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R G U H S · M O D E L A N S W E R B A N K

# RGUHS MD/MS Anatomy — Paper II



M O D E L A N S W E R B A N K

**2 0 0 6 – 2 0 2 6**

*883 recurring topics · Textbook-grounded model answers · cited Recent Advances*

**G R O U N D E D I N :**

Gray's Anatomy (Standring) 41e — spine text  
BD Chaurasia · AK Datta · Moore's Clinically Oriented Anatomy — gross anatomy  
Langman · Moore (Developing Human) · Larsen — embryology  
Thompson & Thompson · Gangane — genetics  
Junqueira · Ross · IB Singh — histology  
Bancroft · Pranab Dey — microscopy & histotechniques  
Halder · Govt Museum Handbook — organ donation & body preservation  
Snell · Vishram Singh · IB Singh — neuroanatomy



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# General embryology (gametogenesis to placenta)



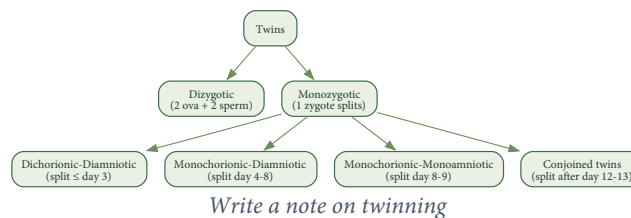
## Write a note on twinning

Asked in: Paper II 28-May-2025 · Paper II 10-Jul-2023 · Paper II Oct 2010 · Paper II May 2010 (4×) — RGUHS MD/MS Anatomy

### Definition / Introduction

Twinning is the phenomenon in which two offspring are produced in a single pregnancy — the commonest form of multiple pregnancy (triplets, quadruplets etc. being rarer variants). Twins are of two fundamental genetic types — **dizygotic** (from two zygotes) and **monozygotic** (from splitting of one zygote) — and spontaneous twinning occurs about once in every 80 births. The clinical importance of twinning lies almost entirely in the **chorionicity and amnionicity** of the pregnancy, which is fixed by the exact embryonic day at which a monozygotic conceptus splits: the later the split, the fewer the membranes shared and the higher the fetal risk, culminating in conjoined twins when splitting is very late.

### 1. Classification of twins



- By zygosity — **dizygotic** (fraternal, biovular) and **monozygotic** (identical, uniovular).
- By chorionicity/amnionicity (monozygotic only) — dichorionic-diamniotic, monochorionic-diamniotic, monochorionic-monoamniotic, conjoined.
- By number of offspring — twins (2), triplets (3), quadruplets (4), quintuplets (5); triplets may arise from one, two or three zygotes.
- Special mechanisms recognised alongside ordinary twinning — superfecundation, superfetation, and semi-identical (polar-body) twinning (below).

### 2. Dizygotic (fraternal) twins

- **Mechanism:** two separate secondary oocytes, released by double ovulation in the same cycle, are fertilised by two different sperm, giving two genetically distinct zygotes; each implants and develops its own placenta, chorion and amnion.
- **Incidence:** 7–10 per 1000 live births, rising with maternal age; population variation is wide — about 6/1000 in Japan up to 12/1000 in Africa, with India intermediate. About 70% of all twins are dizygotic.
- **Genetics/phenotype:** genetically dissimilar (no more alike than ordinary siblings); may be same or different sex — of the three sex combinations, male–female pairs are commonest, followed by female–female, then male–male; overall sex ratio (M:F) is 0.518.

- ▶ **Membranes:** always **dichorionic-diamniotic** — two amnions and two chorions (4 layers at the inter-twin septum). Placentae may be separate, or fuse if implantation sites lie close together (with a firm dividing ridge where the two placental masses abut).
- ▶ **Clinical note:** rarely, exchange of red cells across fused, anastomosing placentae produces **erythrocyte (blood-group) mosaicism** in an otherwise normal dizygotic pair.
- ▶ Increasing rates are linked to ovulation-inducing drugs and assisted reproduction — up to 35% of IVF pregnancies are twin pregnancies.

### 3. Monozygotic (identical) twins — mechanism and chorionicity/amnionicity

- ▶ **Mechanism:** a single zygote (one oocyte + one sperm) splits into two separate cell groups at some point up to the establishment of the embryonic axis and the primitive streak. Splitting of the blastocyst from the zona pellucida ("hatching") is thought to contribute — an incompletely hatched blastocyst may be bisected by the zona, producing two half-blastocysts.
- ▶ **Incidence:** fairly constant across populations, about 3–4 per 1000 live births (unlike dizygotic twinning, it is not much influenced by heredity, age or ART).
- ▶ **Genetics/phenotype:** genetically identical, always same sex; overall M:F sex ratio 0.487, but monochorionic-monoamniotic twins are disproportionately female (M:F 0.231).
- ▶ The timing of the split fixes the chorionicity/amnionicity and hence the outcome:

| Type                       | Time of splitting                                                                | Membrane relations                            | Incidence (of MZ twins)        | Survival / chief risk                                                                              |
|----------------------------|----------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------|
| Dichorionic-diamniotic     | Up to day 3 (2-cell to morula stage)                                             | 2 chorions, 2 amnions, 2 placentas (may fuse) | ~25%                           | Good — comparable to dizygotic twins                                                               |
| Monochorionic-diamniotic   | Day 4–8 (blastocyst stage — inner cell mass splits within one blastocyst cavity) | 1 chorion, 1 placenta, 2 amnions              | ~60–75% (commonest MZ pattern) | ~80% — risk of twin-to-twin transfusion syndrome (placental vascular anastomoses)                  |
| Monochorionic-monoamniotic | ~Day 8–9 (bilaminar germ-disc stage)                                             | 1 chorion, 1 amnion, 1 placenta               | ~1–5% (rare)                   | ~50–60% — transfusion syndrome + umbilical cord entanglement (perinatal mortality approaching 50%) |
| Conjoined twins            | After day 12–13 (incomplete division of the embryonic disc)                      | Single membranes, fused bodies                | Very rare                      | Poor — depends on shared organs                                                                    |

□ Fig 6.8 — Development of the Fetal Membrane in Various Types of Twins (Larsen — Human Embryology — 6e, p.373)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the mechanism-of-twinning schematic above in three parallel columns (dizygotic; early-splitting monozygotic; late-splitting monozygotic), labelling at each level — **Two (or one) zygote(s), Two-cell stage, Splitting at 2-cell stage / Splitting in early blastocyst / Later splitting of one inner cell mass, Two separate inner cell masses, Chorion, Amnion, Placenta** — and end each column with its outcome label: "Separate amnions, chorions and placentas" / "Separate amnions, common chorion and placenta" / "Common amnion, chorion and placenta." Alongside, sketch the four conjoined-twin body diagrams with labels **Craniopagus, Thoracopagus, Omphalopagus, Pyopagus, Ischiopagus** (see figure below).

## 4. Differences between monozygotic and dizygotic twins

| Feature   | Monozygotic                                  | Dizygotic                                        |
|-----------|----------------------------------------------|--------------------------------------------------|
| Origin    | 1 ovum + 1 sperm → 1 zygote that splits      | 2 ova + 2 sperm → 2 zygotes                      |
| Incidence | Less common (~30%)                           | More common (~70%)                               |
| Genotype  | Identical                                    | Dissimilar                                       |
| Phenotype | Similar; strong resemblance                  | Dissimilar                                       |
| Sex       | Always same                                  | Same or different                                |
| Placenta  | Single (shared) or, if early split, separate | Always separate (occasionally secondarily fused) |
| Chorion   | May be single (shared)                       | Always two, separate                             |
| Amnion    | Single or double, depending on time of split | Always two                                       |

## 5. Zygosity determination and genetic/epigenetic aspects of monozygotic twins

- Placental examination alone is **unreliable** for assigning zygosity: about 10% of monozygotic twins (those that split at the 2-cell-to-morula stage) develop two separate placentas and can be wrongly labelled dizygotic at birth. Definitive **zygosity determination** is by **molecular (DNA-marker) analysis**, important before tissue/organ (e.g., bone-marrow) transplantation between twins.
- Despite an identical genotype, monozygotic twins often show **phenotypic discordance**, attributed to: vascular/developmental asymmetry during splitting; post-zygotic somatic mutation; chromosomal aberration arising in one blastocyst after the twinning event; and skewed X-chromosome inactivation in female pairs (one twin preferentially expressing the paternal X, the other the maternal X).
- **Epigenetic influence** (environmentally driven gene switching on/off) accumulates throughout life, so epigenetic discordance is greater in older twin pairs, and greater still if the co-twins are reared apart.

- ▶ **Dermatoglyphics:** monozygotic twins do *not* have identical fingerprints — the pattern of arches, loops and whorls is moulded by differing intrauterine mechanical stresses on each fetus, so broad similarity coexists with fine detailed differences.
- ▶ **Chimerism:** an individual whose body contains cells derived from the co-twin (or mother) is a chimera; detectable by chromosomal comparison in dizygotic pairs, but essentially undetectable in monozygotic pairs.
- ▶ **Mirror-image twins:** a monozygotic pair showing mirror-symmetric features (e.g., opposite handedness); thought to follow a very late split (around day 9).

## 6. Special and rare forms of twinning

- ▶ **Superfecundation** — two (or more) ova ovulated in the same cycle are fertilised by sperm from separate acts of intercourse (potentially different fathers — heteropaternal superfecundation, confirmed by genetic markers); the resulting dizygotic fetuses are of the *same* gestational age.
- ▶ **Superfetation** — an ovum released and fertilised during an *already established* pregnancy, giving fetuses of *different* gestational ages; very rare in humans.
- ▶ **Semi-identical (polar-body/"half-identical") twins** — an extremely rare event in which the twins share identical maternal genes but different paternal genes, postulated to arise from fertilisation of both the ovum and its polar body (or a single ovum fertilised by two sperm) by different spermatozoa followed by splitting; only a handful of confirmed cases exist in the world literature.
- ▶ **Vanishing twin syndrome** — early death and resorption of one member of a twin pair, now commonly detected on serial ultrasonography; may cause discrepancy between prenatal cytogenetic results and the karyotype of the surviving infant.
- ▶ **Parasitic twins / fetus-in-fetu** — asymmetric conjoined twinning in which one twin is rudimentary and vascularly dependent on the well-formed co-twin; when the parasitic twin is entirely enclosed within the host's body, the anomaly is termed *fetus in fetu*.

## Applied / Clinical anatomy

□ Fig 30.3 — Conjoined twins (Sontakke — *Textbook of Human Embryology*, p.316)

- ▶ **Conjoined (Siamese) twins:** arise when division of the embryonic disc is incomplete (split after day 12–13); overall incidence about 1 in 50,000–100,000 births. Classified by site/extent of fusion — **craniopagus** (skull), **thoracopagus** (anterior thoracic and upper abdominal wall to the umbilicus — commonest type; a common pericardial sac is present in ~90% and conjoined hearts in ~75% of cases), **omphalopagus** (lower abdominal wall), **cephalothoracopagus** (head + thorax), **pyopagus/pygopagus** (sacral region, joined dorsally, facing away from each other), and **ischiopagus** (pelvis, classically joined at 180° to the vertebral axis; sub-typed as dipus/tripus/tetrapus by the number of shared lower limbs). Surgical separation is feasible only when no vital organ is shared.
- ▶ **Twin-to-twin transfusion syndrome (TTTS):** complicates monochorionic (chiefly diamniotic) twins that share a single placenta with vascular anastomoses (artery–artery commonest, then artery–vein); an unbalanced shunt makes the **donor** twin small, anaemic and oligohydramniotic, and the **recipient** twin large, polycythaemic, with cardiomegaly and polyhydramnios. It affects up to 30% of monochorionic-diamniotic pairs and is treated by fetoscopic laser ablation of the abnormal anastomoses.

- ▶ **Acardiac twin (TRAP-type)**: unequal division of the embryonic axis or of the placental blood supply in a monochorionic pair can leave one twin without a functioning heart, perfused retrogradely by its co-twin through an arterio-arterial anastomosis.
- ▶ **Monoamniotic pregnancy** carries the highest risk of all — umbilical cord entanglement together with vascular shunting gives a perinatal mortality approaching 50%.
- ▶ Twin pregnancies overall carry higher rates of **pre-eclampsia, preterm delivery, IUGR and congenital anomaly** than singleton pregnancies, and ultrasonographic assessment of chorionicity/amnionicity in the first trimester (before membranes become harder to distinguish) is central to obstetric risk-stratification.

### High-yield exam pointers

- ▶ Spontaneous twinning  $\approx$  1 in 80 births;  $\sim$ 70% dizygotic,  $\sim$ 30% monozygotic.
- ▶ Dizygotic twins are ALWAYS dichorionic-diamniotic; only monozygotic twins show variable chorionicity/amnionicity.
- ▶ Golden rule of timing: split  $\leq$  day 3  $\rightarrow$  dichorionic-diamniotic (25%); day 4–8  $\rightarrow$  monochorionic-diamniotic (60–75%, commonest); day 8–9  $\rightarrow$  monochorionic-monoamniotic (1–5%, cord-entanglement risk); after day 12–13  $\rightarrow$  conjoined twins.
- ▶ Monochorionic-monoamniotic twins carry the highest mortality ( $\sim$ 50%) from cord entanglement and TTTS.
- ▶ TTTS results from unbalanced placental vascular anastomoses in monochorionic twins — donor (small, anaemic, oligohydramnios) vs recipient (large, plethoric, polyhydramnios).
- ▶ Placental appearance alone cannot reliably distinguish zygosity — 10% of monozygotic twins have two separate placentas; DNA-marker testing is definitive.
- ▶ Thoracopagus is the commonest conjoined-twin type; conjoined twins result from incomplete splitting of the embryonic disc after day 12–13.
- ▶ Monozygotic twins are genetically identical but not phenotypically identical (mutation, epigenetics, X-inactivation) — and do NOT share identical fingerprints.
- ▶ Superfecundation (different fathers, same gestational age) vs superfetation (different gestational ages) — a classic differentiator.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Textbook of Anatomy Vol 3 6e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; Larsen — Human Embryology 6e.



## Notochord

Asked in: Paper II 09-May-2022 · Paper II 31-Jul-2021 · Paper II Oct 2009 (3×) — RGUHS MD/MS Anatomy

### Definition / Introduction

The notochord is a solid, midline rod of mesodermal (chordamesodermal) tissue that forms the primary axis of the trilaminar embryo during the third week of intrauterine life. It arises from epiblast cells of the primitive node (Hensen's node) and acts as the principal "organizer" of early development — it induces the overlying ectoderm to form the neural plate/tube and directs the flanking paraxial mesoderm (sclerotome) to form the vertebral column. Although the notochord itself is transient in humans, its inductive influence is permanent; it persists postnatally only as the nucleus pulposus of the intervertebral disc and the apical ligament of the dens.

### Origin and Stages of Formation

Formation proceeds cranial → caudal (the cranial notochord is laid down first as the primitive streak regresses caudally) and passes through four defined stages:

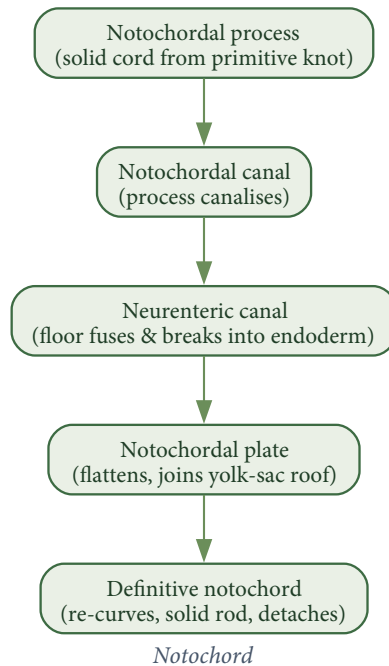
| Stage                   | Event                                                                                                                                                                                                                                                                                  |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Notochordal process  | Proliferating cells of the primitive knot invaginate through the primitive pit (blastopore) and migrate cranially in the midline, between epiblast and hypoblast, up to the prechordal plate — forming a solid cellular cord (head process).                                           |
| 2. Notochordal canal    | The process canalises into a tube; the notochordal canal remains continuous with the primitive pit.                                                                                                                                                                                    |
| 3. Neurenteric canal    | The floor (ventral wall) of the notochordal canal fuses with, and then breaks down into, the underlying endoderm, so the canal transiently communicates with the yolk sac cavity — this transient communication between the amniotic cavity and the yolk sac is the neurenteric canal. |
| 4. Notochordal plate    | The now-open roof of the canal flattens into a plate that is contiguous with the endoderm and forms part of the roof of the yolk sac.                                                                                                                                                  |
| 5. Definitive notochord | The plate re-curves into a tube, proliferates into a solid rod, and detaches completely from the endoderm (endodermal continuity is restored) to form the definitive notochord.                                                                                                        |

The caudal-most notochord (formed later, from the caudal eminence/"caudoneural hinge" after the primitive streak has regressed) arises by a separate process termed secondary neurulation.

 Fig 3.10 — Formation of the Notochordal Process (A, C) Stages showing (Larsen — Human Embryology — 6e, p.185)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw (i) the transverse-section view above (mid and cross-sections through a 17-day embryo) with labels — Amniotic cavity, Ectoderm, Notochordal process, Mesoderm, Endoderm, Yolk sac, Oropharyngeal (buccopharyngeal) membrane, Cloacal membrane, Primitive streak, Prechordal plate, Cardiogenic mesoderm — and (ii) a longitudinal-section series showing the four sequential stages with labels — Primitive knot, Blastopore, Notochordal process, Notochordal canal, Neurenteric canal, Notochordal plate, Definitive notochord, Endoderm restored.



### Molecular Control — the Notochord as Organizer

- ▶ The primitive node is "the organizer"; the **BRACHYURY (T)** gene, expressed in the node, notochordal precursor cells and the notochord, is essential for cell migration through the primitive streak and for notochord formation.
- ▶ The node, notochord and prechordal mesoderm secrete **chordin, noggin and follistatin**, which antagonise BMP4; this "dorsalises" adjacent mesoderm into notochord/paraxial mesoderm and neuralises the overlying ectoderm into the neural plate (default neural-induction model).
- ▶ The notochord, together with the floor plate of the neural tube, later secretes **Sonic hedgehog (SHH)**, which (i) maintains/differentiates the neural floor plate and induces motor neurones, and (ii) induces the ventromedial part of the adjacent somite to become sclerotome (precursor of vertebral bodies and ribs).
- ▶ Experimental removal of the node/notochord abolishes the neural floor plate and motor neurone induction, with ectopic expression of sensory cell types instead — proof of its organizer role.



## Extent, Structure and Relations

- ▶ Extends in the midline from the oropharyngeal (buccopharyngeal) membrane cranially to the region of Hensen's node/primitive streak caudally; it is limited rostrally by the prechordal plate.
- ▶ Lies dorsal to the endoderm (roof of the future foregut) and ventral to the neural tube/neural floor plate.
- ▶ Flanked bilaterally by paraxial mesoderm, which segments into somites and whose ventromedial (sclerotomal) cells later surround both the notochord and the neural tube.
- ▶ Composed of large, turgid, vacuolated cells enclosed by a basal lamina (the perinotochordal sheath); internal cell turgor (osmotic pressure) confers rigidity, giving the notochord a transient skeletal-support function before true vertebrae ossify.
- ▶ The notochord is not a proliferative epithelium once formed, but continues to exert inductive effects on the overlying neural tube and adjacent somites as it elongates.

## Functions of the Notochord

- ▶ Defines the primitive craniocaudal (longitudinal) body axis and marks the future site of the vertebral column.
- ▶ Primary inducer of the neural plate and neural tube from overlying ectoderm (via BMP4 antagonism) — the classical embryonic "organizer."
- ▶ Induces and maintains the floor plate of the neural tube and, together with the floor plate, induces motor neurone differentiation (via SHH).
- ▶ Induces the sclerotomal (ventromedial somite) cells to migrate around the neural tube/notochord and differentiate into the vertebral bodies and ribs (via SHH and noggin).
- ▶ Provides transient axial mechanical support to the embryo before ossification of the vertebral column begins.
- ▶ Provides the central column around which the vertebral bodies and intervertebral discs subsequently develop, without itself contributing cells to the bony vertebra.

## Fate of the Notochord

- ▶ As the sclerotome-derived vertebral bodies condense around it, the notochord within each vertebral body is progressively compressed and degenerates completely — it does **not** contribute to the bony vertebral column.
- ▶ Between successive vertebrae (the future intervertebral disc region) the notochord persists and expands to form the gelatinous **nucleus pulposus** of the intervertebral disc.
- ▶ A small cranial remnant persists as the **apical ligament of the dens** of the axis (C2) vertebra.
- ▶ The notochord is present throughout the phylum Chordata; in lower chordates such as *Amphioxus* it persists life-long as the definitive axial skeleton, but in humans only the above two vestiges remain into adult life.

## Applied / Clinical anatomy

- ▶ **Chordoma**: a slow-growing, locally invasive, bone-infiltrating tumour arising from notochordal remnants; about one-third occur at the cranial base (clivus) and may extend into the



nasopharynx, while the remainder arise in the sacrococcygeal region — the two classical sites correspond exactly to the cranial and caudal extremities of the embryonic notochord.

- ▶ Persistence/abnormal adhesion at the site of the neurenteric canal underlies rare **neurenteric cysts** and the split-notochord malformation spectrum, which is associated clinically with **diastematomyelia** — a bony spicule or fibrous septum splitting the spinal cord/cauda equina longitudinally into two hemicords, often with an overlying cutaneous marker (dimple, hairy patch, or pigmented naevus).
- ▶ **Sacrococcygeal teratoma**, arising from totipotent remnants of the regressing primitive streak/caudal eminence adjacent to the notochord, is the commonest neonatal germ-cell tumour and requires early surgical excision.
- ▶ The **nucleus pulposus**, being of notochordal origin, is gelatinous and avascular (unlike the surrounding fibrocartilaginous annulus fibrosus); its degeneration underlies disc prolapse (herniated nucleus pulposus), a common cause of nerve-root compression.
- ▶ Failure of normal notochord-mediated induction of the neural floor plate is implicated in the pathogenesis of **neural tube defects** (spina bifida, anencephaly); periconceptional folic acid supplementation reduces their incidence.

### High-yield exam pointers

- ▶ Notochord = chordamesoderm; derived from epiblast cells of Hensen's (primitive) node during the 3rd week (stage 7–10 embryo).
- ▶ Four sequential stages: notochordal process → notochordal canal → notochordal plate → definitive notochord, formed cranial-to-caudal.
- ▶ Neurenteric canal = transient communication between amniotic cavity and yolk sac, at the floor of the notochordal canal.
- ▶ Node/notochord secrete chordin, noggin, follistatin (antagonise BMP4) for neural induction; BRACHYURY (T) gene is essential for notochord formation.
- ▶ Notochord + floor plate secrete SHH → induces neural floor plate/motor neurones and sclerotome differentiation.
- ▶ Golden rule: the notochord does **not** form the vertebral column — it only induces and positions it; it persists only as the nucleus pulposus and the apical ligament of the dens.
- ▶ Chordoma arises at the cranial (clivus/nasopharynx) or sacrococcygeal ends of the notochord's original extent.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology.



## Capacitation

Asked in: Paper II May 2018 · Paper II Oct 2008 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** Capacitation is the final, obligatory step in the functional maturation of the spermatozoon, occurring not in the male duct system but inside the female genital tract, that renders an otherwise morphologically mature sperm capable of fertilizing a secondary oocyte. It was first described by **M.C. Chang and Colin Austin independently in 1951**. Freshly ejaculated spermatozoa, though motile and structurally complete, cannot fertilize an oocyte — they must undergo capacitation followed by the acrosome reaction before penetration of the oocyte investments is possible. Capacitation is species-specific and involves no visible morphological change in the sperm, only molecular and membrane-level alterations.

### 1. Site, Duration and Discovery

| Feature            | Detail                                                                                                                                                                                                                                                                    |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Site               | <b>Uterus and uterine tube</b> (starts in the uterus, continues into the tube); cervical mucus and tubal epithelial secretions also contribute conditioning signals                                                                                                       |
| Duration in humans | Approximately <b>7 hours</b>                                                                                                                                                                                                                                              |
| Nature             | <b>Species-specific</b> interaction between sperm and oocyte/female tract secretions                                                                                                                                                                                      |
| Morphology         | <b>No visible morphological change</b> — sperm appear structurally identical before and after                                                                                                                                                                             |
| Discoverer         | Chang and Austin (1951), independently                                                                                                                                                                                                                                    |
| In vitro           | For IVF/ART, capacitation is induced artificially by incubating washed sperm for several hours in a defined medium (e.g. containing $\gamma$ -globulin, follicular fluid, dextran, serum dialysate, adrenal gland extract, or a bicarbonate/albumin-based culture medium) |

### 2. Background — Epididymal Maturation and the "Decapacitation Factor"

Capacitation must be understood against the maturation that precedes it in the male tract:

- ▶ Spermatozoa released from the seminiferous tubules are **immature, non-motile, and incapable of fertilizing an ovum**.
- ▶ During their **2–3 day transit through the epididymis**, glycoproteins of the plasma membrane covering the sperm head are altered and the sperm acquire progressive motility.
- ▶ Crucially, epididymal fluid deposits a surface-associated "**decapacitation factor**" — a coat of glycoproteins/glycoconjugates (with added cholesterol) over the sperm head and acrosome — which **reversibly inhibits the acrosome reaction and fertilizing ability** until it is stripped away.

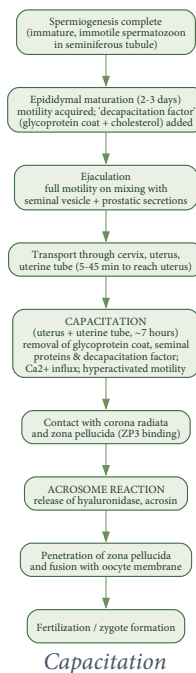
- ▶ Sperm become fully motile only after ejaculation, once mixed with prostatic and seminal vesicle secretions, but they still carry this inhibitory coat and **remain incapable of fertilization** — this coat is exactly what capacitation removes in the female tract.

This explains the key exam point: **maturation (epididymis) confers motility; capacitation (female tract) confers fertilizing capacity** — the two are distinct, sequential processes.

### 3. Molecular and Membrane Changes During Capacitation

- ▶ **Removal of the glycoprotein coat and seminal plasma proteins** overlying the plasma membrane of the sperm head/acrosome, including removal of the decapacitation factor acquired in the epididymis.
- ▶ **Extensive alteration of sperm membrane components** — changes in surface glycoproteins expose the underlying zona-binding proteins that were previously masked, allowing sperm–egg (zona pellucida) binding.
- ▶ **Changes in the sperm cell membrane and signal transduction** — calcium ion influx, altered membrane fluidity/lipid organisation, and release of acrosomal-membrane-associated signalling that primes the acrosome.
- ▶ **Development of hyperactivated motility** — a vigorous, whiplash-type flagellar beat pattern that assists penetration through the cumulus/corona and zona.
- ▶ Capacitation and the subsequent acrosome reaction are regulated in part through **tyrosine-kinase (src-kinase)–mediated signalling** pathways.
- ▶ **Follicular fluid** secreted around ovulation is thought to enhance capacitation.
- ▶ **Completion of capacitation is the prerequisite that permits the acrosome reaction to occur** on contact with the zona pellucida — a capacitated sperm's acrosome binds the zona glycoprotein ZP3, triggering exocytotic release of acrosomal enzymes (hyaluronidase, acrosin) that digest a path through the zona pellucida.

#### 4. Sequence: From Spermatid to Fertilization



#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A simple two-panel schematic of the sperm head, labelled:

- ▶ **Before capacitation:** Plasma membrane → glycoprotein coat + seminal plasma proteins ("decapacitation factor") intact over the acrosomal cap → zona-binding sites masked.
- ▶ **After capacitation:** Glycoprotein coat/seminal proteins stripped away → plasma membrane altered/thinned over acrosome → zona-binding receptors exposed → acrosome primed for the acrosome reaction on ZP3 contact.

Label the acrosomal cap, post-acrosomal (equatorial) region, plasma membrane, outer and inner acrosomal membranes, and nucleus in both panels.

□ Fig 3.5 — A. Scanning electron micrograph of sperm binding to the zona pellucida. B. The three phases of oocyte penetration; inset shows a normal spermatozoon with acrosomal head cap (Langman's Medical Embryology — Sadler — 14e, p.57)

#### 5. Significance of Capacitation

- ▶ It is a **necessary and independent step** for functional fertilizing competence — capacitation status determines fertilizing ability irrespective of a sperm's motility or morphology.
- ▶ Only **capacitated sperm can undergo the acrosome reaction**; uncapacitated sperm carrying the decapacitation factor cannot release acrosomal enzymes on contact with the zona pellucida and hence cannot fertilize.
- ▶ Capacitated sperm show **hyperactivated motility**, which mechanically assists breach of the corona radiata and zona pellucida.
- ▶ Because capacitation is time-limited and species-specific, it also underlies the practical timing windows used in assisted reproduction.

## Applied / Clinical anatomy

- ▶ **Assisted reproduction (IVF/ICSI/IUI):** because natural capacitation requires passage through the uterus and tube, sperm intended for in vitro fertilization or intrauterine insemination must be **capacitated artificially** — washed free of seminal plasma and incubated for several hours in a defined capacitating medium — before they are competent to fertilize an oocyte in vitro.
- ▶ **Sperm timing in the female tract:** since capacitation takes ~7 hours, spermatozoa that "sprint" quickly to the ampulla gain no advantage — they are not yet capacitated and cannot fertilize the oocyte immediately on arrival; effective fertility therefore depends on sperm surviving in the tract long enough to complete capacitation (spermatozoa remain able to fertilize for roughly 1–3 days in the ampulla).
- ▶ **Male infertility work-up:** defects in epididymal maturation (e.g. obstructive azoospermia, congenital absence of vas deferens) or in the capacitation/acrosome-reaction cascade are assessed via semen analysis (motility, morphology) and specialised sperm-function/acrosome-reaction assays; a normal sperm count with poor capacitation or acrosome reaction can still cause unexplained infertility.
- ▶ **Contraceptive relevance:** agents that interfere with tubal/uterine secretions (e.g. progestogen-dominant states that thicken cervical mucus or alter tubal fluid) can impair sperm capacitation and transport, contributing to their contraceptive effect.
- ▶ **ART clinical correlation:** in ICSI, the natural requirement for capacitation and acrosome reaction is bypassed altogether by direct microinjection of a single (even immotile or acrosome-defective) spermatozoon into the oocyte cytoplasm.

## High-yield exam pointers

- ▶ Capacitation = final functional maturation of sperm, occurring in the **female genital tract (uterus + uterine tube)**, taking ~7 hours in humans; discovered by **Chang and Austin, 1951**.
- ▶ No morphological change — purely a **molecular/membrane-level** conditioning process.
- ▶ Core event: **removal of the glycoprotein coat, seminal plasma proteins, and the epididymal "decapacitation factor"** from the sperm plasma membrane overlying the acrosome.
- ▶ Distinguish from **epididymal maturation** (confers motility, occurs in the male tract over 2–3 days) — capacitation confers **fertilizing capacity**, not motility per se, though it does produce hyperactivated motility.
- ▶ Completion of capacitation is the **prerequisite for the acrosome reaction**; only capacitated sperm bind ZP3 and undergo acrosomal enzyme release (hyaluronidase, acrosin).
- ▶ Capacitation is **species-specific**.
- ▶ Clinically induced artificially for **IVF/IUI**; bypassed entirely in **ICSI**.
- ▶ Uncapacitated (freshly ejaculated) sperm cannot fertilize an oocyte even though fully motile.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas; Ross Histology — A Text and Atlas 7e; Junqueira's Basic Histology 17e.



## Chorionic villi

*Asked in: Paper II Nov 2017 · Paper II Oct 2006 (2×) — RGUHS MD/MS Anatomy*

### Definition / Introduction

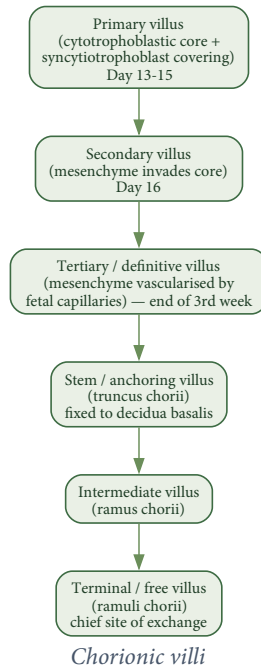
Chorionic villi are finger-like vascular projections of the chorion — the outer, trophoblast-derived fetal membrane — that arise from the chorion frondosum and burrow into the endometrial decidua basalis to build the fetal part of the placenta. They mature through **primary** → **secondary** → **tertiary** stages during the second and third weeks of development, and thereafter branch repeatedly into **stem** (anchoring), **intermediate** and **terminal villi** that persist till term. Bathed externally by maternal blood in the intervillous space (a **haemochorial** arrangement) and carrying fetal blood internally, chorionic villi constitute the sole functional unit of feto-maternal exchange and the principal endocrine tissue of pregnancy.

### 1. Development of chorionic villi

- ▶ **Days 6–9 (pre-lacunar/lacunar stage):** the syncytiotrophoblast erodes decidual glands and maternal spiral arteries; vacuoles coalesce to form **lacunae** within the syncytium, later filled with maternal blood.
- ▶ **Days 13–15 — Primary villi:** cellular columns of cytotrophoblast proliferate and project into the overlying syncytiotrophoblast, covering the entire surface of the chorionic vesicle. A primary villus therefore has a **cytotrophoblastic core covered by syncytiotrophoblast**.
- ▶ **Day 16 — Secondary villi:** extraembryonic (somatic) mesoderm/mesenchyme, derived from the chorionic plate, migrates into and invades the cytotrophoblastic core, converting each primary villus into a **secondary villus** with three layers — syncytiotrophoblast, cytotrophoblast and a central mesenchymal core.
- ▶ **End of 3rd week — Tertiary (definitive) villi:** mesenchymal cells in the villous core differentiate into blood cells and small blood vessels (**villous capillary system**). The villus is now a tertiary or definitive placental villus. Its capillaries make contact with vessels developing in the chorionic plate and connecting stalk, and with the intraembryonic circulation, so that when the **heart begins to beat in the 4th week**, the villous system is already prepared to supply the embryo.
- ▶ Concurrently, cytotrophoblast cells at the villous tips penetrate progressively through the overlying syncytium to reach the maternal decidua, where neighbouring outgrowths meet and fuse to form a spherical **cytotrophoblastic (Langhans') shell**, anchoring the chorion to the

decidua and giving rise to extravillous cytotrophoblastic cell columns that invade the decidua and remodel maternal spiral arteries into low-resistance uteroplacental vessels.

- By the 4th–5th week, villi cover the entire chorionic surface. From about the 8th week, villi facing the **decidua capsularis** degenerate (forming the smooth **chorion laeve**), while villi facing the **decidua basalis** proliferate luxuriantly to form the definitive, bushy **chorion frondosum** — the fetal placenta — which gives rise to ~40–60 stem villi (**truncus chorii**).



## 2. Classification of chorionic villi (branching pattern)

| Type                                                      | Attachment / location                                                                                 | Salient feature                                                                                                                                        |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Stem villus / anchoring villus</b><br>(truncus chorii) | Extends from the chorionic plate to the decidua basalis; tip fixed by a cytotrophoblastic cell column | Main supporting trunk of the villous tree; ~40–60 per placenta, each forming a <b>fetal cotyledon</b> ; carries a main branch of the umbilical vessels |
| <b>Intermediate villus</b> (ramus chorii)                 | Lateral branches given off by the stem villus, projecting freely into the intervillous space          | Conducting/transitional segment between stem and terminal villi                                                                                        |
| <b>Terminal villus / free villus</b><br>(ramuli chorii)   | Finest terminal ramifications, entirely bathed in maternal blood                                      | Maximal surface-to-volume ratio; principal site of feto-maternal exchange; shows thin vasculo-syncytial membranes                                      |

Each stem villus and its arborisation into intermediate and terminal villi forms the essential structural, functional and growth unit of the placenta; the **maternal surface** of the placenta is correspondingly demarcated by cotyledonary (placental) septa into 15–30 lobes (**maternal cotyledons**).

## 3. Microscopic structure of a mature (tertiary) chorionic villus

- Fig 19.18 — Chorionic Villi: Placenta at Five Months. Stain: hematoxylin-eosin. Hi (diFiore's Atlas of Histology — Eroschenko, p.330)

| Layer (outside → inside)                     | Composition                                                                                                                                                      | Functional note                                                                                                                                                                                              |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Syncytiotrophoblast                          | Multinucleated syncytium with no distinct intercellular boundaries; luminal surface bears a dense <b>microvillous brush border</b> facing the intervillous space | Site of transplacental transport and of synthesis/secretion of placental hormones (hCG, hPL, oestrogens, progesterone)                                                                                       |
| Cytotrophoblast (Langhans cells)             | Single, pale-staining, mononuclear cells resting on a basal lamina; joined by desmosomes                                                                         | Germinal layer — proliferates and fuses into overlying syncytium; becomes discontinuous after the 4th month (syncytium covers ~56% of the basal lamina at term)                                              |
| Villous connective-tissue (mesenchymal) core | Fibroblasts, reticulum cells, collagen types I, III, V, VI, and <b>Hofbauer cells</b> (fetal macrophages)                                                        | Structural support; Hofbauer cells are phagocytic/immunomodulatory fetal macrophages                                                                                                                         |
| Fetal capillary endothelium + basal lamina   | Non-fenestrated endothelium with tight and adherens junctions                                                                                                    | In terminal villi the fetal capillary and trophoblast basal laminae fuse to form a thin <b>vasculo-syncytial membrane</b> , reducing the maternal–fetal diffusion distance to as little as 2–3 $\mu\text{m}$ |

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Labelled cross-section of a mature (terminal) chorionic villus floating in the intervillous space — label:

- ▶ Intervillous space with maternal blood
- ▶ Syncytiotrophoblast (with microvillous brush border)
- ▶ Syncytial knot / syncytial sprout
- ▶ Cytotrophoblast (Langhans cell)
- ▶ Trophoblastic basal lamina
- ▶ Villous connective-tissue stroma
- ▶ Hofbauer cell (fetal macrophage)
- ▶ Fetal capillary endothelium + basal lamina
- ▶ Fetal capillary lumen with fetal erythrocytes
- ▶ Vasculo-syncytial membrane (site of fused basal laminae)

#### 4. Placental (villous) membrane / placental barrier

The tissues intervening between maternal blood in the intervillous space and fetal blood in the villous capillaries constitute the placental membrane (barrier), across which all feto-maternal exchange occurs.



| Stage                              | Constituent layers (maternal → fetal side)                                                                                                                                                                                                                                               | Thickness |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Early pregnancy (up to ~4th month) | Syncytiotrophoblast → Cytotrophoblast (with basal lamina) → Villous mesenchyme (connective tissue) → Endothelium of fetal capillary (with basal lamina) — <b>4 layers</b>                                                                                                                | ~0.025 mm |
| Later pregnancy / term             | Cytotrophoblast becomes discontinuous and largely disappears; syncytiotrophoblast thins; stroma becomes oedematous; fetal capillaries migrate peripherally to abut the trophoblast, so the barrier is reduced to <b>syncytiotrophoblast + fused basal lamina + capillary endothelium</b> | ~0.002 mm |

- ▶ Total surface area of the placental membrane ranges from **4 m<sup>2</sup> to 14 m<sup>2</sup>** — comparable to the total absorptive area of the adult intestine — with effective area further increased by syncytiotrophoblastic microvilli.
- ▶ Towards term, patchy **fibrinoid deposits** appear on the villous surface (a repair phenomenon after focal trophoblast loss) and reduce the efficiency of exchange.
- ▶ The placenta is thus **haemochorial** (maternal blood in direct contact with the syncytiotrophoblast), **chorioallantoic** (vascular supply via allantoic/umbilical vessels), **deciduate**, and **discoid, cotyledonous and villous** in gross structure.

## 5. Functions of chorionic villi (placental function mediated through villi)

- ▶ **Respiratory/gas exchange** — simple diffusion of O<sub>2</sub> and CO<sub>2</sub> across the villous membrane; a term fetus extracts ~25 mL O<sub>2</sub>/min from maternal blood.
- ▶ **Nutritive function** — transfer of water, electrolytes, glucose (facilitated diffusion), amino acids and calcium (active transport), and fatty/water-soluble vitamins; water is exchanged at roughly 3.5 L/hour in both directions.
- ▶ **Excretory function** — elimination of CO<sub>2</sub>, urea and other fetal waste products into the maternal circulation.
- ▶ **Endocrine function** — the syncytiotrophoblast synthesises and secretes human chorionic gonadotropin (hCG), human placental lactogen/human chorionic somatomammotropin (hPL/hCS), progesterone and oestrogens; trophoblastic 11β-hydroxysteroid dehydrogenase-2 inactivates maternal cortisol, protecting the fetus from excess glucocorticoid.
- ▶ **Immunological function** — transfer of maternal IgG by receptor-mediated micropinocytosis confers passive immunity (e.g., against diphtheria, measles); the villous trophoblast itself is immunologically tolerogenic to paternal antigens.
- ▶ **Barrier function** — restricts most bacteria, but many viruses (rubella, CMV, HSV, parvovirus) and organisms such as *Toxoplasma gondii* can cross (the **TORCH** group), as can most small lipophilic drugs from ~7 weeks onward — hence its importance in teratology.

- ▶ **Storage function** — glycogen and lipid droplets are stored transiently within the trophoblast layers.

## Applied / Clinical anatomy

- ▶ **Chorionic villus sampling (CVS)**: transabdominal or transcervical aspiration of 5–30 mg of villous tissue (from the mesenchymal core after trypsinisation of external trophoblast) for rapid fetal karyotyping/DNA analysis, typically performed around 8–10 weeks — earlier than amniocentesis. Procedure-related pregnancy loss approaches that of amniocentesis in experienced hands, but CVS carries a small additional risk of limb-reduction defects.
- ▶ **Hydatidiform mole**: cystic, hydropic degeneration of villi with trophoblastic hyperplasia ("bunch of grapes" appearance; "snow-storm" on ultrasound) and grossly elevated hCG. **Complete mole** — androgenetic, no embryonic tissue, higher (10–15%) risk of subsequent choriocarcinoma; **partial mole** — triploid/tetraploid, some fetal tissue present, lower malignant potential.
- ▶ **Disorders of trophoblastic/villous invasion**: failure of extravillous trophoblast to remodel maternal spiral arteries into low-resistance vessels underlies **early-onset pre-eclampsia, miscarriage and fetal growth restriction**; excessive villous invasion into and beyond the myometrium underlies the **placenta accreta spectrum** (accreta/increta/percreta).
- ▶ **Villitis of unknown aetiology / infective villitis**: lymphoplasmacytic infiltration of villous stroma seen with TORCH infections, contributing to fetal loss or growth restriction.
- ▶ **Rh (D) isoimmunisation**: transplacental passage of fetal erythrocytes across damaged villous membrane sensitises an Rh-negative mother, with anti-D IgG subsequently crossing back to cause haemolytic disease of the fetus/newborn.
- ▶ **Choriocarcinoma**: highly malignant, haemorrhagic tumour of villous trophoblast (cyto- + syncytiotrophoblast) that characteristically shows **no villus formation**, arising from a mole, normal pregnancy or abortion; secretes very high hCG used as a tumour marker.

## High-yield exam pointers

- ▶ Villus maturation sequence: **primary** (cytotrophoblast + syncytiotrophoblast) → **secondary** (mesenchymal core added) → **tertiary/definitive** (vascularised by fetal capillaries) — complete by the end of the 3rd week, just before the heart starts beating (4th week).
- ▶ **Stem/anchoring villi (truncus chorii)** fix the placenta to the decidua basalis via the cytotrophoblastic (Langhans') shell; there are ~40–60 stem villi, each the core of a fetal cotyledon; the maternal surface shows 15–30 cotyledons demarcated by placental septa.
- ▶ **Terminal (free) villi** are bathed directly in maternal blood (haemochorial placenta) and are the chief site of feto-maternal exchange.
- ▶ Placental membrane = **4 layers early** (syncytiotrophoblast, cytotrophoblast, mesenchyme, fetal endothelium) reducing to **syncytiotrophoblast + fused basal lamina + endothelium** at term; thickness falls from **0.025 mm to 0.002 mm**; total exchange area **4–14 m<sup>2</sup>**.
- ▶ **Hofbauer cells** = fetal macrophages in the villous stroma.
- ▶ The villous syncytiotrophoblast is the **sole endocrine layer**, secreting hCG, hPL, progesterone and oestrogens.

- Clinically: villi are sampled in CVS for prenatal diagnosis; abnormal villous development underlies **hydatidiform mole**; failed villous/spiral-artery remodelling underlies **pre-eclampsia** and **IUGR**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Sontakke Textbook of Human Embryology and Textbook of Human Histology 2e; Ross Histology — A Text and Atlas 7e; Vishram Singh Textbook of Clinical Embryology; diFiore's Atlas of Histology (Eroschenko) — source of the embedded photomicrograph.



## Fertilization

*Asked in: Paper II 14-Nov-2019 · Paper II Oct 2010 (2×) — RGUHS MD/MS Anatomy*

**Definition / Introduction** Fertilization is the process of fusion of the male and female gametes — the spermatozoon and the secondary oocyte — to form a single-cell **zygote**, the first cell of the new individual. It normally occurs in the **ampulla of the uterine tube**, the widest part of the tube and the one closest to the ovary, within about 12–24 hours of ovulation. Fertilization restores the diploid chromosome number, determines the genetic sex of the embryo, and initiates cleavage; it is therefore the essential biological event on which propagation of the species depends.

### 1. Site, timing, and transport of the gametes

- **Site:** ampulla of the uterine tube (widest, most dilated part, nearest the ovary).
- **Time window:** the oocyte is fertilizable for only about 12–24 hours after ovulation; sperm remain viable in the female tract for several days, so fertilization can follow intercourse from a few days before ovulation up to about a day after it.
- **Sperm transport:** of the 200–300 million spermatozoa deposited in the vagina, only a few hundred (roughly 200–500) reach the site of fertilization — the high ejaculated number compensates for heavy attrition en route. **Prostaglandins in semen** provoke uterine contractions (reinforced by oxytocin) that draw sperm into the uterine cavity; passage from cervix to isthmus (2–7 hours) is mainly by the sperm's own tail action, aided by ciliary currents; sperm quiesce at the isthmus and regain motility at ovulation — probably via **chemoattractants from the cumulus cells** — swimming on to the ampulla. Most sperm die within 24 hours.
- **Oocyte transport:** the ovulated secondary oocyte, arrested in metaphase II and surrounded by the corona radiata, is swept into the ampulla by fimbrial and ciliary action aided by tubal smooth-muscle contraction.

### 2. Capacitation and the acrosome reaction

Before it can fertilize, a spermatozoon must overcome three successive barriers around the oocyte — the **corona radiata**, the **zona pellucida** (a glycoprotein shell made of ZP1, ZP2 and ZP3), and the

oocyte's own **plasma (vitelline) membrane**. This capability is acquired through two sequential functional changes:

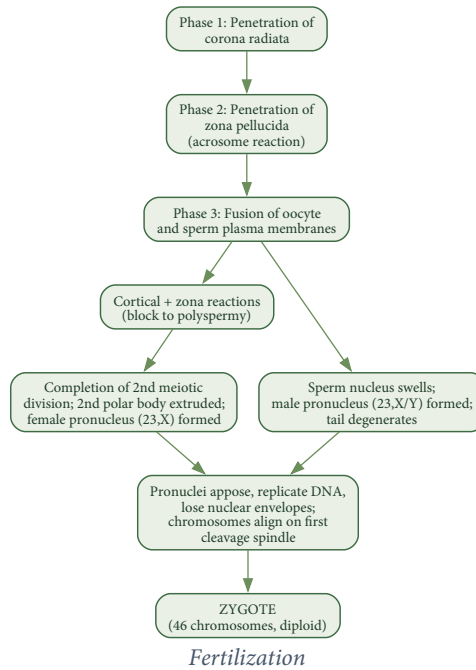
| Step                     | Where it occurs                                                                                                                                                           | What happens                                                                                                                                                                                                                                     |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Capacitation</b>      | Female genital tract (uterus and uterine tube); ~7 hours in the human                                                                                                     | Removal of a glycoprotein coat and adherent seminal-plasma proteins from the plasma membrane overlying the sperm's acrosomal region; only capacitated sperm can traverse the corona radiata and undergo the acrosome reaction                    |
| <b>Acrosome reaction</b> | Induced on contact with the zona pellucida (mediated by the zona glycoprotein <b>ZP3</b> , which acts as both the sperm-binding ligand and the acrosome-reaction inducer) | Vesiculation and shedding of the outer acrosomal membrane, exposing/releasing acrosomal enzymes — <b>hyaluronidase</b> , <b>acrosin</b> , and trypsin-/pepsin-like proteases — which digest a path through the corona radiata and zona pellucida |

*In vitro*, capacitation can be induced artificially by incubating washed sperm in a defined medium, or by exposure to  $\gamma$ -globulin, free serum, follicular fluid, dextran, serum dialysate or adrenal-gland extract — the basis of sperm preparation for IVF/ICSI.

### 3. The three phases of fertilization

| Phase                                                            | Event                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Phase 1 — Penetration of the corona radiata</b>               | Capacitated sperm swim freely through the corona cells using tail movements, aided by hyaluronidase digesting the hyaluronic-acid-rich intercellular matrix                                                                                                                                                                                                                                                                           |
| <b>Phase 2 — Penetration of the zona pellucida</b>               | Zona (ZP3) binding triggers the acrosome reaction; released acrosin/trypsin-like enzymes lyse the zona, letting the sperm reach the perivitelline space and contact the oocyte plasma membrane                                                                                                                                                                                                                                        |
| <b>Phase 3 — Fusion of the oocyte and sperm plasma membranes</b> | Initial adhesion is mediated by <b>integrins</b> on the oocyte and their ligands, <b>disintegrins</b> , on the sperm; because the membrane over the acrosomal cap was already lost, actual fusion occurs between the oocyte membrane and the membrane over the posterior (equatorial) region of the sperm head — both sperm head and tail enter the ooplasm, but the sperm's own plasma membrane is left behind on the oocyte surface |

□ Fig 3.5 — A. Scanning electron micrograph of sperm binding to the zona pellucida (Langman's Medical Embryology — Sadler — 14e, p.57)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the oocyte in the ampulla and label, in sequence: (1) **corona radiata** with capacitated sperm passing through; (2) **zona pellucida** with a sperm head undergoing the **acrosome reaction**; (3) **perivitelline space** and **oocyte plasma (vitelline) membrane** at the site of sperm–oocyte fusion; (4) **cortical granules** discharging beneath the oolemma (cortical reaction); (5) **first polar body** and the **second polar body** being extruded; (6) **female pronucleus (23,X)** and **male pronucleus (23,X/Y)** apposed, with the sperm's degenerating tail; (7) chromosomes of both pronuclei on a common **first cleavage spindle**, labelled the **zygote**.

## 4. Prevention of polyspermy

Only a single spermatozoon normally fertilizes the oocyte, even though several may be found embedded in the zona pellucida. Two coordinated mechanisms block entry of additional sperm as soon as the first sperm fuses with the oocyte membrane:

- ▶ **Cortical reaction:** sperm entry triggers a **calcium wave** in the ooplasm, which causes the enzyme-rich **cortical granules** lining the oocyte plasma membrane to discharge their lysosomal enzymes into the perivitelline space, beginning at the point of sperm fusion and spreading circumferentially.
- ▶ **Zona reaction:** the released cortical-granule enzymes modify the zona pellucida glycoproteins, converting the zona into an impenetrable barrier and inactivating the species-specific sperm receptors on its surface — additional sperm already embedded in the zona can no longer complete penetration.
- ▶ **Vitelline (membrane) block:** the same calcium wave alters the oocyte's own plasma membrane so that it too becomes impermeable to further sperm, reinforcing the zona reaction.

Failure of this block permits **polyspermy** — fertilization by more than one sperm — producing an abnormal (commonly triploid) zygote that is not compatible with normal development; this is one

recognised route to a **hydatidiform mole**, most of which are in fact monospermic (a single sperm fertilizing an "empty" oocyte lacking a female pronucleus, with subsequent duplication of the paternal genome).

## 5. Completion of meiosis, pronuclear formation, and the zygote

As soon as the sperm enters, the egg responds in three coordinated ways:

- ▶ **Cortical and zona reactions** (described above), guarding against polyspermy.
- ▶ **Resumption and completion of the second meiotic division**: the secondary oocyte, arrested in metaphase II since ovulation, now completes meiosis II, producing two very unequal cells — the **second polar body** (almost no cytoplasm) and the **mature (definitive) oocyte**, whose 23 (22 + X) chromosomes condense into a vesicular **female pronucleus**.
- ▶ **Metabolic activation of the egg** — an activating factor carried in by the sperm triggers the cellular and molecular events of early embryogenesis.

Meanwhile the sperm nucleus swells to form the **male pronucleus (23,X or 23,Y)**; its tail detaches and degenerates. The male and female pronuclei — morphologically indistinguishable, each still haploid — approach one another, and each independently **replicates its DNA** (so that each chromosome now consists of two chromatids) before the nuclear envelopes break down and the maternal and paternal chromosomes intermingle on a single **first mitotic (cleavage) spindle**. This restores the diploid number of 46 chromosomes and constitutes formation of the **zygote**, which almost immediately begins its first cleavage division.

## 6. Results / significance of fertilization

| Result                             | Detail                                                                                                                                                                                                                                             |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Restoration of diploid number      | 23 paternal + 23 maternal chromosomes → 46, half from each parent                                                                                                                                                                                  |
| Determination of chromosomal sex   | Oocytes carry only X; sperm are X-bearing (gynosperm) or Y-bearing (androsperm) — an X-sperm gives a female (XX), a Y-sperm a male (XY) embryo, so the <b>father determines the child's sex</b>                                                    |
| Completion of 2nd meiotic division | Second polar body is extruded from the oocyte                                                                                                                                                                                                      |
| Initiation of cleavage             | The zygote begins rapid mitotic division immediately; an unfertilized oocyte instead degenerates within ~24 hours                                                                                                                                  |
| Species variation                  | New combination of maternal and paternal genes makes each zygote genetically unique; interspecies hybrids (e.g., liger — tiger ovum × lion sperm; mule — donkey ovum × horse sperm) illustrate that gamete fusion fixes the offspring's characters |

## Applied / Clinical anatomy

- ▶ **Ectopic pregnancy**: previous **pelvic inflammatory disease** damaging the tubal epithelium (or an IUD/progestin-only contraceptive altering tubal transport) can delay conceptus transport so that implantation occurs within the tube. The **ampulla is the commonest ectopic site**; cornual



(intramural) ectopics risk catastrophic haemorrhage from the rich myometrial vasculature, and rupture may occur as early as 8 weeks. Primary ovarian/abdominal pregnancies are exceptionally rare.

- ▶ **Infertility:** affects ~20% of couples; commonest female cause is **tubal blockage** (often post-PID) preventing sperm reaching the ampulla, commonest male cause is **oligospermia**.
- ▶ **ART:** tubal blockage is bypassed by **IVF** (gonadotrophin-stimulated oocytes aspirated, incubated with artificially capacitated sperm, cleaving embryos transferred to the uterus); severe male-factor infertility is managed by **ICSI** (direct sperm injection into the oocyte), equally successful as routine IVF.
- ▶ **Pregnancy testing:** **hCG**, secreted by the syncytiotrophoblast after implantation, maintains corpus luteal progesterone (essential until the placenta takes over near 8 weeks) and is detectable in maternal blood/urine within days — the basis of the pregnancy test.
- ▶ **Fertility control:** barrier methods, hormonal contraceptives (inhibiting ovulation, thickening cervical mucus) and IUDs (impairing sperm viability/tubal transport, or for copper devices directly impeding fertilization) act at points along the gamete-transport/capacitation/fertilization pathway above.
- ▶ **Abnormal fertilization:** polyspermy or fertilization of a genetically empty oocyte can produce a **hydatidiform mole** (complete — no embryo; partial — some embryonic tissue), 3–5% of which undergo malignant change to **choriocarcinoma**.

### High-yield exam pointers

- ▶ Site of fertilization: **ampulla of the uterine tube**; occurs within ~12–24 hours of ovulation.
- ▶ Two prerequisite sperm changes: **capacitation** (~7 hours, in the female tract) then the **acrosome reaction** (induced by zona protein ZP3), releasing **hyaluronidase** and **acrosin**.
- ▶ Three phases: penetration of **corona radiata** → penetration of **zona pellucida** → **fusion of gamete membranes** (mediated by integrin–disintegrin interaction).
- ▶ Block to polyspermy = **cortical reaction** + **zona reaction** (± vitelline block), all triggered by a **calcium wave**.
- ▶ Fertilization completes the oocyte's **second meiotic division** (second polar body extruded) and triggers formation of male + female **pronuclei**, which fuse to restore the **diploid (46) chromosome number**.
- ▶ **Sex of the child is determined by the father** (X- vs Y-bearing sperm).
- ▶ Fertilization **initiates cleavage**; the unfertilized oocyte degenerates within ~24 hours.
- ▶ Applied correlates: **ampulla** = **commonest ectopic site**; tubal block/oligospermia = commonest infertility causes; **IVF/ICSI** bypass fertilization barriers; **hCG** from syncytiotrophoblast is the basis of the pregnancy test; failed polyspermy block → **hydatidiform mole**.

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Vishram Singh Textbook of Clinical Embryology; Gray's Anatomy (Standring) 41e; Junqueira's Basic Histology 17e (definition cross-check); Moore The Developing Human 9e (site/timing cross-check).



## Notochordal Canal

*Asked in: Paper II May 2018 · Paper II May 2009 (2×) — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The notochordal canal is a transient, midline tubular cavity that develops within the solid **notochordal process (head process)** during the third week of intrauterine life (IUL), as gastrulation converts the flat trilaminar embryo into an organized axial structure. It is formed by canalization of the notochordal process that has grown cranially from **Hensen's node (primitive knot)**, and it briefly re-opens a communication between the amniotic cavity and the yolk sac (umbilical vesicle) — the **neurenteric canal**. The notochordal canal is thus an obligatory intermediate stage between the solid notochordal process and the flattened **notochordal plate**, from which the **definitive notochord** — the primary organizer of the vertebrate body axis — is finally derived.

### 1. Antecedent structures — setting the stage

- ▶ The **primitive streak** appears on day 15 as a linear thickened band of pluripotent epiblast cells in the caudal midline of the bilaminar embryonic disc.
- ▶ Its cranial end is expanded into a rounded elevation, the **primitive knot / primitive node / Hensen's node**, at the centre of which lies a shallow depression, the **primitive pit** — continuous caudally with the primitive groove of the streak.
- ▶ Hensen's node functions as the "**organizer**" of the embryo: it regulates laterality (left–right determination) and drives formation of the notochord, prechordal plate and embryonic endoderm.
- ▶ Cells of the node proliferate and ingress at the primitive pit — this ingressing population is the **prenotochordal cell** population, which will build the axial midline structures in strict cranio-caudal sequence.

### 2. Stepwise formation of the notochordal canal

| Step | Event                                                                                                                                                                                                             |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1    | Prenotochordal cells of Hensen's node invaginate at the primitive pit, producing a central depression — the <b>blastopore</b> .                                                                                   |
| 2    | These cells migrate cranially in the midline, between ectoderm and endoderm, up to the caudal margin of the prochordal (prechordal) plate, forming a solid cord — the <b>notochordal process / head process</b> . |

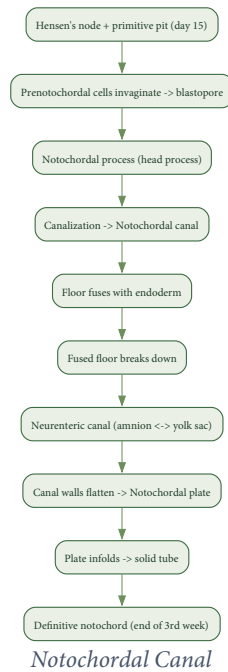


| Step | Event                                                                                                                                                                                                    |
|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3    | The cavity of the blastopore extends forward into the notochordal process, canalizing it into a hollow tube — the <b>notochordal canal</b> , which remains continuous with the blastopore/primitive pit. |
| 4    | The <b>floor of the notochordal canal fuses</b> with the underlying embryonic endoderm forming the roof of the yolk sac.                                                                                 |

- ▶ The notochord lengthens caudally as the primitive streak simultaneously recedes and regresses, so that the most cranial part of the axial rod matures first and canalization proceeds in a strict **cranio-caudal direction**.
- ▶ By Carnegie stage 7 the notochordal process is an established solid cord; canalization to form the notochordal canal is seen through stages 8–9.

### 3. The neurenteric canal — a transient communication

- ▶ The **fused floor** (wall of notochordal canal + adjoining endoderm) breaks down — first as small perforations, which then coalesce into a single opening.
- ▶ The notochordal canal now communicates with the cavity of the **yolk sac** at one end and, via the primitive pit, with the **amniotic cavity** at the other — this transitory passage is the **neurenteric canal**.
- ▶ For a short interval the amniotic cavity and yolk sac are therefore in direct communication with each other through the substance of the embryonic disc.
- ▶ The neurenteric canal is so named because its upper (amniotic) opening lies in the future caudal floor of the neural groove and its lower opening drains into the archenteron (primitive gut); it can still be identified at Carnegie stage 9 and its former site is recognizable at stage 10 (approximately the end of the third week).
- ▶ The **proximal part of the notochordal canal persists temporarily as the neurenteric canal** before obliteration; the region caudal to it — between the neurenteric canal and the cloacal membrane — is the **caudal eminence**, the source of the more caudal (sacroccygeal) segments of the notochord and spinal cord formed later by secondary neurulation.



#### 4. From canal to plate to definitive notochord

- ▶ The walls of the notochordal canal gradually flatten to form the **notochordal plate**, which forms a roof to the secondary yolk sac and remains contiguous with the embryonic endoderm.
- ▶ The notochordal plate then **curves/infolds** to re-form a tube.
- ▶ Proliferation of the cells of this tube converts it into a **solid cord** — **the definitive notochord**; the endoderm below is restored as a continuous layer, and the notochord is now completely separated from the endoderm.
- ▶ The completed notochord runs the length of the embryonic axis from the **oropharyngeal (buccopharyngeal) membrane** to the **cloacal membrane**, lying between the ectoderm (overlying neural plate) and the endoderm.
- ▶ This sequence — process → canal → plate → definitive cord — is complete by the **end of the third week** of IUL.

□ Fig 7.6 — Formation of notochord: (A) At 16th day, cells of primitive node proli (Sontakke — Textbook of Human Embryology, p.61)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A cranio-caudal series of sagittal (and paired transverse) sections through the embryonic disc, days 15–20, labelled in sequence:

- ▶ Ectoderm (epiblast) and endoderm (hypoblast), amniotic cavity above, yolk sac (umbilical vesicle) below
- ▶ **Primitive streak, Hensen's node (primitive knot), primitive pit / blastopore**
- ▶ **Notochordal process (head process)** — solid cord between ectoderm and endoderm
- ▶ **Notochordal canal** — canalized process, continuous with the blastopore
- ▶ **Fused floor** of canal with endoderm → perforations → **neurenteric canal** (draw arrows showing the transient amniotic cavity ↔ yolk sac communication)
- ▶ **Notochordal plate** (flattened, roofing the yolk sac) → infolding → **definitive notochord** (solid rod, endoderm restored beneath)
- ▶ **Oropharyngeal (buccopharyngeal) membrane** cranially and **cloacal membrane** caudally, for orientation

**5. Functions and fate of the notochord**

- ▶ Forms the **central axis** of the developing embryonic disc, defining the future vertebral column.
- ▶ **Induces** the overlying ectoderm to thicken and form the neural plate/neural tube (primary embryonic induction) — the notochord and floor plate of the neural tube develop in matched register.
- ▶ Provides the **central column** around which the vertebral bodies and intervertebral discs subsequently develop.
- ▶ Cells migrating rostral to the node (ahead of the notochord proper) form the **prechordal plate**, a temporary mesenchymal mass beneath the neural plate that assists forebrain induction.
- ▶ **Fate:** the notochord is present in all Chordata; in humans it exists only in embryonic life and later disappears, its only postnatal remnants being the **nucleus pulposus** of each intervertebral disc and the **apical ligament of the dens** of the axis (C2 vertebra).

**Applied / Clinical anatomy**

- ▶ **Chordoma** — a locally aggressive tumour arising from **remnants of the notochord**; occurs either cranially (base of skull/clivus region) or in the **sacroccocygeal region**, corresponding to the two ends of the embryonic notochord.
- ▶ **Sacroccocygeal teratoma** — arises when pluripotent cells of the **primitive streak** fail to degenerate by the end of the fourth week and persist in the sacroccocygeal region; it is the **commonest tumour of the newborn** (about 1 in 37,000 pregnancies), is more frequent in female infants, may cause obstructed labour by its size, and tends to become malignant during infancy — hence surgical excision is recommended **before 6 months of age**.
- ▶ **Diastematomyelia** — a midline cartilaginous/osseous spicule or fibrous septum projecting into the vertebral canal splits the spinal cord or intraspinal nerve roots into two columns; it is

frequently accompanied by a cutaneous marker (dimple, pigmented naevus or hairy patch) over the back at the level of the split, and is associated with cord tethering.

- ▶ **Coverage note:** several standard embryology texts additionally describe a spectrum of "split notochord"/neurenteric-cyst anomalies (persistent dorsal communication between gut and skin/spinal canal) attributed to faulty separation of notochord from endoderm around the site of the regressed neurenteric canal; this specific named entity was not found verbatim in the retrieved chapter text of this corpus, so it is flagged here rather than elaborated, though the underlying embryological logic (incomplete closure of the transient notochordal/neurenteric canal) is standard teaching.

### High-yield exam pointers

- ▶ Day 15: primitive streak appears; its cranial end = **Hensen's node**, the embryonic **organizer**.
- ▶ Prenotochordal cells invaginate at the **primitive pit** → **blastopore** → migrate cranially → solid **notochordal process** (head process).
- ▶ Blastopore cavity extends into the process → canalization → **notochordal canal**.
- ▶ Floor of notochordal canal **fuses with endoderm**, then breaks down → canal opens into both yolk sac and amniotic cavity = **neurenteric canal** (transient amnion–yolk sac communication).
- ▶ Canal walls flatten → **notochordal plate** → infolds → solid **definitive notochord** by end of 3rd week; extends from buccopharyngeal to cloacal membrane.
- ▶ Notochord = **inducer** of the neural tube and **axis** for the future vertebral column; postnatal remnants = **nucleus pulposus** + **apical ligament of the dens**.
- ▶ Applied: **chordoma** (cranial or sacral notochord remnants), **sacroccygeal teratoma** (primitive-streak remnants), **diastematomyelia** (septal splitting of the cord, with cutaneous stigmata).

#### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Gray's Anatomy (Standring) 41e.



## Somites

Asked in: Paper II 14-Nov-2019 · Paper II Oct 2009 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** Somites are paired, transient, ball-like condensations of paraxial mesoderm that form serially, in craniocaudal sequence, on either side of the neural tube and notochord during the third to fifth weeks of development. They are the fundamental metameric (segmental) units of the trunk, and their sequential differentiation into **sclerotome**, **myotome** and **dermatome** underlies the segmental organisation of the vertebral column, trunk/limb musculature, and the dermis and spinal nerves of the back. Somite number is used clinically and embryologically to stage an embryo precisely during the fourth week.

### 1. Origin and formation of somites

- ▶ The intraembryonic mesoderm, once formed at the primitive streak, differentiates on each side of the notochord into three longitudinal columns: **paraxial mesoderm**, **intermediate mesoderm** and **lateral plate mesoderm**.
- ▶ By the beginning of the third week the paraxial mesoderm organises into segments called **somitomeres** — whorled condensations of mesenchymal cells around a central point. Somitomeres appear first in the cephalic (pre-otic) region and formation proceeds cephalocaudally; cranial (pre-otic) somitomeres remain unsegmented and contribute to head mesenchyme, while post-otic somitomeres go on to segment fully into **somites**.
- ▶ The **first pair of somites** appears in the occipital region at approximately **day 20**; new somites are then added in strict craniocaudal sequence at a rate of about **three pairs per day**, so that by the end of the fifth week **42–44 pairs** are present.
- ▶ Cells ingressing through the **primitive node** form the axial cell populations (notochord, prechordal mesenchyme) and the **medial halves** of the somites, while cells ingressing through the more rostral primitive streak form the **lateral halves** of the somites — the two populations later fuse to complete each somite.
- ▶ Because somites appear with a fixed periodicity, **counting somite pairs is used to date an embryo accurately** during the fourth week (e.g., 4 somites ≈ day 21, 20–23 somites ≈ day 26).

**Regional distribution (total 42–44 pairs):**

| Region    | Pairs |
|-----------|-------|
| Occipital | 4     |
| Cervical  | 8     |
| Thoracic  | 12    |
| Lumbar    | 5     |
| Sacral    | 5     |
| Coccygeal | 8–10  |

- ▶ The **first occipital somite** and the **last 5–7 coccygeal somites** subsequently disappear; the remaining somites (≈ 33–35 pairs) go on to form the axial skeleton.

## 2. Molecular regulation — the segmentation clock

- ▶ Somite boundary formation from unsegmented presomitic (paraxial) mesoderm is controlled by a **segmentation clock**: cyclical, oscillating expression of **NOTCH** and **WNT** pathway genes in the presomitic mesoderm. Notch protein accumulates in the mesoderm destined to form the next somite and falls once that somite is established, switching on segment-patterning genes.
- ▶ Superimposed on this clock is a **rostrocaudal gradient**: **retinoic acid (RA)** is high cranially and low caudally, while **FGF8** and **WNT3A** are high caudally and low cranially. The intersection of the clock with this gradient (the "wavefront") fixes where each somite boundary forms.
- ▶ Mutations of clock-pathway genes — **DELTA-LIKE 3 (DLL3)**, **LUNATIC FRINGE (LFNG)**, **MESP2**, **HES7**, **NOTCH1** — disrupt normal somite segmentation and underlie the spondylocostal/spondylothoracic dysostoses discussed below.

## 3. Somite differentiation

- ▶ The newly formed somite is a hollow ball of epithelial cells (a "donut" arranged around a small central lumen).
- ▶ By the beginning of the fourth week, cells of the **ventral and medial wall** lose their epithelial character, become mesenchymal again, and migrate to surround the notochord and neural tube — this population is the **sclerotome**, destined to form the vertebrae, ribs and part of the skull base.
- ▶ The remaining **dorsal epithelial plate** is the **dermomyotome** (dermatome + myotome): cells at its dorsomedial and ventrolateral edges give rise to **myotome** (skeletal muscle precursors), while cells between them form the **dermatome** (dermis of the back); ventrolateral myotome cells also migrate into the parietal layer of lateral plate mesoderm to form the body-wall (external/internal oblique, transversus abdominis) and limb musculature.
- ▶ A **syndetome** (tendon progenitor population) develops between the myotome and sclerotome.
- ▶ **Inductive signalling**: the notochord and floor plate of the neural tube secrete **Sonic hedgehog (SHH)** and **Noggin**, which induce and maintain the ventromedial sclerotome via the transcription factor **PAX1** (mutated in vertebral-defect mouse models). The dorsal neural tube and overlying surface ectoderm secrete **WNTs**, which induce the dermomyotome via **PAX3**. A **BMP4** gradient from the lateral plate mesoderm, modulated by Noggin, further patterns the dermomyotome into medial (epaxial) and lateral (hypaxial/limb) components.
- ▶ The myotome subsequently splits into a dorsal **epimere**, forming the deep epaxial back muscles innervated by the **dorsal ramus**, and a ventral **hypomere**, forming the hypaxial muscles of the ventrolateral body wall and limbs, innervated by the **ventral ramus**. Each myotome and dermatome retains the segmental nerve supply of its somite of origin, wherever its cells subsequently migrate — the basis of dermatomal and myotomal maps.

## 4. Derivatives of the somite — summary

| Somitic component | Principal derivative                                                                 |
|-------------------|--------------------------------------------------------------------------------------|
| Sclerotome        | Vertebral body, vertebral (neural) arch, ribs, part of the occipital bone/skull base |

| Somitic component  | Principal derivative                                                               |
|--------------------|------------------------------------------------------------------------------------|
| Dermatome          | Dermis (and subcutaneous tissue) of the skin of the back                           |
| Myotome (epimere)  | Epaxial (deep back) muscles — dorsal ramus                                         |
| Myotome (hypomere) | Hypaxial muscles — intercostal/abdominal wall and limb musculature — ventral ramus |
| Syndetome          | Tendons linking muscle to sclerotome-derived bone                                  |

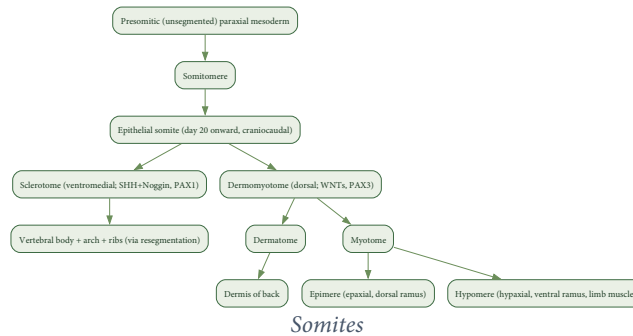


Fig 10.1 — Development of the somite. A. Paraxial mesoderm cells are arranged around (Langman's Medical Embryology — Sadler — 14e, p.166)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a transverse section through the trunk at the level of a differentiating somite and label:

- ▶ Neural tube (dorsal) and notochord (central)
- ▶ Sclerotome — mesenchymal cells surrounding notochord/neural tube (ventromedial)
- ▶ Dermomyotome — epithelial plate (dorsal), subdivided into dermatome and myotome
- ▶ Intermediate mesoderm (lateral to sclerotome)
- ▶ Lateral plate mesoderm — somatopleuric (parietal) and splanchnopleuric (visceral) layers, with intraembryonic coelom between them
- ▶ Surface ectoderm (most superficial)

## 5. Resegmentation and formation of the vertebral column

- ▶ The vertebral column forms not from single somites but by **resegmentation** of adjacent sclerotomes. Each sclerotome (except **occipital somites 1–4**) splits into a **cranial half** and a **caudal half**; the caudal half of one sclerotome fuses with the cranial half of the sclerotome immediately below it to form a single vertebral body.
- ▶ Consequence: **each vertebra is intersegmental**, derived from two adjacent somites, so that spinal nerves and intersegmental (segmental) arteries — which originally ran through the sclerotome — now pass **between** vertebrae rather than through them, exiting at the intervertebral level.
- ▶ Skeletal muscle (myotome), unlike bone, **retains its original single-segment span**, now crossing the intervertebral joint it helps to move — explaining why muscles can act across joints while nerve roots exit segmentally between vertebrae.

- ▶ **Occipital somites 1–4 do not resegment**; instead they fuse together (with the cranial half of the first cervical sclerotome) to form the **exoccipital bone/basiocciput** — hence there are **8 cervical spinal nerves but only 7 cervical vertebrae**, with C1 nerve emerging above the atlas and C8 emerging below C7 vertebra.
- ▶ Fibrous **intervertebral discs** develop from the intrasegmental fissure at the centre of the original sclerotome (nucleus pulposus from residual notochord).

## Applied / Clinical anatomy

- ▶ **Somite counting for staging**: because somite pairs appear with fixed periodicity (day 20 → first pair; ~3 pairs/day thereafter), embryonic age in the fourth week is conventionally expressed and verified by somite number.
- ▶ **Spondylocostal/spondylothoracic dysostosis**: mutations of segmentation-clock genes (**DLL3, LFNG, MESP2, HES7, NOTCH1**) disrupt somite/sclerotome segmentation, producing multiple **hemivertebrae, rib fusions and kyphoscoliosis** — a direct clinical correlate of the molecular clock described above.
- ▶ **Congenital (hemivertebral) scoliosis**: defective/unilateral formation of a vertebral body from abnormal sclerotome induction or resegmentation causes lateral curvature that may require surgical correction.
- ▶ **Klippel–Feil anomaly (cervicothoracic dysostosis)**: fusion of cervical vertebrae from resegmentation failure — short neck, low posterior hairline, restricted neck movement.
- ▶ **Alagille syndrome (JAGGED1/NOTCH2 mutation)**: "butterfly vertebrae" (sagittally-clefted vertebral bodies) in ~60% of cases — reflects failure of the two sclerotomal halves to fuse in the midline.
- ▶ **Spina bifida occulta (cleft vertebra)**: failure of the vertebral (neural) arch — derived from the dorsal sclerotome — to form/fuse around a normally-closed neural tube; distinct from spina bifida aperta, where the primary defect is neural tube closure.
- ▶ **Cervical rib / sacralisation-lumbarisation**: anomalies of costal-process or resegmentation boundaries at the cervicothoracic and lumbosacral junctions, respectively, producing an extra rib from C7 or altered lumbar/sacral vertebral counts.
- ▶ **Segmental (dermatomal/myotomal) maps** used in clinical neurology to localise spinal nerve root lesions are a direct legacy of each somite's fixed segmental nerve supply, regardless of the final position its derivatives migrate to (e.g., diaphragm — C3,4,5 — retains cervical innervation despite its thoracoabdominal position; limb myotomes retain their segmental nerve roots though they migrate far from the trunk).

## High-yield exam pointers

- ▶ Somites = segmented paraxial mesoderm; first pair at day 20 (occipital region); ~3 pairs/day; **42–44 total pairs** (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 8–10 coccygeal).
- ▶ First occipital + last 5–7 coccygeal somites disappear; ~33–35 pairs form the axial skeleton.
- ▶ Each somite differentiates into **sclerotome** (vertebra/rib), **dermatome** (back dermis) and **myotome** (epimere → epaxial/dorsal ramus; hypomere → hypaxial/ventral ramus).



- ▶ Segmentation clock = oscillating NOTCH/WNT expression + opposing RA (cranial) vs FGF8/WNT3A (caudal) gradients.
- ▶ Sclerotome induced by **notochord/floor-plate SHH + Noggin** → **PAX1**; dermomyotome induced by **dorsal neural tube/ectoderm WNTs** → **PAX3**; patterned further by lateral-plate **BMP4**.
- ▶ **Resegmentation**: each vertebra forms from caudal half of one sclerotome + cranial half of the next → vertebrae are intersegmental; nerves/vessels pass between vertebrae; muscles retain original segmental span; occipital somites 1–4 (no resegmentation) form the exoccipital bone.
- ▶ 8 cervical spinal nerves but only 7 cervical vertebrae — direct consequence of occipital-somite fusion.
- ▶ Clinical correlates: spondylocostal dysostosis (DLL3/LFNG/MESP2/HES7/NOTCH1) → hemivertebrae/rib fusion; Klippel–Feil anomaly; butterfly vertebrae in Alagille syndrome; spina bifida occulta; somite counting for embryonic dating.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Gray's Anatomy (Standring) 41e.



## Allantois

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The allantois (allantoenteric diverticulum) is a small, solid endodermal outgrowth that arises from the caudal (dorsocaudal) wall of the yolk sac and projects into the connecting stalk during the third week of intrauterine life. It is one of the extraembryonic (fetal) membranes — along with the amnion, yolk sac, chorion and umbilical cord — and, though functionally vestigial in the human, it is developmentally important because it is the site of origin of the umbilical vessels and gives rise, on its intraembryonic side, to the urachus and median umbilical ligament of the adult bladder.

### 1. Origin and time of appearance

- ▶ Arises as the **allantoenteric diverticulum** — a solid, endoderm-lined outgrowth from the **dorsocaudal wall of the yolk sac**, growing into the mesenchyme of the **connecting stalk**.
- ▶ Appears around **day 16, early in the third week** of development.
- ▶ It soon becomes **canalized** (from a solid cord to a tubular diverticulum).
- ▶ It has **no direct mesothelial (coelomic) covering** of its own — it is embedded within the extraembryonic mesenchyme of the connecting stalk.

### 2. Structure and relations

- ▶ The diverticulum has two parts once the hindgut is formed:
  - **Proximal (enteric) part** — incorporated into the ventral wall of the developing **hindgut/cloaca**.
  - **Distal (allantoic) part** — remains as the **allantoic duct**, continuous with the cloaca, and is carried into the **connecting stalk**.

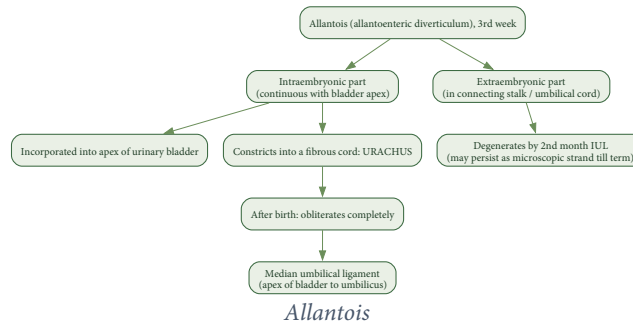
- ▶ With cephalocaudal and lateral folding of the embryo, the allantois becomes partially incorporated into the body of the embryo, contributing to the **cloaca**; its distal portion remains in the connecting stalk.
- ▶ By the **fifth week**, the yolk-sac duct, allantois and umbilical vessels are all restricted to the **umbilical region**, and the connecting stalk + yolk-sac stalk fuse to form the definitive **umbilical cord**.
- ▶ In the fetus, the allantoic duct (confined to the proximal part of the cord) elongates and thins; it may persist as an interrupted series of microscopic epithelial strands within Wharton's jelly until term.

### 3. Functions

| Function                          | Detail                                                                                                                                                                                                                                                                                   |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Angiogenesis                      | The allantois is a principal site of blood-vessel formation; its mesenchyme gives rise to the <b>umbilical arteries</b> (from the dorsal aortae) and <b>umbilical vein</b> (draining the chorionic villi) that carry the fetoplacental circulation — the "chorio-allantoic" circulation. |
| Haemopoiesis                      | Blood formation occurs transiently in the wall of the allantois/yolk sac complex during the <b>3rd–5th weeks</b> , before intraembryonic sites take over.                                                                                                                                |
| Excretory reservoir (comparative) | In <b>birds, reptiles and some lower mammals</b> , the allantois is large and acts as a <b>reservoir for urinary/excretory waste</b> and a respiratory surface (allanto-chorion).                                                                                                        |
| In humans                         | It remains a small, <b>vestigial</b> structure with no excretory reservoir function; its importance is almost entirely as a vascular and positional scaffold.                                                                                                                            |

- ▶ **Comparative significance:** the connecting (body) stalk of the human embryo, because it contains the allantois, is regarded as a **precociously formed allantoic stalk**, homologous with the large, vascular allantoic vesicle of lower mammals that grows out to vascularise the chorion. Consequently, the vessels of the body stalk (the umbilical vessels) are equivalent to the **allantoic vessels** of other mammals, and the human placenta is classified as a **chorio-allantoic placenta**, as are the definitive placentae of all true mammals — even though, in Man, the allantois itself never dilates into a large vesicle and never reaches the chorion.

#### 4. Fate and adult derivatives



| Embryonic structure                      | Adult derivative                                                                               |
|------------------------------------------|------------------------------------------------------------------------------------------------|
| Allantois (intraembryonic part)          | Incorporated into <b>apex of urinary bladder</b>                                               |
| Allantois (constricted, fetal)           | <b>Urachus</b> — thick fibrous cord from bladder apex to umbilicus                             |
| Urachus, after birth                     | <b>Median umbilical ligament</b>                                                               |
| Allantois (extraembryonic part, in cord) | Degenerates in 2nd month IUL; residual strand seen in Wharton's jelly                          |
| Allantoic vessels                        | <b>Umbilical arteries (2) and umbilical vein</b> , seen in cross-section of the umbilical cord |

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 15.15 — Fate of the Allantois: Normally, the allantois becomes occluded to form the urachus or median umbilical ligament (Larsen — Human Embryology — 6e, p.943)

Reproduce a longitudinal (sagittal) section through the caudal end of a 3rd–5th week embryo, labelling:

- ▶ Yolk sac and vitelline (yolk-sac) duct
- ▶ Connecting stalk
- ▶ **Allantois / allantoic duct** running from the cloaca into the connecting stalk
- ▶ Hindgut and cloaca
- ▶ Cloacal membrane
- ▶ Developing urinary bladder (from vesicourethral part of cloaca)
- ▶ Allantoic (umbilical) blood vessels
- ▶ Umbilical cord (definitive, after folding) — with a second panel showing the postnatal fate: bladder apex → urachus → median umbilical ligament → umbilicus.

#### Applied / Clinical anatomy

- ▶ **Congenital anomalies of the urachus** arise when all or part of its lumen fails to obliterate:

| Anomaly                          | Description                                                                                                                                                                                                   |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Urachal fistula (patent urachus) | The entire lumen of the urachus persists, connecting the bladder to the umbilicus; <b>urine discharges through the umbilicus.</b>                                                                             |
| Urachal sinus                    | Only the <b>upper part</b> (near the umbilicus) remains patent; the sinus opens at the umbilicus, blind internally.                                                                                           |
| Urachal cyst                     | Only a <b>small intermediate segment</b> of the urachus remains patent; secretory activity of its epithelial lining produces a cystic dilatation, usually asymptomatic until it enlarges or becomes infected. |

- ▶ **Allantoic cyst:** a remnant of the extraembryonic portion of the allantois that persists between the fetal umbilical vessels; detectable **antenatally on ultrasonography.**
- ▶ Because the allantois is the source of the umbilical vessels, it underlies the surgical/obstetric importance of the umbilical cord contents (2 umbilical arteries, 1 umbilical vein, remnant of allantois, remnant of vitellointestinal duct, all embedded in Wharton's jelly) examined at birth and used clinically (umbilical vessel catheterisation, cord blood sampling).
- ▶ The urachus and median umbilical ligament are important **surgical landmarks** on the internal aspect of the anterior abdominal wall, raising the **median umbilical fold** of peritoneum in the midline between the two medial umbilical folds (obliterated umbilical arteries).

### High-yield exam pointers

- ▶ Allantois = **allantoenteric diverticulum**, endodermal, arises from **caudal wall of yolk sac** into the **connecting stalk**, ~16th day / early 3rd week.
- ▶ It has **no mesothelial covering** of its own.
- ▶ Chief importance in humans: **source of umbilical vessels** (angiogenesis) + site of transient **haemopoiesis** (3rd–5th week).
- ▶ **Vestigial** in humans (unlike birds/reptiles, where it is a urinary/respiratory reservoir).
- ▶ Fate: intraembryonic part → **apex of bladder**; constricts to **urachus**; after birth → **median umbilical ligament**.
- ▶ Extraembryonic part **degenerates by the 2nd month IUL**; may leave a microscopic strand in the cord till term.
- ▶ **Clinical triad of urachal anomalies:** patent urachus/urachal fistula (whole length), urachal sinus (upper end), urachal cyst (intermediate segment) — plus antenatal **allantoic cyst**.
- ▶ Umbilical cord cross-section contents include a **remnant of the allantois** alongside vitellointestinal duct remnant, 2 umbilical arteries, 1 umbilical vein, and Wharton's jelly.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; Hamilton, Boyd & Mossman — Human Embryology; BD Chaurasia — Human Anatomy Vol 2 8e.



## Amnion

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The amnion is the innermost, thin, avascular extraembryonic membrane that arises from the epiblast on day 8 of development and forms a fluid-filled amniotic sac enclosing the embryo, and later the fetus, in amniotic fluid. Together with the chorion, yolk sac, allantois, umbilical cord and placenta, it constitutes the fetal (extraembryonic) membranes, whose collective roles are protection, nutrition, respiration and excretion for the conceptus. By the tenth to twelfth week the expanding amnion contacts and fuses with the chorion to form the chorio-amnion, which persists to term and is expelled as part of the afterbirth.

### 1. Development of the Amnion

- ▶ **Day 8:** the inner cell mass differentiates into a bilaminar germ disc — a high columnar **epiblast** layer (adjacent to the future amniotic cavity) and a cuboidal **hypoblast** layer (adjacent to the blastocyst cavity).
- ▶ A small cleft appears within the epiblast by **cavitation**; this cleft enlarges to become the **amniotic cavity**.
- ▶ Epiblast cells lying adjacent to the cytotrophoblast, at the margin of the germ disc, differentiate into **amnioblasts**; together with the rest of the epiblast they line the amniotic cavity. The amniogenic epithelium covers the **roof and lateral walls** of the sac; the **floor** remains formed by the embryonic disc (epiblast) itself.
- ▶ As amniotic fluid accumulates, the sac enlarges. With **cephalocaudal and lateral folding** of the embryo (during the fourth week), the amnion is drawn around the entire embryo and also envelops the connecting stalk, converting it into the primitive umbilical cord.
- ▶ The amniotic cavity continues to expand at the expense of the surrounding **chorionic (extraembryonic coelomic) cavity**. Between the **10th and 12th weeks**, the amnion makes contact with the chorion and fuses with it to form the **chorio-amnion**, an avascular membrane that persists till term, obliterating the extraembryonic coelom.
- ▶ The amniotic membrane extends along the connecting stalk to form the outer epithelial covering of the umbilical cord.

□ Fig 6.1 — Day 8: Implantation—formation of amniotic cavity. Epiblast cells multiply and amniotic cavity begins to form (Sontakke — Textbook of Human Embryology, p.49)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Section through a day-8 implanted bilaminar blastocyst — label: uterine epithelium and uterine gland; syncytiotrophoblast; cytotrophoblast; **epiblast**; **hypoblast**; **amniotic cavity** (with amnioblasts lining its roof); exocoelomic (Heuser's) membrane; primary yolk sac (exocoelomic cavity); connecting stalk region.

## 2. Structure of the Amnion

| Layer                                          | Composition / features                                                                                                                                                                                                                                           |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Amniotic epithelium (inner, facing the cavity) | Simple cuboidal epithelium derived from amnioblasts (epiblast); microvillous apical surface over a cortical web of intermediate filaments/microfilaments; <b>no tight junctions</b> between cells — only scattered desmosomes, permitting selective permeability |
| Basal lamina                                   | Secreted and maintained by the overlying epithelium                                                                                                                                                                                                              |
| Compact layer                                  | Acellular, collagenous stroma deposited by the epithelium, beneath the basal lamina                                                                                                                                                                              |
| Fibroblast/mesenchymal (outer) layer           | Somatopleuric extraembryonic mesoderm; fuses with the chorionic mesoderm (10–12 weeks) to form the chorio-amnion                                                                                                                                                 |

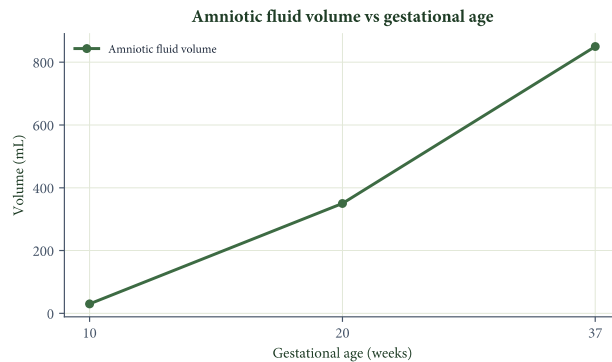
- ▶ The amnion is **avascular** and has **no nerve supply**; it derives nutrition by diffusion from the amniotic fluid and from chorionic vessels it comes to overlie.
- ▶ Amniotic epithelial cells are considered **pluripotent** because they arise so early from the conceptus, and they lack MHC antigens — the amnion can therefore lie in contact with the maternal immune system (at the chorio-amnion) without provoking rejection. This immune-privileged, biologically active membrane is used clinically as a graft for corneal repair after trauma and for vaginal reconstruction in cloacal anomalies.
- ▶ At term the chorio-amnion has a surface area of about 1000–1200 cm<sup>2</sup>, of which roughly 30% overlies the placenta and 70% lies in contact with the decidua. Apoptosis of amniotic cells increases towards term (peaking at 40–41 weeks), contributing to the physiological fragility and eventual rupture of the membranes.

## 3. Amniotic Fluid — Formation, Circulation and Composition

| Source                                       | Contribution                                               |
|----------------------------------------------|------------------------------------------------------------|
| Amniotic epithelium                          | Direct secretion — the initial source in early pregnancy   |
| Diffusion across the amniochorionic membrane | From maternal interstitial fluid in the decidua parietalis |
| Diffusion through the chorionic plate        | From maternal blood in the intervillous space              |

| Source                             | Contribution                                                                                           |
|------------------------------------|--------------------------------------------------------------------------------------------------------|
| Fetal skin (before keratinisation) | Transudation of fetal tissue fluid — amniotic fluid closely resembles fetal tissue fluid at this stage |
| Fetal respiratory tract            | ≈300–400 mL/day                                                                                        |
| Fetal urine (from the 11th week)   | Up to ≈500 mL/day by late pregnancy — the dominant late source                                         |

- **Circulation:** the water content of amniotic fluid is turned over roughly every 3 hours. Water passes through the amniochorionic membrane into maternal uterine capillaries, and is exchanged with fetal blood via the umbilical cord and the placental amnio-chorionic contact zone. In late pregnancy the fetus swallows up to ≈400 mL/day; this is absorbed by the fetal gut and respiratory tract, enters the fetal circulation, and its wastes cross the placental membrane to maternal blood; excess fetal water is excreted by the fetal kidneys back into the sac — a balanced circulatory loop.
- **Composition:** a clear, watery, aqueous solution containing roughly equal parts organic and inorganic constituents (salts). Of the organic fraction, half is protein and the remainder is carbohydrate, fat, enzymes, hormones (including hCG and human placental lactogen) and pigments, together with desquamated fetal epithelial cells suspended in it. As pregnancy advances the composition is altered by the addition of fetal urine and meconium.
- **Volume with gestation:** rises from ≈30 mL at 10 weeks, to ≈350 mL at 20 weeks, to ≈700–1000 mL by 37 weeks (term).



*Amniotic fluid volume rises from ~30 mL (10 wk) to ~350 mL (20 wk) to ~700-1000 mL by term (37 wk) (Moore, The Developing Human 9e).*

#### 4. Functions of the Amnion and Amniotic Fluid

- Permits **symmetric external growth** of the embryo/fetus.
- Acts as a **barrier to infection**.
- Permits normal **fetal lung development** (fetal breathing movements circulate fluid through developing airways).
- **Prevents adherence** of the amnion to the embryo/fetus (loss of this cushion underlies amniotic band syndrome).
- **Cushions** the embryo/fetus, distributing mechanical impacts the mother receives.
- Helps maintain a **constant temperature** for the fetus.



- ▶ Allows **free fetal movement**, aiding musculoskeletal development.
- ▶ Assists in **fluid and electrolyte homeostasis**.
- ▶ Forms the **hydrostatic wedge** ("bag of waters") that helps dilate the cervix at the onset of labour.
- ▶ Provides a medium from which fetal cells, enzymes, hormones and alpha-fetoprotein can be sampled for **antenatal diagnosis**.

### Applied / Clinical anatomy

- ▶ **Amniocentesis**: transabdominal aspiration of amniotic fluid, usually performed at the 14th–15th week, when the sac contains  $\approx 175$ –225 mL of fluid. Used for fetal karyotyping (e.g. trisomy 21/Down syndrome), biochemical enzyme assay (e.g. hexosaminidase-A in Tay–Sachs disease), fetal sex determination, alpha-fetoprotein assay (elevated in open neural tube defects; low in some trisomies), and, later in gestation, the lecithin–sphingomyelin ratio/phosphatidylglycerol for fetal lung maturity.
- ▶ **Oligohydramnios**: amniotic fluid  $< 400$  mL at term (normal term volume 700–1000 mL). Commonest cause is preterm rupture of the amniochorionic membrane (occurring in  $\sim 10\%$  of pregnancies); other causes are renal agenesis and obstructive uropathy (no fetal urinary contribution) and placental insufficiency. Complications include pulmonary hypoplasia, facial and limb deformities from fetal compression (Potter sequence), and umbilical cord compression.
- ▶ **Polyhydramnios**: excessive fluid,  $\geq 2000$  mL. About 60% are idiopathic, 20% maternal (e.g. diabetes), and 20% fetal in origin — classically oesophageal atresia or CNS anomalies such as anencephaly, in which the fetus cannot swallow and absorb fluid normally.
- ▶ **Premature rupture of (fetal) membranes**: the most common event precipitating preterm labour and delivery, and the leading cause of oligohydramnios.
- ▶ **Amniotic band syndrome**: torn strands of amnion wrap around developing digits/limbs, causing constriction rings or amputations, or are swallowed, disrupting facial development; the aetiology of band formation is unknown.
- ▶ **Chorioamnionitis**: infection of the chorio-amnion, usually ascending via the vagina/cervix; more frequent in preterm labour and associated with fetal inflammatory brain injury.
- ▶ **Ventral body wall defects**: in gastroschisis and exomphalos, the reflection of amnion along the forming umbilical cord may be incomplete.
- ▶ **Biomedical use**: the immune-privileged, MHC-negative amnion is used as a biological graft for corneal resurfacing and vaginal reconstruction.

### High-yield exam pointers

- ▶ Amnion = epiblast-derived; amniotic cavity forms by **cavitation within the epiblast on day 8**.
- ▶ Two-layered wall: outer somatopleuric mesoderm + inner amniogenic cuboidal epithelium (no tight junctions); avascular, no nerve supply.
- ▶ Fuses with chorion at **10–12 weeks**  $\rightarrow$  chorio-amnion, obliterating the extraembryonic coelom.
- ▶ Volume:  $\sim 30$  mL (10 wk)  $\rightarrow$  350 mL (20 wk)  $\rightarrow$  700–1000 mL (37 wk, term).
- ▶ **Oligohydramnios**  $< 400$  mL (commonest cause: PROM; also renal agenesis); **polyhydramnios**  $\geq 2000$  mL (commonest: idiopathic; classic cause: oesophageal atresia/anencephaly).



- ▶ **Amniocentesis** at 14–15 weeks (175–225 mL fluid present) for karyotyping/AFP/enzyme assay.
- ▶ Amnion is immune-privileged (no MHC antigen) — clinically used as a biological graft.
- ▶ Amniotic band syndrome causes digit/limb constriction rings and amputations.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore's The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology (figure).



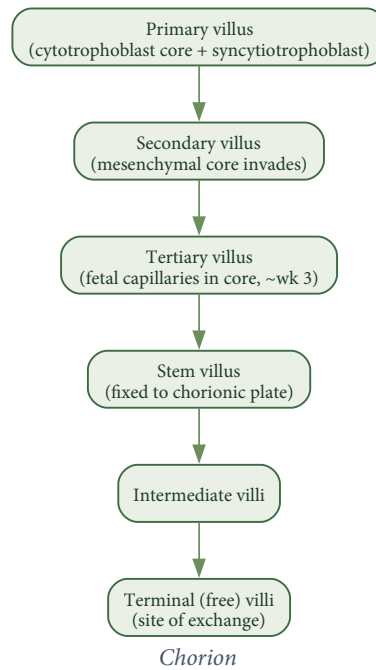
## Chorion

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The chorion is the outermost extraembryonic membrane, formed by the trophoblast (cytotrophoblast and syncytiotrophoblast) lined internally by extraembryonic somatic (somatopleuric) mesoderm. It bounds the chorionic cavity (extraembryonic coelom) that encloses the amniotic cavity, secondary yolk sac and connecting stalk, and it constitutes the fetal contribution to the placenta. Differential growth converts an initially uniform, villus-covered chorionic vesicle into two functionally distinct regions — the villous **chorion frondosum** and the smooth **chorion laeve** — and, by fusing with the amnion, the chorion also forms the avascular amniochorionic membrane of the fetal membranes.

### 1. Development of the Chorion and Its Villi

- ▶ The chorion arises as trophoblast (differentiating into an outer syncytiotrophoblast and inner cytotrophoblast) becomes lined, on its inner aspect, by extraembryonic mesoblast that also reflects over the amnion and yolk sac; the large cavity so enclosed is the **chorionic cavity**, synonymous with the extraembryonic coelom.
- ▶ Chorionic villi develop in an orderly sequence over the whole trophoblastic surface:
  - **Primary villi** — solid columns of cytotrophoblast covered by syncytiotrophoblast, projecting into maternal lacunae.
  - **Secondary villi** — a core of extraembryonic (somatic) mesenchyme grows into the cytotrophoblastic core of each primary villus.
  - **Tertiary (definitive) villi** — angiogenesis within the mesenchymal core produces fetal capillaries; with the onset of the embryonic heartbeat, a primitive fetal circulation is established, and an embryonic–placental circulation begins around week 8 of gestation.
- ▶ From the third week until about the second month, villous stems cover the **entire** chorionic surface, continuous peripherally with the trophoblastic shell apposed to both the decidua capsularis and decidua basalis.
- ▶ Each mature villous stem forms a single trunk attached to the chorion, from which second- and third-order branches (intermediate and terminal villi) arise; terminal villi are the specialised sites of maternofetal exchange.



## 2. Chorion Frondosum and Chorion Laeve

| Feature       | Chorion frondosum (villous chorion)                                                                          | Chorion laeve (smooth chorion)                                                                                           |
|---------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Position      | Apposed to decidua basalis (embryonic pole)                                                                  | Apposed to decidua capsularis (abembryonic pole)                                                                         |
| Villi         | Persist, enlarge, branch profusely                                                                           | Progressively atrophy and disappear by end of 3rd month, as decidua capsularis is compressed and its circulation reduced |
| Composition   | Trophoblast + mesenchyme with well-vascularised, branching villi                                             | Trophoblast + mesenchyme, villus-free, smooth                                                                            |
| Fate          | Together with decidua basalis, forms the <b>definitive placental site</b> (fetal plate)                      | Fuses with the amnion (→ <b>chorio-amnion</b> ) and later with decidua parietalis, obliterating the uterine cavity       |
| Applied point | Abnormal persistence of villi at other sites of this region underlies <b>succenturiate (accessory) lobes</b> | Persistence of the entire villous ring beyond the 2nd month gives <b>placenta membranacea</b>                            |

## 3. Structure of the Definitive Chorion

- **Chorionic plate** — the fetal aspect of the placenta: covered by amniotic epithelium; beneath it a connective-tissue layer (fused amnion + chorion mesenchyme) carrying the main branches of the umbilical vessels; a diminishing cytotrophoblast layer; and an inner syncytial wall bordering the intervillous space. The two umbilical arteries are usually joined by a transverse anastomosis (**Hyrtl's anastomosis**) just before entering the plate.

- ▶ **Villous core** — contains fibroblasts, reticulum cells and macrophages (**Hofbauer cells**); collagen increases from a fine network in early mesenchymal villi to a dense fibrous stroma in stem villi after ~14 weeks.
- ▶ At **term**, the chorion consists of an inner cellular layer (fibroblasts and a reticular layer resembling intermediate-villus mesenchyme) and an outer layer of cytotrophoblast (3–10 cells deep) resting on a pseudo-basement membrane, with occasional obliterated villous remnants of the first-trimester chorion frondosum.
- ▶ The human placenta is **haemochorial** (maternal blood directly bathes the chorion), **chorio-allantoic** (vascularised via allantoic/umbilical vessels of the connecting stalk), **discoid** and **deciduate**.

#### 4. The Placental (Villous) Membrane

- ▶ The barrier separating maternal from fetal blood across a terminal villus is classically described as **four layers** in early pregnancy:
- ▶ **Syncytiotrophoblast** (outer, bathed by maternal blood in the intervillous space)
- ▶ **Cytotrophoblast** (Langhans' cells) — discontinuous, becomes progressively sparse
- ▶ **Connective-tissue core** (villous mesenchyme)
- ▶ **Endothelium** of the fetal capillary
- ▶ From the **fourth month**, the cytotrophoblastic layer becomes discontinuous and the fetal capillary endothelium comes into intimate contact with the syncytium, thinning the membrane to a **vasculo-syncytial membrane** — the maternofetal diffusion distance may fall to as little as 2–3  $\mu\text{m}$ , greatly increasing exchange efficiency. It is loosely called the "placental barrier," though it is not a true barrier — most substances, and several viruses, cross it.

#### 5. Fetal Membranes Formed With the Chorion

- ▶ Between the 10th and 12th weeks, the expanding amniotic cavity contacts the chorion, forming the **amniochorionic membrane** — an avascular membrane that persists to term and ruptures in labour ("breaking of waters").
- ▶ The chorionic cavity (extraembryonic coelom) is progressively obliterated as amnion and chorion fuse.
- ▶ At term, the chorio-amnion has a surface area of ~1000–1200  $\text{cm}^2$ , of which ~30% overlies the placenta and ~70% overlies the decidua parietalis (choriodecidua).

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label a longitudinal schematic of the second-month gravid uterus with: **amniotic cavity** (embryo within amnion) → **chorionic cavity** (extraembryonic coelom) → **chorion frondosum** (villous, facing **decidua basalis**) → **chorion laeve** (smooth, facing **decidua capsularis**) → **decidua parietalis** lining the rest of the uterine cavity → **connecting stalk/umbilical cord** → **myometrium**. Show the uterine cavity obliterated where chorion laeve fuses with decidua parietalis.

□ Fig 8.10 — Relation of fetal membranes to wall of the uterus. A. End of the second month, showing the chorion frondosum and chorion laeve with decidua basalis, capsularis and parietalis. (Langman's Medical Embryology — Sadler, 14e, p.133)

### Applied / Clinical anatomy

- ▶ **Chorionic villus sampling (CVS)**: a biopsy (5–20 mg) of chorion frondosum villi taken transabdominally (needle, ultrasound-guided) or transcervically (catheter) between **10 and 12 weeks** of gestation for fetal karyotyping, inborn errors of metabolism and X-linked disorder diagnosis; risk of fetal loss ~1%, marginally higher than amniocentesis, but results are available several weeks earlier.
- ▶ **Hydatidiform mole**: hydropic, cystic swelling with trophoblastic hyperplasia of chorionic villi; secretes very high hCG and may progress to invasive mole or choriocarcinoma.
- ▶ **Placenta membranacea**: persistence of villi over the entire chorionic sac (failure of chorion laeve to become villus-free) — predisposes to antepartum haemorrhage and abnormal placentation.
- ▶ **Succenturiate (accessory) lobe**: an isolated patch of villi persisting in the chorion laeve, connected to the main placental mass by membranous vessels — risk of retained lobe/postpartum haemorrhage.
- ▶ **Chorioamnionitis / PPROM**: infection ascending through the chorion is associated with chorionic apoptosis, increased matrix metalloproteinase-9 activity and membrane thinning, weakening the amniochorionic membrane and predisposing to preterm rupture.
- ▶ **Rh (D) isoimmunisation**: small numbers of fetal red cells occasionally cross microscopic defects in the thinned villous (placental) membrane, sensitising an Rh-negative mother.
- ▶ **Placenta previa / accreta**: abnormal relation of the chorion frondosum (placental site) to the lower uterine segment/internal os, or abnormal trophoblastic invasion through a deficient decidua basalis.

### High-yield exam pointers

- ▶ Chorion = trophoblast (cyto- + syncytiotrophoblast) + extraembryonic somatic mesoderm; forms the fetal part of the placenta.
- ▶ Villus sequence: primary (trophoblast only) → secondary (mesenchymal core) → tertiary (fetal vessels appear, ~week 3; embryo-placental circulation from ~week 8).
- ▶ **Chorion frondosum** = villous, over decidua basalis, becomes the placenta; **chorion laeve** = smooth, over decidua capsularis, fuses with amnion.
- ▶ Amnion + chorion laeve → **amniochorionic membrane** (10–12 weeks), obliterates the chorionic cavity; ruptures in labour.

- ▶ Placental (villous) membrane: 4 layers early (syncytiotrophoblast, cytotrophoblast, mesenchyme, fetal endothelium) → thins to a vasculo-syncytial membrane from the 4th month (diffusion distance ~2–3  $\mu\text{m}$ ).
- ▶ Human placenta is haemochorial, chorio-allantoic, discoid and deciduate.
- ▶ Chorion (syncytiotrophoblast) secretes hCG, human chorionic somatomammotropin (placental lactogen) and steroid hormones.
- ▶ Applied: CVS (10–12 weeks, from chorion frondosum), hydatidiform mole, placenta membranacea, succenturiate lobe, chorioamnionitis/PPROM.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Ross Histology — A Text and Atlas 7e.



## Definitive yolk sac

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The yolk sac is an endodermal extraembryonic membrane that in humans is vestigial (contains no true nutritive yolk) but is nevertheless essential to early development. It matures through three successive stages — **primary** → **secondary** → **definitive (tertiary) yolk sac** — the last of which forms in the fourth week when embryonic folding pinches off most of the secondary yolk sac into the primitive gut, leaving a small extraembryonic remnant, the **definitive/tertiary yolk sac (umbilical vesicle)**, connected to the midgut by the **vitello-intestinal (omphalomesenteric) duct**. It is a major site of early haemopoiesis and the source of primordial germ cells, and its persistent duct gives rise to Meckel's diverticulum.

### 1. Three stages in the formation of the yolk sac

| Stage                                 | Timing                    | Formation                                                                                                                                                                                                   | Lining                     |
|---------------------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Primary yolk sac (exocoelomic cavity) | End of 2nd week (day 8–9) | Hypoblast cells migrate along the inner surface of the cytotrophoblast to form a thin membrane, the <b>exocoelomic (Heuser's) membrane</b> ; together with the hypoblast this lines the blastocystic cavity | Flattened endodermal cells |

| Stage                          | Timing               | Formation                                                                                                                                                                                                                                                                                                                                                                                                                       | Lining                                                                 |
|--------------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Secondary yolk sac             | 2nd week (day 12–13) | A second wave of hypoblast cells migrates within the primary yolk sac and forms a new, smaller cavity; the primary yolk sac is pushed off peripherally and fragments into <b>exocoelomic cysts</b> within the newly split extraembryonic coelom (chorionic cavity)                                                                                                                                                              | Cuboidal endodermal cells + outer extraembryonic (splanchnic) mesoderm |
| Definitive / tertiary yolk sac | 4th week             | With head-fold, tail-fold and lateral-fold formation, the <b>dorsal (intraembryonic) part of the secondary yolk sac is incorporated into the embryo as the primitive gut</b> (foregut, midgut, hindgut); the <b>extraembryonic part left outside the body</b> , communicating with the midgut by the narrowing <b>vitello-intestinal duct</b> , is the definitive/tertiary yolk sac (also called the <b>umbilical vesicle</b> ) | Endoderm + extraembryonic mesoderm, now much reduced                   |

Some authors (Sadler/Langman, Larsen) use "secondary" and "definitive" yolk sac as synonyms for the day-12–13 structure; Indian curricular texts (IB Singh, Vishram Singh, Sontakke) reserve "**definitive/tertiary yolk sac**" specifically for the small extraembryonic remnant left behind **after folding**, in continuity with the midgut via the vitello-intestinal duct — this is the sense intended by an RGUHS question on the "definitive yolk sac" and is followed through the rest of this answer.

□ Fig 2.3 — Formation of the Secondary (Definitive) Yolk Sac, and Degeneration (Larsen — Human Embryology — 6e, p.144)

## 2. Formation by embryonic folding

- ▶ In the fourth week the flat trilaminar disc converts into a cylindrical embryo by simultaneous **cephalocaudal (head-fold, tail-fold) and lateral folding**.
- ▶ Folding carries the dorsal roof of the secondary yolk sac into the body of the embryo, converting the flat endodermal sheet into a tube — the **primitive gut** — closed cranially by the buccopharyngeal membrane and caudally by the cloacal membrane.
- ▶ The ventral part of the yolk sac that is **not** taken up remains outside the body, suspended in the chorionic (extraembryonic coelomic) cavity; it is pinched into an hour-glass shape at the site of the future umbilicus.

- ▶ The narrow communicating channel between the midgut and this extraembryonic remnant is the **vitello-intestinal (omphalomesenteric/vitelline) duct**; it initially lies free in the extraembryonic coelom and later runs through the developing **umbilical cord** alongside the allantoic diverticulum and umbilical vessels.

### 3. Structure and relations

- ▶ **Wall:** an inner layer of **endoderm** (continuous with gut endoderm through the vitello-intestinal duct) covered externally by **extraembryonic (splanchnic) mesoderm**.
- ▶ **Position:** lies within the chorionic cavity, ventral/caudal to the embryo, attached to it only through the narrow vitello-intestinal duct and, alongside it, the connecting stalk (future umbilical cord).
- ▶ **Vessels:** the mesodermal wall carries a rich capillary plexus drained by paired **vitelline veins** (which enter the septum transversum and contribute to liver sinusoids and the portal system) and supplied by **vitelline arteries** (from the dorsal aortae; they fuse to form the single coeliac, superior mesenteric and inferior mesenteric arteries of the adult gut).
- ▶ **Blood islands:** angiogenic cell clusters appear in the extraembryonic mesoderm of the yolk sac wall around day 18–19; their peripheral cells flatten into endothelium (vasculogenesis) while central cells become the earliest (primitive/yolk-sac) haemopoietic stem cells.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled longitudinal section of a 5th–6th week embryo/umbilical-cord region showing:

- ▶ Amnion / amniotic cavity
- ▶ Connecting stalk (developing umbilical cord)
- ▶ Two umbilical arteries + one umbilical vein
- ▶ Allantoic diverticulum (allantois)
- ▶ Vitello-intestinal (omphalomesenteric) duct
- ▶ Definitive/tertiary yolk sac (umbilical vesicle), with its wall showing blood islands/vitelline vessels
- ▶ Midgut loop herniating into the extraembryonic coelom at the cord
- ▶ Extraembryonic coelom (chorionic cavity)
- ▶ Chorion / placental disc

### 4. Functions of the (definitive) yolk sac

| Function                         | Detail                                                                                                                                                                                                     |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Haemopoiesis                     | Blood islands in its mesodermal wall are the first site of blood-cell and blood-vessel formation in the embryo; it supplies the embryo's blood until the liver takes over haemopoiesis around the 6th week |
| Contributes to the primitive gut | Its dorsal/intraembryonic part is incorporated into the foregut, midgut and hindgut at folding                                                                                                             |



| Function                          | Detail                                                                                                                                                                                                                                           |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Origin of primordial germ cells   | Primordial germ cells arise in the wall of the yolk sac (near the origin of the allantois) and migrate along the dorsal mesentery of the hindgut to the genital ridges between the 4th and 6th weeks, later giving rise to spermatogonia/oogonia |
| Gives rise to the allantois       | A small endodermal diverticulum from its caudal wall, projecting into the connecting stalk; its intraembryonic part contributes to the apex/urachus of the developing urinary bladder, and its vessels form the umbilical arteries and vein      |
| Transport/absorptive role (early) | Before placental circulation is established, it mediates transfer of nutrients between the chorionic cavity and the embryonic gut/circulation                                                                                                    |

### Applied / Clinical anatomy

- ▶ **Ultrasound marker of early pregnancy:** the secondary/definitive yolk sac is the earliest structure identifiable by transvaginal ultrasound within the gestational (chorionic) sac, visible from about the 5th–6th week; it enlarges to a maximum diameter of about 6–7 mm around the 10th week and then regresses, disappearing by mid-trimester. An absent yolk sac in a visible gestational sac, or a yolk sac that is irregular/enlarged (>6–7 mm) or unusually small, is a recognised ultrasound predictor of a **blighted ovum (anembryonic pregnancy)/impending miscarriage**.
- ▶ **Fate of the vitello-intestinal duct:** it normally narrows and disappears by about the 6th week of development, as does the remnant yolk sac (whose vestige may occasionally be seen attached to the fetal surface of the placenta or umbilical cord at term).
- ▶ **Meckel's diverticulum:** the most common anomaly — persistence of the proximal (enteric) part of the vitello-intestinal duct as a true diverticulum of the ileum. Classical "**rule of twos**": ~2% of the population, situated ~2 feet proximal to the ileocaecal junction on the antimesenteric border, ~2 inches long, may contain two types of ectopic mucosa (gastric/pancreatic), and commonly symptomatic by age 2.
- ▶ **Other vitelline-duct anomalies:** a persistent whole duct produces an **umbilico-ileal (vitelline) fistula** discharging faecal matter at the umbilicus; persistence of only the mid-portion gives a **vitelline (enterocystoma) cyst**; a persistent fibrous cord between ileum and umbilicus (**vitelline ligament/band**) can cause volvulus or internal herniation of the midgut.
- ▶ **Physiological umbilical hernia:** because the midgut loop, still connected to the yolk sac remnant via the vitello-intestinal duct, temporarily herniates into the extraembryonic coelom of the cord (6th–10th week) before returning to the abdomen with 90° counter-clockwise rotation — a normal developmental event, not to be confused with an omphalocele.
- ▶ **Yolk-sac (endodermal sinus) tumour:** a malignant germ-cell tumour histologically recapitulating extraembryonic yolk-sac tissue, seen in the gonads (testis/ovary) and occasionally sacrococcygeal/mediastinal sites; it secretes **alpha-fetoprotein (AFP)**, used as a tumour marker.



## High-yield exam pointers

- ▶ Three developmental stages: **primary** → **secondary** → **definitive (tertiary)** yolk sac; the definitive/tertiary stage is the extraembryonic remnant left after folding, in continuity with the midgut via the vitello-intestinal duct.
- ▶ Wall = **endoderm (inner)** + **extraembryonic splanchnic mesoderm (outer)**.
- ▶ Blood islands in its wall → earliest site of **haemopoiesis and vasculogenesis**; drained by vitelline veins, supplied by vitelline arteries.
- ▶ Site of origin of **primordial germ cells**.
- ▶ Gives origin to the **allantois** (→ urachus/umbilical vessels).
- ▶ Communicates with midgut via the **vitello-intestinal (omphalomesenteric) duct**, which normally disappears by the 6th week.
- ▶ Persistence of the duct → **Meckel's diverticulum** (rule of twos), vitelline fistula, vitelline cyst, or fibrous band.
- ▶ Earliest structure visualised on **transvaginal ultrasound** in a gestational sac (~5th–6th week); its absence/abnormal appearance signals a failing pregnancy.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology.



## Development of Notochord. Describe in Detail with a Note on Its Anomalies

*Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The notochord is a solid, rod-like midline structure of **axial mesoderm (chordamesoderm)** that arises from epiblast cells of the primitive node during the third week of intrauterine life. It defines the future craniocaudal axis of the trilaminar embryo and is the classical **primary inductor (organiser)** of development — it converts the overlying ectoderm into neuroectoderm, patterns the somites into sclerotome, and provides the axis around which the vertebral column condenses. Being a defining feature of phylum Chordata, the notochord is present only transiently in humans: it regresses almost completely once the vertebral bodies chondrify around it, persisting in postnatal life only as vestigial remnants (nucleus pulposus, apical ligament of the dens). Its formation, signalling role and the anomalies of its remnants are recurrently tested in the PG curriculum.

### 1. Origin and extent

- ▶ Develops from cells of the **primitive node (Hensen's node/primitive knot)** — the elevated cranial end of the primitive streak that appears on day 15 and surrounds the **primitive pit**.
- ▶ The invaginating node cells constitute the **axial mesoderm/chordamesoderm**, distinguishing them from the general intraembryonic mesoderm formed by streak cells elsewhere.

- **Extent:** from the **prechordal plate** (an area just caudal to the oropharyngeal/buccopharyngeal membrane) cranially to the primitive node caudally; the notochord therefore never extends into the oropharyngeal or cloacal membranes, at both of which ectoderm and endoderm remain fused without intervening mesoderm.
- **Koller's (Rauber's) sickle**, a local thickening of extraembryonic tissue at the caudal edge of the germ disc, induces the adjacent epiblast to form the primitive streak by cell–cell interaction; primitive-streak formation is itself initiated and maintained by expression of the **Nodal** gene (a TGF- $\beta$  superfamily member).

## 2. Stages in formation of the notochord (day 16–22)

Formation proceeds cranial-to-caudal as the regressing primitive streak continuously supplies fresh node cells.

| Stage                                       | Approx. day | Event                                                                                                                                                                                                                             |
|---------------------------------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Notochordal process (head process)       | ~16–17      | Cells of the primitive knot proliferate and invaginate through the primitive pit (blastopore), migrating cranially in the midline between ectoderm and endoderm as a solid cord — the notochordal process                         |
| 2. Notochordal canal                        | ~17–18      | The cavity of the primitive pit extends into the notochordal process, canalising it                                                                                                                                               |
| 3. Fusion with endoderm → neurenteric canal | ~18–20      | The floor of the notochordal canal fuses with, and then breaks down together with, the underlying endoderm, opening a transient <b>neurenteric canal</b> connecting the amniotic cavity (via the primitive pit) with the yolk sac |
| 4. Notochordal plate                        | ~20–21      | The roof of the neurenteric canal flattens to form the <b>notochordal plate</b> , lying in continuity with the endoderm in the roof of the yolk sac                                                                               |
| 5. Definitive notochord                     | ~21–22      | The notochordal plate infolds and its free margins fuse; proliferating cells detach completely from the endoderm to form a solid cord, the <b>definitive notochord</b> ; the endoderm is restored below it as a continuous layer  |

□ Fig 7.6 — Formation of notochord: (A) At 16th day, cells of primitive node proliferate and form notochordal process; (B) extends to oropharyngeal membrane; (C) notochordal canal develops; (D, E) neurenteric canal forms; (F) notochordal plate; (G) folds to form definitive notochord (Sontakke — Textbook of Human Embryology, p.61)

- ▶ The proximal part of the notochordal canal persists only **temporarily** as the neurenteric canal; it normally obliterates completely, and its failure to do so underlies several of the anomalies discussed below.
- ▶ Cilia on the cells of the primitive node generate a leftward fluid flow that establishes left–right (laterality) signalling — a functionally important, though structurally separate, output of the same node population that gives rise to the notochord.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce a longitudinal (sagittal) section through the caudal embryonic disc showing the seven lettered stages (A–G) of notochord formation, labelling in each panel:

- ▶ **Oropharyngeal (buccopharyngeal) membrane and cloacal membrane** — cranial and caudal limits.
- ▶ **Primitive streak, primitive node and primitive pit.**
- ▶ **Ectoderm, mesoderm and endoderm layers.**
- ▶ **Notochordal process** (solid cord stage).
- ▶ **Notochordal canal** (canalised stage) and **allantois**.
- ▶ **Neurenteric canal** connecting amniotic cavity and yolk sac.
- ▶ **Notochordal plate** (flattened, then infolding stage).
- ▶ **Definitive notochord** (final solid rod, separated from endoderm).

### 3. Molecular basis of notochord formation and its inductive signalling

- ▶ **Nodal gene** (TGF- $\beta$  family) drives primitive-streak/node formation; **Brachyury (T gene)** expression marks and is required for notochordal/axial-mesoderm identity — abnormal Brachyury, Wnt or Engrailed gene function produces caudal notochordal/mesodermal deficiency in animal models.
- ▶ **Dorsalising vs ventralising mesodermal patterning:** low **BMP and Wnt** signalling, reinforced by **Noggin, Chordin, Follistatin, Nodal and Cerberus** (dorsalising factors), dorsalises mesoderm and induces notochord formation; high BMP/Wnt signalling ventralises mesoderm instead into lateral plate mesoderm.
- ▶ The notochord (together with the neural-tube floor plate it induces) is itself a signalling centre: it secretes **Sonic Hedgehog (SHH)** and **Noggin**, which induce the ventromedial part of the adjacent somite to differentiate into **sclerotome** and to express **PAX1**, driving chondrogenesis of the future vertebral centra.
- ▶ Notochord-derived **SHH** also induces surrounding mesenchyme to express **VEGF**, contributing to vasculogenesis around the developing axial skeleton.
- ▶ The early notochord maintains and patterns the **neural floor plate** and induces **motor-neurone** identity in the overlying neural tube; experimental removal of the notochord abolishes the floor plate and motor neurones, with the neural tube instead expressing sensory cell types — direct evidence of its primary inductive role.

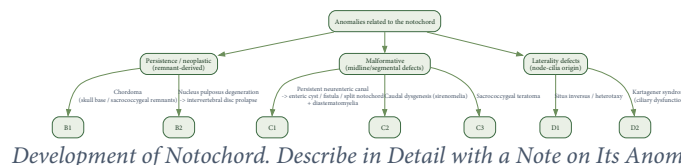
#### 4. Functions (significance) of the notochord

- Defines the **craniocaudal axis** of the embryo and converts the flat, round bilaminar disc into an elongated, polarised structure.
- Acts as the **primary inductor**: induces the overlying ectoderm to differentiate into neuroectoderm, forming the neural plate and, subsequently, the neural tube (neurulation).
- Patterns the **floor plate** and **motor neurones** of the neural tube via SHH signalling.
- Induces the ventromedial somite to form **sclerotome**, which condenses around it to form the vertebral bodies and intervertebral discs.
- Provides the **central axial column** of the embryo around which the axial skeleton is built, although it does not itself ossify or contribute bony tissue.
- Is a defining phylogenetic feature of **phylum Chordata**.

#### 5. Fate of the notochord

- As the sclerotomal mesenchyme of adjoining somites condenses around it to form the vertebral bodies, the notochord degenerates and disappears **within the substance of each developing vertebral body**.
- It **persists only in the region of the future intervertebral disc**, where it expands to form the gelatinous **nucleus pulposus**, later surrounded by the sclerotome-derived annulus fibrosus.
- A cranial remnant persists as the **apical ligament of the dens** of the axis (C2).
- With age, the notochordal cells of the nucleus pulposus degenerate further and are progressively replaced by adjacent mesodermal (fibrocartilaginous) cells; the notochord itself does **not** contribute to the bony vertebral centra.

#### Applied / Clinical anatomy — anomalies related to the notochord



- **Chordoma**: a rare tumour arising from remnants of the notochord, seen either **cranially** (at the base of the skull/clivus, with a tendency to spread into the nasopharynx) or in the **sacrococcygeal** region. It typically occurs in men **beyond 50 years of age**, and roughly **30% of these tumours are malignant**.
- **Nucleus pulposus degeneration and intervertebral disc prolapse**: because the notochord-derived nucleus pulposus is the soft, gelatinous core of the intervertebral disc, its age-related degeneration is the structural basis for disc herniation/prolapse.
- **Persistent neurenteric canal / split notochord syndrome**: the neurenteric canal between the notochordal process and the endoderm is normally transient. Its abnormal persistence, or an abnormal adhesion between notochord and endoderm during early splitting, is the recognised mechanistic basis for a spectrum of dorsal midline anomalies — an enterogenous (neurenteric) cyst or a dorsal enteric fistula tracking from gut to skin, often together with a duplicated (split) segment of notochord and an associated **diastematomyelia** (a midline bony or fibrous septum splitting the spinal cord into two hemicords, usually with an overlying cutaneous marker such as

a dimple, hairy patch or pigmented naevus, and frequently associated vertebral segmentation defects/spina bifida).

- ▶ **Caudal dysgenesis (sirenomelia):** deficient mesoderm formation in the caudalmost (primitive-streak/node) region of the embryo affects the lower limbs, urogenital system and lumbosacral vertebrae together, producing a variable spectrum of hypoplastic/fused lower limbs, renal agenesis, imperforate anus and genital anomalies; it is associated with maternal diabetes, and abnormalities of Brachyury (T), Wnt and Engrailed genes reproduce a similar phenotype in animal models.
- ▶ **Sacroccygeal teratoma:** persistence of pluripotent primitive-streak/node cells in the sacroccygeal region after the fourth week gives rise to a large tumour containing tissue from all three germ layers. It is the **most common tumour of the newborn** (incidence about **1 in 37,000** pregnancies), is commoner in **female** infants, may obstruct labour, and carries malignant potential — it must be excised within the first **6 months** of life.
- ▶ **Laterality defects (situs inversus/heterotaxy):** the same node cells that give rise to the notochord bear motile cilia whose leftward flow establishes the left–right axis; disruption of this ciliary/Nodal–Lefty–Pitx2 signalling produces **situs inversus** (complete mirror-image reversal) or **situs ambiguus/heterotaxy** (discordant/isomeric organ placement, with a high risk of complex congenital heart disease). Roughly one-fifth of complete situs inversus patients have associated ciliary dysfunction (**Kartagener syndrome** — bronchiectasis and chronic sinusitis from immotile cilia).
- ▶ **Neural tube defects:** because the notochord is the obligatory inducer of neurulation, disturbances at this stage contribute to the broader spectrum of midline neural tube defects (spina bifida, with or without diastematomyelia/tethered cord), which are surgically and radiologically significant later in life.

### High-yield exam pointers

- ▶ Notochord = axial mesoderm/chordamesoderm from the primitive node; extends from prechordal plate to the node (never into the oropharyngeal or cloacal membranes).
- ▶ Sequence: notochordal process → notochordal canal → (transient) neurenteric canal → notochordal plate → definitive notochord (days ~16–22).
- ▶ Notochord is the **primary inductor** — induces neural plate/tube formation; SHH + Noggin from notochord/floor plate induce sclerotome and PAX1-driven chondrogenesis.
- ▶ Fate: degenerates within vertebral bodies; persists only as the **nucleus pulposus** of intervertebral discs and the **apical ligament of the dens**.
- ▶ Chordoma = tumour of notochordal remnants, skull base or sacroccygeal, men >50 years, ~30% malignant.
- ▶ Sacroccygeal teratoma: commonest newborn tumour (1:37,000), more common in females, excise within 6 months.
- ▶ Persistent neurenteric canal → split notochord syndrome/enteric cyst-fistula, classically with diastematomyelia.
- ▶ Caudal dysgenesis/sirenomelia: deficient caudal mesoderm, associated with maternal diabetes and Brachyury/Wnt/Engrailed gene defects.

- Node cilia establish laterality — abnormal function gives situs inversus/heterotaxy and Kartagener syndrome.

### SOURCE & COVERAGE

Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Gray's Anatomy (Standing) 41e.



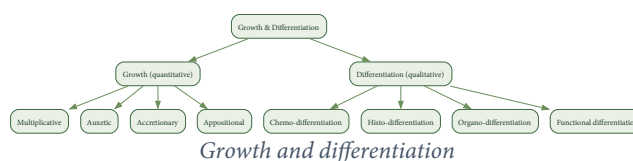
## Growth and differentiation

Asked in: Paper II May 2018 — RGUHS MD/MS Anatomy

**Definition / Introduction** Growth is a **quantitative** change — an increase in the bulk (cell number or cell size) of a tissue. Differentiation is a **qualitative** change — the acquisition of a specialised structure suited to an assigned function. Together with metabolism, growth and differentiation are the two coordinated, interlinked processes that convert a single-celled zygote into a multicellular, organised fetus. Their timing and location are governed by progressive **determination** of cell populations and by **cell-to-cell induction**, mediated by defined families of growth and differentiation factors (GDFs) acting through paracrine and juxtacrine signalling.

### 1. Growth — definition and types

| Type                                 | Mechanism                                                                                  | Example                                                                                                        |
|--------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>Multiplicative</b> (hyperplastic) | Increase in cell number by mitosis, without increase in cell size                          | Blastomeres; predominant type in prenatal life; persists postnatally in epidermis, gut epithelium, blood cells |
| <b>Auxetic</b> (hypertrophic)        | Increase in individual cell size/cytoplasmic content, altering the nucleocytoplasmic ratio | Oocyte (nursed by follicular cells); certain neurons (nursed by satellite cells)                               |
| <b>Accretionary</b> (interstitial)   | Increased accumulation of intercellular/extracellular matrix, increasing length            | Growth in length of bone and cartilage                                                                         |
| <b>Appositional</b>                  | Addition of new layers on a pre-existing surface, at the edges                             | Growth in width of bone by periosteal lamellar apposition                                                      |



### 2. Differentiation and determination

- **Differentiation** — a qualitative structural change conferring an assigned function:

- **Chemo-differentiation** — invisible, molecular-level change; the substances producing it are called **organizers**.
  - **Histo-differentiation** — the first visible ("manifest") differentiation, at tissue level.
  - **Organo-differentiation** (organogenesis) — at organ level; the basis of organ remodelling.
  - **Functional differentiation** — physiological, e.g. haemodynamic changes in developing blood vessels.
- ▶ **Determination** precedes differentiation: it is the progressive, **heritable restriction** of a cell's developmental options. A determined cell will differentiate once environmental (signalling) conditions are suitable.
  - ▶ Hierarchy of restriction as a cell population is progressively determined: **transiently amplifying cells** → **progenitor cells** → **stem cells** → **terminally differentiated cells**.
  - ▶ The state of determination is reflected in the proteins a cell synthesises: **primary/housekeeping proteins** (all cells, essential metabolism) → **secondary proteins** specific to the determined state (e.g. arginase in liver and kidney cells, not muscle) → **tertiary proteins**, unique to one fully differentiated lineage (e.g. haemoglobin in erythrocytes).
  - ▶ **Apoptosis** (programmed cell death) is itself a variety of terminal differentiation — e.g. cell death along the margins of the apical ectodermal ridge and between the digit rays permits separation of the fingers/toes in the developing limb.

### 3. Stem cells and potency

| Potency     | Capacity                                                           | Example                                                                        |
|-------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Totipotent  | Forms embryonic <i>and</i> extra-embryonic (placental) tissue      | Zygote; blastomeres of the first few cleavage divisions                        |
| Pluripotent | Forms all cell types of the body (all 3 germ layers), not placenta | Inner cell mass / human embryonic stem cells (hESCs)                           |
| Multipotent | Forms more than one related cell type                              | Mesenchymal stem cells; cord-blood/adult haemopoietic stem cells               |
| Oligopotent | Forms one category of cells only                                   | Vascular stem cells (endothelium + smooth muscle); lymphoid/myeloid stem cells |
| Unipotent   | Forms only one cell type                                           | Hepatocyte, muscle satellite cell                                              |

Stem cells characteristically undergo **asymmetric division** — one daughter remains a stem cell, the other proceeds along a differentiation pathway — in contrast to the symmetric division of ordinary proliferating (progenitor) cells.

### 4. Control of differentiation — induction and cell signalling

- ▶ **Induction**: one tissue (the **inducer**) causes a second tissue (the **responder**) to change its developmental fate. The capacity of the responder to react is **competence**, conferred by a competence factor; once induced, the tissue loses competence and becomes restricted. **Hans**



**Spemann** (1869–1941) first described this phenomenon as *primary induction* (Nobel Prize, 1935).

- ▶ Two types of tissue interaction:
  - **Permissive** — the signal merely maintains mitotic activity/self-differentiation of an already-determined tissue; no new fate is imposed.
  - **Instructive (directive)** — true induction; the signal changes the fate of the responding tissue (Wessells' four criteria: the response occurs only in the presence of the specific inducer, and a normally different tissue can be redirected to the induced fate by that same inducer). Classic examples: the optic vesicle inducing the lens vesicle from surface ectoderm; gut endoderm–mesenchyme interaction forming liver and pancreas; the ureteric bud inducing nephron formation from metanephric mesenchyme; MyoD/myogenic regulatory factors driving postmitotic myoblast differentiation after induction of myogenic mesenchyme.
- ▶ **Signalling mechanisms** between cells: direct contact via **gap junctions** (connexins); **cell adhesion molecules** (e.g. cadherins); **extracellular-matrix molecule–receptor** interactions (fibronectin/laminin binding **integrins**); and diffusible **growth and differentiation factors** (GDFs) binding cell-surface receptors.
- ▶ GDFs can be delivered by six mechanisms: **endocrine** (blood-borne, distant source), **autocrine** (acts on the secreting cell itself), **paracrine** (acts on an adjacent cell), **juxtacrine** (remains cell-surface-bound, acts on a touching cell), **intracrine** (acts within the cytoplasm/nucleus of the same cell), and **matricrine** (binds and is stored in the extracellular matrix before acting).
- ▶ Major GDF/signalling families: **fibroblast growth factors** (FGFs) acting via FGFR tyrosine-kinase receptors (angiogenesis, mesoderm differentiation, limb development — e.g. FGF8); **Hedgehog family** (Sonic, Indian, Desert — SHH is the "master morphogen", signalling via the Gli transcription factors); **WNT family** acting via frizzled receptors (limb patterning, midbrain, somite/urogenital differentiation); **TGF- $\beta$  superfamily** (TGF- $\beta$ s, bone morphogenetic proteins/BMPs, activins, Müllerian-inhibiting factor — regulating extracellular matrix formation, epithelial branching, and apoptosis); and the juxtacrine **Notch pathway** (Notch–Delta/Jagged binding releases the Notch intracellular domain, which translocates to the nucleus). Positional identity and pattern formation are specified by conserved **Homeobox (Hox)**, **T-box**, **Sox**, and **helix-loop-helix transcription-factor** gene families.

## 5. Organizers

| Organizer | Structure                                     | Induces                                           |
|-----------|-----------------------------------------------|---------------------------------------------------|
| Primary   | Primitive streak/node (blastopore-equivalent) | Notochord and intraembryonic (secondary) mesoderm |
| Secondary | Notochord                                     | Neural tube (brain and spinal cord)               |
| Tertiary  | Neural tube                                   | Segmentation of paraxial mesoderm into somites    |



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a two-part schematic:

- ▶ **Induction loop** — two adjacent tissue blocks, "Inducer (mesenchyme)" and "Responder (competent epithelium)"; an arrow from inducer to responder labelled "paracrine GDF signal — FGF / WNT / Hedgehog / TGF- $\beta$ "; a return arrow labelled "reciprocal crosstalk"; on the responder cell membrane, show ligand–receptor binding with an intracellular kinase cascade arrow reaching a nuclear "transcription factor" box.
- ▶ **Organizer hierarchy chain** — Primitive streak/node (Primary organizer) → arrow "induces" → Notochord (Secondary organizer) → arrow "induces" → Neural tube (Tertiary organizer) → arrow "induces" → Somites; alongside, the potency ladder Zygote (totipotent) → Inner cell mass (pluripotent) → Mesenchymal/haemopoietic stem cell (multipotent) → Vascular/lymphoid stem cell (oligopotent) → Hepatocyte/myocyte (unipotent).

**Applied / Clinical anatomy**

- ▶ **Cancer as a disorder of growth and differentiation control:** mutation of GDF-pathway genes removes normal growth restraint — e.g. constitutive Hedgehog-pathway activation in basal cell carcinoma and medulloblastoma, dysregulated WNT signalling in colorectal carcinoma; anaplastic tumours show reversal along the determination hierarchy toward a less-differentiated state.
- ▶ **Congenital disorders of extracellular-matrix genes:** type I collagen mutation → osteogenesis imperfecta; type II collagen mutation → chondrodysplasias; fibrillin (FBN1) mutation → Marfan syndrome — all reflect disturbed matrix-mediated cell signalling.
- ▶ **Teratogenesis:** an environmental insult (radiation, drugs, infection) acting during the critical inductive window disrupts normal induction/signalling — e.g. thalidomide-related limb defects, folate-deficiency-related neural tube defects.
- ▶ **Twinning:** duplication of the primary organizer (primitive node) produces monozygotic or, if separation is incomplete, conjoined twins.
- ▶ **Failure of regeneration:** terminally differentiated, postmitotic cells (neurons, cardiac myocytes, and myoblasts that have exited the cell cycle under MyoD control) cannot re-enter mitosis — the anatomical basis of irreversible neuronal and myocardial injury and of failed skeletal-muscle regeneration in dystrophic muscle.
- ▶ **Stem-cell therapy:** pluripotent embryonic stem cells are being explored for dopaminergic-neuron replacement in Parkinson disease, islet-cell replacement in diabetes, motor-neurone replacement after acute spinal cord injury, and cardiomyocyte replacement after myocardial infarction; multipotent haemopoietic stem cells from umbilical cord blood are already used clinically as an alternative to bone-marrow transplantation in thalassaemia and leukaemia.
- ▶ **Disorders of fetal growth:** maternal nutrition has the greatest influence on fetal growth; genetic constitution, placental sufficiency, multiple pregnancy, and teratogens (smoking, alcohol, drugs) are other major determinants. Birth weight is categorised as low (<2500 g), very low (<1500 g), and extremely low (<1000 g) birth weight; macrosomia (birth weight >4000 g) follows maternal diabetes, in which fetal hyperinsulinaemia drives excess IGF-I-mediated growth. The

**developmental origins of adult disease (Barker/DOHaD) hypothesis** holds that an altered intrauterine hormonal milieu — a "functional teratogen" — programmes susceptibility to adult hypertension, type 2 diabetes, and dyslipidaemia.

## High-yield exam pointers

- ▶ Growth = quantitative (multiplicative, auxetic, accretionary, appositional); Differentiation = qualitative (chemo-, histo-, organo-, functional).
- ▶ Determination is heritable and precedes differentiation; restriction hierarchy: transiently amplifying → progenitor → stem → terminally differentiated cells.
- ▶ Protein classes mark determination: primary (housekeeping) → secondary (e.g. arginase) → tertiary (e.g. haemoglobin, lineage-unique).
- ▶ Stem-cell potency ladder: totipotent > pluripotent > multipotent > oligopotent > unipotent; division is characteristically asymmetric.
- ▶ Induction = inducer + competent responder; permissive (maintains fate) vs instructive/directive (changes fate — Wessells' criteria).
- ▶ Six GDF delivery modes: endocrine, autocrine, paracrine, juxtacrine, intracrine, matricrine; four major GDF families: FGF, Hedgehog, WNT, TGF- $\beta$ /BMP, plus juxtacrine Notch.
- ▶ Organizer hierarchy: primary (primitive streak/node) → secondary (notochord) → tertiary (neural tube) → somites; Spemann described primary induction (Nobel 1935).
- ▶ Apoptosis is a form of terminal differentiation (e.g. interdigital cell death).
- ▶ Clinically: SHH/WNT pathway mutations → cancer; collagen/fibrillin mutations → congenital connective-tissue disorders; cord-blood stem cells already treat thalassaemia and leukaemia.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Textbook of Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Hamilton, Boyd & Mossman — Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Implantation

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

### Definition / Introduction

Implantation is the process by which the hatched blastocyst attaches to, and then burrows completely into, the endometrium of the uterus, establishing the physical and endocrine connection between the conceptus and the mother from which the placenta subsequently develops. Implantation begins on the 6th–7th day after fertilization (day 20–22 of a 28-day menstrual cycle) and is completed by about the 9th–12th day. Since the blastocyst comes to lie wholly within the endometrial stroma, human implantation is classically described as **interstitial**. Implantation occurs only during a brief hormonally-

defined "**window of implantation**" and is the earliest critical checkpoint of pregnancy — its failure is a major cause of very early, often unrecognized, pregnancy loss.

## 1. Pre-implantation preparation — hatching and the implantation window

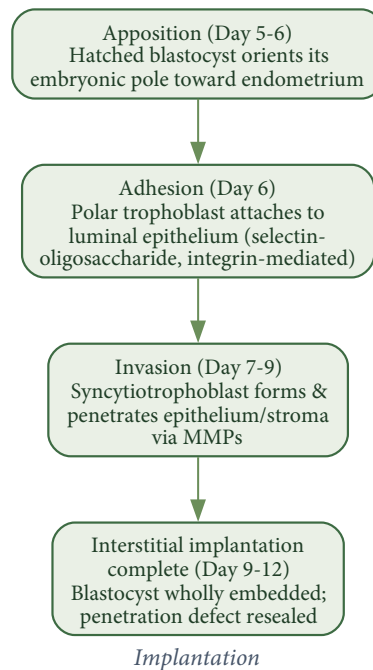
| Event                                    | Timing                     | Detail                                                                                                                                                                                                                                           |
|------------------------------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zona pellucida degeneration ("hatching") | Day 5–6                    | Zona thins and disappears, exposing the trophoblast so it can adhere to endometrium                                                                                                                                                              |
| Free-floating/apposition phase           | ~Day 5–6                   | Blastocyst floats in uterine secretions, deriving nourishment from uterine gland secretions                                                                                                                                                      |
| <b>Window of implantation</b>            | Brief, mid-secretory phase | Uterus cycles through receptive and non-receptive states under oestrogen–progesterone control; oestrogen (via growth factors such as IGF-1) drives endometrial proliferation and prevents epithelial apoptosis only during this receptive window |
| Attachment                               | Day 6                      | Trophoblast at the <b>embryonic pole</b> (polar trophoblast) contacts and adheres to the endometrial luminal epithelium                                                                                                                          |

## 2. Site of normal implantation

- ▶ Normal implantation occurs in the **upper part of the body of the uterus**, in the mid-sagittal plane.
- ▶ Commoner on the **posterior uterine wall** (~55%) than the anterior wall (~45%).
- ▶ The embryonic pole of the blastocyst is the first to contact and invade the endometrium.

## 3. Process of implantation (stages)

Implantation is classically described in three overlapping phases — **apposition, adhesion and invasion**.



- **Day 6:** Polar trophoblast of the hatched blastocyst adheres to the uterine luminal epithelium; binding is assisted by interaction between epithelial-surface oligosaccharide ligands (e.g. Lewis-type/lacto-N-fucopentose determinants) and trophoblast receptors, and by trophoblast expression of **L-selectin** with reciprocal upregulation of selectin-oligosaccharide ligands on maternal epithelium — a mechanism analogous to leukocyte rolling/tethering in vasculogenesis.
- Trophoblast overlying the embryonic pole proliferates and differentiates into an inner **cytotrophoblast** and an outer **syncytiotrophoblast**.
- The syncytiotrophoblast secretes **proteolytic enzymes and matrix metalloproteinases (MMPs)** that erode the endometrial luminal epithelium and basal lamina, and finger-like syncytial processes insinuate between endometrial epithelial cells, drawing the blastocyst progressively into the stroma.
- By **day 9**, the blastocyst is almost completely embedded and the syncytiotrophoblast blankets it except for a small area at the abembryonic pole, covered by a fibrin-containing **coagulation/penetration plug**; the maternal surface epithelium re-seals over this defect.
- The conceptus comes to occupy an uneven **interstitial implantation cavity** in the stroma, erosion continuing until this stage — with concurrent erosion of maternal vascular endothelium and glandular epithelium (phagocytosis of secretory products) that establishes early maternal blood access to trophoblastic lacunae from around day 9.
- Implantation is complete, and the conceptus fully interstitial, by about the **12th day** after fertilization.

### Diagram to draw

Draw the classic three-panel sequence of implantation (7–9 days), labelling:

- Uterine luminal epithelium and underlying endometrial stroma/glands
- Embryonic pole vs abembryonic pole of the blastocyst
- Bilaminar embryonic disc — epiblast (dorsal) and hypoblast (ventral)

- ▶ Amniotic cavity (appearing within epiblast by day 8) and blastocyst/chorionic cavity
- ▶ Cytotrophoblast (inner, cellular) and syncytiotrophoblast (outer, syncytial, invasive)
- ▶ Trophoblastic lacunae opening within the syncytiotrophoblast (from day 9)
- ▶ Coagulation/fibrin plug sealing the penetration site in the resealing luminal epithelium

□ Fig 2.1 — Initial Stages of Implantation (A) At 7 days, the newly hatched blasto (Larsen — Human Embryology — 6e, p.141)

#### 4. Trophoblast lineage and differentiation

The blastocyst/trophoblast lineage gives rise to three principal cell types, visible from Carnegie stages 4–5 onward:

| Trophoblast subtype      | Character                                                                                        | Function                                                                                                                                                                                |
|--------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cytotrophoblast          | Mononuclear, cuboidal, mitotically active                                                        | Germinative population; proliferates throughout pregnancy and fuses to generate syncytiotrophoblast                                                                                     |
| Syncytiotrophoblast      | Multinucleated syncytial mass, no distinct cell boundaries; expresses neither MHC class I nor II | Invasive, erosive front of implantation; forms the epithelial covering of the villous tree; principal endocrine component of the placenta (secretes hCG, later progesterone/oestrogens) |
| Extravillous trophoblast | Non-proliferative, migratory                                                                     | Invades maternal endometrium/myometrium and remodels maternal spiral arteries                                                                                                           |

- ▶ hCG (human chorionic gonadotrophin), secreted by syncytiotrophoblast, is detectable in maternal blood from about **day 8** and in maternal urine from about **day 10** after fertilization — the biochemical basis of the earliest pregnancy tests.
- ▶ hCG rescues and prolongs the **corpus luteum**, which continues secreting progesterone and oestrogens for roughly the first **8 weeks (2 months)** of pregnancy until the placenta itself assumes steroidogenesis.

#### 5. Decidual reaction

- ▶ On successful implantation, menstruation ceases and the endometrial stroma undergoes **decidualization** to form a nutritive, immunologically tolerant bed (the **decidua**) for the conceptus; this transformation may occur even without an intrauterine pregnancy (e.g., ectopic pregnancy, prolonged progesterone therapy, late secretory phase).
- ▶ Decidual change is not evident at the earliest stages of implantation and may take about a further week to become fully established.
- ▶ Decidual (stromal) cells enlarge, become rounded/polygonal, accumulate glycogen, lipid and vimentin filaments, may be bi- or trinucleate, and acquire a characteristic capsular basal lamina; they secrete **IGF-binding protein-1 (IGFBP-1)** and **prolactin**.
- ▶ The decidua contains an abundant leukocyte population — chiefly **uterine natural killer (uNK) cells**, together with macrophages and T cells — which interact with invading extravillous

trophoblast expressing HLA-G/HLA-C, mediating maternal immune tolerance of the semi-allogeneic conceptus.

- Once implantation is complete, three named regions of decidua are recognized:

| Decidual region    | Location                                                                              |
|--------------------|---------------------------------------------------------------------------------------|
| Decidua capsularis | Covers the conceptus, facing the uterine cavity                                       |
| Decidua basalis    | Between the conceptus and the myometrium; site where the definitive placenta develops |
| Decidua parietalis | Lines the rest of the uterine cavity away from the implantation site                  |

## 6. Abnormal (ectopic) sites of implantation

If the blastocyst implants anywhere other than the normal upper-body-of-uterus site, the result is an ectopic pregnancy.

| Site                                                                                              | Approximate frequency       | Note                                                                                  |
|---------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------|
| Tubal — ampullary                                                                                 | ~80% of tubal implantations | Commonest ectopic site overall                                                        |
| Tubal — isthmus                                                                                   | ~12%                        |                                                                                       |
| Tubal — interstitial (intramural part of tube)                                                    | ~0.2%                       | Narrowest part of tube; presents late, high risk of rupture/haemorrhage               |
| Abdominal/peritoneal (ovary, mesentery, rectouterine pouch of Douglas, or any peritoneal surface) | ~1.4%                       | Rare; secondary abdominal pregnancy may follow tubal rupture                          |
| Ovarian                                                                                           | ~0.2%                       |                                                                                       |
| Cervical / near internal os                                                                       | ~0.2%                       | Low uterine implantation predisposes to <b>placenta previa</b> even when intrauterine |

□ Fig 4.12 — Abnormal sites of implantation. Ovarian, tubal, infundibular, cervical (Sontakke — Textbook of Human Embryology, p.40)

## Applied / Clinical anatomy

- **Ectopic (tubal) pregnancy** is the commonest life-threatening complication of abnormal implantation; risk is raised by pelvic inflammatory disease, prior tubal surgery, and prior ectopic pregnancy, all of which delay tubal transport of the morula/blastocyst so that it implants before reaching the uterus.
- Tubal implantation lacks a proper decidual/submucosal bed, so trophoblastic invasion quickly breaches the thin tubal wall, causing **tubal rupture with intraperitoneal haemorrhage** — a surgical emergency.
- **Intrauterine contraceptive devices (IUCDs)** act chiefly by preventing implantation (a sterile foreign-body/inflammatory endometrial reaction), rather than by preventing fertilization.

- ▶ **Placenta previa** results when implantation occurs low in the uterus, near or over the internal os, so the placenta later overlies the cervical os — an important cause of antepartum haemorrhage.
- ▶ The earliest **urine/serum pregnancy test** exploits syncytiotrophoblastic hCG secretion (detectable from day 8 in blood, day 10 in urine) — the clinical correlate of successful implantation.
- ▶ Failure of implantation (due to inadequate corpus luteal progesterone/oestrogen, developmentally impaired embryos inducing decidual endoplasmic-reticulum stress, or a non-receptive endometrium) is a major, often unrecognized, cause of very early spontaneous abortion presenting only as a delayed, heavy menstrual flow.
- ▶ Endometrial receptivity (the implantation window) is clinically exploited/timed in **assisted reproduction** (IVF) for embryo transfer.

### High-yield exam pointers

- ▶ Implantation begins day 6–7, complete by day 9–12; human implantation is **interstitial**.
- ▶ Normal site: upper part of body of uterus, posterior wall > anterior wall.
- ▶ Three phases: **apposition** → **adhesion** → **invasion**.
- ▶ Trophoblast differentiates into **cytotrophoblast** (proliferative, inner) and **syncytiotrophoblast** (invasive, syncytial, outer); later, **extravillous trophoblast** invades the decidua/spiral arteries.
- ▶ Invasion mediated by **MMPs** and **L-selectin**–ligand adhesion.
- ▶ **hCG** from syncytiotrophoblast — detectable blood day 8, urine day 10; rescues corpus luteum till ~8 weeks.
- ▶ Decidua has three named parts: **capsularis**, **basalis** (= **future placental bed**), **parietalis**.
- ▶ Abnormal implantation = **ectopic pregnancy**; tubal (ampulla commonest) > abdominal > ovarian/cervical.
- ▶ IUCDs prevent implantation; low implantation → **placenta previa**.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Sontakke Textbook of Human Embryology; Vishram Singh Textbook of Clinical Embryology; IB Singh Human Embryology (CBME 2021).





## Implantation of the Embryo

*Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Implantation is the process by which the blastocyst attaches to, and subsequently invades and embeds within, the endometrium of the uterus, establishing a nutritive and hormonal relationship between the conceptus and the mother. In the human it begins on the 6th–7th day after fertilization and is completed by about the 12th day (i.e., day 20–22 of the menstrual cycle), the blastocyst becoming completely buried within the endometrial stroma — a pattern termed **interstitial implantation**. Successful implantation requires precise temporal synchrony between a competent blastocyst and a "receptive" endometrium, and its disturbance underlies infertility, ectopic pregnancy and early pregnancy loss.

### Types and Timing of Implantation

- ▶ **Types of implantation** (comparative embryology):
  - **Central implantation** — blastocyst implants within the uterine cavity without eccentric burrowing, e.g. carnivores (cow).
  - **Eccentric implantation** — blastocyst lodges in a uterine crypt, e.g. mouse.
  - **Interstitial implantation** — blastocyst burrows completely into the endometrial stroma, e.g. guinea pig and **human**.
- ▶ **Timing:** begins day 6–7 (once the zona pellucida is shed) and is completed by day 12 post-fertilization.
- ▶ **Site:** the blastocyst reaches the uterus at the 32-cell stage by day 3–4, and makes contact with the endometrium 1–2 days before implantation proper begins (day 5–7).

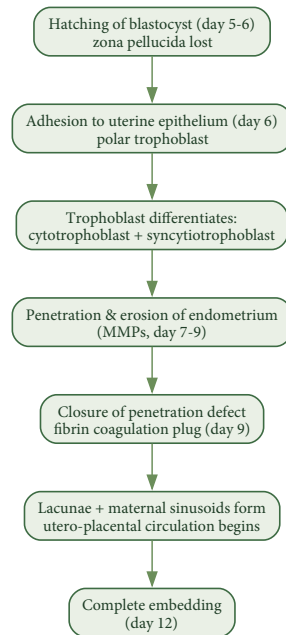
### Endometrial Receptivity — the "Window of Implantation"

- ▶ The endometrium cycles through receptive and non-receptive states; implantation is possible only during a short **implantation window**, under combined oestrogen–progesterone control.
- ▶ **Oestrogen** (via the oestrogen receptor) drives endometrial proliferation (inducing IGF-1) and inhibits epithelial apoptosis; **progesterone** (via the progesterone receptor) induces the transcription factor **Hand2**, which halts further endometrial growth and permits implantation.
- ▶ Receptive change is marked by loss of the anti-adhesive apical glycocalyx/mucin coat, flattening and retraction of microvilli, and formation of apical **pinopodes** on the luminal epithelial cells.
- ▶ The blastocyst matures from an attachment-incompetent to an attachment-competent state, expressing surface **perlecan** (a heparan sulfate proteoglycan); the receptive endometrium up-regulates **HB-EGF** (heparin-binding EGF-like growth factor), which binds the blastocyst's EGF receptor.
- ▶ Molecules mediating the trophoblast–endometrial "dialogue": **L-selectin** on trophoblast with selectin-oligosaccharide ligands on uterine epithelium (initial capture, analogous to leukocyte rolling); **integrins** ( $\alpha 6\beta 4$ ,  $\alpha v\beta 3$ ,  $\alpha v\beta 5$ ) binding laminin (attachment) and fibronectin (migration); the **trophinin–tastin–bystin** adhesion complex; cytokines **LIF** (leukaemia inhibitory factor) and **interleukin-11**; and **matrix metalloproteinases (MMPs)** that degrade the sub-epithelial basal lamina.

- Developmentally competent embryos actively enhance uterine receptivity, whereas impaired embryos trigger endoplasmic-reticulum stress in decidual cells that inhibits implantation.

### Process of Implantation (Stage-by-Stage)

| Day (post-fertilization) | Event                                                                                                                                                                                                                                                                                 |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4–5                      | Blastocyst (with zona pellucida intact) reaches the uterine cavity; blastocyst differentiates into embryoblast (inner cell mass) and trophoblast, with a fluid-filled blastocystic cavity.                                                                                            |
| 5–6                      | <b>Hatching</b> — the zona pellucida thins (trypsin-like enzymatic lysis) and disappears, freeing the trophoblast to make contact with the endometrium.                                                                                                                               |
| 6                        | <b>Adhesion (attachment)</b> — polar trophoblast (overlying the embryoblast) adheres to the columnar uterine epithelium between the mouths of the uterine glands; mediated by L-selectin/integrin interactions.                                                                       |
| 6–8                      | <b>Differentiation of trophoblast</b> into an inner mononucleated, mitotically active <b>cytotrophoblast (Langhans' layer)</b> and an outer multinucleated, non-mitotic <b>syncytiotrophoblast</b> .                                                                                  |
| 7–9                      | <b>Penetration and erosion</b> — proteolytic (MMP) activity from both trophoblast and endometrium erodes the luminal epithelium, stratum compactum and stratum spongiosum; syncytial finger-like processes actively burrow the blastocyst deeper (interstitial implantation).         |
| 9                        | <b>Closure of the penetration defect</b> — the surface epithelial gap is sealed by re-epithelialization and a fibrin <b>coagulation plug</b> .                                                                                                                                        |
| 9–12                     | Spaces ( <b>trophoblastic lacunae</b> ) appear within the syncytiotrophoblast and coalesce; syncytiotrophoblast erodes maternal capillaries, converting them into dilated <b>sinusoids</b> that communicate with the lacunae — establishing the earliest utero-placental circulation. |
| 12                       | Blastocyst <b>completely embedded</b> within the endometrial stroma; menstruation ceases.                                                                                                                                                                                             |



*Implantation of the Embryo*

□ Fig 2.1 — Initial Stages of Implantation (A) At 7 days, the newly hatched blasto (Larsen — Human Embryology — 6e, p.141)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw three successive panels (as above) of the blastocyst embedding in the endometrium, labelling in each:

- ▶ **Uterine gland** and **maternal capillary** (endometrial stroma, unlabelled tan background)
- ▶ **Cytotrophoblast** (inner, cuboidal, mononucleate layer) and **Syncytiotrophoblast** (outer, multinucleate layer) — label both at each stage
- ▶ **Epiblast** and **Hypoblast** (bilaminar embryonic disc)
- ▶ **Amniotic cavity** (appearing by day 8, dorsal to epiblast)
- ▶ By day 9: **trophoblastic lacuna**, **formation of Heuser's membrane**, and the **coagulation plug** sealing the surface defect

### Changes in the Endometrium — Decidual Reaction

- ▶ After successful implantation the endometrium (now the **decidua**) undergoes **decidualization**: stromal cells enlarge, become vacuolated and accumulate glycogen and lipid, becoming **decidual cells** that nourish the early conceptus before placental takeover.
- ▶ Driven by rising maternal **progesterone** and **hCG** from the syncytiotrophoblast; endometrial glands acquire a saw-toothed profile and spiral vessels become tortuous.
- ▶ The decidua contains a large population of leukocytes — chiefly **uterine natural killer (NK) cells**, along with macrophages and T cells — that interact with invading extravillous trophoblast expressing HLA-G/HLA-C, contributing to maternal–fetal immune tolerance.
- ▶ Decidualization can occur even without an intrauterine pregnancy (e.g. ectopic pregnancy, prolonged progesterone therapy, late secretory phase of a non-conception cycle).

**Subdivisions of the decidua** (named once the conceptus is embedded):

| Region                           | Location                                                    | Fate                                                                                                        |
|----------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Decidua basalis (decidual plate) | Between conceptus and the uterine muscular wall             | Forms the maternal component of the placenta; spiral arteries dilate into sinusoids here                    |
| Decidua capsularis               | Thin layer capping the conceptus, facing the uterine cavity | Stretches, degenerates, and by the 3rd month fuses with decidua parietalis, obliterating the uterine cavity |
| Decidua parietalis (vera)        | Remainder of the uterine lining                             | Fuses with capsularis; shed with the placenta and membranes at parturition                                  |

### Site of Implantation — Normal and Abnormal

- **Normal site:** upper part of the body of the uterus, in the midsagittal plane — posterior wall (~55%) slightly more often than the anterior wall (~45%).

| Abnormal/ectopic site       | Approximate frequency               | Note                                                                                                                                                                                             |
|-----------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tubal (uterine tube)        | 95–98% of all ectopic implantations | Ampullary region most common (~80%), then isthmus (~12%); interstitial (narrow intramural part of the tube) rare (~0.2%) but dangerous — deep in myometrium, ruptures later and bleeds massively |
| Abdominal                   | ~1.4%                               | Primary (on peritoneum/mesentery/omentum, e.g. rectouterine pouch of Douglas) or secondary (after tubal abortion/rupture)                                                                        |
| Ovarian                     | ~0.2%                               | May mimic a corpus luteum cyst; can produce an ovarian teratoma-related picture                                                                                                                  |
| Cervical / near internal os | ~0.2%                               | An abnormal <i>uterine</i> (not extrauterine) site; if in the lower uterine segment it causes <b>placenta previa</b>                                                                             |

□ Fig 4.12 — Abnormal sites of implantation. Ovarian, tubal, infundibular, cervical (Sontakke — Textbook of Human Embryology, p.40)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the uterus, tubes and ovary in coronal view and label the six sites exactly as in the plate above: **Abdominal**, **Interstitial**, **Cervical** (on the uterus); **Tubal**, **Ovarian**, **Infundibular** (on the tube/ovary).

**Applied / Clinical anatomy**

- ▶ **Ectopic pregnancy:** tubal pregnancy is the commonest extrauterine pregnancy and a leading cause of first-trimester maternal death; it presents with amenorrhoea, abdominal pain/tenderness and abnormal bleeding, and may mimic acute appendicitis if right-sided.  $\beta$ -hCG rises more slowly than in a normal intrauterine pregnancy, so early assays may be falsely negative; transvaginal ultrasonography aids early diagnosis. A ruptured tubal pregnancy is a surgical emergency (haemoperitoneum).
- ▶ **Placenta previa:** results from abnormal implantation close to or over the internal os in the lower uterine segment; the placenta bridges the os, risking severe antepartum/intrapartum haemorrhage.
- ▶ **Pregnancy test:** hCG secreted by the syncytiotrophoblast is detectable in maternal urine/serum from as early as 10 days after fertilization and is the biochemical basis of the pregnancy test; it also rescues and sustains the corpus luteum (progesterone/oestrogen secretion) for approximately the first two months, until the placenta assumes steroidogenesis.
- ▶ **Immunological tolerance:** the syncytiotrophoblast expresses neither class I nor class II MHC antigens, and uterine NK cells/regulatory mechanisms permit the semi-allogeneic conceptus (50% paternal genome) to evade rejection.
- ▶ **Assisted reproduction:** knowledge of the endometrial "window of implantation" (receptive-phase pinopodes, integrin/HB-EGF expression) guides the timing of embryo transfer in IVF.
- ▶ **Molar pregnancy:** abnormal, purely paternal-genome proliferation of trophoblast (with little/no embryonic tissue) produces a hydatidiform mole with markedly elevated hCG; may become locally invasive or, rarely, choriocarcinomatous.
- ▶ **Menstruation ceases** with successful implantation — the clinical basis of "missed period" as the earliest symptom of pregnancy.

**High-yield exam pointers**

- ▶ Implantation = attachment + invasion of blastocyst into endometrium; begins day 6–7, complete by day 12; type = **interstitial**.
- ▶ Normal site: upper body of uterus, midsagittal plane, posterior (55%) > anterior (45%) wall.
- ▶ Sequence: hatching (zona lost, day 5–6) → adhesion (day 6) → trophoblast differentiates into cyto- + syncytiotrophoblast → penetration/erosion (MMPs) → closure by fibrin coagulation plug (day 9) → lacunae/maternal sinusoids form → complete embedding (day 12).
- ▶ Endometrium in **secretory phase** at implantation; decidualized endometrium = decidua, with three named parts — **basalis** (placental bed), **capsularis** (over conceptus), **parietalis** (rest of cavity) — capsularis fuses with parietalis by the 3rd month.

- ▶ hCG from syncytiotrophoblast: detectable ~10 days post-fertilization; basis of pregnancy test; maintains corpus luteum for ~first 2 months.
- ▶ 95–98% of ectopic pregnancies are tubal (ampulla > isthmus > interstitial); abnormal uterine implantation near internal os → placenta previa.
- ▶ Syncytiotrophoblast lacks MHC class I/II — key to preventing immune rejection of the semi-allograft conceptus.
- ▶ "Window of implantation" — brief receptive period marked by pinopodes, loss of glycocalyx/microvilli, integrin and HB-EGF expression; clinically relevant to IVF embryo-transfer timing.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Methods of dating

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** "Dating" in embryology means estimating the age of a developing conceptus — the interval since fertilization or, clinically, since the first day of the last menstrual period (LMP) — for scientific staging of embryos/fetuses and for antenatal obstetric care. Because the moment of fertilization is almost never known with certainty, age must be estimated indirectly: by morphological staging (somite counts, external form) during the embryonic period, and by biometric measurement (chiefly ultrasound) during the fetal period. Two interconvertible timescales run through the whole subject — the embryological (fertilization/postovulatory) age and the clinical (menstrual/gestational) age — and accurate dating underpins the timing of prenatal diagnostic procedures, interpretation of antenatal screening, and assessment of fetal growth, viability and teratogenic risk.

### 1. Timescales used in dating a pregnancy

- ▶ **Fertilization (postovulatory/postconceptional) age:** reckoned from the actual day of fertilization; used in all embryological descriptions (Carnegie staging).
- ▶ **Menstrual age:** reckoned from the first day of the LMP. Because ovulation occurs around day 14 of a 28-day cycle, menstrual age **overestimates true fertilization age by about 2 weeks**.
- ▶ **Gestational age (obstetric convention):** development from fertilization to full term averages 266 days (9.5 lunar months), but pregnancy counted clinically from the LMP averages **280 days (40 weeks/10 lunar months)** — the extra 2 weeks being the pre-ovulatory part of the cycle.
- ▶ **Estimated date of delivery/confinement (EDD/EDC) — Naegele's rule:** count back **3 calendar months from the first day of the LMP, then add 1 year and 7 days**. Reasonably accurate only with regular 28-day cycles; unreliable with irregular cycles or uncertain LMP recall.

- ▶ **Trimesters:** 1st and 2nd trimesters each span **12 weeks**; the 3rd trimester runs from **24 weeks to delivery**. Term delivery is normal between **37 and 42 weeks**; <37 weeks = preterm, >42 weeks = post-term.
- ▶ If an ultrasound-based ("fetal") ageing system is used instead of LMP-based obstetric staging, its estimate may run **up to 2 weeks less** than the menstrual-age estimate for the same pregnancy.

## 2. Dating the embryonic period (weeks 1–8) — Carnegie staging

- ▶ The embryonic period is defined (Streeter) as **8 weeks post-fertilization = 56 days**. It is subdivided by criterion used:
  - **Pre-somite stage (day 15–20):** age reckoned in days; identified by appearance of the primitive streak, notochord, intraembryonic mesoderm.
  - **Somite stage (day 20–30):** age reckoned by **counting somite pairs** (44 pairs form from paraxial mesoderm; about 3–4 pairs are added per day).
  - **Post-somite stage (day 31–55):** somites too numerous to count reliably; age reckoned by **crown–rump length (CRL)** and pharyngeal-arch/limb-bud development.

| Age (days) | Somite pairs | Correlated structure appearing                      |
|------------|--------------|-----------------------------------------------------|
| 20         | 1–4          | Neural plate, neural folds, neural groove           |
| 21         | 4–8          | Fusion of endocardial heart tubes                   |
| 22         | 8–12         | Otic placode, optic sulcus appear                   |
| 23         | 12–16        | Lens placode forms                                  |
| 24         | 16–20        | 1st & 2nd pharyngeal arches appear                  |
| 25         | 20–24        | Anterior neuropore closes; 3rd–5th arches appear    |
| 26         | 24–28        | Upper limb bud appears; primitive streak disappears |
| 27         | 28–32        | Posterior neuropore closes                          |
| 28         | 32–36        | Lower limb bud appears                              |
| 30         | 40–44        | Face development begins                             |

- ▶ **Carnegie system of embryonic staging:** a numeric system (Streeter, on the Carnegie collection, 1942/45/48; term "Carnegie stage" introduced by O'Rahilly & Müller 1987 to replace Streeter's "developmental horizons"). Stages 1–23 span days 1–56; designation of stage rests on **external and internal morphological criteria, not on length or age** — so it is used internationally to compare specimens irrespective of exact chronological age.
- ▶ Selected milestone stages (age approximate):



| Carnegie stage | Approx. age | Defining external feature                                      |
|----------------|-------------|----------------------------------------------------------------|
| 10             | ~day 22     | 4–12 somites; neural folds fusing, neuropores open             |
| 11             | ~day 24     | 13-somite stage; rostral neuropore closing                     |
| 12             | ~day 26     | 27-somite stage; embryo curved                                 |
| 13             | ~day 28     | Upper limb bud appears; primordial heart large                 |
| 14             | ~day 32     | Second pharyngeal arch prominent                               |
| 17             | ~day 42     | Digital rays visible in the hand                               |
| 19             | ~day 48     | Auricle and external acoustic meatus visible                   |
| 21             | ~day 52     | Feet fan-shaped                                                |
| 23             | ~day 56     | Distinct human appearance; CRL ~30 mm; end of embryonic period |

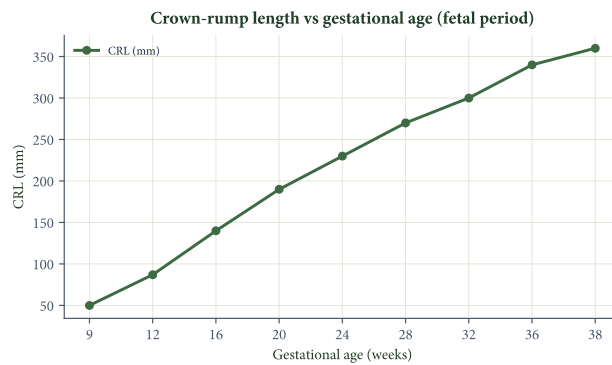
- ▶ **Age-from-length rule:** for CRL in the range 3–30 mm, age (days) can reasonably be estimated as  $\text{CRL (mm)} + 29$  (O'Rahilly & Müller revision).
- ▶ End of the embryonic period was historically marked (Streeter) by the **onset of bone-marrow formation in the humerus**.

### 3. Dating the fetal period (weeks 9–38) — biometric criteria

- ▶ **Crown–rump length (CRL):** sitting height, vertex of skull to midpoint between the buttocks; usable up to about 12–14 weeks ( $\text{CRL} \leq \sim 84 \text{ mm}$ ), beyond which fetal flexion makes it unreliable.
- ▶ **Crown–heel length (CHL):** standing height, vertex to heel; sometimes used from the 8th week onward as an alternative to CRL.
- ▶ After the first trimester, age is estimated from: **biparietal diameter (BPD)**, **head circumference (HC)**, **abdominal circumference (AC)**, **femur length (FL)**, and **foot length**; combined use of multiple parameters is recommended over any single measurement.
- ▶ **BPD is the single most accurate index of fetal menstrual age between 15 and 28 weeks.**
- ▶ **Weight** is a useful but less specific criterion (affected by growth pathology); most fetal weight is gained in the **last 8 weeks** of pregnancy.

| Age (weeks) | CRL (mm) | Foot length (mm) | Weight (g) |
|-------------|----------|------------------|------------|
| 9           | 50       | 7                | 8          |
| 12          | 87       | 14               | 45         |
| 16          | 140      | 27               | 200        |

| Age (weeks) | CRL (mm) | Foot length (mm) | Weight (g) |
|-------------|----------|------------------|------------|
| 20          | 190      | 39               | 460        |
| 24          | 230      | 50               | 820        |
| 28          | 270      | 59               | 1300       |
| 32          | 300      | 68               | 2100       |
| 36          | 340      | 79               | 2900       |
| 38          | 360      | 83               | 3400       |



CRL growth through the fetal period (data: Table of fetal biometric criteria)

#### 4. Sonographic (ultrasound) dating — trimester-wise

□ Fig 77.39 — Transabdominal ultrasound at 12 weeks, showing measurement of the crown–rump length to calculate the gestational age (Gray's Anatomy — Standing — 41e, p.1803)

##### ► First-trimester scan:

- **Gestational sac** — detectable transvaginally at 3–5 weeks; grows at ~1 mm/day; usable for dating only up to a sac diameter of ~14 mm.
- **Yolk sac** — visible from the 5th–6th week; reaches a maximum diameter of ~6 mm at 10 weeks, then regresses; useful only to confirm pregnancy, not for dating.
- **Fetal pole / cardiac activity** — identifiable from about the 6th menstrual week (embryonic length  $\geq 2$  mm).
- **CRL is the most accurate predictor of menstrual age in the first trimester**; ultrasound CRL gives an accuracy of about 1–2 days when measured between the 7th and 14th weeks.
- **Nuchal translucency** — measured at 10–14 weeks as part of first-trimester screening for trisomy 21.

- **Second- and third-trimester scan (18–20-week "anomaly scan" and later):** dating shifts to BPD, HC, AC and FL biometry (each measured in defined standard planes — BPD/HC through the thalami and third ventricle, AC at the point of maximal transverse liver diameter, FL along the ossified femoral diaphysis); ethnic/population-specific reference charts (e.g. the WHO fetal growth study, INTERGROWTH-21st) are recommended over generic ones because maternal age, parity, nutrition and smoking influence fetal biometry.

## 5. Reliability and factors affecting the accuracy of dating

- ▶ **LMP-based (menstrual) dating** is simple but unreliable with irregular cycles, uncertain recall, or bleeding mistaken for menses.
- ▶ **Ultrasound dating is most accurate the earlier in pregnancy it is performed** — CRL in the first trimester is more accurate than any second/third-trimester biometric parameter, because biological variability in fetal size increases with advancing gestation.
- ▶ When LMP-based and ultrasound-based estimates disagree, the discrepancy — and which is adopted — has direct consequences for the calculated EDD, the classification of "preterm"/"post-term," and the diagnosis of growth restriction (fetuses redefined as small-for-gestational-age or large-for-gestational-age depending on which dating method is used).
- ▶ Early routine ultrasound dating increases the **reported rate of preterm delivery** compared with LMP-based dating, largely because delayed ovulation is commoner than early ovulation.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Mid-sagittal schematic of a fetus in utero with measurement lines labelled: (1) **CRL** — vertex of skull to midpoint between the buttocks; (2) **CHL** — vertex to heel; (3) **BPD** — transverse plane through the thalami/third ventricle; (4) **Head circumference** — same plane, outer skull table; (5) **Abdominal circumference** — plane of maximal transverse liver diameter at the portal-vein confluence; (6) **Femur length** — ossified diaphysis + metaphysis; (7) **Foot length** — heel to tip of longest toe. Beneath it, draw a linear Carnegie-stage timeline from **Stage 1 (fertilization, day 0)** to **Stage 23 (day 56, end of embryonic period)**, marking Stage 10 (day 22, somites), Stage 13 (day 28, limb bud), Stage 19 (day 48, auricle) and Stage 23 (day 56, CRL ~30 mm).

## Applied / Clinical anatomy

- ▶ **Teratogen susceptibility windows** depend directly on accurate dating: **0–2 weeks** (pre-differentiation, "all-or-none" period — embryo not sensitive to teratogens but high lethality/spontaneous-abortion risk if damaged); **3–8 weeks** (organogenesis — the most sensitive period, with each organ system having its own critical window); **9–38 weeks** (maturation — a comparatively less sensitive period). Correct dating is what allows a teratogenic exposure to be assigned to the correct window.
- ▶ **Timing of prenatal invasive procedures** rests on accurate dating: chorionic villus sampling at **9–12 weeks**, amniocentesis at **14–20 weeks**, maternal serum screening ( $\beta$ -hCG, AFP, estriol, inhibin-A) from **16 weeks**.
- ▶ **Obstetric decision-making**: dating governs recognition of preterm/post-term delivery, decisions on mode of delivery, and legal limits for medical termination of pregnancy.
- ▶ **Growth assessment**: serial biometry against gestational-age-specific charts is how intrauterine growth restriction (small-for-gestational-age) and macrosomia are diagnosed — both readings are meaningless without a correct denominator (the gestational age).
- ▶ **Medicolegal relevance**: estimating the period of gestation of an aborted/miscarried conceptus (by CRL/somite criteria) or of a recovered fetus is required in criminal-abortion and stillbirth medicolegal examinations.

## High-yield exam pointers

- ▶ Embryonic period = first 8 weeks post-fertilization = 56 days; fetal period = 9th week to birth.
- ▶ Menstrual age overestimates fertilization age by ~2 weeks (ovulation ~day 14).
- ▶ Obstetric gestation (LMP-based) = 280 days/40 weeks; true fertilization-to-term duration = 266 days/9.5 lunar months.
- ▶ Naegele's rule for EDD: LMP – 3 months + 1 year + 7 days.
- ▶ Embryonic age (1–8 wk): somite count (day 20–30) → then CRL/external form (post-somite, day 31–55).
- ▶ Carnegie stages 1–23 (days 1–56) are based on morphological criteria, not length/age; introduced by O'Rahilly & Müller (1987) to replace Streeter's "horizons."
- ▶ Age (days)  $\approx$  CRL (mm) + 29, valid for CRL 3–30 mm.
- ▶ Fetal age (9–38 wk): CRL until ~12–14 weeks, then BPD (most accurate 15–28 weeks), HC, AC, FL and foot length.
- ▶ First-trimester ultrasound CRL is the single most accurate dating method in all of pregnancy (accuracy ~1–2 days).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Hamilton, Boyd & Mossman — Human Embryology.



## Organisers

*Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy*

**Definition / Introduction** An **organiser** is any part of the embryo that exerts a morphogenetic (inductive) stimulus on an adjacent, competent part, directing it to differentiate along a particular pathway that it would not otherwise follow. The phenomenon of one tissue influencing the developmental fate of another is called **embryonic induction**; the ability of the responding tissue to react to the stimulus is called **competence**. The concept was established experimentally by Hans Spemann and Hilde Mangold (1924), who showed that the dorsal lip of the amphibian blastopore, when grafted into another gastrula, could induce formation of an entire secondary embryonic axis — for which Spemann was awarded the Nobel Prize in Physiology or Medicine in 1935. Organisers act in a hierarchy — **primary, secondary and tertiary** — through diffusible signalling molecules, and their orderly, correctly-timed, correctly-placed action underlies normal organogenesis; disordered organiser activity is the basis of several classical developmental anomalies.

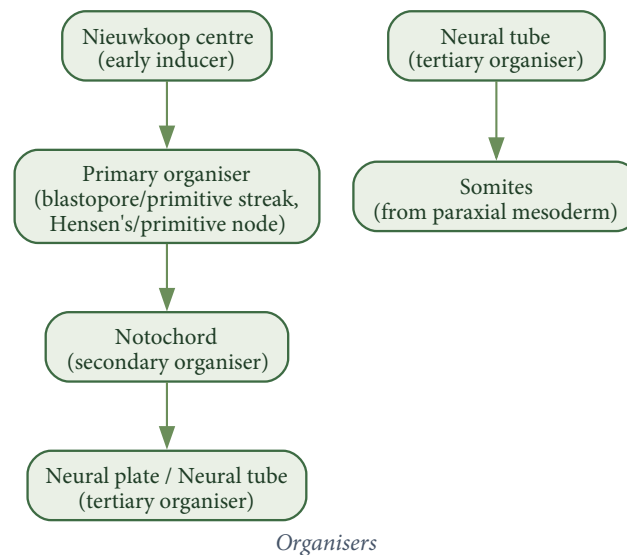
### 1. Induction, Competence and the Evocator

- ▶ **Inductor/organiser** = the tissue exerting the stimulus; **responder** = the tissue reacting to it; **competence** = the responder's capacity to react (competence is time-limited — once a tissue's fate is fixed, i.e. **determined**, it can no longer respond).
- ▶ Induction produces two effects: **evocation** — the actual histological change produced (e.g. neural tissue forms), and **individuation** — the regional character that the induced tissue adopts (e.g. midbrain versus spinal cord).
- ▶ The active principle released by an organiser is termed the **evocator**, envisaged as a morphogenetic-hormone-like diffusible chemical substance.
- ▶ Classic epithelial–epithelial example: the **optic vesicle** (neuroectoderm) induces the overlying surface ectoderm to form the **lens vesicle**; removal of the optic vesicle prevents lens formation, and its ectopic transplantation induces an ectopic lens.
- ▶ Classic epithelial–mesenchymal examples: **endoderm of the gut + adjacent mesoderm** induce liver and pancreas; **ureteric bud (mesonephric duct derivative) + metanephric blastema (mesoderm)** interact reciprocally to induce the nephron.

### 2. Classification of Organisers

| Order               | Organiser structure                                         | Structure(s) induced                                                                                    |
|---------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Primary organiser   | Blastopore / primitive streak (and primitive/Hensen's node) | Notochord and secondary (intraembryonic) mesoderm; also induces overlying ectoderm to form neural plate |
| Secondary organiser | Notochord                                                   | Overlying neuroectoderm → neural plate/neural tube (brain and spinal cord)                              |
| Tertiary organiser  | Neural tube                                                 | Segmentation of adjoining paraxial mesoderm into somites                                                |

- ▶ This hierarchy illustrates **relay/sequential induction**: each newly induced structure becomes, in turn, the organiser for the next event — the essence of orderly craniocaudal morphogenesis.
- ▶ The **primitive streak itself is the primary organiser** in the human embryo, analogous to the amphibian blastopore; its removal causes total failure of embryonic development, exactly as blastopore removal does in amphibian gastrulae.



### 3. The Primary Organiser — Structural Equivalents and Molecular Basis

- ▶ Structurally, the primary organiser is the **dorsal lip of the blastopore** in amphibians, the **embryonic shield** in fish, **Hensen's node** in the chick, the **node** in the mouse, and the **primitive node** in the human — all homologous, all defined by position, by the capacity to induce/pattern an axis, and by characteristic gene expression.
- ▶ An earlier-acting **Nieuwkoop centre** (not structurally distinct, defined by location and gene expression) induces the organiser itself; homologous centres are presumed to exist in all vertebrates including humans, though not yet structurally localised.
- ▶ The organiser patterns the mesoderm (and later the ectoderm) through antagonism between two opposing signal classes:
  - **Ventralising factors** — *Bmp* and *Wnt* — promote lateral-plate-type mesoderm and surface ectoderm.
  - **Dorsalising factors**, secreted by the organiser and its derivatives (notochord, floor plate) — protein products of *noggin*, *chordin*, *folliculin*, *cerberus* and *nodal* — antagonise Bmp/Wnt signalling. Low Bmp/Wnt activity favours notochord; high activity favours lateral plate mesoderm; intermediate levels pattern the somites.
  - The organiser also expresses about a dozen **transcription factors**, of which *gooseoid* is prototypic — its ectopic expression alone can induce a secondary body axis.
- ▶ **Neural induction** follows the same antagonism principle: in the presence of Bmp signalling ectoderm remains surface ectoderm; when Bmp signalling is blocked (by *noggin*/*chordin*/*folliculin*/*cerberus* secreted by the organiser and notochord), ectoderm instead forms **neural plate**.

## 4. Head, Trunk and Tail Organisers

Analysis of the primary organiser shows it is regionally subdivided along the craniocaudal axis:

| Regional organiser | Structure                                                                                                    | Signalling requirement                                                                                                         |
|--------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Head organiser     | Cells first to invaginate — the <b>prechordal plate</b> (mouse-model equivalent: anterior visceral endoderm) | Inhibition of Wnt and Bmp signalling (e.g. via the Wnt-antagonist <i>dickkopf1</i> ); loss causes cranial-structure deficiency |
| Trunk organiser    | The node, formed by later-invaginating chordamesoderm                                                        | Wnt, Fgf and nodal signalling with Bmp inhibition                                                                              |
| Tail organiser     | Ventral margin (zebrafish model)                                                                             | Wnt and nodal signalling, together with Bmp signalling                                                                         |

- ▶ The **prechordal plate** additionally marks the future site of the mouth (buccopharyngeal region) and is an important organiser of the head region.
- ▶ Failure of separation of head-organiser derivatives in the midline underlies **cyclopia** (fused single median eye, holoprosencephaly spectrum) — the eye primordia and their organiser mechanisms fail to split.

## 5. Classic Experimental Evidence for Organiser Activity

- ▶ **Spemann–Mangold graft (1924)**: the dorsal lip of the blastopore, transplanted into the flank of a host gastrula, retained its own fate (invaginating to form notochord/mesoderm) but induced the overlying host ectoderm — which would otherwise have become epidermis — to form neural structures, producing an almost complete **secondary embryonic axis** (experimental "conjoined twin").
- ▶ **Nature of the evocator**: subsequent work (Spemann 1931, 1933) showed the dorsal lip could still induce neural plate formation even after its cells were **crushed** or **boiled**, indicating the active principle is a heat-stable chemical rather than a living-cell interaction alone.
- ▶ **Lack of species specificity**: a chick blastopore/node graft can induce a secondary axis when introduced into an amphibian blastula — organiser action crosses species and even class boundaries.
- ▶ **Regional specificity of induction**: different inducing tissues elicit different regional responses in competent ectoderm — e.g. guinea-pig liver induces archencephalic (forebrain, eye, nose) structures, guinea-pig kidney induces deuterocephalic (midbrain, hindbrain, ear vesicle) structures, and other tissues induce spino-caudal (spinal cord, tail) structures — demonstrating that the evocator is not a single uniform substance but conveys positional/regional information.

□ Fig 7.6 — Formation of notochord: cells of the primitive node proliferate and form the notochordal process, the secondary organiser that induces the overlying neural plate (Sontakke — *Textbook of Human Embryology*, p.61)



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Dorsal view of a 16-day trilaminar embryonic disc — label: **primitive streak** (with primitive groove); **primitive/Hensen's node** (with primitive pit) at its cranial end; the **notochordal process** extending cranially from the node in the midline; **neurenteric canal**; the surrounding **epiblast**; and, in a paired sagittal inset, the **prechordal plate** cranial to the notochord marking the future buccopharyngeal membrane/mouth. Arrows to show ingression/migration of cells through the streak and node.

**Applied / Clinical anatomy**

- ▶ **Abnormal organiser strength/timing** explains a spectrum of malformations: an absent or inadequate inductive stimulus causes **agenesis** (e.g. absence of the lens, of a limb, or of a digit); a weak stimulus or poor tissue response causes **hypoplasia**; a stimulus abnormally divided in space causes **duplication/supernumerary organs** (e.g. polydactyly, double ureter/kidney, polymastia); a stimulus arising or acting in an aberrant site/direction causes an **ectopic organ**.
- ▶ **Cyclopia** (single median eye, part of the holoprosencephaly spectrum): failure of the head-organiser (prechordal plate) mesenchyme to separate the paired eye primordia in the midline.
- ▶ **Twinning** (including conjoined twins): partial or exaggerated subdivision of the primary organiser/inductive stimulus produces two axial centres instead of one; incomplete separation of the two developing axes gives conjoined twins.
- ▶ **Teratoma**: bizarre, disorganised but often well-differentiated tissue masses (e.g. **sacroccygeal teratoma**) are attributed to unco-ordinated/ectopic organiser activity involving pluripotent remnants of the primitive streak, rather than to simple twin-splitting.
- ▶ **Neural tube defects**: because the notochord (secondary organiser) induces the overlying neural plate via Bmp antagonists (noggin/chordin), disturbed notochordal/organiser signalling contributes to failure of neural plate/tube induction and closure.
- ▶ The organiser/induction concept underpins modern regenerative and developmental biology — embryonic stem cell differentiation protocols deliberately mimic organiser signals (Bmp antagonists, Wnt/nodal modulation) to direct lineage-specific differentiation.

**High-yield exam pointers**

- ▶ Organiser = any part of the embryo exerting an inductive (morphogenetic) stimulus on an adjacent competent part; discovered by **Spemann and Mangold, 1924** (dorsal lip of blastopore graft → secondary axis); Spemann — **Nobel Prize 1935**.
- ▶ Three orders: **primary** (primitive streak/node → notochord + intraembryonic mesoderm), **secondary** (notochord → neural plate/tube), **tertiary** (neural tube → somites from paraxial mesoderm).
- ▶ Structural homologues of the primary organiser: dorsal lip of blastopore (amphibia), embryonic shield (fish), Hensen's node (chick), node (mouse), primitive node (human).
- ▶ Molecular antagonism: dorsalisising **noggin/chordin/follistatin/cerberus/nodal** (organiser-secreted) versus ventralising **Bmp/Wnt**; transcription factor **goosecoid** can itself induce a secondary axis.

- ▶ Regional organisers: **head organiser** = prechordal plate/anterior visceral endoderm; **trunk organiser** = node; **tail organiser** = ventral margin (zebrafish).
- ▶ Evocator is chemical, heat-stable (survives boiling/crushing) and not species-specific (cross-species grafts still induce).
- ▶ Applied: cyclopia, conjoined twinning, sacrococcygeal teratoma, agenesis/hypoplasia/duplication/ectopia of organs, neural tube defects — all traceable to disordered organiser/inductive activity.
- ▶ Classic epithelial–epithelial induction example for viva: **optic vesicle** → **lens vesicle**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology (figure).



## Organizers

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** An **organizer** is any region of the embryo that exerts a **morphogenetic (inductive) stimulus** on an adjacent, competent tissue, directing it along a particular developmental pathway that it would not otherwise follow. The concept was established experimentally by **Hans Spemann and Hilde Mangold** in amphibian embryos in the 1920s, for which Spemann alone was awarded the **Nobel Prize in Physiology or Medicine in 1935** — the phenomenon they described is still called **primary induction**. In the human embryo the organizer is represented by the **primitive (Hensen's) node**, and its molecular output (Nodal, Goosecoid, Chordin, Noggin, Follistatin, Brachyury) patterns the mesoderm, induces the neural plate, and establishes the craniocaudal, dorsoventral and left-right body axes.

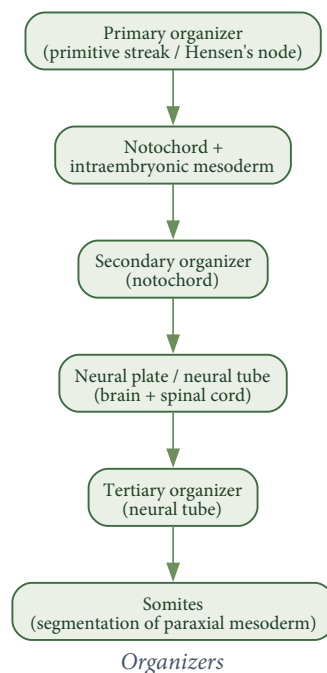
### 1. The classical (Spemann-Mangold) experiment

- ▶ Spemann and Mangold transplanted the **dorsal lip of the blastopore** from a pigmented newt gastrula onto the ventral/lateral side of an unpigmented host gastrula at the same stage.
- ▶ The graft **invaginated normally** and induced the adjacent host ectoderm — which would otherwise have formed skin — to form a **complete second neural axis** (neural tube, somites, notochord), producing **conjoined secondary embryos**.
- ▶ Because host tissue, not just graft tissue, was recruited into the new axis, the graft was shown to act by **induction**, not merely by self-differentiation; Spemann therefore named the dorsal lip the **"organizer."**
- ▶ The organizer was later shown to secrete more than a dozen molecules and to express roughly ten transcription factors; ectopic expression of several of these (e.g. **chordin**, **goosecoid**) is independently sufficient to induce a secondary axis, reproducing the classical graft experiment in molecular terms.

## 2. Definition and classification of organizers

An organizer exerts its effect through diffusible chemical substances — **inductors** (which stimulate differentiation) or **inhibitors** (which restrain it) — that are now known to be gene-controlled growth factors and transcription factors. Three grades are recognised on the basis of the sequence in which one organizer induces the next:

| Grade               | Structure (human/avian embryo)                                                                                                                   | Tissue induced                                                                                                      |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Primary organizer   | Primitive streak / primitive (Hensen's) node — homologous to the <b>dorsal lip of the blastopore</b> (amphibian), <b>embryonic shield</b> (fish) | Notochord and intraembryonic (definitive) mesoderm; also establishes the craniocaudal axis and left-right sidedness |
| Secondary organizer | Notochord                                                                                                                                        | Overlying neuroectoderm → neural plate/neural tube (brain and spinal cord)                                          |
| Tertiary organizer  | Neural tube                                                                                                                                      | Segmentation of adjoining paraxial mesoderm into somites                                                            |



- ▶ A further, more localised example of induction quoted alongside the organizer concept (though not itself graded primary/secondary/tertiary) is the **optic vesicle inducing the lens vesicle** from overlying surface ectoderm — the classical illustration that the inducing tissue is termed the *organizer/inductor* and the responding tissue the *responder*, with **competence** denoting the responder's intrinsic capacity to react to the inductive signal.
- ▶ The **prechordal plate** — the midline mesenchyme derived from cells that migrate cranially through the node, lying between the tip of the notochord and the oropharyngeal membrane — is a distinct, clinically important **organizer of the head/forebrain region**.

### 3. The organizer is homologous across vertebrates

| Species             | Structure equivalent to "the organizer" |
|---------------------|-----------------------------------------|
| Amphibian (Xenopus) | Dorsal lip of the blastopore            |
| Fish                | Embryonic shield                        |
| Chick               | Hensen's node                           |
| Mouse               | The node                                |
| Human               | Primitive node                          |

- The organizer itself is induced by an earlier-acting, **Nieuwkoop center**, an inductive region defined not by a distinct histological structure but by its position and gene-expression pattern; it is well characterised in amphibians and is presumed, from mouse loss-of-function experiments, to have a molecular counterpart in higher vertebrates.
- The organizer, in turn, patterns the newly formed mesoderm along the medial-lateral (dorsoventral) axis and induces the overlying ectoderm to form neural plate rather than surface ectoderm.

### 4. Molecular basis of organizer (node) activity

| Molecule/gene                          | Site of expression                       | Action                                                                                                                                                                                                                     |
|----------------------------------------|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NODAL (TGF- $\beta$ family)            | Primitive streak/node                    | Initiates and maintains the primitive streak; upregulates genes for dorsal/ventral mesoderm and head/tail structures                                                                                                       |
| BMP4                                   | Throughout the bilaminar/trilaminar disc | Together with FGF, <i>ventralises</i> mesoderm (intermediate + lateral plate mesoderm, kidneys, blood, body-wall); would ventralise <b>all</b> mesoderm if unopposed                                                       |
| GOOSECOID                              | Node                                     | Activates chordin; ectopic expression can duplicate the embryonic axis (over-/under-expression $\rightarrow$ head duplications resembling some conjoined-twin defects)                                                     |
| CHORDIN, NOGGIN, FOLLISTATIN, CERBERUS | Node/notochord (BMP antagonists)         | Bind and neutralise BMP4, <i>dorsalising</i> mesoderm into notochord, somites and somitomeres; the same antagonists later act in the notochord to induce the overlying neural plate by blocking BMP signalling in ectoderm |

| Molecule/gene                                  | Site of expression                            | Action                                                                                                                                                                                                        |
|------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BRACHYURY (T)                                  | Node, notochordal precursor cells, notochord  | T-box transcription factor essential for cell migration through the primitive streak; drives dorsal mesoderm formation in middle/caudal regions — its absence shortens the embryonic axis (caudal dysgenesis) |
| HNF-3 $\beta$                                  | Node                                          | Maintains the node and induces regional specificity in fore- and midbrain; loss causes failure of proper gastrulation with absent forebrain/midbrain                                                          |
| OTX2, LIM1, HESX1 + secreted Cerberus, Lefty-1 | Anterior visceral endoderm (AVE), cranial end | Locally inhibit Nodal signalling, thereby establishing the cranial end/head-forming region of the embryo                                                                                                      |
| Wnt / Cdx genes / retinoic acid                | Regressing primitive streak                   | Wnt-driven Cdx expression upregulates posterior Hox genes, imposing craniocaudal identity on neural plate and paraxial mesoderm, opposed by a cranial-high retinoic acid gradient                             |

- ▶ The organizer therefore acts principally as a **BMP-antagonist source**: ectoderm defaults to a neural fate once BMP signalling is blocked, and mesoderm is dorsalised (notochord/somite fate) rather than ventralised (kidney/blood/lateral plate fate) wherever chordin/noggin/follistatin reach it.
- ▶ Distinct **head, trunk and tail organizing activities** exist sequentially along the primitive streak/node as it regresses, so that the mesoderm and neural plate laid down at each level acquire region-specific (forebrain vs hindbrain vs spinal cord; unsegmented head mesoderm vs segmented trunk mesoderm) character.

## 5. Nature of induction and competence

- ▶ Induction may be **instructive** (the inducing tissue directs the responder into a pathway it would not otherwise take, e.g. organizer → neural plate) or **permissive** (the inducer merely allows self-differentiation/mitosis to continue in an already-determined tissue).
- ▶ **Competence** is the responder's intrinsic, time-limited ability to respond to an inductive signal; once a tissue has been induced along a pathway it progressively loses competence and becomes **restricted**.
- ▶ Signalling is mediated by direct cell-cell contact, cell-adhesion molecules, extracellular-matrix molecules, or diffusible growth factors acting in endocrine, paracrine, juxtacrine or autocrine fashion — the organizer's BMP antagonists act paracrine/diffusibly across the disc.

□ Fig 3.21 — *Experiments on the Role of the Organizer* (A) Donor blastopore grafted onto a host embryo induces a complete secondary body axis, resulting in conjoined twins; (B) UV-irradiated (organizer-ablated) embryo injected with goosecoid mRNA shows induction of two embryonic axes (Larsen — *Human Embryology* — 6e, p.209)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

**Spemann-Mangold organizer-graft experiment** Labels: donor gastrula (pigmented) — dorsal lip of blastopore/organizer marked; host gastrula (unpigmented) — ventral/lateral graft site marked; direction of graft transplantation (arrow); resulting embryo — primary (host-derived) neural axis; induced secondary neural axis (from host tissue, graft-induced) with its own neural tube, somites and notochord; label the two conjoined axes as "primary embryo" and "induced secondary embryo."

**Applied / Clinical anatomy**

- ▶ **Conjoined ("Siamese") twins** — experimentally reproduced by organizer grafting/duplication (goosecoid over-expression) in animal models; in humans, incomplete separation of monozygotic twin embryonic discs is the accepted mechanism, and organizer-signalling duplication provides the experimental proof-of-principle for how a single disc can generate two body axes.
- ▶ **Holoprosencephaly** — loss of midline tissue in the **prechordal-plate region** (the head organizer derived from cells migrating through the node) causes failure of the forebrain vesicle to cleave into two cerebral hemispheres, ranging from mild (single central incisor, hypotelorism) to severe (synophthalmia, proboscis, single ventricle) forms — a direct clinical correlate of head-organizer failure.
- ▶ **Neural tube defects** (anencephaly, spina bifida) — failure of the organizer-driven BMP-antagonism that normally converts ectoderm to neural plate, or failure of subsequent neural fold fusion, underlies a proportion of these common CNS malformations.
- ▶ **Caudal dysgenesis/sacral agenesis** — loss of Brachyury (T)-dependent caudal mesoderm formation shortens the embryonic axis, analogous to caudal regression seen clinically (notably associated with maternal diabetes).
- ▶ **Regenerative medicine and cancer biology** — organizer signalling molecules (Nodal, BMP antagonists, Wnt) are re-studied as templates for directing stem-cell differentiation in vitro, and aberrant reactivation of Nodal/TGF- $\beta$  pathways is implicated in tumour invasiveness, giving the century-old organizer concept continuing translational relevance.

**High-yield exam pointers**

- ▶ Organizer = region exerting a morphogenetic/inductive stimulus on adjacent, competent tissue; discovered by **Spemann and Mangold** (dorsal lip of blastopore graft  $\rightarrow$  secondary axis); **Nobel Prize 1935 (Spemann)**.
- ▶ Human/avian equivalent of the organizer = **primitive (Hensen's) node**; other species: dorsal lip of blastopore (amphibian), embryonic shield (fish), the node (mouse).
- ▶ **Grading**: Primary organizer (primitive streak/node)  $\rightarrow$  notochord + mesoderm; Secondary organizer (notochord)  $\rightarrow$  neural tube; Tertiary organizer (neural tube)  $\rightarrow$  somite segmentation.
- ▶ Organizer is itself induced by the **Nieuwkoop center**.
- ▶ Molecular core: **NODAL** maintains the streak; **BMP4** ventralises mesoderm; **GOOSECOID**  $\rightarrow$  **CHORDIN**, plus **NOGGIN** and **FOLLISTATIN**, antagonise BMP4 to dorsalise mesoderm and

induce neural plate; **BRACHYURY (T)** drives caudal dorsal-mesoderm formation; **HNF-3 $\beta$**  maintains the node and patterns fore-/midbrain.

- ▶ The **prechordal plate** is the specific organizer of the head/forebrain region.
- ▶ Clinical correlates: conjoined twins (organizer duplication), holoprosencephaly (prechordal-plate/midline failure), neural tube defects, caudal dysgenesis.

#### SOURCE & COVERAGE

Larsen — Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Gray's Anatomy (Standring) 41e.



## Placenta as a homograft

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

### Definition / Introduction

A **homograft (allograft)** is tissue transferred between genetically non-identical members of the same species, which normally provokes immune rejection. The conceptus, carrying **paternal antigens foreign to the mother**, is genetically such a graft — yet it implants, invades the endometrium, and is retained in intimate contact with maternal blood for the entire duration of gestation without rejection. This paradox — first framed by **Medawar (1953)** as "the immunological problem of pregnancy" — has never been explained by a single mechanism; instead, a combination of anatomical, hormonal and cellular-immunological factors together protect the fetoplacental unit. This remains, in the words of Hamilton, Boyd & Mossman, "the greatest enigma of nature."

### 1. The conceptus as a graft — genetic basis

- ▶ The embryo/trophoblast derives half its genome from the mother and half from the father. With respect to **maternal genes it is an isograft**; with respect to **paternal genes it is a homograft** — the conceptus is therefore simultaneously a **semi-isograft and semi-homograft**, i.e. an **F1-hybrid graft** (Bardawil et al., 1962).
- ▶ The **syncytiotrophoblast** covering the chorionic villi is bathed directly in maternal blood from very early stages; in the mature placenta the total villous surface exposed to maternal blood is enormous (~14 m<sup>2</sup>). Despite this vast area of contact, **no homograft reaction occurs**.
- ▶ Primary graft rejection classically requires three steps — recognition of foreign antigen by circulating lymphocytes, proliferative response in lymphoid organs, and graft destruction by committed lymphocytes/antibody. In pregnancy, the mother mounts only an **ineffective, localised response**: small lymphocyte-like cells infiltrate the decidua around the implantation site, but no destructive reaction follows.

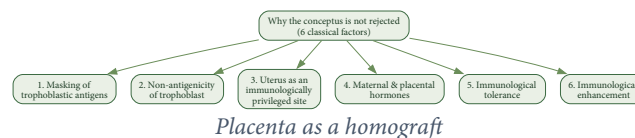


## 2. Medawar's postulates (1953) — the three classical explanations

| Postulate                                        | Basis                                                                                                                                                                                       |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Anatomical/physical separation                | The trophoblast is interposed between fetal and maternal tissue and <b>poorly expresses classical MHC antigens</b> , so it is not efficiently "seen" as foreign                             |
| 2. Antigenic immaturity of the fetus             | The conceptus was proposed to be too immunologically immature to provoke rejection (later shown to be only partly true — transplantation antigens actually appear very early in fetal life) |
| 3. Immunological inertia/tolerance of the mother | Pregnancy induces a state of general immunological quiescence in the mother that specifically spares the conceptus                                                                          |

None of these three postulates alone is sufficient; each is only partly supported by evidence, and modern work shows the real explanation is multifactorial.

## 3. Classical six factors invoked for non-rejection (Hamilton, Boyd & Mossman)



| Factor                                       | Mechanism                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Masking of trophoblastic antigens         | Fibrin/fibrinoid deposited at the junctional zone and villous surface may physically shield trophoblastic antigens from maternal lymphocytes/antibodies; sialic-acid-rich fibrinoid carries a strong negative charge that electrostatically repels similarly-charged lymphocytes                                                                                        |
| 2. Non-antigenicity of the trophoblast       | Trophoblastic giant cells and syncytial sprouts lie in direct contact with maternal tissue yet provoke no cellular reaction; when embryonic tissue and trophoblast are separated and transplanted, the embryonic tissue is destroyed while the trophoblast survives — evidence of a peculiar, reduced antigenicity unique to trophoblast (also seen in choriocarcinoma) |
| 3. Uterus as immunologically privileged site | Proposed by analogy with other lymphatic-poor sites (anterior chamber of eye, CNS); largely refuted, since transplantation immunity can be evoked normally in the uterus, and an <b>ectopic (extra-uterine) pregnancy is also not rejected</b>                                                                                                                          |
| 4. Maternal and placental hormones           | High local concentrations of <b>hCG</b> and <b>oestrogens</b> are lymphopenic and prolong skin-allograft survival in pregnant and choriocarcinoma patients; raised <b>corticosteroids</b> in pregnancy are also lymphopenic                                                                                                                                             |

| Factor                       | Mechanism                                                                                                                                                                                                                                                             |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5. Immunological tolerance   | Bidirectional transplacental trafficking of lymphocytes (mother→fetus and fetus→mother, from as early as the 14th week) exposes each to low, chronic doses of the other's antigens — the classical route (intravenous, low-dose) most effective at inducing tolerance |
| 6. Immunological enhancement | Non-cytotoxic maternal antibodies bind antigenic sites on the trophoblast, sterically blocking access of cytotoxic lymphocytes without themselves damaging the graft                                                                                                  |

#### 4. Modern immunological basis of maternal–fetal tolerance

- ▶ Syncytiotrophoblast expresses neither class I nor class II MHC antigens at all — it is essentially invisible to maternal T cells, the most complete solution to rejection.
- ▶ Extravillous trophoblast (EVT), which invades the decidua and remodels the maternal spiral arteries, does express class I MHC — but only the **non-classical, non-polymorphic HLA-G** (poorly recognised as an alloantigen by T cells) together with HLA-C (polymorphic). HLA-G additionally engages **killer-inhibitory receptors on uterine natural killer (NK) cells**, switching off their cytotoxic function; uterine NK cells are the most numerous decidual leukocyte population and interact directly with HLA-G/HLA-C-bearing EVT cells.
- ▶ **Local immunosuppressive milieu:** decidual cells secrete **prostaglandin E2, TGF- $\beta$  and IL-10**, which block activation of maternal T cells and NK cells locally.
- ▶ **Indoleamine 2,3-dioxygenase (IDO)** in trophoblast catabolises tryptophan, starving activated maternal T cells of this essential amino acid and suppressing local T-cell proliferation; pharmacological inhibition of IDO in pregnant mice causes complement-mediated rejection of allogeneic (but not syngeneic) conceptuses.
- ▶ **Complement regulation:** membrane cofactor protein **CD46** (the human counterpart of murine Crry) blocks activation of complement component C3 at the trophoblast surface, protecting the placenta from complement-mediated damage.
- ▶ **Transient systemic tolerance:** the maternal T-cell (and B-cell) repertoire develops a temporary, pregnancy-specific tolerance to fetal MHC antigens, acting as a backup mechanism.
- ▶ **Deletion of activated maternal leukocytes:** trophoblast expresses apoptosis-inducing ligands that trigger death of activated maternal leukocytes attempting to traffic into the placenta/fetus.

□ Fig 9.6 — Placental barrier. In early foetal life, placental barrier consists of (Sontakke — *Textbook of Human Embryology*, p.86)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A schematic of the maternal–fetal interface, labelled with:

- ▶ **Intervillous space** with maternal blood.
- ▶ **Syncytiotrophoblast** covering the chorionic villus — labelled "MHC class I & II negative — invisible to maternal T cells."
- ▶ **Cytotrophoblast** layer beneath the syncytium.
- ▶ **Fetal capillary** with fetal blood, inside the villous core.
- ▶ **Anchoring villus** → **column of extravillous trophoblast (EVT)** invading the decidua, labelled "expresses HLA-G (non-polymorphic) + HLA-C (polymorphic)."
- ▶ **Decidual (uterine) NK cell** adjacent to EVT, with an arrow labelled "HLA-G → killer-inhibitory receptor → NK cytotoxicity switched OFF."
- ▶ **Remodelled spiral artery**, endovascular EVT plugging its lumen.
- ▶ Small labelled cloud around the interface for **PGE<sub>2</sub>, TGF- $\beta$ , IL-10, IDO** — "local immunosuppressive milieu."

**Applied / Clinical anatomy**

- ▶ **Pre-eclampsia, miscarriage and fetal growth restriction:** failure of adequate EVT invasion and of spiral-artery conversion from narrow musculoelastic vessels to wide, low-resistance channels is a recognised anatomical basis of these complications — an example of what happens when the normal invasive/tolerogenic programme of trophoblast fails.
- ▶ **Choriocarcinoma and hydatidiform mole:** trophoblastic tumours exploit the same "peculiar" immunological privilege of normal trophoblast, growing and even metastasising as a persistent, non-rejected allograft — supporting evidence that trophoblast itself (not just the barrier) has reduced antigenicity.
- ▶ **Rh (D) isoimmunisation:** shows that maternal tolerance is not absolute — when fetal **red cell antigens** (which do carry blood-group antigenicity, unlike the trophoblast surface) cross into the maternal circulation via fetomaternal haemorrhage, the mother does mount an antibody response, underlining that immune privilege is specific to the trophoblast/placental interface rather than to all fetal tissue.
- ▶ **Prolonged skin-allograft/neonatal tolerance:** skin allografts survive longer in pregnant women and in choriocarcinoma patients (hormonal effect); conversely, transplacental passage of maternal lymphocytes to the fetus may render some neonates tolerant of maternal skin grafts.
- ▶ **Transplant immunology relevance:** multiparous women can become sensitised to paternal HLA antigens carried by successive fetuses, which is relevant to cross-matching before solid-organ transplantation.
- ▶ **Obstetric ultrasound/Doppler correlate:** uterine artery Doppler waveform notching is used clinically as a surrogate marker of inadequate trophoblastic spiral-artery remodelling.

## High-yield exam pointers

- ▶ Conceptus = **semi-isograft** (maternal genes) + **semi-homograft/allograft** (paternal genes) = an **F1-hybrid graft**.
- ▶ **Medawar's 3 postulates (1953)**: physical separation, antigenic immaturity of fetus, maternal immunological tolerance.
- ▶ **Hamilton, Boyd & Mossman's 6 classical factors**: masking, non-antigenicity, immunologically privileged uterus (largely refuted), hormones, immunological tolerance, immunological enhancement.
- ▶ **Syncytiotrophoblast is MHC class I and II negative** — the single most important reason it evades T-cell recognition.
- ▶ **Extravillous trophoblast** expresses only **HLA-G** (non-polymorphic) + **HLA-C** — HLA-G engages killer-inhibitory receptors on **uterine NK cells** to switch off cytotoxicity.
- ▶ Local immunosuppressants: **PGE<sub>2</sub>**, **TGF- $\beta$** , **IL-10**, **IDO** (tryptophan depletion); complement is controlled by **CD46 (membrane cofactor protein)**.
- ▶ Failure of EVT invasion/spiral-artery remodelling → **pre-eclampsia, miscarriage, fetal growth restriction**.
- ▶ **Rh isoimmunisation** proves maternal tolerance is compartmentalised to trophoblast, not to all fetal antigens.

### SOURCE & COVERAGE

Hamilton, Boyd & Mossman Human Embryology; Moore The Developing Human 9e; Gray's Anatomy (Standring) 41e; Sontakke Textbook of Human Embryology; Larsen Human Embryology 6e — for the embedded plate, Sontakke Textbook of Human Embryology, Fig 9.6.



## Placenta praevia and its types

*Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — Placenta praevia (*praevia* = "in front of", Latin) is an abnormal implantation of the placenta in which it is attached, partially or completely, over the lower uterine segment so that it lies in relation to, or covers, the internal os of the cervix. It arises when the blastocyst implants close to the internal os instead of in its usual fundal/upper-segment site, and it is one of the most important causes of antepartum haemorrhage (APH) and an indication for caesarean delivery.

### Normal site of placental attachment

- ▶ Normally the blastocyst implants along the **posterior wall** of the body of the uterus (less often the anterior wall), close to the fundus, so that the mature placenta lies in the **upper uterine segment** (upper two-thirds of the body of the uterus).
- ▶ In early pregnancy the placental disc occupies a large part of the uterine cavity and may appear to lie close to the internal os on early scans; in most pregnancies, growth and stretching of the

uterus and the differential development of the lower segment draw the placenta upward, away from the cervix, by the end of pregnancy ("placental migration").

- If, instead, the blastocyst implants in the region of the internal os, the developing placenta remains attached over the **lower uterine segment** (lower one-third of the body of uterus) and the condition of placenta praevia results.

## Aetiology / Incidence

- **Abnormal implantation site:** implantation in the region of the internal os is one of the recognised abnormal implantation sites of the blastocyst, alongside tubal, ovarian and abdominal implantation.
- **Incidence:** quoted as roughly 0.2% of implantations in series of abnormal implantation sites, and about 0.5–1% of **hospital deliveries** when counted as a complication of late pregnancy.
- Incidence **increases with increasing maternal age beyond 35 years.**
- Predisposing factors accepted in standard obstetric-anatomy teaching include multiparity, multiple pregnancy (larger placental surface area), a scarred lower segment from a previous caesarean section/uterine surgery, and previous curettage — all of which favour low implantation or impaired upper-segment vascularity.

## Classification (types) of placenta praevia

Placenta praevia is graded by the degree to which the placenta encroaches on, or covers, the internal os. Two parallel nomenclatures are used in the standard texts; they describe the same spectrum of severity.

| Modern "Type" (I–IV)                  | Description                                                                                                               | Classical "Degree"                                                                                                                          | 3-tier (Hamilton, Boyd & Mossman)                                                      |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Type I — Low-lying                    | Only the lower margin of the placenta encroaches onto the lower uterine segment; it does <b>not</b> reach the internal os | First degree — attachment does not extend to the internal os                                                                                | —                                                                                      |
| Type II — Marginal                    | Placenta reaches the <b>margin</b> of the internal os but does not cover it                                               | Second degree — extends up to the internal os but does not cover it                                                                         | <b>Marginal</b> — part of placenta lies in the lower segment but does not cover the os |
| Type III — Incomplete/Partial central | Placenta <b>partially</b> covers the internal os                                                                          | Third degree — edge covers the internal os, but as the os dilates in labour the placenta no longer occludes it                              | <b>Lateral</b> — placenta partially covers the internal os                             |
| Type IV — Central/Total               | Placenta <b>completely</b> covers the internal os                                                                         | Fourth degree — placenta completely covers/bridges the internal os even when fully dilated; also called " <b>central placenta praevia</b> " | <b>Central</b> — placenta completely overlies the internal os                          |

- ▶ Types III and IV (or third/fourth degree, "central") are the clinically dangerous grades — they mandate delivery by caesarean section because vaginal delivery is mechanically obstructed and provokes catastrophic haemorrhage.
- ▶ As a working rule on imaging: if the placental edge lies **within 1–2 cm of the internal os, or covers it**, delivery by caesarean section is generally indicated.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal section through the gravid uterus, cervix and upper vagina, drawn as **four labelled panels (A–D)**, one for each type/degree, showing:

- ▶ Fundus of uterus
- ▶ Body of uterus / **upper uterine segment**
- ▶ **Lower uterine segment**
- ▶ **Internal os** (mark clearly in every panel)
- ▶ Cervical canal and **external os**
- ▶ Vagina
- ▶ Placenta (shade it), positioned in each panel as:
  - **A — Type I / First degree:** placental margin reaching only into the lower segment, well clear of the internal os
  - **B — Type II / Second degree ("Marginal"):** placental edge just touching the margin of the internal os
  - **C — Type III / Third degree ("Lateral"/incomplete central):** placenta partially overlapping the internal os
  - **D — Type IV / Fourth degree ("Central"/total):** placenta completely covering the internal os

(Based on the classical "types of placenta praevia" figure used in embryology texts — reproduce as four small labelled uterine outlines side by side.)

### Clinical features and diagnosis

- ▶ Classic presentation: **painless, bright-red vaginal bleeding** in the third trimester (after 28 weeks), often recurrent, without associated abdominal pain — placenta praevia is one of the **commonest causes of antepartum haemorrhage**.
- ▶ **Ultrasonography** is the investigation of choice. **Transvaginal ultrasound** is preferred over transabdominal scanning for accurately localising the placental edge and measuring cervical length, and can demonstrate the placenta covering, or lying a measured distance from, the internal os.
- ▶ Because early "low-lying" placentas commonly migrate upward as the lower segment forms and stretches, a diagnosis made on a mid-trimester scan is re-confirmed later in pregnancy before labelling a case as praevia.

## Applied / Clinical anatomy

- ▶ **Mechanism of bleeding:** as the lower uterine segment progressively forms, thins and stretches in the third trimester and during labour, the inelastic placental attachment shears away from the underlying decidua at points where the two layers cannot stretch equally, tearing open the maternal venous sinuses of the placental bed — producing painless bleeding that is entirely **maternal** in origin.
- ▶ **Relation to the lower uterine segment:** the lower uterine segment is thinner, less vascular and less contractile than the body of the uterus, which is why it is the preferred site for the transverse incision of a lower-segment caesarean section; in placenta praevia, however, the placenta itself may directly underlie this incision site, and the poorly contractile lower segment also predisposes to **postpartum haemorrhage** after delivery because it cannot clamp down on open venous sinuses as effectively as the myometrium of the upper segment.
- ▶ **Placenta accreta spectrum:** the decidua of the lower uterine segment is thinner than that of the fundus/body, so trophoblastic tissue more readily invades through the decidua basalis and into (or through) the myometrium — giving rise to a **morbidly adherent placenta**. Superficial invasion into the myometrium is **placenta accreta**, deeper invasion into the myometrium is **placenta increta**, and full-thickness penetration to (and occasionally through) the uterine serosa — sometimes invading the bladder — is **placenta percreta**. Prior uterine surgery, especially **multiple previous caesarean sections**, is the single most significant risk factor, and placenta praevia overlying a caesarean scar is the classic clinical setting in which this spectrum arises.
- ▶ **Vasa praevia:** when fetal vessels (as in a velamentous cord insertion, or vessels connecting to an accessory succenturiate lobe) run within the membranes across the region of the internal os, this is termed vasa praevia; rupture of membranes here can tear a fetal vessel and cause rapid fetal exsanguination — a related but distinct emergency from placenta praevia itself.
- ▶ **Obstetric consequences:** placenta praevia predisposes to **malpresentation** (breech or transverse lie), because the placenta occupies the lower segment and prevents the presenting part from engaging normally; it is an absolute indication for **caesarean section** in the higher grades (types III/IV), and increases the risk of **intrauterine growth restriction** because a "low-lying"/praevia placenta is a placental factor implicated in reduced fetal growth.
- ▶ Retained **succenturiate lobes** (accessory lobes connected to the main placenta by membranes/vessels) can be a further source of postpartum haemorrhage or infection if left in utero after delivery, and are anatomically relevant when the main placental mass is examined for completeness after a praevia delivery.

## High-yield exam pointers

- ▶ **Definition:** placenta attached over the lower uterine segment, encroaching on/covering the internal os; *praevia* = "in front of" (Latin).
- ▶ **Incidence:** ~0.5–1% of hospital deliveries; rises with maternal age beyond 35 years.
- ▶ **Four types (I–IV):** Low-lying → Marginal → Incomplete/Partial central → Central/Total — synonymous with First–Fourth "degree" classification.
- ▶ Types III/IV ("central"/total) = **absolute indication for caesarean section**.



- ▶ **Commonest cause of painless antepartum haemorrhage** (bleeding after 28 weeks, before delivery).
- ▶ **Diagnostic modality:** transvaginal ultrasonography; caesarean indicated if placental edge < 1–2 cm from, or covering, the internal os.
- ▶ **Applied triad to remember:** praevia → thin lower-segment decidua → **placenta accreta/increta/percreta**; also associated with **vasa praevia** and **malpresentation**.
- ▶ Bleeding is due to shearing of placental attachment from decidua as the lower segment stretches — maternal blood, painless.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Brijesh Kumar — Embryology Text & Atlas; Hamilton, Boyd & Mossman — Human Embryology; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021).

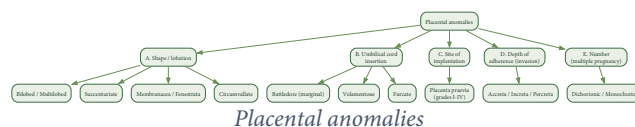


## Placental anomalies

Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The normal placenta is a discoid, haemochorial organ, ~15–20 cm in diameter, ~2–3 cm thick and ~500 g at term, formed by the chorion frondosum (fetal part) fused with the decidua basalis (maternal part), with the umbilical cord inserting near its centre. Deviation from this norm — in shape, number of lobes, site of cord insertion, site of uterine implantation, or depth of trophoblastic invasion — constitutes a placental anomaly. These anomalies matter clinically because they are recurring causes of antepartum and postpartum haemorrhage, fetal hypoxia, and operative delivery, and RGUHS repeatedly tests their classification and applied significance.

### Classification of placental anomalies



### I. Anomalies of shape and lobation

Normally the placenta is a single, circular, discoid mass with 15–30 lobes (cotyledons) separated by incomplete placental septa.

| Type                | Feature                                            |
|---------------------|----------------------------------------------------|
| Discoid (normal)    | Single round/oval disc                             |
| Bilobed / bidiscoid | Placenta consists of two roughly equal lobes/discs |
| Multilobed          | More than two lobes                                |

| Type                           | Feature                                                                                                                                                                                                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Placenta succenturiata         | A small accessory lobe separate from the main disc, connected to it only by membranes and blood vessels; if retained in utero after delivery it causes postpartum haemorrhage (PPH) or infection             |
| Placenta membranacea (diffuse) | Villous chorion frondosum fails to regress and villi persist over the whole chorionic sac, forming a thin, diffuse placenta surrounding the entire gestational sac                                           |
| Placenta fenestrata            | A gap/hole is present in the placental disc (villous tissue is deficient centrally); the central cotyledon may be missing on inspection, risking a false impression of retained placenta                     |
| Circumvallate placenta         | The peripheral edge of the chorionic (fetal) plate is smaller than the basal plate, so the membranes insert centrally and the placental margin is undercut by a raised, thickened ring of decidua and fibrin |

□ Fig 9.7 — Classification of the placenta according to its shape: discoid, bidiscoid, lobed, succenturiate, membranacea, and circumvallate placenta (Sontakke — Textbook of Human Embryology, p.87)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A row of 6 discs labelled: (1) **Discoid** — single normal disc; (2) **Bidiscoid/bilobed** — two equal lobes joined by a vascular bridge; (3) **Multilobed** — 3+ lobes; (4) **Succenturiate** — one small satellite lobe joined to main disc by membranes + vessels; (5) **Membranacea** — thin villous sheet covering the whole chorion; (6) **Circumvallate** — a raised white decidual/fibrin ring set in from the placental edge, with the chorionic plate smaller than the basal plate.

## II. Anomalies of umbilical cord attachment

| Type                           | Feature                                                                                                                                                                                                                                                        |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Central (normal)               | Cord inserts at the centre of the fetal surface                                                                                                                                                                                                                |
| Battledore (marginal) placenta | Cord inserts at or near the placental margin                                                                                                                                                                                                                   |
| Velamentous placenta           | Cord fails to reach the placental disc and terminates in the membranes; the umbilical vessels then run unprotected (no Wharton's jelly) through the chorio-amniotic membranes before reaching and ramifying on the placenta — reported in ~0.2% of pregnancies |
| Furcate placenta               | The umbilical vessels branch before they reach the placental disc                                                                                                                                                                                              |

□ Fig 9.8 — Classification of the placenta according to the attachment of the umbilical cord: normal (central), battledore, and velamentous placenta (Sontakke — Textbook of Human Embryology, p.87)

### III. Anomalies of site of implantation — Placenta praevia

Normal implantation is on the posterior/upper uterine segment; when the blastocyst implants low, near or over the internal os, the resulting placenta praevia occupies ~1% of pregnancies at term and is graded by its relation to the internal os:

| Grade                 | Relation to internal os                                                 |
|-----------------------|-------------------------------------------------------------------------|
| I (low-lying)         | Placental edge in the lower segment but does not reach the internal os  |
| II (marginal)         | Edge reaches the internal os but does not cover it                      |
| III (partial)         | Placenta covers the os when closed but not when the os is fully dilated |
| IV (central/complete) | Placenta completely covers the internal os even when fully dilated      |

Placenta praevia, particularly grade IV, is an important cause of painless antepartum haemorrhage in the third trimester; if the placenta covers the os, or its lower edge is <1–2 cm from the os, delivery is by caesarean section.

### IV. Anomalies of depth of adherence — the accreta spectrum

Normally, cytotrophoblastic invasion is limited by Nitabuch's fibrinoid layer at the interface with decidua basalis, so the placenta separates cleanly at delivery. Abnormally deep trophoblastic invasion produces a morbidly adherent placenta:

| Type              | Depth of invasion                                                                                                                              | Approx. proportion of cases |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Placenta accreta  | Villi adhere to, but do not invade, the myometrium (decidua basalis is deficient)                                                              | ~75%                        |
| Placenta increta  | Villi invade into the substance of the myometrium                                                                                              | ~15%                        |
| Placenta percreta | Villi penetrate the full thickness of the myometrium and reach/breach the uterine serosa, occasionally invading adjacent organs (e.g. bladder) | ~10%                        |

The accreta spectrum occurs in approximately 3 per 1000 births; the single most significant risk factor is prior uterine surgery, especially multiple previous caesarean sections (often coexisting with placenta praevia over the scar). Because the placenta will not separate spontaneously, forcible removal causes torrential haemorrhage, so increta/percreta usually mandate hysterectomy.

□ Fig 9.9 — Types of placenta according to degree of adhesion: (A) normal; (B) placenta accreta; (C) placenta increta; (D) placenta percreta (Sontakke — *Textbook of Human Embryology*, p.88)

### V. Anomalies of number — placentation in multiple pregnancy

- Dizygotic twins always have two separate placentas (dichorionic diamniotic).

- ▶ **Monozygotic** twins usually share one placenta, but placentation depends on the timing of embryonic splitting: split within 3 days → **dichorionic diamniotic** (own placenta and sac each); split after day 3 → **monochorionic diamniotic** (shared placenta, vascular communications between the two fetal circulations); split after day 9 → **monochorionic monoamniotic**; split after day 12 → conjoined twins.

## Applied / Clinical anatomy

- ▶ **Placenta praevia** → painless, recurrent antepartum haemorrhage; diagnosed by ultrasound; delivery by caesarean section when the os is covered or the placental edge is <1–2 cm from it.
- ▶ **Accreta spectrum (accreta/increta/percreta)** → failure of placental separation in the third stage, life-threatening postpartum haemorrhage, and frequently emergency hysterectomy; strongly linked to previous caesarean section and coexisting praevia.
- ▶ **Retained succenturiate lobe** → a common, preventable cause of secondary PPH and puerperal sepsis if the accessory lobe is left in utero after delivery; the placenta and membranes must always be examined for a "missing" vascular bridge.
- ▶ **Velamentous cord insertion** → the unprotected fetal vessels crossing the membranes are vulnerable to compression or tearing; when they cross the internal os this is called **vasa praevia**, and rupture before/during birth causes fetal exsanguination — an obstetric emergency.
- ▶ **Circumvallate placenta** → associated clinically with antepartum bleeding and abruption due to the abnormal marginal attachment of the membranes.
- ▶ **Battledore/furcate insertion** → usually of little clinical consequence alone but predisposes to cord vessel compression/torsion.
- ▶ Ultrasound (grey-scale and colour Doppler) is the mainstay for antenatal detection of praevia, accreta-spectrum disorders, velamentous insertion and vasa praevia.

## High-yield exam pointers

- ▶ Classify placental anomalies under 5 headings: **shape/lobation, cord insertion, site of implantation, depth of adherence, number**.
- ▶ Shape anomalies: bilobed, multilobed, succenturiate, membranacea, fenestrata, circumvallate — know one-line definitions.
- ▶ Cord-insertion anomalies: **battledore** (marginal), **velamentous** (into membranes), **furcate** (vessels branch before reaching the disc).
- ▶ Placenta praevia has **4 grades** (I low-lying → IV central/complete); grade IV causes painless APH.
- ▶ Accreta spectrum: **accreta** (adheres to myometrium), **increta** (invades myometrium), **percreta** (penetrates through serosa) — incidence ~3/1000 births; commonest risk factor is prior caesarean section.
- ▶ **Vasa praevia** = fetal vessels (from velamentous insertion) crossing the internal os — risk of fetal exsanguination on rupture.
- ▶ Retained succenturiate lobe is a classic, testable cause of secondary PPH.
- ▶ Monozygotic twin placentation (dichorionic/monochorionic, diamniotic/monoamniotic) is determined purely by the day of embryonic splitting.

**SOURCE & COVERAGE**

Gray's Anatomy (Standing) 41e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Ross Histology — A Text and Atlas 7e; Brijesh Kumar — Embryology Text & Atlas.



## Placental barrier

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

### Definition / Introduction

The **placental barrier** (placental membrane) is the composite layer of extrafetal tissue that separates maternal blood in the **intervillous space** from fetal blood in the capillaries of the **chorionic (terminal) villi**, across which all materno-fetal exchange of gases, nutrients, waste products, hormones, antibodies and (unintentionally) many drugs and pathogens takes place. Because the maternal blood in the human placenta bathes the chorion directly (no intervening maternal epithelium or endothelium), the human placenta is classified as **haemochorial**. The term "barrier" is a **misnomer** — it is in fact a highly selective, actively remodelling interface that becomes progressively thinner and more efficient as pregnancy advances, rather than a fixed, impermeable wall.

### 1. Structure — layers of the placental barrier

Tissues intervening between a maternal and a fetal erythrocyte constitute the barrier. In the **early part of pregnancy** (up to the 4th–5th month, i.e. ~16–20 weeks — Indian texts state "4th month onward," Moore's *Developing Human* states "until approximately 20 weeks"), it consists of **four principal layers**, each cellular layer resting on its own basement membrane:

| Layer (maternal → fetal side) | Tissue                                                                                          |
|-------------------------------|-------------------------------------------------------------------------------------------------|
| 1                             | <b>Syncytiotrophoblast</b> (outer, in contact with maternal blood; bears absorptive microvilli) |
| 2                             | <b>Cytotrophoblast</b> (Langhans' layer) + its basement membrane                                |
| 3                             | <b>Extraembryonic (villous) mesoderm</b> — connective-tissue core of the villus                 |
| 4                             | <b>Endothelium of the fetal capillary</b> + its basement membrane                               |

(Because layers 2 and 4 each carry a separate basement membrane, some texts — e.g. Vishram Singh's *Clinical Embryology* — enumerate these as **five discrete components**; the four-layer scheme above is the standard teaching answer.)

□ Fig 9.6 — Placental barrier. In early foetal life, placental barrier consists of endothelium of foetal blood vessels, its basement membrane, mesodermal layer, cytotrophoblast and syncytiotrophoblast; from the fourth month, cytotrophoblast and mesoderm thin out, leaving only syncytiotrophoblast and foetal capillary endothelium (Sontakke — Textbook of Human Embryology, p.86)

## 2. Thinning of the barrier — the vasculosyncytial membrane

From the 4th month (some texts: 20th week) onward, the barrier is progressively remodelled to increase transfer efficiency to meet rising fetal demands:

- ▶ The **cytotrophoblast** becomes discontinuous and disappears over large areas of the villi, leaving only patches of syncytiotrophoblast.
- ▶ The **mesodermal core** thins and becomes oedematous.
- ▶ Fetal capillaries **migrate peripherally**, coming to lie immediately beneath the trophoblast.
- ▶ The **basement membranes of the cytotrophoblast and the capillary endothelium fuse**, and the thinned syncytiotrophoblast comes into intimate contact with the capillary endothelium to form a **vasculosyncytial membrane** — in most places the barrier is now reduced to just **two layers** (thin syncytiotrophoblast + fused fetal capillary endothelium).
- ▶ This reduces the maternal-fetal diffusion distance to as little as **2–3  $\mu\text{m}$**  (Gray's Anatomy, 41e), approaching the efficiency of the alveolo-capillary membrane of the lung.
- ▶ **Near term**, a **fibrinoid (Rohr's) deposit** appears on the syncytial surface, which paradoxically **reduces** the efficiency of the membrane again.

## 3. Surface area, thickness and phylogenetic classification

- ▶ **Thickness:** falls from about **0.025 mm (25  $\mu\text{m}$ )** in early pregnancy to about **0.002 mm (2  $\mu\text{m}$ )** at term (IB Singh; Vishram Singh) — consistent with Gray's figure of 2–3  $\mu\text{m}$  for the vasculosyncytial interface.
- ▶ **Total exchange area:** increases from about 4 m<sup>2</sup> early in gestation to roughly **11–14 m<sup>2</sup> at term**, comparable to the total absorptive surface area of the adult small intestine; this large area is achieved chiefly through the numerous **microvilli** on the free surface of the syncytiotrophoblast.
- ▶ **Maternal blood flow:** the intervillous space holds about **150 ml** of maternal blood, replenished **3–4 times per minute**, giving a flow of roughly **500 ml/minute** through the intervillous space (Gray's Anatomy, 41e).
- ▶ **Phylogenetic (Grosser's) classification** — placentae of different mammals are classified by how many maternal tissue layers are eroded before fetal chorion contacts maternal blood:

| Type              | Maternal tissue interposed                       | Example                       |
|-------------------|--------------------------------------------------|-------------------------------|
| Epitheliochorial  | Uterine (endometrial) epithelium intact          | Pig, horse                    |
| Syndesmochorial   | Endometrial connective tissue (stroma) only      | Ruminants (cow, sheep)        |
| Endotheliochorial | Endothelium of maternal vessels only             | Carnivores (dog, cat)         |
| Haemochorial      | None — chorion bathed directly by maternal blood | <b>Human</b> , other primates |

| Type             | Maternal tissue interposed                                                                            | Example                  |
|------------------|-------------------------------------------------------------------------------------------------------|--------------------------|
| Haemoendothelial | None — even the trophoblast is reduced; fetal capillary endothelium directly bathed by maternal blood | Rodents (late gestation) |

The human placenta is thus **haemochorial**, **discoidal**, and **chorio-allantoic** (vascularised by allantoic vessels of the connecting/body stalk via the umbilical vessels).

#### 4. Mechanisms of transfer across the barrier

| Mechanism                                                                    | Substances transported                                                                                                         |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Simple diffusion (down a concentration/electrochemical gradient, no carrier) | O <sub>2</sub> , CO <sub>2</sub> , carbon monoxide, water, urea, uric acid, most electrolytes                                  |
| Facilitated diffusion (carrier-mediated, no energy)                          | Glucose (the principal fetal fuel)                                                                                             |
| Active transport (energy-dependent, against gradient)                        | Amino acids, calcium, iron, water-soluble vitamins (B, C cross rapidly)                                                        |
| Pinocytosis / receptor-mediated transcytosis                                 | Maternal IgG immunoglobulins, some plasma proteins (e.g. transferrin)                                                          |
| Bulk leakage through microscopic breaks                                      | Small numbers of fetal RBCs into maternal blood (and vice versa)                                                               |
| Active (self-propelled) transcellular passage                                | Maternal leukocytes; <i>Treponema pallidum</i>                                                                                 |
| Cellular invasion after creating lesions                                     | <i>Toxoplasma gondii</i> , cytomegalovirus                                                                                     |
| Passive lipid diffusion (small, lipophilic molecules)                        | Most drugs, unconjugated steroid hormones, anaesthetic agents, alcohol, nicotine — cross measurably from ~7 weeks of gestation |

Substances that **cross poorly or not at all** in physiological amounts include heparin (too large/charged), most protein hormones (except a slow trickle of thyroxine/T<sub>3</sub>), maternal insulin, and cholesterol/triglycerides/phospholipids — illustrating that the "barrier" is selective by molecular size, charge and configuration rather than by a fixed anatomical seal.



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

- ▶ Two side-by-side schematic cross-sections of a **chorionic villus** floating in the intervillous space (maternal blood shown stippled around it).
- ▶ **Panel A — early pregnancy:** from outside in, label **syncytiotrophoblast** → **cytotrophoblast** (with its own basement membrane) → **villous mesenchyme** (connective tissue core) → **fetal capillary endothelium** (with its own basement membrane); mark the fetal capillary centrally within the villus.
- ▶ **Panel B — late pregnancy (vasculosyncytial membrane):** show the cytotrophoblast disappearing, the mesoderm thinned/oedematous, and the fetal capillary migrating peripherally to abut a thinned syncytiotrophoblast directly; label "fused basement membranes" and "2–3  $\mu\text{m}$  diffusion distance."
- ▶ Annotate both panels with arrows for **O<sub>2</sub>/nutrients** → **fetus** and **CO<sub>2</sub>/waste** → **mother**, and a small fibrinoid cap on the term syncytium in Panel B.

**Applied / Clinical anatomy**

- ▶ **Rhesus (Rh) isoimmunization:** small numbers of fetal Rh-positive erythrocytes leak into the maternal circulation through microscopic defects in the barrier (increased at parturition/abruption), sensitising an Rh-negative mother; maternal anti-D IgG then crosses back by transcytosis in a subsequent pregnancy to cause erythroblastosis fetalis/fetal hydrops.
- ▶ **TORCH and other congenital infections:** rubella, cytomegalovirus, HIV, and *Treponema pallidum* (syphilis) traverse the barrier (rubella and CMV especially in the first trimester, producing embryopathy); *Listeria*, *Toxoplasma gondii* and *Plasmodium falciparum* invade the trophoblast by creating lesions.
- ▶ **Passive immunity:** maternal IgG crossing by transcytosis protects the neonate against diphtheria, measles and (to a degree) polio, but **not** against chickenpox (varicella) or whooping cough (pertussis), since these are chiefly cell-mediated or IgM-dependent immunities that do not cross.
- ▶ **Teratogen/drug transfer:** the barrier offers little true protection — most drugs cross once lipophilic and small, explaining the teratogenicity of agents such as **thalidomide**, and the transplacental effects of alcohol, opioids and cocaine on the fetus.
- ▶ **Diagnostic/therapeutic correlates:** the barrier's thickness and villous architecture underlie **Doppler assessment of uteroplacental blood flow**, and its breakdown in **pre-eclampsia** (defective trophoblastic invasion, thickened/fibrotic membrane) causes intrauterine growth restriction through impaired diffusion.
- ▶ **Chorionic villus sampling** directly biopsies the villous trophoblast that constitutes this barrier for first-trimester prenatal genetic diagnosis.

**High-yield exam pointers**

- ▶ Early barrier = 4 layers: syncytiotrophoblast, cytotrophoblast, villous mesoderm, fetal capillary endothelium (each cellular layer with its own basement membrane).
- ▶ After the 4th–5th month: cytotrophoblast disappears, mesoderm thins, fetal capillaries migrate peripherally → **vasculosyncytial membrane** (2 layers), diffusion distance reduced to 2–3  $\mu\text{m}$ .

- ▶ Thickness falls from **0.025 mm** → **0.002 mm**; total exchange area rises to **~11–14 m<sup>2</sup>** at term ( $\approx$  small-intestinal absorptive area).
- ▶ Intervillous space holds **~150 ml** maternal blood, replenished 3–4×/min ( $\approx$  **500 ml/min** flow).
- ▶ Human placenta = **haemochorial, discoidal, chorio-allantoic**; phylogenetic series — epitheliochorial → syndesmochorial → endotheliochorial → haemochorial → haemoendothelial.
- ▶ Transport mechanisms: simple diffusion (gases, water), facilitated diffusion (glucose), active transport (amino acids, Ca<sup>2+</sup>, Fe, vitamins), pinocytosis/transcytosis (IgG), leakage (RBCs), self-motile crossing (leukocytes, *Treponema*).
- ▶ The barrier is a **misnomer** — near-complete permeability to lipophilic drugs/most viruses; true impermeability only to a few large/charged molecules (e.g. heparin, insulin, most protein hormones).
- ▶ Fibrinoid (Rohr's) deposition near term **reduces** transfer efficiency despite the thinner membrane.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke Textbook of Human Embryology; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Moore The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e — for the embedded plate, Sontakke Textbook of Human Embryology, Fig 9.6, p.86.



## Placental circulation

*Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The placenta is a **fetomaternal organ** with a fetal component (chorionic plate + chorionic villi, derived from the chorion frondosum) and a maternal component (decidua basalis). "Placental circulation" refers to two separate blood streams that flow side by side within the chorionic villi and the intervillous space, without normally intermixing — the **fetal placental circulation** (umbilical vessels  $\rightleftharpoons$  villous capillaries) and the **maternal (uteroplacental) circulation** (spiral arteries  $\rightleftharpoons$  intervillous space). Because maternal blood bathes the trophoblast directly, the human placenta is classified as **haemochorial**. Exchange of gases, nutrients and waste occurs by diffusion, facilitated diffusion, active transport and pinocytosis across the intervening **placental membrane**, which thins progressively through gestation to maximise transfer efficiency.

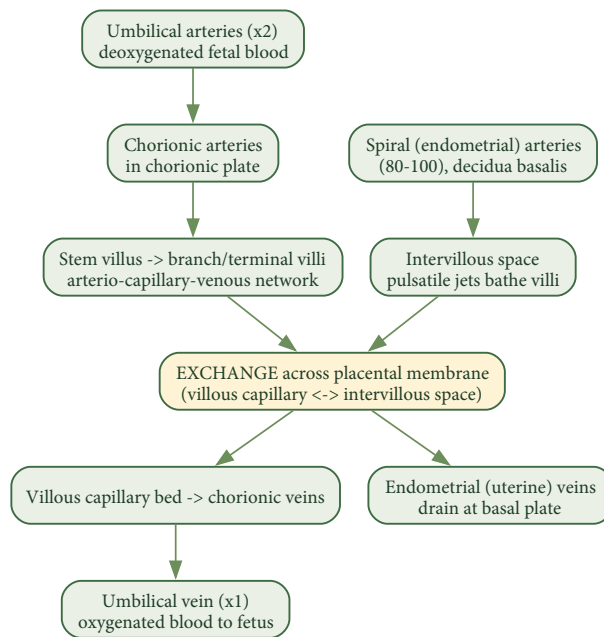
### 1. Fetal placental circulation

- ▶ Poorly oxygenated blood leaves the fetus through **two umbilical arteries** (carrying deoxygenated blood and waste) that run in the umbilical cord to the placenta.
- ▶ At the cord's placental attachment, the umbilical arteries divide into several **radially disposed chorionic arteries** that branch freely in the **chorionic plate** before entering the **stem (main) villi**.

- ▶ Within each chorionic (stem) villus the vessels form an extensive **arterio-capillary-venous network**, extending through branch and terminal villi, bringing fetal blood extremely close to the maternal blood in the intervillous space.
- ▶ Oxygenated, nutrient-rich blood from the villous capillaries collects into thin-walled venules that follow the chorionic arteries back to the cord insertion and converge to form the single **umbilical vein**, which carries oxygen-rich blood to the fetus.
- ▶ There is normally **no intermixing** of fetal and maternal blood; only very small numbers of fetal cells may cross the membrane (fetomaternal micro-haemorrhage), which is the anatomical basis of Rh-isoimmunisation.
- ▶ **Villous development:** primary villi (trophoblastic core only) → secondary villi (extraembryonic mesenchymal core added, ~3rd week) → tertiary villi (mesenchymal core vascularised by fetal capillaries connected to the embryonic circulation, ~end of 3rd week). Villi anchored to the decidua basalis are **anchoring villi**; the majority, bathed freely by maternal blood, are **floating (terminal) villi** — the actual sites of exchange.

## 2. Maternal (uteroplacental) circulation

- ▶ Maternal blood reaches the intervillous space through **80–100 spiral (endometrial) arteries** that pierce the decidua basalis and open into the intervillous space through gaps in the cytotrophoblastic shell.
- ▶ Because these arteries discharge at a pressure considerably higher than that within the intervillous space, blood enters in **pulsatile, jet-like fountains** directed toward the chorionic plate ("roof" of the intervillous space); as the jet pressure dissipates, blood flows slowly over the branch villi (permitting exchange) before draining through **endometrial (uterine) veins** at the basal plate back into the maternal circulation.
- ▶ **Spiral artery remodelling:** extravillous (interstitial and endovascular) trophoblast invades and converts the musculo-elastic spiral arteries into wide-bore, low-resistance uteroplacental vessels. Early in pregnancy endovascular trophoblastic **plugs occlude the artery tips**, permitting only a slow plasma seepage and creating a protective physiological placental hypoxia; between **10–14 weeks** these plugs are progressively dislodged and continuous, free maternal blood flow throughout the placenta begins. Failure of this remodelling underlies early-onset **pre-eclampsia**, fetal growth restriction and miscarriage.
- ▶ From the third month, the decidua basalis sends **placental (cotyledonary) septa** into the intervillous space, dividing the maternal surface into **15–20 (up to 30) lobes or cotyledons**; each cotyledon is the functional, structural and growth unit of the placenta, containing a stem villus and its branches around a portion of the intervillous space.
- ▶ **Flow figures at term** (Gray's 41e): total villous surface area **12–14 m<sup>2</sup>**; uteroplacental circulation carries **~600 mL of maternal blood/minute**; the intervillous space holds **~150 mL of blood**, completely replenished **3–4 times per minute**. There are no lymphatics in the placenta.



Placental circulation

□ Fig 9.7 — The arrangement of the placental tissues from the chorionic plate (fetal side) to the basal plate or decidua basalis (maternal side) (Gray's Anatomy — Standring — 41e, p.262)

### 3. Placental membrane (blood-placental barrier)

The membrane separating the two circulations changes in composition and thickness across gestation:

| Layer                                                              | Before ~20 weeks (4 layers)           | At term (usually 3 layers)                                                                                                                                  |
|--------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Syncytiotrophoblast                                                | Continuous, thicker                   | Thinned; forms multinucleated <b>syncytial knots</b> ; where directly apposed to fetal capillary endothelium, forms a thin <b>vasculosyncytial membrane</b> |
| Cytotrophoblast (Langhans cells)                                   | Continuous single layer               | Discontinuous, disappears over large areas (persists only ~singly by term)                                                                                  |
| Connective tissue core of villus (mesenchyme, with Hofbauer cells) | Present, cellular                     | Becomes oedematous; fetal capillaries pushed toward the <b>periphery</b> of the villus                                                                      |
| Endothelium of fetal capillary                                     | Present, capillaries centrally placed | Present, capillaries peripherally placed, closely apposed to thinned syncytium                                                                              |

- This progressive thinning brings fetal blood extremely close to maternal blood, maximising the efficiency of exchange as fetal metabolic demand rises.
- The term "placental barrier" is imprecise: it restricts transfer only of molecules of a certain size, charge or configuration (e.g. heparin); most drugs, gases, nutrients, and many pathogens/antibodies cross freely.

#### 4. Materno-fetal exchange across the circulation

- ▶ **Mechanisms:** simple diffusion, facilitated diffusion, active transport, and pinocytosis (bulk transport of macromolecules such as IgG).
- ▶ **Mother → fetus:** O<sub>2</sub>, glucose, amino acids, free fatty acids, electrolytes, vitamins, water, maternal IgG (passive immunity), and — undesirably — many drugs, alcohol, and TORCH agents (Toxoplasma, rubella, CMV, HSV), which cross more readily once the maternal circulation to the placenta becomes fully established after the first trimester.
- ▶ **Fetus → mother:** CO<sub>2</sub>, urea, uric acid, bilirubin, and other waste products, plus occasional fetal red cells/antigens (basis of Rh sensitisation) and syncytial knots (shed into maternal blood, filtered out in maternal pulmonary capillaries).
- ▶ **Placental functions subserved by this circulation:** (a) **metabolism** — synthesis of glycogen, cholesterol and fatty acids; (b) **transport** of respiratory gases and nutrients; (c) **endocrine secretion** into the maternal circulation — human chorionic gonadotropin (hCG), human placental lactogen/somatomammotropin, progesterone (maintains pregnancy from the 4th month once the corpus luteum regresses) and oestrogens (promote uterine and mammary growth); (d) **immunological barrier**, selectively transferring maternal IgG while excluding many harmful agents.

#### Applied / Clinical anatomy

- ▶ **Pre-eclampsia / IUGR:** incomplete trophoblastic invasion and failure of spiral artery remodelling leaves narrow, high-resistance vessels, causing reduced, turbulent uteroplacental perfusion — the anatomical basis of early-onset pre-eclampsia, fetal growth restriction and recurrent miscarriage.
- ▶ **Placental insufficiency / IUGR:** maternal malnutrition, diabetes, multiple pregnancy, pre-eclampsia/eclampsia, infection and abnormal implantation all compromise the uteroplacental circulation and restrict fetal growth.
- ▶ **Rh (D) isoimmunisation / erythroblastosis fetalis:** fetal red cells crossing the placental membrane into the maternal circulation can provoke a maternal antibody response; anti-D IgG antibodies then cross back and cause haemolysis in a subsequent Rh-positive fetus.
- ▶ **TORCH transmission:** because the maternal circulation inside the placenta functions fully only from the end of the first trimester, transplacental transmission of Toxoplasma is rare (but severe) early on; rubella crossing in early pregnancy is a major cause of congenital malformation.
- ▶ **Twin-twin transfusion syndrome (TTTS):** in ~15% of monochorionic monozygotic twin placentas, unbalanced vascular anastomoses divert most flow to one twin (recipient) at the expense of the other (donor), with a high combined mortality; treated by fetoscopic laser ablation of the anastomotic vessels.
- ▶ **Morbidly adherent placenta (accreta/incrета/percreta):** deficient decidua basalis allows villi to adhere to, invade, or penetrate the myometrium, compromising normal separation of the maternal circulation at delivery and causing severe postpartum haemorrhage.
- ▶ **Doppler ultrasonography:** uterine and umbilical artery Doppler waveforms (e.g. loss of end-diastolic flow, notching) are used clinically to detect impaired uteroplacental/fetoplacental circulation antenatally.

## High-yield exam pointers

- ▶ Two circulations run side by side, never mixing: **fetal** (umbilical arteries → chorionic arteries → villous capillaries → umbilical vein) and **maternal** (spiral arteries → intervillous space → endometrial veins).
- ▶ Placenta is **haemochorial** — maternal blood directly bathes the syncytiotrophoblast.
- ▶ **80–100 spiral arteries** enter the intervillous space in pulsatile jets; spiral artery remodelling by extravillous trophoblast is complete by **10–14 weeks**.
- ▶ **15–20 (up to 30) cotyledons**, each demarcated by a placental septum, is the functional unit.
- ▶ At term: villous surface area **12–14 m<sup>2</sup>**; uteroplacental flow **~600 mL/min**; intervillous space **~150 mL**, replenished **3–4×/minute**.
- ▶ Placental membrane: **4 layers before 20 weeks** (syncytiotrophoblast, cytotrophoblast, villous connective tissue, fetal capillary endothelium) → **3 layers at term** (cytotrophoblast discontinuous), forming a **vasculosyncytial membrane**.
- ▶ Exchange mechanisms: simple diffusion, facilitated diffusion, active transport, pinocytosis.
- ▶ Failure of spiral-artery remodelling → pre-eclampsia/IUGR; TTTS in monochorionic twins (~15%) from unbalanced vascular anastomoses.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled coronal/schematic section of a full-term placenta in situ, showing:

- ▶ **Umbilical cord** with 2 umbilical arteries + 1 umbilical vein, and **Wharton's jelly**.
- ▶ **Chorionic plate** (fetal surface) covered by amnion, with chorionic vessels radiating from the cord insertion.
- ▶ **Stem (main) villus** with branch and terminal (floating) villi projecting into the intervillous space; one **anchoring villus** shown fixed to the decidua basalis.
- ▶ **Intervillous space** with maternal blood — arrows showing jets from spiral arteries directed toward the chorionic plate, then slow flow back over the villi.
- ▶ **Placental (cotyledonary) septum** demarcating a **cotyledon**.
- ▶ **Decidua basalis** with **spiral (endometrial) arteries** entering and **endometrial veins** draining, sitting on the **myometrium**.
- ▶ Peripheral **smooth chorion (chorion laeve)** and **decidua parietalis/capsularis**.
- ▶ Colour or arrow code: fetal (deoxygenated) blood in blue from umbilical arteries; oxygenated fetal blood in red in the umbilical vein; maternal blood flow direction in the intervillous space.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; IB Singh Textbook of Human Histology 9e; Vishram Singh Textbook of Clinical Embryology.





## Results of foldings of embryo

*Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Folding is the process, occurring during the fourth week, by which the flat trilaminar embryonic disc is converted into a cylindrical, roughly C-shaped embryo. It results from differential growth — the embryo elongates rapidly in its long (cephalocaudal) axis while the peripheral disc fails to keep pace, so the disc buckles around the more slowly growing central axis (the notochord/neural tube). Folding occurs simultaneously in the median plane (producing a **head fold** and a **tail fold**) and in the horizontal plane (producing paired **lateral folds**), with a relative constriction developing at the junction of the embryo and the umbilical vesicle (yolk sac). Together these folds convert the flat endoderm-lined disc into a tubular gut, close the ventral body wall, reposition the septum transversum/heart and the buccopharyngeal/cloacal membranes, and draw the amnion around the embryo to form the umbilical cord — the events that give the embryo its recognisable human body form.

### 1. Cause and planes of folding

- ▶ **Cause:** unequal growth rates — rapid elongation of the neural tube/notochordal axis and rapid expansion of the somites outpaces growth at the periphery of the disc, which curls ventrally around the axial structures.
- ▶ **Median plane folding:** ventral bending of the cranial and caudal ends of the disc → **head fold** and **tail fold**.
- ▶ **Horizontal plane folding:** ventral bending of the two sides of the disc, driven by the rapidly growing neural tube and somites → paired **lateral (lateral body wall) folds**.
- ▶ All three folds proceed **simultaneously**, not sequentially, and are complete by about the end of the fourth week.

### 2. Head fold and its results

The head fold forms as the overgrowing germ disc folds ventrally around the cranial end of the notochord, chiefly driven by the rapidly enlarging forebrain vesicle.

- ▶ **Foregut** is created — the part of the endoderm-lined yolk sac trapped cranially within the head fold (primordium of pharynx, oesophagus, stomach, and lower respiratory tract).
- ▶ **Anterior intestinal portal** — the communication between the foregut and the midgut.
- ▶ **Ventral relations of the foregut:** the buccopharyngeal membrane, the pericardial sac/primitive heart, and the septum transversum are carried onto the ventral surface of the embryo, coming to lie ventral to the foregut.
- ▶ **Dorsal relations of the foregut:** the notochord and the developing brain vesicles now lie dorsal to the foregut.
- ▶ **Cranial relation:** the rapidly growing forebrain vesicle overhangs the foregut and the developing heart, coming to lie cranial to the buccopharyngeal membrane.
- ▶ The **septum transversum**, originally cranial, is carried caudal to the heart, where it later contributes to the central tendon of the diaphragm; the buccopharyngeal membrane ruptures in the fourth week to open the primitive mouth into the foregut.



### 3. Tail fold and its results

The tail fold forms as the overgrowing germ disc folds ventrally around the caudal end of the notochord, driven mainly by the rapid growth of the caudal neural tube (future spinal cord) and the caudal eminence (tail).

- ▶ **Hindgut** is created — the part of the yolk sac trapped caudally within the tail fold (primordium of the descending colon, rectum, and upper anal canal).
- ▶ **Allantois** now communicates with the hindgut and comes to lie ventral to it as the **allantoenteric diverticulum**, which divides the hindgut into a cranial **pre-allantoic** and a caudal **post-allantoic** part.
- ▶ **Posterior intestinal portal** — the communication between the midgut and the pre-allantoic part of the hindgut.
- ▶ **Cloacal membrane** (bilaminar, ecto-endodermal) is carried onto the ventral surface, coming to lie caudal to the connecting stalk; it later subdivides into a ventral urogenital membrane and a dorsal anal membrane.
- ▶ **Dorsal relations of the hindgut:** the notochord and neural tube now lie dorsal to it.
- ▶ **Caudal relations of the hindgut:** the degenerating primitive node and primitive streak come to lie caudal to it.
- ▶ The **primitive streak**, which lay cranial to the cloacal membrane before folding, comes to lie caudal to the membrane after tail folding, and it regresses/disappears by the end of the fourth week.
- ▶ The **connecting stalk** (future umbilical cord) is now attached to the ventral surface of the embryo rather than its caudal end.

### 4. Lateral folds and their results

The lateral folds form as the overgrowing central part of the germ disc rolls the two sides of the disc ventrally, driven by the rapid growth of the neural tube and the somites.

- ▶ **Midgut** is created — the part of the yolk sac trapped by the fusing lateral folds; it stays connected to the shrinking remainder of the yolk sac (now the **umbilical vesicle**) through a narrow **vitello-intestinal (omphalo-enteric/omphalomesenteric) duct**.
- ▶ **Ventral body wall closure:** the somatopleuric (parietal) layer of intraembryonic mesoderm, together with the overlying ectoderm, fuses in the ventral midline — except at the site of the connecting stalk — converting the flat, horseshoe-shaped intraembryonic coelom into paired, later communicating, body cavities.
- ▶ **Dorsal mesentery:** the splanchnopleuric (visceral) mesoderm covering the ventrolateral surface of the gut is carried dorsally and reflects on itself to suspend the gut tube as its dorsal mesentery.
- ▶ **Peritoneal cavity:** with ventral fusion of the somatopleuric mesoderm, the intraembryonic coelom is converted into the definitive peritoneal (and, more cranially, pleural and pericardial) cavity.
- ▶ **Amnioectodermal junction:** the line of attachment of the amnion to the disc margin is drawn ventrally with the lateral folds until it is reduced to a narrow ring on the ventral surface, around the connecting stalk.

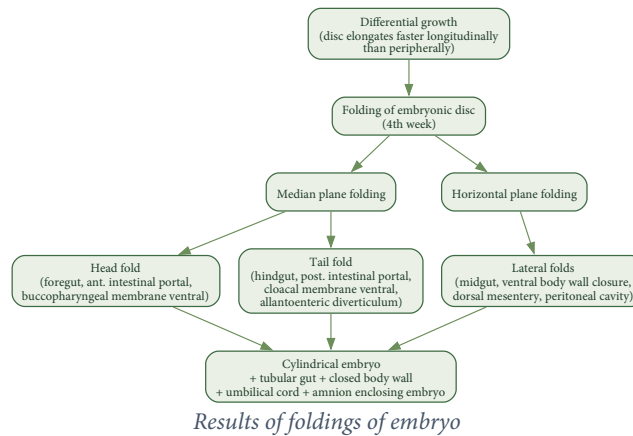
- **Umbilical cord formation:** as the lateral folds fuse ventrally, the amnion is pulled around the embryo and expands to cover the connecting stalk, which is thereby converted into the epithelium-covered umbilical cord containing the yolk stalk, allantois, and umbilical vessels.

## 5. Combined effect of head, tail, and lateral folding

| Feature                       | Head fold                                                                        | Tail fold                                                               | Lateral folds                                                                                    |
|-------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Site                          | Cranial end, around notochord                                                    | Caudal end, around notochord                                            | Both sides of disc                                                                               |
| Principal driver              | Rapidly growing forebrain vesicle                                                | Rapidly growing caudal neural tube/tail                                 | Rapid growth of neural tube & somites                                                            |
| Yolk sac part incorporated    | <b>Foregut</b>                                                                   | <b>Hindgut</b>                                                          | <b>Midgut</b>                                                                                    |
| Communicating portal formed   | Anterior intestinal portal                                                       | Posterior intestinal portal                                             | —                                                                                                |
| Membrane repositioned         | Buccopharyngeal membrane → ventral, cranial-most                                 | Cloacal membrane → ventral, caudal-most                                 | Amnioectodermal junction → umbilical cord                                                        |
| Other structures repositioned | Septum transversum & pericardial sac/heart carried ventral and caudal to foregut | Allantois → allantoenteric diverticulum; primitive streak/node → caudal | Somatopleuric mesoderm fuses ventrally (body wall); splanchnopleuric mesoderm → dorsal mesentery |

### Overall (general) results of folding:

- The flat trilaminar embryonic disc is converted into a cylindrical, C-shaped embryo lying free within the amniotic cavity.
- The dorsal part of the endoderm-lined yolk sac is incorporated as a continuous gut tube divided into **foregut, midgut and hindgut**; the ventral part remains outside as the umbilical vesicle, connected to the midgut via the vitello-intestinal duct.
- The flattened, horseshoe-shaped intraembryonic coelom is converted by ventral fusion of the lateral folds into the definitive **pericardial, pleural and peritoneal cavities**.
- The **ventral body wall** is closed except at the umbilicus, where the connecting stalk perforates it.
- The **amnion**, originally attached only at the disc margin, is drawn around the whole embryo, so the embryo now floats freely in the amniotic cavity.
- The **connecting stalk** is converted into the epithelium-covered **umbilical cord**.
- The **buccopharyngeal membrane** and **cloacal membrane**, originally at opposite poles on the embryonic disc, both come to lie on the **ventral surface** of the embryo (buccopharyngeal cranially, cloacal caudally).
- The **septum transversum, pericardial coelom and primitive heart tube** are relocated to the ventral, cervico-thoracic region, setting the stage for cardiac descent and looping.
- By the end of the fourth week the embryo has acquired the recognisable, curved human body form, attached to the placenta only through the umbilical cord.



□ Fig 4.2 — The Process of Craniocaudal and Lateral Folding That Transforms the Embryo From a Flat Embryonic Disc (Larsen — Human Embryology — 6e, p.225)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw (i) a mid-sagittal section through a 4th-week embryo before and after folding, and (ii) a transverse section through the midgut region after lateral folding. Label:

- ▶ Neural tube, notochord
- ▶ Foregut, midgut, hindgut
- ▶ Anterior intestinal portal, posterior intestinal portal
- ▶ Buccopharyngeal membrane, cloacal membrane
- ▶ Septum transversum, pericardial cavity/heart tube
- ▶ Allantois, allantoenteric diverticulum, connecting stalk
- ▶ Yolk sac (umbilical vesicle), vitello-intestinal duct
- ▶ Amnion, amniotic cavity
- ▶ Somatopleuric mesoderm (ventral body wall), splanchnopleuric mesoderm (dorsal mesentery)
- ▶ Intraembryonic coelom → peritoneal cavity

### Applied / Clinical anatomy

- ▶ **Ectopia cordis**: failure of fusion of the two sternal bars/ventral body wall in the thoracic region (a lateral-fold defect) leaves the heart lying exposed on the surface of the thorax, usually with an open pericardial sac; most affected infants die in the first few days of life.
- ▶ **Sternal cleft/foramen**: incomplete fusion of the paired sternal bars derived from the fusing lateral folds; may range from an asymptomatic sternal foramen to a sternal cleft, occasionally associated with ectopia cordis.
- ▶ **Omphalocele**: persistent herniation of abdominal viscera (intestine ± liver) into the base of the umbilical cord, covered by amnion/peritoneum, due to failure of the lateral folds to complete ventral closure around the umbilical ring; incidence about 1 in 10,000 births, with up to 50% showing chromosomal abnormalities.
- ▶ **Gastroschisis**: a linear defect of the anterior abdominal wall lateral to the umbilicus (usually right-sided) through which viscera extrude directly into the amniotic cavity without a covering

membrane and without involving the umbilical cord — a more localised failure of lateral body wall folding/closure.

- ▶ **Exstrophy of the bladder/cloaca:** a caudal (tail-fold-region) ventral body wall defect in which mesoderm fails to migrate between the ectoderm and the cloacal membrane, so the membrane ruptures prematurely, exposing the bladder mucosa; epispadias is a constant accompanying feature.
- ▶ **Congenital diaphragmatic hernia:** incomplete closure of the pleuroperitoneal canals in the septum-transversum-derived diaphragm (repositioned by head folding) allows abdominal viscera to herniate into the thorax, compressing the developing lung.
- ▶ Understanding these folds also explains why the **heart and septum transversum**, initially cranial structures, are found in the thorax, and why the **cloacal and buccopharyngeal membranes** end up on the ventral, not dorsal, aspect of the fully folded embryo.

### High-yield exam pointers

- ▶ Folding is due to **differential growth** — rapid longitudinal elongation of the embryo relative to the disc periphery; occurs in the **4th week**.
- ▶ Two planes, occurring **simultaneously**: median plane (head fold + tail fold) and horizontal plane (lateral folds).
- ▶ **Head fold** → foregut, anterior intestinal portal, buccopharyngeal membrane and septum transversum/heart carried ventrally.
- ▶ **Tail fold** → hindgut, posterior intestinal portal, cloacal membrane carried ventrally, allantoenteric diverticulum, primitive streak now caudal to cloacal membrane.
- ▶ **Lateral folds** → midgut + vitello-intestinal duct, ventral body wall closure, dorsal mesentery, peritoneal/pleural/pericardial cavities, umbilical cord formation.
- ▶ Net effect: flat trilaminar disc → cylindrical, C-shaped embryo enclosed by amnion, connected to placenta only via the umbilical cord.
- ▶ Failure of ventral wall closure → ectopia cordis, gastroschisis, omphalocele, exstrophy of bladder/cloaca — all classic applied-anatomy correlates of faulty folding.

### SOURCE & COVERAGE

Sontakke — Textbook of Human Embryology; Moore — The Developing Human, 9e; Langman's Medical Embryology (Sadler), 14e; Larsen — Human Embryology, 6e; Vishram Singh — Textbook of Clinical Embryology; Gray's Anatomy (Standring), 41e (terminology/axis-formation cross-reference).



## Spermatogenesis

Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy

**Definition / Introduction.** Spermatogenesis is the sequence of cell divisions and structural transformations by which spermatogonia lying on the basal lamina of the seminiferous tubule are converted into mature spermatozoa. It begins at puberty and continues into old age, occurring exclusively within the germinal (spermatogenic) epithelium of the seminiferous tubule under the physical support of Sertoli cells and the hormonal control of the hypothalamo-pituitary-gonadal axis. The process is conventionally divided into three sequential phases — spermatocytogenesis, meiosis and spermiogenesis — and takes a total of approximately 64–74 days per germ cell, yielding roughly 300 million spermatozoa daily.

### Site and cellular basis

- ▶ Each testicular lobule (≈250 lobules/testis, demarcated by septa from the mediastinum testis) contains 1–4 highly coiled **seminiferous tubules**; their combined length in one testis is approximately 250 metres (Gray's Anatomy).
- ▶ The tubule wall is a complex stratified germinal epithelium, 4–8 cell layers thick, resting on a basal lamina, and made of two cell populations:
  - **Spermatogenic cells** — spermatogonia, primary and secondary spermatocytes, spermatids and spermatozoa — arranged in progressively more mature layers from base to lumen.
  - **Sertoli (sustentacular) cells** — tall columnar, non-dividing supporting cells spanning the full height of the epithelium.
- ▶ **Spermatogonia** (derived from primordial germ cells) are of three morphological types: dark type A (**Ad**, reserve stem cells), pale type A (**Ap**, the proliferating/renewing pool) and **type B** (committed cells that give rise to primary spermatocytes) — Gray's Anatomy; Vishram Singh.
- ▶ A **blood–testis barrier**, formed by tight junctions between adjacent Sertoli cells, divides the epithelium into a **basal compartment** (spermatogonia) and an **adluminal compartment** (spermatocytes, spermatids, spermatozoa), immunologically isolating the haploid germ cells that develop after self-tolerance is established.

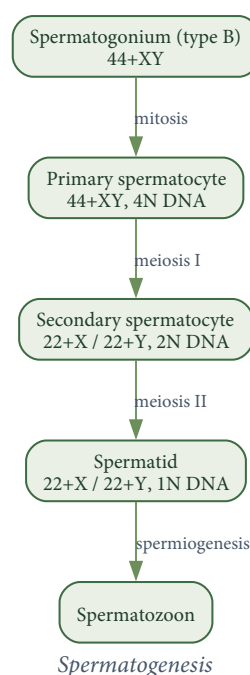
### Stages of spermatogenesis

| Phase               | Cell transition                              | Nature of division | Chromosome/<br>DNA content | Duration |
|---------------------|----------------------------------------------|--------------------|----------------------------|----------|
| Spermatocytogenesis | Type B spermatogonium → primary spermatocyte | Mitosis            | 44+XY (4N DNA)             | ≈16 days |

| Phase                                               | Cell transition                                                                                                                                                                                      | Nature of division                    | Chromosome/<br>DNA content     | Duration |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|--------------------------------|----------|
| <b>Meiosis I + II</b><br>(reductional + equational) | Primary spermatocyte → 2 secondary spermatocytes (1st meiotic division, after a prolonged prophase of ~3 weeks) → 4 spermatids (rapid 2nd meiotic division; secondary spermatocytes are short-lived) | Meiosis                               | 22+X or 22+Y (2N DNA → 1N DNA) | ≈24 days |
| <b>Spermiogenesis</b>                               | Spermatid → spermatozoon                                                                                                                                                                             | Cytodifferentiation, no cell division | 22+X or 22+Y (1N DNA)          | ≈24 days |

(Source of the day-count breakdown: IB Singh Human Embryology. Total figures vary genuinely across texts — ≈64 days per Gray's Anatomy and IB Singh, ≈74 days per Langman's/Sadler, ≈60 days per Vishram Singh — a discrepancy worth stating rather than masking.)

- Each **primary spermatocyte** theoretically yields **four haploid spermatids** — two carrying 22+X and two carrying 22+Y — giving an equal numerical sex ratio at production (Vishram Singh; Gray's Anatomy).
- **Cytoplasmic (intercellular) bridges**: mitotic and meiotic divisions in the clone show incomplete cytokinesis, so successive generations of one type-A spermatogonium remain cytoplasmically interconnected as a syncytium — allowing haploid cells shared access to diploid gene products. The bridges are lost only in the final (maturation) phase of spermiogenesis, when residual bodies are shed (Junqueira; Langman's).



□ Fig 21.6 — Seminiferous tubules: Sertoli cells and spermatogenesis. (Junqueira's Basic Histology — Text & Atlas — 17e, p.1065)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Cross-section of a seminiferous tubule; label from base to lumen: **basal lamina** → **spermatogonia** (Ad/Ap/type B) → **primary spermatocytes** → **secondary spermatocytes** → **early and late spermatids** → **spermatozoa**; show one **Sertoli cell** spanning the full height with its nucleus near the base; mark the **tight-junctional blood–testis barrier** between adjacent Sertoli cells separating the basal from the adluminal compartment; show **Leydig cells** in the surrounding interstitial connective tissue.

## Spermiogenesis and structure of the spermatozoon

Spermiogenesis is the purely cytodifferentiative transformation of a round spermatid into an elongated, motile spermatozoon, described in four phases (Junqueira's Basic Histology):

- ▶ **Golgi phase** — proacrosomal vesicles from the Golgi apparatus coalesce into a single acrosomal cap; centrioles migrate to the pole opposite the cap and organise the axoneme.
- ▶ **Cap phase** — the acrosomal cap spreads over roughly half the condensing nucleus; the acrosome is a specialised lysosome containing hyaluronidase and acrosin.
- ▶ **Acrosome phase** — the nucleus elongates and condenses (histones replaced by protamines); the flagellum grows and mitochondria aggregate around its proximal part to form the middle piece.
- ▶ **Maturation phase** — excess cytoplasm is shed as a **residual body** (phagocytosed by the Sertoli cell); intercellular bridges are lost; structurally mature but still non-motile spermatozoa are released into the tubular lumen (**spermiation**).

**Structure of the mature spermatozoon** (total length  $\approx 50\text{--}60\ \mu\text{m}$ ; Vishram Singh, Gray's Anatomy):

- ▶ **Head** ( $\approx 4 \times 3\ \mu\text{m}$ ) — flattened, condensed nucleus covered anteriorly by the acrosomal cap.
- ▶ **Neck** ( $\approx 0.3\ \mu\text{m}$ ) — connects head to tail; contains the centrioles.
- ▶ **Tail**, in three parts: **middle piece** (axoneme surrounded by a helical mitochondrial sheath, the "powerhouse"), **principal piece** (axoneme within a fibrous sheath, responsible for motility,  $\approx 40\ \mu\text{m}$ ), **end piece** (bare terminal axoneme,  $\approx 5\text{--}7\ \mu\text{m}$ ).
- ▶ Released spermatozoa are structurally mature but non-motile; full motility is acquired in the **epididymis**, and full fertilising capacity only after **capacitation** and the acrosome reaction within the female genital tract (Gray's Anatomy).

## Hormonal control of spermatogenesis

- ▶ Pulsatile hypothalamic **GnRH** drives anterior pituitary gonadotrophs to secrete **LH** and **FSH**.
- ▶ **LH** (also called interstitial cell–stimulating hormone, **ICSH**) binds receptors on **Leydig cells**, stimulating **testosterone** synthesis; testosterone in turn binds Sertoli cells to sustain spermatogenesis (Langman's; BD Chaurasia).
- ▶ **FSH** binds receptors on **Sertoli cells**, stimulating testicular fluid production and synthesis of **androgen-binding protein (ABP)**, which concentrates intraluminal testosterone to the level required for spermiogenesis (Langman's; Junqueira).



- ▶ **Negative feedback:** Sertoli-cell-derived **inhibin B** selectively suppresses pituitary FSH release; testosterone feeds back on the hypothalamus/pituitary to restrain LH/GnRH (Junqueira).

### Sertoli cells — structure and function

Tall columnar cells with a basal, euchromatic, ovoid-to-triangular nucleus and a prominent nucleolus; abundant smooth endoplasmic reticulum and lysosomes reflect their secretory and phagocytic roles. Each Sertoli cell supports 30–50 developing germ cells (Junqueira). Functions:

- ▶ **Structural support and blood–testis barrier** — tight junctions between adjacent Sertoli cells create the basal/adluminal compartments.
- ▶ **Nutrition** of germ cells sequestered from plasma (transport of metabolites, e.g. transferrin).
- ▶ **Phagocytosis** of residual bodies and degenerating germ cells.
- ▶ **Exocrine secretion** of tubular fluid that flushes non-motile sperm toward the rete testis.
- ▶ **Endocrine secretion** — ABP and inhibin B (both FSH-driven), and in fetal life anti-Müllerian hormone (Müllerian-inhibiting substance), which causes regression of the paramesonephric ducts (Junqueira; IB Singh).
- ▶ **Coordination** of synchronous germ-cell development via gap junctions between adjacent Sertoli cells.

### Applied / Clinical anatomy

- ▶ **Cryptorchidism:** arrested testicular descent exposes germ cells to the higher intra-abdominal/inguinal temperature, impairing spermatogenesis while Leydig-cell (testosterone) function is usually preserved; **orchidopexy** is recommended within the first 18 months of life (ideally the first year) to maximise the chance of restoring normal spermatogenic potential — it does not, however, reduce the associated risk of testicular malignancy (Gray's Anatomy; BD Chaurasia).
- ▶ **Varicocele:** dilatation of the pampiniform plexus, characteristically left-sided (longer left testicular vein, right-angled entry into the left renal vein), raises scrotal temperature and is a surgically correctable cause of male subfertility (BD Chaurasia).
- ▶ **Semen analysis** is the first-line investigation of male infertility; abnormal findings (**oligospermia** — low sperm density, generally quoted below 10–20 million/mL — abnormal morphology, or flagellar defects with impaired motility) point to a spermatogenic defect (Junqueira).
- ▶ **Testicular biopsy** distinguishes obstructive azoospermia (normal spermatogenesis, blocked duct system) from primary testicular failure (e.g. maturation arrest or a Sertoli-cell-only pattern).
- ▶ **Radiosensitivity:** rapidly dividing spermatogonia are the most radiosensitive germ cells, whereas Sertoli and Leydig cells are comparatively radioresistant — the rationale for gonadal shielding during pelvic radiotherapy.
- ▶ **Vasectomy** interrupts the ductus deferens; spermatogenesis itself continues unaffected, with sperm resorbed/phagocytosed proximal to the ligation — the anatomical basis of surgical male sterilisation.

## High-yield exam pointers

- ▶ Spermatogenesis = spermatocytogenesis (mitosis) + meiosis (reduction + equational division) + spermiogenesis (cytodifferentiation); total ≈64–74 days; ≈300 million sperm/day.
- ▶ Spermatogonia: dark type A (reserve stem cell) → pale type A → type B (committed).
- ▶ One primary spermatocyte (44+XY, 4N) → 2 secondary spermatocytes (22+X/22+Y, 2N) → 4 spermatids (22+X/22+Y, 1N) — two X-bearing, two Y-bearing.
- ▶ Cytoplasmic bridges keep clonal germ cells interconnected until the maturation phase of spermiogenesis.
- ▶ Spermiogenesis has four phases: Golgi → cap → acrosome → maturation; ends in spermiation of a non-motile spermatozoon.
- ▶ Blood–testis barrier (Sertoli tight junctions) separates basal (spermatogonial) from adluminal (spermatocyte/spermatid) compartments.
- ▶ Hormonal axis: GnRH → FSH (acts on Sertoli cells: ABP, inhibin B) + LH/ICSH (acts on Leydig cells: testosterone).
- ▶ Motility is acquired in the epididymis; fertilising capacity requires capacitation in the female tract.
- ▶ Cryptorchidism and varicocele are the two classic anatomically-correctable causes of impaired spermatogenesis.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Junqueira's Basic Histology — Text & Atlas 17e; BD Chaurasia Human Anatomy Vol 2 8e.



## Structure of sperm

*Asked in: Paper II Nov 2017 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The mature human spermatozoon is the small, highly specialised, motile male gamete produced by **spermiogenesis** — the purely cytodifferentiative transformation of a round, non-motile spermatid within the seminiferous tubule, during which nearly all surplus cytoplasm is shed as a **residual body**. It is a haploid cell (22 autosomes + X or Y) about **50–60 µm** long, sharply polarised into a **head**, carrying the condensed paternal genome and the enzyme-laden acrosome, and a **tail** built almost entirely as a motility apparatus. The whole cell is enclosed throughout by a single continuous plasma membrane, and its shape is dictated entirely by its one function — delivering the paternal genome to the oocyte.

## 1. Overview and regional dimensions

| Region          | Approx. length                            | Principal contents                                                                   | Chief function                                                               |
|-----------------|-------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Head            | ~4 $\mu\text{m}$ $\times$ 3 $\mu\text{m}$ | Nucleus (condensed chromatin) + acrosomal cap                                        | Carries the haploid genome; acrosome enzymes breach the oocyte's investments |
| Neck            | ~0.3 $\mu\text{m}$                        | Connecting piece (9 segmented columns), proximal centriole, remnant distal centriole | Couples head to tail; centriole organises the axoneme                        |
| Middle piece    | ~7 $\mu\text{m}$                          | Axoneme + 9 outer dense fibres + helical mitochondrial sheath                        | ATP generation — the "powerhouse" of the tail                                |
| Principal piece | ~40 $\mu\text{m}$ (longest part)          | Axoneme + outer dense fibres + fibrous sheath                                        | Generates the propulsive, whip-like beat                                     |
| End piece       | ~5–7 $\mu\text{m}$                        | Bare axoneme under plasma membrane alone                                             | Flexible terminal tip                                                        |

The tail (neck + middle + principal + end piece) makes up roughly four-fifths of the total length of the spermatozoon.

□ Fig 2.4 — Structure of sperm (Sontakke — Textbook of Human Embryology, p.18)

## 2. Head of the spermatozoon

- ▶ **Shape:** flattened antero-posteriorly, giving a spade-/spearhead-shaped profile and an oval outline en face; contains minimal cytoplasm.
- ▶ **Nucleus** occupies almost the entire head. Its chromatin is maximally condensed (histones largely replaced by protamines, rendering it transcriptionally inert) — this compaction makes the head highly resistant to mechanical and chemical stress during transit.
- ▶ **Acrosomal cap** (acrosome; also called the anterior nuclear cap or **galea capitis**) — derived from the Golgi complex of the spermatid — is a flattened, membrane-bound sac capping the **anterior two-thirds** of the nucleus.
  - **Contents:** hyaluronidase, acrosin (a trypsin-like protease) and acid phosphatase, among other hydrolytic enzymes.
  - **Function:** sequential release of these enzymes (the acrosome reaction) disperses the corona radiata and digests a path through the zona pellucida during fertilisation.

## 3. Neck (connecting piece)

- ▶ The narrowest segment of the spermatozoon; contains a funnel-shaped **basal plate** applied to the posterior pole of the nucleus.
- ▶ A **proximal centriole** lies just behind the basal plate, oriented roughly at right angles to the axoneme and probably functioning as a basal body.
- ▶ The **distal centriole** is consumed in generating the axoneme and the **annulus** (a ring-like intracytoplasmic structure marking the middle-piece/principal-piece junction).

- **Nine segmented (striated) columns** of the connecting piece encircle the centriole; each is directly continuous, distally, with one of the **nine outer dense fibres** of the tail, mechanically uniting head and tail into a single, torque-resistant unit.

#### 4. Tail — middle piece, principal piece and end piece

A common core — the **axoneme (axial filament)** — runs continuously from just behind the neck to the tip of the tail, but the sheath surrounding it changes along its length:

| Segment         | Covering around the axoneme + outer dense fibres                                                                    | Distinguishing landmark                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Middle piece    | Helical (spiral) sheath of mitochondria arranged end to end                                                         | Begins just distal to the neck; ends at the <b>annulus</b>  |
| Principal piece | <b>Fibrous sheath</b> — two longitudinal columns joined by circumferential ribs, replacing the mitochondrial sheath | Longest tail segment; imparts the whip-like propulsive beat |
| End piece       | None — axoneme denuded of outer dense fibres and fibrous sheath, covered only by plasma membrane                    | Terminal, tapering tip                                      |

#### 5. Ultrastructure of the axoneme (9 + 2 arrangement)

- The axoneme has the same basic plan as a motile respiratory cilium.
- **2 central single microtubules** (the central pair) lie within a central sheath.
- **9 peripheral doublet microtubules** are arranged circularly around the central pair; each doublet bears inner and outer **dynein arms** (the ATPase motor proteins), and neighbouring doublets are linked to each other by nexin links and to the central sheath by radial spokes.
- **9 coarse outer dense fibres** lie external to each doublet through the middle and principal pieces — direct continuations of the nine striated columns of the connecting piece — and reinforce the tail against torque during flagellar bending.
- Dynein-arm ATPase activity, energised by ATP generated in the middle-piece mitochondria, drives sliding of adjacent doublets against one another, producing the flagellar (whip-like) beat of the tail.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Reproduce the labelled longitudinal section of the spermatozoon (as in the plate above), with:

- ▶ **Head:** acrosome cap, nucleus.
- ▶ **Neck:** proximal centriole.
- ▶ **Middle piece:** mitochondria in a spiral sheath, axial filament, annulus (at its distal end).
- ▶ **Principal piece:** fibrous sheath, axial filament.
- ▶ **Tail tip (end piece):** bare axial filament only.
- ▶ **Inset — transverse section of the tail:** central doublet (2 central microtubules), the ring of 9 peripheral doublets, and the 9 coarse (outer dense) fibrils external to them.

**6. Maturation and capacitation — functional correlates of structure**

- ▶ Spermatozoa released into the seminiferous tubule lumen are **structurally mature but functionally non-motile**.
- ▶ During transit through the **epididymis** they progressively acquire motility: sperm in the proximal (caput) epididymis show sluggish, high-amplitude/low-frequency tail movements producing little forward motion, whereas sperm in the cauda epididymis show low-amplitude/high-frequency tail movements that produce effective forward progression. Secretions of the epididymis, seminal vesicles and prostate further condition motility, but spermatozoa display their **full pattern of motility only after ejaculation**.
- ▶ **Capacitation** occurs within the female genital tract: a surface glycoprotein "decapacitation factor" coat (added during epididymal transit) is stripped from the plasma membrane overlying the acrosome, membrane fluidity/permeability changes, and **hyperactivated motility** develops.
- ▶ On contact with the corona radiata/zona pellucida, the capacitated sperm undergoes the **acrosome reaction**: fusion and vesiculation of the plasma membrane with the outer acrosomal membrane releases **hyaluronidase** (which disperses the corona radiata cells) and **acrosin** (a trypsin-like enzyme that digests the zona pellucida), permitting sperm penetration and fertilisation.

**Applied / Clinical anatomy**

- ▶ **Semen analysis:** a single normal ejaculate contains roughly **200–300 million spermatozoa** in about **2.5 mL of semen**; sperm count, motility and morphology (head, mid-piece and tail form) are the principal structural parameters assessed in the work-up of male infertility.
- ▶ **Immotile cilia syndrome (Kartagener syndrome):** an autosomal recessive genetic defect of the **dynein arms** of the 9+2 axoneme. Because the sperm tail and the cilia of the respiratory epithelium share this identical ultrastructure, the same defect produces **immotile spermatozoa (infertility)** together with defective mucociliary clearance, manifesting as recurrent sinusitis and bronchiectasis; embryonic nodal cilia sharing the same motor apparatus explain the associated **situs inversus** seen in many affected patients.
- ▶ **Acrosome and fertilisation:** failure of normal acrosomal enzyme content or of the acrosome reaction is a recognised structural basis of fertilisation failure; **intracytoplasmic sperm injection (ICSI)**, which mechanically delivers the sperm directly into the ooplasm, bypasses the need for

an intact acrosome reaction and normal tail motility, and is used in assisted reproduction where such structural/functional tail or acrosomal defects exist.

- ▶ **Sperm morphology assessment:** abnormalities of head shape (e.g. tapering, amorphous or duplicated heads), mid-piece thickening, or coiled/absent tails, seen on a stained semen smear, correlate directly with the ultrastructural regions described above and are scored as teratozoospermia during infertility evaluation.

## High-yield exam pointers

- ▶ Mature spermatozoon ~50–60  $\mu\text{m}$  long; the tail forms about **four-fifths** of the total length.
- ▶ Parts: **Head**  $\rightarrow$  **Neck**  $\rightarrow$  **Tail** (tail subdivided into **middle piece**, **principal piece**, **end piece**); the whole cell is wrapped in one continuous plasma membrane.
- ▶ **Head** (~4  $\mu\text{m}$   $\times$  3  $\mu\text{m}$ ): condensed haploid nucleus + acrosomal cap (anterior two-thirds) containing **hyaluronidase**, **acrosin**, **acid phosphatase**.
- ▶ **Neck** (~0.3  $\mu\text{m}$ ): connecting piece (9 striated columns) + proximal centriole; distal centriole gives rise to the axoneme and the annulus.
- ▶ **Middle piece** (~7  $\mu\text{m}$ ): axoneme + 9 outer dense fibres + spiral **mitochondrial sheath** — the "powerhouse"; ends at the annulus.
- ▶ **Principal piece** (~40  $\mu\text{m}$ , the longest part): axoneme + outer dense fibres + **fibrous sheath** — the main motile segment.
- ▶ **End piece** (~5–7  $\mu\text{m}$ ): bare axoneme covered only by plasma membrane.
- ▶ **Axoneme = 9 + 2 pattern** (9 peripheral doublets bearing dynein arms + 2 central single microtubules) — identical to a respiratory cilium; a dynein-arm defect causes **Kartagener/immotile cilia syndrome**.
- ▶ Motility begins in the **epididymis**; full fertilising capacity requires **capacitation** and the **acrosome reaction** in the female genital tract.

## SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Histology 2e; IB Singh — Textbook of Human Histology 9e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021) — for the embedded plate, Sontakke — Textbook of Human Embryology, Fig 2.4, p.18.



## Twins

*Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Twins are two offspring produced in a single pregnancy. Twinning is classified on a genetic basis into **dizygotic (binovular, fraternal)** twins, arising from fertilization of two separate ova by two separate sperms, and **monozygotic (uniovular, identical)** twins, arising from splitting of a single fertilized ovum (zygote). The pattern of fetal membranes — number of chorions and amnions — depends on the mechanism of twinning and, in monozygotic twins, on the exact day of embryonic splitting. Spontaneous twinning occurs roughly once in every 80 births, with dizygotic twins accounting for about two-thirds and monozygotic twins for about one-third of all twin births.

### Classification of twins

- ▶ **By number of offspring:** twins (2), triplets (3), quadruplets (4), quintuplets (5).
- ▶ **By genetic/zygosity basis:**
- ▶ **Dizygotic (DZ) twins** — two ova fertilized by two sperms (two zygotes).
- ▶ **Monozygotic (MZ) twins** — one ovum fertilized by one sperm (single zygote) that subsequently splits.
- ▶ **Trizygotic twins** (for higher multiples) — multiple ova fertilized by different sperms.
- ▶ **MZ twins are further classified by the timing of splitting** (see table below), which determines the fetal-membrane pattern — dichorionic-diamniotic, monochorionic-diamniotic, monochorionic-monoamniotic, or conjoined.

### Dizygotic (fraternal) twins

- ▶ **Cause:** two oocytes released in the same ovarian cycle, fertilized by two different sperms; occasionally two oocytes are shed from a single follicle.
- ▶ **Incidence:** about 7–10 per 1000 births; roughly two-thirds of all human twins. Incidence rises with **maternal age** (increases sharply up to 35 years, then declines), **parity**, and **heredity** — a genetically-determined tendency to multiple ovulation ("twinning runs in families"), while monozygotic twinning is largely age- and heredity-independent.
- ▶ **Ovulation-inducing drugs/gonadotrophins and assisted reproductive technology** (multiple blastocyst transfer) sharply raise the DZ twinning rate — IVF pregnancies show a twinning incidence of about 21 per 1000 births.
- ▶ **Membranes:** each embryo implants separately with its own amnion, chorion and placenta — **dichorionic, diamniotic**. Placentae may lie close together and fuse secondarily, in which case the two chorions remain separated by a ridge of firmer tissue formed where the two expanding placental masses abut (four membranes in the dividing septum: two amnia + two choria).
- ▶ Twins are of similar or different sex; phenotypically and genetically dissimilar ("unlike" twins), no more alike than ordinary siblings.

### Monozygotic (identical) twins

- ▶ **Cause:** a single zygote (one ovum + one sperm) whose cells separate into two totipotent groups at some stage before completion of the primitive streak; each group develops into a complete embryo.



- **Incidence:** about 3 per 1000 births (roughly age-independent, fairly constant across populations).
- Twins are always of the **same sex**, with identical genotype (though phenotype may differ due to environmental factors, uneven X-inactivation, post-zygotic mutation, or unequal placental blood supply).
- The fetal-membrane pattern depends entirely on the day of splitting after fertilization:

| Timing of splitting                                                                                            | Type produced                                          | Membranes                                                          | Approx. incidence (of MZ twins) |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------|---------------------------------|
| Up to 3rd day (2-cell/early cleavage stage, before trophoblast differentiates)                                 | <b>Dichorionic, diamniotic</b> (bichorial, biamniotic) | Separate chorion, amnion, placenta for each twin (like DZ twins)   | ~25%                            |
| 4th–7th day (duplication of the inner cell mass within one blastocyst)                                         | <b>Monochorionic, diamniotic</b>                       | Common chorion and single placenta, but two separate amniotic sacs | ~70–75%                         |
| ~8th–12th day (classically ~9th day; duplication of the bilaminar embryonic disc, after the amnion has formed) | <b>Monochorionic, monoamniotic</b>                     | Common chorion, common placenta, single amniotic sac               | ~1–2%                           |
| After the 12th day (incomplete splitting of the primitive streak/embryonic axis)                               | <b>Conjoined (Siamese) twins</b>                       | Common chorion, amnion and placenta; bodies joined                 | Rare                            |

□ Fig 6.8 — Development of the Fetal Membrane in Various Types of Twins (Larsen — Human Embryology — 6e, p.373)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sketch four labelled panels (2-cell stage → morula → blastocyst → fetus in utero) for: (1) **DZ / early-split MZ** — separate zygotes/blastomeres, **separate chorion, separate amnion, separate placenta**, each with its own umbilical cord; (2) **MZ monochorionic-diamniotic** — single blastocyst with **duplicated inner cell mass, common chorion + single placenta, two separate amnia**, dividing membrane = 2 thin amnion layers only; (3) **MZ monochorionic-monoamniotic** — **duplicated embryonic disc, common chorion, common amnion, common placenta**, both cords entering one sac (risk of cord entanglement); (4) **Conjoined twins** — incompletely separated embryonic axis, bodies joined, single set of membranes. Label in each panel: zygote/blastomere, inner cell mass, chorion, amniotic cavity, placenta, umbilical cord.

## Differences between monozygotic and dizygotic twins

| Feature | Monozygotic twins                       | Dizygotic twins              |
|---------|-----------------------------------------|------------------------------|
| Origin  | 1 ovum + 1 sperm → 1 zygote that splits | 2 ova + 2 sperms → 2 zygotes |

| Feature   | Monozygotic twins                                     | Dizygotic twins                                |
|-----------|-------------------------------------------------------|------------------------------------------------|
| Incidence | Less common (~1/3 of twins)                           | More common (~2/3 of twins)                    |
| Sex       | Always same sex                                       | Same or different sex                          |
| Genotype  | Identical (including HLA genes)                       | Genetically dissimilar, like ordinary siblings |
| Phenotype | Identical/very similar in appearance                  | Unlike, fraternal appearance                   |
| Placenta  | Single, usually shared                                | Two separate placentae (may fuse)              |
| Chorion   | May be single (majority monochorionic)                | Always two (dichorionic)                       |
| Amnion    | May be single or double, depending on timing of split | Always two                                     |

### Determination of zygosity

- Zygosity is clinically important for **tissue/organ transplantation** (e.g., bone-marrow transplant between twins) and for **twin studies in genetics** (comparing concordance for a trait in MZ vs DZ pairs to estimate heritability).
- Simple examination of the placenta/membranes at birth is unreliable — a **monochorionic placenta always implies MZ twins**, but a **dichorionic placenta does not exclude MZ twins**: about 35% of MZ twins split early enough (2-cell stage to morula) to be dichorionic-diamniotic, and in a subset of these (~10% of all MZ twins) the two placentae remain completely separate and are indistinguishable on gross examination from dizygotic twins.
- Definitive zygosity determination is now done by **molecular/DNA marker analysis** — dissimilarity at DNA markers proves dizygosity, since true MZ twins are virtually identical at the DNA level.

### Conjoined (Siamese) twins

- Result from **incomplete separation of the embryonic axis/primitive streak** after about the 12th day, or from secondary fusion of two adjacent embryonic discs; classic surviving pair — **Chang and Eng** (joined at the abdomen).
- **Incidence**: roughly 1 in 20,000–50,000 births.
- Classified by the site and extent of fusion:



- Separation is possible only when the twins share **no vital organ**; outcome depends on the extent of shared viscera (thoracopagus with a conjoined heart is generally inseparable).

### Other multiple-pregnancy phenomena

- **Hellin's law**: frequency of triplets = square of the frequency of twins; frequency of quadruplets = cube of the frequency of twins (an approximate rule, not exact).

- ▶ **Superfecundation:** fertilization of two ova (released in the same cycle) by sperm from **two different acts of coitus/different males**, giving dizygotic twins of the same gestational age but different paternity.
- ▶ **Superfetation:** fertilization of a second ovum released **during an already-established pregnancy**, giving twins of clearly different gestational age.
- ▶ **Vanishing twin:** death and resorption of one twin, usually in the first trimester/early second trimester, with the surviving co-twin continuing normal development; a compressed, flattened remnant seen later in pregnancy is a **fetus papyraceus**.

## Applied / Clinical anatomy

- ▶ **Placental type predicts mortality:** monochorionic-monoamniotic twins carry the highest perinatal mortality (approaching 50%), chiefly from **umbilical cord entanglement** and unbalanced inter-twin vascular shunting.
- ▶ **Twin-twin transfusion syndrome (TTTS):** occurs in roughly 10–20% (up to 30% in some series) of monochorionic-diamniotic MZ pregnancies via unbalanced placental vascular anastomoses; the **donor twin** is small, anaemic/pale with oligohydramnios, the **recipient twin** is plethoric/polycythaemic with polyhydramnios and may develop cardiac failure; laser ablation of the anastomoses is a treatment option.
- ▶ **Twin-reversed arterial perfusion (TRAP) sequence:** a rare (~1 in 35,000 births) complication of monochorionic twinning in which a normally-formed "**pump**" twin perfuses an **acardiac/acephalic twin** through placental arterio-arterial anastomoses via reversed flow; the pump twin is at high risk (50–75%) of cardiac failure and death.
- ▶ **Discordance in MZ twins** for anomalies/disease despite identical genotype is explained by unequal placental blood supply, post-zygotic somatic mutation, uneven X-inactivation (in female pairs), and environmental differences.
- ▶ Twinning is a recognized predisposing cause of **polyhydramnios**, preterm labour and intrauterine growth restriction; **ultrasonography** is central to antenatal diagnosis of chorionicity/amnionicity and surveillance for TTTS/TRAP.

## High-yield exam pointers

- ▶ MZ = one zygote splits; DZ = two ova + two sperms; DZ is commoner (~2/3 of twins) than MZ (~1/3).
- ▶ Timing of MZ split decides membranes: ≤3 days → dichorionic-diamniotic; 4–7 days → monochorionic-diamniotic (commonest MZ pattern, ~70–75%); ~8–12 days → monochorionic-monoamniotic; >13 days → conjoined twins.
- ▶ A **monochorionic placenta always means MZ**; a **dichorionic placenta does NOT exclude MZ**.
- ▶ DZ twinning ↑ with maternal age (up to 35y), parity, heredity, ovulation-inducing drugs/ART; MZ twinning rate is largely constant.
- ▶ Monochorionic-monoamniotic twins → highest mortality (~50%, cord entanglement); monochorionic-diamniotic → risk of TTTS (10–30%).
- ▶ Conjoined twins: incomplete splitting after day 13; thoracopagus is the commonest type; separable only if no vital organ is shared.

- ▶ Hellin's law: triplet frequency = (twin frequency)<sup>2</sup>; quadruplet frequency = (twin frequency)<sup>3</sup>.
- ▶ Definitive zygosity testing = DNA/molecular marker analysis (important before twin-to-twin organ/marrow transplantation and for twin studies in genetics).
- ▶ Distinguish superfecundation (two ova, same cycle, different fathers) from superfetation (second ovum fertilized after pregnancy already established).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Larsen — Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Hamilton, Boyd & Mossman — Human Embryology.



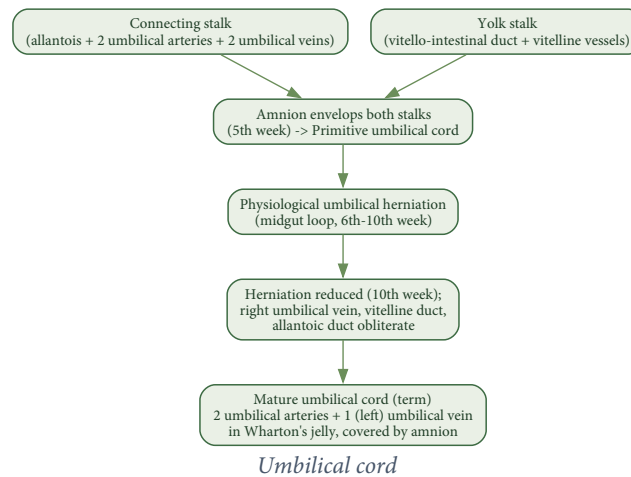
## Umbilical cord

*Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The umbilical cord (funis) is the tubular fetal membrane that connects the fetus (at the umbilicus) to the placenta (at its centre), conveying the umbilical vessels between the two. It develops from the **connecting (body) stalk** and the **yolk stalk**, both being progressively enclosed by the expanding amnion. Functionally it is the sole conduit for fetoplacental exchange — carrying deoxygenated fetal blood to the placenta via the umbilical arteries and oxygenated blood back via the umbilical vein.

### 1. Development (formation) of the cord

- ▶ In the 3rd week, the extra-embryonic mesoderm around the **allantois** vascularises to form the umbilical vessels (initially **2 umbilical arteries + 2 umbilical veins**) within the connecting stalk.
- ▶ With lateral and cephalocaudal folding of the embryo (4th–5th week), the amnio-ectodermal junction (**primitive umbilical ring**) comes to lie ventrally; through it pass (i) the connecting stalk (allantois + umbilical vessels), (ii) the yolk stalk (vitello-intestinal duct + vitelline vessels), and (iii) the canal joining the intra- and extra-embryonic coeloms.
- ▶ The rapidly enlarging amniotic cavity encroaches on the chorionic cavity and envelops the connecting stalk and yolk stalk together, crowding them into a single tube — the **primitive umbilical cord**.
- ▶ Because the abdominal cavity is transiently too small for the elongating midgut loop, gut loops herniate into the proximal cord between the 6th and 10th weeks — the **physiological umbilical hernia** — and are withdrawn back into the abdomen by the 10th week as the cavity enlarges and the liver's relative growth slows.
- ▶ With further development the **right umbilical vein**, the **vitello-intestinal duct** and the **allantoic duct** all obliterate; the mesenchyme of the connecting and yolk stalks fuses and is transformed into the mucoid connective tissue, **Wharton's jelly**, which characterises the mature cord.



## 2. Gross structure and measurements

| Feature            | Detail                                                                                                       |
|--------------------|--------------------------------------------------------------------------------------------------------------|
| Covering           | Single layer of amniotic epithelium (no true skin, no nerve/lymphatic supply)                                |
| Core               | Wharton's jelly — mucoid connective tissue rich in hyaluronic acid and proteoglycans, protecting the vessels |
| Length (full term) | Average ~50 cm; range 20–120 cm                                                                              |
| Diameter           | 1–2 cm                                                                                                       |
| Shape              | Not straight — twisted into a right- or left-handed helix; number of turns ranges from a few to over 300     |
| Attachment         | Fetal end at the umbilicus; placental end usually at/near the centre of the fetal surface of the placenta    |

- The umbilical vessels have a strong muscular coat that, on mechanical stimulation, contracts and produces periodic sharp constrictions of the vessel contour — the **valves of Hoboken**.
- Close to the placental end, the two umbilical arteries are joined by a transverse cross-anastomosis, the **Hyrtl's anastomosis**, which equalises flow between the two placental halves.

embed: ![Fig 24.12 — Histology of umbilical cord. (A) Transverse section of umbilical cord; (B) Wharton's jelly (Sontakke — Textbook of Human Histology — 2e, p.327)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/d8357aed3c8bf4dd.jpg)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a transverse section of the mature umbilical cord:

- ▶ Outer covering — amniotic epithelium
- ▶ Wharton's jelly (mucoid connective tissue) filling the core
- ▶ Two umbilical arteries (thick muscular wall, smaller lumen)
- ▶ One umbilical vein (thin wall, larger lumen) — usually placed centrally
- ▶ Remnant of vitello-intestinal duct (small epithelial-lined space)
- ▶ Remnant of allantoic duct/urachus (near the fetal end)

**3. Contents of the umbilical cord**

| Structure                                               | Origin                                                            | Fate / note                                                                                    |
|---------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 2 umbilical arteries                                    | Allantoic (connecting-stalk) mesenchyme                           | Persist; carry deoxygenated blood, fetus → placenta                                            |
| 1 umbilical vein (left)                                 | Allantoic mesenchyme                                              | Right umbilical vein disappears in utero; left carries oxygenated blood, placenta → fetus      |
| Wharton's jelly                                         | Fused somatopleuric + splanchnopleuric extra-embryonic mesenchyme | Protective mucoid matrix around the vessels                                                    |
| Vitello-intestinal (vitelline) duct + vitelline vessels | Yolk stalk                                                        | Normally obliterates completely by term; persistence → Meckel's diverticulum/vitelline fistula |
| Allantoic duct                                          | Connecting stalk                                                  | Confined to proximal cord; usually reduced to fibrous strands continuous with the urachus      |
| Amniotic covering                                       | Amnion                                                            | Single-layered epithelium, continuous with fetal skin at the umbilicus                         |

**4. Attachment of the cord to the placenta**

| Type                           | Description                                                                                                                    | Note                                                                                                                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Central/eccentric (normal)     | Cord inserts at or near the centre of the fetal surface                                                                        | Commonest pattern                                                                                                         |
| Marginal (battledore placenta) | Cord inserts at the placental margin                                                                                           | Vessels otherwise normal                                                                                                  |
| Velamentous insertion          | Cord inserts into the membranes short of the placental edge; vessels run unsupported in the membranes before reaching the disc | ~0.2% of pregnancies; predisposes to vessel injury/haemorrhage and, if vessels cross the internal os, <b>vasa praevia</b> |

## 5. Fate of the umbilical vessels after birth

| Fetal structure                                    | Adult remnant                                                                                              |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Left umbilical vein (patent part, intra-abdominal) | Ligamentum teres hepatis (round ligament of liver), in the free edge of the falciform ligament             |
| Ductus venosus                                     | Ligamentum venosum                                                                                         |
| Umbilical arteries — distal (obliterated) part     | Medial umbilical ligaments (raise the medial umbilical folds of peritoneum)                                |
| Umbilical arteries — proximal (patent) part        | Superior vesical arteries                                                                                  |
| Allantois/urachus                                  | Median umbilical ligament (raises the median umbilical fold), connecting the bladder apex to the umbilicus |
| Right umbilical vein                               | Obliterates in utero; no adult remnant                                                                     |

### Applied / Clinical anatomy

- ▶ **Single umbilical artery (SUA):** occurs in ~1 in 200 births (agenesis or early degeneration of one artery); associated with a ~20% risk of cardiac and other vascular/renal anomalies — every delivered placenta should have its cord cross-section checked for vessel number.
- ▶ **True knots:** occur in about 0.3% of cords owing to fetal movement through a loop of cord; can tighten during labour and cause acute cord compression and fetal hypoxia. **False knots** are simple local redundancies/varicosities of umbilical vessels or Wharton's jelly with no clinical significance.
- ▶ **Nuchal cord:** an unusually long cord may loop around the fetal neck; usually well tolerated but can compress the vessels during descent.
- ▶ **Cord prolapse:** an excessively long cord (or malpresentation, polyhydramnios, prematurity) may prolapse through the cervix ahead of the presenting part after membrane rupture; the presenting part compresses the cord, causing fetal hypoxia — an obstetric emergency treated by funic replacement or urgent Caesarean section.
- ▶ **Velamentous insertion / vasa praevia:** unsupported fetal vessels in the membranes are vulnerable to rupture during amniotomy or spontaneous labour, causing fetal haemorrhage.
- ▶ **Funisitis:** infection of the cord, associated with chorioamnionitis and adverse neurodevelopmental outcome.
- ▶ **Wall defects and the cord base:** in **exomphalos (omphalocele)**, failure of embryonic midgut return leaves abdominal viscera herniated into the base of the cord, covered by a peritoneum-amnion sac; in **gastroschisis**, the cord insertion is normal and bowel loops evert through a separate paraumbilical defect, floating free in the amniotic fluid.
- ▶ **Percutaneous umbilical cord blood sampling (PUBS)/cordocentesis:** ultrasound-guided puncture of the umbilical vein at the placental cord insertion for fetal blood sampling and intrauterine transfusion.
- ▶ **Umbilical cord blood banking:** cord blood is a rich source of haematopoietic stem cells, used in transplantation for haematological disorders.



- ▶ **Cord clamping:** delayed clamping (ligating 2–3 minutes after birth, or once cord pulsation stops) reduces neonatal iron deficiency and improves ferritin status at 4 months compared with early clamping.
- ▶ **Surgical relevance of postnatal remnants:** the ligamentum teres hepatis is the surgical landmark for locating the umbilical vein for catheterisation (recanalised in portal hypertension); the medial umbilical ligaments and urachal remnant (median umbilical ligament) are laparoscopic landmarks on the anterior abdominal wall.

### High-yield exam pointers

- ▶ Cord develops from **connecting stalk** (allantois + umbilical vessels) + **yolk stalk** (vitelline duct + vessels), enclosed together by the amnion.
- ▶ Mature cord: **2 umbilical arteries + 1 (left) umbilical vein** embedded in **Wharton's jelly**, covered by amnion; right umbilical vein disappears.
- ▶ Average length **~50 cm** (range 20–120 cm); diameter **1–2 cm**; vessels twisted into a helix (up to 300 turns).
- ▶ **Valves of Hoboken** (spiral-muscle constrictions) and **Hyrthl's anastomosis** (inter-arterial cross-link near placental end) are cord-specific eponyms.
- ▶ Cord attachment types: central (normal), marginal/battledore, and **velamentous** (~0.2%) — the last linked to vasa praevia.
- ▶ **Single umbilical artery (1 in 200)** carries ~20% risk of associated cardiac/vascular anomalies — always check vessel number.
- ▶ Postnatal remnants: left umbilical vein → ligamentum teres hepatis; ductus venosus → ligamentum venosum; umbilical arteries → medial umbilical ligaments (distal) + superior vesical arteries (proximal); allantois → median umbilical ligament.
- ▶ Clinical emergencies linked to the cord: true knot, nuchal cord, cord prolapse, vasa praevia rupture — all can cause acute fetal hypoxia.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Sontakke — Textbook of Human Histology 2e; IB Singh — Human Embryology (CBME 2021).



## Zona pellucida

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The zona pellucida is a thick, translucent, acellular glycoprotein coat that surrounds the plasma membrane (oolemma) of the growing oocyte, the fertilised ovum and the early preimplantation embryo up to the blastocyst stage. It is secreted jointly by the oocyte and the surrounding granulosa (follicular) cells during oocyte growth within the primary follicle. Functionally it mediates species-specific sperm binding, induces the acrosome reaction, forms the definitive block to polyspermy after fertilisation, and holds the blastomeres together through cleavage until it is shed ("hatching") just before implantation.

### 1. Structure and composition

- ▶ A continuous, structureless-looking membrane by light microscopy; by electron microscopy it shows a **granular texture with concentric lamination**, reflecting successive layers of glycoprotein deposited as the oocyte enlarges.
- ▶ Fully formed thickness around the human oocyte is approximately **17 micrometres**.
- ▶ Composed of zona-pellucida glycoproteins described classically as **ZP1, ZP2, ZP3** (all synthesised by the oocyte), with human-specific accounts additionally describing a fourth, **ZP4** — together these have different roles in different phases of fertilisation:
  - **ZP3** is the principal sperm-receptor glycoprotein — mediates initial sperm binding and induces the acrosome reaction.
  - **ZP2** plays a key role in sperm binding, gamete recognition and sperm penetration, and (once modified by cortical-granule enzymes) contributes to the block against polyspermy.
  - **ZP1** (and **ZP4**, where described) form part of the structural glycoprotein meshwork that gives the zona its integrity.
- ▶ A fluid-filled **perivitelline space** lies between the zona and the oolemma once the space develops; it contains the extruded polar bodies.
- ▶ **Cytoplasmic processes of the innermost granulosa cells** traverse the zona and make intercellular (gap-junction) contact with **microvilli of the oocyte**, permitting nutrient transport into the growing oocyte — these processes withdraw once the oocyte enters the uterine tube after ovulation.
- ▶ After ovulation, the granulosa cells adherent to the outer zona surface rearrange to form the **corona radiata**.

□ Fig 22.6 — Ultrastructure of primary follicle and zona pellucida. (Junqueira's Basic Histology — Text & Atlas — 17e, p.1108)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A schematic oocyte in cross-section, labelled:

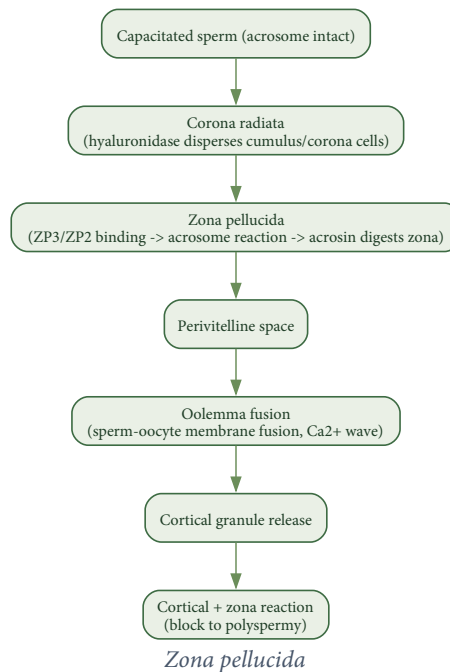
- ▶ Oocyte cytoplasm / ooplasm
- ▶ Oolemma (oocyte plasma membrane)
- ▶ Cortical granules (beneath oolemma)
- ▶ Perivitelline space
- ▶ Zona pellucida (show granular/lamellated texture; label ZP1–ZP4 glycoprotein layer)
- ▶ Cytoplasmic processes of granulosa cells crossing the zona, meeting oocyte microvilli
- ▶ Granulosa cells forming the corona radiata (outer surface)
- ▶ First polar body lying in the perivitelline space
- ▶ A capacitated sperm head approaching/bound to the zona surface

**2. Formation (histogenesis)**

- ▶ Zona material first appears as **irregular patches** between the oocyte and the flattened/cuboidal follicular cells at the **early primary (preantral) follicle** stage.
- ▶ With continued follicular growth (granulosa cells becoming stratified), the patches enlarge and become confluent, producing a **continuous zona pellucida** by the mature primary/antral follicle stage.
- ▶ Both the **oocyte and the granulosa cells contribute glycoprotein** to the zona; deposition continues throughout oocyte growth.
- ▶ Concurrently, follicular-cell cytoplasmic processes and oocyte microvilli grow across the developing zona and remain interdigitated until after ovulation.

**3. Role in fertilisation**

Fertilisation occurs in the ampulla of the uterine tube. The spermatozoon must cross three barriers in sequence — the corona radiata, the zona pellucida, and finally the oolemma:



- **Capacitation** (in the female tract) removes a glycoprotein coat and seminal plasma proteins from the sperm head plasma membrane, enabling it to bind the corona/zona.
- Capacitated sperm traverse the **corona radiata** using surface hyaluronidase.
- Sperm-head glycoprotein receptors bind specific **zona glycoprotein receptors, ZP3 and ZP2**. Interaction with ZP3 **induces the acrosome reaction** — fusion and vesiculation of the outer acrosomal membrane with the overlying sperm plasma membrane, releasing acrosomal enzymes (**acrosin**, trypsin-like substances).
- These enzymes **digest a path through the zona pellucida**, allowing the sperm to reach the **perivitelline space**, where it fuses with oocyte microvilli (via disintegrin–integrin interaction) and then with the oolemma.
- The zona pellucida is **species-specific** — sperm of other species cannot bind or penetrate it, providing a biological barrier to inter-species fertilisation.

#### 4. Cortical and zona reaction — block to polyspermy

- Sperm–oolemma fusion triggers **membrane depolarisation and an intracellular calcium wave** that sweeps across the oocyte within seconds, resuming the oocyte's suspended second meiotic division (completion of meiosis II, extrusion of the second polar body).
- Repetitive calcium pulses trigger **exocytosis of cortical granules** (enzyme-rich secretory granules lying beneath the oolemma) into the perivitelline space/zona.
- Cortical granule enzymes **hydrolyse the ZP3 sperm-receptor**, so the zona can no longer bind or support the acrosome reaction of additional sperm — this alteration is the **zona reaction**.
- The same secretion also modifies the oolemma/vitelline layer, making it resistant to further sperm fusion (an oolemma-level "fast/slow block"), giving a second layer of polyspermy block.
- Net effect: only **one spermatozoon** normally fertilises the oocyte, preventing **polyspermy** (which would produce a non-viable polyploid zygote).

## 5. Zona pellucida through cleavage, hatching and implantation

- ▶ The zona persists around the zygote and **blastomeres through cleavage** (2-cell to morula), keeping them together as a compact mass and preventing premature adhesion of trophoblast to the tubal/endometrial epithelium during transit.
- ▶ From about **day 4**, the zona begins to **thin**; fluid entering the morula from the uterine cavity helps form the blastocystic cavity.
- ▶ The blastocyst "**hatches**" from the zona at around **day 6–7**, aided by a **trypsin-like enzyme**; trophoblast oozes out through a slit in the thinned zona and the hatched blastocyst rapidly expands, deriving nourishment from uterine gland secretions until implantation.
- ▶ Only after the zona has been shed can the trophoblast make direct, intimate contact with — and invade — the endometrial epithelium (**implantation**, day 6–7).

## 6. Functions of the zona pellucida — summary

| Function                                | Mechanism / stage                                                                                                          |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Prevents premature/ectopic implantation | Physically separates trophoblast from endometrium until it is shed on day 6–7                                              |
| Species-specific sperm binding          | ZP3 (primary)/ZP2 receptors bind only conspecific sperm                                                                    |
| Induces acrosome reaction               | ZP3–sperm-head interaction                                                                                                 |
| Block to polyspermy                     | Zona reaction — cortical granule enzymes hydrolyse ZP3 receptors                                                           |
| Maintains blastomere cohesion           | Encloses zygote/blastomeres through cleavage                                                                               |
| Permits nutrient diffusion              | Porous glycoprotein meshwork allows uterine secretions to reach blastomeres/blastocyst cavity                              |
| Immunological barrier                   | Zona lacks histocompatibility antigens, shielding the early conceptus from maternal immune recognition before implantation |

## Applied / Clinical anatomy

- ▶ **Immunological shield:** because the zona pellucida itself is devoid of histocompatibility antigens, it separates genetically "foreign" embryonic tissue from maternal tissue during transit and early development, delaying exposure of the embryo to the maternal immune system until after implantation.
- ▶ **Zona hardening and monozygotic twinning:** the zona pellucida becomes progressively thinner with increasing maternal age; conversely, zona **hardening** during oocyte maturation/cleavage can cause the hatching blastocyst to emerge as a constricted "figure-of-eight" shape, splitting into two cell masses — a proposed mechanism for **monozygotic twinning**, whose frequency rises with maternal age as zona thickness falls.
- ▶ **Assisted reproductive technology (ART):** in **intracytoplasmic sperm injection (ICSI)**, a single sperm is injected directly into the ooplasm, bypassing the natural need for zona binding and

acrosome-mediated zona penetration — used to overcome severe male-factor infertility (oligozoospermia/azoospermia) or a zona-binding/penetration defect.

- ▶ **Preimplantation genetic diagnosis (PGD):** one or two blastomeres are biopsied from a 6–8-cell embryo (whose blastomeres are still held together by the zona) 3–5 days after IVF, for detection of single-gene or chromosomal disorders before uterine transfer.
- ▶ **Abnormal implantation sites:** premature loss/deficiency of the zona can permit premature trophoblastic attachment (e.g. tubal/ectopic implantation), while delayed shedding can delay or prevent implantation.
- ▶ **Diagnostic/embryology correlate:** an oocyte or early embryo is graded in IVF laboratories partly by the integrity and thickness of its zona pellucida; zona abnormalities are a recognised cause of fertilisation failure in vitro.

### High-yield exam pointers

- ▶ Zona pellucida = **acellular glycoprotein coat**, secreted by **oocyte + granulosa cells**, ~17 µm thick, granular/lamellated on EM.
- ▶ Composed of **four glycoproteins** — ZP1, ZP2, ZP3, ZP4; ZP3 = **primary sperm receptor**, inducer of acrosome reaction.
- ▶ Sperm crosses, in order: **corona radiata → zona pellucida → oolemma**.
- ▶ **Acrosin** (released in acrosome reaction) digests the zona to let sperm through.
- ▶ **Cortical granule release → zona reaction → hydrolysis of ZP3 receptor = the block to polyspermy**.
- ▶ Zona persists through **cleavage**, **thins from day 4**, and the blastocyst **hatches on day 6–7** (trypsin-like enzyme) — a prerequisite for implantation.
- ▶ Zona is **species-specific** and **lacks histocompatibility antigens** (immunological barrier).
- ▶ **Zona hardening → figure-of-eight half-hatching** is a proposed cause of **monozygotic twinning**, more frequent with advancing maternal age (thinner zona).
- ▶ Clinically bypassed in ICSI; biopsied through in PGD.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; IB Singh, Human Embryology (CBME 2021); Hamilton, Boyd & Mossman, Human Embryology; Sontakke, Textbook of Human Embryology; Junqueira's Basic Histology, Text & Atlas 17e (figure).



## Teratology & congenital anomalies



## Teratogens

Asked in: Paper II 26-Sep-2025 · Paper II 31-Jul-2021 · Paper II Nov 2018 · Paper II May 2018 · Paper II Apr 2006 (5×)  
— RGUHS MD/MS Anatomy

**Definition / Introduction** — A **teratogen** is any agent — drug, chemical, infectious organism, physical agent or maternal metabolic state — that, acting on the embryo/fetus during a susceptible period of development, can produce a structural or functional **congenital anomaly (birth defect)** or increase the incidence of a defect already present in the population. The science studying such agents and their mechanisms is **teratology**. Until the discovery by N. Gregg (early 1940s) that maternal **rubella** produced fetal abnormalities, congenital defects were assumed to be purely hereditary; W. Lenz (1961) subsequently linked limb defects to the sedative **thalidomide**, establishing that drugs too cross the placenta and act as teratogens. Only about 7–10% of **birth defects** are attributable to recognised environmental teratogens, yet identifying them is critical because most are **preventable**.

### 1. Principles of teratogenesis

Whether an agent produces a defect, and what defect, is governed by five inter-related principles:

- ▶ **Genotype of the conceptus** — susceptibility depends on the genetic constitution of the embryo and how it interacts with the environment (maternal genotype also matters for drug metabolism). Example: only 5–10% of embryos exposed to phenytoin develop the full fetal hydantoin syndrome; roughly a third show partial features, and over half are unaffected.
- ▶ **Stage of development at exposure (critical period)** — susceptibility varies with the developmental stage; most defects are induced during the **3rd–8th week (organogenesis)**, though virtually any defect can be induced during 1st-week axis formation, and post-8-week exposure can still injure the differentiating/growing brain.
- ▶ **Dose and duration of exposure** — a dose–response relationship exists; the lowest dose has no effect and the highest is embryolethal. Animal-derived thresholds do not transfer reliably to humans, so a genuine human teratogen must show a dose–response relationship clinically.
- ▶ **Mechanism-specificity** — teratogens act through specific biochemical/molecular mechanisms (inhibition of a pathway, cell death, reduced proliferation, impaired morphogenetic movement); even for thalidomide, the exact mechanism remains unsettled (>20 hypotheses proposed).
- ▶ **Manifestations of abnormal development** — death, malformation, growth restriction, and functional disturbance are the four possible outcomes of teratogenic insult.

**Proof of teratogenicity** requires either a *prospective* (cohort) study showing increased defect frequency after exposure, or a *retrospective* study showing exposure is disproportionately common in malformed infants; isolated case reports convince only when both agent and defect are rare enough that chance association is implausible.

### 2. Critical periods of human development

- ▶ **Weeks 1–2 (pre-differentiation/pre-implantation period)**: the "all-or-none" law — teratogens either kill the embryo/cause spontaneous abortion, or damage only a few cells that are compensated by the powerful regulative capacity of the early embryo; **no birth defects** are produced in this window.



- **Weeks 3–8 (embryonic period/organogenesis):** the period of **peak vulnerability** — cell division, differentiation and morphogenesis are maximal, and **major structural anomalies** are produced.
- **Weeks 9–38 (fetal period):** sensitivity falls sharply for gross structural defects, but exposure can still cause **growth restriction** and **functional/minor morphological disturbances**, particularly of organs (brain, eye, external genitalia) still differentiating.

| Organ / system     | Critical (most vulnerable) period                                   |
|--------------------|---------------------------------------------------------------------|
| Heart              | Day 20 to day 50 post-fertilisation                                 |
| Upper limb         | Day 24 to 36 post-fertilisation                                     |
| Brain              | 3rd to 16th week (mental deficiency risk continues into fetal life) |
| Palate             | 6th to 12th week                                                    |
| Eye                | 4th to 8th week                                                     |
| Ear                | 4th to 9th (up to 12th) week                                        |
| External genitalia | 7th to 9th week                                                     |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

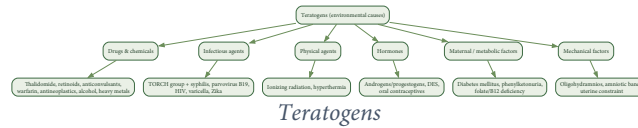
Moore's schematic of critical periods in human prenatal development (horizontal timeline, weeks 1–38 on the x-axis):

- Label the pre-implantation block (weeks 1–2) as "not susceptible to teratogenesis" (dotted/pale shading).
- Draw individual horizontal bars for **CNS, heart, upper limb, lower limb, eye, ear, teeth, palate, external genitalia** spanning their critical windows (weeks 3–9, tapering) — darker shading = highly sensitive period, lighter shading = less-sensitive period.
- Mark "period of dividing zygote, implantation, bilaminar embryo" (weeks 1–2), "embryonic period — major congenital anomalies" (weeks 3–8), and "fetal period — physiological defects and minor anomalies" (weeks 9–38, birth) below the axis.
- Below each organ bar, note the classic defect it corresponds to (e.g., limb bar → amelia/meromelia; heart bar → ASD/VSD; brain bar → mental deficiency).

**Table 20-7 (incidence of major defects per 1000 live births):** Brain 10, Heart 8, Kidneys 4, Limbs 2, all other 6 — total 30:1000.

## 3. Classification of teratogens

Congenital anomalies as a whole arise from genetic, environmental, or combined causes: approximately **80% are multifactorial** (gene–environment interaction), about **10% are exclusively chromosomal/single-gene**, and about **10% are exclusively environmental** (teratogenic). Environmental teratogens are conventionally classified as follows.



#### 4. Drugs and chemicals as teratogens

| Agent                                          | Chief birth defects                                                                                                                                                                                                           |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Thalidomide                                    | Meromelia (phocomelia/amelia of limbs); ear, cardiac, renal, GIT anomalies. Critical window: <b>day 20–36</b> post-fertilisation                                                                                              |
| Alcohol                                        | <b>Fetal alcohol syndrome (FAS)</b> : IUGR, mental deficiency, microcephaly, short palpebral fissures, thin upper lip, joint/cardiac defects — the whole spectrum is now termed <b>fetal alcohol spectrum disorder (FASD)</b> |
| Isotretinoin (13-cis-retinoic acid, vitamin A) | Craniofacial dysmorphism (microtia, micrognathia), cleft palate, thymic aplasia, cardiovascular defects, NTDs; window = 3rd–5th week                                                                                          |
| Warfarin                                       | Nasal/cartilage hypoplasia, stippled epiphyses, CNS defects; most sensitive 6th–12th week                                                                                                                                     |
| Phenytoin                                      | <b>Fetal hydantoin syndrome</b> — IUGR, microcephaly, ridged frontal suture, epicanthal folds, ptosis, broad nasal bridge, distal phalangeal hypoplasia (5–10% of exposed)                                                    |
| Trimethadione                                  | Developmental delay, V-shaped eyebrows, low-set ears, cleft lip/palate                                                                                                                                                        |
| Valproic acid                                  | Craniofacial anomalies, neural tube defects, cardiac/skeletal defects, cognitive delay                                                                                                                                        |
| Aminopterin / methotrexate                     | IUGR; CNS defects (meroencephaly); severe skeletal defects of face, cranium, limbs, vertebrae                                                                                                                                 |
| Androgens/progestogens                         | Masculinisation of female external genitalia (labial fusion, clitoromegaly)                                                                                                                                                   |
| Diethylstilbestrol (DES)                       | Vaginal adenosis, cervical ridges, vaginal clear-cell adenocarcinoma in exposed daughters; epididymal cysts/testicular hypoplasia in exposed sons                                                                             |
| Tetracycline                                   | Staining and enamel hypoplasia of deciduous/permanent teeth                                                                                                                                                                   |
| Lithium carbonate                              | Cardiac and great-vessel defects                                                                                                                                                                                              |
| ACE inhibitors                                 | Oligohydramnios, calvarial hypoplasia, IUGR, renal dysfunction                                                                                                                                                                |
| Methylmercury                                  | Cerebral atrophy, spasticity, seizures, mental deficiency (Minamata disease pattern)                                                                                                                                          |

| Agent                               | Chief birth defects                                                                         |
|-------------------------------------|---------------------------------------------------------------------------------------------|
| Lead / polychlorinated biphenyls    | IUGR, neurobehavioural deficits; skin discolouration (PCBs)                                 |
| Cocaine                             | IUGR, microcephaly, cerebral infarction, urogenital defects, prematurity                    |
| Progestogen–estrogen (OCP) exposure | VACTERL association (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, Limb anomalies) |

## 5. Infectious agents as teratogens

| Agent                  | Hallmark defects                                                                                                                                                                                             |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rubella virus          | Classic triad — cataract, cardiac defect (PDA), sensorineural deafness; also microcephaly, glaucoma. ~20% embryo/fetal infection risk in 1st-trimester maternal infection; risk falls sharply after 5 months |
| Cytomegalovirus        | Commonest congenital viral infection; microcephaly, chorioretinitis, sensorineural deafness, periventricular calcification, hepatosplenomegaly                                                               |
| Herpes simplex virus   | Skin vesicles/scarring, chorioretinitis, hepatomegaly, hydranencephaly (usually acquired at delivery)                                                                                                        |
| Varicella-zoster virus | Cutaneous scarring, limb hypoplasia, cataract, chorioretinitis, CNS defects                                                                                                                                  |
| Toxoplasma gondii      | Microcephaly, hydrocephalus, intracranial calcification, chorioretinitis, mental deficiency                                                                                                                  |
| Treponema pallidum     | Congenital deafness, saddle nose, Hutchinson teeth, hydrocephalus                                                                                                                                            |
| Parvovirus B19         | Non-immune hydrops fetalis, fetal anaemia, fetal death                                                                                                                                                       |
| HIV                    | Growth failure, microcephaly, craniofacial dysmorphism (transmission mainly perinatal)                                                                                                                       |
| Zika virus             | Congenital Zika syndrome — severe microcephaly with redundant scalp, thin calcified cerebral cortex, microphthalmia/coloboma, arthrogryposis                                                                 |

## 6. Physical, hormonal and maternal factors as teratogens

- **Ionizing radiation:** dose- and stage-dependent; atomic-bomb survivor data identify **weeks 8–16** as most sensitive for radiation-induced mental deficiency; doses **>25,000 mrad** are established as harmful to the developing CNS; recommended cumulative maternal whole-body exposure limit for the entire pregnancy is **500 mrad (0.005 Gy)**; routine diagnostic imaging away from the pelvis delivers only a few millirads and is not teratogenic.
- **Hyperthermia** (febrile illness, sauna/hot-tub use): teratogenic, principally disrupting **neurulation** (neural tube defects).

- ▶ **Maternal diabetes mellitus:** 2–3× increase in major defects (cardiac, sacral agenesis, neural tube, skeletal); poor peri-conceptual glycaemic control is the key modifiable risk factor.
- ▶ **Maternal phenylketonuria (untreated):** microcephaly, cardiac defects, mental deficiency, IUGR in offspring — preventable by a phenylalanine-restricted maternal diet before and during pregnancy.
- ▶ **Folate/vitamin B12 deficiency:** increased risk of neural tube defects.
- ▶ **Mechanical factors:** oligohydramnios → limb deformation (e.g., knee hyperextension, clubfoot, hip dislocation); amniotic band rupture → intrauterine amputation/constriction rings.

## Applied / Clinical anatomy

- ▶ **Prevention is the practical payoff of this topic:** avoid all non-essential drugs in the first trimester; pre-conceptual rubella vaccination; periconceptual folic acid; tight glycaemic control before conception in diabetics; phenylalanine-restricted diet in maternal PKU; thalidomide/isotretinoin are absolutely contraindicated in women of childbearing age.
- ▶ **Four clinically distinct types of birth defect** (relevant to how a teratogenic anomaly is classified): **malformation** (intrinsically abnormal developmental process, e.g., cleft lip), **disruption** (breakdown of a previously normal structure, e.g., amniotic band amputation), **deformation** (mechanical distortion of an already-formed part, e.g., oligohydramnios-related clubfoot), and **dysplasia** (abnormal organisation of cells into tissue, e.g., skeletal dysplasias).
- ▶ **Prenatal screening/diagnosis** used to detect teratogen-induced anomalies: ultrasonography (age, anomaly detection, amniotic fluid volume), maternal serum/amniotic alpha-fetoprotein (raised in NTD/abdominal wall defects, low in trisomies), amniocentesis (15th–18th week; karyotype, biochemistry), chorionic villus sampling (10th–12th week), fetoscopy, fetal MRI, and percutaneous umbilical blood sampling (PUBS).
- ▶ **Classic clinical vignettes** (exam favourites): phocomelia/meromelia in a child of a mother given thalidomide for morning sickness in the 1960s; the FAS facial gestalt (thin upper lip, smooth philtrum, short palpebral fissures) in a heavy-drinking mother; congenital rubella triad in an unvaccinated mother infected in the first trimester; VACTERL association after inadvertent OCP use in early pregnancy; vaginal clear-cell adenocarcinoma in a young woman whose mother took DES in pregnancy.

## High-yield exam pointers

- ▶ Three cardinal determinants of teratogenicity: **genotype**, **critical period (developmental stage)**, **dose/duration** of exposure — plus mechanism-specificity and the four possible outcomes (death/malformation/growth restriction/functional disorder).
- ▶ **Weeks 1–2 = all-or-none law** (no malformation); **weeks 3–8 = peak vulnerability (organogenesis)**; fetal period = growth restriction/functional/minor defects only.
- ▶ Only 7–10% of birth defects have a recognised environmental (teratogenic) cause; ~80% are multifactorial.
- ▶ **Thalidomide window = day 20–36** post-fertilisation → phocomelia/amelia/meromelia.
- ▶ **Rubella triad** = cataract + cardiac defect (PDA) + deafness; risk highest in weeks 1–5, negligible after 5 months.

- **Radiation:** most CNS-sensitive at weeks 8–16; safe cumulative limit for pregnancy = 500 mrad; >25,000 mrad is CNS-damaging.
- **Warfarin** (nasal hypoplasia + stippled epiphyses, 6–12 wk) vs **phenytoin** (fetal hydantoin syndrome) vs **valproate** (NTD) — a favourite "match the drug to the defect" table.
- **VACTERL** = Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, Limb.
- Four types of birth defect: **malformation, disruption, deformation, dysplasia**.

#### SOURCE & COVERAGE

Moore's *The Developing Human* 9e (K. L. Moore, T. V. N. Persaud); Langman's *Medical Embryology* (Sadler) 14e; Larsen's *Human Embryology* 6e; IB Singh's *Human Embryology* (CBME 2021). Gray's Anatomy (Standing) 41e was checked but, per its emphasis on structural embryogenesis, discusses teratogens only in passing — the dedicated embryology texts above form the primary grounding for this answer.



## Cleft Palate

Asked in: Paper II Nov 2017 · Paper II Apr 2008 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — Cleft palate is a congenital fissure of the roof of the mouth caused by failure of fusion of the primary palate (premaxilla) with the secondary palate (palatine shelves of the two maxillary prominences), and/or failure of fusion of the two palatine shelves with each other and with the nasal septum, during the 6th–10th week of intra-uterine life. It may occur alone (isolated cleft palate) or combined with cleft lip, and ranges in severity from a bifid uvula to a complete cleft extending through the hard and soft palate into the alveolus and lip. It is one of the commonest craniofacial congenital anomalies and is of major interest to the anatomist because it directly reflects a failure of the normal sequence of facial-process fusion.

### Development of the palate (normal)

| Week (IUL) | Event                                                                                                                                                                                                                               |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4th week   | Frontonasal, maxillary and mandibular prominences identifiable around the stomodeum; nasal (olfactory) placodes appear                                                                                                              |
| 5th week   | Nasal placodes invaginate to form nasal pits, flanked by medial and lateral nasal prominences                                                                                                                                       |
| 6th week   | On each side, a shelf-like <b>palatine process (palatine shelf)</b> grows out from the maxillary prominence and lies <b>vertically</b> , alongside the tongue                                                                       |
| 7th week   | Maxillary prominence fuses with the medial nasal prominence (completing the upper lip); as the mandible grows and the tongue drops down and forward, the palatine shelves reorient to a <b>horizontal</b> position above the tongue |

| Week (IUL)    | Event                                                                                                                                                                                                                                                                                                                                              |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8th–10th week | The two palatine shelves fuse with <b>each other</b> in the midline (fusion proceeds antero-posteriorly), with the <b>primary palate</b> anteriorly, and with the <b>nasal septum</b> superiorly, completing the secondary palate (AK Datta states fusion is complete by the 8th week; IB Singh's timetable places septal fusion at the 10th week) |

- ▶ The **primary palate** develops from the **intermaxillary segment** — the fused product of the two medial nasal prominences — which has three components: a labial part forming the **philtrum** of the upper lip, an upper-jaw part carrying the **four incisor teeth (premaxilla)**, and a palatal part forming the small, triangular **primary palate**. The intermaxillary segment is continuous with the rostral nasal septum (from the frontal prominence).
- ▶ The **secondary palate** is formed by the **palatine processes of the maxilla** (anteriorly, forming the greater part of the hard palate) continuous posteriorly with the **horizontal plates of the palatine bones**.
- ▶ Of the completed (permanent) palate, the **anterior three-fourths ossify** in membrane to form the **hard palate**; the **posterior one-fourth remains unossified** and hangs down as the **soft palate** and uvula.
- ▶ The **incisive foramen** is the key midline landmark marking the junction between the primary and secondary palates — it separates *anterior* (pre-foramen) clefts from *posterior* (post-foramen) clefts.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label a horizontal (axial) section through the developing palate at about the 7th–8th week, showing: **premaxilla (primary palate)**, **incisive foramen**, **palatine process of maxilla (palatine shelf)** — right and left, **nasal septum** (growing down in the midline), **tongue** (dropped below the shelves), **line of fusion** between the two shelves and between each shelf and the primary palate (Y-shaped suture), **primitive/definitive choana**, and the **oronasal membrane** breaking down. A companion frontal section should show the shelves first vertical (alongside the tongue) and then horizontal (above the tongue, fused).

### Embryological basis of the defect

- ▶ Cleft palate results from a failure of the normal fusion process described above, due to:
  - **Smallness of the palatine shelves** (insufficient growth),
  - **Failure of the shelves to elevate** to the horizontal position at the correct time,
  - **Inhibition of the fusion process itself** in shelves that are otherwise normally positioned, or
  - **Failure of the tongue to drop away** from between the vertical shelves — commonly due to **micrognathia** (small mandible), which mechanically blocks shelf elevation. This mechanism underlies **Robin sequence**, in which poor growth of the mandible leaves the tongue posteriorly placed between the shelves, preventing their fusion; the classic triad is **micrognathia + cleft palate + glossoptosis** (incidence  $\approx 1/8500$  births).

- Clefts **anterior** to the incisive foramen (lateral cleft lip, cleft jaw, cleft between primary and secondary palate) arise from failure of fusion of the maxillary prominence with the medial nasal prominence.
- Clefts **posterior** to the incisive foramen (cleft of the secondary/soft palate, cleft uvula) arise from failure of fusion of the two palatine shelves with each other and/or with the nasal septum.
- A combination of anterior and posterior clefts may co-exist (e.g., unilateral cleft lip with cleft of the entire secondary palate).
- Cleft lip with/without cleft palate and isolated cleft palate are regarded as **etiologically and pathogenetically distinct** entities, not different severities of one process.

### Classification of cleft palate

| Category         | Type                          | Embryological defect                                                                                                                                                                                         |
|------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Complete cleft   | Bilateral complete cleft      | Both palatine processes fail to fuse with the premaxilla → a <b>Y-shaped cleft</b> between primary and secondary palate and between the two halves of the secondary palate; usually with bilateral cleft lip |
|                  | Unilateral complete cleft     | One palatine process fails to fuse with the premaxilla (the other side fuses normally) → unilateral cleft, usually with unilateral cleft lip                                                                 |
| Incomplete cleft | Cleft of hard and soft palate | The two palatine shelves fail to fuse with each other in the midline; premaxilla/lip unaffected                                                                                                              |
|                  | Cleft of soft palate only     | Limited to the unossified posterior segment                                                                                                                                                                  |
|                  | Bifid uvula                   | Cleft limited to the uvula alone — the mildest form, usually of no functional/clinical significance                                                                                                          |

- An older severity-graded scheme (AK Datta) describes **four degrees**: 1st degree = bifid uvula; 2nd degree = un-united palatine processes (isolated cleft palate); 3rd degree = un-united palatine processes with a cleft on **one** side of the premaxilla (unilateral complete cleft lip and palate); 4th degree = un-united palatine processes with clefts on **both** sides of the premaxilla (bilateral complete cleft lip and palate).

□ Fig 12.5 — Cleft lip and cleft palate. Non-fusion of the median and later palatine processes result (Sontakke — Textbook of Human Embryology, p.123)



## Muscles of the soft palate and their relevance

| Muscle                                                                  | Nerve supply                                                                                                              | Relevance to cleft palate                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tensor veli palatini                                                    | Trunk of the <b>mandibular nerve</b> via the otic ganglion (without relay), carrying fibres destined for medial pterygoid | Its tendon normally hooks around the pterygoid hamulus and tenses the palate; anomalous attachment in a cleft impairs its action on the pharyngotympanic (Eustachian) tube                                                                                                         |
| Levator veli palatini, palatoglossus, palatopharyngeus, musculus uvulae | <b>Pharyngeal plexus</b> (vagus, with cranial accessory contribution)                                                     | Normally form a transverse muscular sling that elevates the soft palate against the pharyngeal wall (velopharyngeal closure); in a cleft, these fibres run antero-posteriorly and insert into the abnormal cleft margins instead of the midline raphe, so the sling action is lost |

## Etiology and genetic basis

- Most cases are **multifactorial**. Incidence of cleft lip with/without cleft palate is about **1 in 700 births**, commoner in **males (65%)**, with the highest population rates in Asians and Native Americans (3.5/1000) and the lowest in African Americans (1/1000).
- **Isolated cleft palate** is less frequent, about **1 in 1500 births**, and is commoner in **females (55%)** — attributed to palatal shelves fusing about a week later in female embryos, widening the window for a disruptive insult.
- Recurrence risk after one affected child is low (of the order of a few percent) and is **not related to maternal age**.
- **Genetic associations**: mutations in **IRF6** (interferon regulatory factor 6), expressed at the fusing medial edge of the palatal shelves, cause **Van der Woude syndrome** (autosomal dominant), the commonest syndrome associated with cleft lip with/without cleft palate — most affected infants also have characteristic lower-lip pits. **MSX1** mutations are also implicated. **22q11.2 deletion syndrome** (velocardiofacial/DiGeorge syndrome) is associated with bifid uvula and velopharyngeal insufficiency.
- **Teratogens**: anticonvulsants (particularly **valproic acid**), and maternal cigarette smoking during pregnancy increase risk.

## Applied / Clinical anatomy

- **Feeding difficulty**: loss of the intact bony/muscular palatal partition between the oral and nasal cavities causes nasal regurgitation of milk/fluids in the neonate and impaired generation of negative intra-oral (suck) pressure.
- **Speech**: absent or deficient velopharyngeal sphincter action (from the disrupted muscular sling) produces **hypernasal speech** and a **nasal twang**; this is the same clinical picture seen in isolated **vagus nerve palsy of the palate** (paralysis of levator veli palatini and the pharyngeal-plexus-supplied muscles), which additionally shows flattening of the palatal arch and **deviation of the uvula to the normal side** — a useful comparison for the anatomy of palatal muscle action.

- ▶ **Otitis media:** because tensor veli palatini cannot act normally on the pharyngotympanic tube in a cleft, mucociliary clearance and pressure equalisation of the middle ear are impaired, predisposing to recurrent secretory otitis media.
- ▶ **Airway/associated anomalies:** a small, retruded mandible (micrognathia) causing tongue-based airway obstruction, and glossoptosis, should be looked for, since failure of tongue descent is itself a cause of cleft palate.
- ▶ **Landmarks for classifying severity:** the incisive foramen (primary/secondary palate junction) and the posterior nasal spine (hard/soft palate junction) are the anatomical reference points used clinically to describe the extent of a cleft.
- ▶ **Surgical anatomy note:** repair aims to reconstruct the normal transverse orientation of the levator veli palatini sling across the midline (rather than leaving it running antero-posteriorly along the cleft margins) to restore velopharyngeal competence.

### High-yield exam pointers

- ▶ Primary palate = intermaxillary segment (philtrum + premaxilla + triangular primary palate); secondary palate = palatine shelves of the maxillary prominence + horizontal plate of palatine bone.
- ▶ Incisive foramen = the dividing landmark between primary (anterior) and secondary (posterior) palate/clefts.
- ▶ Palatine shelves are vertical at 6th week, become horizontal at 7th week (as the tongue drops with mandibular growth), and fuse with each other, the primary palate, and the nasal septum by the 8th–10th week.
- ▶ Anterior three-fourths of the palate ossify (hard palate); posterior one-fourth stays unossified (soft palate).
- ▶ Classic classification: complete (bilateral/unilateral, with cleft lip) vs incomplete (hard+soft palate/soft palate only/bifid uvula alone).
- ▶ Cleft lip ± palate and isolated cleft palate are distinct entities — different sex ratios, different incidences.
- ▶ Tensor veli palatini alone is supplied by the mandibular nerve (via otic ganglion); all other palatal muscles are supplied by the pharyngeal plexus (vagus) — key to explaining Eustachian tube dysfunction and vagal-palsy findings.
- ▶ IRF6 → Van der Woude syndrome; MSX1; 22q11.2 deletion → bifid uvula/VPI; teratogens — valproic acid, smoking.
- ▶ Failure of tongue descent (micrognathia) is a mechanical cause of cleft palate.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; IB Singh — Human Embryology (CBME 2021); AK Datta — Human Anatomy Vol 2 (Head & Neck); BD Chaurasia — Human Anatomy Vol 3–4; Sontakke — Textbook of Human Embryology; Larsen — Human Embryology 6e; Gray's Anatomy (Standring) 41e.



## Developmental defects in abdominal diaphragm

Asked in: Paper II Nov 2017 · Paper II Sep 2007 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — The diaphragm is a composite musculotendinous partition that forms between the 4th and 12th weeks of intra-uterine life by fusion of **four embryonic components**: the septum transversum, the paired pleuroperitoneal membranes, the dorsal mesentery of the oesophagus, and mesoderm of the body wall. Failure of development or fusion of any one component produces a spectrum of developmental defects, of which the **postero-lateral (Bochdalek's) hernia** is the commonest and most clinically important. Other defects include the retrosternal (Morgagni's) hernia, congenital hiatus hernia, central (septum-transversum) defects, and eventration of the diaphragm.

### Normal development of the diaphragm — the basis for its defects

| Component                          | Origin / position                                                                            | Contribution to adult diaphragm                                                                                                                       |
|------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Septum transversum                 | Mesenchymal plate below the pericardial cavity, opposite C3–C5 somites in the 4th week       | Cranial part → <b>central tendon</b> ; caudal part is invaded by the liver bud                                                                        |
| Paired pleuroperitoneal membranes  | Caudal ridges that grow from the dorsolateral body wall to close the pleuroperitoneal canals | Fuse with the septum transversum and dorsal mesentery of oesophagus by the end of the 6th week; form a relatively small part of the newborn diaphragm |
| Dorsal mesentery of the oesophagus | Mesentery around the developing oesophagus                                                   | Median part of the diaphragm; gives rise to the <b>crura</b>                                                                                          |
| Mesoderm of the body wall          | Lateral thoracic body wall, invaded by myoblasts during the 9th–12th week                    | Peripheral rim of the diaphragm, external to the pleuroperitoneal-membrane-derived parts                                                              |

- ▶ **Sequence**: pleuroperitoneal folds appear in the 4th–5th week → by the end of the 6th week they fuse ventromedially with the septum transversum and dorsal mesentery of the oesophagus, separating the pleural from the peritoneal cavities → myoblasts migrate in from the body wall during the 9th–12th week to complete the muscular peripheral diaphragm.
- ▶ The **right pleuroperitoneal canal closes earlier than the left** — the single most important fact explaining why almost all developmental diaphragmatic defects are left-sided.
- ▶ **Innervation**: when the dorsal border of the septum transversum lies opposite the 4th cervical segment, the **phrenic nerve (C3, C4, C5)** and corresponding myotomal fibres grow into it and accompany it during its later caudal migration to the level of L1 — hence the diaphragm's long intrathoracic phrenic nerve course. The peripheral, body-wall-derived rim additionally receives **sensory** fibres from the lower intercostal (thoracic) nerves, reflecting its separate somatopleuric origin.

□ Fig 17.5 — Development of abdominothoracic diaphragm. Central tendon of diaphragm develops from septum transversum (Sontakke — Textbook of Human Embryology, p.171)

## Classification of developmental defects of the diaphragm

| Type                                           | Embryological basis                                                                                                                                     | Site                                              | Approx. frequency (of all CDH)              |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------|
| Postero-lateral (Bochdalek's) hernia           | Failure of fusion of the pleuroperitoneal membrane with the other three components                                                                      | Postero-lateral, usually left                     | 85–90% (unilateral in 95%, bilateral in 5%) |
| Central defect                                 | Defect within the septum transversum itself                                                                                                             | Central tendon                                    | Rare, midline                               |
| Retrosternal / parasternal (Morgagni's) hernia | Abnormally large gap between the sternal and costal slips of origin (foramen of Morgagni)                                                               | Anteromedial, sternocostal triangle               | 1–2%, rare                                  |
| Congenital hiatus hernia                       | Excessively large/patulous oesophageal hiatus (crural defect) around the oesophagus and vagal trunks                                                    | Oesophageal opening                               | Uncommon                                    |
| Eventration of the diaphragm                   | Myoblasts from the body wall fail to invade the pleuroperitoneal membrane on one side — musculature remains thin and membranous (not a true herniation) | Usually one entire hemidiaphragm, more often left | Uncommon                                    |

## Congenital diaphragmatic hernia (Bochdalek's hernia) — the clinically important defect

- **Definition:** herniation of abdominal viscera (stomach, small bowel, colon, spleen, occasionally liver) into the pleural cavity through a persistent postero-lateral pleuroperitoneal canal, because the pleuroperitoneal membrane fails to fuse with the septum transversum, dorsal mesentery of the oesophagus and body-wall mesoderm.
- **Pathogenesis — two views:** classically attributed to failure of pleuroperitoneal membrane fusion; increasing evidence, however, suggests the **primary abnormality is pulmonary hypoplasia**, with herniation of the abdominal contents being a secondary event — an important shift with implications for antenatal treatment.
- **Timing link with physiological gut herniation:** the midgut, which physiologically herniates into the umbilical cord, returns to the abdominal cavity at about the **10th week**. If a pleuroperitoneal canal is still patent at that time, the returning intestine (and often stomach/spleen) passes into the thoracic cavity instead of the abdomen.
- **Laterality:** left-sided in ~80–90% of cases because the right pleuroperitoneal canal closes earlier than the left.

- ▶ A **non-muscular membranous sac**, derived from the wall of the persisting pleuroperitoneal canal, covers the herniated viscera in 10–15% of cases — evidence that the lesion arises very early in development.
- ▶ **Genetics**: a candidate gene region has been mapped to **chromosome 15q26**; CDH may be associated with **trisomy 13 and 18** and can occur as part of several malformation syndromes.
- ▶ **Incidence**: about 1 in 3000–5000 live births; prenatal incidence approximately 1 in 2000.
- ▶ **Consequence**: herniated viscera compress the developing lung, producing **pulmonary hypoplasia** (with abnormal ipsilateral and contralateral airway branching in the first 16 weeks) and a muscularised, reactive pulmonary vasculature causing **persistent pulmonary hypertension** — together the chief causes of neonatal death, rather than the diaphragmatic defect itself.

□ Fig 17.6 — Congenital diaphragmatic hernia: normal diaphragmatic openings compared with absence of the left pleuroperitoneal membrane (Bochdalek hernia) and an enlarged foramen of Morgagni (Morgagni hernia) (Sontakke — Textbook of Human Embryology, p.172)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the inferior surface of the diaphragm twice, side by side (normal vs defective), with these exact labels:

- ▶ Sternum, costal cartilages (anterior rim)
- ▶ Central tendon of diaphragm
- ▶ Caval opening (with inferior vena cava)
- ▶ Oesophageal opening (with oesophagus)
- ▶ Aortic opening (with aorta), right and left crus
- ▶ On the "defect" panel: **enlarged foramen of Morgagni** → **Morgagni hernia** (antero-medial, between sternal and costal slips) and **absence of the left pleuroperitoneal membrane** → **Bochdalek hernia** (postero-lateral, left side)

### Other developmental defects

- ▶ **Retrosternal / Morgagni's hernia**: an abnormally large sternocostal hiatus (the normal gap through which the superior epigastric vessels pass) between the sternal and costal slips of the diaphragm; usually small, right-sided, and often asymptomatic; may permit herniation of intestine into the pericardial sac, or occasionally displacement of part of the heart into the epigastrium.
- ▶ **Congenital hiatus hernia**: herniation of part of the fetal stomach through an excessively large oesophageal hiatus formed by the right crus; a distinct, rarer developmental lesion from the common acquired sliding hiatus hernia of adult life, though it predisposes to it.
- ▶ **Eventration of the diaphragm: not a true hernia** — the diaphragm remains anatomically continuous, but its musculature on one side (usually left) stays thin, aponeurotic and membranous because myoblasts fail to invade the pleuroperitoneal membrane; the thinned hemidiaphragm balloons superiorly, displacing abdominal viscera into the thoracic pouch. It produces an abnormal medial bulge on chest X-ray with paradoxical diaphragmatic movement on fluoroscopy, and may be a benign incidental finding or occasionally require surgical plication.

## Applied / Clinical anatomy

- ▶ **Clinical triad at birth (CDH):** breathlessness, cyanosis, and an unusually flat (scaphoid) abdomen (due to absent abdominal viscera); bowel sounds may be auscultated over the affected (usually left) hemithorax, and the heart sounds/apex beat are displaced (mediastinal shift) — a classical case scenario for viva/theory.
- ▶ **Antenatal diagnosis:** ultrasonography (from about 18 weeks onward) shows loops of bowel or liver within the thorax, mediastinal shift, and sometimes polyhydramnios; fetal MRI confirms and quantifies pulmonary hypoplasia. Severe cases may be candidates for fetoscopic endoluminal tracheal occlusion to promote lung growth.
- ▶ **Postnatal management principle:** immediate nasogastric decompression and avoidance of bag-mask ventilation (which distends herniated bowel and worsens lung compression), followed by stabilisation of pulmonary hypertension and surgical reduction with repair of the diaphragmatic defect (primary suture or prosthetic patch) once the neonate is stable.
- ▶ **Applied anatomy of the long phrenic course:** because the phrenic nerve is dragged down from the neck (C3–C5) with the descending diaphragm, diaphragmatic or subphrenic (e.g., gallbladder, subphrenic abscess) irritation is classically **referred to the C4 dermatome — the tip of the shoulder**.
- ▶ **Radiological correlate:** a plain chest/abdominal radiograph in CDH characteristically shows bowel loops (with a paucity of gas in the abdomen) in the affected hemithorax with contralateral mediastinal shift — a key image for the exam.

## High-yield exam pointers

- ▶ Diaphragm develops from **four** components: septum transversum, paired pleuroperitoneal membranes, dorsal mesentery of oesophagus, and body-wall mesoderm.
- ▶ **Bochdalek's hernia** = postero-lateral, commonest (85–90%), left-sided because the right pleuroperitoneal canal closes first.
- ▶ **Morgagni's hernia** = anterior/retrosternal, through the sternocostal hiatus, rare (1–2%).
- ▶ **Eventration ≠ hernia** — the diaphragm is intact but thinned/membranous, not truly defective.
- ▶ Congenital hiatus hernia is due to an abnormally large oesophageal hiatus — distinct from the acquired sliding hiatus hernia of adults.
- ▶ Chief cause of neonatal death in CDH = **pulmonary hypoplasia and pulmonary hypertension**, not the hernia per se.
- ▶ Candidate gene region for CDH: **chromosome 15q26**; associations with trisomy 13 and 18.
- ▶ Diaphragm's motor (and central) sensory supply = **phrenic nerve (C3, 4, 5)**; peripheral rim receives sensory supply only from lower intercostal nerves — the embryological basis of shoulder-tip referred pain.
- ▶ Antenatal ultrasound can detect CDH from about 18 weeks of gestation.



**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Moore's The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh Textbook of Clinical Embryology; IB Singh Human Embryology (CBME 2021); Sontakke Textbook of Human Embryology.



## Alpha foetoproteins

*Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Alpha-fetoprotein (AFP) is the major serum glycoprotein of the fetus, structurally and functionally related to albumin, with which it shares a common cell lineage of synthesis. It is produced sequentially by the secondary yolk sac, the fetal liver and, to a lesser extent, the fetal gut, and it diffuses into the amniotic fluid and, via the placenta, into the maternal circulation. Because its concentration rises sharply whenever the fetal serum is exposed directly to amniotic fluid — as happens through an open neural tube defect or a ventral body-wall defect — and falls in certain chromosomal trisomies, AFP assay (in amniotic fluid as AFAFP or in maternal serum as MSAFP) is a cornerstone biochemical screening test in antenatal care. It is therefore a favourite embryology short-essay linking developmental biology with applied obstetric screening.

### 1. Molecular nature and biochemistry

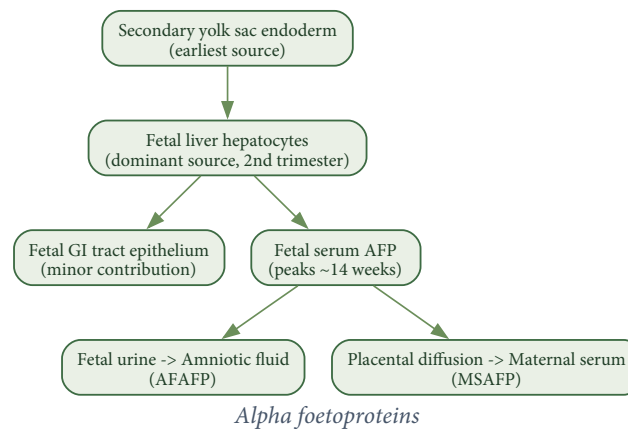
- ▶ AFP is a single-chain fetal **glycoprotein**.
- ▶ It belongs to the same family of serum proteins as **albumin**: yolk-sac epithelium and fetal hepatocytes synthesize AFP together with albumin, **α1-antitrypsin**, **pre-albumin** and **transferrin** — i.e. AFP and albumin share a common secretory lineage and largely overlapping developmental regulation.
- ▶ At the molecular level, hepatic induction of the ventral foregut endoderm (by BMP and FGF signals from the cardiogenic mesoderm/septum transversum) switches on the hepatocyte gene programme, of which **albumin and AFP are the classical co-expressed markers**; the same signals repress the alternative pancreatic fate (Pdx1 pathway) in adjacent endoderm.
- ▶ Because of this shared ancestry, AFP is often loosely described as the **fetal counterpart of albumin**.

### 2. Embryological source and developmental time-course

- ▶ **Secondary (definitive) yolk sac** — the endodermally-derived epithelium lining the yolk-sac cavity is the earliest site of AFP synthesis; the same cells synthesize AFP, albumin, α1-antitrypsin, pre-albumin and transferrin in common with the fetal liver.
- ▶ **Fetal liver** — hepatocytes become the dominant site of AFP production from early organogenesis and remain so through the second trimester, once the liver bud (hepatic diverticulum from the foregut endoderm) has differentiated.
- ▶ **Fetal gastrointestinal tract epithelium** contributes a smaller, additional share of synthesis, particularly by the second trimester.



- ▶ As the yolk sac regresses, hepatic synthesis progressively takes over as the major source — a graded "yolk sac → liver → gut" handover that is a classic teaching point linking extra-embryonic and intra-embryonic development.



### 3. Physiological functions

- ▶ Serves as the principal **fetal plasma protein**, analogous to the role albumin plays in the adult, contributing to fetal plasma oncotic pressure.
- ▶ Acts as a **carrier/binding protein**, in keeping with its albumin-like structure.
- ▶ Synthesis is essentially confined to the embryonic/extra-embryonic compartments; only trace amounts normally reach the maternal circulation, so a disproportionate rise signals a breach in the normal fetal-amniotic barrier.

### 4. Kinetics — fetal, amniotic and maternal AFP levels across gestation

- ▶ **Fetal serum AFP** rises through early gestation and **peaks at approximately 14 weeks**, thereafter declining.
- ▶ **Amniotic fluid AFP (AFAFP)** reflects fetal urinary excretion and diffusion, and is compared against gestational-age-specific normal ranges.
- ▶ **Maternal serum AFP (MSAFP)**, which reaches the maternal blood through the placenta and amniotic membranes, **increases through the second trimester and then declines steadily after about 30 weeks**.
- ▶ This differing fetal-versus-maternal time-course underlies the timing of screening tests described below.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Sketch a labelled line graph — x-axis "Gestational age (weeks)" from 8 to 40, y-axis "AFP concentration (relative units)". Draw two curves: (i) **Fetal serum AFP** — rising steeply from early gestation to a peak at ~14 weeks, then falling; (ii) **Maternal serum AFP (MSAFP)** — low early, rising through the second trimester, and declining after ~30 weeks. Shade a vertical band at 15–20 weeks (optimal 16–18 weeks) and label it "screening window for MSAFP/amniocentesis".

**5. Antenatal diagnostic applications**

| Test                       | Sample                           | Timing                                             | Purpose                                                                                                                                            |
|----------------------------|----------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| MSAFP (maternal serum AFP) | Maternal venous blood            | ~16 weeks (part of 2nd-trimester quadruple screen) | Non-invasive screen for open neural tube defects and, when combined with hCG, unconjugated estriol (uE3) and inhibin A, for trisomy 21/18          |
| AFAFP (amniotic fluid AFP) | Amniotic fluid via amniocentesis | 15–20 weeks (typically 16–18 weeks)                | Confirmatory/definitive test for open NTD in high-risk pregnancies; combined with amniotic fluid acetylcholinesterase assay to sharpen specificity |
| Quadruple screen           | Maternal serum                   | 2nd trimester                                      | hCG, MSAFP, uE3 and inhibin A together — all four analytes are depressed in trisomies except hCG, which is raised                                  |
| Detailed ultrasonography   | —                                | 18–19 weeks                                        | Used alongside AFAFP; together identifies ~99% of open spina bifida and virtually all cases of anencephaly                                         |

- ▶ AFP is measured by a simple, inexpensive **immunoassay**, applicable to any amniotic fluid or serum sample regardless of the indication for testing.
- ▶ Screening (MSAFP) is a triage step; a positive result is followed by detailed ultrasonography and, if needed, amniocentesis for AFAFP and karyotyping/chromosomal microarray.
- ▶ MSAFP screening has retained its place even alongside newer non-invasive prenatal screening (cell-free DNA) methods, because NTD detection specifically still depends on AFP measurement.

## 6. Causes of altered AFP concentration

| Elevated AFP (amniotic fluid / maternal serum)                                               | Decreased AFP (maternal serum)          |
|----------------------------------------------------------------------------------------------|-----------------------------------------|
| Open neural tube defects — spina bifida, anencephaly                                         | Down syndrome (trisomy 21)              |
| Ventral wall defects — omphalocele, gastroschisis                                            | Trisomy 18                              |
| Bladder/cloacal exstrophy                                                                    | Triploidy                               |
| Intestinal atresia / GI obstruction                                                          | Sex-chromosome abnormalities            |
| Congenital skin defects, pilonidal cysts                                                     | Gestational age younger than calculated |
| Sacroccygeal teratoma, cystic hygroma                                                        | Increased maternal weight               |
| Renal anomalies — polycystic/absent kidney, congenital nephrosis, urinary obstruction        |                                         |
| Amniotic band syndrome                                                                       |                                         |
| Fetal death, fetal blood contamination of sample                                             |                                         |
| Multiple gestation, oligohydramnios, low birth weight, gestational age older than calculated |                                         |

## Applied / Clinical anatomy

- ▶ **Neural tube defects:** an open spina bifida or anencephaly leaves fetal cerebrospinal fluid/serum in direct contact with amniotic fluid through the exposed neural placode or defective cranial vault, allowing AFP (and acetylcholinesterase) to leak into amniotic fluid in excess — the anatomical basis for the raised-AFP screening principle.
- ▶ **Ventral body-wall defects** (omphalocele, gastroschisis): herniated bowel or viscera lack the normal peritoneal/skin covering, so fetal serum proteins leach directly into amniotic fluid, again raising AFP — mechanistically parallel to the neural tube mechanism.
- ▶ **Down syndrome and trisomy 18:** mechanism of the low MSAFP is less anatomical and more placental/physiological (altered placental and fetal protein handling), but the depression is reproducible enough to be diagnostically useful when combined with hCG, uE3 and inhibin A (quadruple screen) or with nuchal translucency-based first-trimester screening.
- ▶ **Multiple gestation** raises MSAFP simply by summation of AFP contributed by more than one fetus — a pitfall the sonographer/embryologist must correct for before interpreting a "positive" screen.
- ▶ AFP is also of general medical relevance as an **oncofetal protein**: it is normally almost undetectable in adult serum but reappears in yolk-sac (endodermal sinus) germ-cell tumours and in hepatocellular carcinoma, reflecting re-expression of the same yolk-sac/hepatocyte developmental programme — a useful cross-link for the PG candidate between embryology and pathology.

- ▶ Practical antenatal work-up sequence: MSAFP (with hCG/uE3/inhibin A) at ~16 weeks → if abnormal, detailed ultrasonography at 18–19 weeks → amniocentesis for AFAFP and karyotype if ultrasonography is inconclusive.

## High-yield exam pointers

- ▶ AFP = fetal serum **glycoprotein**, structurally/functionally analogous to **albumin**; both are co-expressed hepatocyte/yolk-sac markers.
- ▶ Sequential source: **secondary yolk sac** → **fetal liver (dominant)** → **fetal gut (minor)**.
- ▶ Fetal serum AFP peaks at ~14 weeks; MSAFP rises through the 2nd trimester and declines after ~30 weeks.
- ▶ Screening window: MSAFP/amniocentesis at 15–20 weeks (optimal 16–18 weeks); ultrasonography confirmatory at 18–19 weeks.
- ▶ Raised in open neural tube defects, omphalocele/gastroschisis, other ventral wall/GI/renal defects, multiple gestation.
- ▶ Lowered in Down syndrome (trisomy 21) and trisomy 18.
- ▶ Quadruple screen = hCG + MSAFP + uE3 + inhibin A (all depressed in trisomies except hCG, which rises).
- ▶ Amniotic fluid **acetylcholinesterase** assayed alongside AFP increases specificity for open NTDs.
- ▶ AFP assay method: simple **immunoassay**; combined with USG, detects ~99% of open spina bifida and nearly all anencephaly.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Thompson & Thompson — Genetics in Medicine 8e; Gangane — Human Genetics 5e; Brijesh Kumar — Embryology Text & Atlas.



## Anencephaly

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Anencephaly (synonyms: meroencephaly, meroanencephaly, cranioschisis) is a lethal neural tube defect in which the cranial vault (calvaria) is completely or largely absent (**acrania**) and the underlying brain, rather than being wholly absent, is reduced to a degenerated, spongy, vascular mass exposed to the amniotic fluid. It results from failure of closure of the **rostral (cranial) neuropore** during the fourth week of intrauterine life. It is the most common serious congenital anomaly of the central nervous system encountered in stillborn fetuses and is uniformly incompatible with life.

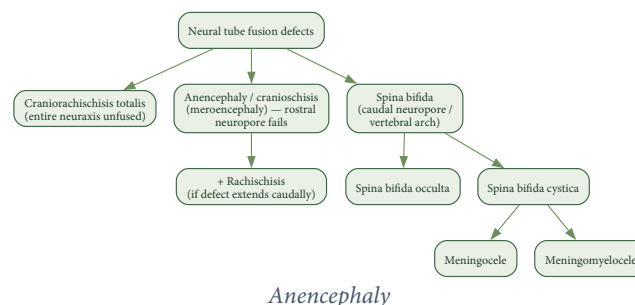
### 1. Embryological basis — neurulation and neuropore closure

- ▶ Neural plate → neural folds → neural groove → neural tube: primary neurulation occurs through the 3rd–4th week.

- Fusion of the neural folds begins at the level of the future cervical cord (about the 4th somite) and proceeds simultaneously craniad and caudad, leaving two transient openings continuous with the amniotic cavity: the **rostral neuropore** and the **caudal neuropore**.
- **Multiple closure-site theory** (Moore, Sadler) — up to five discrete sites of fusion initiation are proposed along the neuraxis:
  - Failure of site 1 → spina bifida cystica.
  - Failure of site 2 → **meroencephaly (anencephaly)**.
  - Failure of sites 1, 2 and 4 together → craniorachischisis.
  - Site 3 non-fusion is rare.
- Rostral neuropore closes at the **18–20 somite stage** (≈ **day 25**); caudal neuropore closes ≈ **3 days later** (**day 27–28**). Closure of each neuropore coincides with establishment of a vascular supply to the neural tube wall.
- Anencephaly follows directly from failure of rostral neuropore closure at this stage — the still-open forebrain region remains exposed to amniotic fluid before the brain vesicles fully differentiate.
- Gray's Anatomy notes that anencephalic fetuses additionally show disturbed shape, position and ossification of the **basichondrocranium** and an abnormal course of the intracranial notochord — i.e., the defect is not simply a failure of dorsal fusion.

## 2. Classification of neural tube fusion defects

| Defect                                      | Level of failure                         | Essential feature                                                     |
|---------------------------------------------|------------------------------------------|-----------------------------------------------------------------------|
| Craniorachischisis totalis                  | Entire neuraxis                          | Neural tube unfused dorsally from brain to sacrum                     |
| Cranioschisis / anencephaly (meroencephaly) | Rostral neuropore (cranial)              | Spinal cord closes normally; brain and calvaria fail to fuse dorsally |
| Spina bifida (occulta / cystica)            | Caudal neuropore and/or vertebral arches | Local non-fusion of spinal neural tube and/or vertebral laminae       |



- **Exencephaly** → **anencephaly sequence**: initially the malformed brain is exposed/extruding through the calvarial defect (exencephaly); mechanical trauma and prolonged exposure to amniotic fluid cause progressive necrosis, converting it into the degenerated vascular mass seen at term. Hence "anencephaly" is technically a misnomer — brain tissue (usually hindbrain

remnants) is rarely completely absent — and Moore's *The Developing Human* prefers the term **meroencephaly**.

### 3. Gross morphological features

□ Fig 13.3 — Neural tube defect "anencephaly". (Gangane — Human Genetics — 5e, p.228)

- ▶ **Acrania** — complete or partial absence of the neurocranium/vault of the skull (a constant finding).
- ▶ Brain reduced to a spongy, vascular, degenerated mass composed mostly of hindbrain remnants; the forebrain, midbrain and most of the hindbrain and calvaria are absent.
- ▶ Characteristic facies — prominent, bulging eyes and a short/absent neck, giving the appearance of the chin being continuous with the chest.
- ▶ Spinal cord may be open in the cervical region when craniorachischisis co-exists.
- ▶ Trunk and limbs are otherwise normally formed.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

**A. Neurulation — closure of the neural tube (dorsal view, ~day 24–26)** Labels: neural fold; neural groove; somites (numbered); site of initial fusion ( $\approx$ 4th somite level); direction of closure (arrows — cranial and caudal); rostral (cranial) neuropore (open, continuous with amniotic cavity); caudal neuropore (open, continuous with amniotic cavity); cut edge of amnion.

**B. Gross appearance of an anencephalic fetus (lateral view)** Labels: absent cranial vault (acrania); degenerated vascular brain remnant exposed on the skull base; bulging/prominent eyes; short/absent neck — chin continuous with chest; normally formed trunk and limbs;  $\pm$  open cervical spinal cord (if craniorachischisis).

### 5. Associated findings

- ▶ **Polyhydramnios** — a near-constant association; the absent fetal swallowing reflex (loss of brain/brainstem control of deglutition) prevents normal absorption of amniotic fluid through the fetal gut, so fluid accumulates to about **1500–2000 mL** (against  $\sim$ 500–1000 mL at term normally).
- ▶ **Rachischisis** — co-existing open spinal defect in severe (craniorachischisis) cases.
- ▶ Facial clefting (cleft lip/palate) has been reported in association in some cases.
- ▶ Because of the destroyed cranial contour, standard fetal cranial biometry (e.g., biparietal diameter, head circumference) cannot be obtained.

### 6. Etiology, epidemiology and genetics

- ▶ **Multifactorial inheritance** (polygenic + environmental, threshold model), as with other common isolated malformations; overall population incidence of neural tube defects is quoted as **2–10 per 1000 births** (Thompson & Thompson).
- ▶ Anencephaly specifically is quoted as  **$\approx$ 1 per 1000 births** (Moore) to  **$\approx$ 1 per 5000 births** (Langman), with marked geographic variation — as high as **1 in 200 births** in parts of northern China.

- ▶ **Sex ratio** — anencephaly (meroencephaly) is distinctly more common in females, **2–4 times** that in males.
- ▶ About **90% of infants** born with a neural tube defect have **no family history** of the disorder — the rationale for universal (rather than only "high-risk") maternal screening.
- ▶ Risk factors: maternal **folate deficiency**; maternal **hyperthermia** (febrile illness, sauna/hot-tub exposure).
- ▶ Folic acid fortification of flour (USA, 1998) reduced the birth prevalence of neural tube defects by **≈25%** (to about 1 in 1500 births) — direct evidence for the preventive role of periconceptual folate.
- ▶ Emerging evidence links some neural tube closure defects to disorders of **primary cilium** structure/function (ciliopathies), which also disturb cortical development (Gray's Anatomy 41e).

## 7. Antenatal diagnosis

| Test / modality                                   | Finding in anencephaly                                                                                                               |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Maternal serum alpha-fetoprotein (AFP)            | Raised; screening performed at <b>16–18 weeks'</b> gestation                                                                         |
| Amniotic fluid AFP (transabdominal amniocentesis) | Raised — confirmatory                                                                                                                |
| Detailed obstetric ultrasonography                | Absence of the cranial vault visualised from the late first/early second trimester; definitive on the <b>18–20 week</b> anomaly scan |
| MRI                                               | Adjunct, typically at 20–22 weeks; gives especially clear delineation of the defect                                                  |
| Fetoscopy / radiography                           | Additional modalities demonstrating the absent calvaria and brain                                                                    |

- ▶ Elevated maternal serum AFP is **not specific** to neural tube defects — also seen in twin pregnancy and threatened/missed abortion — so a raised value is followed by ultrasonography ± amniocentesis for confirmation.

## Applied / Clinical anatomy

- ▶ **Prognosis** — uniformly fatal; affected infants are stillborn or survive only a few hours to days after birth.
- ▶ Once the diagnosis is confirmed antenatally, **termination of pregnancy** is advised/offered.
- ▶ **Prevention** — periconceptual folic acid supplementation (400 µg/day, before conception and through early pregnancy) reduces the risk of anencephaly and other neural tube defects; population-level food fortification has demonstrably lowered birth prevalence.
- ▶ **Screening policy** — maternal serum AFP at 16–18 weeks is recommended universally, since ~90% of affected pregnancies occur in families with no prior history; a positive screen is followed by detailed USG ± amniocentesis.
- ▶ Increasing use of 3-D ultrasonography now permits detection of anencephaly even earlier, in the late first/early second trimester, alongside other lethal anomalies for which termination may be offered.



## High-yield exam pointers

- ▶ Anencephaly = failure of closure of the **rostral (cranial) neuropore** during the 4th week.
- ▶ Rostral neuropore closes at the 18–20 somite stage (day 25); caudal neuropore  $\approx$  3 days later (day 27–28).
- ▶ Multiple-closure-site theory: failure of **site 2**  $\rightarrow$  meroencephaly/anencephaly; failure of sites 1+2+4  $\rightarrow$  craniorachischisis.
- ▶ More correctly termed **meroencephaly** — brain tissue (hindbrain remnants) is rarely completely absent.
- ▶ **Acrania is a constant feature**; may co-exist with rachischisis (craniorachischisis).
- ▶ Most common serious CNS defect in stillborn fetuses; 2–4 $\times$  more common in females; incidence ranges 1/1000–1/5000 births by population.
- ▶ **Polyhydramnios** results from absent fetal swallowing reflex.
- ▶ Diagnosis: raised maternal serum/amniotic-fluid **AFP** (16–18 weeks) + confirmatory detailed USG.
- ▶ Prevention: periconceptional **folic acid 400  $\mu$ g/day**; uniformly fatal once established.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Vishram Singh — Clinical Neuroanatomy 4e; IB Singh — Human Embryology (CBME 2021); Gangane — Human Genetics 5e; Thompson & Thompson — Genetics in Medicine 8e.



## Annular pancreas

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Annular pancreas is a rare congenital anomaly of pancreatic development in which a thin, flat band (collar) of otherwise histologically normal pancreatic tissue completely — or occasionally incompletely — encircles the second (descending) part of the duodenum, usually at or close to the level of the major duodenal papilla. It arises from an aberration in the migration of the normally bifid ventral pancreatic bud during the 4th–7th weeks of intrauterine life, so that its two limbs come to encircle the duodenum before fusing with the dorsal pancreatic bud, instead of fusing with each other first. It is of considerable applied importance because the encircling tissue may compress and obstruct the duodenum, presenting as neonatal (or, less often, adult) duodenal obstruction, and because — since true pancreatic ductules run within the ring — surgical treatment must bypass rather than divide the annulus.

### 1. Normal development of the pancreas — brief recap

- ▶ The pancreas develops from two **endodermal outgrowths of the caudal foregut** (at the foregut–midgut junction) — the **dorsal and ventral pancreatic buds** — appearing around the **4th week** of intrauterine life.

- ▶ The **dorsal pancreatic bud** arises first, from the dorsal wall of the duodenal foregut, growing directly into the **dorsal mesentery (dorsal mesoduodenum)**; it becomes the larger contribution to the gland — the antero-superior part of the head, plus the body and tail.
- ▶ The **ventral pancreatic bud** arises slightly later as an outgrowth of the **hepatic (bile) duct** itself, close to the developing liver and gallbladder, lying initially in the **ventral mesentery**; it is commonly **bifid** (two small lobes) — a recognised normal variant.
- ▶ With **differential growth of the duodenal wall**, the duodenum rotates to the right and becomes C-shaped; the ventral bud, carried together with the bile duct, is swept **dorsally** and comes to lie **posterior to (below) the dorsal bud**.
- ▶ By about the **7th week**, the two buds meet and **fuse**: the ventral bud contributes the **uncinate process** and the postero-inferior part of the head; the dorsal bud contributes the rest of the gland.
- ▶ Their duct systems anastomose: the **main pancreatic duct (of Wirsung)** = duct of the ventral bud + distal part of the duct of the dorsal bud, opening with the bile duct at the **major duodenal papilla**; the proximal part of the dorsal duct usually persists as the **accessory pancreatic duct (of Santorini)**, opening about 2 cm cranially at the **minor duodenal papilla**.
- ▶ Islets of Langerhans ( $\alpha$ ,  $\beta$ ,  $\delta$ , PP cells) differentiate from the ductal epithelium; insulin secretion begins by about the 10th week.

## 2. Definition, incidence and gross morphology of the anomaly

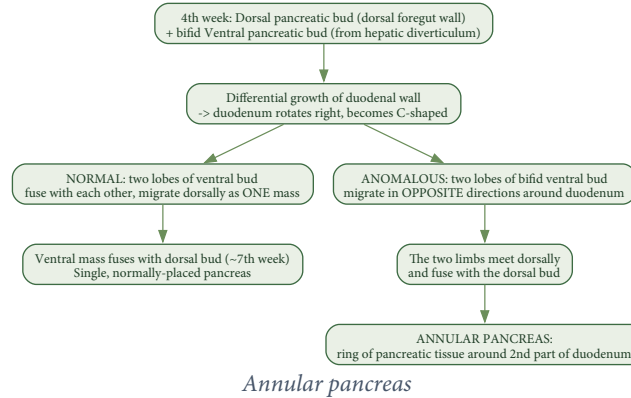
- ▶ **Annular pancreas**: a thin, flat collar of normal pancreatic parenchyma that surrounds the **second (descending) part of the duodenum**, typically at the level of the major duodenal papilla.
- ▶ **Incidence**: rare — about 1 in 12,000–15,000 live births.
- ▶ **Sex**: reported to be **more common in females**.
- ▶ The ring may be **complete** (a closed collar, the classical form) or, less often, **incomplete** (only a partial arc of tissue around the duodenal wall).
- ▶ The tissue forming the ring is **ordinary, mature pancreatic parenchyma** — it is not ectopic or neoplastic tissue, merely a normal gland that has come to lie in an abnormal (encircling) position.

## 3. Embryological basis (pathogenesis)

- ▶ The best-accepted mechanism is based on the **bifid ventral pancreatic bud** — normally, both of its lobes migrate together dorsally with the bile duct and fuse with each other before joining the dorsal bud.
- ▶ In annular pancreas, the **two lobes of the bifid ventral bud migrate in opposite directions around the duodenum** — one following the normal course toward the dorsal bud, the other migrating in the reverse direction — so that the two limbs meet on the far (dorsal) side of the duodenum and **encircle it like a collar** before fusing with the dorsal bud.
- ▶ **Gray's Anatomy** expresses this more concisely: failure of the ventral pancreatic diverticulum to migrate normally results in an "anular" pancreas that constricts the duodenum locally.
- ▶ **Molecular correlate (animal data)**: disturbed **Hedgehog signalling** is implicated — loss of **Indian hedgehog (Ihh)** causes ectopic branching of the ventral pancreatic bud that wraps around the duodenum, and loss of **Sonic hedgehog (Shh)** in some mouse strains also produces an

annular pancreas; Shh-mutant mice additionally show **duodenal stenosis and imperforate anus**, defects that are likewise associated with annular pancreas in humans.

- Because the ring incorporates genuine pancreatic ductules continuous with the main/accessory duct system, it **cannot safely be divided surgically** without risking a pancreatic fistula.



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 15.7 — Formation of annular pancreas. There may be two ventral pancreatic buds that fuse with dorsal pancreatic bud surrounding duodenum to form annular pancreas (Sontakke — Textbook of Human Embryology, p.155)

Reproduce a schematic transverse/oblique diagram at the level of the second part of the duodenum, labelling:

- **Stomach and second (descending) part of duodenum**, in situ
- **Dorsal pancreatic bud** — forming body, tail and antero-superior part of the head
- **Bifid ventral pancreatic bud** — right lobe and left lobe
- **Bile duct** opening into the duodenum
- Right lobe of ventral bud migrating along the **normal (dorsal) course**
- Left lobe of ventral bud migrating in the **opposite (anomalous) direction**
- The two limbs meeting on the dorsal aspect and fusing with the dorsal bud
- Final **ring of pancreatic tissue (annular pancreas)** completely encircling the second part of duodenum
- **Main pancreatic duct** and **accessory pancreatic duct** opening at the major and minor duodenal papillae respectively

## 4. Normal fusion vs annular pancreas — comparison

| Feature              | Normal pancreatic development                                             | Annular pancreas                                                                     |
|----------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Ventral bud lobes    | Bifid (two lobes) fuse with <b>each other first</b> , migrate as one mass | Two lobes migrate in <b>opposite directions</b> , fail to fuse with each other first |
| Path around duodenum | Ventral mass rotates dorsally, comes to lie posterior to the dorsal bud   | The two limbs pass around the duodenum in opposite directions and meet dorsally      |

| Feature              | Normal pancreatic development                                                                              | Annular pancreas                                                                  |
|----------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Relation to duodenum | Pancreas lies adjacent to (postero-superior to) the duodenum; does not encircle it                         | A ring/collar of tissue completely (or partly) encircles the 2nd part of duodenum |
| Duct elements        | Main duct (Wirsung) = ventral duct + distal dorsal duct; accessory duct (Santorini) = proximal dorsal duct | Same duct elements present, but ductules also traverse the encircling collar      |
| Clinical consequence | None — normal gland                                                                                        | May compress and obstruct the duodenum                                            |

## 5. Associated anomalies

- ▶ Down syndrome (trisomy 21)
- ▶ Intestinal malrotation
- ▶ Congenital cardiac defects
- ▶ Annular pancreas is classified as an **extrinsic** cause of duodenal obstruction; intrinsic causes (duodenal atresia, stenosis, a duodenal web) are distinct anomalies that may nonetheless **coexist** at the same level.
- ▶ Related but **distinct** pancreatic anomalies (important for differentiation, not to be confused with the annular pancreas mechanism above):
  - **Pancreas divisum** — failure of **fusion of the dorsal and ventral duct systems** (not of bud migration); occurs in roughly 9–10% of individuals; usually asymptomatic but can predispose to recurrent pancreatitis.
  - **Ectopic/accessory pancreatic tissue** — heterotopic pancreatic tissue in the wall of the stomach, duodenum, jejunum, Meckel's diverticulum, gallbladder or spleen.
  - **Inversion of the pancreatic duct** — an uncommon variant in which the main pancreatic duct is formed by the dorsal duct and opens at the minor papilla, while the ventral duct joins the bile duct and opens at the major papilla.

## Applied / Clinical anatomy

- ▶ **Presentation:** most often diagnosed in the **neonatal period** with vomiting (bilious or non-bilious depending on whether the obstruction lies distal or proximal to the ampulla) within the first hours to days of life, from partial or complete duodenal obstruction.
- ▶ **Antenatal clue:** **polyhydramnios**, because the fetus cannot adequately swallow and absorb amniotic fluid past the obstructed duodenum; this is often the finding that prompts antenatal ultrasound.
- ▶ **Imaging:** plain abdominal radiograph or ultrasound shows the classic "**double bubble**" sign — two gas/fluid-filled shadows corresponding to the distended stomach and the dilated proximal duodenum, proximal to the site of obstruction.
- ▶ **Delayed presentation:** an incomplete ring, or a lesser degree of obstruction, may remain silent for years and present later in childhood or adulthood with recurrent vomiting, epigastric pain,

peptic ulceration, or duodenal blockage precipitated by **inflammation (pancreatitis)** developing **within the annular tissue**.

- ▶ **Management:** surgical **bypass** of the obstructed duodenal segment, classically by **duodenojejunostomy**. The encircling pancreatic collar itself is **never incised or resected**, because pancreatic ductules run within it and division risks a pancreatic fistula and persistent obstruction from oedema/pancreatitis.
- ▶ **Differential diagnosis** of neonatal duodenal obstruction (an important applied-anatomy distinction, since the anatomical cause differs): intrinsic duodenal atresia/stenosis/web, malrotation with Ladd's bands, and annular pancreas.

## High-yield exam pointers

- ▶ Annular pancreas = a ring of **normal** pancreatic tissue encircling the **2nd (descending) part of duodenum**, at/near the major duodenal papilla.
- ▶ Mechanism: the **bifid ventral pancreatic bud** — its two limbs migrate in **opposite directions** around the duodenum before fusing with the dorsal bud (Gray's Anatomy: "failure of the ventral pancreatic diverticulum to migrate").
- ▶ Incidence  $\approx$  **1 in 12,000–15,000 births**; **more common in females**.
- ▶ Associated with **Down syndrome, intestinal malrotation, and cardiac defects**.
- ▶ Clinical picture: neonatal bilious/non-bilious vomiting; antenatal **polyhydramnios**; **"double bubble" sign** on imaging.
- ▶ Treatment = **bypass** (duodenojejunostomy) — the pancreatic ring is **never divided** (risk of pancreatic fistula, since ducts run within the collar).
- ▶ Differentiate from **pancreas divisum** (failure of *duct* fusion, not bud migration) and from **ectopic/accessory pancreatic tissue**.
- ▶ Molecular note: disturbed **Hedgehog (Shh/Ihh) signalling** implicated in animal models of annular pancreas.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology.



## Anomalies of placenta

*Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy*

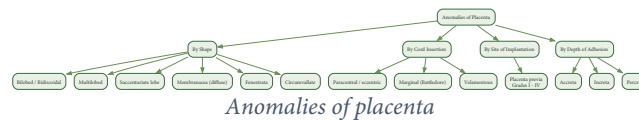
### Definition / Introduction

A normal placenta is a single, discoid, **haemochorial** organ formed by the chorion frondosum (fetal part) and decidua basalis (maternal part), attached to the **upper uterine segment** with the umbilical cord inserted **centrally** on its fetal surface. At term it measures **200–220 mm** in diameter and **~25 mm**

thick and weighs a mean of **470 g** (commonly rounded in teaching to 15–20 cm/500 g/3 cm). Placental anomalies are deviations from this norm and are conventionally grouped under four heads — **shape**, **site of attachment of the umbilical cord**, **site of implantation in the uterus**, and **depth of trophoblastic adhesion/invasion** — each with distinct developmental basis and obstetric significance, chiefly antepartum/postpartum haemorrhage.

## 1. Developmental basis of placental anomalies

- ▶ The chorionic villi initially cover the whole chorionic vesicle. From the **2nd month**, villi related to the **decidua capsularis** regress to form the smooth, avillous **chorion laeve**, while villi related to the **decidua basalis** proliferate to form the bushy **chorion frondosum** — the definitive placental site.
- ▶ **Failure of complete regression** of the chorion laeve villi at scattered points leaves isolated patches of functioning villi outside the main disc, connected to it only by membranous vessels — the basis of an **accessory/succenturiate lobe**.
- ▶ **Failure of regression of the entire villous ring** beyond the 2nd month leaves villi persisting all around the gestational sac, producing a thin, diffuse **placenta membranacea** instead of a compact disc.
- ▶ Abnormal, low implantation of the blastocyst near or over the internal os (instead of along the posterior/upper segment) produces **placenta previa**; because the lower segment develops a thinner decidua, it also predisposes to abnormally deep adhesion (**accreta spectrum**).
- ▶ Eccentric growth of the villous mass relative to the site of attachment of the body/connecting stalk explains **paracentral**, **marginal (battledore)** and **velamentous** cord insertions.



## 2. Anomalies of shape

| Type                                                         | Description                                                                                                                                   |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bilobed / bidiscoidal</b>                                 | Placenta consists of two nearly equal discs connected by a bridge of membranes carrying the vessels; cord often inserts between the two lobes |
| <b>Multilobular</b>                                          | Placenta consists of more than two lobes                                                                                                      |
| <b>Placenta succenturiata</b> (succenturiate/accessory lobe) | A small part of the placenta is separated from the main mass but remains connected to it through fetal blood vessels running in the membranes |
| <b>Placenta membranacea</b> (diffuse placenta)               | Chorionic villi persist all round the blastocyst instead of regressing, so the placenta is thin, diffuse and not disc-shaped                  |
| <b>Placenta fenestrata</b>                                   | A hole or opening is present in the placental disc (a cotyledon fails to develop)                                                             |

| Type                   | Description                                                                                                                                  |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Circumvallate placenta | The peripheral edge of the placenta is covered/overlapped by a circular fold of decidua, giving a raised, opaque ring set in from the margin |

### 3. Anomalies of umbilical cord insertion

| Type                           | Description                                                                                                                                                                         |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Normal                         | Cord inserted centrally on the fetal surface                                                                                                                                        |
| Paracentral / eccentric        | Cord inserted away from the centre but still on the placental disc                                                                                                                  |
| Marginal (Battledore) placenta | Cord attached at the very margin of the placenta, resembling the bat used in the medieval game of battledore and shuttlecock                                                        |
| Velamentous insertion          | Umbilical vessels leave the cord and run unsupported (without Wharton's jelly) between the amnion and chorion before spreading onto the placenta, which they reach only at its edge |

Distribution of the umbilical vessels over the chorionic plate is further described as **disperse** (dichotomous branching with progressive reduction in calibre), **magistral** (vessels retain a uniform calibre to the periphery) or **furcate** (the umbilical vessels divide before reaching the placental disc, leaving an unsupported segment vulnerable to injury).

□ Fig 77.47 — A battledore placenta showing the marginal insertion of the umbilical cord into the placenta (Gray's Anatomy — Standring — 41e, p.1807)

□ Fig 77.48 — Velamentous insertion of the umbilical cord, showing the cord inserting into the chorioamnion before its vessels reach the placental edge (Gray's Anatomy — Standring — 41e, p.1807)

### 4. Anomalies of site of implantation — placenta previa

Normally the blastocyst implants along the posterior/upper two-thirds of the body of the uterus. When implantation occurs close to the internal os so that the developed placenta lies wholly or partly in the lower uterine segment, the condition is called **placenta previa**, graded into four degrees:

| Grade | Feature                                                                                                                             |
|-------|-------------------------------------------------------------------------------------------------------------------------------------|
| I     | Attachment of the placenta does not extend up to the internal os (low-lying)                                                        |
| II    | Attachment extends up to the internal os but does not cover it (marginal)                                                           |
| III   | The placental edge covers the internal os, but with dilatation of the os at childbirth the placenta no longer occludes it (partial) |
| IV    | Placenta completely covers/bridges the internal os even when it is fully dilated ( <b>central placenta previa</b> )                 |



Grade IV previa is the most severe and is a major cause of painless antepartum haemorrhage and of obstructed labour, usually requiring delivery by caesarean section.

## 5. Anomalies of adhesion — the morbidly adherent placenta

| Type              | Depth of villous invasion                                                                                                                           |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Placenta accreta  | Chorionic villi are pathologically adherent directly to the myometrium (decidua basalis deficient), without invading its substance                  |
| Placenta increta  | Villi penetrate into the substance of the myometrium                                                                                                |
| Placenta percreta | Villi penetrate the full thickness of the myometrium, reaching or breaching the perimetrium (and occasionally adjacent viscera such as the bladder) |

Because these placentas fail to separate normally after delivery of the fetus, forcible removal causes severe, difficult-to-control postpartum haemorrhage; the risk is markedly increased when a previous caesarean scar coincides with a low-lying (previa) placenta.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Shape panel** — six labelled outline sketches side by side: normal discoid; bilobed/bidiscoidal (two discs + connecting membrane bridge with vessels); succenturiate (small satellite lobe joined to main disc by vessels running in the membrane); membranacea (thin villous layer covering the entire decidua); fenestrata (central gap in the villous disc); circumvallate (raised greyish ring of doubled amnion-chorion set in from the placental edge).
- ▶ **Cord-insertion panel** — fetal surface of placenta showing four insertion sites: central (normal), paracentral, marginal/battledore (at the rim), velamentous (vessels coursing in the membranes before reaching the disc — label "no Wharton's jelly, vulnerable to rupture").
- ▶ **Placenta previa panel** — sagittal section of a gravid uterus and cervix, four small diagrams labelled Grade I–IV, each showing the placenta's relation to the internal os and cervical canal.
- ▶ **Adhesion panel** — cross-section of the uterine wall (endometrium/decidua basalis → myometrium → perimetrium) with villi shown stopping at the decidua (accreta), invading the myometrium (increta), and breaching the perimetrium (percreta).

## Applied / Clinical anatomy

- ▶ **Antepartum haemorrhage:** placenta previa (all grades) and circumvallate placenta are important anatomical causes of painless/recurrent bleeding in the third trimester; diagnosis is by transvaginal ultrasonography.
- ▶ **Vasa previa:** when velamentous umbilical vessels cross the region of the internal os, they are vulnerable to tearing when the membranes rupture, causing rapid fetal exsanguination and fetal death — an obstetric emergency requiring elective caesarean section.

- ▶ **Retained accessory (succenturiate) lobe:** if a succenturiate lobe is left behind after delivery of the main placenta, it is a preventable cause of secondary postpartum haemorrhage; the placenta and membranes must always be inspected for a "missing" vessel running to a torn edge.
- ▶ **Placenta accreta spectrum (accreta/increta/percreta):** the commonest cause of massive, life-threatening postpartum haemorrhage requiring emergency (often peripartum) hysterectomy; strongly associated with placenta previa overlying a previous caesarean-section scar.
- ▶ **Circumvallate placenta:** associated with antepartum haemorrhage, intrauterine growth restriction and preterm labour.
- ▶ **Imaging correlate:** colour-flow Doppler ultrasonography is used antenatally to define the placental site, cord insertion, and any velamentous/vasa-previa vessels crossing the os.

### High-yield exam pointers

- ▶ Four broad groups: **shape, cord-insertion site, implantation site (previa), depth of adhesion (accreta spectrum).**
- ▶ Shape anomalies: **bilobed/bidiscoidal, multilobular, succenturiate, membranacea, fenestrata, circumvallate** — succenturiate and membranacea both arise from failure of chorion laeve villi to regress (focal vs complete).
- ▶ Cord-insertion anomalies: **paracentral** → **marginal (battledore)** → **velamentous**; velamentous vessels crossing the os = **vasa previa**.
- ▶ **Placenta previa** — 4 grades: I low-lying, II marginal, III partial (occludes only when os undilated), IV central/total.
- ▶ **Adhesion spectrum** — 3 grades by depth: accreta (myometrial surface), increta (into myometrium), percreta (through perimetrium).
- ▶ Normal placenta at term (Gray's 41e): diameter 200–220 mm, thickness ~25 mm, weight ~470 g; commonly taught as ~15–20 cm/500 g.
- ▶ Retained succenturiate lobe and the accreta spectrum are the two leading anatomical causes of postpartum haemorrhage; previa and vasa previa are the leading causes of antepartum haemorrhage.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; Moore The Developing Human 9e; Hamilton, Boyd & Mossman Human Embryology; Brijesh Kumar Embryology Text & Atlas — for the embedded plates, Gray's Anatomy (Standring) 41e, Fig 77.47–77.48.



# Foetus in foetu

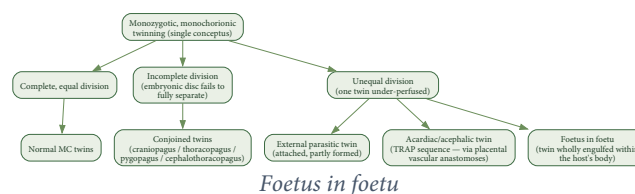
Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy

**Definition / Introduction** Foetus in foetu (FIF) is a rare congenital anomaly in which a **malformed, non-viable twin** becomes wholly enclosed within the body of its otherwise normal co-twin (the host or "autosite"), and continues to grow as a parasitic, vascular-pedicle-dependent mass — most often discovered as a retroperitoneal lump in infancy. It represents the most extreme point on the spectrum of **unequal monozygotic, monochorionic twinning**, and its chief practical importance for the anatomist/pathologist is distinguishing it from a far commoner lesion it can mimic radiologically and grossly — the **teratoma**.

## 1. Embryological basis / Pathogenesis

- ▶ FIF arises from a **single fertilised ovum (monozygotic, monochorionic, usually diamniotic) conceptus** in which the embryonic disc/axis divides **unequally** rather than completely, analogous to — but more extreme than — the division that produces conjoined or acardiac twins.
- ▶ Gray's Anatomy describes this shared mechanism: "*Late separation of twins from a single conceptus may result in conjoined twins; these may be equal or unequal, as in acardia,*" and unequal division of the embryonic axis or of its blood supply can produce an **acardiac monster**; FIF is regarded as an even more extreme unequal division in which the smaller, weaker twin is not merely attached externally but becomes **internalised/engulfed** within the larger host twin.
- ▶ The smaller twin (acardiac, lacking independent circulation) survives only because it remains attached to the host by a **vascular pedicle**, through which it continues to receive nourishment — allowing partial, disorganised growth of axial and limb structures while never achieving independent viability.
- ▶ The included twin comes to lie enclosed within a body cavity of the host — usually the **retroperitoneum** — where it can enlarge slowly over months to years, encased in its own membranous sac.

## 2. Classification — spectrum of monozygotic twinning anomalies



- ▶ **Conjoined twins**: equal but incomplete separation; classified by site/extent of fusion — **craniopagus** (heads), **thoracopagus** (thorax), **cephalothoracopagus** (head + thorax), **pygopagus** (sacral region); separable surgically only if no vital organs are shared.
- ▶ **Parasitic twin**: markedly asymmetric conjoining — a small, rudimentary twin, under-perfused, grows attached to (but external on) a well-formed co-twin.
- ▶ **Acardiac/acephalic twin (TRAP sequence)**: an extreme monochorionic vascular anomaly (~1 in 35,000 births) in which a "pump twin" perfuses a twin lacking a functioning heart via placental arterio-arterial anastomoses; the acardiac twin cannot survive independently.

- **Foetus in foetu**: the parasitic twin is not merely attached but **totally enclosed** within the host's body — the rarest and most extreme variant.

### 3. Common sites

| Site                                                                                        | Frequency | Notes                                               |
|---------------------------------------------------------------------------------------------|-----------|-----------------------------------------------------|
| <b>Retroperitoneum</b> (near upper pole of kidney/adrenal, or in relation to the mesentery) | Commonest | Presents as a slowly enlarging abdominal mass       |
| Cranial cavity (intracranial)                                                               | Rare      | May mimic an intracranial tumour                    |
| Oral cavity / oropharynx                                                                    | Rare      | May cause airway or feeding difficulty              |
| Sacrococcygeal region                                                                       | Rare      | Must be differentiated from sacrococcygeal teratoma |
| Scrotum                                                                                     | Rare      | Presents as a scrotal/inguinal mass                 |

### 4. Clinical features and investigations

- Almost all cases present **within the first year of life** (occasionally later) as a **slowly growing, otherwise asymptomatic mass** at one of the sites above; the host twin (autosite) is itself healthy and structurally normal.
- On examination the mass may be firm/irregular; larger masses can cause pressure symptoms (abdominal distension, feeding or respiratory difficulty depending on site).
- **Imaging is diagnostic**: plain radiographs may show recognisable **vertebral/limb bony elements** within the mass — the key diagnostic clue; ultrasonography/CT/MRI confirm an **encapsulated mass containing skeletal elements and soft-tissue organisation**, supplied by a **discrete vascular pedicle** arising from the host rather than an independent circulation.
- Serum tumour markers (e.g. alpha-fetoprotein) are typically **not markedly elevated**, unlike many teratomas, and help support the diagnosis pre-operatively.

### 5. Foetus in foetu vs teratoma — key differentiating points

| Feature               | Foetus in foetu                                                                                                                                          | Teratoma                                                                                                                                                     |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Origin                | A highly differentiated <b>included monozygotic twin</b> (unequal twinning defect)                                                                       | A <b>germ-cell tumour</b> — totipotent/primordial germ cells or primitive-streak remnants persisting after normal regression                                 |
| Internal organisation | An <b>organised vertebral axis (spine)</b> , with limb buds and other organs arranged around it in a body-like pattern (Willis' criterion for diagnosis) | <b>Disorganised, haphazard mixture</b> of tissue from all three germ layers (bone, tooth, hair, gut epithelium, neural tissue) with <b>no vertebral axis</b> |

| Feature             | Foetus in foetu                                                                                                              | Teratoma                                                                                   |
|---------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Covering/capsule    | Enclosed in its own <b>limiting membrane/sac</b> , separate from host tissue, with a distinct vascular pedicle from the host | Arises <b>within host tissue</b> , may show local infiltration; no separate membranous sac |
| Common sites        | Retroperitoneum > cranial > oral > sacrococcygeal > scrotal                                                                  | Sacrococcygeal region (commonest overall), gonads, mediastinum                             |
| Malignant potential | Rare                                                                                                                         | Can be malignant, particularly sacrococcygeal teratoma if not excised early in infancy     |
| Treatment           | Complete surgical excision — curative                                                                                        | Complete surgical excision; malignant elements need oncological follow-up                  |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Outline of the **host (autosite) twin's trunk**, normal external form.
- ▶ Within the **retroperitoneum** (most testable site), draw the **encapsulating sac** of the included twin.
- ▶ Inside the sac, show a rudimentary **vertebral column/axial skeleton** with one or two **limb buds** arranged around it, and a **vascular pedicle** connecting the mass to the host's aorta/mesenteric vessels (labelled "nourishment from host circulation").
- ▶ Beside it, a small comparison box for **teratoma**: an unencapsulated mass with scattered, disorganised elements (tooth, hair, bone spicules) and **no vertebral axis** — to visually anchor the differentiating point.

### Applied / Clinical anatomy

- ▶ FIF is a **surgical diagnosis confirmed on imaging** — the presence of an organised vertebral axis with limb elements, seen on plain film/CT/MRI, distinguishes it pre-operatively from a teratoma at the same site.
- ▶ **Complete surgical excision, including the vascular pedicle**, is curative; recurrence is rare when excision is complete.
- ▶ Because FIF and sacrococcygeal/retroperitoneal teratoma can coexist as differentials at overlapping sites (sacrococcygeal, retroperitoneal), careful **gross and histopathological examination for an organised vertebral axis** is essential to confirm the diagnosis and guide follow-up (teratomas, unlike FIF, carry a real risk of malignant change if incompletely excised).
- ▶ Radiologically, FIF may initially be mistaken for a calcified teratoma, neuroblastoma, or other retroperitoneal mass in an infant — recognising organised skeletal parts within a discrete capsule is the key differentiator.

## High-yield exam pointers

- ▶ FIF = an **included, wholly internalised parasitic twin** — the extreme end of the unequal monozygotic-twinning spectrum (conjoined twin → external parasitic twin → acardiac/TRAP twin → foetus in foetu).
- ▶ The included twin is nourished via a **vascular pedicle from the host**, not an independent circulation.
- ▶ **Retroperitoneum** is the classic and commonest site; also cranial, oral, sacrococcygeal, scrotal.
- ▶ **Willis' criterion**: presence of an **organised vertebral axis with limb buds/organs** around it — this is what separates FIF from a teratoma.
- ▶ Teratoma = disorganised germ-layer-derived tissue from **primordial germ cells/primitive-streak remnants**, no vertebral axis, higher malignant potential.
- ▶ Diagnosis is confirmed by **imaging showing recognisable skeletal elements** within an encapsulated mass.
- ▶ Treatment for both FIF and teratoma is **complete surgical excision**; FIF has an excellent prognosis after complete removal.
- ▶ Related but distinct monochorionic-twinning anomaly to know for comparison: **TRAP sequence/acardiac twin** — a pump twin perfusing a heart-less co-twin via placental vascular anastomoses.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Textbook of Anatomy Vol 3 (Chapter: Twinning — Monozygotic and Dizygotic Twins); Hamilton, Boyd & Mossman — Human Embryology; IB Singh — Human Embryology (CBME 2021); Larsen — Human Embryology 6e (TRAP sequence/acardiac twinning). **Coverage note:** "Foetus in foetu" as a named entity is only briefly mentioned in the sampled corpus (a one-line definition each in Vishram Singh's Clinical Embryology and IB Singh's Anatomy Vol 3, plus historical case citations in Hamilton, Boyd & Mossman's reference list). The embryological mechanism (unequal monozygotic twinning, the acardia/TRAP spectrum) is corpus-grounded via Gray's Anatomy and Larsen; the differentiating criterion from teratoma (organised vertebral axis — Willis' criterion) and standard clinical/imaging/treatment details are drawn from universally-accepted embryology-pathology teaching, since this rare topic is not covered in depth by any single textbook in the library.



## Mode of action of teratogenic agents

Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy

**Definition / Introduction** Teratology (Gr. *teratos* = monster) is the study of the causation, mechanisms, and patterns of abnormal prenatal development. A **teratogen** is any agent — genetic, infectious, physical, chemical, or metabolic — that can produce a structural or functional birth defect, or increase the incidence of a defect in the population, when the conceptus is exposed to it. Major structural anomalies occur in about 3% of liveborn infants (minor anomalies in a further 15%) and birth defects account for roughly 25% of infant deaths. Of all congenital malformations, about 15% are purely environmental, 30% purely genetic, and 55% arise from gene–teratogen (multifactorial) interaction. Teratogens act through defined principles, defined critical periods, and definable cellular/molecular mechanisms, which form the basis of this answer.

### 1. Principles governing teratogenic action

| Principle                              | Explanation                                                                                                                                                                                                                                                                  |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Genotype of the conceptus (and mother) | Susceptibility to a given teratogen depends on the genetic constitution of the embryo; the maternal genome also matters for drug metabolism, placental transfer, and resistance to infection. Two individuals exposed to an identical dose may show very different outcomes. |
| Stage of development at exposure       | Susceptibility varies with the developmental stage — governed by "critical periods" of each organ system (see below).                                                                                                                                                        |
| Dose and duration of exposure          | Manifestations depend on how much of the agent reaches the conceptus and for how long; a genuine human teratogen must show a dose–response relationship (greater exposure → more severe phenotype).                                                                          |
| Specific mechanism of action           | Each teratogen acts in a defined way (mechanism) on developing cells/tissues to initiate abnormal embryogenesis (pathogenesis) — inhibition of a specific biochemical/molecular process, followed by a cellular response such as cell death or altered proliferation.        |
| Manifestations of abnormal development | The four possible outcomes of teratogenic insult are: death of the conceptus, structural malformation, growth retardation, and functional/behavioural disorder.                                                                                                              |

### 2. Critical periods of susceptibility

Susceptibility is not uniform through gestation; each organ/tissue has its own "window" of maximum vulnerability, which usually precedes its visible morphological differentiation by a few days because biochemical differentiation always precedes structural differentiation.

- **Pre-differentiation period (fertilisation to end of 2nd week):** the "all-or-none" law — the teratogen either kills the embryo (early spontaneous abortion) or the blastocyst's regenerative



capacity compensates fully. Exception: axis formation (cranio-caudal, left–right) begins in week 1, so disruption here can still cause a wide range of defects — no stage is entirely "safe."

- ▶ **Embryonic period / organogenesis (3rd–8th week):** the period of **peak susceptibility** — cell division, differentiation, and morphogenesis are maximal, and most major structural malformations are induced here. Several organs differentiate together, so one teratogen can strike several systems at once (rubella → eye + ear + heart defects together; thalidomide → limb + cardiac + renal defects together). The exact defect also depends on *when within* the window exposure occurs — thalidomide early in the limb critical period (day 24–36) causes severe meromelia/amelia, later exposure only mild radius/ulna hypoplasia.
- ▶ **Fetal period (9th week to term):** gross structural defects become uncommon (organs have passed their critical period), but growth restriction and **functional disturbance** persist — especially of the brain, which keeps differentiating to and beyond birth, so late exposure can still cause intellectual disability. Enamel remains vulnerable to tetracyclines to age 16 years; the skeleton's critical period extends into childhood.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A horizontal timeline of gestation (weeks 1–38) in three labelled blocks: (1) weeks 1–2, "pre-differentiation — all-or-none; exception = axis-formation defects"; (2) weeks 3–8, "embryonic period/organogenesis — peak sensitivity, most structural defects," with small tick-marks for organ-specific windows (heart 3–6 wk, limbs 24–36 days, CNS 3–16 wk, palate to 7th week); (3) weeks 9–38, "fetal period — growth retardation and functional/CNS disturbance rather than gross malformation." Mark a dashed line at "first prenatal visit (~8 wk)" to show it falls after the critical period for most structural defects — the rationale for pre-conceptional counselling.

### 3. Cellular and molecular mechanisms of teratogenic action

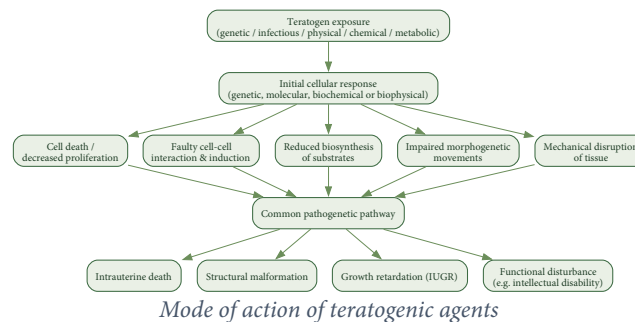
A teratogen's initial action on the conceptus may be genetic, molecular, biochemical, or biophysical in nature. Whatever the trigger, it is believed to funnel into a limited set of **cellular pathogenetic mechanisms**, which then converge on a common final pathway to produce the defect:

- ▶ **Cell death** — excessive cell death (beyond the normal programmed apoptosis of morphogenesis) removes cell populations needed to build a structure.
- ▶ **Decreased cell proliferation / reduced biosynthesis of substrates** — slowing of mitotic rate or of the synthesis of substrates (e.g., matrix components, enzymes) needed for normal growth of a primordium.
- ▶ **Faulty cellular interaction and induction** — failure of the normal inductive signalling between adjacent tissues (e.g., epithelial–mesenchymal interactions) that is essential for morphogenesis.
- ▶ **Impaired morphogenetic movements** — abnormal cell migration or folding movements (e.g., neural crest cell migration, palatal shelf elevation) that are essential to shape a structure.
- ▶ **Mechanical disruption of already-formed tissue** — as in amniotic band disruptions.

These cellular lesions converge on one of four end results — intrauterine death, structural malformation, growth retardation, or functional disturbance. At the molecular level this is increasingly explained by **disruption of the gene-expression cascades that pattern the embryo**: retinoic acid

(vitamin A) alters the normal domain of homeobox gene expression and thereby disrupts morphogenesis — the basis of the severe teratogenicity of its analogue isotretinoin. A worked example is **alcohol**, which recent evidence suggests acts partly by **down-regulating Sonic Hedgehog (SHH) signalling** (interfering with SHH binding to cholesterol), causing abnormal forebrain development and neural-crest cell death — producing the craniofacial and CNS features of fetal alcohol syndrome. **Ionizing radiation** acts more directly, killing rapidly proliferating cells and acting as a germ-cell mutagen. Even the precise mechanism of the prototype human teratogen, **thalidomide**, remains unsettled after six decades — over 20 molecular hypotheses have been proposed — showing that epidemiological proof of teratogenicity can precede a full mechanistic explanation by decades.

### Graphviz — mechanism cascade



## 4. Classes of teratogenic agents and their characteristic defects

| Category          | Representative agent(s) | Characteristic malformations                                                                                                   |
|-------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Infections        | Rubella virus           | Cataract, glaucoma, congenital heart defects, sensorineural deafness                                                           |
|                   | Cytomegalovirus         | Microcephaly, cerebral (periventricular) calcification, visual/hearing impairment, intellectual disability                     |
|                   | Toxoplasma gondii       | Hydrocephalus, cerebral calcifications, microphthalmia, chorioretinitis                                                        |
|                   | Varicella virus         | Limb hypoplasia, cutaneous scarring, eye and CNS defects                                                                       |
| Physical agents   | Ionizing radiation      | Microcephaly, intellectual disability, skeletal anomalies, cataracts (kills rapidly dividing cells; dose- and stage-dependent) |
|                   | Hyperthermia            | Neural tube defects (anencephaly, spina bifida) via disrupted neurulation                                                      |
| Drugs / chemicals | Thalidomide             | Meromelia/amelia of limbs; cardiac, renal, ocular defects                                                                      |

| Category                   | Representative agent(s)                                     | Characteristic malformations                                                                                                      |
|----------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
|                            | Phenytoin (diphenylhydantoin)                               | Fetal hydantoin syndrome — facial clefts, microcephaly, intellectual disability                                                   |
|                            | Valproic acid                                               | Neural tube defects (spina bifida), craniofacial and cardiac anomalies                                                            |
|                            | Warfarin                                                    | Nasal hypoplasia, stippled epiphyses, limb hypoplasia                                                                             |
|                            | Isotretinoin (vitamin-A analogue)                           | Craniofacial defects, small/abnormal ears, cleft palate, cardiac and CNS defects                                                  |
|                            | ACE inhibitors                                              | Growth retardation, renal dysfunction, oligohydramnios (2nd/3rd-trimester exposure)                                               |
|                            | Alcohol                                                     | Fetal alcohol syndrome — microcephaly, short palpebral fissures, cardiac and intellectual defects                                 |
| Hormones                   | Androgens, high-dose progestogens, diethylstilbestrol (DES) | Masculinisation of female external genitalia; uterine/vaginal malformation, vaginal clear-cell carcinoma in DES-exposed daughters |
| Maternal metabolic disease | Uncontrolled maternal diabetes                              | Neural tube and cardiac defects, caudal dysgenesis (sirenomelia)                                                                  |
|                            | Maternal phenylketonuria                                    | Intellectual disability, microcephaly, cardiac defects                                                                            |
| Nutritional deficiency     | Iodine deficiency                                           | Endemic cretinism (stunted mental/physical growth)                                                                                |

## 5. Dose–response and genotype interaction

For an agent to be accepted as a genuine human teratogen, a **dose–response relationship** must be demonstrable — the greater the exposure, the more severe the phenotypic effect; the doses used to demonstrate teratogenicity in animal models are usually far higher than typical human exposures, which limits direct extrapolation from animal to human data. Superimposed on dose is the **genotype-dependence** of the response: with phenytoin, for example, only about 5–10% of exposed embryos develop the full fetal hydantoin syndrome, roughly one-third show only some features, and the rest are unaffected — the same maternal dose therefore produces a spectrum of outcomes depending on the genetic constitution of the individual conceptus (and of the mother, via differences in drug metabolism).

## Applied / Clinical anatomy

- ▶ **Historical foundations:** N. Gregg's early-1940s recognition that maternal rubella caused congenital cataract, cardiac defects, and deafness first proved environmental agents (not only heredity) cause birth defects; W. Lenz's 1961 link of thalidomide to limb meromelia/amelia proved drugs cross the placenta, founding the discipline of teratology and the Teratology Society.
- ▶ **Radiation — human data:** among pregnant Hiroshima/Nagasaki survivors, 28% spontaneously aborted, 25% had offspring who died in year 1, and 25% had children with severe CNS defects — the developing brain's extreme radiosensitivity.
- ▶ **Pre-conception prevention:** the critical period for most structural defects (weeks 3–8) ends before most women's first antenatal visit (~week 8); counselling (avoid isotretinoin/valproate/warfarin/alcohol; peri-conceptional folic acid; strict glycaemic/phenylalanine control in diabetic/PKU mothers) must therefore begin *before* conception.
- ▶ **Repurposed teratogens:** thalidomide and isotretinoin remain therapeutic (myeloma/leprosy/graft-versus-host disease; cystic acne) but only under strict pregnancy-prevention programmes.
- ▶ **Prenatal diagnosis:** once teratogen exposure is known/suspected, ultrasonography, maternal serum AFP, amniocentesis, or chorionic villus sampling detect the resulting anomaly early.

## High-yield exam pointers

- ▶ Teratogen = any genetic/infectious/physical/chemical/metabolic agent producing (or increasing the incidence of) a birth defect; teratology = its study.
- ▶ Causes of birth defects: ~15% environmental, ~30% genetic, ~55% multifactorial (gene–teratogen interaction).
- ▶ Five principles of teratogenesis: genotype, developmental stage/critical period, dose & duration, specific mechanism, and the four possible manifestations (death, malformation, growth retardation, functional disorder).
- ▶ Pre-embryonic period (weeks 1–2) = "all-or-none"; embryonic period (weeks 3–8) = peak sensitivity/organogenesis; fetal period = growth retardation and functional (especially CNS) disturbance rather than gross structural defect.
- ▶ Cellular mechanisms: cell death, faulty cell–cell induction, reduced biosynthesis, impaired morphogenetic movement, mechanical disruption — converging on a common pathogenetic pathway.
- ▶ Molecular examples: retinoic acid alters homeobox gene expression domains; alcohol down-regulates Sonic Hedgehog signalling.
- ▶ Dose–response relationship is mandatory to label an agent a human teratogen; genotype of embryo/mother explains variable expressivity at the same dose (e.g., phenytoin, 5–10% full syndrome).
- ▶ Landmark teratogens to name with their defects: thalidomide (phocomelia/meromelia), rubella (Gregg triad — cataract, cardiac defect, deafness), isotretinoin, phenytoin, valproate, warfarin, alcohol (FAS).

- Prevention is a pre-conceptional strategy, since most structural damage occurs before pregnancy is even diagnosed.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e — Chapter on Birth Defects and Prenatal Diagnosis (Principles of Teratology, environmental causes and Table of teratogens); Moore's The Developing Human 9e — Human Birth Defects chapter (Principles of Teratogenesis, critical-period figure and tables, cellular/molecular mechanisms); IB Singh's Human Embryology (CBME 2021) — "Mode of Action of Teratogens" section (stage of action, genetic/metabolic influence, dose and duration; classification of environmental causes).



## Mode of actions of the teratogenic agents

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** A **teratogen** is any agent — genetic, infectious, physical, chemical or hormonal — that acts on the embryo/fetus to produce a permanent structural or functional birth defect, or increases the incidence of such a defect in the population; the study of these agents and the malformations they cause is **teratology**. Major structural anomalies affect about 3% of liveborn infants and are responsible for roughly 25% of infant deaths. Of all birth defects, approximately 15% are attributable to purely environmental (teratogenic) causes, 30% to purely genetic causes, and 55% to a multifactorial gene–environment interaction. Understanding *how* teratogens act — their mode of action — explains why the same agent can be harmless, lethal, or grossly malformative depending on the genotype, timing and dose of exposure.

### 1. General principles governing the mode of action of teratogens

| # | Principle                                     | Explanation                                                                                                                                                                                                                                                                                     |
|---|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Genotype of the conceptus and maternal genome | Susceptibility to a given teratogen depends on the genetic constitution of the embryo; the maternal genome also matters because it governs drug metabolism, placental transfer and resistance to infection. A fetus of one genotype may be far more susceptible than another to the same agent. |

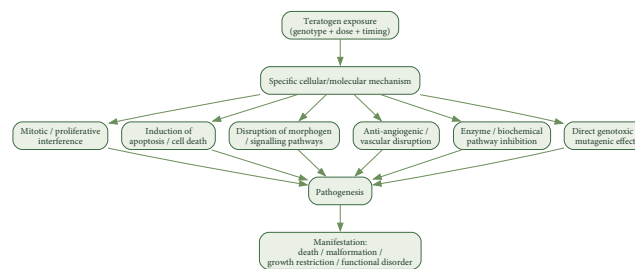
| # | Principle                                                | Explanation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2 | Developmental stage at exposure (critical period)        | Susceptibility varies sharply with the stage of development. Insults before the third week (pre-differentiation/blastocyst stage) classically follow an <b>"all-or-none" law</b> — the conceptus either dies and is resorbed, or recovers completely — although disruptions of cranio-caudal/left-right axis signalling in this period can still cause severe defects. The <b>critical period for most structural defects is the 3rd–8th week (organogenesis)</b> , when each organ passes through its own window of peak sensitivity (e.g. the cranial neuropore closes by day 25 and the caudal neuropore ~3 days later, while the limb bud is most vulnerable at 24–36 days after fertilisation). After the 8th week, gross structural defects are uncommon, but the brain continues to differentiate throughout the fetal period and remains sensitive to functional/growth insults — so <b>no stage of gestation is entirely safe</b> . |
| 3 | Dose and duration of exposure                            | Manifestations follow a <b>dose–response relationship</b> : the greater the exposure (higher dose, longer duration, repeated exposure), the more severe the phenotypic effect.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 4 | Specific mechanism (mode of action) on cells and tissues | Teratogens act through <b>defined biochemical or molecular mechanisms</b> that initiate abnormal embryogenesis (pathogenesis) — commonly by inhibiting a specific molecular pathway, and the resulting pathogenesis may involve cell death, decreased cell proliferation, or other cellular phenomena (see table below).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 5 | Manifestations of abnormal development                   | The end-result of teratogenic action is one of four outcomes: <b>death, malformation, intrauterine growth restriction, or a functional disorder</b> (e.g. intellectual disability), singly or in combination.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

□ Fig 9.2 — Graph showing the times in gestation versus the risks of birth defects (Langman's Medical Embryology — Sadler — 14e, p.148)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A "risk of birth defect vs weeks of gestation" curve (X-axis: weeks 1 → 38; Y-axis: increasing risk, unlabelled scale):

- ▶ Shade/label weeks 1–2 as the period of axis formation (yellow zone — "all-or-none," but any type of defect possible if axis signalling is disrupted).
- ▶ Shade/label weeks 3–8 as the embryonic period/organogenesis (blue zone — peak risk of major structural malformations).
- ▶ Show a declining curve from week 8 to term (fetal period) — structural-defect risk falls, but mark the brain as remaining sensitive throughout (functional/growth defects).
- ▶ Mark an arrow at week 8, labelled "first prenatal visit" — to emphasise that most women present for antenatal care only after the critical window has passed.



Mode of actions of the teratogenic agents

## 2. Cellular and molecular mechanisms — the actual "mode of action"

| Mechanism                                                 | Representative teratogen(s) | How it produces the defect                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interference with cell proliferation (mitotic inhibition) | Ionizing radiation          | Kills rapidly proliferating embryonic cells outright; virtually any defect can result depending on dose and stage (Hiroshima/Nagasaki survivors exposed in utero: 28% spontaneous abortion, 25% infant death in the first year, 25% severe CNS defects).                                                             |
| Induction of apoptosis / cell death                       | Zika virus; alcohol         | Zika targets <b>neural progenitor cells</b> , causing decreased proliferation and increased necrosis → severe microcephaly. Alcohol down-regulates <b>Sonic Hedgehog (SHH)</b> signalling by interfering with SHH binding to cholesterol, causing death of <b>neural crest cells</b> and abnormal brain development. |



| Mechanism                                             | Representative teratogen(s)                              | How it produces the defect                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Disruption of morphogen/signalling pathways           | Retinoic acid (isotretinoin, vitamin A); alcohol         | Retinoic acid is a potent teratogen that <b>targets neural crest cells</b> , producing craniofacial, cardiac and CNS malformations (isotretinoin embryopathy); alcohol acts via the SHH-cholesterol pathway as above.                                                                                                                          |
| Anti-angiogenic / vascular disruption                 | Thalidomide                                              | Inhibits <b>angiogenesis</b> (new blood-vessel formation) in the developing limb bud; it also promotes <b>degradation of the SALL4 transcription factor</b> , whose mutation independently produces an overlapping limb phenotype (Duane Radial Ray/Holt-Oram syndromes) — giving thalidomide two converging mechanisms for amelia/phocomelia. |
| Enzyme/biochemical pathway inhibition                 | Folate antagonists (aminopterin, methotrexate); warfarin | Folate antagonists inhibit dihydrofolate reductase, blocking the nucleic-acid synthesis needed for neural tube closure and craniofacial development. Warfarin interferes with hepatic vitamin-K-dependent carboxylation, disturbing skeletal (epiphyseal/nasal cartilage) matrix protein synthesis.                                            |
| Altered maternal metabolic milieu reaching the embryo | Maternal diabetes; hyperthermia                          | Poorly controlled maternal hyperglycaemia (altered glucose levels, not insulin itself) raises risk of neural tube and cardiac defects three- to four-fold. Hyperthermia (fever, sauna, hot-tub use) characteristically disturbs <b>neurulation</b> , producing anencephaly and spina bifida.                                                   |
| Direct genotoxic/mutagenic effect                     | Ionizing radiation                                       | Beyond killing cells, radiation is mutagenic to germ cells, so it can also cause heritable genetic alterations transmitted to the next generation (male-mediated teratogenesis).                                                                                                                                                               |

| Mechanism                                | Representative teratogen(s)                     | How it produces the defect                                                                                                                                                                                                                                                              |
|------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endocrine disruption (receptor-mediated) | Diethylstilbestrol (DES); androgenic progestins | DES interferes with normal oestrogen-receptor signalling in the developing Müllerian system, causing uterine/tubal/vaginal malformation and later vaginal/cervical carcinoma; androgenic progestins (ethisterone, norethisterone) masculinise the external genitalia of female fetuses. |
| "Functional" (epigenetic) teratogenesis  | Altered maternal hormonal milieu                | Abnormal concentrations of endogenous hormones during critical periods can act as <b>functional teratogens</b> , producing lasting epigenetic ("fetal programming") effects on adult health without a gross structural anomaly.                                                         |

□ Fig 9.5 — A,B. Examples of phocomelia. Limb defects characterized by loss of the (Langman's Medical Embryology — Sadler — 14e, p.150)

### 3. Classification of teratogenic agents (by category, with resulting defects)

| Category       | Agent              | Chief malformations                                                     |
|----------------|--------------------|-------------------------------------------------------------------------|
| Infectious     | Rubella            | Cataract, glaucoma, congenital heart disease, sensorineural deafness    |
|                | Cytomegalovirus    | Microcephaly, intellectual disability, hepatosplenomegaly               |
|                | Toxoplasma gondii  | Hydrocephalus, cerebral calcification, microphthalmia                   |
|                | Varicella zoster   | Skin scarring, limb hypoplasia, CNS/eye defects                         |
|                | Zika virus         | Severe microcephaly, cerebral calcification, arthrogryposis             |
| Physical       | Ionizing radiation | Microcephaly, spina bifida, cleft palate, limb defects, malignancy risk |
|                | Hyperthermia       | Anencephaly, spina bifida, intellectual disability                      |
| Chemical/drugs | Thalidomide        | Amelia/phocomelia, cardiac malformation                                 |

| Category                   | Agent                        | Chief malformations                                                |
|----------------------------|------------------------------|--------------------------------------------------------------------|
|                            | Isotretinoin/vitamin A       | Craniofacial, cardiac, CNS malformation (isotretinoin embryopathy) |
|                            | Phenytoin, trimethadione     | Fetal hydantoin/trimethadione syndrome — facial clefts             |
|                            | Valproic acid, carbamazepine | Neural tube defects (spina bifida)                                 |
|                            | Warfarin                     | Nasal hypoplasia, stippled epiphyses, limb hypoplasia              |
|                            | ACE inhibitors               | Renal dysfunction, oligohydramnios, growth restriction             |
|                            | Alcohol                      | Fetal alcohol syndrome/spectrum disorder                           |
| Hormonal                   | Diethylstilbestrol           | Uterine/vaginal anomaly, later genital-tract carcinoma             |
|                            | Androgenic progestins        | Masculinisation of female external genitalia                       |
| Maternal disease/metabolic | Diabetes mellitus            | Neural tube defects, cardiac defects, caudal dysgenesis            |

### Applied / Clinical anatomy

- **Antenatal-care timing gap:** because the critical period for most structural defects (weeks 3–8) precedes the first prenatal visit for the majority of women, **preconception counselling** is emphasised for women with epilepsy, diabetes or planned isotretinoin/warfarin use.
- **Preventive practice:** periconceptual **folate supplementation** lowers neural tube defect incidence and also reduces hyperthermia-induced defects; strict **preconception glycaemic control** in diabetics and dietary control in phenylketonuria reduce malformation rates to near-baseline; **rubella vaccination** has virtually eliminated congenital rubella syndrome; **iodine supplementation** prevents cretinism.
- **Recognisable dysmorphic patterns** (viva-relevant): fetal alcohol syndrome (short palpebral fissures, smooth philtrum, thin upper lip, microcephaly), fetal hydantoin syndrome, warfarin embryopathy, thalidomide phocomelia/amelia, isotretinoin embryopathy (small dysplastic ears, mandibular hypoplasia).
- **Male-mediated teratogenesis:** paternal exposure to mutagens (radiation, ethylnitrosourea, alcohol, lead) can damage germ-cell DNA, linking to spontaneous abortion, low birth weight and birth defects — a reminder that teratogenic mechanisms are not confined to maternal exposure.
- **Prenatal diagnosis** (ultrasonography, maternal serum screening, amniocentesis, chorionic villus sampling) allows early detection of structural anomalies once a teratogenic exposure is suspected, guiding counselling and management.

## High-yield exam pointers

- ▶ Teratogen = any agent (genetic/infectious/physical/chemical/hormonal) causing a birth defect or raising its incidence; teratology = its study.
- ▶ Environmental causes ≈15% of birth defects, genetic ≈30%, multifactorial ≈55% (Langman).
- ▶ Four determinants of teratogenic action: **genotype, developmental stage/critical period, dose–duration, specific cellular mechanism** → manifestations = death/malformation/growth restriction/functional disorder.
- ▶ Critical period for most structural defects = **3rd–8th week (organogenesis)**; weeks 1–2 largely "all-or-none" except for axis-formation defects; brain remains vulnerable throughout gestation.
- ▶ Key mechanisms to name: mitotic/proliferative inhibition (radiation), apoptosis/cell death (Zika, alcohol via SHH–cholesterol), neural-crest targeting (retinoic acid, alcohol), anti-angiogenesis + SALL4 degradation (thalidomide), enzyme/pathway inhibition (folate antagonists, warfarin), altered maternal metabolic milieu (diabetes, hyperthermia), direct mutagenesis (radiation), receptor-mediated endocrine disruption (DES).
- ▶ Dose–response relationship is a defining feature of teratogenic action.
- ▶ Remember at least one worked example per mechanism for the viva: thalidomide (dual mechanism) and alcohol (SHH pathway) are examiner favourites.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Larsen Human Embryology 6e; Brijesh Kumar Embryology Text & Atlas; Thompson & Thompson Genetics in Medicine 8e; Moore The Developing Human 9e; Gray's Anatomy (Standring) 41e.



## Neural tube defects

*Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Neural tube defects (NTDs) are a group of congenital malformations of the central nervous system that result from failure of normal **neurulation** — incomplete fusion, or non-closure, of the neural folds into a neural tube during the third and fourth weeks of intrauterine life. They are the commonest major congenital malformations of the CNS, and the defect always involves the overlying meninges, vertebral/cranial neural arches, muscle and skin in continuity with the neural tissue itself. The spectrum ranges from a trivial, asymptomatic bony gap (spina bifida occulta) to a totally open neuraxis that is incompatible with life (craniorachischisis totalis).

### Normal neurulation — the developmental basis of NTDs

- ▶ The **neural plate** forms in the third week as a midline thickening of ectoderm induced by the underlying notochord; it invaginates to form the **neural groove**, flanked by elevating **neural folds**.

- ▶ The neural folds meet and fuse in the dorsal midline first at the level of **somites 1–2** (future rhombencephalon, 4–6 somite stage), and fusion then proceeds **bidirectionally** — rostrally and caudally — in a "zippering" fashion (**primary neurulation**).
- ▶ **Rostral neuropore** closure is completed at the 19–20 somite stage (about day 25); two fusion sites are described — the dorsal lip ( $\alpha$ ) and terminal lip ( $\beta$ ) of the rostral neuropore.
- ▶ **Caudal neuropore** closure begins at about the 29-somite stage (day 28), at the level of the future S2 vertebra.
- ▶ Below this level (sacroccygeal cord), the neural tube forms by **secondary neurulation** — canalisation of a solid mesenchymal cell mass (the caudal eminence/caudal cell mass) rather than by fold-and-fuse.
- ▶ Once the tube closes, a continuous surface ectoderm re-forms over it, and the surrounding paraxial mesenchyme (sclerotome) condenses around the tube and notochord to form the vertebral centra and neural arches.
- ▶ Failure of any of these steps — **non-fusion of the folds, or failure of the overlying mesenchyme/arch to close over an otherwise normally fused tube** — produces the corresponding NTD.

### Classification / spectrum of neural tube defects

| Defect                          | Level of failure                          | Essential description                                                                                                     |
|---------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Craniorachischisis totalis      | Entire neural tube (both neuropores fail) | Whole neuraxis remains open dorsally; most severe form, incompatible with life                                            |
| Anencephaly (cranioschisis)     | Rostral neuropore                         | Neural tube fuses in the cord but stays open in the brain; cranial vault fails to form; exposed neural tissue degenerates |
| Encephalocele (cranium bifidum) | Localised skull-vault ossification defect | Meninges $\pm$ brain tissue herniate through a bony gap, usually occipital                                                |
| Spina bifida                    | Caudal neuropore / vertebral arch         | Failure of fusion of one or more vertebral (neural) arches, with or without herniation of neural tissue                   |
| Iniencephaly                    | Cranio-cervical junction                  | Occipital bone defect + cervical spina bifida + fixed retroflexion of the head                                            |

### Spina bifida — types and morphology

- ▶ **Spina bifida occulta** — a defect confined to the vertebral arches (commonly S1–S2), covered by intact skin; the spinal cord and meninges remain in normal position. Affects about 5–10% of an otherwise normal population; often marked by a hairy patch, dimple, dermal sinus or pigmented naevus over the site; usually an incidental radiological finding.
- ▶ **Spina bifida cystica** — a cystic swelling protrudes through the bony defect:

- **Meningocele** — only the CSF-filled meninges (arachnoid + pia, covered by skin) herniate; the spinal cord remains in its normal position within the canal.
- **Myelomeningocele (meningomyelocele)** — the most common and most severe cystic form; spinal cord and/or nerve roots herniate into the sac together with the meninges, producing neurological deficit below the lesion level (motor/sensory loss, bladder involvement).
- ▶ **Myeloschisis / rachischisis** — the neural folds fail to elevate and fuse at all; a flattened, ribbon-like plaque of neural tissue lies exposed on the surface with no covering sac — the most severe spinal-level defect, often becoming necrotic in utero. When this open defect extends cranially into the brain it is termed **craniorachischisis**.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

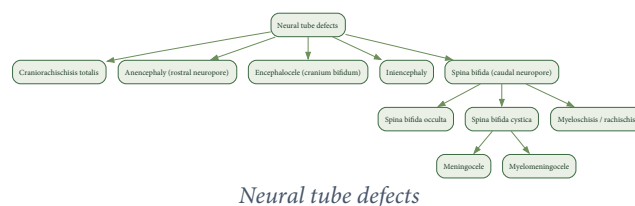
□ Fig 44.14 — The spectrum of spina bifida. A, Intact neural tube. B, Open spina bifida – myelocele. C, Open spina bifida – myelomeningocele. D, Closed spina bifida with meningocele. (Gray's Anatomy — Standring — 41e, p.1024)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce the four-panel spectrum in cross-section, left to right:

- ▶ **A — Normal:** closed neural tube, intact skin and fused vertebral (neural) arch dorsal to it.
- ▶ **B — Myelocele:** neural arch open; flattened neural plaque exposed directly to the surface, no covering sac.
- ▶ **C — Myelomeningocele:** neural arch open; CSF-filled sac herniating dorsally, with neural tissue/cord incorporated into the sac wall.
- ▶ **D — Meningocele:** neural arch open; CSF-filled meningeal sac only, covered by skin, with the spinal cord remaining in its normal position within the canal.

Label in each panel: skin, vertebral (neural) arch, dura/arachnoid, spinal cord/neural placode, CSF.



## Aetiopathogenesis

- ▶ **Multifactorial** in origin — an interaction of genetic susceptibility and environmental/nutritional factors; recurrence risk rises significantly (multifactorial threshold effect) once one affected child has been born.
- ▶ **Folate (vitamin B9) deficiency** is the single most important, and most preventable, cause — folate is essential for DNA/RNA synthesis, cell division and closure of the neural folds.
- ▶ **MTHFR (methylenetetrahydrofolate reductase) gene mutation** — a thermolabile enzyme variant that impairs folate metabolism — is a well-established genetic association with NTDs.

- ▶ **Teratogens:** maternal hyperthermia (fever, sauna/hot-tub use), anticonvulsant **valproic acid**, and **hypervitaminosis A**.
- ▶ **Ossification defects** of the skull vault (commonly the squamous occipital bone) underlie most **encephaloceles**.
- ▶ **Epidemiology:** birth prevalence of NTDs varies widely by population — as high as 1/200 births in parts of northern China; in the USA it fell by about 25% to roughly 1/1500 births after mandatory folic-acid fortification of flour (1998). **Anencephaly** occurs in about 1/5000 births and is about four times more common in females.

### Associated anomalies

- ▶ **Hydrocephalus** develops in 80–90% of children with severe (open) NTDs, most often secondary to an **Arnold–Chiari (type II) malformation** — downward herniation of the cerebellar vermis/tonsils through the foramen magnum. As the vertebral column elongates in later fetal life, the cord (tethered by the spinal defect) fails to ascend normally, dragging the hindbrain caudally and obstructing CSF outflow.
- ▶ **Tethered cord syndrome / diastematomyelia** — a bony or fibrous septum may split the cord and roots into two columns (diastematomyelia); patients typically show a cutaneous marker (dimple, hairy patch, naevus) at the level of tethering, with delayed presentation of urinary or gait symptoms as the child grows.
- ▶ **Dandy–Walker malformation** may coexist — atresia of the foramina of Magendie and Luschka causes fourth-ventricle dilation with cerebellar vermal agenesis.
- ▶ **Exencephaly–anencephaly sequence** — the primary defect is exencephaly (open cranial vault with malformed brain exposed to amniotic fluid); the exposed tissue undergoes progressive mechanical/chemical necrosis in utero, leaving the classic anencephalic appearance (absent cranial vault and cerebral hemispheres, with the brainstem often relatively intact).
- ▶ **Encephalocele subtypes**, in increasing severity: **meningocele-type** (meninges only), **meningoencephalocele** (meninges + brain tissue), and **meningohydroencephalocele** (meninges + brain tissue + part of a ventricle); overall incidence about 1/12,000 births, occipital region most common.
- ▶ Anencephaly is regularly accompanied by **polyhydramnios** in the last trimester because the fetus lacks a functioning swallowing reflex.

### Applied / Clinical anatomy

- ▶ **Antenatal screening/diagnosis:** raised **maternal serum and amniotic fluid alpha-fetoprotein (AFP)**, combined with obstetric **ultrasonography**. Vertebral ossification centres can be visualised from about 12 weeks; a detailed anomaly scan is routinely performed at 18–20 weeks, assessing the three ossification centres of each vertebra (centrum + bilateral lamina–pedicle junctions) in axial, coronal and sagittal planes — normally these appear as parallel "rail-track" lines in coronal section, but in spina bifida the posterior centres splay abnormally into a U- or V-shape.
- ▶ Spina bifida and related vertebral anomalies are among the commonest fetal malformations detected on antenatal scan; population surveys report a total birth/termination prevalence in the range of roughly 12–18 per 10,000 pregnancies.



- ▶ **Prevention:** peri-conceptual **folic acid supplementation** — 0.4 mg/day from at least one month (ideally three months) before conception through the first trimester reduces NTD occurrence by 50–70%; women with a previously affected pregnancy or family history are advised a higher dose (up to 4 mg/day) over the same peri-conceptual window.
- ▶ **Treatment:** postnatal surgical closure of the defect; a **ventriculoperitoneal shunt** is used for the associated hydrocephalus; experimental **fetal (in-utero) surgical repair** has been performed from as early as 22 weeks of gestation.
- ▶ **Surface anatomy correlate:** the level of the vertebral/cutaneous marker in occult spina bifida (commonly lumbosacral, S1–S2) predicts the likely site of a tethered cord or diastematomyelia and guides MRI/surgical planning.
- ▶ Because the vertebral (bony) defect in myelomeningocele typically extends cranially beyond the neural lesion, vertebrae at and above the level may show wedging, hemivertebra formation, or rib fusion/absence — relevant to orthopaedic assessment of scoliosis in these children.

### High-yield exam pointers

- ▶ NTDs arise from failure of neurulation in the 3rd–4th week; rostral neuropore closes about day 25, caudal about day 28.
- ▶ Folic acid deficiency and MTHFR mutation are the key preventable/genetic causes; 400 µg/day peri-conceptionally cuts risk by 50–70%.
- ▶ Classic spectrum: craniorachischisis totalis > anencephaly (rostral) / spina bifida (caudal), with encephalocele and iniencephaly as regional variants.
- ▶ Spina bifida = occulta (skin-covered, cord normal) vs cystica = meningocele (meninges only) vs myelomeningocele (meninges + cord, commonest/most severe cystica type); myeloschisis/rachischisis = totally exposed flattened cord.
- ▶ Anencephaly begins as exencephaly, with secondary necrosis of exposed neural tissue; associated with polyhydramnios (no swallowing reflex).
- ▶ 80–90% of severe NTDs develop hydrocephalus, chiefly via Arnold–Chiari II malformation from cord tethering.
- ▶ Screening: raised maternal serum/amniotic AFP + ultrasound (12-week vertebral visualisation; 18–20-week anomaly scan; abnormal U/V-shaped posterior ossification centres).
- ▶ Teratogens to remember: valproic acid, hyperthermia, hypervitaminosis A.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Larsen Human Embryology 6e.



## Teratogenic agents

Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** A **teratogen** (Gr. *teratos* = monster) is any agent — drug, chemical, infectious organism, physical factor, hormone or maternal metabolic state — that acts on the embryo/fetus in utero to produce a structural or functional **congenital anomaly (birth defect)**, or that increases the incidence of such a defect in the population; **teratology** is the study of abnormal development and its causation. Major structural malformations affect ~3% of **live-born infants** and are a leading cause of infant mortality (~25% of infant deaths); of all birth defects, **15% are purely environmental, 30% purely genetic/chromosomal**, and **55% multifactorial** (gene–teratogen interaction, including many of unknown cause). The discovery by N. Gregg (early 1940s) that maternal **rubella** causes fetal malformation, and by W. Lenz (1961) that **thalidomide** causes limb defects, established that environmental agents — not only heredity — cause human birth defects and founded the science of teratology.

### 1. Principles of teratogenesis

| Principle                                   | Explanation                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Genotype of the conceptus (and mother)      | Susceptibility to a given teratogen varies with the genetic constitution of the embryo and the maternal genome (which governs drug metabolism, infection resistance); the same dose of phenytoin produces full fetal hydantoin syndrome in only 5–10% of exposed embryos, some features in ~one-third, and no effect in over half — genotype determines response. |
| Critical (developmental) period at exposure | The stage of development when the agent acts determines the type and severity of defect produced; each organ has its own window of peak sensitivity.                                                                                                                                                                                                              |
| Dose and duration of exposure               | A dose–response relationship exists — greater/longer exposure produces a more severe phenotype; a threshold dose is generally required.                                                                                                                                                                                                                           |
| Mechanism/pathogenesis                      | Teratogens act by specific biochemical/molecular mechanisms (e.g., inhibition of a signalling pathway, cell-cycle block) producing cell death, reduced proliferation, or impaired morphogenetic movement.                                                                                                                                                         |
| Manifestations of abnormal development      | Four possible outcomes of teratogenic insult: <b>death, malformation, growth restriction, and functional disorder</b> .                                                                                                                                                                                                                                           |

### 2. Critical periods of development

- **Pre-differentiation/pre-implantation period (fertilization to end of 2nd week)** — governed by the classic "**all-or-none**" law: an insult either kills the conceptus (spontaneous abortion, often before pregnancy is recognised) or the powerful regulative capacity of the early embryo allows full, undamaged recovery; no birth defects are attributed to insults in this window under the

classical teaching, although axis (cranio-caudal/left-right) specification begins in this period and some anomalies of laterality can still originate here.

- ▶ **Embryonic period / period of organogenesis (3rd–8th week)** — the **most critical period**; cell division, differentiation and morphogenesis are at their peak, so most **major structural malformations** are induced now (this is also, unfortunately, before many women recognise their pregnancy).
- ▶ **Fetal period (9th week to term)** — organ systems have already formed, so gross structural defects are uncommon; however, the **brain continues to differentiate and grow throughout gestation**, so exposure in this period chiefly causes **growth restriction, minor morphological anomalies, and functional/intellectual disturbance** rather than gross malformation. **No stage of gestation is entirely free of teratogenic risk.**
- ▶ Individual organs retain their own susceptibility window: **CNS is sensitive from the 3rd to at least the 16th week** (and remains vulnerable to functional injury through the fetal period); the **critical period for limb development is 24–36 days post-fertilization** (early limb-bud stage); the **palate** can be disrupted at several distinct points — blastocyst stage (day 6), gastrulation (day 14), limb-bud stage (5th week), or palatal-shelf fusion (7th week); permanent **tooth** development (enamel) remains vulnerable to tetracycline from **18 weeks in utero to 16 years postnatally**. Classic teaching also assigns comparable narrow windows to the developing heart, eye, ear and external genitalia, coinciding with their respective organogenetic periods.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

No genuine matching real plate was found in the figure library for this specific composite timeline chart (a schematic, not a photographed structure), so reproduce Moore's classic "**Critical periods of human development**" timeline freehand:

- ▶ Draw a horizontal axis marked in **weeks of gestation, 1 to 38**, with "fertilization" at one end and "birth (38 wk)" at the other.
- ▶ Mark **weeks 1–2** as the "period of the dividing zygote, implantation and bilaminar embryo" — hatch this zone and label "**not susceptible to teratogenesis (all-or-none)**."
- ▶ Mark **weeks 3–8** as the "**embryonic period**" — shade darkest and label "**highly sensitive period — major structural anomalies**."
- ▶ Mark **weeks 9–38** as the "**fetal period**" — shade lightly and label "**less sensitive period — minor anomalies and functional/CNS disturbance**."
- ▶ Below the axis, draw separate horizontal bars for **CNS, heart, eye, limb, ear, teeth, palate, external genitalia**, each positioned over its own organogenetic window (CNS spanning the longest, from week 3 into the fetal period); shade the busiest part of each bar dark and its tail light, and annotate 1–2 defects each bar can produce (e.g., limb bar → "amelia/meromelia"; heart bar → "ASD/VSD/TGA"; eye bar → "cataract/microphthalmia"; palate bar → "cleft lip/palate").

### 3. Classification of teratogenic agents (with examples and defects produced)

| Category          | Agents                                                                                                                                                | Principal defects                                                                                                                                                                                                                                                                                                                                        |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infectious agents | Rubella (congenital rubella syndrome), cytomegalovirus, herpes simplex virus, varicella, Toxoplasma gondii, Treponema pallidum (syphilis), Zika virus | Cataract, cardiac defects (PDA), sensorineural deafness (rubella); microcephaly, cerebral (periventricular) calcification, chorioretinitis (CMV, toxoplasmosis); limb hypoplasia and skin scarring (varicella); microcephaly with overlapping sutures and calcifications (Zika); congenital deafness, abnormal teeth and bones, hydrocephalus (syphilis) |
| Physical agents   | Ionizing radiation (diagnostic/therapeutic X-rays, nuclear fallout — Hiroshima/Nagasaki, Chernobyl), hyperthermia (maternal fever, sauna/hot-tub use) | Microcephaly, mental deficiency, skeletal anomalies, growth restriction, cataract (radiation); neural tube defects such as anencephaly and spina bifida via disrupted neurulation (hyperthermia)                                                                                                                                                         |

| Category                        | Agents                                                                                                                                                                                                                                                                     | Principal defects                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical/pharmaceutical agents  | Thalidomide, isotretinoin/vitamin A analogues, anticonvulsants (phenytoin, valproic acid, trimethadione, carbamazepine), anticoagulant warfarin, ACE inhibitors, lithium, SSRIs, mycophenolate mofetil, cancer chemotherapeutics (aminopterin/methotrexate), tetracyclines | Meromelia/amelia (thalidomide); isotretinoin embryopathy — microtia, mandibular hypoplasia, cardiac and CNS defects; fetal hydantoin syndrome, trimethadione syndrome (facial clefts); neural-tube and skeletal defects (valproate); nasal hypoplasia and stippled epiphyses (warfarin); Ebstein anomaly (lithium); stained teeth/enamel hypoplasia (tetracycline) |
| Social/recreational agents      | Alcohol, tobacco, cocaine, opioids, marijuana                                                                                                                                                                                                                              | Fetal alcohol syndrome/fetal alcohol spectrum disorder — growth restriction, microcephaly, short palpebral fissures, smooth philtrum, thin upper lip, cardiac and CNS defects (alcohol interferes with sonic-hedgehog signalling); orofacial clefts and cardiac defects (smoking); neurobehavioural disturbance (cocaine)                                          |
| Hormones / endocrine disruptors | Androgenic progestins, diethylstilbestrol (DES)                                                                                                                                                                                                                            | Masculinisation of female external genitalia (clitoral hypertrophy, labial fusion); DES — vaginal/cervical adenocarcinoma and uterine/testicular malformation in offspring exposed in utero                                                                                                                                                                        |
| Maternal metabolic disease      | Maternal (pregestational) diabetes, maternal phenylketonuria, maternal obesity                                                                                                                                                                                             | Neural tube defects, congenital heart disease, caudal dysgenesis/sirenomelia (diabetes); microcephaly and intellectual disability (untreated maternal PKU)                                                                                                                                                                                                         |
| Nutritional deficiency/excess   | Iodine deficiency, folate deficiency, excess vitamin A                                                                                                                                                                                                                     | Endemic cretinism (iodine); neural tube defects (folate deficiency — preventable); isotretinoin-type embryopathy at high dose (vitamin A)                                                                                                                                                                                                                          |
| Miscellaneous                   | Heavy metals (organic mercury, lead), advanced paternal age/male-mediated exposures                                                                                                                                                                                        | Cerebral palsy-like neurological syndrome (organic mercury, e.g. Minamata Bay); growth restriction and neurological disorder (lead); increased de novo mutations and structural defects with advanced paternal age                                                                                                                                                 |

#### 4. Landmark example and mechanism — thalidomide

□ Fig 9.5 — Examples of phocomelia: limb defects with loss of the long bones of the limb, commonly produced by the drug thalidomide (Langman's Medical Embryology — Sadler — 14e, p.150)

- ▶ Thalidomide, an antinauseant/hypnotic used in the late 1950s–60s, produces **meromelia and amelia** (partial/complete absence of long bones) when taken early in the critical period of limb development, and milder hypoplasia of the radius/ulna when taken later in the same window — illustrating how timing within a single organ's critical period grades the severity of the defect.
- ▶ It also causes cardiac, renal, ocular and facial anomalies, confirming that a single teratogen can affect several organ systems developing concurrently.
- ▶ Its precise molecular mechanism is still debated (over 20 hypotheses proposed), underlining that teratogens act through specific, often still incompletely understood, biochemical pathways rather than nonspecific toxicity.

#### Applied / Clinical anatomy

- ▶ **Prenatal diagnosis** (ultrasonography, maternal serum  $\alpha$ -fetoprotein, amniocentesis, chorionic villus sampling) allows detection of many teratogen-induced structural defects (neural tube defects, abdominal-wall defects, cardiac and facial anomalies) and underpins genetic counselling in a suspected teratogen exposure.
- ▶ **Prevention** is the principal clinical application of teratology: peri-conceptual **folate** supplementation reduces neural tube defects; iodised salt prevents cretinism; strict glycaemic control before and during pregnancy in diabetic/PKU mothers reduces malformation risk toward background levels; avoidance of retinoids, valproate and alcohol in women of reproductive age reduces isotretinoin embryopathy, fetal valproate syndrome and FASD.
- ▶ **Male-mediated teratogenesis**: paternal occupational exposure to mercury, lead, solvents and ionizing radiation, and advancing paternal age, are linked to increased spontaneous abortion, low birth weight and de novo structural/chromosomal defects — prevention strategies must therefore also target the father before conception.
- ▶ **Fetal programming** ("functional teratogenesis"): altered maternal hormonal/nutritional milieu during critical developmental windows can programme adult-onset disease (insulin resistance, hypertension) in offspring without producing a structural malformation — an extension of the teratogenic concept recognised in Gray's Anatomy (Standring) 41e.
- ▶ Clinicians must weigh the risk of an untreated maternal illness (e.g., epilepsy, fever) against drug teratogenicity — abrupt cessation of an anticonvulsant is itself dangerous, so the least teratogenic effective agent and dose is chosen rather than no treatment at all.

#### High-yield exam pointers

- ▶ Teratogen = agent producing a birth defect or raising its population incidence; teratology = its study; ~3% of live births show a major malformation.
- ▶ Causation split: **15% environmental, 30% genetic, 55% multifactorial** (Langman); Gregg (rubella, early 1940s) and Lenz (thalidomide, 1961) are the two landmark discoveries founding teratology.

- ▶ Three governing principles: **critical period of exposure, dose/duration, and embryo–maternal genotype** (plus mechanism and the four possible manifestations — death, malformation, growth restriction, functional disorder).
- ▶ **3rd–8th week (organogenesis) = most critical/vulnerable period** for major structural defects; weeks 1–2 follow the "all-or-none" law; fetal period (9 wk–term) mainly gives growth restriction and functional (especially CNS) deficits.
- ▶ Classic categories: **infectious (TORCH + Zika), physical (radiation, hyperthermia), chemical/drugs (thalidomide, retinoids, anticonvulsants, warfarin), hormonal (DES, androgens), maternal metabolic disease (diabetes, PKU), nutritional (iodine, folate, vitamin A), miscellaneous (heavy metals, paternal factors).**
- ▶ **Thalidomide** → meromelia/amelia; **rubella** → cataract, deafness, PDA; **isotretinoin** → craniofacial + cardiac embryopathy; **alcohol** → FAS/FASD (via SHH pathway disruption); **phenytoin** → fetal hydantoin syndrome; **warfarin** → nasal hypoplasia + stippled epiphyses; **lithium** → Ebstein anomaly.
- ▶ Prevention = the clinical payoff of teratology: peri-conceptional folate, iodised salt, pre-pregnancy glycaemic control, and avoidance of known teratogens in women of child-bearing age.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Larsen — Human Embryology 6e; Gray's Anatomy (Standring) 41e.



## Treacher Collins Syndrome

*Asked in: Paper II May 2018 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Treacher Collins syndrome (TCS) — also called mandibulofacial dysostosis, or Franceschetti–Zwahlen–Klein syndrome — was first described by the English surgeon Edward Treacher Collins in 1900. It is the prototype **first (and second) arch syndrome**: a bilateral, essentially symmetrical craniofacial malformation caused by disturbed development of structures derived from the first and second pharyngeal arches. TCS is inherited as an autosomal dominant trait, most often due to haploinsufficiency of the **TCOF1** gene at chromosome **5q32**, and presents classically with malar and mandibular hypoplasia, down-slanting palpebral fissures with lower-lid coloboma, and external/middle-ear anomalies with conductive deafness.

### Classification — a first (and second) arch syndrome

- ▶ Congenital facial malformations arise either early, from **abnormal migration, proliferation and/or apoptosis of cranial neural crest cells**, or later, during the morphogenetic phase of facial development.
- ▶ **First arch cartilage (Meckel's cartilage)**: its dorsal end ossifies into the **malleus and incus**; its ventral part is surrounded by membrane bone to form the **mandible**; the intervening



perichondrium persists as the **anterior ligament of malleus** and **sphenomandibular ligament**. The maxillary process (also first-arch) forms the **maxilla and zygomatic bone**.

- ▶ **Second arch cartilage (Reichert's cartilage)**: its dorsal end ossifies into the **stapes**; more caudally it forms the **styloid process**; ventrally the **lesser cornu and upper body of the hyoid**; the intervening perichondrium persists as the **stylohyoid ligament**.
- ▶ TCS results from deficient neural-crest ectomesenchyme in **both the first and second arches** — which is why it damages the malleus/incus (1st arch) together with the stapes (2nd arch), and why it is termed "mandibulofacial dysostosis" rather than a purely "first-arch" defect.
- ▶ Together with **Pierre Robin sequence**, TCS is one of the two principal first-arch syndromes of the standard embryology curriculum; DiGeorge syndrome (3rd/4th pouch), hemifacial microsomia (Goldenhar syndrome), and craniofrontonasal syndrome are related neural-crest craniofacial disorders often discussed alongside it.

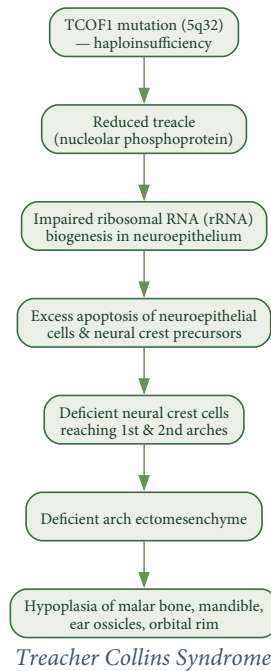
## Genetics of Treacher Collins syndrome

- ▶ **Inheritance**: Autosomal dominant.
- ▶ **Incidence**: approximately **1 in 50,000** live births.
- ▶ **New mutation rate**: about **60%** of cases arise from a fresh (de novo) mutation — one of the higher new-mutation rates among autosomal dominant disorders (comparable to achondroplasia 80%, tuberous sclerosis 80%, neurofibromatosis 40%).
- ▶ **Penetrance and expressivity**: recent family studies show **near-complete (almost 100%) penetrance**, but **markedly variable expressivity** — severity ranges from barely perceptible facial asymmetry to severe mandibulofacial deformity, even within the same family.
- ▶ **Gene**: TCOF1 (Treacher Collins–Franceschetti 1), located at **chromosome 5q32**; the disorder results from **haploinsufficiency** of this gene (one functional copy is insufficient for normal craniofacial development).
- ▶ Because most cases are sporadic new mutations, the majority of affected individuals are born to unaffected parents; an affected parent, however, transmits the dominant allele to each child with **50% risk**.

## Molecular pathogenesis

- ▶ The TCOF1 gene encodes a nucleolar phosphoprotein called **treacle**.
- ▶ Treacle is required for the **biogenesis of ribosomal RNA (rRNA)** in the neuroepithelium of the developing hindbrain and in migrating cranial neural crest cells.
- ▶ Loss of one functional TCOF1 allele (haploinsufficiency) impairs ribosome biogenesis, which triggers **excessive apoptosis of neuroepithelial cells and their neural crest progeny** destined for the first and second pharyngeal arches.
- ▶ Crucially, treacle acts on **cell survival and proliferation, not on the migratory machinery** — neural crest cells that do survive migrate into the arches normally; the defect is a **quantitative deficiency** of crest-derived ectomesenchyme reaching the arches, not a mis-migration.
- ▶ The resulting **ectomesenchymal deficiency** in the first and second arches manifests as hypoplasia of the arch-derived skeletal, cartilaginous, and soft-tissue structures — the zygomatic complex, mandible, and ear ossicles.

- Phenocopies of the syndrome can be produced experimentally in animals by teratogenic doses of retinoic acid, indicating that some sporadic human cases may have an environmental as well as a genetic basis.



## Clinical features

| Region              | Anomaly                                                                                                                |
|---------------------|------------------------------------------------------------------------------------------------------------------------|
| Orbit / eyes        | Down-slanting (antimongoloid) palpebral fissures; <b>coloboma of the lower eyelid</b> ; incomplete/notched orbital rim |
| Malar region        | <b>Malar hypoplasia</b> — underdeveloped zygomatic bone with absent cheek prominence                                   |
| Mandible            | <b>Mandibular hypoplasia</b> — micrognathia/retrognathia; agnathia in extreme cases                                    |
| External ear        | Deformed or absent pinna (microtia/anotia); preauricular tags, fistulae, or cysts                                      |
| Middle ear          | Malformed auditory ossicles (malleus, incus) → <b>bilateral conductive hearing loss</b>                                |
| Oral cavity         | <b>Cleft palate</b> in a proportion of cases; occasional macrostomia (first-arch spectrum)                             |
| Systemic (uncommon) | Occasional congenital heart disease, cryptorchidism, mental deficiency                                                 |

## Differential diagnosis of related craniofacial (neural-crest) syndromes

| Syndrome                                      | Genetics                           | Key distinguishing features                                                                                                                    |
|-----------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Treacher Collins (mandibulofacial dysostosis) | AD; TCOF1 haploinsufficiency, 5q32 | Bilateral symmetrical malar + mandibular hypoplasia, down-slanting fissures with lower-lid coloboma, ear anomalies with conductive deafness    |
| Pierre Robin sequence                         | Sporadic/heterogeneous             | Triad of <b>micrognathia, glossoptosis, and cleft palate</b> (often U-shaped); small mandible is the primary defect obstructing tongue descent |
| Hemifacial microsomia (Goldenhar syndrome)    | Usually sporadic                   | <b>Unilateral</b> small mandible ± absent temporomandibular joint, malformed/absent ear with accessory tags, facial clefts                     |
| DiGeorge (22q11.2 deletion) syndrome          | Microdeletion 22q11.2              | Thymic and parathyroid aplasia, conotruncal cardiac defects — 3rd/4th pouch, not arch, disorder                                                |
| Craniofrontonasal syndrome                    | EFNB1 gene deletion                | Broad forehead, hypertelorism, coronal suture synostosis, central nasal groove                                                                 |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 6.4 — A girl with Treacher Collin syndrome. (Gangane — Human Genetics — 5e, p.123)

For hand reproduction in the exam, sketch a frontal facial outline and label:

- ▶ Down-slanting (antimongoloid) palpebral fissures
- ▶ Coloboma of the lower eyelid
- ▶ Malar hypoplasia — flattened cheek (underdeveloped zygomatic bone)
- ▶ Mandibular hypoplasia — receding chin (micrognathia)
- ▶ Deformed/small pinna (microtia) with preauricular tag
- ▶ Notched/incomplete lower orbital rim
- ▶ Macrostomia or high-arched/cleft palate (if present)

### Applied / Clinical anatomy

- ▶ **Airway risk:** mandibular hypoplasia narrows the oropharyngeal airway, predisposing to **difficult mask ventilation and intubation** and to obstructive sleep apnoea in infancy — a key anaesthetic concern during craniofacial surgery.
- ▶ **Hearing rehabilitation:** middle-ear ossicular anomalies cause bilateral conductive deafness; early audiological assessment and hearing aid/bone-anchored hearing device fitting are essential to prevent speech-language delay.

- ▶ **Surgical reconstruction:** staged craniofacial surgery — malar/zygomatic augmentation (bone graft or alloplastic implant), mandibular distraction osteogenesis, lower-eyelid coloboma repair, and auricular (pinna) reconstruction — follows the same first/second arch skeletal derivatives affected embryologically.
- ▶ **Genetic counselling:** because TCS is autosomal dominant with near-complete penetrance but variable expressivity, an affected parent's offspring carry a 50% recurrence risk regardless of how mildly the parent is affected; however, since ~60% of cases are de novo mutations, most affected children have unaffected parents, and recurrence risk to such parents is low (though germline mosaicism is a recognised, if rare, exception). TCOF1 mutation analysis allows confirmatory and prenatal/preimplantation testing in known families.
- ▶ **Prenatal detection:** severe cases with marked micrognathia and orbital/malar deficiency may be suspected on antenatal ultrasound, prompting planned delivery with airway back-up available.

### High-yield exam pointers

- ▶ TCS = mandibulofacial dysostosis = Franceschetti–Zwahlen–Klein syndrome; described by Edward Treacher Collins, 1900.
- ▶ Autosomal dominant; incidence ≈ 1:50,000 births; ~60% new (de novo) mutations.
- ▶ Gene: TCOF1, chromosome 5q32; product = **treacle**, a nucleolar protein required for rRNA biogenesis.
- ▶ Mechanism: haploinsufficiency → impaired rRNA biogenesis → **apoptosis** of neuroepithelial cells and neural crest precursors (survival/proliferation defect, **not** a migration defect) → deficient ectomesenchyme in 1st and 2nd arches.
- ▶ Near-complete penetrance but highly variable expressivity — even within one family.
- ▶ Classic tetrad: **malar hypoplasia + mandibular hypoplasia + down-slanting palpebral fissures with lower-lid coloboma + ear anomalies with conductive deafness.**
- ▶ Involves BOTH first and second arch neural-crest derivatives (not first arch alone).
- ▶ Grouped with Pierre Robin sequence as the two classic "first arch syndromes"; distinguish from DiGeorge (pouch, not arch, disorder) and hemifacial microsomia (unilateral).
- ▶ Airway and hearing are the two most important applied-anatomy concerns for management.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Gangane — Human Genetics 5e; Brijesh Kumar — Embryology Text & Atlas.

♦ ♦ ♦

## Systemic embryology - cardiovascular

♦ ♦ ♦

## Development of Interventricular septum

Asked in: Paper II 26-Sep-2025 · Paper II May 2019 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — The single primitive ventricle of the tubular heart is partitioned into separate right and left ventricles by growth of the **interventricular (IV) septum** between the 4th and 7th intrauterine weeks. Three components — a thick **muscular part**, a **bulbar (conal) part**, and a thin **membranous part** — arise from different embryonic sources and progressively fuse around a crescentic **interventricular foramen**, which finally closes by the end of the 7th week to give the definitive four-chambered heart. Abnormal fusion of these components, most often at the membranous part, produces the **ventricular septal defect (VSD)**, the commonest congenital cardiac malformation.

### 1. Sources of the interventricular septum

| Component           | Origin                                                                                                                                                                                                                                                            | Nature                                                  |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Muscular part       | Apposition and fusion of the medial (facing) walls of the two dilating primitive ventricles, at the floor of the bulboventricular cavity                                                                                                                          | Thick, myocardial                                       |
| Bulbar (conal) part | Fusion of the <b>right and left bulbar ridges</b> that arise in the wall of the bulbus cordis (conus region), continuous above with the truncal ridges                                                                                                            | Muscular; forms the <b>proximal bulbar/conal septum</b> |
| Membranous part     | Proliferation of subendocardial tissue from (a) the right side of the fused atrioventricular (AV) endocardial cushions (septum intermedium), plus (b) the right and (c) the left bulbar ridges, filling the gap between the bulbar septum and the muscular septum | Thin, fibrous; closes the interventricular foramen      |

*Note on terminology:* Indian embryology texts (Sontakke, IB Singh) describe three named parts as above. Western texts (Sadler/Langman, Moore) describe only two named parts — muscular and membranous — with the same right/left bulbar-ridge tissue counted as two of the three contributors that fuse to form the single membranous part. The underlying developmental events are identical; only the nomenclature differs.

### 2. Formation of the muscular part

- By the end of the **4th week**, the two primitive ventricular pouches begin to expand on either side of the floor of the bulboventricular cavity.
- Their medial walls become apposed and gradually merge, raising a median muscular ridge — the **muscular interventricular septum** — that grows from near the cardiac apex toward the atrioventricular canal.

- ▶ Growth is due initially to **passive dilatation** of the two ventricles on either side of the septum, and later to **active proliferation of myoblasts** within the septum itself, so the septum is formed more by outward growth of the ventricular cavities than by its own active growth.
- ▶ Its free margin is **concave, crescentic and twisted**, presenting a dorsal and a ventral horn: the dorsal horn fuses with the right edge of the dorsal (inferior) AV cushion, and the ventral horn with the left edge of the ventral (superior) AV cushion.
- ▶ A gap persists between this free edge and the fused AV cushions — the **interventricular foramen** — permitting free communication between both ventricles until it closes.
- ▶ Externally, the site of septum formation corresponds to the **bulboventricular sulcus** (interventricular groove).
- ▶ Occasionally the two ventricular walls do not merge completely, leaving a deep apical cleft between the ventricles.

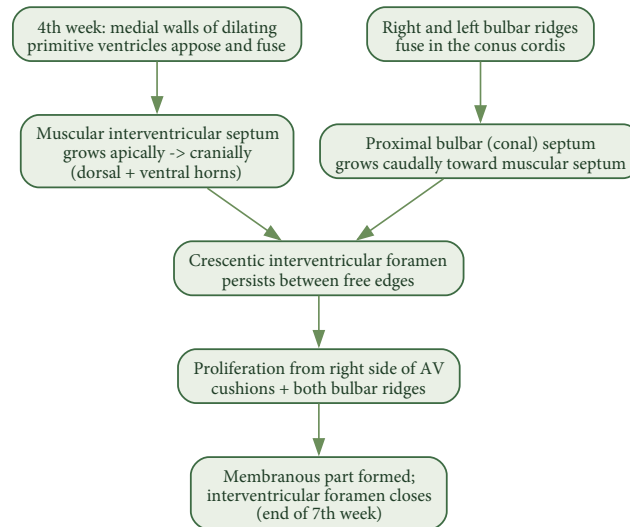
### 3. Formation of the bulbar (conal) part

- ▶ Two ridges — the **right bulbar ridge** (from the dorsal and right wall, cephalic to the right AV orifice) and the **left bulbar ridge** (from the ventral and left wall) — appear in the conus (bulbar) portion of the bulbus cordis, in continuity above with the **truncal ridges** that will form the spiral aortopulmonary septum.
- ▶ The two bulbar ridges grow toward each other and fuse to form the **proximal bulbar (conal) septum**.
- ▶ The right bulbar ridge lies in line with the dorsal horn, and the left ridge with the ventral horn, of the muscular septum — this alignment ensures the pulmonary trunk eventually communicates with the right ventricle and the aorta with the left ventricle.
- ▶ The bulbar septum grows downward toward the muscular septum but does **not quite reach it**, leaving a residual gap.

### 4. Formation of the membranous part and closure of the interventricular foramen

- ▶ The remaining gap — between the free edge of the muscular septum, the lower edge of the bulbar septum, and the fused AV cushions — is filled by **proliferation of tissue from the right side of the AV cushions (septum intermedium)** together with contributions from **both bulbar ridges**.
- ▶ This proliferating tissue fuses with the aortopulmonary (conotruncal) septum above and the muscular septum below, forming the thin **membranous part** of the interventricular septum and permanently sealing the interventricular foramen — normally complete by the **end of the 7th week**.
- ▶ Because the interatrial and interventricular septa do not meet the AV cushions in exactly the same plane, the membranous septum is described as having two components: an **anterior (interventricular) part** separating the right and left ventricles, and a **posterior (atrioventricular) part** separating the left ventricle from the right atrium — the latter is also called the "AV septum".
- ▶ Once closure is complete, the pulmonary trunk communicates exclusively with the right ventricle and the aorta exclusively with the left ventricle.

## 5. Sequence of septation events



*Development of Interventricular septum*

□ Fig 18.11 — Development of the interventricular septum. Muscular part of the interventricular septum develops from muscular ridge, bulbar part from right and left bulbar ridges, and membranous part from proliferation of AV cushion (Sontakke — Textbook of Human Embryology, p.185)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Frontal/coronal section of the embryonic heart at 5–7 weeks showing: primitive right and left ventricles; **muscular interventricular septum** with its concave free margin and dorsal/ventral horns; **right bulbar ridge** and **left bulbar ridge** fusing into the **bulbar (conal) septum**; fused **atrioventricular (AV) endocardial cushions (septum intermedium)**; the **interventricular foramen** as a gap between all three; the **membranous part** filling the gap; continuity with the **aorticopulmonary (conotruncal) septum** above.
- ▶ Label the pulmonary trunk opening into the right ventricle and the aorta into the left ventricle after septation is complete.

## Applied / Clinical anatomy

- ▶ **Ventricular septal defect (VSD)** is the **most common congenital malformation of the heart** ( $\approx$  one-fifth to one-quarter of all congenital heart defects), more frequent in males than females; the isolated form has an incidence of about **12 per 10,000 live births**.
- ▶ Embryological basis: failure of complete fusion of the right and left bulbar ridges with the atrioventricular cushions — the defect most commonly, and most seriously, involves the **membranous part** of the septum.
- ▶ Clinico-anatomical classification of VSD (as seen from the right ventricle):

| Type           | Anatomical basis                                                                                                                    |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Perimembranous | Abuts the central fibrous body/membranous septum; can extend into the inlet, apical trabecular or outlet components; commonest type |
| Muscular       | Lies entirely within the muscular septum; may be multiple, producing a "Swiss-cheese" septum                                        |



| Type                              | Anatomical basis                                                                                                                                                 |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Doubly committed (juxta-arterial) | Lies beneath the conjoined facing leaflets of the aortic and pulmonary valves, due to failure of formation of the free-standing subpulmonary infundibular septum |

- ▶ **Surgical importance:** in perimembranous defects, the **atrioventricular bundle (of His)** and its branches always run along the **postero-inferior margin** of the defect (the membranous septum forms part of the central fibrous body that the bundle penetrates) — surgical closure must avoid this margin to prevent iatrogenic **complete heart block**.
- ▶ About 30–50% of small (usually muscular) VSDs close spontaneously within the first year of life.
- ▶ Associated malformations from disordered bulbar/conotruncal septation:
  - **Tetralogy of Fallot** — VSD + overriding aorta + infundibular pulmonary stenosis + right ventricular hypertrophy, from unequal (anterior/cephalad) deviation of the conotruncal (bulbar) septum.
  - **Taussig–Bing anomaly** — double-outlet right ventricle with a subpulmonary VSD.
  - **Eisenmenger complex/syndrome** — a large VSD with pulmonary hypertension and eventual right-to-left shunt reversal with cyanosis.
  - Complete failure of septum formation gives a **common/single ventricle (cor triloculare biatriatum)** — rare.
  - **Holt–Oram syndrome** (TBX5 gene mutation) combines atrial/ventricular septal defects with preaxial upper-limb anomalies, reflecting the shared role of TBX5 in cardiac septation and limb patterning.
- ▶ Clinically, membranous VSDs are best auscultated as a pansystolic murmur at the left lower sternal border and are assessed echocardiographically for size, shunt direction and associated conotruncal anomalies.

### High-yield exam pointers

- ▶ Interventricular septum has **three sources**: muscular (myocardial fusion of ventricular walls), bulbar/conal (fusion of right & left bulbar ridges), membranous (proliferation from AV cushions + both bulbar ridges).
- ▶ Muscular part begins forming by the **end of the 4th week**; its free edge has **dorsal and ventral horns**.
- ▶ Membranous part forms from **three tissues**: right AV cushion tissue, right bulbar ridge, left bulbar ridge.
- ▶ Interventricular foramen normally closes by the **end of the 7th week**, completing septation.
- ▶ VSD is the **commonest congenital heart defect**; the **membranous part** is the commonest and most serious site.
- ▶ Perimembranous VSD is closely related to the **AV bundle of His** running along its postero-inferior margin — key surgical hazard (heart block).
- ▶ Associated anomalies to recall: **Tetralogy of Fallot, Taussig–Bing anomaly, Eisenmenger complex/syndrome, cor triloculare biatriatum, Holt–Oram syndrome**.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Sontakke's Textbook of Human Embryology; IB Singh's Human Embryology (CBME 2021); Gray's Anatomy (Standring) 41e. Coverage note: Gray's Anatomy's dedicated embryology chapter carries little developmental detail on the interventricular septum specifically (confirmed by targeted search); the developmental sequence and figure are grounded in Langman/Moore/Sontakke/IB Singh, while the VSD clinical classification and AV-bundle relation are grounded in Gray's adult-heart and congenital-heart-disease chapters.



## Aorto-pulmonary septum

Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy

**Definition / Introduction** The aorticopulmonary (aortopulmonary) septum — also called the **spiral septum** — is the spirally-twisted partition that divides the common arterial outflow channel of the primitive heart, the **truncus arteriosus**, into the **ascending aorta** and the **pulmonary trunk**. It arises in the 5th week of intrauterine life from fusion of two **truncal ridges**, built predominantly of **cardiac neural crest**-derived mesenchyme, that are continuous below with the **bulbar (conotruncal) ridges** of the bulbus cordis. Its 180° spiral course explains why the aorta and pulmonary trunk wind around one another in the adult, and mal-formation or mal-orientation of this septum underlies an important group of conotruncal congenital cardiac anomalies.

### 1. Site and embryological origin

- ▶ The truncus arteriosus is the most cranial (distal) of the primitive subdivisions of the embryonic heart tube (sinus venosus, primitive atrium, primitive ventricle, bulbus cordis/conus cordis, truncus arteriosus) — continuous distally with the **aortic sac** and proximally with the **bulbus cordis (conus cordis)**.
- ▶ The septum is built by **cardiac neural crest cells**, which originate at the edges of the neural folds in the hindbrain (rhombomeric) region and **migrate through pharyngeal arches 3, 4 and 6** into the walls of the truncus and conus, where they proliferate to form the truncal and bulbar ridges.
- ▶ **Timing**: active mesenchymal proliferation and ridge formation begins in the **5th week**; the ridges fuse and septation is essentially complete by about the 6th–7th week.
- ▶ Lengthening/patterning of the outflow tract itself is driven by the **second heart field (SHF)**; migration and proliferation of the neural crest cells within it are, in turn, regulated by the SHF acting through **NOTCH signalling**.

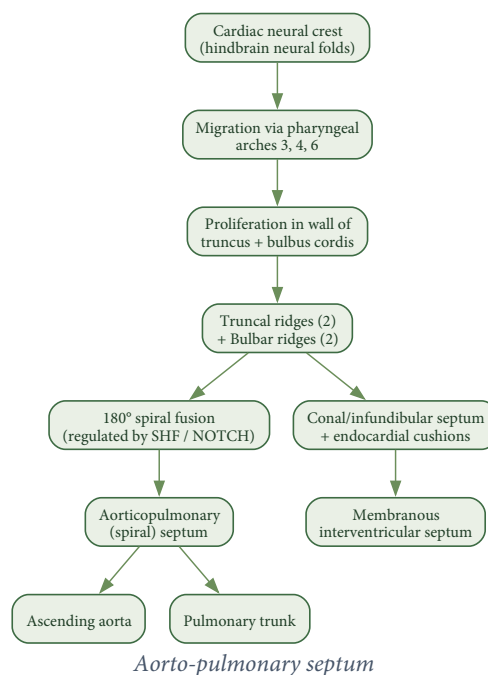
### 2. Formation of the truncal and bulbar (conotruncal) ridges

| Ridge                                                                     | Location                       | Forms                                                    |
|---------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------|
| <b>Truncal ridges</b> (2 — a right-superior and a left-inferior swelling) | Wall of the truncus arteriosus | Fuse to form the <b>aorticopulmonary (spiral) septum</b> |

| Ridge                                                               | Location                          | Forms                                                                                                                                                                                                |
|---------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bulbar (conal) ridges (2, continuous below with the truncal ridges) | Wall of the bulbus cordis (conus) | Fuse to form the <b>conal/infundibular septum</b> , which — together with the endocardial cushions — closes the interventricular foramen and completes the <b>membranous interventricular septum</b> |

- The truncal ridges grow toward the conical part of the ventricle and fuse with each other to form the spiral septum. Because the plane of fusion twists through 180°, the relationship of the aorta to the pulmonary trunk differs at different levels of the outflow tract — a frequently tested point:

| Level of septum                | Plane           | Relationship of great vessels                                                                       |
|--------------------------------|-----------------|-----------------------------------------------------------------------------------------------------|
| Lower (close to the ventricle) | Coronal         | Pulmonary trunk lies <b>anterior</b> , ascending aorta <b>posterior</b>                             |
| Middle                         | Sagittal        | Aorta and pulmonary trunk lie <b>side by side</b> — aorta on the right, pulmonary trunk on the left |
| Upper (near the aortic sac)    | Coronal (again) | Aorta lies <b>anterior</b> , pulmonary trunk <b>posterior</b>                                       |



### 3. Continuity with the rest of the outflow-tract septum

- **Below:** the truncal ridges are continuous with the bulbar (conotruncal) ridges; their fusion forms the conotruncal/infundibular septum, which joins tissue from the endocardial cushions of the atrioventricular canal to close the membranous part of the interventricular septum — this is why a defect of the aorticopulmonary/conotruncal septum is so often paired with a VSD.

- ▶ **Above:** the spiral septum extends into the **aortic sac**, fusing with its posterior wall so that the right and left horns of the aortic sac come to lie in continuity with the pulmonary trunk and aorta respectively, connecting onward to the aortic-arch-artery derivatives.
- ▶ **Semilunar valves:** once truncal septation is almost complete, subendocardial swellings appear around each new orifice (derived in part from the truncal ridges, in part from intercalated swellings) and hollow out on their upper surface to form the cusps of the **aortic and pulmonary semilunar valves**; neural crest cells contribute to these valve cusps as well.

□ Fig 18.12 — Development of truncus arteriosus. Spiral aorticopulmonary septum divi (Sontakke — Textbook of Human Embryology, p.186)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label a transverse-section series through the truncus arteriosus at three levels (lower/coronal, middle/sagittal, upper/coronal), showing:

- ▶ Truncus arteriosus (undivided) with **right-superior and left-inferior truncal ridges** approaching each other
- ▶ **Bulbar ridges** continuous below with the truncal ridges, in the conus of the right ventricle
- ▶ The completed **aorticopulmonary (spiral) septum**, coloured to show its spiral twist
- ▶ **Ascending aorta** and **pulmonary trunk** labelled at each level with their changing anteroposterior/side-by-side relationship
- ▶ **Semilunar valve cusps** (3 each) forming around the newly separated orifices
- ▶ An arrow/label indicating **cardiac neural crest cell migration** from the pharyngeal arches into the ridges

### Applied / Clinical anatomy

- ▶ **Persistent (common) truncus arteriosus:** the truncal ridges/aorticopulmonary septum fail to develop at all, so the truncus remains undivided — a single great vessel (with a single, often abnormal, semilunar valve) overrides both ventricles and gives origin to the aorta, pulmonary arteries, and coronary arteries; it is **always accompanied by a VSD** because the conotruncal septum also fails to contribute to the membranous interventricular septum.
- ▶ **Aorticopulmonary window (aortopulmonary septal defect):** a localized failure of fusion of the septum leaving a communication ("aortic window") between the ascending aorta and pulmonary trunk near the valves; distinguished from persistent truncus arteriosus by the presence of two separate, normally formed semilunar valves and an intact interventricular septum.
- ▶ **Transposition of the great vessels (TGA):** results from **non-spiral (straight) development** of the aorticopulmonary septum, due to abnormal migration of neural crest cells in the truncal ridges — the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle; survival after birth requires a shunt (PDA, ASD, or VSD) to permit mixing of the two circulations.
- ▶ **Unequal partitioning of the truncus:** asymmetric growth of the septum makes one great vessel large and the other small/stenotic; the aorticopulmonary septum then fails to align with the interventricular septum, producing a VSD with the larger vessel overriding it — the basis of

**pulmonary/aortic valvular stenosis or atresia** and of the outflow-tract component of **Tetralogy of Fallot** (pulmonary stenosis, overriding aorta, VSD, right ventricular hypertrophy).

- ▶ **DiGeorge sequence (22q11 deletion syndrome)**: deficient cardiac neural crest migration into pharyngeal arches 3, 4 and 6 causes conotruncal septal defects (persistent truncus arteriosus, tetralogy of Fallot, interrupted aortic arch type B), together with thymic and parathyroid hypoplasia and craniofacial anomalies — because the same neural crest population patterns both the face and the outflow-tract septum.
- ▶ **Teratogenicity**: retinoic acid (vitamin A) is a potent neural-crest teratogen; excess exposure in early pregnancy can produce craniofacial defects together with conotruncal anomalies such as transposition of the great vessels.

### High-yield exam pointers

- ▶ Aorticopulmonary (spiral) septum = fusion product of **two truncal ridges** in the truncus arteriosus.
- ▶ Ridges are formed by **cardiac neural crest cells** migrating through **pharyngeal arches 3, 4, 6**; migration/proliferation is regulated by the **SHF via NOTCH signalling**.
- ▶ The septum is **spiral**, not straight — hence the changing coronal/sagittal/coronal relationship of aorta and pulmonary trunk from below upward, and their twisted course in the adult.
- ▶ Continuous below with the **bulbar/conotruncal ridges**, which help close the **membranous interventricular septum**.
- ▶ **Failure of the septum** → **persistent truncus arteriosus** (always with a VSD); **localized failure** → **aorticopulmonary window** (valves and IV septum intact — key differentiator).
- ▶ **Non-spiral development** → **transposition of the great vessels**.
- ▶ **Unequal partitioning** → **pulmonary/aortic stenosis or atresia**, and the outflow component of **Tetralogy of Fallot**.
- ▶ **DiGeorge/22q11 deletion** = neural crest deficiency linking conotruncal heart defects with craniofacial and thymic/parathyroid anomalies.
- ▶ Semilunar valve cusps develop from subendocardial swellings once truncal septation is nearly complete.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Vishram Singh, Textbook of Clinical Embryology; IB Singh, Human Embryology (CBME 2021); Sontakke, Textbook of Human Embryology (figure); Gray's Anatomy (Standring) 41e.



## Cardinal system of veins

Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy

**Definition / Introduction** The cardinal system of veins is the paired **somatic (parietal) venous system** of the early embryo, one of the three primitive venous complexes (vitelline, umbilical and cardinal) that drain into the horns of the sinus venosus. It is called "cardinal" (Latin *cardo* — hinge/important) because it forms the principal venous drainage of the embryonic body wall before the adult caval system is established. It appears in the 4th week as paired **anterior (precardinal)** and **posterior (postcardinal)** cardinal veins that unite on each side to form a short **common cardinal vein (duct of Cuvier)**; from the 5th–7th weeks this primary system is progressively remodelled by three subsidiary channels — the **subcardinal, supracardinal and azygos-line veins** — whose asymmetric survival and regression construct the definitive **superior and inferior venae cavae, azygos system, renal and gonadal veins**.

### Formation of the primary cardinal venous system (4th week)

- ▶ Represented, on each side, by two vessels: the **anterior (precardinal) cardinal vein**, rostral to the heart, draining the head, neck and forelimb bud; and the **posterior (postcardinal) cardinal vein**, caudal to the heart, draining the trunk, mesonephros and hindlimb bud.
- ▶ On each side the anterior and posterior cardinal veins unite to form a short **common cardinal vein**, which runs ventrally, lateral to the pleuropericardial canal, and opens into the corresponding (right or left) **horn of the sinus venosus**.
- ▶ At this stage the system is perfectly **symmetrical** — each sinus horn receives, from medial to lateral, the vitelline vein, the umbilical vein and the common cardinal vein.
- ▶ The cranial part of the anterior cardinal vein constitutes the **primary head vein**, which runs ventral to the neural tube alongside the trigeminal ganglion and drains a superficial and a deep dural venous plexus (future dural sinuses and cerebral veins).
- ▶ The posterior cardinal veins alone are insufficient to drain the rapidly enlarging mesonephros, gonads and body wall, so from the 5th week they are progressively supplemented — and largely replaced — by the subcardinal and supracardinal systems described below.

### Secondary (subsidiary) venous channels that supplement/replace the posterior cardinal veins

| Channel             | Site                                                                                                      | Chief drainage                                                                           | Later fate                                                     |
|---------------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Subcardinal veins   | Ventromedial part of the mesonephric ridge, linked to the postcardinal veins by transverse vessels        | Mesonephros; intercommunicate by a <b>pre-aortic (intersubcardinal) anastomosis</b>      | Renal segment of the IVC; renal, suprarenal and gonadal veins  |
| Supracardinal veins | Dorsolateral to the aorta, lateral to the sympathetic trunk ("thoracolumbar" or lateral-sympathetic line) | Takes over intersegmental (intercostal/lumbar) drainage from the posterior cardinal vein | Postrenal (infrarenal) segment of IVC; azygos/hemiazygos veins |

| Channel                      | Site                                                                                   | Chief drainage                                                                   | Later fate                                                      |
|------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Azygos-line veins            | Dorsolateral to the aorta, medial to the sympathetic trunk ("medial sympathetic line") | Joins cranially with the persisting cranial ends of the posterior cardinal veins | Arch/terminal part of the azygos vein                           |
| Subcentral veins             | Directly dorsal to the aorta, between paired intersegmental arteries                   | Communicate with the azygos-line veins                                           | Retro-aortic parts of the left lumbar veins and hemiazygos vein |
| Precostal (lumbocostal) line | Anterior to the costal element, posterior to the supracardinal vein                    | Inconstant                                                                       | Possible origin of the ascending lumbar vein                    |

- The most cranial of the supracardinal–subcardinal and inter-subcardinal anastomoses, together with the caudal continuation, complete a venous ring around the aorta just below the origin of the superior mesenteric artery — the "**renal collar**." Persistence of both anterior and posterior limbs of this collar underlies retro-aortic/circumaortic renal-vein anomalies (see Applied anatomy).

### Fate of the anterior and common cardinal veins — formation of the SVC and its tributaries

- An oblique (transverse) intercardinal anastomosis forms between the two anterior cardinal veins, proximal to their junction with the developing subclavian veins; this diverts venous return from the left side of the head and left upper limb to the right, and is the single most important event asymmetrizing the cranial cardinal system.
- The caudal part of the left anterior cardinal vein and the whole of the left common cardinal vein retrogress after this shunt is established, leaving only small residual vessels.

| Adult structure                            | Embryological derivation                                                                          |
|--------------------------------------------|---------------------------------------------------------------------------------------------------|
| Superior vena cava — intrapericardial part | Right common cardinal vein                                                                        |
| Superior vena cava — extrapericardial part | Right anterior cardinal vein, caudal to the intercardinal anastomosis                             |
| Right brachiocephalic vein                 | Right anterior cardinal vein, between the anastomosis and the right subclavian vein junction      |
| Left brachiocephalic vein                  | Oblique intercardinal anastomosis + corresponding part of left anterior cardinal vein             |
| Internal jugular veins                     | Anterior cardinal veins, cranial to the subclavian vein junction (each side)                      |
| External jugular veins                     | Secondary channels formed in situ in the face — <b>not</b> cardinal-vein derivatives              |
| Subclavian veins                           | Intersegmental veins draining the developing upper limb bud that join the anterior cardinal veins |



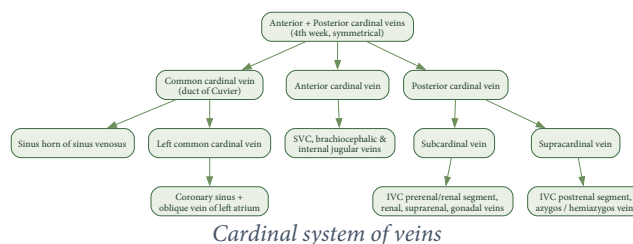
| Adult structure                               | Embryological derivation                                                                                            |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Left superior intercostal vein                | Left anterior cardinal vein (caudal to the anastomosis) + the most cranial part of the left posterior cardinal vein |
| Coronary sinus                                | Left horn of the sinus venosus + proximal part of the left common cardinal vein                                     |
| Oblique vein of the left atrium (of Marshall) | Distal (remaining) part of the left common cardinal vein                                                            |

### Fate of the posterior/subcardinal/supracardinal veins — formation of the IVC, renal and gonadal veins

- The inferior vena cava is a composite vessel assembled from four segments, each of separate embryological origin:

| Segment of IVC                        | Embryological origin                                                              |
|---------------------------------------|-----------------------------------------------------------------------------------|
| Hepatic segment                       | Right vitelline vein / right hepatocardiac channel (through the developing liver) |
| Prerenal (suprarenal) segment         | Right subcardinal vein                                                            |
| Renal segment                         | Right supracardinal–subcardinal ("suprasubcardinal") anastomosis                  |
| Postrenal (infrarenal/caudal) segment | Right supracardinal vein                                                          |

- **Common iliac veins:** the right forms from the most caudal part of the right posterior cardinal vein; the left forms from the **iliac (transverse) anastomosis** that develops between the two posterior cardinal veins.
- **Renal veins:** the right renal vein is a mesonephric tributary draining directly into the subcardinal-derived IVC. The left renal vein is composite — part mesonephric vein, part residual left subcardinal vein, and part the **intersubcardinal (pre-aortic) anastomosis** — which is why it crosses in front of the aorta.
- **Suprarenal and gonadal veins** are remnants of the subcardinal veins above and below, respectively, the intersubcardinal anastomosis; this asymmetric origin explains why the right suprarenal and gonadal veins drain directly into the IVC while their left-sided counterparts drain into the left renal vein.
- **Azygos vein:** chiefly the right supracardinal vein (thoracic part) together with the cranial (arch) end of the right posterior cardinal vein.
- **Hemiazygos vein:** the corresponding left-sided supracardinal (thoracolumbar-line) derivative, draining into the azygos vein through the retro-aortic subcentral/azygos-line anastomoses.



□ Fig 19.15 — Development of inferior vena cava. Segments of inferior vena cava develop by anastomosis of anterior/posterior cardinal, subcardinal and supracardinal veins (Sontakke — Textbook of Human Embryology, p.205)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A four-panel schematic (week 6 → week 7 → week 8 → at birth) of the paired longitudinal channels flanking the aorta, labelled with:

- ▶ Sinus venosus and common cardinal vein at the cranial end
- ▶ Anterior (precardinal) vein and posterior (postcardinal) vein on each side
- ▶ Right vitelline vein / hepatocardiac channel and developing liver
- ▶ Right and left subcardinal veins, with the subcardinal (intersubcardinal) anastomosis
- ▶ Supracardinal veins, with the supra-subcardinal anastomosis
- ▶ Posterior cardinal (iliac) anastomosis at the caudal end
- ▶ Final labelled adult vessel: superior vena cava, azygos vein, hemiazygos vein, hepatic/prerenal/renal/postrenal segments of the IVC, left renal vein, left suprarenal vein, left gonadal vein, common iliac veins

### Applied / Clinical anatomy

- ▶ **Double (duplicated) inferior vena cava:** persistence of the left supracardinal vein alongside the right, so that a left-sided IVC (draining into the left renal vein) runs parallel to the normal right-sided IVC below the renal veins — an important incidental CT finding before retroperitoneal or aortic surgery.
- ▶ **Absence of the (hepatic segment of the) IVC with azygos continuation:** failure of the right subcardinal vein to connect with the hepatic (vitelline) channel; venous return from the lower body bypasses the liver via the azygos vein into the SVC, while hepatic veins drain directly into the right atrium — classically associated with polysplenia/left-isomerism syndromes.
- ▶ **Double superior vena cava:** persistence of the left anterior cardinal vein with failure of the oblique intercardinal (future left brachiocephalic) anastomosis to form; the persistent left SVC usually drains into the right atrium via an enlarged **coronary sinus**.
- ▶ **Left-sided (single) SVC:** persistence of the left anterior and common cardinal veins with obliteration of the right-sided vessels — rare, but the coronary sinus is again the usual drainage route.
- ▶ **Retro-aortic / circumaortic left renal vein:** the left renal vein normally forms from an anterior (intersubcardinal) and a posterior (subcentral/retro-aortic) limb of the "renal collar"; persistence of the posterior limb alone gives a solitary retro-aortic left renal vein, and persistence of both gives a circumaortic (venous ring) renal vein — relevant to nutcracker syndrome and to safe clamping/ligation during aortic and renal surgery.
- ▶ **Left renal vein ligation:** because it receives the left gonadal and suprarenal veins as collaterals, the left renal vein can be ligated (medial to these tributaries) during aortic aneurysm repair without renal compromise; the right renal vein has no such collateral and cannot be ligated safely.

- ▶ **Left superior intercostal vein ("aortic nipple")**: the derivative of the left anterior/posterior cardinal remnant seen as a small bulge on the aortic knuckle on a chest radiograph, prominent when azygos/hemiazygos flow is obstructed.

### High-yield exam pointers

- ▶ Cardinal system = paired **somatic** venous drainage of the embryo; one of the three primitive venous systems (vitelline, umbilical, cardinal) entering the sinus venosus.
- ▶ Primary system (4th week): **anterior + posterior cardinal veins** → **common cardinal vein (duct of Cuvier)** → **sinus horn**; symmetrical at this stage.
- ▶ Subsidiary systems (5th–7th week) that remodel the posterior cardinal veins: **subcardinal, supracardinal, azygos-line, subcentral, precostal**.
- ▶ **SVC** = right common cardinal vein (intrapericardial) + right anterior cardinal vein (extrapericardial); **left brachiocephalic vein** = oblique intercardinal anastomosis.
- ▶ **IVC has four segments** of different origin: hepatic (vitelline/hepatocardiac), prerenal (right subcardinal), renal (suprasubcardinal anastomosis), postrenal (right supracardinal).
- ▶ **Left renal vein** is composite (mesonephric vein + left subcardinal remnant + intersubcardinal anastomosis) — hence its pre-aortic course and its collateral gonadal/suprarenal tributaries.
- ▶ **Coronary sinus** = left sinus horn + proximal left common cardinal vein; **oblique vein of left atrium (Marshall)** = distal left common cardinal vein.
- ▶ **Azygos vein** = right supracardinal + cranial posterior cardinal remnant; **hemiazygos** = left-sided supracardinal counterpart.
- ▶ Classic anomalies: double IVC, IVC agenesis with azygos continuation, double/left SVC, retro-aortic or circum-aortic left renal vein — each traceable directly to failure of a specific cardinal-vein anastomosis or regression step.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; Brijesh Kumar — Embryology Text & Atlas.



## Changes in the foetal circulation after birth, and the factors affecting each change

Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy

**Definition / Introduction.** In the fetus the lungs are collapsed and non-functional and the liver receives only a small hepatic-artery inflow, so blood is diverted around both organs by three physiological **shunts** — the **ductus venosus**, the **foramen ovale**, and the **ductus arteriosus** — while gas and nutrient exchange occurs across the **placenta** via the paired **umbilical arteries** and the **umbilical vein**. At birth, two nearly simultaneous events — **aeration of the lungs** with the first breath, and **cessation of umbilical/placental flow** on clamping of the cord — trigger a cascade of pressure and chemical changes that converts this single fetal circuit into the mature, **series-arranged pulmonary and systemic circulations**. Each shunt closes in two stages, an immediate **functional closure** followed later by a slower **anatomical (structural) closure**, and each is driven by its own distinct set of mechanical and humoral factors.

### 1. The fetal pattern being replaced

- ▶ The **placenta** is the fetal organ of respiration, nutrition and excretion; well-oxygenated blood returns to the fetus in the **umbilical vein**, and deoxygenated, waste-laden blood is returned to the placenta by the paired **umbilical arteries** (branches of the internal iliac arteries).
- ▶ Three shunts allow blood to bypass the non-aerated lungs and the immature liver:
- ▶ **Ductus venosus** — carries oxygenated umbilical venous blood directly into the inferior vena cava, bypassing the hepatic sinusoids (about half the umbilical venous return takes this route; the rest perfuses the liver via the left portal vein).
- ▶ **Foramen ovale** — the flap-valve gap in the interatrial septum through which the crista dividens directs the more highly oxygenated inferior-vena-caval stream from the right atrium into the left atrium.
- ▶ **Ductus arteriosus** — connects the pulmonary trunk to the aortic arch just distal to the left subclavian artery, carrying the bulk of right-ventricular output directly into the descending aorta since the collapsed fetal lungs offer very high vascular resistance.
- ▶ Because of this arrangement, the fetal pulmonary and systemic circuits work essentially **in parallel**, not in series, and the two ventricles pump almost equal, admixed volumes.

□ Fig 19.18 — Foetal circulation. Blood shunts three times in foetus at following places: Ductus arteriosus, foramen ovale and ductus venosus, to bypass lungs and liver (Sontakke — Textbook of Human Embryology, p.208)

### 2. The two master triggers of change at birth

- ▶ **Aeration of the lungs at the first breath** — alveolar expansion and the sharp rise in arterial oxygen tension cause a dramatic **fall in pulmonary vascular resistance** and a correspondingly **large rise in pulmonary blood flow**; more blood now returns through the pulmonary veins, raising left atrial pressure.
- ▶ **Clamping/separation of the umbilical cord** — abrupt cessation of the low-resistance placental circuit removes the large venous return that had been entering the inferior vena cava and right atrium, so **right atrial pressure falls**, and the driving pressure that had kept the ductus venosus and umbilical vessels open disappears.

- Acting together, these two events reverse the atrial pressure gradient, raise systemic vascular resistance (loss of the low-resistance placental bed), and expose the ductal wall to a sharply higher local oxygen tension — the combination that closes every fetal shunt.

### 3. Vessel-by-vessel changes and the factors responsible

| Fetal structure             | Fetal role                                                                         | Principal factors/mechanism of closure                                                                                                                                                                                                                      | Timing of closure                                                                                                                                     | Adult remnant                                                                                             |
|-----------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Umbilical arteries (paired) | Carry deoxygenated, waste-laden blood from fetus to placenta                       | Reflex contraction of the thick muscular wall at birth, potentiated by <b>bradykinin</b> (released as the cord cools and from the aerating lung)                                                                                                            | Functional closure within seconds of cord clamping; anatomical obliteration of the lumen over about 2–3 months                                        | Distal part → <b>medial umbilical ligament</b> ; proximal (patent) stump → <b>superior vesical artery</b> |
| Umbilical vein              | Carries oxygenated, nutrient-rich blood from placenta to fetus                     | Contracts a few minutes <i>after</i> the arteries — this delay lets residual placental blood drain into the newborn before flow ceases; cessation of flow after cord clamping                                                                               | Functional closure within minutes; the lumen often stays patent for weeks (used clinically for exchange transfusion/umbilical venous catheterisation) | <b>Ligamentum teres hepatis</b> (round ligament of the liver)                                             |
| Ductus venosus              | Shunts oxygenated umbilical-venous blood into the IVC, bypassing hepatic sinusoids | Loss of umbilical venous inflow removes the pressure head keeping it open; withdrawal of locally-acting <b>prostaglandins</b> that maintained its patency in fetal life; contraction of an intrinsic sphincter at its junction with the left umbilical vein | Functional closure within minutes–hours; structural closure in about 3–7 days                                                                         | <b>Ligamentum venosum</b>                                                                                 |

| Fetal structure                                  | Fetal role                                                                                           | Principal factors/mechanism of closure                                                                                                                                                                                                                                                                                                                                                                                      | Timing of closure                                                                                                                                                                                    | Adult remnant                                                                                 |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Foramen ovale</b><br>(valve of septum primum) | Directs the oxygen-rich IVC stream from right atrium to left atrium                                  | Reversal of the atrial pressure gradient — increased pulmonary venous return raises left atrial pressure while loss of umbilical/IVC flow lowers right atrial pressure, pressing the flexible septum-primum valve against the rigid septum secundum                                                                                                                                                                         | Functional closure at the first breath; anatomical fusion of the two septa is progressive (fewer than 3% fused by 2 weeks, about 87% by 4 months, essentially complete within about a year)          | <b>Fossa ovalis</b> (floor = septum primum; rim = limbus fossae ovalis, from septum secundum) |
| <b>Ductus arteriosus</b>                         | Shunts right-ventricular/pulmonary-trunk output into the descending aorta, bypassing collapsed lungs | Rise in arterial $pO_2$ (to about 50 mmHg) on lung aeration causes ductal smooth-muscle contraction, reinforced by a fall in circulating <b>prostaglandin <math>E_2</math>/prostacyclin (<math>PGI_2</math>)</b> (loss of the placental source), a rise in <b>catecholamines</b> and <b>bradykinin</b> , and a fall in <b>adenosine</b> ; later, endothelial damage and platelet-plug formation, then intimal proliferation | Functional closure over hours (about 20% closed by 24 h, 80% by 48 h, essentially 100% by 96 h in term infants); anatomical closure/fibrosis by about 2–3 weeks, complete by the 12th postnatal week | <b>Ligamentum arteriosum</b>                                                                  |

#### 4. Ductus arteriosus — the closure mechanism in detail

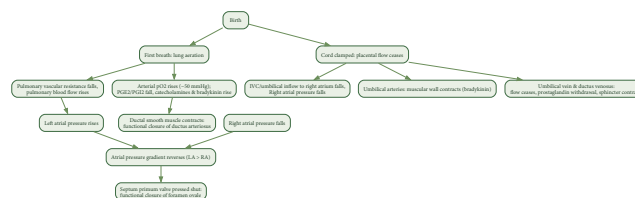
- **Oxygen is the single most important factor.** In fetal life the low  $pO_2$  of the blood passing through the duct, together with locally produced  **$PGE_2$  and  $PGI_2$** , keeps ductal smooth muscle relaxed. At birth, reversed flow of highly oxygenated aortic blood raises local  $pO_2$  sharply, suppressing prostacyclin synthesis and exposing the duct to unopposed contractile prostaglandin endoperoxides.

- **Bradykinin**, released from the lung on its initial inflation, is a potent additional constrictor acting synergistically with the rise in oxygen tension; a fall in circulating adenosine contributes similarly.
- **TGF- $\beta$**  is implicated in the later, permanent anatomical closure; a platelet plug (responding to endothelial ischaemic damage from the constriction itself) is also required, in addition to smooth-muscle contraction, for complete occlusion.
- **Factors that keep the duct open** (exploited clinically) mirror the closure factors exactly: hypoxia, prematurity, and circulating prostaglandins.

## 5. Foramen ovale and ductus venosus — closure mechanism in detail

- **Foramen ovale closure** is a purely mechanical (pressure) event, not a chemical one — no local vasoactive mediator is needed, unlike the ductus arteriosus. Both halves of the pressure reversal (rising LA pressure from the pulmonary side, falling RA pressure from the umbilical/systemic side) must occur together; if pulmonary expansion is delayed, the gradient may not reverse and a functional right-to-left shunt persists.
- **Premature in-utero narrowing/closure of the foramen ovale** causes right ventricular volume/pressure overload, fetal right ventricular hypertrophy and, if severe, hydrops.
- **Ductus venosus closure** follows (a) abrupt loss of umbilical venous inflow on cord clamping, removing its functional necessity, and (b) withdrawal of the prostaglandins that maintained its patency in utero; the precise signal for its active postnatal constriction is not fully understood, but a normal hepatic portal circulation is established within a few days.

## 6. Sequence of postnatal circulatory adaptation



*Changes in the foetal circulation after birth, and the factors affecting each change*



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a schematic of the neonatal thorax/abdomen showing the postnatal derivatives, labelling in sequence:

- ▶ SVC/IVC entering the **right atrium**; **fossa ovalis** with its **limbus** in the interatrial septum (in place of the foramen ovale)
- ▶ **Pulmonary trunk**, with the **ligamentum arteriosum** running from the left pulmonary artery to the **arch of the aorta** (in place of the ductus arteriosus); **descending aorta** to the internal iliac arteries
- ▶ The **liver**, showing the **ligamentum teres hepatis** from umbilicus to porta hepatis (in place of the left umbilical vein), and the **ligamentum venosum** within the liver joining the left portal vein to the IVC (in place of the ductus venosus)
- ▶ The **anterior abdominal wall**, umbilicus to bladder, showing the midline **median umbilical ligament** (urachus), the paired **medial umbilical ligaments** (obliterated umbilical arteries) continuing proximally as **superior vesical arteries**, and the **lateral umbilical folds** (inferior epigastric vessels, not a vascular remnant) for contrast

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- ▶ **Patent ductus arteriosus (PDA)** — the commonest anomaly of postnatal adaptation; failure of closure produces a continuous "machinery" murmur and left-to-right shunting. 2–3 times more common in females; strongly linked to **prematurity** (virtually universal <28 weeks/<1750 g in the first 24 hours), **high altitude/hypoxia**, and **maternal rubella**. Since closure is prostaglandin-dependent, **PGE<sub>1</sub> infusion** keeps the duct open in duct-dependent lesions awaiting surgery, while **indomethacin/ibuprofen** (prostaglandin-synthesis inhibitors) promote closure of a symptomatic preterm PDA.
- ▶ **Patent foramen ovale (PFO)** — incomplete fusion of septum primum to septum secundum leaves a valve-competent but potential atrial communication that is usually of no functional consequence, but is an important route for **paradoxical embolism** (e.g., venous thrombus crossing to the systemic/cerebral circulation) and can shunt right-to-left with any transient rise in right atrial pressure (Valsalva, crying, straining).
- ▶ **Premature closure of the foramen ovale in utero** causes right ventricular pressure/volume overload, fetal right ventricular hypertrophy, and can progress to fetal hydrops.
- ▶ **Umbilical vein catheterisation/exchange transfusion** exploits the fact that the umbilical vein's lumen frequently remains patent for some weeks after birth; this route is used for exchange transfusion in **erythroblastosis fetalis** and for central venous/umbilical arterial access in the neonate.
- ▶ **Recanalised ligamentum teres** in portal hypertension re-establishes a paraumbilical collateral (**caput medusae**, Cruveilhier–Baumgarten syndrome), reflecting its embryological origin as the obliterated left umbilical vein.
- ▶ **Peritoneal folds of the internal aspect of the anterior abdominal wall** directly reflect these vascular remnants and are a favourite viva correlate: the **median umbilical fold** overlies the median umbilical ligament (urachus), the **medial umbilical folds** overlie the obliterated

umbilical arteries, and the **lateral umbilical folds** overlie the inferior epigastric vessels (not a fetal-circulation remnant) — the intervening suprapubic and medial/lateral inguinal fossae are potential hernial sites.

### High-yield exam pointers

- ▶ Two master triggers of every change: **lung aeration** (raises pulmonary flow/LA pressure, raises arterial pO<sub>2</sub>) and **cord clamping** (abolishes umbilical/placental flow, falls RA pressure).
- ▶ Every fetal shunt closes in **two stages** — an immediate **functional** closure, followed by a slower **anatomical/structural** closure (fibrosis/intimal proliferation) over days to months.
- ▶ **Foramen ovale** closes purely by **pressure reversal** (mechanical); the **ductus arteriosus** closes **chemically/humorally** — rising pO<sub>2</sub>, falling PGE<sub>2</sub>/PGI<sub>2</sub>, rising catecholamines and bradykinin, falling adenosine.
- ▶ **Ductus venosus and umbilical vessels** close because their driving flow (umbilical venous inflow) simply ceases, aided by intrinsic sphincteric/muscular contraction and prostaglandin withdrawal.
- ▶ Remnants to recall as pairs: umbilical arteries → **medial umbilical ligaments** (+ superior vesical arteries proximally); umbilical vein → **ligamentum teres hepatis**; ductus venosus → **ligamentum venosum**; ductus arteriosus → **ligamentum arteriosum**; foramen ovale → **fossa ovalis**.
- ▶ Clinically exploitable: PGE<sub>1</sub> **keeps the duct open**; **indomethacin/ibuprofen close it** — mirrors the same prostaglandin axis responsible for physiological closure.
- ▶ **PDA** — prematurity, maternal rubella, high altitude, female preponderance; **premature FO closure** — fetal RV hypertrophy/hydrops; **PFO** — paradoxical embolism risk.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore's The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke's Textbook of Human Embryology; IB Singh's Human Embryology (CBME 2021); BD Chaurasia's Human Anatomy Vol 2 8e (peritoneal folds correlate).



## Congenital anomalies of heart

Asked in: Paper II Nov 2017 — RGUHS MD/MS Anatomy

**Definition / Introduction** — Congenital heart disease (CHD) comprises structural cardiovascular malformations present at birth, resulting from disruption of the tightly-timed sequence of cardiac looping, septation and outflow-tract division that occurs between the 4th and 8th weeks of intra-uterine life. CHD is the commonest category of human birth defect, with an incidence of about 8 per 1000 live births, rising to nearly 2% among stillbirths, and accounts for roughly one-quarter of all developmental anomalies. Most defects are multifactorial (genetic-plus-environmental); only a minority are attributable purely to a single chromosomal, single-gene or teratogenic cause. Anomalies are conventionally grouped as disorders of atrial/ventricular septation, disorders of the endocardial cushions and AV canal, disorders of outflow-tract (conotruncal) division, anomalies of the great vessels, and anomalies of cardiac position.

### 1. Aetiology and pathogenesis

- ▶ **Chromosomal** — ~12% of CHD infants have a chromosomal abnormality; conversely 33% with a chromosomal abnormality have CHD (e.g. AV septal defect in ~20% of Down syndrome).
- ▶ **Single-gene mutations** — *NKX2.5* (5q35): secundum ASD, tetralogy of Fallot, AV conduction delay; *TBX5*: Holt–Oram syndrome (ASD/VSD + radial limb defects); *JAG1*: Alagille syndrome with tetralogy of Fallot; **22q11 deletion** (DiGeorge): truncus arteriosus, tetralogy of Fallot, interrupted aortic arch type B.
- ▶ **Neural crest / second heart field insults** — impair outflow-tract septation, producing truncus arteriosus, tetralogy of Fallot, VSD, transposition and double-outlet right ventricle.
- ▶ **Teratogens** (~2%) — rubella, thalidomide, retinoic acid, alcohol; **maternal diabetes**.
- ▶ **Multifactorial** — the majority; ~30% of CHD infants have additional major malformations; low monozygotic-twin concordance but higher recurrence with consanguinity.

### 2. Classification of congenital heart disease

| Group                                                          | Mechanism                                                                                                                                             | Examples                                                                           |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Acyanotic — left-to-right shunt</b>                         | Communication allows oxygenated blood to re-enter the pulmonary circuit, causing volume overload and, if uncorrected, pulmonary arterial hypertension | ASD, VSD, patent ductus arteriosus (PDA), AV septal defect                         |
| <b>Acyanotic — obstructive</b>                                 | Narrowing of a valve or vessel without shunting                                                                                                       | Pulmonary/aortic valve stenosis, coarctation of the aorta, interrupted aortic arch |
| <b>Cyanotic — reduced pulmonary flow / right-to-left shunt</b> | Obstruction to right ventricular outflow or discordant connections force desaturated blood into the systemic circulation                              | Tetralogy of Fallot, tricuspid atresia, pulmonary atresia                          |

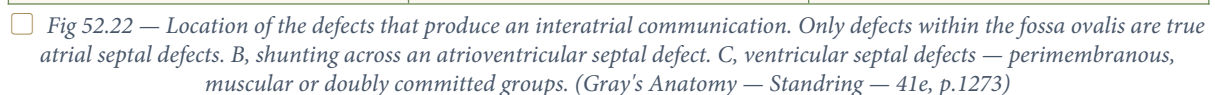
| Group                             | Mechanism                                                | Examples                                                                                                                                                         |
|-----------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cyanotic — complex/mixing lesions | Parallel or abnormal circulations with obligatory mixing | Transposition of the great arteries (TGA), persistent truncus arteriosus, total anomalous pulmonary venous return (TAPVR), hypoplastic left/right heart syndrome |

Overall frequency (Gray's Anatomy): VSD is the single commonest lesion (~1/5 of all cases), followed in descending order by PDA, coarctation of the aorta, pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, aortic stenosis, and hypoplasia of the left heart.

### 3. Atrial septal defects (ASD)

ASD (overall incidence ~6.4/10,000 births, female preponderance) is a persistent communication between the atria; only a defect truly within the fossa ovalis is a "true" ASD.

| Type                                                    | Embryological basis                                                                                                                                              | Notes                                                                                                                                                                                                |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ostium secundum</b> (commonest, within fossa ovalis) | Excessive resorption of septum primum, or deficient/short septum secundum, so the flap valve fails to cover the oval fossa                                       | Well tolerated in childhood; may present with pulmonary hypertension in the 30s; surgical closure mortality <1%                                                                                      |
| <b>Ostium primum</b> (AV septal defect)                 | Septum primum fails to fuse with the AV endocardial cushions                                                                                                     | Usually combined with a cleft in the anterior mitral leaflet; when cushions fail to fuse completely, a common AV orifice results (complete AV canal defect) — strongly associated with Down syndrome |
| <b>Sinus venosus defect</b> (superior or inferior)      | Incomplete absorption of the sinus venosus into the right atrium; superior type near SVC entry, inferior type near IVC entry                                     | Superior type commonly associated with partial anomalous pulmonary venous connection                                                                                                                 |
| <b>Coronary sinus defect / common atrium</b>            | Deficiency of the wall separating coronary sinus from left atrium; complete absence of septum primum + secundum = common atrium (cor triloculare biventriculare) | Common atrium always accompanied by other severe cardiac defects                                                                                                                                     |

 Fig 52.22 — Location of the defects that produce an interatrial communication. Only defects within the fossa ovalis are true atrial septal defects. B, shunting across an atrioventricular septal defect. C, ventricular septal defects — perimembranous, muscular or doubly committed groups. (Gray's Anatomy — Standring — 41e, p.1273)

### 4. Ventricular septal defects (VSD) and AV septal defect

VSD is the commonest isolated congenital cardiac malformation (isolated incidence ~12/10,000 births).

| Type                            | Site                                                                                                                                             | Comments                                                                                                                                                                                                                                              |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Perimembranous (commonest)      | Around the membranous septum, abutting the central fibrous body below the aortic vestibule; related to the septal leaflet of the tricuspid valve | Often combines with aortic override and right ventricular outflow obstruction (the tetralogy-of-Fallot combination); if the pulmonary trunk instead overrides, this is the Taussig-Bing anomaly; the AV bundle runs along its postero-inferior margin |
| Muscular                        | Entirely within the muscular septum; may be multiple ("Swiss-cheese" septum)                                                                     | Small muscular VSDs frequently close spontaneously in the first year                                                                                                                                                                                  |
| Doubly-committed juxta-arterial | Beneath the conjoined facing leaflets of the aortic and pulmonary valves                                                                         | Failure of formation of the free-standing sub-pulmonary infundibulum                                                                                                                                                                                  |

An AV (atrioventricular) septal defect ("complete AV canal") arises from failure of fusion of the endocardial AV cushions, producing a single common AV orifice with a shared valve bridging both ventricles, and a combined atrial + ventricular communication; strongly linked to trisomy 21.

## 5. Cyanotic (outflow-tract / great-vessel) anomalies

| Anomaly                                                          | Embryological defect                                                                                                                   | Key features                                                                                                                                                                                                  |
|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tetralogy of Fallot (commonest cyanotic CHD; ~9.6/10,000 births) | Anterior deviation of the conotruncal (outflow) septum                                                                                 | Four components: (1) infundibular pulmonary stenosis, (2) large VSD, (3) aorta overriding the septal defect, (4) right ventricular hypertrophy; associated with <i>JAG1</i> /Alagille syndrome (90% of cases) |
| Persistent (common) truncus arteriosus                           | Truncal/spiral septum cushions fail to fuse — no division of the outflow tract                                                         | Single arterial trunk with a common valve straddles a large VSD; a right aortic arch is a frequent association                                                                                                |
| Transposition of the great arteries (TGA)                        | Conotruncal (spiral) septum fails to follow its normal spiral course and descends straight — discordant ventriculo-arterial connection | Aorta arises from the right ventricle, pulmonary trunk from the left; survival requires a shunt (PFO/ASD, VSD or PDA) allowing mixing; commonest cause of cyanotic CHD in the newborn                         |
| Tricuspid atresia                                                | Obliteration/fusion of the right AV orifice                                                                                            | Always with patent oval foramen, VSD, hypoplastic right ventricle, hypertrophied left ventricle                                                                                                               |
| Total anomalous pulmonary venous return (TAPVR)                  | Abnormal position of the dorsal mesocardium so pulmonary veins fail to join the left atrium                                            | Veins drain to right atrium, SVC/brachiocephalic vein, or below the diaphragm; often with heterotaxy                                                                                                          |

| Anomaly                               | Embryological defect                                                  | Key features                                                                                                                             |
|---------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Hypoplastic left/right heart syndrome | Under-development of one ventricle, its AV valve and its great artery | Left-sided form: atretic/stenotic mitral & aortic valves, tiny left ventricle, PDA-dependent systemic flow; ductus-dependent circulation |

□ Fig 12.38 — Tetralogy of Fallot: (A) infundibular pulmonary stenosis, (B) VSD with an overriding aorta, (C) right ventricular hypertrophy — the four classic components (Larsen — Human Embryology — 6e, p.742)

## 6. Anomalies of the great vessels and cardiac position

- ▶ **Patent ductus arteriosus (PDA)** — commonest great-vessel anomaly (~8/10,000 births), especially in preterm infants; functional closure (smooth-muscle contraction, bradykinin-mediated) within hours of birth, anatomical closure (intimal proliferation → ligamentum arteriosum) over 1–3 months; large aortopulmonary pressure gradients impede closure.
- ▶ **Coarctation of the aorta** (~3.2/10,000 births) — narrowing of the aortic lumen distal to the left subclavian artery; **pre-ductal type** (ductus persists) versus the commoner **post-ductal type** (ductus usually obliterated; collateral flow via hypertrophied intercostal/internal thoracic arteries — "rib notching").
- ▶ **Interrupted aortic arch (IAA)** — the extreme expression of coarctation; type A (30–40%), type B (40–50%, often with 22q11 deletion), type C (~4%); always with a PDA and a VSD.
- ▶ **Anomalies of cardiac position** — **dextrocardia**, with or without **situs inversus totalis** or Kartagener syndrome; **isomerism** — right isomerism with asplenia (complex defects), left isomerism with polysplenia (simpler defects); **ectopia cordis** (failure of ventral body-wall closure).
- ▶ **Coronary anomaly** — anomalous left coronary artery from the pulmonary trunk (Bland–White–Garland syndrome) — myocardium perfused with desaturated blood, presenting as infantile cardiac failure.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a four-chamber schematic heart in coronal section and label:

- ▶ Right atrium, left atrium, right ventricle, left ventricle, interatrial septum, interventricular septum (membranous + muscular parts)
- ▶ On the atrial septum, mark the four ASD sites: **fossa ovalis (ostium secundum) defect**, **ostium primum (AV septal) defect**, **superior/inferior sinus venosus defect**, **coronary sinus defect**
- ▶ On the ventricular septum, mark: **perimembranous VSD**, **muscular VSD**, **doubly-committed juxta-arterial VSD**
- ▶ Adjacent panel — Tetralogy of Fallot with the four labelled components: **infundibular pulmonary stenosis** → **overriding aorta** → **large VSD** → **right ventricular hypertrophy** (draw arrows showing right-to-left shunt across the VSD)
- ▶ Adjacent panel — **patent ductus arteriosus** and **coarctation of aorta** (pre-ductal vs post-ductal) on an aortic-arch outline, with the ligamentum arteriosum labelled

**Applied / Clinical anatomy**

- ▶ **Eisenmenger complex/syndrome** — large VSD with pulmonary hypertension and a normal/dilated pulmonary trunk (no true pulmonary stenosis); any long-standing large left-to-right shunt can reverse to right-to-left once pulmonary resistance exceeds systemic resistance, producing late cyanosis and clubbing.
- ▶ **Ductus-dependent circulation** — duct-dependent lesions (critical pulmonary/aortic atresia, hypoplastic left heart, IAA, some TGA) need prostaglandin E1 to keep the duct open pending surgery; NSAIDs hasten closure of an unwanted PDA.
- ▶ **Diagnosis** — the antenatal four-chamber echocardiographic view (chamber symmetry, AV "cross" integrity, great-vessel origin, situs) detects most CHD; postnatal echocardiography is primary, catheterization/angiography reserved for pressure/saturation data.
- ▶ **Clinical presentation** — "tet spells" in tetralogy of Fallot are relieved by the knee-chest position (raises systemic resistance, reduces right-to-left shunt); differential cyanosis suggests PDA with reversed flow distal to a coarctation/IAA.
- ▶ **Radiology & genetics** — right aortic arch with tetralogy of Fallot/truncus arteriosus; rib notching with coarctation; "boot-shaped" heart (coeur en sabot) with tetralogy of Fallot; heart-hand pattern (Holt–Oram), hypocalcaemia + thymic hypoplasia (22q11) should prompt cardiac screening.

**High-yield exam pointers**

- ▶ CHD incidence ≈ 8/1000 live births; VSD is the commonest lesion overall, tetralogy of Fallot the commonest cyanotic lesion, TGA the commonest cause of cyanosis in the newborn.
- ▶ Four ASD types: ostium secundum (commonest), ostium primum (AV septal defect, Down syndrome), sinus venosus (superior/inferior), coronary sinus defect.
- ▶ Three VSD types: perimembranous (commonest), muscular ("Swiss cheese"), doubly-committed juxta-arterial.



- ▶ Tetralogy of Fallot = pulmonary infundibular stenosis + VSD + overriding aorta + RV hypertrophy (anterior deviation of conotruncal septum).
- ▶ TGA = failure of the spiral course of the aorticopulmonary/conotruncal septum → parallel great vessels.
- ▶ PDA and coarctation are the classic ductus-related anomalies; pre-ductal vs post-ductal coarctation.
- ▶ 22q11 deletion (DiGeorge) → conotruncal defects (truncus arteriosus, tetralogy of Fallot, IAA type B); *NKX2.5* → ASD + TOF; *TBX5* → Holt–Oram.
- ▶ Situs/positional anomalies: dextrocardia, situs inversus totalis, right isomerism–asplenia vs left isomerism–polysplenia.
- ▶ Neural crest and second heart field are the key embryonic cell populations for outflow-tract septation — their disruption is the common thread linking truncus arteriosus, tetralogy of Fallot, VSD and TGA.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e.



## Congenital malformations of Heart

*Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Congenital malformations of the heart are structural defects of the heart and great vessels arising from disturbances of normal cardiogenesis during the third to eighth weeks of intra-uterine life. They form the commonest group of congenital anomalies, with an incidence of about **8 per 1000 live births**, rising to as much as **2% of stillbirths**. Only a minority are ascribed to single-gene mutations (~4%) or chromosomal aberrations (~6%) or to specific teratogens (~5%); the great majority (80–85%) are **multifactorial**, resulting from an interaction between the individual's genetic susceptibility and environmental/epigenetic influences. Understanding the malformations requires understanding the normal septation events they interrupt.

### 1. Embryological basis — septation events disrupted in CHD

| Developmental event         | Normal process                                                                                         | Malformation if disrupted                                                          |
|-----------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Cardiac looping (day 22–28) | Straight heart tube bends rightward (D-loop), bringing the four chambers into correct spatial register | Leftward looping → dextrocardia; indeterminate looping → situs ambiguus/heterotaxy |

| Developmental event                                                           | Normal process                                                                                                                                                                                                                                                                                                                                                                          | Malformation if disrupted                                                                                                                                                                                     |
|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Atrial septation                                                              | <b>Septum primum</b> grows down from the roof, its dorsal free edge fusing with the endocardial cushions to close the <b>foramen primum</b> ; before closure, the upper part of septum primum breaks down to form the <b>foramen secundum</b> . A second, thicker <b>septum secundum</b> then grows to the right of septum primum, leaving an oblique opening, the <b>foramen ovale</b> | Short septum secundum / large foramen secundum → <b>ostium secundum ASD</b> ; failure of septum primum to close foramen primum → <b>ostium primum ASD</b>                                                     |
| Ventricular septation                                                         | <b>Muscular part</b> grows up from the floor of the primitive ventricle; <b>bulbar part</b> from fused right and left bulbar ridges; <b>membranous part</b> fills the residual interventricular foramen by proliferation of tissue from the AV cushions and bulbar ridges (complete by the 8th week)                                                                                    | Failure of fusion of any of the three parts (commonly the membranous part) → <b>VSD</b>                                                                                                                       |
| <b>Endocardial-cushion fusion</b> (dorsal + ventral cushions of the AV canal) | Forms the septum intermedium, dividing the AV canal into tricuspid and mitral orifices and contributing to the membranous IV septum                                                                                                                                                                                                                                                     | Failure of fusion → <b>persistent common AV canal / atrioventricular septal defect (AVSD)</b>                                                                                                                 |
| <b>Outflow-tract (conotruncal) septation</b>                                  | Right and left <b>bulbar ridges</b> and <b>truncal ridges</b> fuse in a spiral course to form the <b>aortopulmonary (conotruncal) septum</b> , dividing the truncus arteriosus into aorta and pulmonary trunk                                                                                                                                                                           | Failure of septum to form → <b>persistent truncus arteriosus</b> ; unequal/anterior malalignment of the septum → <b>tetralogy of Fallot</b> ; reversed spiralling → <b>transposition of the great vessels</b> |
| <b>Ductus arteriosus closure</b>                                              | Functional closure within hours of birth (bradykinin-mediated smooth-muscle constriction); anatomical closure by 3 months (TGFβ-mediated intimal proliferation) → ligamentum arteriosum                                                                                                                                                                                                 | Failure of closure → <b>patent ductus arteriosus (PDA)</b>                                                                                                                                                    |

## 2. Genetic and syndromic associations

| Gene / condition | Associated cardiac defect                                                 |
|------------------|---------------------------------------------------------------------------|
| NKX2.5           | Atrial septal defect + cardiac conduction defects                         |
| GATA4            | Atrial septal defect, pulmonary valve stenosis                            |
| TBX20            | Atrial/ventricular septal defects, valve defects, abnormal chamber growth |

| Gene / condition                                               | Associated cardiac defect                                                                              |
|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| CRELD1                                                         | Atrioventricular septal defect                                                                         |
| TBX5 (Holt–Oram syndrome)                                      | ASD + preaxial (radial-ray) limb defect; autosomal dominant                                            |
| PTPN11 (Noonan / LEOPARD syndrome)                             | Pulmonary trunk stenosis, atrioventricular septal defects, conduction anomalies                        |
| JAGGED1 / NOTCH1 / NOTCH2 (Alagille syndrome)                  | Pulmonary/aortic stenosis, septal defects, tetralogy of Fallot, aortic coarctation                     |
| TBX1 / 22q11.2 deletion (DiGeorge / velocardiofacial syndrome) | Conotruncal defects — tetralogy of Fallot, persistent truncus arteriosus, interrupted aortic arch, VSD |
| Trisomy 21 (Down syndrome)                                     | Atrial septal defect / atrioventricular septal defect (near-universal accompaniment)                   |
| Turner syndrome                                                | Coarctation of the aorta — its commonest cardiovascular anomaly                                        |

Known teratogens producing heart defects include **lithium, alcohol and retinoic acid**, and maternal **diabetes and rubella infection**.

### 3. Classification of congenital heart malformations



Physiologically, defects are grouped by the direction of shunt:

| Group                                   | Defects                                                                                                   | Basic haemodynamics                                                                                                                          |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Acyanotic (left-to-right shunt)         | ASD, VSD, persistent AV canal, PDA                                                                        | Oxygenated blood recirculates through the lungs → pulmonary plethora, right heart/pulmonary volume overload, eventual pulmonary hypertension |
| Acyanotic (obstructive, no shunt)       | Semilunar valve stenosis, coarctation of aorta                                                            | Pressure overload proximal to the obstruction → ventricular hypertrophy                                                                      |
| Cyanotic (right-to-left shunt / mixing) | Tetralogy of Fallot, transposition of the great vessels, persistent truncus arteriosus, tricuspid atresia | Deoxygenated blood bypasses/mixes into the systemic circulation → central cyanosis from birth or infancy                                     |

#### 4. Individual malformations — basis, incidence and effect

| Malformation                  | Embryological basis                                                                                       | Incidence (per 10,000 live births)             | Chief effect                                                                                                                                                                             |
|-------------------------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ostium secundum ASD           | Short septum secundum fails to cover an enlarged foramen secundum                                         | 6.4 (F:M $\approx$ 2:1)                        | L→R shunt; RA/RV enlargement; late atrial arrhythmia, pulmonary hypertension                                                                                                             |
| Ostium primum ASD             | Septum primum fails to close the foramen primum; often with an endocardial-cushion defect                 | (rarer subtype)                                | Similar L→R shunt; may coexist with AV-valve malformation                                                                                                                                |
| Persistent AV canal (AVSD)    | Failure of fusion of dorsal and ventral endocardial cushions                                              | Characteristic of trisomy 21                   | Combined ASD + VSD + malformed AV valves; early pulmonary hypertension/CHF if severe                                                                                                     |
| Ventricular septal defect     | Failure of fusion of muscular, bulbar and (commonest) membranous components                               | 12 — the <b>commonest isolated CHD</b> ; M > F | L→R shunt; may close spontaneously in infancy                                                                                                                                            |
| Patent ductus arteriosus      | Failure of physiological and anatomical (TGF $\beta$ -mediated intimal) closure of the ductus arteriosus  | 8                                              | Continuous L→R shunt (aorta → pulmonary artery); maintained by prostaglandins, closed by indomethacin                                                                                    |
| Coarctation of aorta          | Medial thickening narrowing the aorta near the ductus arteriosus (juxtaductal); pre-ductal or post-ductal | 3.2                                            | Commonest CVS anomaly in <b>Turner syndrome</b> ; preductal → differential cyanosis after ductal closure; postductal → collateral circulation via intercostal/internal thoracic arteries |
| Persistent truncus arteriosus | Truncal/bulbar ridges fail to form the aortopulmonary septum at all                                       | ~1                                             | Obligatorily accompanies a VSD; mixing of blood → pulmonary hypertension; fatal within 2 years if uncorrected                                                                            |

| Malformation                       | Embryological basis                                                                                                            | Incidence (per 10,000 live births)                        | Chief effect                                                                                                                                                                                                  |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Transposition of the great vessels | Reversed (non-spiral) course of the aorticopulmonary septum, or disturbed second-heart-field contribution to the outflow tract | ~5                                                        | Aorta arises from the right ventricle, pulmonary trunk from the left — parallel (not in-series) circulations; fatal unless a shunt (PDA/ASD/VSD) permits mixing; leading cause of cyanotic death under 1 year |
| Tetralogy of Fallot                | Unequal division of the conus cordis, with anterior malalignment of the outlet (conotruncal) septum                            | ~9.6–10; <b>commonest cyanotic CHD</b> (6–10% of all CHD) | Four components — pulmonary infundibular stenosis, VSD, overriding aorta, right ventricular hypertrophy; boot-shaped ("coeur en sabot") heart on chest X-ray                                                  |
| Tricuspid atresia                  | Abnormal remodelling of the right AV canal — the tricuspid orifice fails to develop/communicate with the right ventricle       | —                                                         | Functionally a univentricular (left-ventricle-driven) heart; right ventricle hypoplastic; survival needs a patent foramen ovale plus a VSD and/or PDA                                                         |

Additional named entities confirmed in the corpus: **double-outlet right ventricle** (both great vessels arise from the RV, almost always with a VSD; incidence  $\approx 1$  in 3000); **Taussig–Bing anomaly** (a double-outlet right ventricle with a sub-pulmonic VSD); **Eisenmenger complex** (hypoplasia of the pulmonary capillary bed  $\rightarrow$  pulmonary hypertension, dilated pulmonary trunk, RV hypertrophy — termed **Eisenmenger's syndrome** when it complicates a pre-existing ASD/VSD, producing late shunt reversal and cyanosis).

□ Fig 18.15 — Tetralogy of Fallot. It includes pulmonary stenosis, right ventricular (Sontakke — Textbook of Human Embryology, p.189)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a coronal section of the four-chambered heart with these exact labels:

- ▶ **Right atrium, right ventricle, left atrium, left ventricle**
- ▶ **Pulmonary trunk with infundibular stenosis** (narrowed pulmonary outflow)
- ▶ **Ventricular septal defect** — gap in the membranous interventricular septum
- ▶ **Overriding aorta** straddling the VSD, receiving mixed blood from both ventricles
- ▶ **Right ventricular hypertrophy** — thickened RV wall
- ▶ A dashed arrow showing right-to-left shunting of blood through the VSD into the overriding aorta

**5. Anomalies of cardiac position**

- ▶ **Dextrocardia**: the commonest positional anomaly of the heart; incidence  $\approx 1$  in 7000. Classified as (a) **isolated dextrocardia** — only the heart lies on the right, or (b) **dextrocardia situs inversus** — reversal of all thoracic and abdominal viscera. Cause: abnormal (leftward instead of rightward) looping of the heart tube.
- ▶ **Ectopia cordis**: a rare anomaly in which the heart lies exposed on the anterior thoracic wall due to non-union of the sternal halves; postnatal surgical repositioning carries high mortality. It may occur as one element of **Pentalogy of Cantrell** (supraumbilical abdominal wall defect, diaphragmatic hernia, pericardial defect, sternal cleft, intracardiac anomaly).
- ▶ **Aortic arch anomalies** (from abnormal regression/persistence of the paired dorsal aortae and fourth arch arteries): **right aortic arch** (persistence of the right, regression of the left fourth arch — seen in a substantial minority of tetralogy of Fallot and transposition cases), **double aortic arch** (persistence of both, forming a vascular ring around the trachea/oesophagus), and **interrupted aortic arch** (both fourth arch arteries obliterated — lower body perfused only via a patent ductus arteriosus).

**Applied / Clinical anatomy**

- ▶ **Fetal detection**: real-time ultrasonography can detect major cardiac anomalies from as early as the 16th week; fetal echocardiography with Doppler between the **18th and 22nd weeks** is the standard screening window for structural heart disease.
- ▶ **Cyanotic presentation**: the "**blue baby**" — cyanosed lips and nail beds — with easy fatigability; "**Tet spells**" in tetralogy of Fallot are acute hypoxic episodes with breathlessness, cyanosis, agitation and syncope, classically relieved by the squatting posture (which raises systemic vascular resistance and reduces the right-to-left shunt).
- ▶ **Radiology**: the boot-shaped ("**coeur en sabot**") cardiac silhouette on chest X-ray is characteristic of tetralogy of Fallot.
- ▶ **Anomalous coronary origin**: an anomalous left coronary artery arising from the right aortic sinus (or, in ALCAPA, from the pulmonary artery) can become compressed between the great vessels during systole, causing exertional myocardial ischaemia and sudden cardiac death in an apparently healthy young person — a reminder that coronary arterial development itself can be a site of congenital malformation.

- ▶ **Surgical/interventional correction:** ASD and VSD may be closed surgically or by a percutaneous occluding device; PDA closure is promoted pharmacologically by prostaglandin-synthesis inhibitors (e.g., indomethacin) or by surgical/catheter ligation; tetralogy of Fallot is corrected by relieving the pulmonary outflow obstruction and patching the VSD; persistent truncus arteriosus requires VSD closure with a valved conduit from the right ventricle to the pulmonary arteries.
- ▶ **Genetic screening trigger:** presentation with a conotruncal defect (tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, VSD) should prompt testing for a **22q11.2 microdeletion**.

### High-yield exam pointers

- ▶ CHD incidence  $\approx$  8 per 1000 live births (up to 2% of stillbirths);  $\sim$ 80–85% multifactorial in origin.
- ▶ **VSD is the commonest isolated CHD (12/10,000); tetralogy of Fallot is the commonest cyanotic CHD ( $\sim$ 10/10,000).**
- ▶ Tetralogy of Fallot's embryological basis: anterior malalignment of the conotruncal (aorticopulmonary) septum  $\rightarrow$  pulmonary stenosis + VSD + overriding aorta + RV hypertrophy.
- ▶ Ostium secundum ASD = failure of septum secundum to cover the foramen secundum; ostium primum ASD = failure of septum primum to close the foramen primum.
- ▶ Persistent truncus arteriosus and transposition of the great vessels both result from abnormal aorticopulmonary septum formation — absent in the former, reversed/parallel in the latter.
- ▶ Turner syndrome  $\rightarrow$  coarctation of aorta; trisomy 21  $\rightarrow$  ASD/AVSD; 22q11.2 deletion (DiGeorge)  $\rightarrow$  conotruncal defects.
- ▶ Dextrocardia (commonest positional anomaly, 1/7000) results from reversed cardiac looping; ectopia cordis results from non-union of the sternal halves.
- ▶ Eisenmenger's syndrome = late reversal of a left-to-right shunt (ASD/VSD) once pulmonary vascular resistance exceeds systemic resistance.
- ▶ Fetal echocardiography (18–22 weeks) is the standard antenatal screening window for structural CHD.

### SOURCE & COVERAGE

Larsen — Human Embryology, 6e; Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler), 14e; Gray's Anatomy (Standring), 41e; Thompson & Thompson — Genetics in Medicine, 8e.





## Congenital malformations of the heart

Asked in: Paper II Nov 2018 — RGUHS MD/MS Anatomy

**Definition / Introduction** — Congenital heart defects (CHDs) are structural anomalies of the heart and great vessels present at birth, arising from faults in cardiac looping, septation of the atria/ventricles/outflow tract, or partitioning of the aortic arch system during the fourth to eighth weeks of intrauterine life. They are the commonest group of major congenital malformations. Ventricular septal defect (VSD) is the single most frequent lesion (about one-fifth of all cases), followed in frequency by patent ductus arteriosus (PDA), coarctation of the aorta, pulmonary stenosis, Fallot's tetralogy, transposition of the great arteries, aortic stenosis and hypoplasia of the left heart. CHDs occur more often in siblings and in children of consanguineous marriages, and molecular defects of key cardiac transcription factors (NKX2-5, TBX5, PITX2) underlie many familial cases.

### 1. Embryological basis (recap of normal septation)

- ▶ **Cardiac looping (day 22–28):** the straight heart tube bends so the primitive ventricle moves ventrally and to the right while the atrial region moves dorsally and to the left, converting the tube into the definitive S-shaped loop.
- ▶ **Atrial septation:** the crescentic **septum primum** grows from the dorsocranial atrial roof towards the fusing atrioventricular endocardial cushions, transiently leaving the **foramen primum**; before this closes, apoptotic perforation of the upper septum primum creates the **foramen secundum**. A second in-folding of the atrial roof to the right of this, the **septum secundum**, overlaps the foramen secundum, and the persisting oblique passage through both septa is the **foramen ovale**.
- ▶ **Ventricular septation:** the muscular interventricular septum grows from the ventricular floor towards the endocardial cushions; the gap between its free edge and the fused (dorsal + ventral) atrioventricular cushions is closed by tissue derived from the **right and left bulbar (conal) ridges plus the posterior endocardial cushion**, forming the membranous septum — the last part to close and of **neural crest origin**.
- ▶ **Outflow tract septation:** the truncocoanal (bulbar) ridges grow in a spiral fashion and fuse to form the **aorticopulmonary (spiral) septum**, dividing the truncus arteriosus into the aorta and pulmonary trunk and aligning each with its own ventricle.
- ▶ Failure, malalignment or incomplete fusion at any one of these steps produces the corresponding named defect described below.

### 2. Classification of congenital heart defects

| Category                        | Mechanism                                                                                                                | Examples                                                                                                                    |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Acyanotic — left-to-right shunt | Pressure in systemic (left-sided) chambers exceeds pulmonary (right-sided) chambers; no early cyanosis                   | Atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), atrioventricular septal defect |
| Cyanotic — right-to-left shunt  | Obstruction to pulmonary outflow or malposition of great vessels forces deoxygenated blood into the systemic circulation | Tetralogy of Fallot, transposition of the great arteries, persistent truncus arteriosus, tricuspid atresia                  |

| Category                                                        | Mechanism                        | Examples                                                                                              |
|-----------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------|
| Obstructive (may be acyanotic or produce differential findings) | Narrowing of a valve or vessel   | Coarctation of the aorta, pulmonary/aortic valve stenosis or atresia, hypoplastic left heart syndrome |
| Malposition/situs anomalies                                     | Faulty lateralisation or looping | Dextrocardia, situs inversus, isomerism/heterotaxy                                                    |



### 3. Septal defects — atrial, ventricular and atrioventricular

| Defect                                                       | Site / embryological fault                                                                                        | Key feature                                                                                                                           |
|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ostium secundum ASD</b><br>(commonest ASD)                | Excessive resorption of septum primum, or deficient septum secundum, leaving an over-sized foramen ovale/secundum | Isolated left-to-right shunt at atrial level; incidence $\approx$ 6.4/10,000 births, female:male $\approx$ 2:1                        |
| <b>Ostium primum ASD</b> (an atrioventricular septal defect) | Failure of the leading edge of septum primum to fuse with the atrioventricular endocardial cushions               | Interatrial communication low in the septum, close to the AV valves; often a common AV valve/'cleft' component                        |
| <b>Sinus venosus defect</b>                                  | Defective incorporation of the sinus venosus/anomalous drainage of a caval vein                                   | Opening near the entry of the SVC (or IVC), usually with anomalous right pulmonary venous drainage                                    |
| <b>Coronary sinus defect</b>                                 | Deficiency of the wall separating the coronary sinus from the left atrium                                         | Interatrial shunt through the mouth of the coronary sinus                                                                             |
| <b>Complete AV septal defect</b>                             | Failure of fusion of the (superior + inferior) atrioventricular endocardial cushions                              | Common AV orifice, single bridging AV valve, shunting at atrial and/or ventricular level; classically associated with Down syndrome   |
| <b>Perimembranous VSD</b><br>(commonest VSD)                 | Defective closure of the membranous septum (bulbar ridges + posterior/dorsal endocardial cushion fail to fuse)    | Abuts the central fibrous body; conducting bundle lies along its posteroinferior margin; may extend to inlet/outlet/trabecular septum |
| <b>Muscular VSD</b>                                          | Multiple deficiencies within the muscular septum                                                                  | Can be multiple — "Swiss-cheese" septum                                                                                               |
| <b>Doubly-committed juxta-arterial VSD</b>                   | Failure of the free-standing subpulmonary infundibulum to form                                                    | Defect lies beneath both the aortic and pulmonary valve orifices                                                                      |

Real captured plate — Gray's Anatomy: locations of interatrial communications and the three anatomical types of VSD:

□ Fig 52.22 — Location of the defects that produce an interatrial communication; shunting across an AV septal defect; ventricular septal defects classified as perimembranous, muscular or doubly-committed (Gray's Anatomy — Standring — 41e, p.1273)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A four-chamber schematic heart (coronal section) labelled with: **right atrium, left atrium, right ventricle, left ventricle; fossa ovalis/septum secundum (ASD site); membranous interventricular septum (VSD site); tricuspid and mitral valves; aorta and pulmonary trunk arising side by side (normal) vs twisted (TGA);** arrows showing the direction of shunt (left→right for ASD/VSD; right→left across an overriding aorta for Fallot's tetralogy).

## 4. Cyanotic heart defects

- ▶ **Tetralogy of Fallot** — four components: (1) **pulmonary infundibular stenosis** (from anterosuperior/forward deviation of the conotruncal septum obstructing the right ventricular outflow tract), (2) **VSD** (perimembranous, from the same malaligned septum), (3) **overriding/dextroposed aorta** straddling the VSD and receiving blood from both ventricles, and (4) **right ventricular hypertrophy** (secondary to the outflow obstruction). Rarely, the pulmonary trunk is normal or dilated with this same combination — the **Eisenmenger complex**. A right aortic arch is found most often with Fallot's tetralogy.
- ▶ **Persistent truncus arteriosus (common arterial trunk)** — failure of fusion of the spiral (aortopulmonary) outflow cushions leaves a single undivided arterial trunk with a common truncal valve astride a juxta-arterial VSD; the pulmonary arteries arise from the common trunk (confluent or separately) before it continues as the ascending aorta. Linked to abnormal neural-crest cell migration into the outflow cushions.
- ▶ **Transposition of the great arteries (TGA)** — the aortopulmonary/conotruncal septum fails to spiral, so the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle (discordant ventriculo-arterial connection), producing two parallel, non-communicating circuits. Survival requires a mixing lesion (ASD/VSD/PDA); it is the leading cause of death from cyanotic heart disease in infants under one year, though surgically correctable with good prognosis. A discordant atrioventricular connection coexisting with this is termed **congenitally corrected transposition**.
- ▶ **Taussig–Bing anomaly** — a perimembranous/doubly-committed VSD with the pulmonary trunk overriding the muscular septum (a form of double-outlet right ventricle).
- ▶ **Tricuspid atresia** — absence of the tricuspid valvular orifice (no right atrium–right ventricle communication); accompanied by ASD/VSD, right ventricular hypoplasia with left ventricular hyperplasia, and PDA; survival depends entirely on these associated shunts.
- ▶ **Hypoplastic left heart syndrome** — atresia/stenosis of the aortic and/or mitral valve with a diminutive left ventricle and ascending aorta; linked to misexpression of the Hand1/Hand2 transcription factors that regulate ventricular growth; systemic circulation is duct-dependent.

## 5. Anomalies of the great vessels and aortic arch

- ▶ **Patent ductus arteriosus (PDA)** — persistence beyond the neonatal period of the sixth-arch-derived ductus arteriosus (normally closes functionally within hours via smooth-muscle

contraction, and anatomically over 2–3 weeks to form the ligamentum arteriosum); allows continued aorta-to-pulmonary-trunk flow, producing pulmonary hypervolaemia; classically associated with maternal rubella infection.

- ▶ **Coarctation of the aorta** — congenital narrowing of the aortic arch/isthmus in relation to the ductus arteriosus, with two variants:
  - **Preductal coarctation** — narrowing proximal to the ductus; the distal aorta is perfused via the (still patent) ductus with deoxygenated blood, producing **differential cyanosis** of the lower body.
  - **Postductal coarctation** — narrowing distal to the ductus; collateral flow develops through dilated intercostal arteries, producing radiologically visible **rib notching**.
- ▶ **Right aortic arch / vascular rings** — persistence of the right (rather than left) fourth arch, seen with Fallot's tetralogy or persistent truncus arteriosus; a double or right arch encircling the trachea/oesophagus can compress them (**dysphagia lusoria**).
- ▶ **Anomalous venous connections** — persistent left superior vena cava draining via a dilated coronary sinus; totally anomalous pulmonary venous connection; interruption of the abdominal IVC with azygos continuation (often with left atrial appendage isomerism).

## 6. Anomalies of cardiac looping and position

- ▶ **Dextrocardia** — the heart lies in the right hemithorax because the primary heart tube loops to the *left* instead of the normal rightward loop; it may occur in **isolation** (usually with other associated cardiac anomalies) or together with **situs inversus** (complete mirror-image reversal of all thoraco-abdominal viscera), in which case the heart itself is often otherwise structurally normal and prognosis is comparatively good.
- ▶ **Situs inversus / heterotaxy (situs ambiguus)** — disturbance of the normal left–right (situs solitus) patterning; partial reversal (heterotaxy) carries a substantially higher risk of associated cardiac malformation than complete situs inversus.
- ▶ **Molecular basis:** the cardiac master transcription factor **NKX2-5** is expressed uniformly over the early heart tube; human mutations cause **ASD with disturbances of atrioventricular conduction**. **TBX5** acts later and directs septation and caudocranial chamber patterning. **PITX2**, expressed in left-sided lateral plate mesoderm downstream of Nodal/left–right signalling, governs the direction of cardiac looping; its ectopic expression or loss produces dextrocardia/situs inversus and associated septal defects.

## Applied / Clinical anatomy

- ▶ **Auscultation correlates:** ASD — wide, fixed splitting of S2; VSD — harsh pansystolic murmur at the left lower sternal border; PDA — continuous "machinery" murmur below the left clavicle; coarctation — radiofemoral delay with weak/absent femoral pulses and hypertension in the upper limbs.
- ▶ **Radiology:** rib notching (postductal coarctation, from dilated posterior intercostal arteries), "boot-shaped" heart (Fallot's tetralogy, from right ventricular hypertrophy with a concave pulmonary bay), "egg-on-a-string" cardiac silhouette (TGA), and cardiomegaly with plethoric lung fields (large L→R shunts).

- ▶ **Surgical anatomy:** knowledge of the perimembranous VSD's posteroinferior conduction bundle relationship is essential to avoid heart block during surgical closure; PDA ligation requires care to protect the closely related left recurrent laryngeal nerve.
- ▶ **Eisenmenger syndrome:** any large, uncorrected left-to-right shunt (VSD, ASD, PDA) can progressively raise pulmonary vascular resistance until the shunt reverses direction (right-to-left), producing late cyanosis.
- ▶ **Associations:** complete AV septal defect with Down syndrome (trisomy 21); Fallot's tetralogy/persistent truncus arteriosus with 22q11 deletion (neural crest-related); PDA with maternal rubella and prematurity.

### High-yield exam pointers

- ▶ VSD is the single commonest congenital heart defect overall; PDA, coarctation, pulmonary stenosis, Fallot's tetralogy and transposition follow in decreasing frequency.
- ▶ Membranous interventricular septum = right + left bulbar ridges + posterior (dorsal) endocardial cushion; it is of neural crest origin and the last part of the septum to close.
- ▶ Tetralogy of Fallot = PS + VSD + overriding aorta + RVH — all four trace to one primary defect: anterosuperior deviation/malalignment of the outflow (conotruncal) septum.
- ▶ TGA results from failure of spiralling of the aorticopulmonary septum; survival needs an obligatory shunt (ASD/VSD/PDA).
- ▶ Preductal coarctation → differential cyanosis; postductal coarctation → rib notching (collateral intercostal arteries).
- ▶ Foramen primum closes as septum primum fuses with the AV cushions; foramen secundum then forms by apoptotic perforation of septum primum; septum secundum overlaps it to leave the valve-like foramen ovale.
- ▶ Dextrocardia = heart loops left instead of right; isolated dextrocardia carries a worse prognosis (more associated defects) than dextrocardia with full situs inversus.
- ▶ NKX2-5 mutation → ASD + AV conduction defect; PITX2 controls the direction of cardiac looping and left-right patterning.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Brijesh Kumar — Embryology Text & Atlas; BD Chaurasia — Human Anatomy Vol 1; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Moore — The Developing Human 9e.



## Describe in detail "Aortic Arch Arteries" and mention about the resulting anomalies

Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** The aortic arch (pharyngeal arch) arteries are six paired vessels that develop within the mesenchymal cores of the successive pharyngeal arches, each connecting the **aortic sac** (the fused cranial end of the primitive heart tube) ventrally to the paired **dorsal aortae** dorsally. They appear in strict **cranio-caudal sequence** during the 4th–5th weeks of intrauterine life and are never all present together — the first two arches have already regressed by the time the sixth appears. Through a highly ordered, asymmetric programme of persistence and regression, this transient six-arch system is remodelled into the definitive great arteries of the head, neck and thorax — the arch of the aorta, brachiocephalic, subclavian, common/internal/external carotid, and pulmonary arteries, and the ductus arteriosus. Disturbance of the normal pattern of disappearance/persistence produces a well-recognised group of vascular anomalies, several of which form vascular rings around the trachea and oesophagus.

### Origin and sequential development

- ▶ Each primitive dorsal aorta has three parts: a **ventral (aortic sac) part**, an **arched part** within the pharyngeal arch, and a **dorsal part** lying dorsal to the foregut.
- ▶ After fusion of the paired endocardial heart tubes, the two ventral aortae partially fuse to form the single midline **aortic sac**, the unfused cranial ends persisting as its **right and left horns**.
- ▶ The **first aortic arch artery** forms first (4th week), as a dorsoventral loop connecting the aortic sac to the dorsal aorta within the mandibular (1st pharyngeal) arch.
- ▶ A further series of arch arteries then appears in the **2nd to 6th pharyngeal arches**, each connecting the aortic sac (via the right or left horn) ventrally to its own-sided dorsal aorta.
- ▶ The **fifth aortic arch artery** either never forms completely or regresses almost as soon as it appears; it gives rise to **no adult derivative** in humans.
- ▶ The **paired dorsal aortae** fuse in the midline caudal to the pharyngeal region to form the single **descending (dorsal) aorta**.

### Fate of the individual aortic arch arteries

| Arch      | Fate / adult derivative                                                                                                                                                                                                                              |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I         | Mostly disappears; represented in adult life by the <b>maxillary artery</b>                                                                                                                                                                          |
| II        | Mostly disappears; persists transiently in fetal life as the <b>stapedial artery</b> , which may contribute to the <b>external carotid artery</b>                                                                                                    |
| III       | Proximal part → <b>common carotid artery</b> ; distal part, together with the cranial part of the dorsal aorta, → <b>internal carotid artery</b> ; the <b>external carotid artery</b> buds off from the 3rd arch artery (not a true arch derivative) |
| IV — left | → <b>Arch of the aorta</b> , between the origins of the left common carotid and left subclavian arteries                                                                                                                                             |



| Arch       | Fate / adult derivative                                                              |
|------------|--------------------------------------------------------------------------------------|
| IV — right | → Proximal part of the right subclavian artery                                       |
| V          | Regresses without forming any artery                                                 |
| VI — left  | Proximal part → left pulmonary artery; distal part persists as the ductus arteriosus |
| VI — right | Proximal part → right pulmonary artery; distal part disappears                       |

### Remodelling into the adult arterial pattern

- ▶ **Aortic sac:** right horn → **brachiocephalic (innominate) artery**; left horn, continuous with the left 4th arch artery, → proximal **arch of aorta**; **descending aorta** is derived from the left dorsal aorta (below the 4th arch attachment) together with the fused dorsal aortae.
- ▶ **Right subclavian artery:** proximal part from the **right 4th arch artery**, distal part from the **right 7th cervical intersegmental artery**, the two joined by a short surviving segment of the **right dorsal aorta**. **Left subclavian artery** is formed *entirely* from the **left 7th cervical intersegmental artery**, arising opposite the 4th arch attachment.
- ▶ The **carotid duct (ductus caroticus)** — dorsal aorta between the 3rd and 4th arch attachments — normally **disappears on both sides**.
- ▶ The **right dorsal aorta**, between the right 7th intersegmental artery and its junction with the left dorsal aorta, normally **disappears**; its persistence produces a double aortic arch (see below).
- ▶ Each 6th arch artery gives a branch to the developing **lung bud**; on the right, the segment beyond this branch disappears, while on the left it persists patent as the **ductus arteriosus**, becoming the **ligamentum arteriosum** after birth.
- ▶ Cephalic flexion and neck elongation drag the heart caudally, so the carotid/brachiocephalic arteries elongate and the left subclavian origin shifts progressively higher.

### Relationship to the nerves of the head and neck

- ▶ The nerve of each pharyngeal arch is initially **lateral** to its corresponding arch artery.
- ▶ Nerves of the **1st, 2nd and 3rd arches** (trigeminal, facial, **glossopharyngeal**) retain this lateral position.
- ▶ Disappearance of the ductus caroticus lets the nerve of the **4th arch (superior laryngeal)** move **medially**, coming to lie deep to the great vessels of the neck.
- ▶ The nerve of the **6th arch (recurrent laryngeal)**, a branch of the vagus, lies at first caudal to its arch artery; as the heart descends it hooks around this arch artery and ascends back to the larynx — its classical **recurrent course**.
  - On the **right**, once the distal part of the 6th arch (and the 5th arch) disappear, the right recurrent laryngeal nerve hooks around the **right subclavian artery** (the 4th arch derivative).
  - On the **left**, the nerve does not migrate, remaining hooked around the persisting distal 6th arch — the **ductus arteriosus/ligamentum arteriosum**.



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

embed: ![Fig 36.9 — Aortic arch arteries and their derivatives. (Gray's Anatomy — Standring — 41e, p.840)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/19de1f65f4ef481d.jpg)

Reproduce the aortic arch artery schema by hand with these labels:

- ▶ Aortic sac with its **right and left horns**; paired **dorsal aortae**
- ▶ Six numbered arch arteries (I–VI) drawn in the pharyngeal arches, noting that I, II and V are shown fading/regressed
- ▶ **III** → common carotid + internal carotid (with external carotid as a separate sprout)
- ▶ **IV left** → arch of aorta; **IV right** → proximal right subclavian artery
- ▶ **VI left** → left pulmonary artery + ductus arteriosus; **VI right** → right pulmonary artery (distal part fading)
- ▶ **7th cervical intersegmental arteries** (right and left) feeding into the right and left subclavian arteries
- ▶ **Carotid duct** segment (III–IV, dorsal aorta) shown disappearing on both sides
- ▶ Right dorsal aorta segment (7th intersegmental artery to midline fusion) shown disappearing

### Anomalies of the aortic arch arteries

Anomalies arise when a part that normally disappears **persists**, or a part that normally persists **disappears**.

embed: ![Fig 13.20 — A Double Aortic Arch Results From Failure of the Right Dorsal Aorta to (Larsen — Human Embryology — 6e, p.798)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/ed3d30fb66240c6f.jpg)

| Anomaly            | Embryological basis                                                                                                                             | Clinical feature                                                                                                                                      |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Double aortic arch | Right dorsal aorta (between 7th intersegmental artery and its junction with the left dorsal aorta) fails to regress, so both 4th arches persist | Complete <b>vascular ring</b> around trachea and oesophagus → dyspnoea and dysphagia in infancy                                                       |
| Right aortic arch  | Left 4th arch and left dorsal aorta obliterate; mirror-image right-sided vessels take over                                                      | Usually asymptomatic; if the ligamentum arteriosum lies on the left and passes behind the oesophagus, it may still cause a partial ring and dysphagia |

| Anomaly                                                                  | Embryological basis                                                                                                                                                                                                                                       | Clinical feature                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aberrant (retro-oesophageal) right subclavian artery — "arteria lusoria" | Right 4th arch and proximal right dorsal aorta obliterate; artery instead forms from the distal right dorsal aorta + right 7th intersegmental artery, arising as the last branch of the aortic arch and crossing the midline <b>behind the oesophagus</b> | Usually asymptomatic; occasionally compresses the oesophagus → <b>dysphagia lusoria</b> . The right recurrent laryngeal nerve does <i>not</i> hook around this artery — it runs directly to the larynx (a "non-recurrent" laryngeal nerve), a point of surgical importance in neck dissection/thyroidectomy                                               |
| Persistent ductus caroticus                                              | Segment of dorsal aorta between the 3rd and 4th arches fails to disappear                                                                                                                                                                                 | Left internal carotid arises directly from the aortic arch; right internal carotid arises from the subclavian artery                                                                                                                                                                                                                                      |
| Patent ductus arteriosus (PDA)                                           | Distal left 6th arch derivative fails to close functionally/anatomically after birth                                                                                                                                                                      | One of the commonest great-vessel anomalies (~8/10,000 births); continuous "machinery" murmur, left-to-right shunt                                                                                                                                                                                                                                        |
| Coarctation of the aorta                                                 | Localised narrowing of the aortic media near the ductal attachment; <b>pre-ductal</b> or <b>post-ductal</b> types                                                                                                                                         | ~3.2/10,000 births; post-ductal type causes rib-notching (dilated collateral intercostal arteries) and upper-limb hypertension with weak/delayed femoral pulses                                                                                                                                                                                           |
| Interrupted aortic arch (IAA)                                            | Abnormal regression of both 4th arch arteries → complete discontinuity between the arch and descending aorta                                                                                                                                              | Rare (~3/1,000,000 births); Type A (break distal to left subclavian origin), Type B (break between left common carotid and left subclavian, most common), Type C (break between the two common carotids, rarest); almost always accompanied by a VSD + a duct-dependent PDA; Type B is strongly associated with <b>DiGeorge syndrome (22q11 deletion)</b> |
| Variant branching of the arch                                            | E.g. left common carotid arising from the brachiocephalic trunk ("bovine arch"), or left common carotid and left subclavian arising by a common stem                                                                                                      | Usually an incidental radiological/surgical finding                                                                                                                                                                                                                                                                                                       |

## Applied / Clinical anatomy

- **Vascular rings** (double aortic arch; retro-oesophageal right subclavian artery with a left ligamentum arteriosum) present in infancy with **stridor, dyspnoea, wheeze and dysphagia** from tracheo-oesophageal compression; barium swallow shows a posterior oesophageal indentation, confirmed on CT/MR angiography before surgical division of the ring.

- ▶ **PDA** is closed pharmacologically (indomethacin/ibuprofen in the premature infant) or surgically/by catheter-delivered device in the term infant/child; the **left recurrent laryngeal nerve**, hooked around the ligamentum arteriosum, is at risk during surgical ligation.
- ▶ **Coarctation of the aorta** presents with upper-limb hypertension and diminished, delayed femoral pulses ("radiofemoral delay"); enlarged collateral intercostal arteries produce **rib notching** (3rd–8th ribs) on a chest radiograph.
- ▶ **Aortic knuckle/arch aneurysm**: on a PA chest film the arch produces the "aortic knuckle"; an aneurysm may compress the **left recurrent laryngeal nerve** (hoarseness, cardiovocal/Ortner's syndrome) or cause the mediastinal syndrome of dyspnoea, dysphagia and dysphonia.
- ▶ The arch of aorta, a content of the superior mediastinum, gives off (right to left) the brachiocephalic trunk, left common carotid and left subclavian arteries — the "**ABC**" mnemonic.
- ▶ **22q11 deletion (DiGeorge) screening** is indicated whenever an interrupted aortic arch (especially Type B) or other conotruncal cardiac anomaly is diagnosed, given the shared neural-crest developmental field.

### High-yield exam pointers

- ▶ Six paired aortic (pharyngeal) arch arteries connect the aortic sac to the dorsal aortae; never all present simultaneously; the 5th gives no derivative in humans.
- ▶ Right subclavian = right 4th arch + right 7th cervical intersegmental artery; left subclavian = left 7th cervical intersegmental artery alone.
- ▶ Left recurrent laryngeal nerve hooks around the ligamentum arteriosum; right recurrent laryngeal nerve hooks around the right subclavian artery — explains its absence in an aberrant right subclavian artery.
- ▶ Persistence of the right dorsal aorta → double aortic arch (vascular ring); persistence of the right 4th arch alone (with left obliterating) → right aortic arch.
- ▶ Aberrant retro-oesophageal right subclavian artery = "arteria lusoria" → dysphagia lusoria; a non-recurrent right laryngeal nerve is a surgical trap.
- ▶ Coarctation of aorta: pre-ductal vs post-ductal; rib notching and radiofemoral delay are classic clinical signs.
- ▶ Interrupted aortic arch (Type B commonest) is linked to 22q11 deletion/DiGeorge syndrome; always accompanied by VSD + PDA.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; BD Chaurasia — Human Anatomy Vol 1 8e; Brijesh Kumar — Embryology Text & Atlas.



## Describe in detail about the Development of Heart

Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy

**Definition / Introduction** The cardiovascular system is the **first system to become functional** in the embryo — it begins developing in the third week when increasing nutritional demand outstrips simple diffusion. The heart forms from splanchnopleuric (splanchnic) mesoderm of the cardiogenic area, begins beating on day 22, and circulates blood by day 24. Through cardiac looping and a coordinated series of septations of the atrioventricular canal, atria, ventricles and outflow tract, the single primitive heart tube is remodelled into the definitive four-chambered heart, essentially complete by the **10th week (start of the 3rd month)** of intrauterine life.

### 1. Establishment of the cardiogenic area and heart fields

- ▶ In the third week, cardiac progenitor cells lying just lateral to the primitive streak migrate cranially through the streak into the splanchnopleuric mesoderm, forming a horseshoe-shaped **primary heart field (PHF)** cranial to the neural folds (cardiogenic area).
- ▶ The **secondary heart field (SHF)**, in splanchnic mesoderm ventral to the pharynx, lengthens both poles of the tube: it forms the **right ventricle and outflow tract** (conus cordis, truncus arteriosus) at the arterial pole, and contributes to the atria and sinus venosus at the venous pole. The PHF forms the left ventricle and most of both atria.
- ▶ Pharyngeal endoderm induces vasculogenesis in the cardiogenic area; blood islands unite to form paired **endothelial heart tubes** (future endocardium).
- ▶ Splanchnopleuric mesoderm surrounding the tubes condenses into a **myoepicardial mantle**, which differentiates into **myocardium** and **epicardium** (visceral pericardium); somatopleuric mesoderm forms the **parietal pericardium**.
- ▶ **Molecular control:** foregut endoderm secretes **BMP2/BMP4**, inducing **NKX2.5** (master gene for heart development) in splanchnic mesoderm; neural-tube WNT proteins inhibit cardiogenesis elsewhere. Laterality is set by the **Nodal–Lefty–2–Pitx2** cascade (serotonin as trigger); disruption causes dextrocardia and complex malformations.
- ▶ With lateral and cephalocaudal folding of the embryo, the paired tubes are brought together ventral to the foregut and fuse (day 21) into a **single heart tube**, suspended in the developing pericardial cavity by the **dorsal mesocardium**.

### 2. Formation and folding of the heart tube (cardiac looping)

- ▶ The fused tube shows **five fusiform dilatations**, cranial to caudal: **truncus arteriosus** → **bulbus cordis** → **primitive ventricle** → **primitive atrium** → **sinus venosus**. The cranial end is the arterial end; the caudal end is the venous end.
- ▶ The tube elongates faster than the pericardial cavity can accommodate, so it **bends ventrally and to the right** (dextral/D-looping) — this is the **bulboventricular (U) loop**, formed by day 23–24.
- ▶ The **dorsal mesocardium** breaks down, leaving a gap — the future **transverse sinus of the pericardium** — while the arterial and venous ends remain fixed.
- ▶ As the primitive atrium and sinus venosus (freed from the septum transversum) come to lie dorsocranial to the ventricle, an **S-shaped cardiac loop** is completed (the atrioventriculobulbar

loop, days 25–28); the atrium expands on either side of the truncus arteriosus to form the **auricles**.

- ▶ The **bulboventricular sulcus** separating bulbus cordis from the primitive ventricle later disappears as the two fuse into a single chamber.

□ Fig 18.3 — Development of heart. External views (Sontakke — Textbook of Human Embryology, p.178)

**Table 1 — Fate of the segments of the primitive heart tube**

| Heart-tube segment           | Adult derivative                                                                 |
|------------------------------|----------------------------------------------------------------------------------|
| Truncus arteriosus           | Ascending aorta; pulmonary trunk                                                 |
| Bulbus cordis (conus cordis) | Conus arteriosus (smooth outflow of RV); aortic vestibule (smooth outflow of LV) |
| Primitive ventricle          | Trabeculated part of right and left ventricles                                   |
| Primitive atrium             | Trabeculated part of right and left atria + auricles                             |
| Sinus venosus — right horn   | Sinus venarum (smooth part of right atrium)                                      |
| Sinus venosus — left horn    | Coronary sinus + oblique vein of left atrium                                     |

### 3. The atrioventricular canal and sinus venosus

- ▶ Two **endocardial (AV) cushions** — ventral and dorsal — develop as subendocardial mesenchymal thickenings around the AV canal; they grow and fuse to form the **septum intermedium**, dividing the canal into right and left AV orifices.
- ▶ Each horn of the sinus venosus receives, from lateral to medial: the **common cardinal vein** (body wall), **umbilical vein** (placenta) and **vitelline vein** (yolk sac).
- ▶ A **sinoatrial fold** develops at the sinoatrial orifice; its right and left margins form the **right and left venous valves**. Cranial fusion of the valves forms the **septum spurium**; caudal fusion forms the **sinus septum**.
- ▶ With systemic venous return shifting to the right, the **right horn** is absorbed into the right atrium as the smooth-walled **sinus venarum**; the **right venous valve** gives rise to the **crista terminalis**, valve of the IVC and valve of the coronary sinus. The **left venous valve** fuses with the interatrial septum.
- ▶ The **left horn**, now only a tributary, becomes the **coronary sinus** and **oblique vein of the left atrium**.

### 4. Septation of the atria

The interatrial septum develops during the 5th week from two overlapping folds:

- ▶ **Septum primum** grows from the roof of the primitive atrium toward the AV cushions (septum intermedium), sickle-shaped; the shrinking gap ahead of it is the **foramen primum**.
- ▶ Septum primum fuses with the AV cushions, closing the foramen primum; simultaneously, perforations coalesce to open the **foramen secundum** in the body of septum primum.
- ▶ A thicker, crescentic **septum secundum** grows from the atrial roof to the right of septum primum, overlapping the foramen secundum.

- ▶ The persisting oblique passage between the two septa is the **foramen ovale**; its flap-valve (thin septum primum on the left, thick septum secundum on the right) permits right-to-left shunting only, allowing blood to bypass the non-aerated lungs.
- ▶ At birth, pulmonary flow and left-atrial pressure rise, pressing septum primum against septum secundum → **physiological closure**, followed by anatomical fusion; failure of fusion (~20% of individuals) leaves a **probe-patent foramen ovale**. The closed foramen becomes the **fossa ovalis**; the free margin of septum secundum forms the **annulus ovalis**.

## 5. Septation of the ventricles and outflow tract

- ▶ **Bulbus cordis** differentiates into three parts: proximal third fuses with the primitive ventricle (→ trabeculated RV); middle third is the **conus cordis** (→ smooth outflow of both ventricles); distal third is the **truncus arteriosus** (→ aorta and pulmonary trunk).
- ▶ **Interventricular septum — three components:**
  - **Muscular part** — grows upward from the floor of the bulboventricular cavity, leaving an **interventricular foramen** below the AV cushions; patency of this foramen is essential until the outflow tract itself is septated.
  - **Bulbar (conal) part** — right and left **bulbar ridges** in the conus cordis fuse and grow caudally to meet the muscular septum.
  - **Membranous part** — closes the residual interventricular foramen by tissue proliferating from the AV cushions together with the bulbar ridges (~7th–8th week); its anterior part separates the two ventricles, its posterior (atrioventricular) part separates the right atrium from the left ventricle.
- ▶ **Aorticopulmonary (spiral) septum:** paired **truncal ridges** in the truncus arteriosus fuse and, aligning with the bulbar ridges, spiral through 180°, dividing the truncus into the **ascending aorta** and **pulmonary trunk** and ensuring the aorta connects to the LV and the pulmonary trunk to the RV. Reversed spiralling produces **transposition of the great vessels**.

## 6. Development of the cardiac valves

- ▶ **Atrioventricular valves:** subendocardial cushions proliferate around each AV canal — three on the right (anterior, posterior, septal) and two on the left (anterior, posterior); excavation of these cushions carves out the valve cusps, giving the **tricuspid valve** on the right and **bicuspid (mitral) valve** on the left. Cusps remain tethered to papillary muscles of the ventricular wall by **chordae tendineae**.
- ▶ **Semilunar valves:** right and left, then additional anterior/posterior cushions appear in the truncus arteriosus; as the spiral septum divides the truncus, each pair of cushions splits, and excavation forms the cusps — **aortic valve** (one anterior, two posterior cusps) and **pulmonary valve** (one posterior, two anterior cusps).

## 7. Development of the conducting system

- ▶ **SA node** — differentiates in the 5th week from primary myocardium at the junction of the sinus venosus and right atrium; once the sinus venosus is absorbed, it comes to lie near the SVC opening.

- ▶ **AV node and bundle of His** — derived from the dorsal endocardial cushion of the AV canal (near the coronary sinus opening) in the 6th week.
- ▶ **Purkinje fibres** — the bundle of His divides into right and left bundle branches, terminating as the subendocardial Purkinje network.

### Applied / Clinical anatomy

- ▶ **Dextrocardia** — heart points to the right due to reversed (leftward) looping of the heart tube; may be isolated or part of **situs inversus** (dextrocardia invertus).
- ▶ **Ectopia cordis** — heart lies exposed on the anterior chest wall from failure of sternal fusion; surgical repositioning carries high mortality.
- ▶ **Atrial septal defects (ASDs)** — commonest is **ostium secundum defect** (short septum secundum/excess resorption of septum primum → large persistent foramen ovale); **ostium primum defect** (failed closure of foramen primum, often with AV-cushion defect); **sinus venosus ASD** (incomplete absorption of sinus venosus near SVC opening); rarely **common atrium** (no septal development). Gene: NKX2.5.
- ▶ **Ventricular septal defect (VSD)** — commonest congenital cardiac anomaly; usually **membranous**, from failed fusion of bulbar ridges with AV cushions.
- ▶ **Tetralogy of Fallot (TOF)** — commonest cyanotic CHD, from unequal (anterior) division of the conus cordis: **pulmonary stenosis, VSD, overriding aorta, RV hypertrophy**; classic "**coeur en sabot**" boot-shaped heart on X-ray.
- ▶ **Transposition of the great vessels** — reversed spiralling of the aorticopulmonary septum.
- ▶ **Taussig–Bing anomaly** — double-outlet right ventricle with a subpulmonic VSD.
- ▶ **Holt–Oram syndrome** — autosomal-dominant TBX5 mutation: radial limb defects with ASD.
- ▶ **Eisenmenger syndrome** — long-standing left-to-right shunt (ASD/VSD) reversing to right-to-left with cyanosis.
- ▶ **Probe-patent foramen ovale** — anatomical fusion fails in ~20% despite physiological closure at birth; usually asymptomatic.
- ▶ **Antenatal detection**: ultrasound identifies cardiac anomalies from the 16th week; fetal echocardiography/Doppler is used at 18–22 weeks.



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

**Development of the interatrial septum** (sagittal section of the developing atrium, viewed from the right side, in 4 sequential stages) — label:

- ▶ Sinus venosus opening / septum spurium
- ▶ Superior vena cava opening; inferior vena cava opening
- ▶ Endocardial (AV) cushions
- ▶ **Septum primum** and **foramen primum** (Stage A)
- ▶ Right primitive atrium; primitive ventricle
- ▶ **Foramen secundum** in septum primum (Stage B–C)
- ▶ **Septum secundum** (Stage C)
- ▶ Opening of the coronary sinus
- ▶ **Foramen ovale** and direction of right-to-left shunt (Stage D)

**High-yield exam pointers**

- ▶ Heart is the **first functioning organ**; beats from **day 22**, circulation from **day 24**.
- ▶ Five primitive dilatations (cranial→caudal): **truncus arteriosus**, **bulbus cordis**, **primitive ventricle**, **primitive atrium**, **sinus venosus**.
- ▶ Looping is **dextral (rightward)**; abnormal looping → dextrocardia.
- ▶ Interatrial septum = **septum primum** + **septum secundum**; **foramen ovale** allows only right-to-left flow in utero.
- ▶ Interventricular septum has **muscular** + **bulbar** + **membranous** parts; membranous part is the commonest VSD site.
- ▶ Aorticopulmonary septum is a **spiral septum** from truncal + bulbar ridges — reversed spiralling causes TGA.
- ▶ Master gene: **NKX2.5**; limb-heart gene: **TBX5** (Holt–Oram).
- ▶ **TOF** = pulmonary stenosis + VSD + overriding aorta + RV hypertrophy — commonest cyanotic CHD.
- ▶ SA node from primary myocardium at the sinus venosus–right atrium junction; AV node/bundle of His from the dorsal AV endocardial cushion.

**SOURCE & COVERAGE**

Sontakke, *Textbook of Human Embryology*; Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen, *Human Embryology* 6e; IB Singh, *Human Embryology* (CBME 2021); Vishram Singh, *Textbook of Clinical Embryology*.



## Describe in detail the different stages in the development of the ventricles of heart. Add a note in congenital anomalies of the ventricles of the heart with relevant correlation

*Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction.** The definitive right and left ventricles arise from two adjoining dilatations of the primary heart tube — the **primitive ventricle** and the proximal (trabeculated) third of the **bulbus cordis** — after the tube undergoes rightward **cardiac looping** in the fourth week. Each ventricle acquires a rough, trabeculated **inflow (rough) part** from these primary dilatations and a smooth-walled **outflow (smooth) part** from the more distal bulbus cordis/conus cordis. The two chambers are then separated internally by the **interventricular (IV) septum** — a composite structure built from three embryologically distinct components (muscular, bulbar and membranous) that must fuse precisely with the atrioventricular endocardial cushions and the conotruncal septum. Failure of septation at any of these junctions is the single commonest cause of congenital heart disease.

### 1. The primary heart tube and its regionalisation (3rd–4th week)

- ▶ The straight primary heart tube forms by fusion of paired endocardial tubes derived from the **first (primary) heart field** of splanchnic mesoderm, and is organised craniocaudally, arterial to venous end: **truncus arteriosus → conus cordis → bulbus cordis → primitive ventricle → primitive atrium → sinus venosus**.
- ▶ A **second heart field (SHF)** medial/caudal to the first, adds myocardium at both poles as the tube elongates — its cranial segment lengthens the arterial pole (conus cordis/outflow tract and much of the right ventricle), its caudal segment adds to the venous pole (atria); markers **NKX2.5** and **GATA4** mark this proliferation.
- ▶ The tube is suspended by the **dorsal mesocardium**; its breakdown creates the future **transverse pericardial sinus**.

### 2. Cardiac looping — positioning the future ventricles

- ▶ From **day 23**, the tube bends into a C-shape directed to the right (torsional displacement of the ventral wall), producing the **bulboventricular (D-shaped) loop**.
- ▶ With rupture of the dorsal mesocardium and continued elongation at both poles, the tube becomes **S-shaped**: the bulbus cordis (future RV) is carried caudally, ventrally and to the right; the primitive ventricle (future LV) shifts left; the primitive atrium comes to lie dorsocranial to the ventricles.
- ▶ Looping is complete by **day 28**, positioning all four future chambers correctly for septation. The external **bulboventricular sulcus** corresponds internally to the narrow **primary interventricular foramen**.
- ▶ *Clinical correlation*: reversed (leftward) looping gives **dextrocardia**; correct rightward looping is a prerequisite for normal septation, so looping defects predispose to combined septal/valvar anomalies.

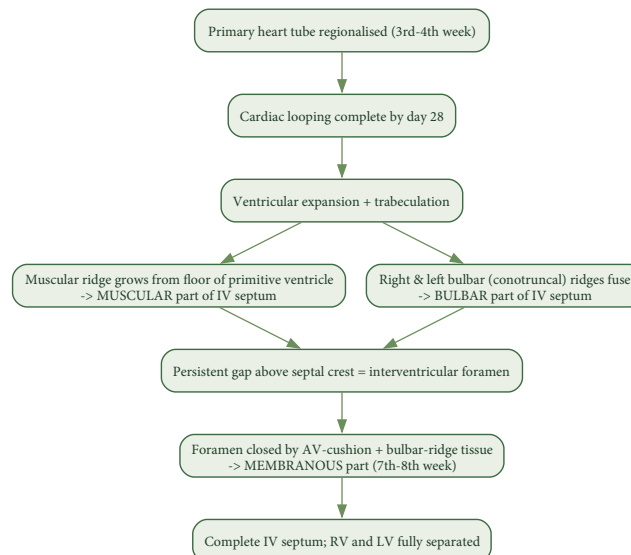
### 3. Expansion, trabeculation and fate of the primitive ventricle and bulbus cordis

| Embryonic component                             | Adult derivative                                                                                                                                          |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primitive ventricle                             | Trabeculated (rough) part of <b>both</b> right and left ventricles                                                                                        |
| Bulbus cordis — proximal 1/3                    | Trabeculated (rough) part of the <b>right ventricle</b> ; fuses with the primitive ventricle to form the bulboventricular chamber                         |
| Bulbus cordis — middle 1/3 (conus cordis)       | Smooth outflow parts of both ventricles — <b>infundibulum (conus arteriosus)</b> of the right ventricle and <b>aortic vestibule</b> of the left ventricle |
| Bulbus cordis — distal 1/3 (truncus arteriosus) | Roots of ascending aorta and pulmonary trunk, later divided by the spiral aorticopulmonary septum                                                         |

- From the end of the 4th week the ventricular/bulbus cordis wall proliferates in two layers: an inner **trabecular layer** (aids nutrition/gas exchange before coronary vessels form) and an outer **compact layer** (thickens under epicardial retinoic-acid/FGF signalling). Excess trabeculation at the compact layer's expense produces **isolated ventricular non-compactation**, a recognised cause of heart failure.

### 4. Partitioning of the ventricle — the interventricular septum

The IV septum has **three developmentally distinct parts**, and its completion is the key septation event of ventricular development:



*Describe in detail the different stages in the development of the ventricles of heart. Add a note in congenital anomalies of the ventricles of the heart with relevant correlation*

- **Muscular part** (largest, forms first): a crescentic myocardial ridge grows from the floor of the primitive ventricle near its apex from the end of the 4th week (first appears **day 28**), dividing the common ventricular cavity into two. It grows towards, but does not reach, the fused AV (endocardial) cushions, leaving a residual gap.

- ▶ **Bulbar part:** right and left **bulbar (conotruncal) ridges**, largely **neural-crest-derived**, grow towards each other from the conus cordis and fuse in a spiralling manner, extending the septum caudally towards the muscular part.
- ▶ **Membranous part:** the residual gap between the muscular and bulbar parts — the **interventricular foramen** — is closed by tissue from **three sources**: the right side of the fused AV endocardial cushions, and the right and left bulbar ridges. Closes by the **7th–8th week**; its anterior part separates the two ventricles, a small posterior (atrioventricular) part separates the right atrium from the left ventricle.

The two ventricles communicate through the **interventricular foramen** until this membranous closure — the only outlet for the left ventricle before conotruncal septation is complete, so membranous closure and truncal spiral septation are mechanistically linked.

**Embedded figure (real plate):**

□ Fig 18.11 — Development of the interventricular septum. Muscular part of the interventricular septum develops from muscular ridge arising from the floor of primitive ventricle. Bulbar part develops from right and left bulbar ridges arising from conus cordis, whereas membranous part develops from the proliferation of AV cushion that fills the gap between muscular and bulbar parts (Sontakke — Textbook of Human Embryology, p.185)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Frontal section of the developing heart at (a) an early stage and (b) end of 7th week, labelling: Aorta, Pulmonary trunk, Truncus arteriosus, right & left **bulbar ridge**, Left/Right atrium, superior & inferior **endocardial (AV) cushion**, **interventricular foramen**, **muscular/bulbar/membranous parts** of IV septum, tricuspid orifice, Right ventricle, Left ventricle.

### 5. Formation of the ventricular valves

- ▶ **Atrioventricular valves:** subendocardial mesenchymal proliferation around the AV canal (endocardial cushions) forms the valve leaflets; remodelling and erosion of the underlying ventricular myocardial wall frees the leaflets, leaving thin strands that become **chordae tendineae** attached to **papillary muscles**. Three cushions on the right give the **tricuspid valve**; two cushions on the left give the **mitral (bicuspid) valve**.
- ▶ **Semilunar valves:** proliferation of subendocardial connective tissue in the truncus arteriosus produces swellings that are remodelled into the cusps of the **aortic** and **pulmonary** valves after division of the truncus by the spiral aorticopulmonary septum.

### 6. Molecular regulation of ventricular septation (brief)

- ▶ **NKX2.5/GATA4** mark the proliferating second heart field; NKX2.5 mutation is linked to atrial septal and conduction defects.
- ▶ **Neural-crest cells** populate the conotruncal (bulbar) ridges and are essential for their fusion; their experimental ablation produces persistent truncus arteriosus and VSD.
- ▶ **TBX5** determines atrial/left-ventricular chamber identity; human TBX5 mutation causes **Holt–Oram syndrome** (limb defects with septal/conduction anomalies).
- ▶ Epicardium-derived **retinoic acid/FGF signalling** drives compact-layer proliferation; its failure gives a thin compact layer and dilated cardiomyopathy.

## Applied / Clinical anatomy — Congenital anomalies of the ventricles, with developmental correlation

| Step that fails                                          | Resulting anomaly                                             | Key features                                                                                                                     | Incidence (grounded)                        |
|----------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Rightward cardiac looping                                | <b>Dextrocardia /</b> ventricular inversion                   | Mirror-image heart; usually isolated unless full situs inversus                                                                  | ≈ 1 in 7000                                 |
| Muscular IV septum fails to develop at all               | <b>Single (common) ventricle</b> — cor triloculare biatriatum | Both atria empty into one ventricular chamber; aorta and pulmonary trunk both arise from it, usually with transposition          | Rare                                        |
| Membranous part fails to close the IV foramen            | <b>Ventricular septal defect (VSD)</b>                        | Commonest CHD, usually <b>membranous</b> ; left-to-right shunt → pulmonary plethora, failure to thrive, cardiac failure if large | ≈ 12 in 10,000 (isolated); ≈ 25% of all CHD |
| Excessive cavitation of the muscular septum              | <b>Muscular VSD</b> ("Swiss-cheese" septum)                   | Multiple small defects; many close spontaneously                                                                                 | Less common than membranous                 |
| Dorsal + ventral endocardial cushions fail to fuse       | <b>Persistent AV canal (AV septal defect)</b>                 | Combined ASD + VSD + malformed (often single) AV valve; early pulmonary hypertension                                             | —                                           |
| Conotruncal ridges fail to form/fuse                     | <b>Persistent (common) truncus arteriosus</b>                 | No aorticopulmonary septum; single vessel overrides a VSD; early cyanosis                                                        | ≈ 1 in 10,000                               |
| Anterior/superior malalignment of the conotruncal septum | <b>Tetralogy of Fallot</b>                                    | Infundibular pulmonary stenosis + membranous VSD + overriding aorta + RVH; "coeur en sabot" on X-ray                             | ≈ 9.6 in 10,000; 6–10% of all CHD           |
| Reversed (straight, not spiral) aorticopulmonary septum  | <b>Transposition of great arteries (TGA)</b>                  | Aorta from RV, pulmonary trunk from LV; needs an associated shunt to survive                                                     | ≈ 4.8 in 10,000                             |
| Deficient SHF lengthening/malalignment of outflow tract  | <b>Double-outlet right ventricle (DORV)</b>                   | Both great arteries from RV, almost always with VSD; cyanosis, poor weight gain                                                  | ≈ 1 in 3000                                 |
| Maldevelopment of right AV canal/tricuspid valve         | <b>Tricuspid atresia</b>                                      | RV hypoplastic; functional single (LV-driven) circulation via ASD + VSD/PDA                                                      | —                                           |

| Step that fails                                  | Resulting anomaly                      | Key features                                                                    | Incidence (grounded) |
|--------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|----------------------|
| Severe underdevelopment of LV and aortic outflow | Hypoplastic left heart syndrome (HLHS) | Tiny LV and aortic outflow; duct-dependent — collapse/cyanosis as ductus closes | —                    |

- ▶ **Eisenmenger syndrome:** late complication of any large uncorrected left-to-right shunt (VSD > ASD/PDA) — pulmonary hypertension reverses the shunt to right-to-left, causing cyanosis; preventable by timely closure.
- ▶ Antenatal 4-chamber echocardiographic view (from the 2nd trimester) should show two similarly sized ventricles with an intact IV septum — the standard screening view for VSD, single-ventricle and hypoplastic-ventricle anomalies.

### High-yield exam pointers

- ▶ Ventricles arise from **two** primary dilatations: the primitive ventricle (mainly first heart field) and the proximal bulbus cordis (added by the second heart field), each contributing a rough inflow part; the middle third (conus cordis) gives the smooth outflow part of both ventricles.
- ▶ Cardiac looping (D-loop, then S-loop) is complete by **day 28** and correctly positions the future ventricles for septation.
- ▶ IV septum = **3 parts** — muscular (ventricular floor), bulbar (right & left conotruncal ridges, neural-crest derived), membranous (AV cushion + both bulbar ridges) — closing by the **7th–8th week**.
- ▶ VSD is the commonest congenital heart defect ( $\approx 25\%$  of all CHD); membranous site is commonest and clinically most significant; muscular ("Swiss-cheese") defects often close spontaneously.
- ▶ Single (common) ventricle results from total failure of the muscular septum to form — rare, usually with transposition.
- ▶ Tetralogy of Fallot = anterior conotruncal malalignment giving VSD + pulmonary stenosis + overriding aorta + RVH — commonest cyanotic CHD.
- ▶ Persistent truncus arteriosus and TGA both stem from abnormal aorticopulmonary (spiral) septation, and both are invariably associated with a VSD.
- ▶ Eisenmenger syndrome = late shunt-reversal complication of any large uncorrected left-to-right shunt.

**SOURCE & COVERAGE**

Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas; Larsen — Human Embryology 6e; Moore — The Developing Human 9e. *Coverage note:* Gray's Anatomy (Standring) 41e was grepped as spine text, but its early-embryonic-circulation chapter covers only the pre-looping stage; septation/anomaly detail is drawn from the specialty embryology texts, as expected for this Paper II topic.



## Describe the foetal circulation. Discuss the changes that occur at birth

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The foetal circulation is the pattern of blood flow unique to intrauterine life, modified so that the **placenta** — and not the lungs or, to a large extent, the liver — serves as the organ of respiration, nutrition and excretion. It is characterised by **five special vascular adaptations** (two umbilical arteries, one umbilical vein, the ductus venosus, the foramen ovale and the ductus arteriosus) that shunt blood around the fluid-filled, non-aerated fetal lungs and, partially, around the liver. At birth, exclusion of the placental circuit and the onset of pulmonary respiration trigger a coordinated sequence of pressure and flow changes that close these shunts and convert the fetal pattern into the definitive adult circulation.

### 1. Special adaptations of the fetal circulation

| Structure                                                                       | Course / connections                                                                                                                                     | Function                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Umbilical vein</b> (single; left — the right umbilical vein regresses early) | Placenta → umbilical cord → umbilicus → along the free edge of the falciform ligament → joins the <b>left branch of the portal vein</b>                  | Carries highly oxygenated, nutrient-rich blood (~80% saturated) from the placenta to the fetus                                                                                                                      |
| <b>Ductus venosus</b>                                                           | Arises opposite the umbilical vein –portal vein junction, ascends behind the liver, joins the <b>left hepatic vein</b> near the inferior vena cava (IVC) | Shunts most umbilical-vein blood <b>around the hepatic sinusoids</b> directly into the IVC; a sphincter at its origin regulates flow and protects the heart from sudden volume overload during uterine contractions |
| <b>Foramen ovale</b>                                                            | A valve-like (flap) communication between the two atria, guarded by the free edge of the <b>septum primum</b> against the <b>septum secundum</b>         | Directs richly oxygenated IVC blood preferentially from the right atrium (RA) into the left atrium (LA), bypassing the non-aerated lungs                                                                            |
| <b>Ductus arteriosus</b>                                                        | Direct continuation of the pulmonary trunk at its bifurcation → joins the aortic arch at 30–35°, just distal to the origin of the left subclavian artery | Shunts most right-ventricular output away from the high-resistance pulmonary vessels directly into the systemic (descending aortic) circulation                                                                     |



| Structure                   | Course / connections                                                                                        | Function                                                                                   |
|-----------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Umbilical arteries (paired) | Branches of the <b>internal iliac arteries</b> → along the sides of the bladder → umbilical cord → placenta | Return deoxygenated, waste-laden fetal blood to the placenta for gas and nutrient exchange |

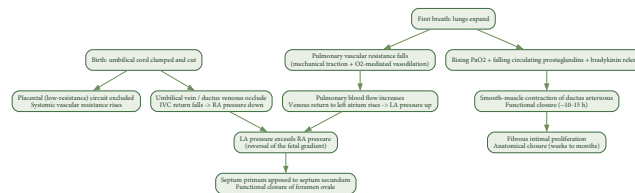
## 2. Course and oxygenation of fetal blood

- ▶ Placental blood (~80% O<sub>2</sub> saturated) reaches the fetus by the **umbilical vein**; on approaching the liver, most bypasses the sinusoids via the **ductus venosus** directly into the IVC, while a smaller portion perfuses the liver and rejoins via the hepatic veins.
- ▶ In the IVC, this blood mixes with desaturated blood from the lower limbs, pelvis and kidneys (**mixing point I**) and enters the **right atrium**.
- ▶ The **valve of the IVC** and the **crista dividens** (lower edge of septum secundum) direct the larger, better-oxygenated stream through the **foramen ovale** into the left atrium, where it mixes with a small desaturated pulmonary venous return (**mixing point II**); a smaller stream remains in the RA and mixes with desaturated superior-vena-caval blood (**mixing point III**).
- ▶ From the LA → left ventricle → **ascending aorta**; because the coronary and carotid arteries are its first branches, the **heart and brain receive the best-oxygenated blood** ("preferential streaming").
- ▶ Desaturated RA blood → right ventricle → pulmonary trunk; since pulmonary vascular resistance is high in the collapsed fetal lung, most of this flows through the **ductus arteriosus** into the descending aorta, mixing with proximal aortic blood (**mixing point IV**).
- ▶ The descending aorta supplies the trunk, abdominal viscera and lower limbs, and continues via the two **umbilical arteries** back to the placenta; oxygen saturation in the umbilical arteries is ~58%.

## 3. Peculiarities of the fetal circulation

- ▶ Blood is shunted **three times** to bypass the liver and lungs: at the **ductus venosus**, the **foramen ovale** and the **ductus arteriosus**.
- ▶ Oxygenated and deoxygenated blood mix at **four sites**: the liver, the IVC, the right atrium and the left atrium (and again where the ductus arteriosus joins the descending aorta).
- ▶ Blood crosses the interatrial septum (**trans-septal circulation**) via the foramen ovale, right atrium to left atrium.
- ▶ The two ventricles work essentially **in parallel** rather than in series, both contributing to the combined systemic/placental output.
- ▶ The **upper limb is relatively better oxygenated** than the lower limb (aortic arch branches vs post-ductal descending aorta), which is one explanation offered for the upper limb bud receiving more blood and its slightly more advanced growth in utero.
- ▶ The heart is fully functional from the end of the **second month** of intrauterine life, long before the lungs take over gas exchange.

## 4. Circulatory changes at birth — mechanism



Describe the foetal circulation. Discuss the changes that occur at birth

- **Umbilical arteries** close first — within minutes, by smooth-muscle contraction triggered by thermal, mechanical and oxygen-tension stimuli (mediated by **bradykinin**); this preserves the neonate's blood volume.
- The **umbilical vein and ductus venosus** close a little later than the arteries, so placental transfusion may continue briefly after birth (the anatomical basis for delayed cord clamping).
- **Lung expansion** lowers pulmonary vascular resistance and raises pulmonary venous return to the LA; simultaneously, occlusion of the umbilical vein/ductus venosus reduces IVC return to the RA. The reversal of the interatrial pressure gradient presses the septum primum against the septum secundum, producing **functional closure of the foramen ovale**; this is initially reversible — crying (a Valsalva-like manoeuvre) can transiently reopen it and cause brief neonatal cyanosis.
- The **ductus arteriosus** closes by active smooth-muscle contraction, driven by a rising arterial  $PO_2$ , a fall in circulating prostaglandins ( $E_2$ ,  $I_2$ ) after loss of the placental source, and bradykinin released from the newly aerated lungs; flow through it **transiently reverses** (left-to-right) before it seals.

## 5. Closure of fetal shunts — timing and adult derivatives

| Fetal structure                    | Functional closure                         | Anatomical (structural) closure          | Adult derivative                                   |
|------------------------------------|--------------------------------------------|------------------------------------------|----------------------------------------------------|
| Umbilical vein (left)              | Few minutes after birth                    | ~2–3 months                              | Ligamentum teres hepatis (round ligament of liver) |
| Ductus venosus                     | Shortly after the umbilical vessels        | Weeks                                    | Ligamentum venosum                                 |
| Foramen ovale                      | Immediately–few days (reversible early on) | ~1 year (probe-patent in ~20% of adults) | Fossa ovalis                                       |
| Ductus arteriosus                  | ~10–15 hours                               | 2–3 weeks to 3 months                    | Ligamentum arteriosum                              |
| Umbilical arteries — distal part   | Few minutes after birth                    | ~2–3 months                              | Medial umbilical ligaments                         |
| Umbilical arteries — proximal part | Remains patent                             | —                                        | Superior vesical arteries                          |

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

□ Fig 10.19 — Foetal circulation (Vishram Singh — General Anatomy — 4e, p.470)

Reproduce a schematic plan of the fetal circulation (after Gray's Fig 52.19), labelling with arrows showing the direction of blood flow:

- ▶ Placenta with two **umbilical arteries** entering and one **umbilical vein** leaving
- ▶ **Ductus venosus** bypassing the liver (left lobe and right lobe of liver shown, with the **portal vein**)
- ▶ **Inferior vena cava** and **superior vena cava** entering the **right atrium**
- ▶ **Foramen ovale** between right and left atria
- ▶ **Right ventricle** → **pulmonary trunk** → **right and left lung** (small flow) and **ductus arteriosus** → **arch of aorta** (major flow)
- ▶ **Left atrium** → **left ventricle** → **aorta**
- ▶ **Aorta** → **bladder region** → **left/right umbilical arteries** → **placenta** (completing the circuit)

**Applied / Clinical anatomy**

- ▶ **Patent ductus arteriosus (PDA)**: failure of postnatal closure; occurs in roughly 8 per 10,000 births; kept open pharmacologically with **prostaglandin E<sub>1</sub> (PGE<sub>1</sub>)** infusion in duct-dependent congenital heart disease (e.g. transposition of the great arteries, critical coarctation), and closed with **indomethacin/ibuprofen** (prostaglandin-synthesis inhibitors) when premature closure is desired.
- ▶ **Coarctation of the aorta** is classified relative to the ductus arteriosus insertion: **pre-ductal** (proximal to the duct — duct-dependent for lower-body perfusion) and **post-ductal** (distal to the duct).
- ▶ **Atrial septal defect (ASD)**: incomplete fusion of septum primum with septum secundum; a small **probe-patent foramen ovale** persists harmlessly in about 20% of adults, but a true ASD permits a haemodynamically significant left-to-right shunt.
- ▶ **Persistent pulmonary hypertension of the newborn ("persistent fetal circulation")**: if the neonate becomes hypoxic or acidotic before pulmonary vascular remodelling is complete, pulmonary vascular resistance rises again, the foramen ovale and ductus arteriosus reopen, and right-to-left shunting causes profound hypoxaemia.
- ▶ **Single umbilical artery** occurs in about 1% of pregnancies and is associated with an increased incidence of other congenital (especially renal and cardiac) anomalies, warranting detailed anomaly scanning.
- ▶ **Umbilical vessel catheterisation** (umbilical arterial and venous catheters) exploits the patent umbilical vessels in the neonatal period for vascular access, blood-gas sampling and exchange transfusion in the NICU.
- ▶ **Ligamentum teres hepatis and ligamentum venosum** are important surgical landmarks in liver anatomy — the ligamentum venosum lies in the fissure separating the **caudate lobe** from the **left lobe**, and the ligamentum teres runs in the free edge of the falciform ligament to the porta hepatis; the **medial umbilical ligaments** (obliterated umbilical arteries) raise the medial

umbilical folds and are landmarks for the internal inguinal ring/laparoscopic extraperitoneal dissection, while the patent proximal stumps continue as the **superior vesical arteries** supplying the bladder.

### High-yield exam pointers

- ▶ Three fetal shunts — **ductus venosus, foramen ovale, ductus arteriosus** — all bypass non-functioning organs (liver, lungs).
- ▶ Only **one** functional umbilical vein (left; right regresses); **two** umbilical arteries (branches of the internal iliac arteries).
- ▶ Oxygen saturation: umbilical vein ~80%; umbilical arteries ~58%.
- ▶ "Preferential streaming": IVC valve + crista dividens direct the best-oxygenated blood through the **foramen ovale** → LA → LV → **coronary and cerebral circulation** ("brain- and heart-sparing").
- ▶ Order of closure after birth: **umbilical arteries first (minutes)** → umbilical vein/ductus venosus → ductus arteriosus (functional, ~10–15 h) → **foramen ovale last (anatomically, ~1 year)**.
- ▶ Ductus arteriosus patency in utero is maintained by **prostaglandins** (E<sub>2</sub>, I<sub>2</sub>); closure follows rising PaO<sub>2</sub>, falling prostaglandins and bradykinin release.
- ▶ Adult remnants: umbilical vein → **ligamentum teres hepatis**; ductus venosus → **ligamentum venosum**; ductus arteriosus → **ligamentum arteriosum**; foramen ovale → **fossa ovalis**; umbilical arteries → **medial umbilical ligaments** (distal) + **superior vesical arteries** (proximal).
- ▶ Clinical correlates to remember: **PDA** (PGE<sub>1</sub>-dependent CHD, indomethacin closure), **pre-/post-ductal coarctation**, **probe-patent foramen ovale** (~20%), **persistent fetal circulation/PPHN**, **single umbilical artery** (~1%, anomaly association).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; BD Chaurasia — Human Anatomy Vol 1 8e; Sontakke — Textbook of Human Embryology; Vishram Singh — General Anatomy 4e.



## Describe the formation and fate of Aortic Arches

Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The **aortic arches** (pharyngeal/branchial arch arteries) are a craniocaudally-appearing series of paired vessels that connect the **aortic sac** (the most distal, undivided part of the truncus arteriosus) to the paired **dorsal aortae**. Each arch develops within the mesenchymal core of its corresponding pharyngeal arch, alongside that arch's own cranial nerve, during the **4th and 5th weeks** of intrauterine life. Although a total of six pairs is described (numbered I–VI), the fifth either never forms or forms incompletely and regresses immediately, and no more than three or four arches are ever present together, since the earlier arches involute before the later ones are complete. Asymmetric, sequential remodelling of this originally symmetrical system between the 4th and 8th weeks converts it into the adult pattern of the aortic arch, its major branches, the pulmonary arteries and the ductus arteriosus.

### 1. Origin and general plan of the aortic arch system

- ▶ The **aortic sac** is the dilated, unpaired distal end of the truncus arteriosus; it gives off a new paired branch to each pharyngeal arch as that arch forms, so that a total of five pairs of aortic arch arteries eventually arises from it.
- ▶ Each arch runs within its pharyngeal arch and drains into the **dorsal aorta** of its own side; the dorsal aortae are paired opposite the arches but fuse into a single midline vessel caudal to this region.
- ▶ The arches appear **cranial to caudal** and are **not all present simultaneously** — by the time arch VI is forming, arch I has already largely disappeared; by the 29th day, arches I and II have disappeared while III, IV and VI are the large, functional vessels.
- ▶ **Neural crest cells** that migrate into each pharyngeal arch form the smooth muscle and connective-tissue coat of that arch's vessel and also regulate its patterning; signals from the overlying ectoderm/endoderm (e.g., **FGF8** in arch ectoderm) are essential for normal fourth-arch development, and **PITX2**, expressed in the aortic sac, secondary heart field and arch mesenchyme, is the master gene that imposes the left–right asymmetry seen in the final pattern.
- ▶ Division of the **truncus arteriosus** by the spirally growing **aorticopulmonary (aortopulmonary) septum** separates the outflow tract into the ventral aorta and the pulmonary trunk; the aortic sac itself then splits into a **right horn**, which becomes the **brachiocephalic artery**, and a **left horn**, which becomes the **proximal part of the arch of the aorta**.

### 2. Fate of the individual arches

| Arch | Fate / adult derivative                                                                     |
|------|---------------------------------------------------------------------------------------------|
| I    | Largely disappears by day 27; a small part persists as the <b>maxillary artery</b>          |
| II   | Disappears soon after forming; remnants form the <b>hyoid</b> and <b>stapedial</b> arteries |

| Arch       | Fate / adult derivative                                                                                                                                                                                         |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III        | Forms the <b>common carotid artery</b> and the proximal (first) part of the <b>internal carotid artery</b> ; the <b>external carotid artery</b> is a new sprout from the third arch, not a true arch derivative |
| IV — left  | Forms part of the <b>arch of the aorta</b> , between the origins of the left common carotid and left subclavian arteries                                                                                        |
| IV — right | Forms the <b>proximal part of the right subclavian artery</b>                                                                                                                                                   |
| V          | Never forms completely, or forms and regresses immediately — no adult derivative                                                                                                                                |
| VI — left  | Proximal part contributes to the <b>left pulmonary artery</b> ; distal part persists throughout fetal life as the <b>ductus arteriosus</b>                                                                      |
| VI — right | Proximal part becomes the <b>right pulmonary artery</b> ; distal part loses its connection to the dorsal aorta and disappears                                                                                   |

- ▶ The **internal carotid artery** beyond its proximal segment (from the third arch) is formed by the cranial continuation of the dorsal aorta, not by an aortic arch.
- ▶ The **distal part of the right subclavian artery** and the whole of the **left subclavian artery** are not arch derivatives at all — both form from the **seventh cervical intersegmental arteries** of their respective sides.

### 3. Accompanying changes in the dorsal aortae

- ▶ The paired dorsal aortae persist opposite the arches but fuse into one vessel caudally; the segment between the third and fourth arches, the **carotid duct**, gradually narrows and disappears.
- ▶ The **right dorsal aorta** disappears between the origin of the right seventh intersegmental artery and the point where it would join the left dorsal aorta; the **left dorsal aorta** in this same region persists and becomes the **descending (thoracic) aorta**.
- ▶ From the fourth arch to the origin of the seventh intersegmental artery, the **right dorsal aorta** contributes to the distal right subclavian artery.
- ▶ A localized narrowing, the **aortic isthmus**, may be seen in the aorta between the origin of the left subclavian artery and the entry of the ductus arteriosus — the classic site of coarctation.
- ▶ As the head and neck elongate and the heart descends into the thorax, the **common carotid** and **brachiocephalic** arteries lengthen considerably, and the origin of the **left subclavian artery** progressively shifts to a point closer to the left common carotid artery.

### 4. Relationship to the recurrent laryngeal nerves

- ▶ Both recurrent laryngeal nerves are initially symmetrical branches of the vagus that hook around the **sixth aortic arch** on their own side before ascending to the larynx — this loop is what gives them their "recurrent" course.

- ▶ On the **right side**, once the distal part of the sixth arch (and the vestigial fifth arch) disappears, the right recurrent laryngeal nerve moves cranially and comes to hook around the **right subclavian artery** (the fourth-arch derivative).
- ▶ On the **left side**, the distal part of the sixth arch persists as the **ductus arteriosus** (later the **ligamentum arteriosum**), so the left recurrent laryngeal nerve remains at its original level, hooking around the **ligamentum arteriosum** and the arch of the aorta.

## 5. Molecular and pharyngeal-arch correlation (brief)

- ▶ Each aortic arch is topographically tied to a pharyngeal arch and its cranial nerve: arch III with the glossopharyngeal (9th) nerve territory, arches IV and VI with the vagus (10th) and its laryngeal branches.
- ▶ Neural-crest-derived cardiac crest cells populate the arches 3, 4 and 6 and are indispensable for normal septation of the outflow tract and patterning of the great vessels; their depletion underlies conotruncal and arch anomalies seen in **22q11 deletion (DiGeorge) syndrome**.

□ Fig 36.9 — Aortic arch arteries and their derivatives. (Gray's Anatomy — Standring — 41e, p.840)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw two paired panels — (A) the symmetrical embryonic pattern and (B) the definitive adult pattern — and label:

- ▶ Aortic sac with **right horn** and **left horn**
- ▶ Arches I, II, III, IV, (V rudimentary), VI on both sides, embedded in their pharyngeal arches
- ▶ Paired **dorsal aortae**, the **carotid duct**, and the fused **descending aorta**
- ▶ Derivatives: **maxillary artery** (I); **hyoid/stapedial arteries** (II); **common carotid + proximal internal carotid** (III); **arch of aorta** (left IV) and **proximal right subclavian artery** (right IV); **pulmonary arteries** (both VI) and **ductus arteriosus** (left VI, distal)
- ▶ **7th intersegmental arteries** forming the distal right and the whole left subclavian arteries
- ▶ Both **recurrent laryngeal nerves**, shown hooking around the right subclavian artery and the ligamentum arteriosum respectively



## Applied / Clinical anatomy

- ▶ **Patent ductus arteriosus (PDA)**: failure of the distal left sixth arch (ductus arteriosus) to close after birth; one of the commonest great-vessel anomalies (~8/10,000 births), more frequent in preterm infants; a continuous "machinery" murmur is classical.
- ▶ **Coarctation of the aorta**: significant narrowing of the aortic lumen distal to the left subclavian artery, at the aortic isthmus, related to an abnormality of the aortic media; ~3.2/10,000 births.
  - **Preductal type**: narrowing proximal to the ductus, which remains patent; lower body perfused partly via the persistent ductus.



- **Postductal type** (more common): ductus obliterates; collateral flow to the lower body develops through enlarged intercostal and internal thoracic arteries — producing the classical clinical picture of upper-limb hypertension with diminished, delayed femoral pulses.
- ▶ **Aberrant (retro-oesophageal) right subclavian artery**: the right fourth arch and proximal right dorsal aorta are obliterated, so the right subclavian artery forms instead from the distal right dorsal aorta and the seventh intersegmental artery; it must then cross the midline behind the oesophagus to reach the right arm — **dysphagia lusoria** when it compresses the oesophagus.
- ▶ **Double aortic arch**: abnormal persistence of the distal right dorsal aorta creates a complete **vascular ring** around the trachea and oesophagus, causing stridor and dysphagia in infancy.
- ▶ **Right aortic arch**: the left fourth arch and left dorsal aorta obliterate and are replaced functionally by their right-sided counterparts; usually asymptomatic unless the ligamentum arteriosum crosses behind the oesophagus.
- ▶ **Interrupted aortic arch (IAA)**: rare (~3/1,000,000 live births) failure of continuity between the arch and descending aorta from abnormal regression of the fourth arch; always accompanied by a VSD and a PDA supplying the lower body.
  - **Type A** (~30–40%): interruption distal to the left subclavian artery.
  - **Type B** (~40–50%, generally the commonest): interruption between the left common carotid and left subclavian arteries.
  - **Type C** (~4%): interruption between the two common carotid arteries.
  - Strongly associated with **22q11 deletion (DiGeorge) syndrome** — present in about half of IAA cases (chiefly type B).
- ▶ **Vascular ring anomalies** as a group (double arch, aberrant subclavian, right arch with left ligamentum) explain most cases of neonatal stridor/dysphagia caused by great-vessel malformation and are demonstrated on barium swallow/CT angiography as extrinsic oesophageal/tracheal compression.

### High-yield exam pointers

- ▶ Aortic arches connect the **aortic sac** to the **dorsal aortae**, embedded in pharyngeal arches; five pairs form (arch V rudimentary/absent), not all present together.
- ▶ Right horn of aortic sac → **brachiocephalic artery**; left horn → **proximal aortic arch**.
- ▶ III → common + proximal internal carotid; IV (L) → arch of aorta; IV (R) → proximal right subclavian; VI → pulmonary arteries (+ **left VI distal** → ductus arteriosus).
- ▶ Distal right subclavian and entire left subclavian come from the **7th intersegmental arteries**, not from an arch.
- ▶ Right recurrent laryngeal nerve hooks the **right subclavian artery**; left hooks the **ligamentum arteriosum** — direct consequence of asymmetric arch/dorsal-aorta regression.
- ▶ Neural crest cells populate arches 3, 4, 6 and pattern the great vessels — deficiency underlies **22q11 (DiGeorge) arch anomalies**.

- ▶ Key anomalies to remember: PDA, coarctation (pre-/post-ductal), aberrant right subclavian (dysphagia lusoria), double aortic arch (vascular ring), right aortic arch, interrupted aortic arch (types A/B/C).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology.



## Development of Arch of Aorta

*Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The arch of aorta develops as part of the **pharyngeal (aortic) arch arterial system** — six pairs of bilaterally symmetrical vessels that connect the aortic sac (the cranial, arterial end of the developing heart tube) to the paired dorsal aortae. Development begins in the 3rd–4th week with formation of the primitive heart tube, aortic sac and dorsal aortae, and the pharyngeal arch arteries appear sequentially through the 4th–5th weeks as the pharyngeal arches form. Through the 6th–8th weeks, asymmetric regression of some segments and persistence of others converts this symmetrical embryonic plan into the definitive, asymmetric adult arterial pattern. The definitive **arch of aorta is derived specifically from the left fourth aortic arch artery together with the left horn of the aortic sac**; faulty remodelling of this same system underlies most clinically important aortic-arch anomalies.

### 1. Formation of the primitive aortic arch system

- ▶ Blood vessel formation begins in the 3rd week by **vasculogenesis** (new vessels from mesenchymal angioblasts) and **angiogenesis** (endothelial sprouting/budding).
- ▶ By the 4th week the embryo has a heart tube whose arterial end is the **truncus arteriosus**, continuing into the **aortic sac**; the fused, midline part of the primitive ventral aortae forms the aortic sac, while the unfused cranial part on each side forms a **right and left horn of the aortic sac**.
- ▶ Paired **dorsal aortae** run the length of the embryo dorsal to the foregut and fuse in the midline caudal to the 6th arch to form a single dorsal aorta (future descending aorta).
- ▶ As the pharyngeal arches appear craniocaudally (4th–5th week), each is traversed by a **pharyngeal (aortic) arch artery** connecting the aortic sac to the ipsilateral dorsal aorta — six pairs in all, numbered I–VI craniocaudally.
- ▶ All six pairs are **never present simultaneously** — cranial arches are already regressing while caudal ones are still forming. By day 27 the first two arches have largely disappeared while the 3rd is prominent and the 4th and 6th are still forming; by day 29 the 3rd, 4th and 6th arches are all well formed.
- ▶ The **fifth pair** either forms only rudimentarily and then degenerates, or never forms at all — in about 50% of embryos it is absent altogether, and it leaves **no derivative** in either case.
- ▶ **Neural crest cells** migrating through the pharyngeal arches populate the walls of the arch arteries and the conotruncal (outflow tract) cushions; the transcription factor **Tbx1** (expressed in 4th–

arch pharyngeal endoderm/mesoderm) regulates this neural-crest contribution — its loss underlies the arch-artery and conotruncal anomalies of **22q11 deletion (DiGeorge) syndrome**, the commonest human microdeletion syndrome.

- By the **8th week** the symmetrical embryonic pattern has been transformed into the final fetal arterial arrangement.

## 2. Fate of the six pairs of pharyngeal (aortic) arch arteries

| Arch artery         | Fate — right side                                                                                                                                                                                                                                 | Fate — left side                                                                                                                                              |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I                   | Mostly disappears; a small remnant contributes to the <b>maxillary artery</b>                                                                                                                                                                     | Same                                                                                                                                                          |
| II                  | Mostly disappears; remnants form the <b>hyoid</b> and <b>stapedial</b> arteries                                                                                                                                                                   | Same                                                                                                                                                          |
| III                 | Proximal part → <b>common carotid artery</b> ; distal part joins the dorsal aorta to form the proximal <b>internal carotid artery</b> . (External carotid artery is a new sprout from the 3rd arch artery, not itself an arch-artery derivative.) | Same                                                                                                                                                          |
| IV                  | Proximal part of the <b>right subclavian artery</b> only                                                                                                                                                                                          | Part of the <b>arch of aorta</b> , between the left common carotid and left subclavian arteries                                                               |
| V                   | Rudimentary/never completes; <b>disappears without any derivative</b> (absent in ~50% of embryos)                                                                                                                                                 | Same                                                                                                                                                          |
| VI (pulmonary arch) | Proximal part → proximal <b>right pulmonary artery</b> ; distal part <b>degenerates</b>                                                                                                                                                           | Proximal part → proximal <b>left pulmonary artery</b> ; distal part persists prenatally as the <b>ductus arteriosus</b> (→ ligamentum arteriosum after birth) |

## 3. Specific formation of the definitive arch of aorta

- The **proximal (ascending) part** of the arch develops from the **left horn of the aortic sac**.
- The main body of the arch — the segment between the origins of the **left common carotid** and **left subclavian** arteries — is formed by the **left 4th aortic arch artery**.
- The **right horn of the aortic sac** forms the **brachiocephalic (innominate) trunk**, the first and largest branch of the definitive arch.
- The **left common carotid artery** arises directly from the aortic sac, just distal to the brachiocephalic origin.
- The **left subclavian artery** is not a pharyngeal-arch derivative at all — it forms from the **left 7th cervical intersegmental artery**; differential growth of the neck progressively shifts its origin cranially until it lies close to that of the left common carotid.

- ## DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

For hand reproduction, draw a ventral schematic of the aortic sac and its two horns giving off six numbered paired arch arteries (I–VI) into a common dorsal aorta, then label:

- [illegible]

- **Coarctation of aorta** — congenital narrowing of the aorta, most often **juxtaductal** (directly opposite the ductus arteriosus in ~90% of cases). Classified as **preductal** (proximal to the ductus — a longer, more severe narrowing; before birth the ductus supplies the lower body) and

**postductal** (distal to the ductus — permits fetal collateral circulation via intercostal arteries). Twice as common in males; associated with a **bicuspid aortic valve** in ~70% of cases and with **Turner syndrome**. Three proposed embryologic mechanisms: (i) ductal smooth muscle incorporated into the aortic wall constricts along with the ductus at birth; (ii) abnormal involution of a segment of the left dorsal aorta, later carried cranially with the left subclavian artery; (iii) persistence of the normally narrow "isthmus" between the left subclavian artery and the ductus, which fails to widen after ductal closure.

- ▶ **Interrupted aortic arch (IAA)** — very rare (~3 per 1,000,000 live births), from abnormal regression of the right and/or left 4th aortic arch — the extreme end of the coarctation spectrum, where the arch is split rather than merely narrowed. Type A (30–40%), Type B (40–50%, strongly linked (~50%) to **22q11 deletion/DiGeorge syndrome**), and Type C (~4%); always accompanied by a VSD and a PDA that perfuses the lower body.
- ▶ **Double aortic arch** — persistence of the entire right dorsal aorta (instead of its normal involution) alongside the normal left arch, so that both a right and left arch of aorta arise from the ascending aorta and encircle the trachea and oesophagus, forming a true **vascular ring**; the right arch is usually the larger and passes posterior to the trachea/oesophagus, causing stridor/dysphagia.
- ▶ **Right aortic arch** — the entire right dorsal aorta persists while the distal left dorsal aorta involutes. Two types: (a) *without* a retro-oesophageal component — the ductus/ligamentum runs from the right pulmonary artery to the right arch; no vascular ring, usually asymptomatic; (b) *with* a retro-oesophageal component — a small left arch has involuted, leaving the right arch posterior to the oesophagus, and the ligamentum arteriosum completes a constricting ring.
- ▶ **Aberrant (retro-oesophageal) right subclavian artery** — the right 4th arch artery and right dorsal aorta disappear cranial to the 7th intersegmental artery; the right subclavian artery then forms from the right 7th intersegmental artery and courses posterior to the trachea and oesophagus as the last branch of the arch. Fairly common; forms a loose vascular ring that is rarely clinically significant.
- ▶ **Recurrent laryngeal nerve asymmetry** is a direct consequence of 6th-arch-artery fate: the nerves originally hook around the 6th pair of arch arteries; on the right, the distal 6th arch degenerates, so the right recurrent laryngeal nerve moves cranially and hooks around the right subclavian artery (a 4th-arch derivative); on the left, the distal 6th arch persists as the ductus arteriosus, so the left nerve remains looped around the ductus/ligamentum arteriosum and the arch of aorta.
- ▶ **Patent ductus arteriosus (PDA)** — failure of postnatal closure of the ductus arteriosus (persisting distal left 6th arch artery), incidence ~8 in 10,000 births; kept patent by prostaglandins, closed by prostaglandin-synthesis inhibitors (e.g., indomethacin).

### High-yield exam pointers

- ▶ Arch of aorta = **left 4th aortic (pharyngeal) arch artery** (definitive arch segment) + **left horn of aortic sac** (proximal/ascending part).
- ▶ Right 4th arch artery forms **only the proximal right subclavian artery**, not any part of the arch, because the distal right dorsal aorta disappears.

- ▶ **Left subclavian artery is not an arch-artery derivative** — it is the left 7th cervical intersegmental artery.
- ▶ **5th arch artery** is rudimentary or never forms — leaves no derivative (absent in ~50% of embryos).
- ▶ **Right horn of aortic sac** → **brachiocephalic trunk**; hence definitive branches, right to left: brachiocephalic trunk, left common carotid, left subclavian.
- ▶ Recurrent laryngeal nerve asymmetry is entirely explained by differential fate of the 6th arch artery (persists as ductus on the left; degenerates distally on the right).
- ▶ Coarctation is juxtaductal in ~90%; linked to bicuspid aortic valve (70%) and Turner syndrome.
- ▶ Double aortic arch (persistent right dorsal aorta), retro-oesophageal right aortic arch, and aberrant right subclavian artery are the classic vascular-ring/near-ring anomalies of the 4th-arch system.
- ▶ 22q11 deletion (DiGeorge) syndrome — Tbx1/neural-crest defect — classically produces interrupted aortic arch (especially type B) and other conotruncal/4th-arch anomalies.

#### SOURCE & COVERAGE

Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; Gray's Anatomy (Standing) 41e.



## Development of Inferior vena cava

*Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The inferior vena cava (IVC) is not a single embryonic vessel but a composite structure, assembled piecemeal from four different fetal veins that are joined end to end. It develops between the 6th and 8th weeks through a sequence of anastomoses among three paired venous systems of the trunk — the **posterior cardinal**, **subcardinal**, and **supracardinal veins** — together with the **right vitelline vein**. The guiding principle is a progressive **shift of venous return from a bilaterally symmetrical pattern to an asymmetric, predominantly right-sided channel**. Because the process involves so many transient anastomoses and regressions, the IVC is one of the most anomaly-prone vessels in the body.

### 1. Primordial (paired) venous system — 4th week

- ▶ At the end of the 4th week the embryo has a **bilaterally symmetrical** system of three paired veins draining into the sinus venosus through short **common cardinal veins (ducts of Cuvier)**:
  - **Anterior cardinal veins** — drain the cephalic part of the embryo (head, neck, upper limb buds).
  - **Posterior cardinal veins** — drain the caudal part of the embryo; they are primarily the veins of the **mesonephros** and largely disappear with it.



- **Vitelline veins** — carry blood from the yolk sac; the **right vitelline vein** persists to form the hepatic portal system and a segment of the IVC, while the left regresses.
- **Umbilical veins** — carry oxygenated placental blood; the right umbilical vein and the cranial part of the left disappear, the persisting caudal left umbilical vein becomes **the umbilical vein**, and the **ductus venosus** develops within the liver connecting it to the IVC.

## 2. Three additional paired veins (5th–7th week)

As the mesonephros regresses, the posterior cardinal veins are progressively replaced/supplemented by two new paired systems that develop in sequence, and their fates are summarised below.

| System                                     | When it appears                                 | Course / relations                                                                                                                                         | Principal adult derivatives                                                                                     |
|--------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Posterior cardinal veins                   | 4th week (earliest)                             | Lateral to the mesonephros                                                                                                                                 | Terminal (root) of the <b>azygos vein</b> ; anastomosis between the two forms the <b>common iliac veins</b>     |
| Subcardinal veins                          | Appear first of the two new systems (~5th week) | Ventromedial to the mesonephros; joined by an <b>intersubcardinal (subcardinal) anastomosis</b> , and to the posterior cardinals via mesonephric sinusoids | <b>Renal, suprarenal, and gonadal (testicular/ovarian) veins</b> ; a segment of the IVC                         |
| Supracardinal veins (thoraco-lumbar veins) | Develop last (~7th week)                        | Dorsal to the posterior cardinal veins; communicate cranially and caudally with them, and join the subcardinals just below the renal veins                 | <b>Azygos and hemiazygos/accessory hemiazygos veins</b> ; the <b>infrarenal (post-renal) segment</b> of the IVC |

## 3. The left-to-right shift

- ▶ Formation of the vena caval system is characterised by a series of **anastomoses that channel blood from the left side to the right**, after which the corresponding left-sided vessel regresses.
- ▶ The anastomosis between the two subcardinal veins becomes the **left renal vein**; once this is established the **left subcardinal vein disappears**, leaving only its distal remnant as the **left gonadal vein** — the right subcardinal vein becomes the dominant channel and forms the **renal segment of the IVC**.
- ▶ The anastomosis between the two posterior cardinal veins forms the **left common iliac vein**; the right posterior cardinal vein's terminal part contributes to the **postrenal/terminal segment** of the IVC and to the **azygos vein**.
- ▶ With obliteration of most of the posterior cardinal veins, the **supracardinal veins take over body-wall (intercostal) drainage**, forming the azygos–hemiazygos system on each side.



#### 4. The four segments of the definitive inferior vena cava

The mature IVC is conventionally described, from its termination in the right atrium down to the common iliac veins, as being made up of **four segments**, each derived from a different fetal vessel:

| Segment (cranial → caudal)                 | Embryonic origin                                                       |
|--------------------------------------------|------------------------------------------------------------------------|
| Hepatic segment                            | Right vitelline vein (hepatocardiac channel) + hepatic sinusoids       |
| Renal segment                              | Right subcardinal vein (and the subcardinal–supracardinal anastomosis) |
| Post-renal (infrarenal) segment            | Right supracardinal vein                                               |
| Terminal segment / common iliac confluence | Anastomosis between the two posterior cardinal veins                   |

□ Fig 19.15 — Development of inferior vena cava. Segments of inferior vena cava develop by anastomosis of cardinal, subcardinal, and supracardinal veins (Sontakke — Textbook of Human Embryology, p.205)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A schematic (ventral view) of the cardinal venous system at the stage just before fusion, with the four numbered IVC segments marked on the adult pattern:

- ▶ Right and left **anterior cardinal veins** + their anastomosis (→ left brachiocephalic vein)
- ▶ Right and left **posterior cardinal veins** + caudal anastomosis (→ common iliac veins)
- ▶ Right and left **subcardinal veins** + intersubcardinal anastomosis
- ▶ Right and left **supracardinal veins** + supracardinal–subcardinal anastomosis
- ▶ **Right vitelline vein / hepatocardiac channel** entering the sinus venosus
- ▶ Number the four IVC segments 1 (hepatic) → 2 (renal) → 3 (post-renal) → 4 (terminal/common iliac) on the final adult scheme
- ▶ Label derivative branches: renal vein, gonadal vein, suprarenal vein, azygos vein, hemiazygos vein

#### 5. Related venous derivatives formed in the same process

- ▶ **Renal veins** — right renal vein is simply the persisting mesonephric vein draining into the right subcardinal vein; the **left renal vein** is composite — part mesonephric vein, part left subcardinal vein remnant, part intersubcardinal anastomosis (this last component explains its normal **pre-aortic** course).
- ▶ **Gonadal veins** — remnants of the subcardinal veins below the intersubcardinal anastomosis; hence the **right gonadal vein drains directly into the IVC**, the **left into the left renal vein**.
- ▶ **Suprarenal veins** — remnants of the subcardinal veins above the intersubcardinal anastomosis, with the same right/left asymmetry as the gonadal veins.
- ▶ **Azygos and hemiazygos veins** — from the supracardinal veins (with a contribution from the posterior cardinal veins on the right), draining the posterior intercostal veins once the posterior cardinal veins have largely obliterated.

- **Common iliac veins** — right from the terminal part of the right posterior cardinal vein, left from the posterior cardinal anastomosis.

## Applied / Clinical anatomy

Because so many transient channels and anastomoses are involved, IVC anomalies are relatively common and are almost always explicable from the developmental scheme above.

| Anomaly                                     | Embryological basis                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Double (duplicated) inferior vena cava      | Persistence of the <b>left supracardinal vein</b> below the renal level instead of its normal regression, so that a left-sided infrarenal IVC persists alongside the normal right-sided one; duplication is limited to the infrarenal segment, and the left channel usually drains into the left renal vein                                                                |
| Left-sided (transposed) IVC                 | The infrarenal segment develops entirely from the left supracardinal vein while the right one regresses (mirror-image of normal)                                                                                                                                                                                                                                           |
| Absence of the IVC with azygos continuation | Failure of the anastomosis between the right subcardinal vein and the right hepatocardiac channel (i.e., the <b>hepatic segment fails to form</b> ); caudal blood then ascends via the azygos vein into the SVC, while the hepatic veins open separately into the right atrium at the normal IVC ostium — often associated with other cardiac/laterality (situs) anomalies |
| Preureteric (retrocaval) ureter             | The infrarenal IVC develops from the <b>subcardinal vein</b> (which lies anterior to the ureter) instead of the supracardinal vein (which lies posterior to it); the right ureter is then hooked behind the vena cava, predisposing to obstructive hydronephrosis                                                                                                          |
| Circumaortic / retro-aortic left renal vein | Persistence of both the ventral and dorsal (intersubcardinal) components of the anastomosis that normally forms the left renal vein, producing a venous ring around the aorta, or a solitary retro-aortic channel                                                                                                                                                          |

□ Fig 19.16 — Double inferior vena cava (Sontakke — *Textbook of Human Embryology*, p.206)

- These variants matter surgically — retroperitoneal, aortic, and renal transplant surgery, IVC filter placement, and retroperitoneal lymph-node dissection in testicular tumours all require pre-operative recognition of caval anomalies on CT/MR venography.
- Awareness of the segment of origin explains why a **retrocaval ureter** is a caval (not a ureteric) developmental anomaly, and why an interrupted IVC with azygos continuation is frequently accompanied by **polysplenia/asplenia and other left–right patterning defects**.

## High-yield exam pointers

- IVC = composite vessel from **4 sources**: right vitelline vein (hepatic segment), right subcardinal vein (renal segment), right supracardinal vein (post-renal segment), posterior-cardinal anastomosis (terminal/common iliac segment).

- ▶ Three paired veins involved, in order of appearance: **posterior cardinal** → **subcardinal** → **supracardinal**.
- ▶ General rule: **subcardinal veins** → **renal/suprarenal/gonadal veins**; **supracardinal veins** → **azygos/hemiazygos system + infrarenal IVC**; **posterior cardinal veins** → **root of azygos + common iliac veins**.
- ▶ Left renal vein is pre-aortic because it incorporates the **intersubcardinal anastomosis**.
- ▶ Right gonadal/suprarenal veins drain directly into the IVC; left ones drain into the left renal vein — always asymmetric, and this is exam-favourite applied anatomy.
- ▶ Double IVC = persistent left supracardinal vein (infrarenal only); Absent IVC with azygos continuation = failed subcardinal–hepatocardiac anastomosis (hepatic segment missing); Retrocaval ureter = infrarenal IVC from subcardinal instead of supracardinal vein.
- ▶ The overall developmental "logic" is a **progressive left-to-right shift** of venous drainage — remember this as the unifying theme for the whole question.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; IB Singh, Human Embryology (CBME 2021); Sontakke, Textbook of Human Embryology; Brijesh Kumar, Embryology Text & Atlas; Vishram Singh, Textbook of Clinical Embryology.



## Development of inferior venacava

*Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The inferior vena cava (IVC) is not derived from any single embryonic vessel. It is a **composite structure**, assembled piecemeal and in a craniocaudal sequence, from segments of **three paired systemic veins** of the 4th–8th week embryo — the **posterior cardinal**, **subcardinal** and **supracardinal veins** — together with the **right vitelline vein**. Because the definitive IVC is built almost entirely from right-sided derivatives (the corresponding left-sided vessels mostly regress), its adult form comprises several segments of different embryological origin joined end to end. This complex, multi-step origin explains both the asymmetric venous drainage pattern of the abdomen (e.g., why the right gonadal/suprarenal veins drain directly into the IVC while the left ones drain via the left renal vein) and the wide range of congenital anomalies of the IVC seen clinically. In the adult, the IVC is formed by union of the two common iliac veins anterior to the body of L5, about 1 cm to the right of the midline, and ascends to open into the right atrium.

## 1. The three paired embryonic venous systems

| System                   | Site of development                                                                                                                              | Principal role                                                                                                               | Key fate                                                                                                                                                                                                                                                                          |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Posterior cardinal veins | Paired veins running the length of the trunk, draining into the <b>common cardinal veins</b> (ducts of Cuvier) which open into the sinus venosus | Chief venous drainage of the trunk and mesonephros in the 4th –5th week                                                      | Regress almost completely; caudal-most parts persist as the <b>common iliac veins</b> and the extreme caudal tip of the IVC; cranial/thoracic remnant contributes to the root of the <b>azygos vein</b>                                                                           |
| Subcardinal veins        | Form ventromedial to the mesonephric ridge (future site of the kidney), connected to the posterior cardinals by numerous channels                | Take over drainage of the mesonephros; intercommunicate in the midline by a <b>pre-aortic (intersubcardinal) anastomosis</b> | Right subcardinal vein → <b>prerenal segment of IVC + right suprarenal vein</b> ; left subcardinal vein (cranial to the anastomosis) → <b>left suprarenal vein</b> ; the pre-aortic anastomosis persists as the part of the <b>left renal vein</b> crossing anterior to the aorta |
| Supracardinal veins      | Form dorsolateral to the aorta and posterior cardinal veins (also called the thoracolumbar veins)                                                | Take over intersegmental (lumbar and intercostal) venous drainage from the posterior cardinal veins                          | Right supracardinal vein → <b>postrenal segment of IVC</b> , and (with the posterior cardinal remnant) most of the <b>azygos vein</b> ; left supracardinal vein → <b>hemiazygos</b> and <b>accessory hemiazygos veins</b> ; rest disappears                                       |

Cranially and caudally, the subcardinal and supracardinal veins on each side anastomose with one another; this **subcardinal–supracardinal (suprasubcardinal) anastomosis**, together with the pre-aortic intersubcardinal anastomosis, completes a venous ring around the aorta just below the origin of the superior mesenteric artery — the "**renal collar**."

## 2. Segment-wise origin of the definitive IVC

| Segment (caudal → cranial)       | Embryonic origin                                                                                                                                                                                                                         |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Caudal (infrarenal-most) segment | Caudal part of the <b>right posterior cardinal vein</b> (between the transverse iliac anastomosis of the two posterior cardinals and the point where the right supracardinal vein joins it); continues below into the common iliac veins |
| Postrenal segment                | <b>Right supracardinal vein</b>                                                                                                                                                                                                          |

| Segment (caudal → cranial)      | Embryonic origin                                                                                                                         |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Renal segment                   | Right subcardinal–supracardinal (renal collar) anastomosis; receives the renal veins here                                                |
| Prerenal segment                | Right subcardinal vein                                                                                                                   |
| Hepatic segment                 | Anastomosis between the <b>right subcardinal vein</b> and the <b>right vitelline vein</b> (right hepatocardiac channel)                  |
| Suprahepatic (terminal) segment | <b>Right vitelline vein / right hepatocardiac channel</b> ; the left hepatocardiac channel and most of the left vitelline vein disappear |

Several standard texts group these into the commonly quoted "**four main segments**" of the IVC — **hepatic, prerenal, renal and postrenal** — by folding the caudal-most part into the postrenal segment and the suprahepatic part into the hepatic segment; both descriptions are testable and refer to the same underlying sequence.

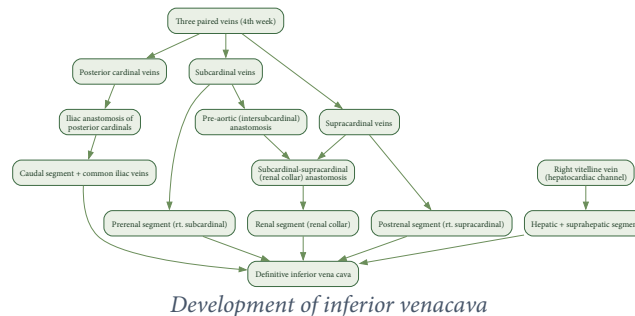
□ Fig 19.15 — Development of inferior vena cava. Segments of inferior vena cava develops by anastomosi (Sontakke — *Textbook of Human Embryology*, p.205)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the three paired longitudinal venous channels flanking the dorsal aorta with these exact labels:

- ▶ **Posterior cardinal veins** (paired, shown regressing/dashed except at the caudal and cranial ends)
- ▶ **Subcardinal veins** (paired, ventromedial, in relation to the mesonephric ridge)
- ▶ **Supracardinal veins** (paired, dorsolateral to the aorta)
- ▶ **Pre-aortic (intersubcardinal) anastomosis**
- ▶ **Subcardinal–supracardinal (renal collar) anastomosis**
- ▶ **Right vitelline vein / right hepatocardiac channel**
- ▶ **Common iliac veins** (from the iliac anastomosis of the posterior cardinals)
- ▶ **Renal veins entering at the renal segment**
- ▶ **Right gonadal vein and right suprarenal vein opening directly into the IVC; left gonadal and left suprarenal veins opening into the left renal vein**
- ▶ **Label the definitive IVC in four coloured bands: hepatic – renal – prerenal – postrenal segments** (caudal to cranial as drawn top to bottom, or cranial to caudal per convention used)

### 3. Sequence of formation



### 4. Fate of parts of the three systems NOT incorporated into the IVC

| Structure                                                           | Fate                                                                                                                        |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Bulk of the posterior cardinal veins                                | Regress; only the caudal ends (common iliac veins) and a cranial/thoracic remnant (root of azygos vein) persist             |
| Right and left common cardinal veins (with anterior cardinal veins) | Right → part of the <b>superior vena cava</b> ; left → <b>oblique vein of the left atrium</b> and the <b>coronary sinus</b> |
| Left subcardinal vein (cranial part)                                | <b>Left suprarenal vein</b>                                                                                                 |
| Left gonadal vein                                                   | Drains into the <b>left renal vein</b> (via the persisting pre-aortic/intersubcardinal channel)                             |

| Structure                                                | Fate                                                                                |
|----------------------------------------------------------|-------------------------------------------------------------------------------------|
| Right gonadal vein                                       | Drains directly into the IVC (via the persisting right subcardinal-derived channel) |
| Left suprarenal vein                                     | Drains into the <b>left renal vein</b>                                              |
| Left supracardinal vein                                  | <b>Hemiazygos and accessory hemiazygos veins</b>                                    |
| Right supracardinal + posterior cardinal (thoracic part) | Most of the <b>azygos vein</b>                                                      |

### Applied / Clinical anatomy

- ▶ **Double (duplicated) infrarenal IVC** — persistence of the left supracardinal vein instead of its normal regression; the left-sided vessel usually joins the left renal vein and drains into the normal right-sided IVC across the midline.
- ▶ **Absence of the hepatic segment of the IVC with azygos continuation** — failure of the anastomosis between the right subcardinal vein and the right hepatocardiac channel; infrarenal venous blood then returns to the heart via the azygos/hemiazygos system into the superior vena cava, while the hepatic veins open separately into the right atrium. Important in cardiac catheterisation/IVC-filter planning when a femoral approach is used, and is classically associated with left atrial isomerism/polysplenia.
- ▶ **Left-sided IVC** — persistence of the left supracardinal vein with regression of the right supracardinal vein; the vessel crosses to the right at the renal level to join the normal suprarenal (hepatic) segment; may occur in isolation or with situs inversus.
- ▶ **Retrocaval (postcaval) ureter** — the infrarenal IVC develops abnormally from the persisting right subcardinal vein (which lies ventral to the ureter) rather than the supracardinal vein (which lies dorsal to it), so the right ureter comes to lie behind the cava; presents clinically as ureteric obstruction/hydronephrosis.
- ▶ **Circumaortic or retro-aortic left renal vein** — persistence of both limbs of the "renal collar" (the dorsal supracardinal-subcardinal anastomosis in addition to the normal ventral pre-aortic anastomosis) instead of only the ventral limb surviving; surgically relevant during aortic aneurysm repair and live-donor nephrectomy.
- ▶ **Surgical/radiological relevance** — knowledge of the segmental origin explains why the hepatic segment can be spared/reconstructed separately in liver transplantation (piggyback technique), why IVC anomalies must be excluded before IVC filter placement, and why these variants are frequently tested on contrast CT/MR venography.

### High-yield exam pointers

- ▶ The IVC is a **composite vessel** built from **three paired veins** (posterior cardinal, subcardinal, supracardinal) + the **right vitelline vein** — never describe it as arising from one single embryonic vein.
- ▶ Craniocaudal segments: **hepatic** (right vitelline/hepatocardiac channel) → **renal** (subcardinal-supracardinal/renal-collar anastomosis) → **prerenal** (right subcardinal vein) → **postrenal** (right supracardinal vein); caudal-most tip from the right posterior cardinal vein.



- ▶ The definitive IVC is right-sided by convention because the corresponding left-sided channels of each paired system regress.
- ▶ **Renal collar** = ring of venous anastomoses around the aorta below the origin of the SMA (pre-aortic/intersubcardinal + subcardinal-supracardinal anastomoses); its persistence pattern explains left renal vein variants.
- ▶ Right gonadal and right suprarenal veins drain **directly into the IVC**; the corresponding left veins drain into the **left renal vein** — a direct, testable consequence of subcardinal asymmetry.
- ▶ Classic tested anomalies: **double IVC**, **left-sided IVC**, **azygos continuation of the IVC** (absent hepatic segment), **retrocaval ureter**, and **circumaortic/retro-aortic left renal vein** — each traceable to a specific failure of the normal regression/persistence pattern.
- ▶ Adult IVC begins anterior to the body of **L5** (union of the common iliac veins), about 1 cm to the right of the midline; normal calibre up to ~30 mm.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Brijesh Kumar — Embryology Text & Atlas; IB Singh — Human Embryology (CBME 2021).



## Development of Interatrial septum

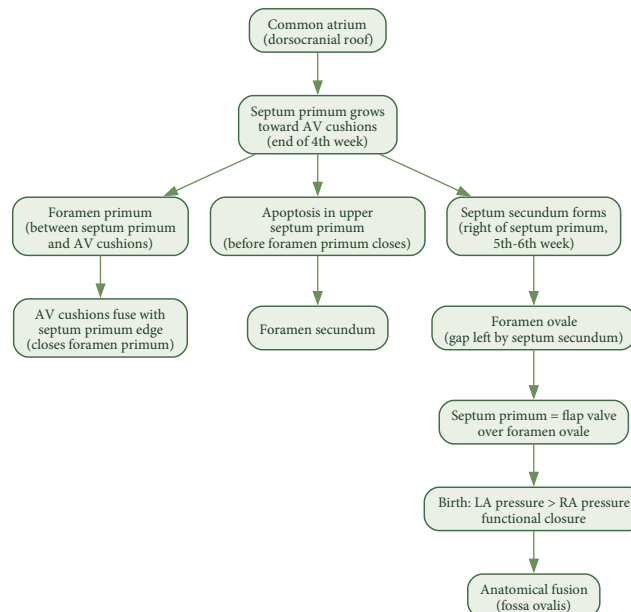
*Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The interatrial (atrial) septum is the partition that converts the single common atrium of the tubular embryonic heart into separate right and left atrial chambers. It is built between the 4th and 7th weeks of intrauterine life by the sequential, overlapping growth of two incomplete septa — the **septum primum** and the **septum secundum** — whose non-aligned openings (foramen primum, foramen secundum and foramen ovale) keep a valve-like right-to-left communication patent throughout fetal life, essential for shunting oxygenated placental blood, while preventing reverse flow. At birth, a reversal of interatrial pressure presses the two septa together, converting the fetal shunt functionally, and later anatomically, into the adult **fossa ovalis**.

### 1. Sequence of development — overview

- ▶ **End of the 4th week (~day 28):** a sickle/crescent-shaped fold, the **septum primum** (primary atrial septum), grows from the dorsocranial roof of the common atrium toward the atrioventricular (AV) canal.
- ▶ **Before the end of the 5th week:** programmed cell death (apoptosis) in the upper part of septum primum creates the **foramen secundum**, before the lower opening (**foramen primum**) has closed.
- ▶ **5th–6th week:** the **septum secundum** begins to form as a thick, muscular crescentic infolding of the atrial roof, to the right of septum primum.

- **6th–7th week:** the free, concave edge of septum secundum overlaps the foramen secundum, leaving a residual gap — the **foramen ovale**; septum primum comes to act as its flap valve.
- **At birth:** pressure reversal presses septum primum against septum secundum — **functional closure**; **anatomical fusion** follows over the following weeks to months.



*Development of Interatrial septum*

## 2. Septum primum, the mesenchymal cap and the foramen primum → foramen secundum sequence

- Septum primum grows from the atrial roof downward, just to the right of the entrance of the (developing) pulmonary vein, separated from the left sinuatrial (venous) valve by the interseptovalvular space.
- Its leading (lower) edge carries a **mesenchymal cap**, in continuity dorsally with the **dorsal mesenchymal protrusion (DMP)**, also called the **spina vestibuli** — a second-heart-field-derived mesenchymal mass that enters the atrium via the dorsal mesocardium.
- The ventral horn of septum primum reaches the ventral (superior) AV cushion and the dorsal horn reaches the dorsal (inferior) AV cushion; the gap between the free edge of septum primum and the AV cushions is the **foramen (ostium) primum** — the sole interatrial communication at this stage.
- As the foramen primum narrows, fusion of the mesenchymal cap, the DMP and the fusing AV cushions forms the **atrioventricular mesenchymal complex**, which eventually occludes the foramen primum in the midline and also contributes to the atrioventricular septum (septum intermedium), dividing the common AV canal into right and left AV orifices.
- **Before** the foramen primum is finally sealed, programmed cell death produces multiple small perforations in the **upper** part of septum primum; their coalescence forms a new opening, the **foramen (ostium) secundum**, completed before the end of the 5th week — this guarantees an uninterrupted right-to-left shunt as one opening closes and another opens.

### 3. Septum secundum and the foramen ovale

- ▶ As the right atrium enlarges by incorporation of the right horn of the sinus venosus, a second, thicker and more muscular crescentic fold — the **septum secundum** — develops from the atrial roof immediately to the right of septum primum.
- ▶ Septum secundum never forms a complete partition: its free, concave edge grows to overlap the foramen secundum but stops short of the atrioventricular mesenchymal complex, leaving a persistent gap near the floor of the right atrium — the **foramen ovale**.
- ▶ On the right side, the **septum spurium** (formed where the right and left venous valves join cranial to the sinuatrial orifice) and the **left venous valve** fuse with septum secundum, contributing to its substance.
- ▶ Blood therefore crosses from right to left atrium along an obliquely staggered course: under the crescentic free edge of septum secundum, then through the foramen secundum in septum primum — the thin, flexible septum primum acts as a **one-way flap valve**, collapsing away from the stiffer septum secundum to allow right-to-left flow but apposing against it to block reverse flow.

□ Fig 18.8 — Development of interatrial septum. Sagittal section of the developing heart (Sontakke — Textbook of Human Embryology, p.182)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal/coronal series through the developing atria (3 stages: septum-primum stage → septum-sekundum stage → foramen-ovale stage), labelling:

- ▶ **Common atrium** with dorsocranial roof
- ▶ **Septum primum** growing toward the AV cushions, with its **mesenchymal cap**
- ▶ **Dorsal mesenchymal protrusion (spina vestibuli)** and developing **pulmonary vein**
- ▶ **Foramen (ostium) primum** — gap below septum primum
- ▶ **Superior and inferior AV endocardial cushions** fusing to form the AV septum
- ▶ **Foramen (ostium) secundum** — perforations in the upper septum primum
- ▶ **Septum secundum** — thick muscular fold to the right of septum primum
- ▶ **Foramen ovale** — residual gap in septum secundum, with septum primum as its flap valve
- ▶ **Right and left venous valves / septum spurium**, and **sinus venosus** opening

### 4. Contribution of the sinus venosus and pulmonary veins to atrial topography

- ▶ The **right venous valve** persists (forming the crista terminalis, valve of the IVC, and valve of the coronary sinus); the **left venous valve** and **septum spurium** fuse with septum secundum and largely disappear, so the smooth-walled part of the adult right atrium (sinus venarum) derives from the absorbed right sinus horn.
- ▶ Simultaneously, the developing pulmonary vein — carried into the left atrial wall by growth and movement of the dorsal mesenchymal protrusion — is progressively incorporated, so that the smooth-walled part of the adult left atrium derives from the absorbed pulmonary vein, ultimately opening by four separate pulmonary venous orifices.

## 5. The foramen ovale in fetal circulation

- ▶ Highly oxygenated blood returning from the placenta via the umbilical vein and ductus venosus enters the inferior vena cava (IVC) and is preferentially directed by the **crista dividens** (the free, lower edge of septum secundum) through the foramen ovale into the left atrium.
- ▶ The valve of the IVC (Eustachian valve) helps direct roughly three-quarters of this richly oxygenated blood toward the foramen ovale and left atrium, where it mixes with the small pulmonary venous return, ensuring the best-oxygenated blood reaches the left ventricle, aorta, and coronary/cerebral circulation preferentially.
- ▶ In the neonate, the foramen ovale lies at about the level of the 3rd intercostal space in the median plane, and measures roughly 4–6 mm vertically by 3–4 mm transversely.

## 6. Closure of the foramen ovale at birth

- ▶ With the first breaths, pulmonary vascular resistance falls and pulmonary venous return to the left atrium rises sharply, while loss of placental flow lowers right-sided venous return; **left atrial pressure exceeds right atrial pressure**, pressing the flap-valve of septum primum against septum secundum — **functional closure**, which occurs after functional closure of the ductus arteriosus.
- ▶ **Anatomical (structural) closure** by fusion of septum primum to the rims of the foramen ovale is gradual: it is complete in fewer than 3% of infants by 2 weeks, and in about 87% by 4 months after birth.
- ▶ Fusion remains incomplete in a substantial minority: a **probe-patent oval foramen** (through which a probe can be passed from one atrium to the other, without a true tissue deficit) persists in roughly 25–30% of otherwise normal adult hearts and is not, by itself, a haemodynamically significant defect.

## Applied / Clinical anatomy

| Anomaly                                                          | Embryological basis                                                                                                   | Key features                                                                                                                     |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Ostium secundum ASD</b><br>(commonest significant ASD)        | Excessive resorption/short septum primum, and/or deficient/short septum secundum, so the foramen ovale is not covered | Defect in the region of the fossa ovalis; well tolerated in childhood, symptoms (pulmonary hypertension) often appear in the 30s |
| <b>Ostium primum ASD</b> (partial AV/endocardial cushion defect) | Failure of septum primum to fuse with the AV endocardial cushions → persistent foramen primum                         | Low atrial septal defect, usually combined with a cleft in the anterior mitral (or tricuspid) leaflet                            |
| <b>Complete AV septal defect</b>                                 | Complete failure of fusion of the AV endocardial cushions                                                             | Continuous interatrial + interventricular communication with a common AV valve; occurs in ~20% of Down syndrome patients         |
| <b>Sinus venosus ASD</b>                                         | Incomplete absorption of the sinus venosus into the right atrium and/or abnormal septum secundum development          | High defect near the SVC entry; commonly associated with partial anomalous pulmonary venous connection                           |

| Anomaly                                                | Embryological basis                                                          | Key features                                                                                                                                                        |
|--------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Common atrium</b> (cor triloculare biventriculare)  | Combined failure of septum primum and septum secundum to develop at all      | Rare; always accompanied by other serious cardiac defects                                                                                                           |
| <b>Probe-patent (patent) foramen ovale</b>             | Incomplete apposition/fusion of septum primum to septum secundum after birth | No true septal deficit; present in ~25–30% of adults; usually asymptomatic but a route for paradoxical embolism, platypnoea-orthodeoxia, and decompression sickness |
| <b>Premature closure of the foramen ovale in utero</b> | Foramen ovale seals before birth                                             | Massive right atrial/ventricular hypertrophy with left heart underdevelopment; usually fatal soon after birth                                                       |

- **Genetics:** mutations of **NKX2.5** (chromosome 5q35) cause secundum-type ASD with atrioventricular conduction delay, inherited as autosomal dominant; mutations of **TBX5** cause **Holt–Oram syndrome** (ASD with preaxial/radial limb defects), also autosomal dominant, incidence ~1/100,000 live births.
- **Epidemiology:** ASD overall incidence ≈ 6.4/10,000 live births, with a 2:1 female preponderance.
- **Clinical relevance of the fossa ovalis:** the thin floor of the fossa ovalis (septum primum remnant) is the standard site for **transseptal puncture** during cardiac catheter interventions (e.g., mitral valvuloplasty, left-sided ablation) and for percutaneous **device closure of secundum ASD/PFO**.
- The adult **limbus fossae ovalis**, though traditionally equated with the septum secundum edge, is largely formed by infolding of the atrial wall incorporating extracardiac fat rather than a discrete septal structure — a nuance worth noting in gross/gross-applied answers.

### High-yield exam pointers

- Two septa, **septum primum** (thin, membranous, forms first) and **septum secundum** (thick, muscular, forms second, to its right).
- Three openings in sequence: **foramen primum** → **foramen secundum** → **foramen ovale** — never a moment without a right-to-left channel.
- Foramen primum closes by fusion of septum primum with the **AV endocardial cushions**; foramen secundum forms by **apoptosis** in septum primum before that closure is complete.
- Foramen ovale = gap in septum secundum, valved on its left-atrial side by septum primum (crista dividens directs IVC flow through it).
- **Functional closure at birth** (pressure reversal, flap-valve apposition) vs **anatomical closure** (fusion, complete in only ~87% by 4 months) — a frequently tested distinction.
- Probe-patent oval foramen in ~25–30% of normal adults ≠ a true ASD.
- **NKX2.5** (5q35) → secundum ASD + AV block; **TBX5** → Holt–Oram syndrome (ASD + limb defects).
- Ostium primum/AV septal defects are cushion-based (often Down syndrome-associated); ostium secundum/sinus venosus/common atrium defects are septum-primum/secundum-based.

- ▶ Adult fossa ovalis = septum primum remnant (floor) + limbus (mostly atrial-wall infolding) — clinical site for transseptal puncture and device closure.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen, Human Embryology 6e; Moore, The Developing Human 9e; Sontakke, Textbook of Human Embryology (figure); Vishram Singh, Textbook of Clinical Embryology; IB Singh, Human Embryology (CBME 2021).



## Development of the inferior vena cava

*Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The inferior vena cava (IVC) is not the derivative of a single embryonic vein but a **composite vessel**, assembled piecemeal between the 4th and 8th weeks from four successive sets of paired venous channels of the trunk — the **vitelline veins** and the three "cardinal" venous complexes, the **posterior cardinal**, **subcardinal** and **supracardinal veins**. Each system contributes one segment of the definitive IVC, so the adult vessel is, from below upward, a chain of vessels of different embryological origin joined end to end. This multi-source, right-sided origin explains both the segmental topography used in cross-sectional imaging and the wide range of congenital venous anomalies seen clinically.

### 1. The three primary paired venous systems (4th week)

- ▶ **Vitelline veins** — drain the yolk sac and primitive gut; as the liver bud invades the septum transversum they break up into a plexus around the duodenum and into hepatic sinusoids; the right vitelline vein persists as the **right hepatocardiac (common hepatic) channel**, which later forms the terminal/hepatic part of the IVC, while the left hepatocardiac channel disappears with regression of the left sinus horn. The extrahepatic vitelline plexus forms the **portal vein** and **superior mesenteric vein**.
- ▶ **Umbilical veins** — carry oxygenated placental blood; the right umbilical vein and the proximal part of the left disappear, leaving the left umbilical vein as the sole conduit; a sinusoidal short-circuit, the **ductus venosus**, connects it to the right hepatocardiac channel (becomes the ligamentum venosum after birth; the left umbilical vein becomes the ligamentum teres hepatis).
- ▶ **Anterior and posterior cardinal veins** — the anterior cardinal veins drain the head, the posterior cardinal veins drain the rest of the body; on each side they unite as a short **common cardinal vein** opening into the corresponding horn of the sinus venosus. This is the initial *symmetrical* venous plan of the embryo.

### 2. Secondary venous complexes that replace the posterior cardinal veins (5th–7th week)

Because the posterior cardinal veins alone cannot cope with the venous return from the enlarging mesonephros, gonads and body wall, two further paired plexuses appear and largely replace them:



- **Subcardinal veins** — lie ventromedial to the mesonephric ridges; drain the mesonephros, gonads and suprarenal glands; the two subcardinal veins intercommunicate by a **pre-aortic intersubcardinal anastomosis**, which becomes the part of the left renal vein that crosses in front of the aorta.
- **Supracardinal veins** (thoracolumbar/lateral sympathetic-line veins) — lie dorsolateral to the aorta and lateral to the sympathetic trunk; they take over intersegmental (intercostal/lumbar) drainage of the body wall from the regressing posterior cardinal veins, and connect with the subcardinal veins by a **supracardinal–subcardinal (suprasubcardinal) anastomosis** just below the developing renal veins.
- Together, the intersubcardinal anastomosis, the suprasubcardinal anastomosis and the supracardinal–azygos connections complete a venous ring around the aorta below the origin of the superior mesenteric artery, the "**renal collar**."
- The posterior cardinal veins themselves regress almost completely; only the caudal-most part of the right vein and the interposterior-cardinal anastomosis (between the two posterior cardinal veins) persist.

### 3. Segmental assembly of the definitive IVC (caudal → cranial)

| Segment                         | Level                                                  | Embryonic source                                                                                                                                           |
|---------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Post-renal (infrarenal) segment | From the common iliac confluence up to the renal veins | Right <b>supracardinal vein</b> , together with the terminal part of the right posterior cardinal vein and the right supracardinal–subcardinal anastomosis |
| Renal segment                   | At the level of the renal veins                        | Right <b>supracardinal–subcardinal (suprasubcardinal) anastomosis</b>                                                                                      |
| Prerenal (subhepatic) segment   | Between the renal veins and the liver                  | Right <b>subcardinal vein</b>                                                                                                                              |
| Hepatic segment                 | Within the liver, up to the sinus venosus/right atrium | Subcardinal–hepatocardiac anastomosis continuing as the right <b>vitelline vein</b> (right hepatocardiac/common hepatic channel)                           |

- **Common iliac veins** (continuous caudally with the IVC): the **right** common iliac vein is the caudal-most part of the right posterior cardinal vein; the **left** common iliac vein is the interposterior-cardinal anastomosis.
- Some texts (e.g. Sontakke) further split the hepatic segment into a "hepatic" part (subcardinal–hepatocardiac anastomosis) and a terminal "suprahepatic" part (the right vitelline/hepatocardiac channel itself); Sadler (Langman) separately names the postrenal plexus a **sacrocardinal vein**. Terminology differs slightly between texts, but the sequence of contributing veins is identical.

### 4. Why the renal, gonadal and suprarenal veins are asymmetric

- The **right renal, right suprarenal and right gonadal veins** are tributaries of the right subcardinal vein and so open directly into the subcardinal-derived (prerenal) segment of the IVC.



- The **left renal vein** is formed from the mesonephric tributary that drained into the left subcardinal vein, a small part of the left subcardinal vein itself, and the intersubcardinal anastomosis — hence it lies in front of the aorta. Because the left subcardinal vein itself regresses once this anastomosis is established, the **left suprarenal and left gonadal veins** drain not into the IVC directly but into the **left renal vein**.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 19.15 — *Development of inferior vena cava. Segments of inferior vena cava develop by anastomosis channels of cardinal veins (Sontakke — Textbook of Human Embryology, p.205)*

Reproduce as a labelled sequence (week 6 → week 7 → early week 8 → late week 8 → at birth), with these exact labels:

- Week 6: sinus venosus, common cardinal vein, anterior cardinal (precardinal) vein, right vitelline vein, hepatic sinusoids, developing liver, aorta, right subcardinal vein, right posterior cardinal (postcardinal) vein, left posterior cardinal (postcardinal) vein, left subcardinal vein
- Week 7: right hepatocardiac channel, right vitelline vein, subcardinal anastomosis, right gonadal vein, left gonadal vein, posterior cardinal veins anastomosis (iliac region)
- Early/late week 8: supracardinal vein, subcardinal vein, supra-subcardinal anastomosis, external iliac vein, internal iliac vein
- At birth: superior vena cava, azygos vein, hemiazygos vein, suprahepatic segment, hepatic segment, prerenal segment (subcardinal), renal segment (suprasubcardinal anastomosis), postrenal segment (supracardinal vein), caudal segment (supracardinal vein), left suprarenal vein, renal vein, gonadal veins, common iliac vein

### Applied / Clinical anatomy

- **Double IVC** — persistence of both the left subcardinal and left supracardinal veins below the renal level (failure of the interposterior-cardinal anastomosis to take over), so an infrarenal IVC persists on the left side as well as the right; the left channel usually drains into the left renal vein.
- **Absence of the (hepatic segment of the) IVC with azygos continuation** — the subcardinal–hepatocardiac anastomosis fails to develop; venous return from below the liver is then diverted through the persisting supracardinal/azygos system into the superior vena cava, while the hepatic veins open into the right atrium at the usual IVC orifice.
- **Left-sided IVC** — the infrarenal segment develops from the left supracardinal vein instead of the right (with regression of the normal right-sided channel); may occur in isolation or with situs inversus.
- **Retrocaval (preureteric/circumcaval) ureter** — if the infrarenal IVC develops from the right subcardinal vein (which lies anterior to the ureter) instead of the normal right supracardinal vein (which lies posterior to it), the ureter comes to hook behind and then anterior to the cava, usually near the lower border of the third part of the duodenum; incidence quoted as about 1 in 1500.
- **Retro-aortic left renal vein** — persistence of the posterior (dorsal) limb of the renal collar with regression of the normal anterior (intersubcardinal) limb places the left renal vein behind rather

than in front of the aorta; surgically relevant during ligation of the left renal vein (gonadal/suprarenal collaterals usually protect the kidney; the right renal vein has no such collateral and must not be ligated).

- ▶ The embryological segments map directly onto the **CT/radiological segmental nomenclature** used in trauma and oncological staging — retrohepatic, infrahepatic (peritonealized), renal and infrarenal segments — reflecting the hepatic, prerenal, renal and postrenal segments described above.

## High-yield exam pointers

- ▶ IVC is built from **four** embryonic sources (caudal→cranial): posterior cardinal (common iliac/caudal-most part) → supracardinal (postrenal) → suprasubcardinal anastomosis (renal) → subcardinal (prerenal) → right vitelline/hepatocardiac channel (hepatic).
- ▶ **Right-sided dominance:** the vessels of the right side persist while their left-sided counterparts largely regress — the single most important organizing principle.
- ▶ Intersubcardinal anastomosis → crossing part of left renal vein; suprasubcardinal anastomosis → renal segment of IVC; together with supracardinal–azygos link they form the "**renal collar**."
- ▶ Left gonadal/suprarenal veins drain into the left renal vein; right gonadal/suprarenal veins drain directly into the IVC — a direct consequence of subcardinal vein asymmetry.
- ▶ Right common iliac vein = caudal right posterior cardinal vein; left common iliac vein = interposterior-cardinal anastomosis.
- ▶ Congenital anomalies (double IVC, absent/azygos-continued IVC, left IVC, retrocaval ureter, retro-aortic left renal vein) are all directly explainable from failure/persistence of specific embryonic segments — always link the anomaly to the missing/persisting vein.
- ▶ Left umbilical vein + ductus venosus persist antenatally and obliterate at birth to form the ligamentum teres hepatis and ligamentum venosum respectively.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Brijesh Kumar — Embryology Text & Atlas.



## Development of ventricles of heart

Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy

**Definition / Introduction.** The definitive right and left ventricles arise from two adjacent dilatations of the primary heart tube — the **primitive ventricle** and the proximal (trabeculated) part of the **bulbus cordis** — after the tube undergoes rightward cardiac looping in the fourth week. Each ventricle acquires a rough, trabeculated **inflow part** from these primary dilatations and a smooth-walled **outflow part** from the more distal bulbus cordis. The two chambers are separated internally by the **interventricular (IV) septum**, a composite structure built from three embryologically distinct components — muscular, bulbar and membranous — that must fuse correctly with the atrioventricular endocardial cushions and the conotruncal (aorticopulmonary) septum for normal septation; failure at any of these three junctions is the commonest cause of congenital heart disease.

### 1. Primary heart tube and cardiac looping

- ▶ The straight primary heart tube (formed by end of 3rd week from the cardiogenic mesoderm) is organised craniocaudally, from arterial to venous end, into: **truncus arteriosus** → **conus cordis** → **bulbus cordis** → **primitive ventricle** → **primitive atrium** → **sinus venosus**.
- ▶ The tube is tethered by the **dorsal mesocardium**; as this degenerates a gap forms — the future **transverse pericardial sinus**.
- ▶ **Cardiac looping**: from day 23, the tube begins to bend — the cephalic (bulbo-conal) part bends ventrally, caudally and to the right, while the atrial (caudal) part shifts dorsocranially and to the left. This produces the **bulboventricular (D-shaped) loop**, and, as the atrium/sinus venosus come to lie dorsocranial to the ventricle, an **S-shaped cardiac loop**. Looping is complete by **day 28**.
- ▶ The **bulboventricular sulcus**, marking the external junction between bulbus cordis and primitive ventricle, corresponds internally to the narrow **primary interventricular foramen**.
- ▶ *Clinical note*: reversed (leftward) looping produces **dextrocardia**, often with situs inversus.

### 2. Heart-field contribution — why the two ventricles differ in origin

- ▶ The **primary/first heart field** contributes the greater part of the primitive ventricle, which becomes largely the **left ventricle**.
- ▶ The **secondary (anterior) heart field** is added progressively to the cranial (arterial) end of the tube during looping, lengthening the outflow tract; this added tissue forms the **right ventricle and outflow tract (conus cordis, truncus arteriosus)**.
- ▶ This explains why failure of adequate SHF-driven lengthening produces right-ventricular/outflow anomalies — double-outlet right ventricle, VSD, tetralogy of Fallot, pulmonary atresia/stenosis.

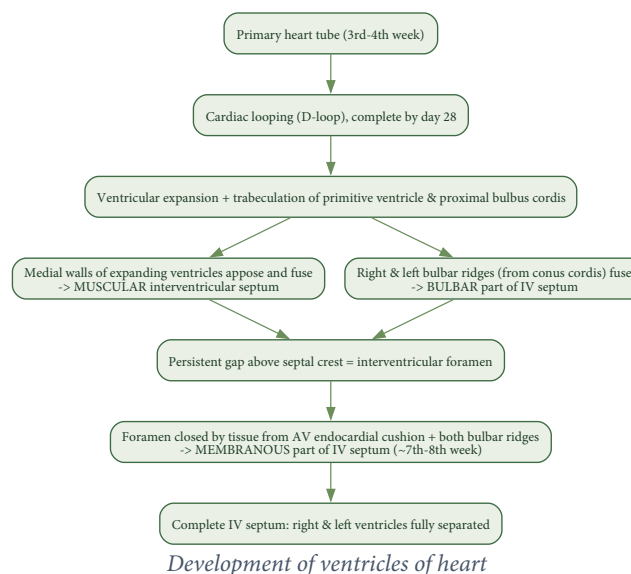
### 3. Fate of the primitive ventricle and bulbus cordis (rough vs smooth parts)

By the end of the 4th week the two primitive ventricles begin to expand — by continued myocardial growth externally and by trabeculation/diverticulation internally — while the bulbus cordis remains temporarily smooth-walled.

| Embryonic component                             | Adult derivative                                                                                                                              |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Primitive ventricle                             | Trabeculated (rough, inflow) part of <b>both</b> right and left ventricles                                                                    |
| Bulbus cordis — proximal 1/3                    | Trabeculated part of the <b>right ventricle</b> (fuses with primitive ventricle to form the bulboventricular chamber)                         |
| Bulbus cordis — middle 1/3 (conus cordis)       | Smooth outflow part of both ventricles: <b>infundibulum/conus arteriosus</b> of right ventricle and <b>aortic vestibule</b> of left ventricle |
| Bulbus cordis — distal 1/3 (truncus arteriosus) | Roots of ascending aorta and pulmonary trunk (divided by the spiral aortopulmonary septum)                                                    |

- ▶ The **left ventricle** therefore = inflow rough part (primitive ventricle) + outflow smooth part, aortic vestibule (conus cordis).
- ▶ The **right ventricle** = inflow rough part (proximal bulbus cordis) + outflow smooth part, infundibulum (conus cordis).
- ▶ The conotruncal portion, initially to the right of the pericardial cavity, is brought to a more medial position by paired transverse dilatations of the atrium bulging on either side of the bulbus cordis.

#### 4. Development of the interventricular septum



The IV septum has **three developmentally distinct parts**:

- ▶ **Muscular part** (largest, forms first): a crescentic myocardial ridge grows upward from the floor of the primitive ventricle near its apex, dividing the common ventricular cavity into two; it grows towards, but does not fully reach, the fused AV (endocardial) cushions, leaving a gap above its free, sickle-shaped margin.
- ▶ **Bulbar part**: right and left **bulbar ridges** develop from the conical (conal) part of the bulbus cordis, grow towards each other and fuse, extending the septum caudally towards the muscular part.

- **Membranous part:** by about the 7th–8th week, the residual gap between the muscular and bulbar parts — the **interventricular foramen** — is closed by proliferating mesenchymal tissue derived from **three sources**: the right side of the (inferior/dorsal) AV endocardial cushion, and the right and left bulbar ridges. This thin membranous part completes septation; its anterior (interventricular) portion separates the two ventricles, and a small posterior (atrioventricular) portion separates the right atrium from the left ventricle.

The muscular septum's crest marks the position of the original primary heart tube and later becomes the site of the **atrioventricular (His) bundle**. Persistence of patency of the interventricular foramen is essential until septation of the bulbus/truncus is complete, since it is the only outlet for the left ventricle before conotruncal septation.

**Embedded figure (real plate):**

□ Fig 18.11 — Development of the interventricular septum. Muscular part develops from a ridge on the floor of the primitive ventricle; bulbar part from right and left bulbar ridges; membranous part from AV-cushion tissue filling the gap between them (Day 41 and end of 7th week) (Sontakke — Textbook of Human Embryology, p.185)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce two frontal sections of the developing heart (as above), labelling:

- **Day-41 stage:** Aorta, Pulmonary trunk, Truncus arteriosus, right & left **Bulbar ridge**, Left atrium, Right atrium, **Superior and Inferior endocardial cushion**, **Interventricular foramen**, **Interventricular septum** (single ridge), Right AV canal/tricuspid orifice, Right ventricle, Left ventricle.
- **End-of-7th-week stage:** Aorta, Pulmonary trunk, **Bulbar part**, **Membranous part**, **Muscular part** of the interventricular septum, Tricuspid orifice, Right ventricle, Left ventricle.

### 5. The interventricular foramen — significance and closure

- Lies **cranial/dorsal to the crest of the muscular septum**, between the free margins of the muscular and bulbar septal components and the fused AV cushions.
- Permits communication between right and left ventricles throughout most of the embryonic period; before conotruncal division it is the **only route by which blood from both ventricles can reach the aortic sac**.
- Its closure (formation of the membranous septum) is intimately linked with **conotruncal (spiral aortopulmonary) septation** — the same right/left bulbar-ridge tissue contributes to both. This is why membranous VSDs cluster with outflow-tract (conotruncal) anomalies such as tetralogy of Fallot.

### Applied / Clinical anatomy

- **Ventricular septal defect (VSD)** — the single most common congenital cardiac malformation (isolated incidence  $\approx 12/10,000$  live births). By site: the majority are small **muscular** defects (often close spontaneously with growth); **membranous (perimembranous)** defects are less numerous but clinically more significant, since they reflect faulty fusion of AV-cushion and bulbar-ridge tissue and are frequently associated with conotruncal malalignment.

- ▶ **Tetralogy of Fallot** ( $\approx 9.6/10,000$  births) — anterior displacement of the conotruncal septum causing (1) infundibular pulmonary stenosis, (2) a large (perimembranous) VSD, (3) an overriding aorta, and (4) right ventricular hypertrophy; associated in many cases with a *JAG1* (Notch pathway) mutation in Alagille syndrome.
- ▶ **Persistent (common) truncus arteriosus** ( $\approx 0.8/10,000$  births) — failure of the conotruncal ridges to form/fuse, so no outflow septum forms; invariably accompanied by a VSD because the same ridges normally contribute to the membranous septum.
- ▶ **Transposition of the great arteries** ( $\approx 4.8/10,000$  births) — reversed (straight instead of spiral) growth of the aorticopulmonary septum, so the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle; survival requires an associated shunt (PDA/ASD/VSD).
- ▶ **Double-outlet right ventricle (DORV)** — both great arteries arise predominantly from the right ventricle, due to failure of adequate lengthening/rightward shift of the outflow tract (second heart field deficiency).
- ▶ **Single (primitive) ventricle / cor biloculare** — failure of the muscular septum to develop, producing a common ventricular chamber.
- ▶ Functionally, the interventricular septum is conventionally regarded as belonging to the left ventricle (myocardial fibre orientation), though its cellular lineage is mixed; the RV:LV+septum weight ratio is used echocardiographically/at autopsy to assess right-ventricular hypertrophy.
- ▶ On antenatal ultrasound, the four-chamber view (up to  $\sim 28$  weeks) should show two ventricles of equal size with an intact IV septum and equal contraction — the standard screening view for VSD and single-ventricle anomalies.

### High-yield exam pointers

- ▶ Ventricles derive from **two** primary dilatations: primitive ventricle (LV, mainly PHF) and proximal bulbus cordis (RV, added by SHF).
- ▶ Each ventricle has a **rough inflow part** (from primitive ventricle/proximal bulbus cordis) and a **smooth outflow part** (infundibulum/aortic vestibule, from conus cordis).
- ▶ IV septum = **3 parts**: muscular (from ventricular floor) + bulbar (right & left bulbar ridges) + membranous (AV cushion + both bulbar ridges) — **membranous part has 3 contributors**.
- ▶ Cardiac looping complete by **day 28**; muscular septum begins end of 4th week; membranous septum (and hence complete septation) by **7th–8th week**.
- ▶ Interventricular foramen closure is mechanistically linked to conotruncal (spiral) septation — explains co-occurrence of membranous VSD with tetralogy of Fallot / truncus anomalies.
- ▶ VSD = commonest congenital cardiac malformation; muscular defects are more numerous, membranous defects more clinically significant.
- ▶ The septal crest becomes the site of the AV (His) bundle — clinically relevant to conduction blocks after VSD repair.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Larsen — Human Embryology 6e (cross-checked for heart-tube regionalisation/looping figures).



## Discuss the formation and fate of aortic arches. Explain the embryological basis, when recurrent laryngeal nerve on the right side is not recurrent

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The aortic (pharyngeal) arch arteries are six paired vessels that develop transiently within the mesenchyme of the pharyngeal arches during the 4th–5th weeks, connecting the **aortic sac** (the distal, forked continuation of the truncus arteriosus) to the paired **dorsal aortae**. All six are never present together — cranial arches begin regressing before the caudal ones finish forming — and asymmetric, side-specific persistence or obliteration of these vessels converts the symmetrical embryonic plan into the adult asymmetric great-vessel pattern. This same asymmetric remodelling explains why the two recurrent laryngeal nerves (RLNs) — vagal branches originally running below the sixth arch arteries — come to hook around different structures on each side, and why, when the normal right-sided remodelling fails, the right RLN can end up not "recurring" at all.

### Formation of the aortic arch arteries

- ▶ Develop during the 4th–5th weeks in cranio-caudal sequence as each pharyngeal arch forms, so all six arches are never present simultaneously.
- ▶ Arise as branches of the **aortic sac**, the most distal part of the truncus arteriosus; a new branch is added as each arch forms, and every arch artery terminates in the paired **dorsal aortae** (fusing into one midline vessel caudal to the arches, from the fourth week).
- ▶ Only **five** arch-artery pairs ever form completely — I, II, III, IV and VI — because the **fifth arch** either never forms, or forms incompletely and then regresses, leaving no derivative.
- ▶ Each arch artery is embedded in the mesenchyme of its own pharyngeal arch; **neural crest cells** supply its smooth-muscle/connective-tissue coverings and regulate patterning — ectodermal **FGF8** is specifically required for 4th-arch development, and **PITX2** (aortic sac, second heart field, arch mesoderm) is the master gene of left–right asymmetry of the remodelling.
- ▶ The aorticopulmonary septum divides the outflow tract into the ventral aorta and pulmonary trunk; the aortic sac develops **right and left horns** — right → **brachiocephalic artery**, left → **proximal arch of the aorta**.

### Fate of the six aortic arches

| Arch | Fate                                                                                    |
|------|-----------------------------------------------------------------------------------------|
| I    | Largely disappears by day 27; a small remnant forms part of the <b>maxillary artery</b> |



| Arch                        | Fate                                                                                                                                                                                                                                                           |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| II                          | Disappears soon after; remnants form the <b>hyoid</b> and <b>stapedial</b> arteries                                                                                                                                                                            |
| III                         | Forms the <b>common carotid artery</b> and the proximal (first) part of the <b>internal carotid artery</b> (the rest of the internal carotid is from the cranial dorsal aorta); the <b>external carotid artery</b> sprouts from the third arch as a new vessel |
| IV — right                  | Forms the <b>proximal part of the right subclavian artery</b> (its distal part is formed by the right dorsal aorta + right 7th cervical intersegmental artery)                                                                                                 |
| IV — left                   | Forms part of the <b>arch of the aorta</b> , between the origins of the left common carotid and left subclavian arteries                                                                                                                                       |
| V                           | Never forms completely, or regresses without leaving a derivative                                                                                                                                                                                              |
| VI — right (pulmonary arch) | Proximal part → proximal <b>right pulmonary artery</b> ; distal part loses its connection with the dorsal aorta and disappears                                                                                                                                 |
| VI — left (pulmonary arch)  | Proximal part → <b>left pulmonary artery</b> ; distal part persists through fetal life as the <b>ductus arteriosus</b> (→ ligamentum arteriosum after birth)                                                                                                   |

□ Fig 19.12 — Fetal aortic arches showing development of arch arteries (BD Chaurasia — Human Anatomy Vol 1 — 8e, p.341)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Fetal aortic-arch scheme, labelled: aortic sac (right & left horn) — truncus arteriosus — arch I and arch II (regressed, shown dotted) — arch III → common carotid artery + internal carotid artery, with external carotid artery as a new sprout — arch IV right → proximal right subclavian artery — arch IV left → arch of aorta — arch V (rudimentary/absent) — arch VI right → right pulmonary artery (distal part regresses) — arch VI left → left pulmonary artery + ductus arteriosus — right and left dorsal aortae — right 7th cervical intersegmental artery → distal right subclavian artery — carotid duct (obliterated dorsal-aortic segment between arches III and IV).

### Associated remodelling of the dorsal aortae

- ▶ The **carotid duct** (dorsal aorta between the third and fourth arches) is obliterated on both sides.
- ▶ The **right dorsal aorta disappears** between the right 7th intersegmental artery and its junction with the left dorsal aorta; caudal to this, the fused dorsal aortae persist as the **descending thoracic and abdominal aorta**.
- ▶ The remaining left dorsal aorta (after loss of the left carotid duct) persists as the **descending part of the arch of the aorta**.
- ▶ With cephalic flexure, neck elongation and caudal descent of the heart, the **left subclavian artery** — fixed distally in the limb bud, originally at the level of the 7th intersegmental artery — shifts its

origin progressively cranially to just distal to the left common carotid, giving the adult three-branch arch pattern (brachiocephalic trunk, left common carotid, left subclavian).

### Embryological basis of the recurrent course of the laryngeal nerves

- ▶ The **recurrent laryngeal nerves** are vagal branches that, in the early embryo, are given off in relation to the **sixth (pulmonary) aortic arch** and pass below it to reach the developing larynx.
- ▶ As the heart and great vessels descend caudally into the thorax, both nerves get caught (hooked) below the sixth arch arteries and must ascend again to reach the larynx — this caudal capture-and-reascent is what makes their course "recurrent."
- ▶ **Left side:** the distal part of the left sixth arch persists throughout intra-uterine life as the **ductus arteriosus** (later the ligamentum arteriosum); the left RLN therefore stays fixed in the thorax, hooking below the arch of the aorta and behind the ligamentum arteriosum, then ascending in the left tracheo-oesophageal groove.
- ▶ **Right side:** the distal part of the right sixth arch (and the vestigial fifth arch) disappears completely, so no vessel remains in the thorax for the nerve to loop under; the right RLN instead moves up in the neck and hooks around the next persisting vessel at that level — the **right subclavian artery** (derived from the right fourth arch + right dorsal aorta + right 7th intersegmental artery) — reaching the larynx via the right tracheo-oesophageal groove.

□ Fig 8.34 — Relation to recurrent laryngeal nerve (BD Chaurasia — Human Anatomy Vol 3-4 — 8e, p.196)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Scheme of the recurrent laryngeal nerves and the aortic arch derivatives, labelled: right and left vagus nerves — right and left recurrent laryngeal nerves — arch of aorta — ligamentum arteriosum (left side only) — right subclavian artery — trachea — oesophagus — right and left tracheo-oesophageal grooves — thyroid gland (inferior pole).

### Embryological basis of the "non-recurrent" right recurrent laryngeal nerve

- ▶ A rare anomaly, seen only on the right side, in which the right RLN arises **directly from the vagus trunk high in the neck** and passes almost transversely into the larynx close to the inferior pole of the thyroid gland, without any recurrent/hooks course.
- ▶ It occurs **only** in association with an **aberrant (retro-oesophageal) right subclavian artery**, i.e. when the normal right-sided arch-IV remodelling fails: instead of persisting, the **right fourth aortic arch and the proximal part of the right dorsal aorta are obliterated**, so the proximal right subclavian artery cannot form from arch IV as it normally does.
- ▶ The right subclavian artery is then reconstituted entirely from the **distal right dorsal aorta + right seventh intersegmental artery**, arising as the **last (most distal) branch of the aortic arch** beyond the left subclavian, with the brachiocephalic trunk absent and the right common carotid arising directly from the arch. As its stem is the persisting right dorsal aorta, this vessel crosses the midline **behind the oesophagus** to reach the right upper limb — the **arteria lusoria**, which may compress the oesophagus (**dysphagia lusoria**).

- ▶ Consequence for the nerve: the vessel the right RLN would normally hook beneath — the arch-IV-derived proximal right subclavian artery — never forms. With no local vessel to loop under, the right vagus's laryngeal branch runs straight into the larynx from its point of origin in the neck: it never "recurs," giving the **non-recurrent laryngeal nerve**.
- ▶ The anomaly is exclusively right-sided because it is the right dorsal aorta/right fourth-arch remodelling — not the left, which forms the aortic arch itself — that is subject to this developmental failure.

## Applied / Clinical anatomy

- ▶ **Surgical importance:** an unrecognised non-recurrent laryngeal nerve is vulnerable to injury during thyroidectomy, parathyroidectomy and lateral neck dissection, since the surgeon does not expect a laryngeal nerve running transversely at that level; it may also be compressed by small thyroid tumours.
- ▶ **Aberrant right subclavian artery (arteria lusoria):** the commonest congenital anomaly of the aortic arch arteries; usually asymptomatic, but may cause **dysphagia lusoria** (oesophageal compression), seen as a posterior oesophageal indentation on barium swallow and confirmed on CT angiography.
- ▶ **Patent ductus arteriosus:** failure of closure of the distal left sixth-arch derivative; continuous "machinery" murmur; associated with prematurity/maternal rubella; kept patent with prostaglandin E1, closed with indomethacin.
- ▶ **Coarctation of the aorta:** narrowing near the ductus/ligamentum arteriosum (pre-ductal and, more commonly, post-ductal types); post-ductal type develops intercostal/internal-thoracic collaterals causing rib notching; upper-limb hypertension with diminished femoral pulses.
- ▶ **Double aortic arch:** persistence of the distal right dorsal aorta creates a vascular ring around the trachea and oesophagus, causing stridor/dysphagia in infancy.
- ▶ **Right aortic arch:** the left fourth arch and left dorsal aorta are obliterated and replaced by their right-sided counterparts; a left-sided ligamentum arteriosum passing behind the oesophagus can cause dysphagia.
- ▶ **Interrupted aortic arch:** rare, from abnormal regression of the fourth arches; strongly associated with 22q11 deletion (**DiGeorge) syndrome**, with a VSD and PDA.

## High-yield exam pointers

- ▶ Six paired aortic arch arteries form in cranio-caudal sequence during weeks 4–5 from the aortic sac to the dorsal aortae; arch V never completes.
- ▶ Arch III → common + internal carotid artery; arch IV (left) → arch of aorta, arch IV (right) → proximal right subclavian artery; arch VI (left) → left pulmonary artery + ductus arteriosus, arch VI (right) → right pulmonary artery (distal part regresses).
- ▶ Both recurrent laryngeal nerves originally hook below the sixth arch; the left stays hooked around the ligamentum arteriosum (persisting ductus arteriosus) in the thorax, the right moves up to hook around the right subclavian artery (persisting arch IV) in the root of the neck.

- ▶ Non-recurrent right laryngeal nerve = right RLN arises directly from the vagus in the neck with no hooking course; it is always associated with an aberrant right subclavian artery (obliteration of the right 4th arch + proximal right dorsal aorta).
- ▶ The aberrant right subclavian artery arises as the last branch of the aortic arch, crosses behind the oesophagus, and the brachiocephalic trunk is absent — causing dysphagia lusoria.
- ▶ The left recurrent laryngeal nerve is never non-recurrent, because the aortic arch itself (not merely a branch) is formed from the left fourth arch.
- ▶ Clinically important: risk of iatrogenic injury to an unrecognised non-recurrent laryngeal nerve during thyroid/parathyroid surgery.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e (formation and fate/derivatives of the aortic arches, dorsal-aortic remodelling, embryological basis of the recurrent and non-recurrent laryngeal nerve course, aortic arch anomalies); Gray's Anatomy (Standring) 41e (aortic sac/dorsal aorta remodelling, aortic isthmus, gross relations of the recurrent laryngeal nerves to the arch of the aorta and ligamentum arteriosum, the non-recurrent laryngeal nerve); BD Chaurasia — Human Anatomy Vol 1 & Vol 3–4, 8e (development-of-arteries summary; relation of the recurrent laryngeal nerve to the aortic arches); Vishram Singh — Textbook of Clinical Embryology (aberrant right subclavian artery, dysphagia lusoria); Larsen — Human Embryology 6e (cross-check on timing/sequence of arch formation).



## Fate of aortic arches

*Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The aortic (pharyngeal) arch arteries are six paired vessels that arise from the aortic sac and run through the mesenchyme of the corresponding pharyngeal arches to drain into the paired dorsal aortae. They appear in cranio-caudal sequence during the 4th–5th weeks, are never all present simultaneously, and the 5th pair never forms completely. Selective persistence, regression and asymmetric (right vs left) remodelling of this originally symmetrical six-arch system produces the definitive great vessels of the neck and thorax — the carotid, subclavian and pulmonary arteries and the arch of the aorta. Knowledge of this transformation explains the arch of aorta's asymmetric branching pattern, the recurrent course of the laryngeal nerves, and a family of clinically important vascular-ring anomalies.

## Origin and general plan of the aortic arch system

- ▶ Each of the five/six pharyngeal arches, as it forms in cranio-caudal sequence during the 4th and 5th weeks, receives its own cranial nerve and its own artery — the aortic arch artery.
- ▶ All aortic arches arise from the **aortic sac**, the most distal (most cranial) part of the truncus arteriosus, and terminate in the **right and left dorsal aortae**; in the region of the arches the dorsal aortae remain paired, but caudal to this they fuse into a single midline vessel.

- ▶ Because the arches appear sequentially, not simultaneously, the aortic sac gives off a new branch to each arch as it forms — a total of five pairs of arteries, conventionally numbered **I, II, III, IV and VI** (the 5th either never forms or forms incompletely and regresses without leaving a derivative).
- ▶ **Neural crest cells** populating each arch form the tunica media/adventitia of the arch vessels and regulate their patterning; their ablation causes persistent truncus arteriosus and arch anomalies.
- ▶ Molecular control: **FGF8** (arch ectoderm/endoderm) drives 4th-arch development; **PITX2**, the master sidedness gene in the aortic sac/secondary heart field/arch mesoderm, governs the left-right asymmetric remodelling.
- ▶ The aorticopulmonary septum divides the truncus outflow into a ventral aorta and pulmonary trunk; the aortic sac then forms **right and left horns** — right horn → **brachiocephalic artery**, left horn → proximal **arch of the aorta**.

### Fate of the individual aortic arches

By the end of the 4th week the 1st and 2nd arches have already disappeared while the 3rd, 4th and 6th arches are still enlarging; from this point the system loses its original symmetry and is remodelled into the definitive pattern below.

| Arch                         | Fate (arterial derivative)                                                                                                                                                                                                                                                    |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st                          | Largely disappears by day 27; a small remnant persists as the <b>maxillary artery</b>                                                                                                                                                                                         |
| 2nd                          | Disappears soon after formation; remnants form the <b>hyoid and stapedial arteries</b>                                                                                                                                                                                        |
| 3rd                          | Forms the <b>common carotid artery</b> and the <b>proximal (first) part of the internal carotid artery</b> ; the rest of the internal carotid is formed by the cranial part of the dorsal aorta; the <b>external carotid artery</b> sprouts as a new branch from the 3rd arch |
| 4th — left                   | Persists as part of the <b>arch of the aorta</b> , between the origin of the left common carotid and left subclavian arteries                                                                                                                                                 |
| 4th — right                  | Forms the <b>most proximal segment of the right subclavian artery</b> (its distal part is formed by the right dorsal aorta and the 7th intersegmental artery)                                                                                                                 |
| 5th                          | Never forms, or forms incompletely and regresses — <b>no derivative</b>                                                                                                                                                                                                       |
| 6th (pulmonary arch) — left  | Proximal part forms the <b>left pulmonary artery</b> ; distal part persists throughout intrauterine life as the <b>ductus arteriosus</b>                                                                                                                                      |
| 6th (pulmonary arch) — right | Proximal part forms the <b>proximal right pulmonary artery</b> ; the distal part loses its connection with the dorsal aorta and disappears                                                                                                                                    |

- ▶ Four vessels summarise the whole system for viva purposes: the **carotid arteries** (3rd arches), the **arch of the aorta** (left 4th arch), the **pulmonary artery** (6th arches, connected to the aorta via the

ductus arteriosus in fetal life), and the **right subclavian artery** (right 4th arch + distal right dorsal aorta + 7th intersegmental artery).

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the paired ventral aortic sac and paired dorsal aortae joined by six numbered transverse arches (I–VI, mark 5th as absent/dashed) embedded in the six pharyngeal arches; then, alongside it, the definitive adult pattern derived from it. Label:

- ▶ Aortic sac → right horn (brachiocephalic artery) and left horn (proximal arch of aorta)
- ▶ Arch I → maxillary artery; Arch II → hyoid/stapedial artery
- ▶ Arch III → common carotid + proximal internal carotid; external carotid as a new sprout
- ▶ Arch IV (L) → arch of aorta (between left common carotid and left subclavian); Arch IV (R) → proximal right subclavian
- ▶ Arch V → absent (dashed, no derivative)
- ▶ Arch VI (L) → left pulmonary artery + ductus arteriosus (→ ligamentum arteriosum after birth); Arch VI (R) → proximal right pulmonary artery, distal part disappears
- ▶ Dorsal aorta segments: carotid duct (between 3rd and 4th arches, obliterated), right dorsal aorta between 7th intersegmental artery and midline fusion (obliterated), 7th intersegmental arteries (→ subclavian arteries)
- ▶ Recurrent laryngeal nerves looping under the 6th arch derivatives (ductus arteriosus on left, right subclavian artery on right)

□ Fig 36.9 — Aortic arch arteries and their derivatives. (Gray's Anatomy — Standring — 41e, p.840)

## Remodelling of the dorsal aortae and related structures

Alongside the arch changes, three further changes complete the transformation:

- ▶ The **dorsal aorta between the 3rd and 4th arches**, called the **carotid duct**, is obliterated on both sides.
- ▶ The **right dorsal aorta disappears** between the origin of the 7th intersegmental artery and its junction with the left dorsal aorta; the fused right and left dorsal aortae caudal to this persist as the definitive **descending thoracic and abdominal aorta**.
- ▶ **Cephalic folding, forebrain growth and neck elongation** draw the heart down into the thorax; the carotid and brachiocephalic arteries elongate accordingly, and the **left subclavian artery** (fixed distally in the limb bud, originally arising at the level of the 7th intersegmental artery) shifts its point of origin progressively cranially until it lies close to the left common carotid artery.
- ▶ Gray's Anatomy additionally describes an **aortic isthmus** — a physiological constriction of the aorta between the origin of the left subclavian artery and the entry of the ductus arteriosus — the classic site later affected in coarctation of the aorta.
- ▶ The **7th intersegmental arteries** on each side contribute the distal right and the whole left subclavian artery.



## Course of the recurrent laryngeal nerves — a direct consequence of arch remodelling

- ▶ The recurrent laryngeal nerves are branches of the vagus that initially supply the 6th pharyngeal arch and hook around the corresponding 6th aortic arch before ascending to the larynx — hence their "recurrent" course.
- ▶ **Right side:** once the distal part of the right 6th arch (and the non-existent 5th arch) disappears, the nerve moves cranially and hooks around the next persisting vessel below it — the **right subclavian artery**.
- ▶ **Left side:** the distal part of the left 6th arch persists as the **ductus arteriosus**, so the left recurrent laryngeal nerve does not migrate and remains hooked around the arch of the aorta at the ligamentum arteriosum (post-natal fate of the ductus).
- ▶ This asymmetry is the embryological basis for the different surgical/anatomical course of the two recurrent laryngeal nerves in the neck and superior mediastinum.

## Applied / Clinical anatomy

- ▶ **Patent ductus arteriosus (PDA)** — failure of the left 6th arch derivative to close after birth; one of the commonest great-vessel anomalies (~8/10,000 births), more frequent in preterm infants; large aortic-pulmonary pressure differences (e.g. with other cardiac defects) sustain flow through the duct and prevent closure.
- ▶ **Coarctation of the aorta** — narrowing of the aortic lumen around the aortic isthmus (below the left subclavian origin), ~3.2/10,000 births; **preductal** (duct persists) or **postductal** (duct usually obliterated; commoner, with collateral flow to the lower body via enlarged intercostal and internal thoracic arteries); presents with upper-limb hypertension and diminished femoral pulses.
- ▶ **Aberrant (retro-oesophageal) right subclavian artery / "arteria lusoria"** — the right 4th arch and proximal right dorsal aorta are obliterated; the right subclavian artery instead arises from the distal right dorsal aorta + 7th intersegmental artery and must cross the midline behind the oesophagus to reach the arm — occasionally producing dysphagia (**dysphagia lusoria**).
- ▶ **Double aortic arch** — persistence of the right dorsal aorta between the 7th intersegmental artery and its junction with the left dorsal aorta, so both a right and left arch persist; forms a **vascular ring** around the trachea and oesophagus causing stridor/dysphagia.
- ▶ **Right aortic arch** — the left 4th arch and left dorsal aorta are obliterated and replaced functionally by the corresponding right-sided vessels; usually asymptomatic, but if the ligamentum arteriosum lies to the left and passes behind the oesophagus it can cause dysphagia.
- ▶ **Interrupted aortic arch (IAA)** — rare (~3/1,000,000 live births), from abnormal regression of the 4th arches bilaterally, producing a gap between the arch and descending aorta; a VSD and a PDA (supplying the lower body) are typically associated. Type A (interruption distal to the left subclavian, ~30–40%), Type B (between left common carotid and left subclavian, ~50–60%, the commonest type), Type C (between the two common carotid arteries, rare ~4%). **Type B IAA is strongly associated with DiGeorge syndrome (22q11 deletion)** — consistent with the cardiac neural crest origin of arch-vessel connective tissue.



- ▶ **Surface/clinical correlate:** the differing nerve loops (right subclavian vs left ligamentum arteriosum) explain why a left-sided aortic aneurysm or bronchogenic carcinoma more often causes recurrent laryngeal nerve palsy/hoarseness than an equivalent right-sided lesion.

### High-yield exam pointers

- ▶ Six paired aortic arches arise from the aortic sac and end in the paired dorsal aortae, embedded in the pharyngeal arches; they appear cranio-caudally and are never all present together.
- ▶ The **5th arch never forms completely** and leaves no derivative — arches are numbered I, II, III, IV, VI.
- ▶ **1st** → maxillary; **2nd** → hyoid & stapedial; **3rd** → common + proximal internal carotid; **4th (L)** → arch of aorta; **4th (R)** → proximal right subclavian; **6th (L)** → left pulmonary artery + ductus arteriosus; **6th (R)** → proximal right pulmonary artery.
- ▶ Distal right subclavian artery + entire left subclavian artery come from the **7th intersegmental arteries**, not from an aortic arch.
- ▶ **Carotid duct** = dorsal aorta segment between 3rd and 4th arches — obliterated bilaterally.
- ▶ Right dorsal aorta disappears distal to the 7th intersegmental artery — this is why the right side needs a "made-up" subclavian artery from three different sources.
- ▶ Ductus arteriosus = distal part of the **left 6th arch**; becomes the **ligamentum arteriosum** after functional (hours) and anatomical (1–3 months) closure.
- ▶ Recurrent laryngeal nerve asymmetry (hooks right subclavian vs left ligamentum arteriosum) is a direct, frequently-tested consequence of arch remodelling.
- ▶ Neural crest cells form the vessel wall media/adventitia of arch derivatives — their disruption underlies conotruncal and arch anomalies seen in 22q11 deletion (DiGeorge) syndrome.
- ▶ Clinically important anomalies to recall together: PDA, coarctation (pre-/post-ductal), aberrant right subclavian artery (dysphagia lusoria), double aortic arch, right aortic arch, and interrupted aortic arch (Types A/B/C).

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e — primary source for arch formation, the derivatives table, dorsal aorta remodelling, recurrent laryngeal nerve course and the arterial-system anomalies (PDA, coarctation, aberrant right subclavian artery, double/right aortic arch, interrupted aortic arch). Gray's Anatomy (Standring) 41e — spine text, used for the aortic-sac horns, carotid duct, aortic isthmus and Fig. 36.9 (embedded above). Cross-checked against Larsen's Human Embryology 6e and Sontakke's Textbook of Human Embryology for consistency of the numbered-arch derivatives table.

♦ ♦ ♦

## Fate of sinus venosus

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **sinus venosus** is the most caudal of the four primitive dilatations of the developing heart tube, appearing in the fourth week as the confluence of the vitelline, umbilical and common cardinal veins on each side. It contributes nothing to the ventricular mass; its entire "fate" is venous and atrial. Through an asymmetric, left-to-right dextral shift, the enlarging **right horn** is incorporated into the wall of the right atrium (giving the smooth-walled sinus venarum, the crista terminalis and the sinuatrial node), while the regressing **left horn** is reduced to the coronary sinus and the oblique vein of the left atrium. This sequence is the embryological basis of several important congenital systemic-venous anomalies and of the site of origin of the cardiac pacemaker.

### 1. Formation of the primitive sinus venosus (4th week)

- ▶ Formed at the caudal (venous) end of the primitive heart tube, just distal to the primitive atrium, within the septum transversum.
- ▶ Consists of a small median **body** and two lateral **horns** — **right and left**, initially of equal size.
- ▶ Each horn receives three paired tributary veins:

| Tributary vein                        | Source drained                                                        |
|---------------------------------------|-----------------------------------------------------------------------|
| Vitelline (omphalomesenteric) vein    | Yolk sac and developing gut/liver                                     |
| Umbilical vein                        | Placenta (oxygenated blood)                                           |
| Common cardinal vein (duct of Cuvier) | Union of anterior and posterior cardinal veins draining the body wall |

- ▶ At this stage the sinus venosus and the primitive atrium communicate through a wide **sinuatrial orifice**, transversely placed in the midline of the posterior atrial wall.

### 2. Mechanism of the dextral (rightward) shift

- ▶ From the fifth week, progressive **left-to-right shunting** of blood remodels the paired venous inflow into an asymmetric single-channel system:
  - **5th week** — the right umbilical vein and the left vitelline vein are obliterated; the left horn begins to lose importance as most blood is now diverted into the right horn.
  - **10th week** — the left common cardinal vein is obliterated; all that now remains of the left horn is the oblique vein of the left atrium and the coronary sinus.
- ▶ Because the right horn becomes the sole venous channel returning blood to the heart, it enlarges greatly and the sinuatrial orifice migrates from its original midline, transverse position to a vertical opening on the right side of the atrium.
- ▶ This dextral shift is the pivotal event that converts an originally symmetrical, paired structure into two functionally and anatomically unequal derivatives.

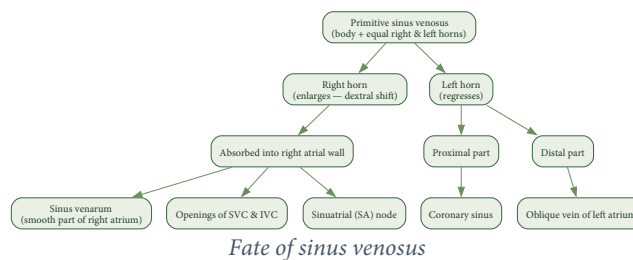
### 3. Fate of the two sinus horns

| Horn                | Regressive events                                                                                                                              | Adult derivative                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Right horn (+ body) | Enlarges progressively → becomes the sole inflow channel → absorbed into the wall of the right atrium                                          | <b>Sinus venarum</b> — the smooth posterior part of the right atrium, demarcated from the rough, trabeculated part (derived from the primitive atrium) by the <b>crista terminalis</b> ; carries the openings of the SVC and IVC; the site of origin of the <b>sinuatrial (SA) node</b> , since pacemaker tissue is carried, along with the incorporated sinus, to lie near the entry of the SVC |
| Left horn           | Right umbilical vein and left vitelline vein obliterate (5th week); left common cardinal vein obliterates (10th week) → progressive regression | Proximal part → <b>coronary sinus</b> ; distal part → <b>oblique vein of the left atrium</b> (vein of Marshall)                                                                                                                                                                                                                                                                                  |

### 4. Fate of the sinuatrial (venous) valves and septum spurium

- ▶ Once the sinuatrial orifice has shifted to the right, it is guarded on either side by two folds — the **right and left venous valves**.
- ▶ Dorsocranially the two valves fuse to form a low ridge, the **septum spurium**.
- ▶ **Left venous valve + septum spurium** fuse with the developing septum secundum/interatrial septum and are incorporated into it, largely disappearing as free structures.
- ▶ **Right venous valve** — stretched out and subdivided by two muscular ridges (superior and inferior limbic bands) into three parts, named from above downward:
- ▶ **Crista terminalis** (upper part)
- ▶ **Valve of the inferior vena cava** — the Eustachian valve (middle part)
- ▶ **Valve of the coronary sinus** — the Thebesian valve (lower part)
- ▶ Net result: the smooth, sinus-derived part of the right atrium (sinus venarum) is separated from the rough, primitive-atrium-derived part by the crista terminalis, while the Eustachian and Thebesian valves persist as small flaps guarding the openings of the IVC and coronary sinus respectively.

### 5. Diagrammatic summary



embed: ![Fig 18.6 — Development of sinus venosus and pulmonary veins (Sontakke — Textbook of Human Embryology, p.181)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/87a16cbc015fac18.jpg)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce the four-stage dorsal-view sequence (4 weeks → 7 weeks → 8 weeks → end of 8 weeks) with these exact labels:

- ▶ 4-week stage: **sinus venosus (body), right horn, left horn, common cardinal vein, anterior cardinal vein, posterior cardinal vein, left/right umbilical vein, left/right vitelline vein**
- ▶ 7-week stage: anastomosis (future **brachiocephalic vein**), degenerating left umbilical vein, degenerating left vitelline vein, degenerating right umbilical vein
- ▶ 8-week stage: **left horn of sinus venosus (→ coronary sinus)**, buds of pulmonary veins, degenerating left anterior/posterior cardinal vein, **superior vena cava, root of azygos vein**
- ▶ End of 8-week (adult pattern): **superior vena cava, inferior vena cava, root of azygos vein, coronary sinus, oblique vein of left atrium, pulmonary veins**
- ▶ Also label, on a right-atrium cut-away inset: **sinuatrial orifice, septum spurium, right venous valve → crista terminalis / valve of IVC / valve of coronary sinus, left venous valve → fused with septum secundum**

### Applied / Clinical anatomy

- ▶ **Persistent left SVC:** failure of obliteration of the left anterior cardinal and left common cardinal veins leaves a left SVC that drains into the right atrium via a dilated **coronary sinus** (the left horn derivative) — the commonest congenital systemic-venous anomaly; usually asymptomatic but important during central-line and pacemaker-lead placement, and in cardiac surgery.
- ▶ **Double SVC:** the left anterior cardinal vein persists and the left brachiocephalic (communicating) vein fails to form; both cavae drain independently, the left again via the coronary sinus.
- ▶ **Unroofed coronary sinus:** partial or complete deficiency of the wall separating the coronary sinus from the left atrium, producing an interatrial shunt; frequently coexists with a persistent left SVC.
- ▶ **Absent infrahepatic IVC with azygos continuation:** failure of the hepatic segment of the IVC; lower-body venous return reaches the heart via the azygos vein and SVC, while the hepatic veins open directly into the right atrium at the old IVC site.
- ▶ **Cor triatriatum dexter:** abnormal persistence of an excessively large right venous valve as a fenestrated membrane that partitions the right atrium into two chambers.
- ▶ **Chiari network / prominent Eustachian or Thebesian valve:** redundant fibrous remnants of the right venous valve seen in the adult right atrium, usually an incidental echocardiographic finding.
- ▶ **Sinus venosus–type ASD:** an interatrial defect near the SVC–right atrial junction related to faulty septation at the sinus horn, often associated with partial anomalous pulmonary venous connection of the right upper lobe vein.

- ▶ The **SA node** is embryologically derived from sinus-venosus tissue carried, with the incorporated right horn, to lie near the SVC opening — the developmental basis for discussing sick-sinus syndrome and ectopic atrial pacemakers alongside anomalies of this region.

### High-yield exam pointers

- ▶ Sinus venosus = median body + right and left horns; each horn receives vitelline, umbilical and common cardinal veins.
- ▶ Dextral shift is driven by sequential obliteration: right umbilical vein + left vitelline vein (5th week), then left common cardinal vein (10th week).
- ▶ Right horn → absorbed into right atrium → **sinus venarum** + **crista terminalis** + **SA node**.
- ▶ Left horn → proximal part = **coronary sinus**; distal part = **oblique vein of left atrium**.
- ▶ Right venous valve → crista terminalis + valve of IVC (Eustachian) + valve of coronary sinus (Thebesian).
- ▶ Left venous valve + septum spurium → fuse with the septum secundum/interatrial septum.
- ▶ Persistent left SVC draining via an enlarged coronary sinus is the classic clinical correlate of an incompletely regressed left horn.
- ▶ Cor triatriatum dexter and Chiari network both reflect abnormal persistence of the right venous valve.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas.



## Foetal circulation and circulatory changes after birth

*Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The foetal circulation is the pattern of blood flow peculiar to intra-uterine life, in which the non-functional lungs and liver are largely bypassed by three specialised shunts and gaseous/nutrient exchange occurs at the placenta instead of the lungs and gut. Oxygenated, nutrient-rich blood is carried to the fetus by a single umbilical vein and returned, after use, by paired umbilical arteries. At birth, clamping of the cord and aeration of the lungs abolish placental flow and reverse the pressure gradients across the atria and the ductus arteriosus, converting this shunt-dependent, parallel circuit into the adult in-series pulmonary-and-systemic circulation over minutes to months.

### 1. Special peculiarities of the foetal circulation

Five structures are "improvised" in the fetus that have no counterpart in the adult circulation.

| Structure                                                                          | Course / connection                                                                                                                                              | Function                                                                                                                                                                                        |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Umbilical vein</b> (single; left umbilical vein persists, right one disappears) | Placenta → umbilical cord → umbilicus → free edge of falciform ligament → joins the left branch of the portal vein                                               | Carries well-oxygenated, nutrient-rich blood <b>from</b> the placenta to the fetus                                                                                                              |
| <b>Ductus venosus</b>                                                              | Arises opposite the porto-umbilical junction, ascends behind the liver to join the left hepatic vein near its entry into the IVC                                 | Shunts a large part of umbilical venous blood past the hepatic sinusoids directly into the IVC; guarded by a physiological sphincter that prevents cardiac overload during uterine contractions |
| <b>Foramen ovale</b>                                                               | A valvular gap in the septum primum, at the free (lower) edge of the septum secundum ( <b>crista dividens</b> ), between right and left atrium                   | Diverts the well-oxygenated IVC stream directly into the left atrium, bypassing the right ventricle and lungs                                                                                   |
| <b>Ductus arteriosus</b>                                                           | Direct continuation of the pulmonary trunk at its bifurcation, joining the aortic arch just distal to the left subclavian artery origin                          | Shunts most of the right ventricular output from the pulmonary trunk into the aorta, bypassing the collapsed, high-resistance fetal lungs                                                       |
| <b>Umbilical arteries</b> (paired)                                                 | Arise from the internal iliac arteries, ascend along the sides of the bladder and anterior abdominal wall to the umbilicus, then run in the cord to the placenta | Return deoxygenated, waste-laden blood <b>from</b> the fetus to the placenta for re-oxygenation                                                                                                 |

## 2. Course of blood flow in the fetus

- Placental blood reaches the fetus via the **umbilical vein**, joins the left branch of the **portal vein**, and — after a small hepatic-sinusoidal contribution — bypasses the liver mainly through the **ductus venosus** to reach the **inferior vena cava (IVC)**, mixing with deoxygenated blood from the lower body.
- This still-rich IVC stream enters the **right atrium**, where the **crista dividens** (lower rim of septum secundum) and the IVC valve direct most of it through the **foramen ovale** into the **left atrium** → **left ventricle** → **ascending aorta**, preferentially supplying the coronary vessels, head, neck and upper limbs.
- The smaller IVC fraction that stays in the right atrium mixes with deoxygenated **superior vena cava**/coronary-sinus blood, passes to the **right ventricle** and out via the **pulmonary trunk**.
- Because fetal pulmonary vascular resistance is high, only a small share of pulmonary-trunk blood perfuses the collapsed lungs; the rest is shunted through the **ductus arteriosus** into the descending aorta, beyond the branches supplying the upper body.
- The descending aorta thus carries mixed, moderately-oxygenated blood to the abdominal viscera and lower limbs, with a large share returning via the **umbilical arteries** to the placenta for re-oxygenation.

### 3. Preferential streaming and differential oxygenation

| Segment                                                                     | Oxygenation                                                                                                                        | Basis                                 |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Umbilical vein → ductus venosus                                             | Highest — freshly arterialised at the placenta                                                                                     | Standard, confirmed across the corpus |
| Right atrium: IVC stream at the crista dividens                             | The inferior vena cava is so placed as to direct 75% of its richly oxygenated blood through the foramen ovale into the left atrium | Gray's Anatomy 41e                    |
| Left atrium → left ventricle → ascending aorta                              | Moderately high; preferentially perfuses the heart, brain, head/neck and upper limb                                                | Gray's Anatomy 41e                    |
| Right atrium (SVC + residual IVC blood) → right ventricle → pulmonary trunk | Medium content                                                                                                                     | Moore, <i>The Developing Human</i> 9e |
| Pulmonary trunk → lungs                                                     | Only about 10% of this flow                                                                                                        | Moore 9e                              |
| Pulmonary trunk → ductus arteriosus → descending aorta                      | The remainder (bulk of right ventricular output)                                                                                   | Moore 9e                              |
| Descending aorta → umbilical arteries → placenta                            | 65% of descending-aortic flow                                                                                                      | Moore 9e                              |
| Descending aorta → lower body/viscera                                       | Remaining 35%                                                                                                                      | Moore 9e                              |

This asymmetric ("preferential") streaming ensures the heart, brain and upper limbs get the best-oxygenated blood — cited as the reason fetal upper limbs grow slightly ahead of the lower limbs.

□ Fig 52.19 — A plan of the fetal circulation. The arrows indicate the direction of blood flow (Gray's Anatomy — Standring — 41e, p.1270)



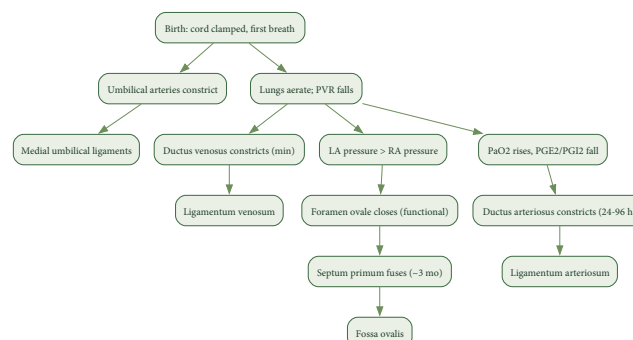
### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce the fetal-circulation plan with these labels, arrows showing direction of flow, and colour-coding (red = well oxygenated, purple/pink = mixed, blue = poorly oxygenated):

- ▶ Placenta; umbilical cord (2 umbilical arteries + 1 umbilical vein)
- ▶ Umbilical vein → liver → **ductus venosus** → hepatic vein → **inferior vena cava**
- ▶ Portal vein / hepatic sinusoids (small side-branch of umbilical vein)
- ▶ Right atrium → **crista dividens** → **foramen ovale** → left atrium → left ventricle → ascending aorta → arch → carotid/subclavian vessels
- ▶ Superior vena cava → right atrium → right ventricle → pulmonary trunk → **ductus arteriosus** → descending aorta
- ▶ Descending aorta → common iliac → internal iliac → **umbilical arteries** → placenta

## 4. Circulatory changes at birth

- ▶ **Cord clamping** stops umbilical flow; the thick muscular wall of the **umbilical arteries** contracts within seconds, preventing blood loss to the placenta, while the umbilical vein/ductus venosus stay patent a minute longer to drain residual placental blood back to the neonate.
- ▶ **Lung aeration** with the first breath sharply lowers pulmonary vascular resistance and raises pulmonary blood flow, so left atrial pressure rises while loss of umbilical inflow lowers IVC/right-atrial pressure.
- ▶ The reversed gradient (LA > RA) presses the foramen-ovale valve shut (**functional closure**), aided by synchronised atrial/SVC muscle contraction; per Gray's Anatomy this follows functional closure of the ductus arteriosus.
- ▶ Falling pulmonary resistance reverses **ductus arteriosus** flow (aorta → pulmonary trunk); rising pO<sub>2</sub> (constriction begins near ~50 mmHg), falling prostaglandins (PGE<sub>2</sub>, PGI<sub>2</sub>) and bradykinin from the aerating lungs constrict it — ~20% functionally closed by 24 h, 80% by 48 h, virtually all by 96 h (term infants).
- ▶ The **ductus venosus** sphincter constricts within minutes (structural closure in 3–7 days), so portal/splanchnic blood must now traverse the hepatic sinusoids.



*Foetal circulation and circulatory changes after birth*

## 5. Closure of the fetal shunts and their adult derivatives

| Fetal structure             | Adult remnant                                                                                                               | Mechanism / timing                                                                                                                                                                                                                                                             |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Umbilical vein (left)       | <b>Ligamentum teres hepatis</b> (round ligament of liver), in the free edge of the falciform ligament                       | Lumen thromboses and fibroses over weeks; the vein may remain patent long enough for neonatal exchange transfusion                                                                                                                                                             |
| Ductus venosus              | <b>Ligamentum venosum</b>                                                                                                   | Functional closure within minutes (sphincteric muscle contraction); structural (fibrous) closure in 3–7 days                                                                                                                                                                   |
| Foramen ovale               | <b>Fossa ovalis</b> , with the septum-primum remnant forming its floor/valve                                                | Functional closure at birth as LA pressure exceeds RA pressure; anatomical fusion of septum primum to septum secundum is gradual — fewer than 3% closed at 2 weeks, about 87% by 4 months (Gray's Anatomy 41e); fusion is sometimes incomplete, leaving a probe-patent foramen |
| Ductus arteriosus           | <b>Ligamentum arteriosum</b> (connects the left pulmonary artery to the aortic arch)                                        | Functional constriction 24–96 h after birth (mediated by oxygen, falling prostaglandins, bradykinin); fibrous obliteration over the following 2–3 weeks                                                                                                                        |
| Umbilical arteries (paired) | Proximal patent segment → <b>superior vesical arteries</b> ; distal obliterated segment → <b>medial umbilical ligaments</b> | Thick muscular wall contracts within seconds of birth, preventing blood loss to the placenta                                                                                                                                                                                   |

### Applied / Clinical anatomy

- **Patent ductus arteriosus (PDA)**: failure of closure, commoner in preterm infants and with maternal rubella; continuous "machinery" murmur. Indomethacin/ibuprofen (prostaglandin-synthesis inhibitors) promote closure; conversely, **PGE<sub>1</sub> infusion** keeps the duct open in duct-dependent CHD (transposition, hypoplastic left heart, critical coarctation) pending surgery.
- **Patent foramen ovale / ASD**: incomplete septal fusion leaves a usually-silent atrial communication (valve-like septum primum), but is a route for paradoxical embolism; ASDs form around a fifth of all congenital cardiac lesions (Gray's Anatomy).
- **Persistent fetal circulation**: neonatal hypoxia/acidaemia re-raises pulmonary vascular resistance, re-opening the foramen ovale and ductus arteriosus with right-to-left shunting and profound hypoxaemia.
- **Single umbilical artery** (usually left absent), ~1 in 200 births, carries a 15–20% incidence of associated cardiovascular/renal anomalies — prompts detailed anomaly screening.
- **Umbilical vein catheterisation**: used for emergency neonatal venous access and exchange transfusion (e.g., erythroblastosis fetalis).

- ▶ **Surgical landmarks:** ligamentum teres in the free edge of the falciform ligament; ligamentum venosum in the fissure for the ductus venosus; medial umbilical ligaments raising the medial umbilical folds — laparoscopic port landmarks.
- ▶ **Ligamentum arteriosum:** the left recurrent laryngeal nerve hooks around it — at risk in PDA ligation and aortic arch aneurysm.
- ▶ **Fossa ovalis** is the standard landmark for trans-septal puncture to access the left atrium.

### High-yield exam pointers

- ▶ Three fetal shunts and what each bypasses: **ductus venosus** (liver), **foramen ovale** (right ventricle/lungs), **ductus arteriosus** (lungs).
- ▶ **Crista dividens** = free lower edge of septum secundum; splits the IVC stream at the cavo-atrial junction, sending ~75% through the foramen ovale (Gray's Anatomy 41e).
- ▶ Best-oxygenated blood is delivered preferentially to the heart, brain, head/neck and upper limbs via the ascending aorta.
- ▶ Postnatal closure timing: ductus venosus (minutes) → ductus arteriosus (functional 24–96 h) → foramen ovale (functional closure follows ductus arteriosus closure, per Gray's Anatomy); foramen ovale fusion complete by ~3–4 months.
- ▶ Five derivatives: umbilical vein → ligamentum teres hepatis; ductus venosus → ligamentum venosum; foramen ovale → fossa ovalis; ductus arteriosus → ligamentum arteriosum; umbilical arteries → medial umbilical ligaments.
- ▶ Prostaglandins (PGE<sub>2</sub>, PGI<sub>2</sub>) keep the ductus arteriosus patent in utero; oxygen, bradykinin and falling prostaglandin levels close it after birth.
- ▶ Single umbilical artery (~1 in 200 births) is a marker for associated congenital anomalies.
- ▶ Ductus arteriosus is histologically muscular (not elastic) unlike the great arteries it connects, and the left recurrent laryngeal nerve loops around it.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 1 8e; Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — General Anatomy 4e; Sontakke — Textbook of Human Embryology.



## Formation of portal vein

Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The portal vein is a valveless venous trunk that is formed, in the adult, behind the neck of the pancreas by the union of the splenic vein and the superior mesenteric vein at the level of the L2 vertebra; it carries nutrient-rich, deoxygenated blood from the gastrointestinal tract, spleen, pancreas and gallbladder to the liver sinusoids and supplies about 80% of total hepatic blood flow. Developmentally, the portal vein and its immediate tributaries are built almost entirely from the paired **vitelline (omphalomesenteric) veins** of the fourth–fifth week embryo, through selective regression of venous segments and the formation of three transverse anastomoses around the duodenum. This question tests that embryological sequence.

### 1. Primitive venous system of the embryo

- ▶ By the fifth week three symmetrical pairs of veins drain into the sinus venosus:
- ▶ **Vitelline (omphalomesenteric) veins** — carry blood from the yolk sac.
- ▶ **Umbilical veins** — carry oxygenated blood from the chorionic villi/placenta.
- ▶ **Cardinal veins** (anterior + posterior, joining as the common cardinal vein/duct of Cuvier) — drain the body of the embryo proper.
- ▶ Before reaching the sinus venosus, the right and left vitelline veins run on either side of the developing duodenum, form a plexus around it, and then pass through the **septum transversum**.
- ▶ The liver cords growing into the septum transversum break up the vitelline (and umbilical) veins into an extensive vascular network — the **hepatic sinusoids**.

### 2. Division of the vitelline veins into three parts

The invading liver tissue divides each vitelline vein into three functional segments, whose separate fates together generate the portal vein, the hepatic veins, and part of the inferior vena cava (IVC):

| Segment           | Level                                  | Principal fate                                                                                                                        |
|-------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Suprahepatic part | Between liver and sinus venosus        | Right side enlarges into the <b>right hepatocardiac channel</b> → becomes the hepatic (terminal) part of the IVC; left side regresses |
| Intrahepatic part | Within the septum transversum/liver    | Broken up by liver cords into the <b>hepatic sinusoids</b>                                                                            |
| Infrahepatic part | Below the liver, flanking the duodenum | Interconnected by three transverse anastomoses → reorganised into the <b>portal vein and its immediate tributaries</b>                |

- ▶ Within the intrahepatic plexus, the afferent radicles draining into the sinusoids are called **venae advehentes** — these become the intrahepatic **branches of the portal vein**; the efferent radicles draining out of the sinusoids are the **venae revehentes** — these become the tributaries of the **hepatic veins**.

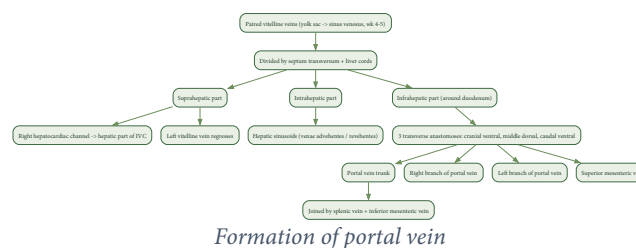
- ▶ With regression of the left sinus horn, blood from the left side of the liver is progressively rechannelled to the right, so the right vitelline vein (right hepatocardiac channel) enlarges while the proximal part of the left vitelline vein disappears.

### 3. The duodenal (infrahepatic) anastomoses — formation of the portal vein proper

- ▶ Around the duodenum the right and left vitelline veins become interconnected by **three transverse anastomotic channels**, forming a "figure-of-8" venous plexus:
- ▶ **Cranial (proximal) ventral anastomosis**
- ▶ **Middle dorsal (intermediate) anastomosis**
- ▶ **Caudal (distal) ventral anastomosis**
- ▶ The independently-developing **splenic vein** (draining the spleen) and, later, the **superior mesenteric vein**'s more proximal tributaries converge on and join the **left end of the middle dorsal anastomosis**.
- ▶ Selective persistence and disappearance of segments of this plexus then produces the definitive channels:

| Definitive structure                                           | Embryonic origin                                                                                                                                                                                                                             |
|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Trunk of the portal vein                                       | Middle dorsal anastomosis + adjoining segment of the left vitelline vein (between the splenic-vein junction and the dorsal anastomosis) + adjoining segment of the right vitelline vein (between the dorsal and cranial ventral anastomoses) |
| Right branch of portal vein                                    | Part of the right vitelline vein cranial (proximal) to the cranial ventral anastomosis, continuing up to the liver                                                                                                                           |
| Left branch of portal vein                                     | Cranial ventral anastomosis + adjoining segment of the left vitelline vein                                                                                                                                                                   |
| Superior mesenteric vein                                       | Distal (caudal) part of the right vitelline vein, draining the primary intestinal loop                                                                                                                                                       |
| Splenic vein / inferior mesenteric vein                        | Later, independently-formed channels that secondarily join the left end of the dorsal anastomosis/portal vein trunk                                                                                                                          |
| Caudal ventral anastomosis + redundant vitelline vein segments | Atrophy and disappear, along with the left hepatocardiac channel                                                                                                                                                                             |

□ Fig 19.13 — Development of portal vein (Sontakke — Textbook of Human Embryology, p.201)



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the duodenum in transverse section with the right and left vitelline veins running along either side; label:

- ▶ Right vitelline vein / Left vitelline vein
- ▶ Cranial (proximal) ventral anastomosis, middle dorsal anastomosis, caudal (distal) ventral anastomosis (the "figure-of-8")
- ▶ Splenic vein joining the left end of the dorsal anastomosis
- ▶ Superior mesenteric vein (continuation of the right vitelline vein)
- ▶ Resulting **portal vein trunk, right branch and left branch**, with arrows showing which segments contribute to each
- ▶ Liver/septum transversum above, with the right hepatocardiatic channel and left umbilical vein draining into it

**4. Umbilical veins and the ductus venosus**

- ▶ The umbilical veins initially pass on each side of the liver; some branches connect to the hepatic sinusoids.
- ▶ The proximal part of both umbilical veins, and the whole of the **right** umbilical vein, disappear — leaving the **left umbilical vein** as the sole channel carrying oxygenated placental blood to the liver.
- ▶ As placental flow increases, a wide direct channel — the **ductus venosus** — forms between the left umbilical vein and the right hepatocardiatic channel (equivalently, opening into the left branch of the portal vein), bypassing the sinusoidal plexus of the liver.
- ▶ **Postnatal fate:** the left umbilical vein obliterates to form the **ligamentum teres hepatis** (round ligament, in the free edge of the falciform ligament); the ductus venosus obliterates to form the **ligamentum venosum**.

**5. The definitive (adult) portal vein**

- ▶ Formed **behind the neck of the pancreas** by union of the **splenic vein** and **superior mesenteric vein** at the level of **L2 vertebra**.
- ▶ About 7.5 cm (3 inches) long; ascends behind the first part of the duodenum into the right free margin of the lesser omentum (as part of the **portal triad**, with the bile duct and hepatic artery, anterior to the epiploic foramen of Winslow).
- ▶ Ends at the porta hepatis by dividing into a shorter, wider **right branch** (receives the cystic vein) and a longer, narrower **left branch** (unites with the ligamentum teres and ligamentum venosum, receives paraumbilical veins).
- ▶ Other tributaries: left and right gastric veins, superior pancreaticoduodenal vein.
- ▶ Devoid of valves; carries about one-third of total body blood volume within its tributaries at any time.

## Applied / Clinical anatomy

- ▶ **Portocaval (portosystemic) anastomoses** — clinically important sites where the valveless portal system communicates with the systemic venous system; these dilate as collateral channels in portal obstruction:
  - Lower end of oesophagus: left gastric vein (portal) with oesophageal tributaries of the azygos system (systemic) → **oesophageal varices**, which may rupture causing haematemesis.
  - Umbilicus: paraumbilical veins (of Sappey, portal) with superficial abdominal wall veins (systemic) → **caput medusae**.
  - Anal canal: superior rectal vein (portal) with middle/inferior rectal veins (systemic) → **haemorrhoids (piles)**.
  - Bare area of the liver and retroperitoneal surfaces of the duodenum/ascending/descending colon: minor portal–systemic communications.
- ▶ **Portal hypertension**: portal venous pressure rises above the normal 5–15 mmHg (commonly quoted threshold >40 mmHg), most often due to alcoholic cirrhosis of the liver; produces splenomegaly, ascites, oesophageal varices, caput medusae and haemorrhoids.
- ▶ **Predoduodenal portal vein**: a rare recognised congenital anomaly in which the portal vein lies anterior instead of posterior to the duodenum, due to abnormal persistence of a ventral (rather than the dorsal) vitelline anastomosis; it may cause duodenal obstruction and is often associated with other foregut/pancreatic anomalies.
- ▶ The left and right hepatic portal veins and the ductus venosus are routinely visualised on the **second-trimester obstetric ultrasound** at the plane used to estimate fetal abdominal circumference.
- ▶ Carcinoma of the head of the pancreas may compress or invade the portal vein because of its close posterior relation.
- ▶ Recanalisation of the obliterated left umbilical vein (ligamentum teres) in portal hypertension explains the clinical sign of caput medusae.

## High-yield exam pointers

- ▶ Portal vein develops chiefly from the **paired vitelline (omphalomesenteric) veins** that drain the yolk sac (4th–5th week).
- ▶ Growing liver cords in the septum transversum divide each vitelline vein into **suprahepatic, intrahepatic and infrahepatic parts**.
- ▶ Infrahepatic parts are linked by **three anastomoses around the duodenum** — cranial ventral, middle dorsal, caudal ventral — a classic "figure-of-8".
- ▶ **Portal trunk** = middle dorsal anastomosis + adjoining vitelline vein segments; **left branch** incorporates the cranial ventral anastomosis; **right branch** = right vitelline vein proximal to it; **superior mesenteric vein** = distal right vitelline vein.
- ▶ Splenic and inferior mesenteric veins are later, independently-formed tributaries that join the portal system secondarily.
- ▶ Right suprahepatic vitelline vein → hepatic part of the IVC; left vitelline vein largely regresses.



- ▶ Intrahepatic vitelline vein plexus (venae advehentes/revehentes) → intrahepatic portal vein radicles and hepatic veins respectively.
- ▶ **Ductus venosus** connects the left umbilical vein to the right hepatocardiac channel/left branch of portal vein, bypassing hepatic sinusoids; becomes the **ligamentum venosum** after birth (left umbilical vein → ligamentum teres hepatis).
- ▶ Adult portal vein: formed behind the neck of pancreas by union of splenic + superior mesenteric veins at L2; ~7.5 cm; valveless; carries ~80% of hepatic blood flow.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2 4e; Larsen — Human Embryology 6e.



## Inter atrial septal defects

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

### Definition / Introduction

An inter-atrial (atrial) septal defect (ASD) is a persistent abnormal communication between the right and left atria resulting from defective septation of the primitive common atrium during the fifth and sixth weeks of intra-uterine life. It occurs in about 6.4 per 10,000 live births with a female-to-male prevalence of roughly 2:1, and is one of the commonest forms of congenital heart disease encountered in adult life because many types remain asymptomatic through childhood. Understanding an ASD therefore requires first recalling the normal step-wise formation of the septum primum and septum secundum, since every clinical variety of ASD is simply an arrest or exaggeration of one of these normal steps.

### 1. Normal septation of the atria — the developmental basis

- ▶ **Septum primum** — on about day 26–28 (4th week), a sickle-shaped crescent grows from the dorsal-cranial roof of the common atrium toward the fused endocardial (atrioventricular) cushions/septum intermedium. Its leading edge carries the mesenchymal dorsal mesenchymal cap.
- ▶ **Foramen (ostium) primum** — the shrinking gap between the growing septum primum and the endocardial cushions; it permits obligatory right-to-left shunting of oxygenated placental blood.
- ▶ **Foramen (ostium) secundum** — before the foramen primum is sealed by fusion of the septum primum with the atrioventricular cushions, programmed cell death perforates the upper part of the septum primum; the coalescing perforations create a new opening so that shunting is never interrupted.
- ▶ **Septum secundum** — a thick, muscular crescentic fold that grows down from the roof of the right atrium just to the right of the septum primum during the 5th–6th week. It never completes a full partition, leaving an opening — the **foramen ovale** — near the floor of the right atrium.

- **Valve of the foramen ovale** — the thin, mobile remnant of the upper septum primum that overlaps the stiffer septum secundum, acting as a one-way flap permitting right-to-left flow only.
- **Closure at birth** — expansion of the pulmonary vasculature and cessation of umbilical flow raise left atrial pressure above right atrial pressure, pressing the septum primum against the septum secundum (functional closure); anatomical fusion follows over subsequent months.

| Fetal structure                 | Adult correlate                                                                                                                     |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Septum primum (floor of septum) | Floor of the <b>fossa ovalis</b>                                                                                                    |
| Free margin of septum secundum  | <b>Limbus (annulus) of the fossa ovalis</b>                                                                                         |
| Foramen ovale                   | Obliterated; may persist as a <b>probe-patent oval foramen</b> in up to a quarter to a third of normal adult hearts (no true shunt) |

## 2. Classification of inter-atrial septal defects

| Type                                                  | Embryological defect                                                                                                  | Typical location                            | Key association                                                                                                          |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Probe-patent oval foramen</b>                      | Incomplete adhesion of valve of foramen ovale to septum secundum after birth                                          | Floor of fossa ovalis                       | Not a true ASD; no haemodynamic shunt unless right atrial pressure rises                                                 |
| <b>Ostium secundum ASD</b>                            | Excessive resorption of septum primum and/or deficient growth of septum secundum, so the foramen ovale is not covered | Fossa ovalis region                         | Commonest significant ASD; female:male $\approx$ 3:1                                                                     |
| <b>Ostium primum ASD</b> (partial AV septal defect)   | Septum primum fails to fuse with the endocardial cushions — persistent foramen primum                                 | Low in the septum, just above the AV valves | Cleft in anterior mitral leaflet; part of the endocardial-cushion-defect spectrum                                        |
| <b>Sinus venosus defect</b>                           | Incomplete absorption of the sinus venosus into the right atrium and/or abnormal septum secundum development          | High in the septum, near the SVC orifice    | Commonly associated with partial anomalous pulmonary venous connection                                                   |
| <b>Common atrium</b> (cor triloculare biventriculare) | Complete failure of both septum primum and septum secundum to develop                                                 | Entire septum absent                        | Combination of ostium primum + secundum + sinus-venosus type failure; always accompanied by other severe cardiac defects |

□ Fig 18.10 — Atrial septal defects involve the defective formation of interatrial s (Sontakke — *Textbook of Human Embryology*, p.184)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Reproduce the panel of coronal heart schemes (normal septum + four defect types) with these exact labels:

- ▶ **A — Normal interatrial septum:** superior vena cava, sinus venarum, valve of inferior vena cava, valve of coronary sinus, septum secundum, foramen ovale, septum primum, inferior endocardial cushion.
- ▶ **B — Ostium secundum defect:** septum secundum, wide-open foramen ovale/septum-primum gap.
- ▶ **C — Ostium primum defect:** septum primum failing to reach the endocardial cushions, persistent foramen primum.
- ▶ **D — Endocardial cushion defect:** septum primum, inferior endocardial cushion, combined atrial + AV-valve defect.
- ▶ **E — Common atrium (cor triloculare biventriculare):** complete absence of the septum.

**3. Ostium secundum ASD — the commonest significant type**

- ▶ Site: within the area of the oval fossa; may involve deficiency of septum primum, septum secundum, or both.
- ▶ Mechanism: (i) abnormal resorption of septum primum leaving it fenestrated/net-like, or excessively short; or (ii) an abnormally large oval foramen from defective septum secundum growth.
- ▶ Clinically well tolerated through childhood; symptoms such as pulmonary hypertension typically appear only in the third decade or later.
- ▶ Defects may be multiple; in symptomatic older children/adults defects of 2 cm or more are not unusual.
- ▶ Surgical/device closure carries a mortality of less than 1%.
- ▶ Genetic association: mutations of **NKX2.5** (human ortholog maps to chromosome 5q35.2) are linked to atrial septal defects together with conduction-system defects.

**4. Ostium primum ASD and the endocardial-cushion-defect spectrum**

- ▶ Results from a deficiency of the endocardial cushions/AV septum, so the septum primum fails to fuse with them and a patent foramen (ostium) primum persists.
- ▶ Usually accompanied by a **cleft in the anterior cusp of the mitral valve**.
- ▶ In its complete form, failure of fusion of the dorsal and ventral endocardial cushions produces a **persistent common atrioventricular canal (complete AV septal defect)** — a continuous interatrial-and-interventricular defect with markedly abnormal, often single, AV valve; this complete form occurs in about 20% of individuals with **Down syndrome (trisomy 21)**.
- ▶ Genetic association: **Holt-Oram syndrome** — an autosomal dominant disorder due to **TBX5** mutation, combining a congenital heart defect (often an ASD) with variable upper-limb/thumb anomalies.

## 5. Sinus venosus defect and common atrium

- ▶ **Sinus venosus ASD:** a high septal defect close to the entry of the superior vena cava, caused by incomplete absorption of the sinus venosus into the right atrium and/or abnormal septum secundum development; frequently accompanies partial anomalous pulmonary venous connection.
- ▶ **Common atrium (cor triloculare biventriculare):** the rarest and most serious type — complete absence of the atrial septum from combined failure of septum primum and septum secundum formation; invariably associated with other severe cardiac malformations.
- ▶ **Premature closure of the foramen ovale** (before birth) is a distinct, rare anomaly: it causes marked right atrial/ventricular hypertrophy with underdevelopment of the left heart, usually fatal soon after birth.

## Applied / Clinical anatomy

- ▶ **Haemodynamics:** an uncorrected ASD produces a left-to-right shunt (higher systemic than pulmonary venous pressure), causing right atrial and right ventricular volume overload and increased pulmonary blood flow; long-standing large shunts lead to pulmonary hypertension and, if untreated, shunt reversal (Eisenmenger physiology) with cyanosis.
- ▶ **Clinical signs:** wide, fixed splitting of the second heart sound (equalised right and left atrial compliance across the defect) and an ejection systolic murmur of relatively increased flow across the pulmonary valve.
- ▶ **Radiology:** chest radiograph shows cardiomegaly with pulmonary plethora; echocardiography (subcostal/four-chamber views) is the investigation of choice to localise and size the defect and to detect associated anomalous pulmonary venous drainage.
- ▶ **Surgical anatomy:** the surgeon closing an ostium primum or AV-canal type defect must respect **Koch's triangle** (bounded by the septal leaflet of the tricuspid valve, the tendon of Todaro, and the orifice of the coronary sinus) as it overlies the atrioventricular node; injury here risks heart block. Most isolated ostium secundum defects are now closed by a trans-catheter occluder device via the femoral vein rather than open surgery.
- ▶ **Probe-patent oval foramen:** present in up to a quarter to a third of normal adults; though not a true ASD, it is clinically relevant as a conduit for **paradoxical embolism** (venous thrombus crossing to the systemic/cerebral circulation) and in decompression illness in divers.
- ▶ **Associated syndromes:** trisomy 21 (complete AV septal defect), Holt-Oram syndrome (TBX5), and rubella embryopathy are recurring exam associations linking ASD to genetics/teratology.

## High-yield exam pointers

- ▶ ASD = persistent defect of the interatrial septum from faulty fusion/growth of septum primum and septum secundum; incidence  $\approx 6.4/10,000$  births, female preponderance.
- ▶ Four clinically significant types: **ostium secundum, ostium primum, sinus venosus, common atrium** — plus the non-shunting probe-patent oval foramen.
- ▶ Adult correlate: floor of fossa ovalis = septum primum; limbus of fossa ovalis = septum secundum edge.

- ▶ Ostium secundum = commonest, located at the fossa ovalis, asymptomatic till adulthood, low surgical mortality.
- ▶ Ostium primum = fails to fuse with endocardial cushions, cleft mitral leaflet, part of the AV septal defect spectrum, linked to Down syndrome.
- ▶ Sinus venosus type = high septal defect near SVC, associated with partial anomalous pulmonary venous connection.
- ▶ Common atrium = complete septal failure, worst prognosis, combined with other severe defects.
- ▶ Genetics: NKX2.5 (5q35.2) and TBX5/Holt-Oram syndrome are the classical gene associations.
- ▶ Surgically important landmark for ASD closure: Koch's triangle (AV node location).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Thompson & Thompson — Genetics in Medicine 8e.



## Peculiarities of Foetal Circulation

*Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The foetal circulation is a temporary pattern of blood flow that operates while the placenta, and not the lung, is the organ of respiration for the conceptus. Because the lungs are collapsed and fluid-filled in utero, pulmonary vascular resistance is very high, and the portal circulation is functionally of little significance. Three unique vascular shunts — the **ductus venosus**, the **foramen ovale** and the **ductus arteriosus** — together with the paired **umbilical vessels**, bypass the liver and lungs so that the best-oxygenated blood reaches the heart and brain preferentially. At birth, cessation of placental flow and the onset of respiration reverse these pressure relationships, converting the foetal pattern into the adult circulation over minutes to months.

### 1. Basis of the peculiarities

- ▶ Blood is oxygenated in the **placenta**, not the lungs; gaseous exchange occurs across the placental villi.
- ▶ The lungs are collapsed during foetal life, so resistance to flow through the pulmonary vessels is high; only a small fraction of right-ventricular output actually perfuses the lung.
- ▶ The **portal (hepatic) circulation is of little functional significance** — most umbilical-venous blood is shunted past the liver sinusoids.
- ▶ Three shunts (ductus venosus, foramen ovale, ductus arteriosus) plus the paired umbilical arteries and single umbilical vein together convert the circulation from a purely "in-series" adult pattern into one with major parallel short-circuits.

## 2. The umbilical vessels and the three foetal shunts

| Structure                 | Course / connection                                                                                                                     | Function                                                                                                                                                                                                                            |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Left umbilical vein       | Placenta → umbilical cord → umbilicus → free edge of falciform ligament → joins the <b>left branch of the portal vein</b>               | Carries highly oxygenated blood ( $\approx 80\%$ saturated) from placenta to fetus                                                                                                                                                  |
| Ductus venosus            | Left branch of portal vein → <b>inferior vena cava</b> , bypassing the hepatic sinusoids                                                | Shunts most umbilical-venous blood past the liver directly into the IVC; a <b>sphincter mechanism</b> near the entry of the umbilical vein narrows during a uterine contraction, protecting the heart from a sudden volume overload |
| Foramen ovale             | Right atrium → left atrium, through the septum secundum                                                                                 | Directs the stream of well-oxygenated IVC blood preferentially into the left atrium and thence to the systemic (coronary + cerebral) circulation, bypassing the lungs                                                               |
| Ductus arteriosus         | Pulmonary trunk (via the left pulmonary artery, its developmental origin being the left 6th aortic arch artery) → arch/descending aorta | Shunts most right-ventricular output away from the high-resistance pulmonary vessels into the systemic circulation                                                                                                                  |
| Paired umbilical arteries | Internal iliac arteries → along the anterior abdominal wall → umbilicus → placenta                                                      | Carry deoxygenated fetal blood ( $\approx 58\%$ saturated) back to the placenta for re-oxygenation                                                                                                                                  |

## 3. Course of oxygenated blood from placenta to fetus

- ▶ Oxygen-rich blood ( $\sim 80\%$  saturated) leaves the placenta in the **left umbilical vein**, traverses the cord and enters the abdomen at the umbilicus.
- ▶ At the liver it joins the left portal vein; the **greater part bypasses the liver via the ductus venosus** into the IVC, a small portion passing through the hepatic sinusoids to mix with portal blood.
- ▶ The **inferior vena cava** opens into the right atrium, its stream guided by the **valve of the IVC (Eustachian valve)** toward the foramen ovale.
- ▶ Most IVC blood passes directly through the **foramen ovale into the left atrium**; a smaller part is deflected by the free lower edge of the septum secundum — the **crista dividens** — and stays in the right atrium, mixing with desaturated blood from the head and arms via the superior vena cava.
- ▶ From the left atrium (mixing with a little desaturated pulmonary-venous blood), blood passes to the **left ventricle and ascending aorta**. Since the **coronary and carotid arteries are the first branches of the aorta**, the heart muscle and brain receive the most oxygenated blood in the fetus.

#### 4. Streaming and sites of admixture

- ▶ The **valve of the IVC** and the **crista dividens** (lower free edge of the septum secundum) together "stream" the IVC flow, splitting it into a larger foramen-ovale-bound portion and a smaller portion that stays in the right atrium.
- ▶ Classically, oxygenated placental blood progressively loses its saturation by admixture at **five sites**: (I) the liver, mixing with portal blood; (II) the IVC, mixing with deoxygenated blood from the lower limbs/pelvis/kidneys; (III) the right atrium, mixing with SVC blood; (IV) the left atrium, mixing with pulmonary-venous blood; and (V) the junction of the ductus arteriosus with the descending aorta.

#### 5. Course of deoxygenated blood back to the placenta

- ▶ Desaturated blood from the head and upper limb returns via the **superior vena cava** (unguided, unlike the IVC) into the right atrium and passes to the **right ventricle**.
- ▶ From the right ventricle, blood enters the **pulmonary trunk**; since pulmonary resistance is high in fetal life, only a small volume perfuses the collapsed lungs, and the **greater part is shunted through the ductus arteriosus into the descending aorta**, mixing with proximal aortic blood.
- ▶ This mixed blood is distributed by the descending aorta and iliac arteries to the pelvis/lower limbs, and returns to the placenta via the **paired umbilical arteries** ( $\approx 58\%$  saturated) for re-oxygenation.

#### 6. Differential oxygenation of upper and lower body

- ▶ Because the coronary, carotid and subclavian arteries arise **proximal** to the entry of the ductus arteriosus, the **heart, brain and upper limbs receive the best-oxygenated blood** in the fetus.
- ▶ The ductus arteriosus adds relatively desaturated right-ventricular blood to the aorta just distal to the left subclavian artery, so the **trunk and lower limbs receive blood of lower oxygen saturation**.
- ▶ This physiological gradient is traditionally cited as the reason the **upper limbs grow relatively longer than the lower limbs in the fetus** (IB Singh).

#### 7. Changes in the circulation at birth

| Fetal structure   | Trigger / mechanism of closure                                                                                                                                                                   | Functional vs anatomical closure                                                                                           | Adult remnant         |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Ductus arteriosus | Rise in blood O <sub>2</sub> tension and withdrawal of placental prostaglandin E, aided by <b>bradykinin</b> released from the lungs on their first inflation → contraction of its muscular wall | Functional closure almost immediately after birth; anatomical obliteration by intimal proliferation over <b>1–3 months</b> | Ligamentum arteriosum |



| Fetal structure                   | Trigger / mechanism of closure                                                                                                                                                     | Functional vs anatomical closure                                                                                                                                                                                                                                                                                                                                                    | Adult remnant                                                                                                |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Foramen ovale                     | Pulmonary venous return increases → <b>left atrial pressure rises</b> ; placental flow ceases → <b>right atrial pressure falls</b> → septum primum apposed against septum secundum | Functional closure with the first breath, but <b>reversible in the first few days</b> (crying produces a transient right-to-left shunt and neonatal cyanosis); anatomical fusion of the septa over about <b>1 year</b> — a probe-patent foramen persists in up to ~20% of adults (Langman), and Gray's Anatomy notes a patent slit may be found in up to one-third of normal hearts | Fossa ovalis                                                                                                 |
| Umbilical arteries                | Thermal and mechanical stimuli plus rising oxygen tension → contraction of the thick muscular wall                                                                                 | Functional occlusion within minutes of birth (prevents fetal blood loss into the placenta); anatomical obliteration over <b>2–3 months</b>                                                                                                                                                                                                                                          | Distal parts → medial umbilical ligaments; proximal parts remain patent as the superior vesical arteries     |
| Umbilical vein and ductus venosus | Occlude a little later than the umbilical arteries, allowing placental blood still in the cord time to drain back to the newborn                                                   | Functional closure within minutes to a few hours                                                                                                                                                                                                                                                                                                                                    | Umbilical vein → ligamentum teres hepatis (round ligament of the liver); ductus venosus → ligamentum venosum |

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

□ Fig 52.19 — A plan of the fetal circulation. The arrows indicate the direction of blood flow (Gray's Anatomy — Standring — 41e, p.1270)

For hand reproduction, label: placenta; umbilical cord with **umbilical vein** (single) and **umbilical arteries** (paired); ductus venosus bypassing the liver; portal vein; inferior vena cava with the valve of the IVC and crista dividens; superior vena cava; right atrium and left atrium with the **foramen ovale**; right ventricle and left ventricle; pulmonary trunk with right/left pulmonary arteries; the **ductus arteriosus** joining the pulmonary trunk to the arch of the aorta; ascending aorta with its three branches (brachiocephalic trunk, left common carotid, left subclavian); descending aorta; and the internal iliac arteries continuing as the umbilical arteries. Shade or arrow-code the vessels to show the gradient of oxygenation (best in the umbilical vein/ductus venosus/left heart outflow, poorest in the umbilical arteries/descending aorta beyond the ductus).

**Applied / Clinical anatomy**

- ▶ **Patent ductus arteriosus (PDA)**: one of the commonest anomalies of the great vessels ( $\approx 8/10,000$  births), classically seen in premature (especially female) infants and those whose mothers had rubella infection early in pregnancy. Patency is sustained by circulating **prostaglandin E** and intrauterine hypoxia; **prostaglandin-synthesis inhibitors** (e.g. **indomethacin**) promote pharmacological closure, while persistent PDA is treated surgically by ligation and division. Conversely, in **duct-dependent congenital heart lesions** (severe coarctation/aortic interruption), a **prostaglandin infusion** is used to keep the ductus open until surgery.
- ▶ **Patent (probe) foramen ovale**: a common, usually asymptomatic, incidental finding; it becomes clinically important when right atrial pressure is transiently raised (e.g. Valsalva, crying in the neonate), permitting a right-to-left shunt and paradoxical embolism.
- ▶ **Coarctation of the aorta**: narrowing of the aortic lumen may lie proximal (**preductal/infantile type**) or opposite/just distal (**postductal/adult type**) to the ductus arteriosus. In the preductal type the lower body is duct-dependent for perfusion, and there is no time for collaterals to develop — these infants need urgent prostaglandin infusion and surgery. The **postductal type is more common**, permits years of normal life, and is associated with a rich collateral circulation (high vascularity of the thoracic wall via intercostal and internal thoracic anastomoses); it presents clinically with **upper-limb hypertension, weak or absent femoral pulses (radiofemoral delay)** and an increased risk of cerebral haemorrhage.
- ▶ **Umbilical vein catheterisation**: the umbilical vein, and to a lesser extent the umbilical arteries, remain patent for a short period after birth, which is exploited clinically for emergency neonatal vascular access.
- ▶ Failure of the ductus venosus, ductus arteriosus or foramen ovale to close/regress appropriately, or persistence of the double aortic arch (encircling the trachea/oesophagus), underlies several important paediatric cardiovascular and vascular-ring anomalies.

## High-yield exam pointers

- ▶ Three fetal shunts — **ductus venosus** (bypasses liver), **foramen ovale** (bypasses lungs, RA→LA), **ductus arteriosus** (bypasses lungs, PA→aorta) — plus the paired umbilical arteries and single umbilical vein.
- ▶ Oxygen saturation: umbilical vein ≈80%; umbilical arteries ≈58%.
- ▶ **Crista dividens** = free lower edge of septum secundum; splits IVC stream at the foramen ovale.
- ▶ Five sites of admixture: liver, IVC, right atrium, left atrium, junction of ductus arteriosus with descending aorta.
- ▶ Heart, brain and upper limb get the best-oxygenated blood (coronary/carotid arteries are the first aortic branches, before the ductus arteriosus joins).
- ▶ Closure sequence at birth: functional closure of DA and umbilical vessels within minutes–hours; foramen ovale closes functionally with the first breath (reversible early — crying causes transient cyanosis); anatomical closure of all structures takes 2–3 months (umbilical vessels/ductus arteriosus) to about 1 year (foramen ovale).
- ▶ Postnatal remnants: umbilical vein → ligamentum teres hepatis; ductus venosus → ligamentum venosum; ductus arteriosus → ligamentum arteriosum; foramen ovale → fossa ovalis; umbilical arteries → medial umbilical ligaments (distal) + superior vesical arteries (proximal).
- ▶ Clinical correlation triad: PDA (indomethacin closes; PGE keeps duct-dependent lesions open), patent foramen ovale, and preductal vs postductal coarctation.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology.



## Sinus venosus

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The sinus venosus is the most caudal of the four dilatations of the primitive heart tube (bulbus cordis, ventricle, atrium, sinus venosus, from cranial to caudal) and constitutes the venous end of the developing heart. It appears embedded within the septum transversum in the middle of the fourth week and initially receives blood symmetrically through paired right and left sinus horns, each draining three great veins. Because of a progressive left-to-right shift of venous return, the right horn is incorporated into the right atrium (forming its smooth-walled part, the sinus venarum) while the left horn regresses to the coronary sinus and the oblique vein of the left atrium. The sinuatrial node, the definitive cardiac pacemaker, differentiates in the wall of the right horn near the site of entry of the superior vena cava.

### 1. Origin and early position

- ▶ The sinus venosus develops as the caudal-most chamber of the tubular heart, lying within the mesenchyme of the **septum transversum**, immediately caudal to the primitive pericardial cavity (Langman; IB Singh).

- ▶ In the middle of the fourth week it presents **paired right and left sinus horns**, symmetrically placed, opening into the primitive atrium through a single median **sinuatrial orifice** that is, at this stage, wide (Langman).
- ▶ The sinus venosus is the site where the **retinoic-acid (RA) signalling pathway** first specifies the venous pole of the heart tube — mesoderm adjacent to the presumptive sinus venosus and atria produces RA, and these structures then express retinaldehyde dehydrogenase and acquire venous identity (Langman).

## 2. Tributaries of the sinus horns

Each sinus horn receives **three important veins** on its own side (Langman; IB Singh; AK Datta):

| Vein draining into the horn           | Origin / course                                                                                                                                              |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vitelline (omphalomesenteric) vein    | Carries blood from the yolk sac; passes through the septum transversum, where it is broken up by the invading liver cords into the hepatic sinusoidal plexus |
| Umbilical vein                        | Carries oxygenated blood from the chorionic villi/placenta; also traverses the septum transversum                                                            |
| Common cardinal vein (duct of Cuvier) | Formed by union of the anterior (precordial) and posterior (postcardinal) cardinal veins of that side; drains the body of the embryo proper                  |

- ▶ The umbilical and vitelline veins are essentially interrupted within the liver-forming septum transversum and reconstituted as right/left **hepatocardiac channels**; the right hepatocardiac channel persists as the terminal (suprahepatic) part of the definitive inferior vena cava, while the left one disappears with regression of the left horn (IB Singh).

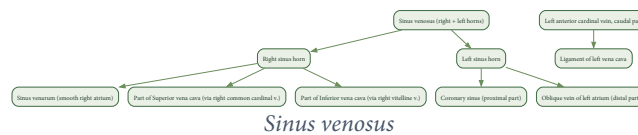
## 3. The shift of the sinuatrial orifice to the right

- ▶ From the fourth to the fifth week, a series of **left-to-right shunts** in the venous system progressively redirects flow into the right horn, so that the entrance of the sinus venosus into the atrium shifts to the right (Langman).
- ▶ Key obliterative events driving this shift:
  - **5th week** — the **right umbilical vein** and the **left vitelline vein** are obliterated.
  - **10th week** — the **left common cardinal vein** is obliterated.
- ▶ With these changes the **right sinus horn and its veins enlarge greatly**, becoming the sole communication between the sinus venosus and the atrium, while the left horn rapidly loses importance (Langman).

## 4. Fate of the sinus venosus and its horns

The right horn is incorporated bodily into the wall of the right atrium; the left horn regresses to two small venous remnants. This is summarised below (Langman; IB Singh; Sontakke; AK Datta):

| Embryonic structure                        | Adult derivative                                                                        |
|--------------------------------------------|-----------------------------------------------------------------------------------------|
| Right sinus horn (+ body of sinus venosus) | <b>Sinus venarum</b> — the smooth-walled part of the right atrium                       |
| Right common cardinal vein                 | Part of the <b>superior vena cava</b> (intrapericardial part)                           |
| Right vitelline vein (suprahepatic part)   | Terminal part of the <b>inferior vena cava</b>                                          |
| Left sinus horn — proximal part            | <b>Coronary sinus</b>                                                                   |
| Left sinus horn — distal part              | <b>Oblique vein of the left atrium</b> (of Marshall)                                    |
| Left common cardinal vein                  | Obliterated — represented by the oblique vein of the left atrium                        |
| Left anterior cardinal vein, caudal part   | <b>Ligament of the left vena cava</b> (of Marshall), in the plica venae cavae sinistrae |



□ Fig 18.6 — Development of sinus venosus and pulmonary veins (Sontakke — Textbook of Human Embryology, p.181)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a dorsal view of the developing heart in two panels (~24 days and ~35 days), each with an inset transverse section, and label:

- ▶ **Sinuatrial junction**, with the sinuatrial orifice shown wide (24 days) then shifted right (35 days)
- ▶ **Right sinus horn** and **left sinus horn**
- ▶ On each side: **vitelline vein**, **umbilical vein**, **common cardinal vein** entering the horn
- ▶ **Anterior (precardinal) vein** and **posterior (postcardinal) vein** uniting to form the common cardinal vein
- ▶ In the final-stage panel: **superior vena cava**, **inferior vena cava**, **coronary sinus**, **oblique vein of left atrium**

## 5. Venous valves, septum spurium and crista terminalis

- ▶ As the right horn is incorporated into the right atrium, its orifice (the **sinuatrial orifice**) is flanked on each side by a valvular fold — the **right and left venous valves** (Langman).
- ▶ Dorsocranially the two valves fuse to form a ridge, the **septum spurium**.
- ▶ **Right venous valve**: its superior part disappears entirely; its inferior part splits into two — the **valve of the inferior vena cava** (Eustachian valve) and the **valve of the coronary sinus** (Thebesian valve) (Langman; Moore).
- ▶ **Left venous valve** and the **septum spurium** fuse with the developing atrial septum (septum secundum) and are incorporated into it.

- ▶ The **crista terminalis** marks the former sinuatrial junction — it forms the dividing line, in the adult right atrium, between the smooth-walled **sinus venarum** (derived from the right sinus horn) and the rough, pectinate-muscle-bearing part derived from the original primitive atrium (Langman; Moore).

## 6. Formation of the sinuatrial node

- ▶ The heart begins to beat at about day 21; the earliest pacemaker activity resides in the caudal part of the left side of the primitive cardiac tube.
- ▶ As development proceeds, this pacemaker function is progressively taken over by the **sinus venosus**.
- ▶ When the sinus venosus (right horn) is incorporated into the right atrial wall, its residual pacemaker tissue comes to lie near the opening of the superior vena cava — this focus constitutes the definitive **sinuatrial node (SAN)** (Langman).
- ▶ The **atrioventricular node (AVN)**, by contrast, develops from cells around the atrioventricular canal and is not a sinus-venosus derivative.

## Applied / Clinical anatomy

- ▶ **Sinus venosus-type atrial septal defect:** a high ASD situated in the superior part of the interatrial septum close to the SVC orifice, resulting from incomplete absorption of the sinus venosus into the right atrium and/or abnormal fusion of septum primum/septum secundum; it typically produces a bi-atrial connection of the involved caval vein and is frequently associated with partial anomalous drainage of the right pulmonary veins into the cavo-atrial junction (Moore; Gray's Anatomy). Comparatively rare compared with ostium secundum ASD, but important to distinguish on echocardiography/CT because closure technique differs.
- ▶ **Unroofed coronary sinus:** an interatrial communication through the mouth of the coronary sinus, due to deficiency of the walls that normally separate the sinus from the left atrium — a direct consequence of incomplete left-horn/left-atrial wall separation (Gray's Anatomy). It is characteristically associated with a persistent left superior vena cava draining into the coronary sinus.
- ▶ **Persistent left superior vena cava:** failure of regression/obliteration of the left anterior and common cardinal veins allows a left SVC to persist, draining into the right atrium via a dilated coronary sinus (a direct left-sinus-horn pathway); the normal right SVC may be reduced or absent (IB Singh).
- ▶ **Cor triatriatum and related sinus venosus-derivative anomalies:** abnormal persistence or malposition of the right venous valve/septum spurium tissue can leave a residual membrane within the right atrium, a rare cause of a functionally "triatrial" right heart.
- ▶ **Prominent Eustachian/Thebesian valves:** exaggerated persistence of the valve of the inferior vena cava or valve of the coronary sinus (remnants of the right venous valve) can be mistaken on echocardiography for an intra-atrial mass or can predispose to a **Chiari network**.
- ▶ **Surgical/radiological landmark:** the crista terminalis, marking the former sinuatrial junction, is an important electrophysiological landmark — it is a common site of origin of focal atrial

tachycardias and forms one boundary of the cavotricuspid isthmus targeted in atrial flutter ablation.

## High-yield exam pointers

- ▶ Sinus venosus = most caudal of the 4 **primitive cardiac dilatations**; lies within the **septum transversum**; appears in the **4th week**.
- ▶ Each horn receives 3 **veins**: vitelline, umbilical, common cardinal (duct of Cuvier).
- ▶ Sinuatrial orifice shifts **right** because of obliteration of the **right umbilical vein + left vitelline vein** (5th week) and the **left common cardinal vein** (10th week).
- ▶ **Right horn** → sinus venarum (smooth part of right atrium); **left horn** → coronary sinus (proximal) + oblique vein of left atrium (distal).
- ▶ Venous valves: right + left, fusing dorsocranially into the **septum spurium**; right valve → valve of IVC + valve of coronary sinus; left valve + septum spurium fuse into the atrial septum.
- ▶ **Crista terminalis** = boundary between sinus-venosus-derived smooth part and primitive-atrium-derived trabeculated part of the right atrium.
- ▶ **Sinuatrial node** forms in the wall of the incorporated right horn, near the SVC opening.
- ▶ Clinically: **sinus venosus ASD** (near SVC opening, associated with anomalous right pulmonary venous drainage), **unroofed coronary sinus**, and **persistent left SVC draining via coronary sinus** are the classical sinus-venosus-related anomalies.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Gray's Anatomy (Standring) 41e.



## Vitelline veins

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The vitelline (omphalomesenteric) veins are a paired set of primitive embryonic veins that drain the capillary plexus in the splanchnopleuric mesenchyme of the secondary yolk sac. Together with the umbilical veins they constitute the "visceral" group of embryonic veins, distinct from the "somatic" cardinal venous system that drains the body of the embryo proper. Although transient as named vessels, the vitelline veins are of major applied importance because their selective persistence and regression sculpt three permanent adult structures: the hepatic sinusoids, the hepatic segment of the inferior vena cava, and the entire hepatic portal venous system (stem, right branch and left branch of the portal vein).

### 1. Origin and early course

- ▶ Arise from the capillary plexus in the wall of the yolk sac (splanchnopleuric mesenchyme) — hence also called **omphalomesenteric veins**.



- ▶ Belong to the **visceral group** of primitive veins (with the umbilical veins); the **somatic group** comprises the anterior, posterior and common cardinal veins.
- ▶ Each vitelline vein runs cranially on either side of the developing foregut (oesophagus, stomach, duodenum), pierces the **septum transversum**, and opens into the corresponding (same-side) horn of the sinus venosus.
- ▶ Within the sinus horn the three venous systems terminate side by side in a fixed order — the vitelline vein lies **most medial**, the umbilical vein lies lateral to it, and the common cardinal vein lies **most lateral**, having encircled the pleuroperitoneal canal.
- ▶ This early symmetrical arrangement is present by the end of the fourth week and is progressively remodelled as the liver, gut and heart develop.

## 2. Relation to the developing liver — formation of the hepatic sinusoids

- ▶ As the hepatic bud grows into the septum transversum, the proliferating **liver cords** interrupt the intrahepatic course of the vitelline veins (and, slightly later, of the umbilical veins), breaking them up into an extensive anastomotic capillary network — the **hepatic sinusoids**.
- ▶ Once the liver primordium appears, each vitelline vein is conveniently described in **three parts**:
- ▶ **Infrahepatic part** — around the duodenum, below the liver.
- ▶ **Intrahepatic part** — broken up by liver cords into hepatic sinusoids.
- ▶ **Suprahepatic (terminal) part** — draining the sinusoids into the sinus venosus; these terminal segments are now called the **right and left hepatocardiac channels**.

## 3. Fate of the suprahepatic (terminal) segments

- ▶ With progressive enlargement of the right sinus horn and regression of the left, the **left hepatocardiac channel disappears**.
- ▶ The **right hepatocardiac channel** enlarges and persists, becoming the channel through which all hepatic sinusoidal blood (and later, placental blood) reaches the heart. It ultimately forms the **hepatic segment of the inferior vena cava** (i.e., the short suprahepatic/intrahepatic IVC segment that receives the hepatic veins).

## 4. The three transverse anastomoses and formation of the portal vein

In the infrahepatic part, the two vitelline veins lie one on either side of the duodenum and become interconnected by **three transverse anastomotic channels**: two ventral to the duodenum and one dorsal to it. The superior mesenteric and splenic veins, which develop independently in the dorsal mesentery, join the **left vitelline vein** a short distance caudal to the dorsal anastomosis (some texts describe the superior mesenteric vein itself as a right-vitelline derivative — the precise vitelline contribution is described with minor variation across textbooks, but all agree the tributary drains into the same confluence).

| Anastomosis     | Position relative to duodenum | Ultimate fate                                                                                          |
|-----------------|-------------------------------|--------------------------------------------------------------------------------------------------------|
| Cranial ventral | Ventral                       | Becomes, with the adjoining vitelline segment cranial to it, the <b>left branch of the portal vein</b> |

| Anastomosis     | Position relative to duodenum | Ultimate fate                                            |
|-----------------|-------------------------------|----------------------------------------------------------|
| Caudal ventral  | Ventral                       | Obliterates and disappears                               |
| Middle (dorsal) | Dorsal                        | Becomes part of the <b>stem/trunk of the portal vein</b> |

With selective involution of the remaining vein segments:

- ▶ **Veins that disappear:** the part of the right vitelline vein caudal to the dorsal anastomosis; the part of the left vitelline vein caudal to the entry of the superior mesenteric and splenic veins; the caudal ventral anastomosis itself.
- ▶ **Veins that persist, forming the portal vein:**
  - **Stem** = left vitelline vein (segment between the entry of the superior mesenteric/splenic veins and the dorsal anastomosis) + the dorsal anastomosis + right vitelline vein (segment between the dorsal anastomosis and the cranial ventral anastomosis).
  - **Right branch** = right vitelline vein cranial to the cranial ventral anastomosis.
  - **Left branch** = cranial ventral anastomosis + left vitelline vein cranial to it.

Because the trunk of the adult portal vein is thus assembled from alternating segments of the right and left vitelline veins joined across the ventral and dorsal aspects of the duodenum, the portal vein takes its characteristic **oblique, spiralling course** as it ascends behind the neck of the pancreas and the first part of the duodenum toward the porta hepatis — a classical embryological explanation for its adult surgical relations.

□ Fig 19.14 — Development of portal vein. Plexus around the duodenum develops hepatic sinusoid and ductus venosus. Terminal parts of the right and left vitelline veins form right and left hepatocardiac channels respectively (Sontakke — Textbook of Human Embryology, p.202)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the classical schema of portal vein development (as in IB Singh/Sontakke), labelling:

- ▶ Right vitelline vein and Left vitelline vein (flanking the duodenum)
- ▶ Duodenum (centrally placed)
- ▶ Cranial ventral anastomosis, Caudal ventral anastomosis (both ventral to duodenum)
- ▶ Middle dorsal anastomosis (dorsal to duodenum)
- ▶ Entry of superior mesenteric vein and splenic vein (into left vitelline vein, caudal to dorsal anastomosis)
- ▶ Right hepatocardiac channel → hepatic segment of inferior vena cava
- ▶ Left hepatocardiac channel (disappearing, shown as broken line)
- ▶ Hepatic sinusoids (within liver substance)
- ▶ Sinus venosus
- ▶ Resulting Portal vein — stem, right branch, left branch
- ▶ Left umbilical vein and Ductus venosus joining the right hepatocardiac channel

**5. Vitelline vein vs umbilical vein**

| Feature                     | Vitelline vein                                                                | Umbilical vein                                                                                                                                                |
|-----------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source                      | Capillary plexus of the yolk sac (splanchnopleuric mesenchyme)                | Placental capillary plexus (somatopleuric mesenchyme)                                                                                                         |
| Position in sinus horn      | Terminates most medially                                                      | Terminates lateral to the vitelline vein                                                                                                                      |
| Principal adult derivatives | Hepatic sinusoids, hepatic segment of IVC, portal vein (stem + both branches) | Left umbilical vein persists as the vessel carrying placental blood; its proximal part unites with the right hepatocardiac channel to form the ductus venosus |
| Postnatal remnant           | None named separately (incorporated into portal system)                       | Ligamentum teres hepatis (obliterated left umbilical vein)                                                                                                    |

- ▶ The **ductus venosus** develops as an enlarged sinusoidal channel linking the point of entry of the **left umbilical vein** to the **right hepatocardiac channel** (the persistent terminal part of the right vitelline vein), providing a bypass around the hepatic sinusoidal plexus. It is therefore not itself a vitelline-vein segment, but its systemic end is grafted directly onto the vitelline-derived right hepatocardiac channel.

**Applied / Clinical anatomy**

- ▶ **Azygos continuation of the inferior vena cava:** the hepatic segment of the IVC may fail to develop if the anastomosis between the right subcardinal vein and the right hepatocardiac channel (the vitelline-derived channel) does not form. Upper abdominal venous return is then diverted along the azygos vein into the superior vena cava, while the hepatic veins open directly into the right atrium at the usual site of the IVC.

- ▶ **Portal vein physiology:** the portal vein is valveless and carries roughly 70–80% of total hepatic blood flow (the remainder via the hepatic artery), delivering nutrient-rich, deoxygenated blood from the gut, spleen and pancreas to the liver sinusoids.
- ▶ **Portal hypertension and portosystemic anastomoses:** because the portal vein and its tributaries lack valves, any obstruction to flow (e.g., cirrhosis) raises portal pressure and dilates the naturally occurring portosystemic anastomoses — most notably at the **umbilicus** via the paraumbilical veins running in the ligamentum teres (giving the radiating dilated veins of "caput medusae"), as well as at the lower oesophagus and rectum.
- ▶ **Ligamentum teres hepatis** (the obliterated left umbilical vein, running from the umbilicus to the left branch of the portal vein) and **ligamentum venosum** (the obliterated ductus venosus, connecting the left branch of the portal vein to the IVC) are important surface and laparoscopic landmarks on the visceral surface of the liver, both being anatomically continuous with vitelline/portal derivatives.
- ▶ **Surgical anatomy of the porta hepatis:** knowledge that the portal vein trunk is a composite of both vitelline veins joined by the dorsal anastomosis explains its fixed retropancreatic, retroduodenal course (posterior to the neck of the pancreas and the first part of the duodenum, anterior to the IVC) — relevant during pancreaticoduodenal and hepatobiliary surgery and portal vein imaging.

### High-yield exam pointers

- ▶ Vitelline (omphalomesenteric) veins drain the yolk-sac capillary plexus and belong to the **visceral** venous group (with umbilical veins), as opposed to the **somatic** cardinal group.
- ▶ They terminate **most medially** in the sinus venosus horns (vitelline vein medial to umbilical vein, which is medial to the common cardinal vein).
- ▶ Growing liver cords break up their intrahepatic course into the **hepatic sinusoids**.
- ▶ **Three transverse anastomoses** form around the duodenum: cranial ventral, caudal ventral, and middle dorsal.
- ▶ The **right hepatocardiac channel** (persistent terminal right vitelline vein) becomes the **hepatic segment of the IVC**; the left hepatocardiac channel disappears.
- ▶ **Portal vein = stem (dorsal anastomosis + adjoining vitelline segments) + right branch (right vitelline vein) + left branch (cranial ventral anastomosis + left vitelline vein).**
- ▶ Superior mesenteric and splenic veins join the **left** vitelline vein just caudal to the dorsal anastomosis.
- ▶ **Ductus venosus** links the left umbilical vein to the right hepatocardiac channel, bypassing the hepatic sinusoids; it becomes the **ligamentum venosum** after birth.
- ▶ Failure of the right subcardinal–right hepatocardiac anastomosis causes **azygos continuation of the IVC**.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; IB Singh Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Sontakke Textbook of Human Embryology; Brijesh Kumar Embryology Text & Atlas; Hamilton, Boyd & Mossman Human Embryology; Vishram Singh Textbook of Anatomy Vol 2 4e and BD Chaurasia Human Anatomy Vol 2 8e (adult gross/clinical correlation).



## Systemic embryology - gastrointestinal & hepatobiliary



### Development of Anal Canal

*Asked in: Paper II May 2018 · Paper II Oct 2010 (2×) — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The anal canal has a **dual embryological origin**: its upper two-thirds is an **endodermal** derivative of the terminal hindgut (primitive rectum), and its lower one-third is an **ectodermal** derivative of the proctodeum (anal pit). Both parts arise after the **urorectal septum** divides the cloaca into a ventral primitive urogenital sinus and a dorsal primitive rectum, and correspondingly splits the cloacal membrane into a urogenital membrane and an anal membrane. The junction of the endodermal and ectodermal components is marked in the adult by the **pectinate (dentate) line**, above and below which the arterial supply, venous drainage, lymphatic drainage, nerve supply and epithelial lining all differ — a dual origin that underlies almost every clinically important fact about the anal canal.

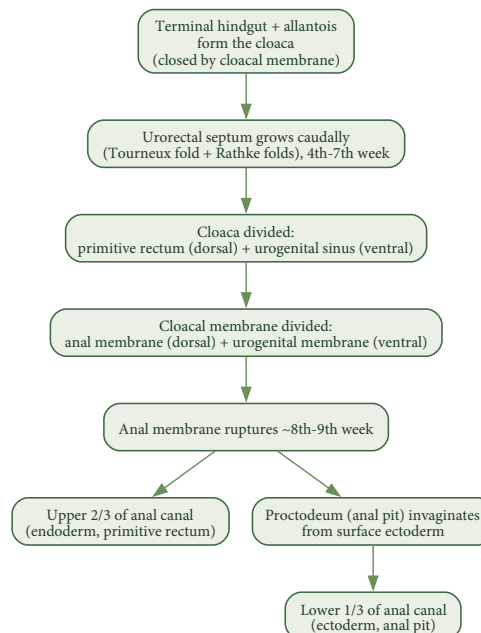
### Formation of the cloaca and the cloacal membrane

- ▶ The terminal, dilated part of the hindgut that receives the **allantois** ventrally is the **cloaca** — a common endoderm-lined chamber for the developing gut and urogenital systems.
- ▶ The cloaca is closed externally by the **cloacal membrane**, a bilaminar disc formed where the endoderm of the cloaca is directly apposed to the surface ectoderm, with no intervening mesoderm.
- ▶ A small, transient caudal extension of the hindgut, the **postanal gut**, projects beyond the cloacal membrane in the 4th–5th week; it normally regresses and disappears before the end of the 5th week.
- ▶ Proliferation of mesenchyme and endoderm in the angle between the hindgut and the allantois initiates the **urorectal septum**, the structure that will partition the cloaca.

### Partitioning of the cloaca by the urorectal septum

- ▶ Classically the urorectal septum is described as forming from two contributions: a cranial vertical element, the **fold of Tourneux**, growing caudally between the hindgut and the allantois/urogenital sinus, and a pair of lateral **folds of Rathke**, growing inward from the lateral walls of the cloaca to fuse in the midline.

- ▶ Between the **4th and 7th weeks**, the growing urorectal septum progressively separates the cloaca into a dorsal **primitive rectum** (which forms the rectum and the upper part of the anal canal) and a ventral, broader **primitive urogenital sinus** (which forms the urinary bladder and urethra).
- ▶ As the septum approaches the cloacal membrane, it correspondingly divides the membrane into an anterior **urogenital membrane** and a posterior **anal membrane**; the point where the tip of the septum meets the membrane becomes the **perineal body**, the fibromuscular node of the perineum.
- ▶ The urogenital membrane breaks down first; the anal membrane persists a little longer and ruptures about the **8th–9th week**, bringing the hindgut lumen into continuity with the amniotic cavity and establishing the primitive anal opening.
- ▶ Current embryological work (Larsen; Moore) refines this classical picture: some studies suggest the urorectal septum and cloacal membrane never truly fuse, and that the "anal membrane" is better regarded as a **transient epithelial plug** that occludes the anorectal lumen before disappearing by apoptosis — offered as a refinement of, not a replacement for, the septum/membrane description still used for teaching congenital anomalies.



*Development of Anal Canal*

## Dual origin of the anal canal — endodermal and ectodermal parts

- ▶ The **proctodeum (anal pit)** is a depression of surface ectoderm just outside the ruptured anal membrane; mesenchyme heaped up around it proliferates to deepen the pit, which invaginates to meet the endodermal hindgut.
- ▶ The **upper two-thirds** of the anal canal (above the pectinate line) is thus derived from the **endodermal primitive rectum**, and the **lower one-third** (below the pectinate line) from the **ectodermal proctodeum**.
- ▶ The former site of the anal membrane is represented in the adult by the **anal valves**, whose line of attachment constitutes the **pectinate (dentate) line** — the surface marker of the endoderm–ectoderm junction.

- This dual germ-layer origin dictates a systematic difference in blood supply, venous and lymphatic drainage, nerve supply and epithelial lining on either side of the line:

| Feature            | Above pectinate line (upper part)                                      | Below pectinate line (lower part)                                                   |
|--------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Germ layer origin  | Endoderm                                                               | Ectoderm                                                                            |
| Develops from      | Endodermal cloaca (primitive rectum/hindgut)                           | Proctodeum (anal pit)                                                               |
| Epithelium         | Columnar (hindgut-type)                                                | Stratified squamous                                                                 |
| Arterial supply    | Superior rectal artery (from inferior mesenteric artery)               | Inferior rectal artery (from internal pudendal artery)                              |
| Venous drainage    | Superior rectal vein → inferior mesenteric vein → <b>portal</b> system | Inferior rectal vein → internal pudendal vein → <b>systemic</b> (caval) system      |
| Lymphatic drainage | Inferior mesenteric / internal iliac nodes                             | Superficial inguinal nodes                                                          |
| Nerve supply       | Autonomic (visceral afferents — poorly localised pain)                 | Somatic, inferior rectal nerve (pudendal) — well localised pain, touch, temperature |

□ Fig 14.12 — Development of the anal canal. Urogenital septum divides cloaca into v (Sontakke — Textbook of Human Embryology, p.144)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Midsagittal/schematic series showing partitioning of the cloaca and formation of the anal canal — label:

- Hindgut (dorsal) and allantois (ventral) entering the cloaca
- Cloacal membrane (ectoderm + endoderm, no mesoderm)
- Urorectal septum (fold of Tourneux + folds of Rathke) growing caudally
- Primitive urogenital sinus (ventral) and primitive rectum (dorsal)
- Urogenital membrane (anterior) and anal membrane (posterior)
- Perineal body — site where the tip of the septum meets the membrane
- Proctodeum (anal pit) — ectodermal invagination
- Pectinate line (anal valves) — junction of endoderm and ectoderm
- Upper two-thirds of anal canal (endoderm) vs lower one-third (ectoderm) — shade differently

### Molecular regulation and clinically relevant refinements

- Septation of the cloaca and normal perineal development depend on **Sonic hedgehog (Shh)** signalling, which maintains mesenchymal proliferation in the urorectal septum and pericloacal mesenchyme; loss of Shh signalling in animal models abolishes cloacal division, and mutations of hedgehog-pathway genes in humans are linked to anorectal malformations.
- **Fibroblast growth factor-10 (Fgf-10)** has similarly been implicated in hindgut birth defects.



- Formation of the **anal sphincter mechanism** is reported to be under **Hox D** genetic control.
- Approximately 2 cm above the anus lies the **anocutaneous line** ("**white line**" of Hilton), close to where the anal epithelium completes its change from columnar to fully keratinised stratified squamous (true perianal skin) — a short transitional zone therefore intervenes between the pectinate line proper and true skin.

### Applied / Clinical anatomy

| Anomaly                                                          | Embryological basis                                                                                                                | Key feature                                                                                                  |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Persistent anal membrane</b><br>(minor imperforate anus)      | Failure of the anal membrane to rupture                                                                                            | Anus and canal form normally; membrane bulges with retained meconium; corrected by simple membrane excision  |
| <b>Membranous atresia</b>                                        | Failure of perforation of the thin epithelial (anal) plug at end of the 8th week                                                   | Thin bluish membrane (meconium visible through it) bulges on straining                                       |
| <b>Anal stenosis</b>                                             | Slight dorsal deviation of the urorectal septum as it grows caudally                                                               | Anus in normal position but anus/anal canal abnormally narrow                                                |
| <b>Anorectal (anal) agenesis</b> — commonest <b>high</b> anomaly | Incomplete separation of the cloaca from the urogenital sinus by the urorectal septum; rectum ends <b>superior to puborectalis</b> | Usually associated with a fistula — rectovesical/rectourethral (male), rectovaginal/rectovestibular (female) |
| <b>Rectal atresia</b>                                            | Defective blood supply or faulty recanalisation                                                                                    | Anal canal and rectum both present but separated by a gap, sometimes joined by a fibrous cord                |
| <b>Ectopic anus</b>                                              | Abnormal division of the cloacal membrane by the growing perineal body                                                             | Anal opening in the vestibule (female) or at the base of the scrotum/bulbar urethra (male)                   |
| <b>Low vs high anomalies</b>                                     | Classified by whether the rectum ends inferior (low) or superior (high) to <b>puborectalis</b> , the key muscle of continence      | Low lesions have a better functional prognosis; >90% of low anomalies have an external fistula               |

- Overall incidence of imperforate anus is about **1 in 5000 live births**, commoner in males; anorectal anomalies may cluster with the **VATER association** (Vertebral, Anal, Tracheo-oesophageal, Renal anomalies).
- **Pectinate line** — **clinical significance**: internal haemorrhoids (dilated tributaries of the superior rectal vein in the anal columns, classically at the 3, 7 and 11 o'clock positions) lie **above** the line and are painless (visceral innervation, columnar mucosa); external haemorrhoids lie **below** the line and are painful (somatic innervation, squamous epithelium). Malignancy above the line tends to be adenocarcinoma spreading to internal iliac/pararectal nodes, whereas malignancy below the line is typically squamous cell carcinoma spreading to superficial inguinal nodes — a direct clinical consequence of the dual developmental origin.

- ▶ **Hirschsprung's disease** (congenital megacolon), due to failure of craniocaudal migration of vagal neural-crest cells with resulting aganglionosis of the myenteric/submucosal plexuses, is not an anal-canal anomaly proper but is an important differential for neonatal obstruction/delayed passage of meconium tested alongside anorectal malformations.

### High-yield exam pointers

- ▶ Anal canal = **dual origin**: upper 2/3 endoderm (primitive rectum/hindgut), lower 1/3 ectoderm (proctodeum/anal pit).
- ▶ **Urorectal septum** (Tourneux fold + Rathke folds) divides the cloaca into primitive rectum (dorsal) + urogenital sinus (ventral), and the cloacal membrane into anal membrane (dorsal) + urogenital membrane (ventral); its tip forms the **perineal body**.
- ▶ **Pectinate (dentate) line** = surface marker of the endoderm–ectoderm junction = former site of the anal membrane = line of the anal valves.
- ▶ Above pectinate line: superior rectal artery, portal venous drainage, autonomic nerves, columnar epithelium, painless lesions. Below: inferior rectal artery, systemic venous drainage, somatic (pudendal) nerves, stratified squamous epithelium, painful lesions.
- ▶ Anal membrane ruptures about the **8th–9th week** of intrauterine life.
- ▶ Imperforate anus classified as **low or high relative to puborectalis**; anorectal agenesis is the commonest high anomaly and is usually fistulous.
- ▶ Molecular control: **Shh** and **Fgf-10** for cloacal septation; **Hox D** genes for anal sphincter formation.
- ▶ Postanal gut is a transient 4th–5th week structure that normally disappears — not to be confused with the definitive anal canal.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology (figure); Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); BD Chaurasia — Human Anatomy Vol 2 8e (haemorrhoids/pectinate-line clinical correlation).



## Development of Duodenum

Asked in: Paper II 14-Nov-2019 · Paper II Nov 2018 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — The duodenum has a **dual embryological origin**: its proximal part is a derivative of the **caudal foregut** and its distal part of the **cranial midgut**, the junction lying at (or just distal to) the opening of the bile duct into the second part. Around this junction the hepatic diverticulum and the ventral and dorsal pancreatic buds bud off, so the duodenum's rotation, mesenteric fate and vascular pattern are inseparable from those of the developing stomach, liver and pancreas. It ends as a **C-shaped, secondarily retroperitoneal** tube clasping the head of the pancreas.

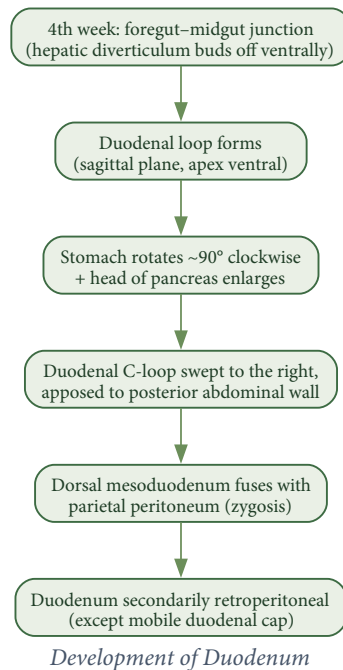
### Dual origin and segmental blood supply

- ▶ The duodenum develops partly from the **terminal (caudal) foregut** and partly from the **cephalic (cranial) midgut**; the junction of the two is directly distal to the origin of the hepatic (liver) bud, i.e., at the opening of the bile duct (major/hepatopancreatic papilla) in the second part.
- ▶ **First part + upper half of second part** (up to the bile-duct opening) → **foregut** derivative → supplied by the **coeliac trunk** (via the gastroduodenal → superior pancreaticoduodenal artery).
- ▶ **Lower half of second part + third + fourth parts** → **midgut** derivative → supplied by the **superior mesenteric artery** (via the inferior pancreaticoduodenal artery).
- ▶ This dual arterial supply (foregut vessel proximally, midgut vessel distally) is the classical embryological explanation for the duodenum's watershed blood supply and is a favourite viva point.

| Duodenal segment                                     | Germ-layer origin     | Arterial supply                                                  |
|------------------------------------------------------|-----------------------|------------------------------------------------------------------|
| D1 + upper half of D2 (up to major duodenal papilla) | Foregut (caudal-most) | Coeliac trunk → superior pancreaticoduodenal artery              |
| Lower half of D2 + D3 + D4                           | Midgut (cranial-most) | Superior mesenteric artery → inferior pancreaticoduodenal artery |

### Formation of the C-shaped loop and rotation

- ▶ Early in the **4th week**, rapid proliferation at the foregut–midgut junction produces a **duodenal loop** that initially lies in the **sagittal plane**, with its apex directed ventrally at the point where the hepatic diverticulum arises.
- ▶ As the **stomach rotates** (approximately 90° clockwise about its longitudinal axis, viewed from the cranial end) and the head of the pancreas enlarges, the loop is swung to the **right side of the abdomen**; its original right surface comes to lie against the posterior abdominal wall.
- ▶ The final **C-shaped** configuration has its concavity clasping the head of the pancreas and its convexity directed to the right — the arrangement seen in the adult.
- ▶ This positional shift is compounded by migration of the bile duct and ventral pancreatic duct around the duodenal wall until they open on its postero-medial aspect (the major duodenal papilla in D2).



### Mesenteric fate — ventral and dorsal mesoduodenum

- ▶ A **ventral mesoduodenum**, continuous cranially with the ventral mesogastrium, is attached only to the short foregut portion of the duodenum; it carries the hepatic diverticulum and ventral pancreatic bud.
- ▶ A thick **dorsal mesoduodenum**, continuous cranially with the dorsal mesogastrium and caudally with the dorsal mesentery of the midgut, anchors the duodenum — it acts as a **suspensory ligament** that fixes the duodenum's position while the rest of the midgut elongates into the physiological umbilical herniation (6th week).
- ▶ Following rotation, the dorsal mesoduodenum and the overlying parietal peritoneum fuse and are absorbed (**zygosis**), so that almost the whole duodenum — apart from a short initial segment — becomes **secondarily retroperitoneal (sessile)**, fixed to the posterior abdominal wall.
- ▶ The short proximal segment near the pylorus retains a free mesentery and stays mobile/partly intraperitoneal; this is the **duodenal cap**, seen radiologically as a triangular shadow on a barium-meal study.

### Relation to the developing pancreatic buds and bile duct

- ▶ The **hepatic diverticulum** buds from the **ventral wall** of the duodenum at the foregut–midgut junction; it gives rise to the liver, cystic duct/gallbladder, and also gives off the **ventral pancreatic bud**.
- ▶ The **dorsal pancreatic bud** evaginates independently from the **dorsal wall** of the duodenum, slightly cranial to the hepatic diverticulum, growing directly into the dorsal mesoduodenum.
- ▶ Differential growth of the duodenal wall, together with duodenal rotation, carries the ventral bud (and the bile duct within it) posteriorly around the right side of the duodenum until it lies **below and behind** the dorsal bud; the two buds then **fuse**.
- ▶ The ventral bud forms the **uncinate process and inferior part of the head** of the pancreas; the dorsal bud forms the rest of the head, body and tail. The bile duct comes to open, together with

the main pancreatic duct, at the **major duodenal papilla** on the postero-medial wall of the second part.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Transverse section through the developing duodenal loop and pancreatic primordia (5th–6th week) — label:

- ▶ Foregut (caudal end) / Midgut (cranial end) — foregut–midgut junction
- ▶ Hepatic diverticulum (liver bud)
- ▶ Ventral pancreatic bud (with bile duct)
- ▶ Dorsal pancreatic bud
- ▶ Ventral mesoduodenum
- ▶ Dorsal mesoduodenum
- ▶ Stomach (undergoing rotation)
- ▶ Duodenal C-loop — convexity to the right, concavity clasping the pancreas
- ▶ Posterior abdominal wall (site of peritoneal fusion/zygosis)
- ▶ Duodenal cap (short mobile segment retaining its mesentery)

### Luminal recanalization

- ▶ During the **2nd month**, rapid endodermal proliferation transiently **obliterates the duodenal lumen** (the "solid stage"), most marked in the duodenum among all gut regions.
- ▶ The lumen is subsequently **re-established by vacuolation and coalescence** ("recanalization"); by 9 weeks the duodenum has developed villi. Failure or incompleteness of this process underlies duodenal atresia/stenosis (classical Tandler theory, still the standard teaching used to explain these anomalies).
- ▶ *Note:* Gray's Anatomy (41e) records a more recent view that true secondary luminal occlusion may not occur, and that the "solid" appearance instead reflects crowding of the epithelium during villus cytodifferentiation — offered as a refinement, not a replacement, of the classical recanalization concept taught for the atresia/stenosis mechanism.

### Applied / Clinical anatomy

- Fig 15.7 — Formation of annular pancreas. There may be two ventral pancreatic buds that fuse with the dorsal bud, one passing anterior and one posterior to the duodenum, forming a ring of pancreatic tissue (Sontakke — Textbook of Human Embryology, p.155)

| Anomaly              | Embryological basis                                                                                                                                                             | Site / feature                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Duodenal atresia     | Complete failure of recanalization                                                                                                                                              | Almost always at/just distal to the major duodenal (hepatopancreatic) papilla, occasionally D3; bilious vomiting within hours of birth (block is distal to the bile-duct opening); antenatal <b>polyhydramnios</b> (failure of amniotic-fluid absorption); postnatal " <b>double bubble</b> " sign on X-ray/USG (dilated stomach + proximal duodenum); ~1/3 of cases have <b>Down syndrome</b> ; also associated with annular pancreas, cardiac anomalies, malrotation. Incidence ~1 in 5000 live births |
| Duodenal stenosis    | Incomplete/partial recanalization                                                                                                                                               | Commonly affects D3/D4; produces partial obstruction, presenting later than atresia                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Annular pancreas     | Bifid ventral pancreatic bud — one part rotates anterior, the other posterior to the duodenum before fusing with the dorsal bud, encircling D2 with a ring of pancreatic tissue | May cause external duodenal compression/obstruction, or pancreatitis within the ring; associated with Down syndrome, intestinal malrotation, cardiac defects; reported to affect females more often                                                                                                                                                                                                                                                                                                      |
| Duodenal diverticula | Persistent focal weakness/redundancy of the developing wall                                                                                                                     | Seen along the inner (concave) border of the second and third parts                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Duodenal cap         | Persistence of a short free mesentery near the pylorus after zygosis elsewhere                                                                                                  | Triangular shadow on barium-meal radiograph; the only mobile, intraperitoneal part of the adult duodenum                                                                                                                                                                                                                                                                                                                                                                                                 |

- Surgical correction of duodenal atresia is by **duodeno-duodenostomy** (bypassing the obstructed segment), often performed alongside correction of associated anomalies.
- Awareness of the foregut/midgut vascular divide (coeliac vs superior mesenteric) is clinically relevant in duodenal ischaemia and in planning pancreatoduodenal resections.

### High-yield exam pointers

- Foregut–midgut junction of the duodenum = at/just distal to the **bile-duct (major duodenal) papilla** in the second part.
- Proximal segment (foregut) → coeliac trunk; distal segment (midgut) → superior mesenteric artery — dual blood supply is the hallmark fact.
- Ventral mesoduodenum is limited to the short foregut segment and carries the hepatic diverticulum + ventral pancreatic bud; dorsal mesoduodenum is thick and fixes the duodenum (acts as its "suspensory ligament").

- ▶ Zygosis (fusion/absorption of dorsal mesoduodenum with parietal peritoneum) renders the duodenum **secondarily retroperitoneal**, except the mobile **duodenal cap**.
- ▶ Ventral pancreatic bud rotates dorsally with the bile duct to fuse behind the dorsal bud → forms the **uncinate process**; failure of normal (single) rotation → **annular pancreas**.
- ▶ Transient solid-stage occlusion followed by recanalization (2nd month) explains **duodenal atresia** (complete failure) and **stenosis** (partial failure).
- ▶ Classic triad for duodenal atresia in the exam/viva: **bilious vomiting** + "**double bubble**" sign + **Down syndrome association**.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; BD Chaurasia — Human Anatomy Vol 2 8e; Sontakke — Textbook of Human Embryology (figure).



## Describe physiological hernias with its congenital malformations

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Physiological (umbilical) herniation is a normal event of the sixth week of intrauterine life in which the rapidly elongating primary intestinal (midgut) loop, unable to be accommodated by the small coelomic abdominal cavity crowded by the bulky developing liver, temporarily herniates into the extraembryonic coelom of the umbilical cord. While herniated, the loop rotates part-way around the axis of the superior mesenteric artery (SMA); it returns to the abdominal cavity by the tenth to twelfth week, completing rotation and settling into the adult disposition. Faults at any step of this timed herniation-rotation-return sequence produce a well-defined group of congenital malformations — ventral wall defects, vitello-intestinal duct remnants, rotation anomalies with volvulus, and intestinal atresias — all of surgical and radiological importance.

### 1. Physiological Umbilical Herniation — Cause and Timing

- ▶ The **midgut** extends from the opening of the bile duct in the duodenum to the junction of the proximal two-thirds and distal one-third of the transverse colon; it is supplied throughout by the **superior mesenteric artery**.
- ▶ Rapid elongation of the gut and its mesentery forms the **primary intestinal (midgut) loop**, suspended from the posterior abdominal wall by a short mesentery and remaining in open communication with the yolk sac at its apex via the narrow **vitelline (yolk-stalk) duct**.
- ▶ The loop has two limbs:
  - **Cephalic (cranial) limb** → distal duodenum, jejunum, and part of ileum.
  - **Caudal limb** → remaining ileum, caecum, appendix, ascending colon, and proximal two-thirds of transverse colon; it bears the **caecal bud**, a small conical dilatation appearing about the sixth week.



- ▶ Cause: disproportionate rapid growth of the midgut loop together with rapid enlargement of the liver makes the abdominal cavity **temporarily too small** to contain the intestinal loops.
- ▶ Result: during the **sixth week**, the loops herniate into the extraembryonic coelom within the **umbilical cord** — the **physiological umbilical hernia**.
- ▶ Coiling of the small-intestinal loops and formation of the caecum both occur while the gut is herniated.
- ▶ Duration: herniation persists from about the **6th week until the 10th week**, when return begins; the process is complete by the **12th week** (early third month).

## 2. Rotation of the Midgut Loop

- ▶ The loop rotates around an axis formed by the **superior mesenteric artery**.
- ▶ Viewed from the front, rotation is **anticlockwise (counterclockwise)** and totals **270°** when complete.
- ▶ Rotation occurs in two temporally distinct phases, together sometimes taught as three sequential 90° turns:

| Phase | Timing                            | Rotation                            | Key change                                                                                                                          |
|-------|-----------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| I     | During herniation (6th–10th week) | 90° anticlockwise                   | Transverse (caudal-limb) colon swings anterior to the duodenum; loop enters the umbilical coelom already rotated 90°                |
| II    | Early return (~10th week)         | further 90° (of the remaining 180°) | Returning proximal jejunal loops pass to the left; caecal bud lies transiently subhepatic in the right upper quadrant               |
| III   | Late return (10th–12th week)      | final 90° (total 270° reached)      | Caecum descends from the subhepatic position into the right iliac fossa; ascending colon and hepatic flexure take up the right side |

- ▶ Even during rotation, the small-intestinal (jejunoileal) limb continues to elongate and becomes thrown into coiled loops; the large-intestinal limb elongates but does **not** coil.

## 3. Return of the Herniated Loops and Final Disposition

- ▶ Return begins in the **10th week**, aided by regression of the mesonephric kidney, slowing of hepatic growth, and enlargement of the abdominal cavity.
- ▶ Sequence: **proximal jejunum returns first**, settling on the **left**; progressively later loops settle more to the **right**. The **caecal bud returns last**, lying transiently subhepatic (right upper quadrant) before **descending into the right iliac fossa**, carrying the ascending colon and hepatic flexure with it; its narrowed distal end forms the **appendix**, hence the appendix's frequently **retrocaecal/retrocolic** (~50%) position.

- Mesenteric fate: the dorsal mesentery twists around the SMA origin and remains continuous from the duodenojejunal flexure to the mesorectum, but is **free** over the jejunum/ileum, transverse and sigmoid mesocolon and mesoappendix, while that of the **ascending/descending colon fuses to the posterior parietal peritoneum** (fascia of Toldt), rendering them secondarily retroperitoneal.
- End result: **duodenojejunal flexure left of L1/L2 (ligament of Treitz)**, **caecum/appendix in the right iliac fossa**, definitive C-shaped colon.

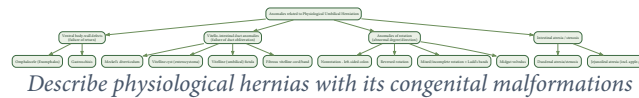
### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 14.13 — *Herniation and Rotation of the Intestine (A, B) At the end of the (Larsen — Human Embryology — 6e, p.868)*

Reproduce a 3-panel sequence (based on Langman Figs 15.25–15.27):

- **Panel A** — loop *before* rotation: cephalic and caudal limbs, apex at the **vitelline duct**, SMA as axis, arrow showing anticlockwise direction.
- **Panel B** — loop *herniated* after 90° rotation: transverse colon anterior to duodenum; label **caecal bud**, coiled jejunoileal loops, umbilical cord.
- **Panel C** — loop *after full 270° rotation* and return: caecum/appendix in right iliac fossa, ascending colon right, descending colon left, duodenojejunal flexure left, transverse colon crossing anteriorly.

## 4. Classification of Congenital Malformations of Physiological Herniation



## 5. Ventral Body-Wall Defects — Omphalocele vs Gastroschisis

| Feature   | Omphalocele<br>(Exomphalos)                                                          | Gastroschisis                                                                                       |
|-----------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Mechanism | Failure of the herniated bowel to return to the body cavity during the 6th–10th week | Defect in closure of the ventral body wall lateral to the umbilical ring (para-umbilical ischaemia) |
| Site      | Through the <b>umbilical ring</b> itself                                             | <b>Para-umbilical</b> , usually to the <b>right</b> of the umbilicus                                |
| Covering  | Herniated viscera covered by <b>peritoneum internally and amnion externally</b>      | <b>No covering membrane</b> — bowel exposed directly to amniotic fluid                              |
| Contents  | May include liver, small/large intestine, stomach, spleen, gallbladder               | Usually small and large intestine only                                                              |
| Incidence | ~2.5/10,000 births                                                                   | ~1/10,000 births (rising, especially in mothers <20 years)                                          |

| Feature             | Omphalocele (Exomphalos)                                                                                                      | Gastroschisis                                                                                                   |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Associations        | High mortality (~25%); cardiac anomalies (~50%); neural tube defects (~40%); chromosomal abnormalities in ~15% of live births | <b>Not</b> associated with chromosomal or other severe defects; bowel may be damaged by amniotic-fluid exposure |
| Prognosis           | Guarded, due to associated anomalies                                                                                          | Excellent, unless complicated by volvulus                                                                       |
| Antenatal diagnosis | Ultrasound — rounded mass with membrane                                                                                       | Ultrasound — ragged, uncovered loops                                                                            |

## 6. Vitello-Intestinal (Vitelline) Duct Anomalies

The duct normally obliterates completely; in 2–4% of people a remnant persists as one of four patterns:

| Anomaly                        | Basis                                                                                                                                                                                                                           |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Meckel's (ileal) diverticulum  | <b>Proximal</b> end persists as a true diverticulum on the antimesenteric border of the ileum, <b>40–60 cm from the ileocaecal junction</b> ; may contain ectopic gastric/pancreatic mucosa → ulceration, bleeding, perforation |
| Vitelline cyst (enterocystoma) | Both ends fibrose into cords while the <b>middle segment</b> persists and dilates into a cyst attached to umbilicus and ileum by vitelline ligaments                                                                            |
| Vitelline (umbilical) fistula  | <b>Entire duct</b> remains patent, giving direct ileum–umbilicus communication with faecal discharge at the umbilicus                                                                                                           |
| Fibrous vitelline cord/band    | Complete obliteration to a cord (no diverticulum), but the cord can entrap or twist loops, causing <b>strangulation/volvulus</b>                                                                                                |

About one-third of symptomatic cases have an associated atresia, imperforate anus, gastroschisis or omphalocele.

## 7. Anomalies of Rotation, Volvulus and Intestinal Atresia

- **Nonrotation:** only 90° of rotation instead of 270°; colon/caecum return first and settle **left**, later loops moving right — a **left-sided colon**.
- **Reversed rotation:** 90° clockwise instead of anticlockwise; transverse colon passes **behind** the duodenum and lies posterior to the SMA; caecum may lie inferior to the pylorus.
- **Incomplete rotation with a high (subhepatic) caecum:** **Ladd's bands** (peritoneal bands fixing the caecum) may cross and compress the duodenum, causing duodenal stenosis/obstruction.
- Failure of peritoneal fixation may leave the mesentery attached at only two points, or create a **retrocolic pocket** behind the ascending colon (retrocolic hernia); both predispose to **midgut volvulus** with vascular compromise and gut necrosis.

- ▶ **Diagnosis:** barium study shows the ligament of Treitz displaced from left of L1/L2; ultrasound in volvulus classically shows the **superior mesenteric vein rotated to lie left of the artery** (reversal of the normal right-sided relationship).
- ▶ **Intestinal atresia/stenosis:** occur anywhere — **most in the duodenum, fewest in the colon, equal numbers in jejunum/ileum** ( $\approx 1/1500$  births). Duodenal atresia reflects failed recanalisation; those distal to it are attributed to **intrauterine vascular accidents** (from malrotation/volvulus/gastroschisis/omphalocele) and HOX/FGF gene misexpression. Morphology: bowel segment lost (50%), fibrous cord (20%), mucosal diaphragm/stenosis (20%), multiple atresias/stenoses (10%). **Apple-peel atresia** ( $\approx 10\%$  of atresias) affects the proximal jejunum, with the short distal bowel coiled around a mesenteric remnant.

## Applied / Clinical anatomy

- ▶ **Bilious vomiting in a neonate** is midgut volvulus until proven otherwise — twisting of a malrotated, narrow-based mesentery around the SMA threatens the entire midgut's blood supply.
- ▶ **Ladd's procedure** for malrotation/volvulus divides Ladd's bands, widens the mesenteric base, positions the bowel in nonrotation, and includes an incidental appendectomy.
- ▶ Antenatal ultrasound distinguishes **omphalocele** (membrane-covered, midline, karyotyping warranted) from **gastroschisis** (uncovered, para-umbilical, isolated, excellent prognosis).
- ▶ A **retrocaecal/retrocolic appendix** ( $\approx 50\%$ ), a result of caecal descent, alters the clinical presentation of appendicitis.
- ▶ **Meckel's diverticulum** — commonest small-intestinal anomaly; differential for painless rectal bleeding, intussusception, diverticulitis; ectopic gastric mucosa is localised on a **Tc-99m pertechnetate scan**.
- ▶ A patent vitelline duct presents as faeculent umbilical discharge and needs surgical excision.
- ▶ The **ligament of Treitz** position on a barium meal is the standard check for malrotation.

## High-yield exam pointers

- ▶ Physiological umbilical herniation occurs at the **6th week**, due to rapid midgut elongation outpacing a liver-crowded abdominal cavity; herniated loops return by the **10th–12th week**.
- ▶ Total midgut rotation = **270° anticlockwise** around the **SMA** axis: 90° during herniation + 180° during return.
- ▶ Return order: **proximal jejunum first (goes left) → caecal bud last (transiently subhepatic, then descends to right iliac fossa)**.
- ▶ **Omphalocele** = covered (peritoneum + amnion), midline, high association with cardiac/NTD/chromosomal anomalies; **gastroschisis** = uncovered, para-umbilical (right), isolated, excellent prognosis.
- ▶ Vitelline duct remnants (in 2–4%): Meckel's diverticulum (proximal end persists, 40–60 cm from ileocaecal valve), vitelline cyst (middle segment), vitelline fistula (whole duct patent), fibrous cord.

- ▶ Rotation defects: **nonrotation** (90° only, left-sided colon), **reversed rotation** (90° clockwise, colon behind duodenum), **incomplete rotation with Ladd's bands** (duodenal obstruction) — all predispose to **midgut volvulus**.
- ▶ Atresias are commonest in the **duodenum** (recanalisation failure) and equal in **jejunum/ileum** (vascular-accident theory); **apple-peel atresia** is a distinctive proximal-jejunal variant.
- ▶ The **ligament of Treitz** (duodenojejunal flexure) to the left of L1/L2 is the key radiological landmark for normal rotation.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology.



## Describe the development and derivatives of the midgut

*Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The midgut is the segment of the primitive gut tube that, in the adult, extends from immediately distal to the entry of the bile duct into the duodenum up to the junction of the proximal two-thirds and distal one-third of the transverse colon. It is supplied throughout its length by the **superior mesenteric artery (SMA)**, the vitelline artery of the midgut loop. Its development is characterised by four sequential events — formation of the **primary intestinal loop**, **physiological umbilical herniation** (6th–10th week), **270° counter-clockwise rotation** around the SMA axis, and **return with fixation** of the loops in the abdominal cavity — and it gives rise to most of the small intestine and the proximal half of the large intestine.

### Extent, boundaries and arterial supply

- ▶ **Proximal limit:** junction of the 2nd (descending) and 3rd (horizontal) parts of the duodenum, i.e. immediately distal to the major duodenal papilla (opening of the bile and main pancreatic ducts) — this point also marks the foregut–midgut junction.
- ▶ **Distal limit:** junction of the proximal two-thirds and distal one-third of the transverse colon.
- ▶ **Artery of the midgut:** the **superior mesenteric artery**, which forms the fixed axis around which the midgut loop rotates; it corresponds to the embryonic **vitelline artery**. (Foregut = coeliac artery; hindgut = inferior mesenteric artery.)
- ▶ At the 5-week stage the midgut is suspended by a short dorsal mesentery and communicates with the yolk sac through the narrow **vitelline duct (yolk stalk)**, which arises from the apex/summit of the loop.

### Formation of the primary intestinal loop

- ▶ Rapid, disproportionate **elongation of the gut tube and its mesentery** (faster than the elongation of the embryo itself) forces the midgut to bulge ventrally, deviating from the median plane — this bulge is the **primary intestinal (midgut) loop**.

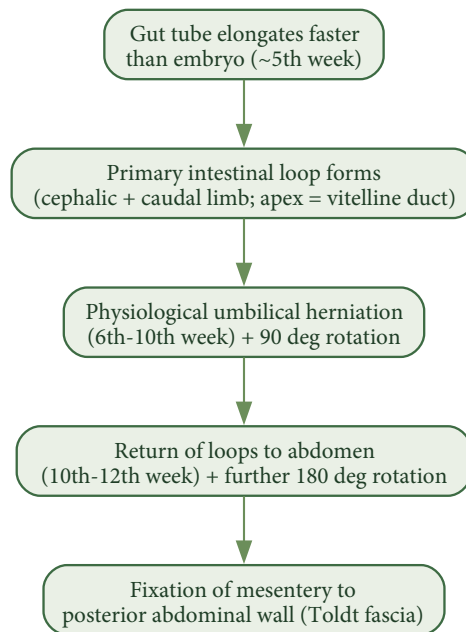
- ▶ The loop remains in continuity with the yolk sac at its apex via the vitelline duct.
- ▶ Two limbs are recognised:
  - **Cephalic (cranial) limb** — the more rapidly elongating limb.
  - **Caudal limb** — on which a small conical dilatation, the **caecal bud**, appears at about the 6th week, caudal to the origin of the yolk stalk; this bud marks the future ileocaecal junction.
- ▶ The **superior mesenteric artery** runs in the mesentery of the loop and forms its fixed axis.

### Physiological umbilical herniation (6th–10th week)

- ▶ The liver and mesonephros grow rapidly and occupy most of the abdominal cavity, which becomes **temporarily too small** to contain the rapidly elongating midgut loop.
- ▶ Consequently, from about the **6th week**, the loop herniates into the extra-embryonic coelom within the proximal umbilical cord — the **physiological (umbilical) hernia**.
- ▶ Coiling of the jejunal and ileal loops, and formation of the caecal bud, occur while the gut lies in this extra-embryonic position.
- ▶ The herniated loop already carries the first **90° of its total rotation** at this stage.

### Rotation of the midgut loop

- ▶ Rotation occurs around an axis formed by the **superior mesenteric artery**, and — viewed from the front — is **counter-clockwise**, totalling 270° when complete.
- ▶ It occurs in two stages:
  - ▶ ~90° during herniation (6th–10th week) — the caudal (colic) limb swings to the embryo's left and the transverse colon comes to pass ventral to the duodenum.
  - ▶ ~180° during return of the loops to the abdominal cavity (10th–12th week), completing the 270° total.
- ▶ Net effect: the small intestine (from the cephalic limb) comes to lie centrally/on the left, while the caecum, ascending colon and transverse colon (from the caudal limb) come to lie on the right and superiorly — the normal disposition of the gut.



*Describe the development and derivatives of the midgut*

### Return (reduction) of herniated loops and fixation

- ▶ From the **10th week**, the herniated loops return to the enlarging abdominal cavity as the liver's relative growth slows and the mesonephros regresses.
- ▶ **Sequence of return:** the proximal jejunal loop returns first and settles to the **left**; progressively later-returning loops settle more to the **right**, so that jejunum lies predominantly left and ileum predominantly right of the root of the mesentery.
- ▶ The **caecal bud is the last part to return**; it lies transiently in the right upper quadrant beneath the right lobe of the liver, then **descends into the right iliac fossa**, carrying the ascending colon and hepatic flexure to the right side; during this descent its distal end narrows to form the **vermiform appendix**.
- ▶ **Fixation:** as the ascending and descending colon come to lie against the posterior abdominal wall, their dorsal mesentery fuses with the parietal peritoneum (with an intervening fascial plane, **Toldt's fascia**), rendering these segments secondarily retroperitoneal. The **transverse mesocolon, mesentery proper (of jejunum/ileum) and sigmoid mesocolon remain free**, though the entire dorsal mesentery is one continuous sheet from the oesophagus to the rectum.

### Derivatives of the midgut

| Limb of primary loop     | Adult structure formed                                                                                       |
|--------------------------|--------------------------------------------------------------------------------------------------------------|
| Cephalic (proximal) limb | Distal (post-ampullary) part of the duodenum · Jejunum · Proximal/greater part of the ileum                  |
| Caudal (distal) limb     | Terminal ileum · Caecum · Vermiform appendix · Ascending colon · Proximal two-thirds of the transverse colon |

- ▶ Over-all, the midgut therefore accounts for **most of the small intestine and roughly the proximal half of the large intestine**.



- ▶ **Epithelial lining and glands** of all these segments are endodermal; muscularis and serosa derive from splanchnic mesoderm.
- ▶ Villi appear cranio-caudally: duodenum/proximal jejunum from ~7 weeks, remaining ileum by ~11 weeks; Brunner's glands appear in the duodenum from ~15 weeks; muscularis mucosae is seen from ~18 weeks. (Occlusion-and-recanalisation of the lumen is **no longer considered accurate**; luminal patency reflects epithelial cyto-differentiation, not a solid-to-recanalised sequence.)

## Applied / Clinical anatomy

- ▶ **Meckel's ("Rule of 2") diverticulum** — persistence of the proximal part of the vitelline duct: occurs in ~2% of people, is about **2 inches (5 cm)** long, lies about **2 feet (60 cm)** proximal to the ileocaecal junction on the **antimesenteric border** of the ileum, is **twice as common in males**, and may contain **2 types of ectopic tissue** (gastric mucosa, pancreatic tissue). It may cause painless bleeding, peptic ulceration/perforation from ectopic gastric mucosa, or inflammation mimicking acute appendicitis.
- ▶ **Other vitelline-duct remnants**: a persistent duct patent along its entire length gives an **umbilical (vitelline) fistula** with faeculent discharge at the umbilicus; obliteration of both ends with a persistent midportion produces a **vitelline (entero-) cyst**, tethered by fibrous cords that can cause volvulus/strangulation of loops that twist around them; partial closure near the umbilicus gives an **umbilical sinus**.
- ▶ **Malrotation (90° rotation only)**: colon and caecum return first and settle on the **left**, giving a left-sided colon with the small bowel to the right — predisposes to **midgut volvulus** and to **obstructive (Ladd's) bands**.
- ▶ **Reversed (clockwise) rotation**: the loop rotates 90° **clockwise** instead of counter-clockwise; the transverse colon then passes **dorsal** to the duodenum and lies behind the SMA.
- ▶ **Non-fixation anomalies**: failure of the ascending colon to fuse to the posterior wall gives a **mobile caecum/colon**, predisposing to **caecal volvulus**; incomplete fusion can leave **retrocolic pockets**, the site of a **retrocolic (paraduodenal-type) internal hernia**.
- ▶ **Omphalocele (exomphalos)**: failure of the herniated midgut loops to return to the abdominal cavity by the 10th week; viscera protrude through the umbilical ring **covered by amnion/peritoneum**; strongly associated with chromosomal and cardiac anomalies.
- ▶ **Gastroschisis**: a para-umbilical (usually right-sided) full-thickness body-wall defect from failure of lateral body-fold fusion; bowel loops protrude **without** a covering sac, directly exposed to amniotic fluid; not chromosomally associated.
- ▶ **Gut duplication cysts**, most often on the mesenteric border of the ileum.
- ▶ **Surgical/radiological correlate**: because the midgut's mesentery is one continuous sheet, the plane of Toldt's fascia is the surgical plane exploited for mobilising the ascending/descending colon; a persistent Meckel's diverticulum is classically seen incidentally at laparotomy or on a **Meckel's (technetium-99m pertechnetate) scan** when it contains ectopic gastric mucosa.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the **midgut loop** after its **270° counter-clockwise rotation**, viewed anteriorly, with the following exact labels:

- ▶ Superior mesenteric artery (axis of rotation, drawn centrally)
- ▶ Cephalic limb — coiled jejunal and ileal loops (to the left/centre)
- ▶ Caudal limb — caecal bud, ascending colon, hepatic flexure, transverse colon (to the right, arching superiorly)
- ▶ Vitelline duct/yolk stalk at the apex of the loop (before obliteration)
- ▶ Position of the future appendix at the tip of the caecal bud
- ▶ Arrow indicating the counter-clockwise direction of rotation

□ Fig 15.27 — A. Anterior view of the intestinal loops after 270° counterclockwise r (Langman's Medical Embryology — Sadler — 14e, p.266)

**High-yield exam pointers**

- ▶ Midgut extent: **major duodenal papilla** → **junction of proximal 2/3 and distal 1/3 of transverse colon**; artery = **SMA**.
- ▶ Total rotation = **270° counter-clockwise**: **90°** during herniation (6th–10th week) + **180°** during return (10th–12th week).
- ▶ **Caecal bud** appears at ~6th week on the caudal limb; it is the **last** part to re-enter the abdomen and gives the caecum + appendix.
- ▶ Derivatives = **distal duodenum, jejunum, ileum, caecum, appendix, ascending colon, proximal 2/3 transverse colon**.
- ▶ **Meckel's diverticulum** — **Rule of 2**: 2% incidence, 2 inches long, 2 feet from ileocaecal junction, antimesenteric border, 2× commoner in males, 2 ectopic tissue types.
- ▶ **90° rotation only** → **left-sided colon/malrotation**; **90° reversed (clockwise) rotation** → **transverse colon behind duodenum and SMA**.
- ▶ **Omphalocele** = covered defect (amnion-covered, failure of return) vs **gastroschisis** = uncovered para-umbilical defect (body-wall fusion failure) — classic differentiator.
- ▶ Fixation of ascending/descending colon mesentery to the posterior wall occurs via **Toldt's fascia**; transverse mesocolon, mesentery proper and sigmoid mesocolon remain free.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2 4e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Brijesh Kumar — Embryology Text & Atlas.

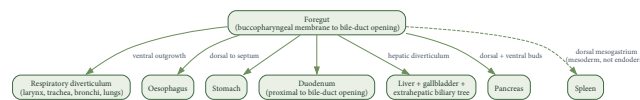
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## Describe the development of all derivatives of foregut. Add a note on the related anomalies

Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy

### Definition / Introduction

Cranio-caudal and lateral folding of the trilaminar embryo in the **4th week** creates the primitive gut tube, divided into **foregut**, **midgut** and **hindgut**. The **foregut** runs from the **oropharyngeal (buccopharyngeal) membrane** to the **opening of the hepatic (bile) duct into the duodenum**, suspended by a **dorsal and ventral mesentery** (the ventral mesentery persists only here, since the liver grows into it). Its cranial-most (pharyngeal) part is conventionally described with head-and-neck embryology; the remainder — this answer's focus — gives rise to the **lower respiratory tract, oesophagus, stomach, duodenum proximal to the bile-duct opening, liver, gallbladder, extrahepatic biliary apparatus and pancreas**, together with the **spleen**, which develops in the foregut mesentery though it is mesodermal, not endodermal. The whole territory is supplied by the **coeliac trunk**.



*Describe the development of all derivatives of foregut. Add a note on the related anomalies*

### 1. Development of the oesophagus

- ▶ The **tracheo-oesophageal septum** grows caudally in the 4th week, partitioning the cranial foregut into a **ventral respiratory diverticulum** and **dorsal oesophagus**.
- ▶ Initially short, the oesophagus **elongates rapidly** (with descent of the heart/diaphragm) to bring the stomach into the abdomen; failure of elongation keeps the stomach thoracic, producing a **congenital hiatus hernia**.
- ▶ The lining epithelium proliferates, transiently **occluding the lumen**, which **recanalises** by the end of the embryonic period.
- ▶ Muscle layers: **upper third striated** (branchial-arch/pharyngeal mesoderm), **middle third mixed**, **lower third smooth** like the rest of the gut.

### 2. Development of the stomach

- ▶ The stomach appears in the 4th week as a **fusiform dilatation of the foregut** just caudal to the respiratory diverticulum.
- ▶ **Longitudinal-axis rotation** — **90° clockwise**: original left side becomes anterior, right side posterior. Hence **left vagus** → **anterior wall**, **right vagus** → **posterior wall** of the adult stomach. The (faster-growing) original posterior wall forms the **greater curvature**; the anterior wall forms the **lesser curvature**.
- ▶ **Antero-posterior-axis rotation** — the caudal (pyloric) end swings **right and upward**, the cephalic (cardiac) end **left and slightly downward**, giving the stomach its final oblique axis.
- ▶ **Mesenteries** — the stomach hangs from the **dorsal mesogastrium** (to the posterior wall) and **ventral mesogastrium** (septum transversum, to liver/ventral wall). As the liver grows into the ventral mesogastrium, this thins into the **lesser omentum** (stomach–liver) and **falciform ligament** (liver–ventral wall).

- ▶ Rotation pulls the dorsal mesogastrium left, opening a space behind the stomach — the **omental bursa (lesser sac)** — and pulls the lesser omentum right; the **epiploic foramen of Winslow** connects lesser and greater sacs.
- ▶ In the **5th week** the **spleen** condenses between the two leaves of the dorsal mesogastrium (section 6), splitting it into the **gastrosplenic** and **lienorenal/splenorenal** ligaments; further downward growth forms the apron-like **greater omentum**, its posterior layer fusing with the transverse mesocolon.

□ Fig 14.6 — Development of transverse mesocolon and lesser sac (omental bursa) (Sontakke — Textbook of Human Embryology, p.139)

### 3. Development of the duodenum

- ▶ Formed from the **terminal (distal) foregut** and the **cephalic midgut**; the junction lies just distal to the **opening of the hepatic diverticulum (bile duct)** — hence the duodenum has a **dual blood supply**, coeliac trunk (foregut part) and superior mesenteric artery (midgut part).
- ▶ As the stomach rotates, the duodenum is thrown into a **C-shaped loop** and, together with the growing head of pancreas, swings to the **right** of the midline; it and the pancreatic head then become fixed to the posterior body wall (become **secondarily retroperitoneal**), except for a short mobile duodenal cap.
- ▶ The lumen is transiently **obliterated by epithelial proliferation** in the 2nd month and **recanalises** shortly after — failure of recanalisation underlies duodenal atresia (see anomalies).

### 4. Development of the liver, gallbladder and extrahepatic biliary apparatus

- ▶ The **hepatic diverticulum (liver bud)** appears in the **middle of the 3rd week** as an endodermal outgrowth from the distal foregut, growing into the mesoderm of the **septum transversum**.
- ▶ Four embryonic sources: (1) liver-bud endoderm → hepatocytes and intrahepatic biliary epithelium; (2) septum transversum mesoderm → fibrous (Glisson's) capsule, connective-tissue stroma, **Kupffer cells**; (3) vitelline and umbilical veins → hepatic sinusoids; (4) ventral mesentery/mesogastrium → **lesser omentum, falciform, coronary and triangular ligaments**.
- ▶ The stalk connecting diverticulum to foregut narrows into the **bile duct**; a small ventral outgrowth from it forms the **cystic duct and gallbladder**, which joins the hepatic duct to form the **common bile duct** — this comes to pass **posterior** to the duodenum as the duodenum rotates.
- ▶ The cranial liver surface, applied to the diaphragm's central tendon, is never peritonealised — the **bare area**, bounded by coronary and triangular reflections.
- ▶ The liver is a major fetal **haematopoietic organ** (~10% of body weight at 10 weeks, ~5% at birth); it begins secreting **bile by the 12th week**.
- ▶ **Molecular regulation**: cardiac-mesoderm **FGF2** plus septum-transversum **BMPs** override notochordal inhibition to specify the hepatic field; **HNF3/HNF4** then drive hepatocyte and biliary differentiation.

□ Fig 15.1 — Development of the liver and gall bladder. The liver develops in the ventral mesogastrium (Sontakke — Textbook of Human Embryology, p.150)

## 5. Development of the pancreas

- Forms from **two endodermal buds** off the duodenal foregut lining: a larger **dorsal pancreatic bud** (in the dorsal mesentery) and a **ventral pancreatic bud** (paired with the bile duct).
- As the duodenum rotates right into its C-shape, the **ventral bud swings dorsally** with the bile duct to lie **below and behind** the dorsal bud, where the two **fuse** in both parenchyma and ducts.

| Pancreatic component                     | Embryonic origin                                                                                      |
|------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Uncinate process + inferior part of head | Ventral bud                                                                                           |
| Body, tail, superior part of head        | Dorsal bud                                                                                            |
| Main pancreatic duct (of Wirsung)        | Distal dorsal duct + entire ventral duct — opens with bile duct at the <b>major papilla</b>           |
| Accessory pancreatic duct (of Santorini) | Proximal dorsal duct (persists as a small channel; may be absent) — opens at the <b>minor papilla</b> |

- Islets of Langerhans differentiate from parenchymal tissue from the **3rd month**; insulin secretion begins by the **5th month**. Molecular regulation: notochord/dorsal-aorta **FGF2 and Activin** repress SHH in dorsal-bud endoderm and upregulate **PDX1**; **PAX4 + PAX6** specify  $\beta$ ,  $\delta$  and PP cells, **PAX6 alone** specifies  $\alpha$  (glucagon) cells.

## 6. Development of the spleen

- **Not a true (endodermal) gut derivative** — arises from **mesenchymal condensations** ("splenculi") in the **dorsal mesogastrium** during the **5th week**, which fuse into a single lobulated mass; **persistent splenic notches** on the adult superior border are a relic of this.
- Mesoderm differentiates into capsule, trabeculae, reticular framework and haematopoietic/lymphoid cells; the spleen is a fetal **haematopoietic organ**.
- Splenic growth divides the dorsal mesogastrium into the **gastrosplenic** (to the stomach) and **lienorenal/splenorenal** (to the posterior wall, carrying splenic vessels) ligaments; fusion of the posterior leaf with the parietal peritoneum and stomach rotation bring the spleen to its final left hypochondriac position.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Foregut derivative map** — a sagittal outline of the primitive gut tube with the tracheo-oesophageal septum splitting the ventral respiratory diverticulum from the dorsal oesophagus; label oesophagus, stomach (fusiform dilatation), hepatic diverticulum, dorsal and ventral pancreatic buds, and the point marking the foregut–midgut junction (opening of the bile duct).
- ▶ **Stomach rotation panel** — three transverse-section sketches at the level of the stomach: (a) before rotation (dorsal/ventral mesogastria symmetrical); (b) during rotation (dorsal mesogastrium ballooning left = developing omental bursa, spleen condensing within it, lesser omentum pulled right); (c) after rotation (final position — greater curvature left/posterior-derived, lesser curvature right/anterior-derived, gastrosplenic and lienorenal ligaments labelled).
- ▶ **Liver–pancreas–duodenum panel** — the C-shaped duodenal loop with the hepatic diverticulum growing into the septum transversum (label falciform ligament, lesser omentum), the bile duct and cystic duct/gallbladder outgrowth, and the ventral pancreatic bud shown migrating dorsally with the bile duct to fuse below the dorsal bud; label main (Wirsung) and accessory (Santorini) ducts and major/minor papillae.

### Applied / Clinical anatomy

| Anomaly                                                 | Basis / feature                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oesophageal atresia ± tracheo-oesophageal fistula (TEF) | Posterior deviation/incomplete formation of the TE septum; <b>commonest pattern</b> (~85–90%) = blind proximal pouch + distal segment fistulous to trachea near the carina (4 rarer variants make up the rest). Causes <b>polyhydramnios</b> ; postnatally, choking on first feed with air in the stomach (X-ray). Often part of <b>VACTERL</b> (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, Limb) |
| Oesophageal stenosis                                    | Incomplete recanalisation or a vascular insult, usually lower third                                                                                                                                                                                                                                                                                                                                           |
| Congenital hiatus hernia                                | Failure of oesophageal elongation pulls the stomach through the oesophageal hiatus                                                                                                                                                                                                                                                                                                                            |
| Congenital hypertrophic pyloric stenosis                | Hypertrophy of circular (± longitudinal) pyloric muscle; incidence ~1 in 150 male / 1 in 750 female infants; <b>non-bilious projectile vomiting</b> after feeds, palpable "olive" mass                                                                                                                                                                                                                        |
| Duodenal atresia/stenosis                               | Failure of recanalisation; ~1 in 5000 births; 20% with annular pancreas, some with bile-duct anomalies; 40–60% complete (pancreatic tissue fills lumen); polyhydramnios + "double bubble" sign; linked to <b>Down syndrome</b>                                                                                                                                                                                |

| Anomaly                                               | Basis / feature                                                                                                                                                                                                                  |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Annular pancreas                                      | Bifid ventral bud — one part migrates normally, the other opposite way — rings the 2nd part of duodenum; ~1 in 12,000–15,000; causes duodenal obstruction/double-bubble; treated by duodeno-jejunostomy, not resection           |
| Pancreas divisum                                      | Failure of dorsal–ventral duct fusion (~10% of cases) leaves a double-duct system                                                                                                                                                |
| Ectopic (accessory) pancreatic tissue                 | Anywhere from lower oesophagus to Meckel diverticulum; commonest in gastric mucosa and Meckel diverticulum                                                                                                                       |
| Biliary atresia                                       | <i>Extrahepatic</i> — failed recanalisation of solid-stage ducts, ~1 in 15,000; 15–20% have a correctable patent proximal segment, rest need transplant. <i>Intrahepatic</i> — rarer (~1 in 100,000), may follow fetal infection |
| Gallbladder/duct duplication, accessory hepatic ducts | Common, usually asymptomatic biliary-outgrowth variants                                                                                                                                                                          |
| Accessory spleen (spleniculus)                        | Failed fusion of a splenculus; found at the hilum, gastrosplenic/lienorenal ligament, pancreatic tail, along splenic vessels, or rarely the spermatic cord — a missed one causes relapse after splenectomy                       |
| Lobulated spleen                                      | Incomplete fusion of splenculi (persistent fetal lobulation)                                                                                                                                                                     |
| Asplenia / polysplenia                                | Laterality (isomerism) disorders: right isomerism → <b>asplenia</b> , left isomerism → <b>polysplenia</b> , both with complex cardiac/situs anomalies                                                                            |

### High-yield exam pointers

- Foregut = buccopharyngeal membrane → opening of the bile duct into the duodenum; supplied by the coeliac trunk.
- Derivatives: lower respiratory tract, oesophagus, stomach, duodenum (proximal to bile duct), liver + biliary tree, pancreas; the spleen develops in the dorsal mesogastrium but is mesodermal, not a true gut derivative.
- Stomach rotates 90° clockwise (longitudinal axis) — left vagus → anterior wall, right vagus → posterior wall; rotation about the antero-posterior axis brings the pylorus right/up and cardia left/down.
- Rotation of the stomach creates the omental bursa (lesser sac); the spleen condenses in the dorsal mesogastrium, splitting it into gastrosplenic and lienorenal ligaments.
- Liver has 4 embryonic sources: hepatic-bud endoderm (hepatocytes/bile ducts), septum transversum mesoderm (capsule/Kupffer cells), vitelline+umbilical veins (sinusoids), ventral mesentery (ligaments).
- Pancreas = dorsal bud (body, tail, most of head) + ventral bud (uncinate process, inferior head); main duct = distal dorsal + all of ventral duct; accessory duct = proximal dorsal duct.



- Key anomalies to name with one fact each: **TEF** (~85–90% type = **proximal blind pouch + distal fistula**), **pyloric stenosis** (projectile vomiting), **duodenal atresia** (double bubble, Down syndrome), **annular pancreas** (double bubble too, duodeno-jejunostomy), **biliary atresia** (extrahepatic 1/15,000 vs intrahepatic 1/100,000), **accessory spleen/asplenia-polysplenia** (isomerism).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Larsen Human Embryology 6e; Sontakke Textbook of Human Embryology; Vishram Singh Textbook of Clinical Embryology — for the embedded plates, Sontakke Textbook of Human Embryology, Fig 14.6 (p.139) and Fig 15.1 (p.150).



## Development of Glands in Relation with the Digestive System

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The major glands opening into the alimentary canal — the three paired **salivary glands**, the **liver** (with gallbladder and extrahepatic biliary tree), and the **pancreas** — all arise as solid epithelial buds/diverticula off the primitive gut tube that proliferate and branch into the surrounding splanchnic mesenchyme. With the sole exception of the **parotid gland** (ectodermal, from the stomodeal lining), every one of these glands is an **endodermal derivative of the foregut**. In each gland the secretory parenchyma and duct system are epithelial in origin while the capsule, septa, connective-tissue stroma and smooth muscle are supplied by the surrounding mesenchyme — the general plan of exocrine gland morphogenesis from the gut tube.

### 1. General plan of digestive-gland morphogenesis

- Each gland begins as a **solid cord of epithelial cells** budding from the gut/stomodeal lining into the adjacent mesenchyme (branching morphogenesis).
- The cords later **canalise** to form the duct system; the rounded, blind, terminal ends of the cords differentiate into the **secretory acini** (parenchyma).
- The **capsule, interlobular septa and connective-tissue stroma** of every one of these glands are mesodermal in origin.
- Branching pattern and cytodifferentiation are controlled by **reciprocal epithelio-mesenchymal induction** — demonstrated in detail for the liver (FGF2/BMP/HNF pathway) and pancreas (Shh/PDX1/PAX pathway), described below.

| Gland   | Epithelial (parenchymal) origin                                   | Germ layer |
|---------|-------------------------------------------------------------------|------------|
| Parotid | Ectodermal outgrowth from the cheek at the angle of the stomodeum | Ectoderm   |

| Gland                                            | Epithelial (parenchymal) origin                        | Germ layer |
|--------------------------------------------------|--------------------------------------------------------|------------|
| Submandibular, sublingual, minor salivary glands | Outgrowths from the floor of the stomodeum/oral cavity | Endoderm   |
| Liver, gallbladder, extrahepatic biliary tree    | Hepatic diverticulum of the distal foregut             | Endoderm   |
| Pancreas                                         | Dorsal + ventral buds of the duodenal foregut          | Endoderm   |

## 2. Development of the major and minor salivary glands

All three pairs of major salivary glands begin as **epithelial cords** that grow into the surrounding mesoderm; the cords canalise to form the duct system while their bulbous terminal ends become the secretory acini, and the mesoderm forms the capsule and septa.

| Gland                 | Source                                                                                            | Time of appearance                   | Outgrowth site / duct outcome                                                                                                                                                                        |
|-----------------------|---------------------------------------------------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Parotid               | Ectodermal outgrowth from the cheek at the angle of the stomodeum                                 | 5th week                             | Grows outward between the mandibular and maxillary processes; the ectodermal furrow tubulises into the <b>parotid duct</b> , medial end opening at the angle of the primitive mouth                  |
| Submandibular         | Endodermal outgrowth from the floor of the stomodeum (alveolo-lingual groove)                     | 6th week                             | Solid cord grows posteriorly lateral to the tongue; a linear groove closes from behind forward to form the <b>submandibular duct</b> , opening on the sublingual papilla beside the frenulum linguae |
| Sublingual            | Multiple endodermal outgrowths from the linguogingival sulcus and the submandibular duct          | 8th week (~2 weeks after the others) | Each outgrowth canalises <b>independently</b> , opening on the summit of the sublingual fold; some may join to form a single sublingual duct                                                         |
| Minor salivary glands | Similar endodermal/ectodermal outgrowths, distributed through the oral mucosa except the gingivae | —                                    | Little or no branching; open <b>independently</b> onto the oral mucosa                                                                                                                               |

- Elongation of the jaws elongates the **parotid duct**, but the gland itself stays put at its site of origin.

- ▶ Fusion of the mandibular and maxillary processes shifts the angle of the mouth medially; in the adult, the parotid papilla opposite the **upper second molar** marks the position of the primitive oral angle.

### 3. Development of the liver, gallbladder and extrahepatic biliary apparatus

- ▶ **Hepatic diverticulum (liver bud):** appears in the **middle of the third week** as a ventral endodermal outgrowth of the foregut at the foregut–midgut junction; it grows into the ventral mesogastrium and penetrates the **septum transversum** (the mesodermal plate between the pericardial cavity and the yolk-sac stalk).
- ▶ The diverticulum divides into two parts: a large cranial **pars hepatica**, which forms the liver parenchyma and hepatic ducts, and a small caudal **pars cystica**, which forms the **gallbladder** and **cystic duct**. Narrowing of the stalk connecting the diverticulum to the duodenum forms the **bile duct**; the cystic duct joins the hepatic duct to complete the (common) bile duct.
- ▶ **Three tissue sources** contribute to the liver: (1) **parenchyma** (hepatocytes + biliary epithelium) from the endodermal hepatic cords; (2) **fibrous stroma, capsule, Kupffer cells and haemopoietic cells** from septum-transversum mesenchyme; (3) **hepatic sinusoids** from the disrupted vitelline and umbilical veins within the septum transversum.
- ▶ **Peritoneal relations:** mesoderm on the liver surface differentiates into visceral peritoneum except over the **bare area**, where the liver is in direct contact with the central tendon of the diaphragm (bounded by the anterior/posterior coronary and triangular reflections). Septum-transversum mesenchyme between the liver and the foregut, and between the liver and the anterior abdominal wall, becomes membranous to form the **lesser omentum** and **falciform ligament** respectively.
- ▶ **Functional milestones:** haemopoiesis dominates early liver activity — at 10 weeks the liver is ~10% of total body weight, falling to ~5% at birth as haemopoiesis subsides; **bile secretion begins around the 12th week**, once the gallbladder, cystic duct and bile duct are patent.
- ▶ **Molecular regulation:** all foregut endoderm has the latent capacity to express liver genes, but this is repressed by the notochord, ectoderm and non-cardiac mesoderm. **FGF2** from the adjacent cardiac mesoderm blocks these inhibitors, while **BMPs** from the septum transversum enhance the endoderm's competence to respond to FGF2 — together these signals specify the hepatic field. Downstream, **hepatocyte nuclear transcription factors HNF3 and HNF4** direct differentiation into hepatocyte and biliary cell lineages.

### 4. Development of the pancreas

- ▶ The pancreas forms from **two endodermal buds** arising from the duodenal foregut: a larger **dorsal pancreatic bud** in the dorsal mesentery (appears ~day 30), and a smaller **ventral pancreatic bud** close to the bile duct (appears shortly after, ~day 32–35).
- ▶ As the duodenum rotates to the right and becomes C-shaped, the **ventral bud swings dorsally** (in step with the migrating bile-duct entrance) to come to lie **immediately below and behind** the dorsal bud by about day 42; the parenchyma and duct systems of the two buds then fuse.

- ▶ The **ventral bud** forms only the **uncinate process** and the inferior/posterior part of the head of the pancreas; the **remainder of the gland** (body, tail, and the rest of the head) is derived from the **dorsal bud**.
- ▶ **Duct fusion:** the **main pancreatic duct (of Wirsung)** is formed by the distal part of the dorsal duct plus the entire ventral duct, opening with the bile duct at the **major duodenal papilla**; the proximal part of the dorsal duct either regresses or persists as the **accessory pancreatic duct (of Santorini)**, opening at the minor papilla. In about **10% of cases the two duct systems fail to fuse**, and the original double system persists (pancreas divisum).
- ▶ **Pancreatic mesenchyme** (from splanchnopleuric coelomic epithelium around the dorsal bud, and from septum-transversum-related mesenchyme around the ventral bud) determines the ductal branching pattern and acinar architecture, and also supplies pancreatic connective tissue and smooth muscle.
- ▶ **Endocrine differentiation:** islet cells differentiate in **two phases** — Phase I (weeks 9–15), proliferation of polyhormonal precursor cells; Phase II (from week 16), differentiation into monohormonal cells.  **$\beta$  cells (insulin, amylin)** appear first, followed by  **$\alpha$  cells (glucagon)**, then  **$\delta$  cells (somatostatin)** after 30 weeks; functional **insulin secretion begins around the 5th month**. The **dorsal bud** contributes predominantly  $\alpha$  cells, the **ventral bud** predominantly pancreatic-polypeptide (PP)-secreting cells.
- ▶ **Molecular regulation:** FGF2 and Activin (from the notochord and dorsal-aortic endothelium) repress **Shh** expression in the endoderm destined for the dorsal bud, permitting pancreatic specification; the ventral bud is induced independently by visceral mesoderm. Both events upregulate **PDX1** (pancreatic and duodenal homeobox 1); combinatorial expression of **PAX4 + PAX6** specifies the  $\beta/\delta/PP$  lineages, while **PAX6 alone** specifies the  $\alpha$ -cell lineage.

□ Fig 14.9 — Development of the Liver, Gallbladder, Pancreas, and Their Duct Systems From Endodermal outgrowths of the foregut, shown at 30, 32, 35 and 42 days (Larsen — Human Embryology — 6e, p.857)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A schematic of salivary gland primordia in the floor/wall of the stomodeum, labelling:

- ▶ Stomodeum with mandibular process and maxillary process
- ▶ Angle of the stomodeum → **ectodermal outgrowth (parotid primordium)** growing between the two processes
- ▶ Floor of the stomodeum (alveolo-lingual groove) → **endodermal outgrowth (submandibular primordium)**, with the linear groove closing behind-to-front into the submandibular duct opening at the sublingual papilla
- ▶ Linguogingival sulcus and submandibular duct → multiple **endodermal outgrowths (sublingual primordia)** opening independently on the sublingual fold
- ▶ Developing tongue in the floor of the mouth for orientation

### Applied / Clinical anatomy

- ▶ **Extrahepatic biliary atresia:** the solid-phase biliary ducts normally recanalise; failure of recanalisation gives extrahepatic biliary atresia, incidence ~1 in 15,000 live births — presents with progressive neonatal cholestatic jaundice.

- ▶ **Gallbladder/duct variants:** accessory hepatic ducts and duplication of the gallbladder are common, usually asymptomatic developmental variants of the pars cystica.
- ▶ **Annular pancreas:** if the bifid ventral bud's two components migrate in opposite directions, pancreatic tissue encircles the duodenum; it may compress the duodenum externally and is found in ~20% of cases of duodenal atresia (itself occurring in ~1/5000 live births).
- ▶ **Pancreas divisum:** persistence of the separate dorsal and ventral duct systems (failure of fusion in ~10% of individuals) — the dorsal duct then drains the bulk of the gland through the minor papilla, a recognised predisposing anatomical variant for recurrent pancreatitis.
- ▶ **Ectopic/heterotopic pancreatic tissue:** may be found anywhere from the distal oesophagus to the tip of the primary intestinal loop, most often in the gastric mucosa or a Meckel diverticulum, sometimes showing the full histological architecture of the pancreas.
- ▶ **Ranula:** a mucous extravasation/retention cyst arising from the multiple independent ducts of the developing sublingual gland or minor salivary glands in the floor of the mouth.
- ▶ **Ectopic parotid tissue/duct anomalies** reflect the variable course of the migrating ectodermal furrow between the mandibular and maxillary processes during the 5th week.

### High-yield exam pointers

- ▶ **Parotid is the only major salivary gland of ectodermal origin** (from the stomodeum); submandibular, sublingual and minor salivary glands are all endodermal.
- ▶ Order of appearance: **parotid (5th week) → submandibular (6th week) → sublingual (8th week).**
- ▶ **Liver bud = hepatic diverticulum**, mid third week, from the distal foregut → **pars hepatica** (liver) + **pars cystica** (gallbladder, cystic duct).
- ▶ **Three sources of the liver:** endoderm (parenchyma), septum-transversum mesenchyme (stroma/Kupffer/haemopoietic cells), vitelline + umbilical veins (sinusoids).
- ▶ **Bare area of the liver** = the only part not covered by peritoneum, related to the diaphragm.
- ▶ **Pancreas = dorsal bud (bulk of gland) + ventral bud (uncinate process + part of head only);** ventral bud rotates dorsally with the bile duct to fuse below the dorsal bud.
- ▶ **Main pancreatic duct (Wirsung)** = distal dorsal duct + whole ventral duct → major papilla; **accessory duct (Santorini)** = proximal dorsal duct remnant → minor papilla.
- ▶ **Annular pancreas and pancreas divisum** are the two classic applied anomalies of pancreatic bud/duct fusion.
- ▶ **PDX1, PAX4, PAX6** = key pancreatic transcription factors; **HNF3, HNF4** = key hepatic transcription factors; **FGF2/BMP** and **FGF2/Activin–Shh** are the respective inductive signalling axes for liver and pancreas.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology; Larsen — Human Embryology 6e (figure); Gray's Anatomy (Standring) 41e.



## Describe the formation, rotation and derivatives of mid gut

*Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The midgut is the middle of the three primitive divisions of the embryonic gut tube, extending from just distal to the opening of the bile duct into the second part of the duodenum (the anterior intestinal portal region) to the junction of the proximal two-thirds and distal one-third of the transverse colon (the posterior intestinal portal region). It is vascularised entirely by the **superior mesenteric artery (SMA)**, which also forms the fixed axis around which the midgut undergoes its characteristic 270° counter-clockwise rotation. Understanding midgut formation and rotation is essential because errors at any stage produce clinically important anomalies — malrotation, volvulus, omphalocele and Meckel's diverticulum.

### Formation of the midgut — primary intestinal loop

- ▶ By the 5th week, the midgut is a straight tube suspended from the posterior abdominal wall by a short dorsal mesentery and connected ventrally, at its apex, to the yolk sac through the narrow **vitellointestinal (vitelline) duct**.
- ▶ The gut lengthens far faster than the embryonic abdomen can accommodate, so it is thrown into a ventral, hairpin-shaped fold — the **primary intestinal (midgut) loop**.
- ▶ The **superior mesenteric artery** runs down the mesentery in the long axis of the loop and divides it into two segments:
  - **Prearterial (cranial/proximal) segment** — lies cranial and to the right of the artery.
  - **Postarterial (caudal/distal) segment** — lies caudal and to the left of the artery; near its apex (at the site of the vitelline duct) it bears a small conical outgrowth, the **cecal bud**.
- ▶ At this stage the loop is oriented in the sagittal (antero-posterior) plane: prearterial segment cranial and ventral, postarterial segment caudal and dorsal to the SMA axis.

### Physiological umbilical herniation

- ▶ During the 6th week, rapid elongation of the prearterial segment, combined with the concurrently enlarging liver and mesonephric kidneys, makes the embryonic abdominal cavity too small to contain the midgut loop.
- ▶ The loop herniates through the umbilical ring into the extraembryonic coelom that persists within the proximal umbilical cord — the **physiological umbilical hernia**.
- ▶ Outside the abdomen, the prearterial segment elongates enormously and coils to form the future jejunum and ileum (the **jejunal–ileal loops**), while the postarterial segment elongates without coiling.
- ▶ Around the **10th week**, the herniated loops begin returning to the abdominal cavity as the liver's relative growth slows and the mesonephros regresses, enlarging the definitive abdominal cavity. Return is complete by about the end of the 3rd month (12th week).

### Rotation of the midgut loop

Viewed from the front, the midgut loop undergoes a **total rotation of 270° in the counter-clockwise (anticlockwise) direction** around the axis of the superior mesenteric artery — never 360°. This total

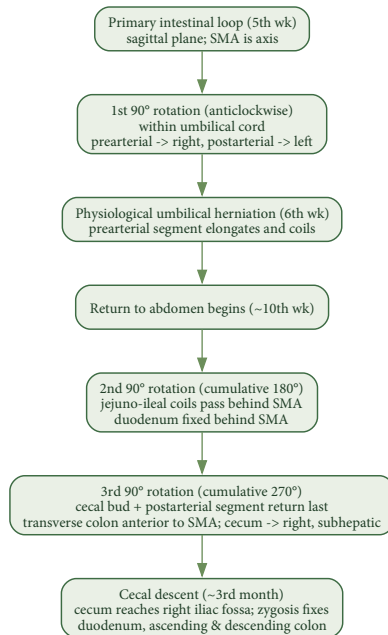


rotation occurs in three equal stages of 90° each: the first 90° occurs during herniation (outside the abdomen), and the remaining 180° occurs during return of the loop into the abdominal cavity.

| Stage            | Rotation                            | Timing / location                                            | What happens                                                                                                                                                                                         |
|------------------|-------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st 90°          | 90° anticlockwise (cumulative 90°)  | Within the umbilical cord, as the loop herniates (~6th week) | Loop swings from the sagittal to the horizontal plane; prearterial segment moves to the <b>right</b> of the SMA, postarterial segment moves to the <b>left</b>                                       |
| Elongation phase | —                                   | 6th–10th week, in the extraembryonic coelom                  | Prearterial segment elongates greatly, coiling into jejunal–ileal loops that lie to the right of the SMA, still outside the abdomen                                                                  |
| 2nd 90°          | 90° anticlockwise (cumulative 180°) | Early part of return to abdomen (from ~10th week)            | Coils of jejunum and ileum pass <b>behind</b> the SMA; the duodenum is carried behind the artery and becomes fixed on the posterior abdominal wall                                                   |
| 3rd 90°          | 90° anticlockwise (cumulative 270°) | Postarterial segment returns last                            | Cecal bud and postarterial segment rotate last; the <b>transverse colon comes to lie anterior to the SMA</b> ; the cecum comes to lie on the right side, initially just below the liver (subhepatic) |

- After the third stage, the cecum gradually **descends** from its subhepatic position to the right iliac fossa as the ascending colon elongates.
- Following completion of rotation, the mesenteries of the duodenum (beyond the first inch), ascending colon, descending colon and rectum fuse with the parietal peritoneum of the posterior abdominal wall (**zygosis**) and these segments become secondarily retroperitoneal. The original dorsal mesentery persists as the mesentery of the small intestine proper, the transverse mesocolon, the sigmoid mesocolon and the mesoappendix.





Describe the formation, rotation and derivatives of mid gut

! [Fig 15.25 — A. Primary intestinal loop before rotation [lateral view]. The superior (Langman's Medical Embryology — Sadler — 14e, p.265)] (C:/Users/Harshad/Documents/anatomy-notes/references/figures/LangmansMedicalEmbryology/figp2652.png)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the midgut loop as a U-shaped tube suspended from the posterior abdominal wall, in three successive panels:

- ▶ **Before rotation** — sagittal view: label *stomach*, *duodenal loop*, **prearterial segment** (cranial), **superior mesenteric artery (axis)**, **postarterial segment** (caudal) with the **cecal bud** at its apex, and the **vitellointestinal duct** connecting the apex to the yolk sac.
- ▶ **After 1st 90° (herniated)** — label prearterial segment now to the *right* of the SMA forming coiled *jejunal-ileal loops*, postarterial segment to the *left*, all lying outside the abdomen in the umbilical cord.
- ▶ **After full 270° (final position)** — label *duodenum* (retroperitoneal, behind SMA), coiled *jejunum* and *ileum* (left/inferior), *cecum* and *appendix* (right iliac fossa), *ascending colon*, *hepatic flexure*, *transverse colon* (anterior to SMA), *splenic flexure*, *descending colon*.

### Derivatives of the midgut

| Segment             | Adult derivative                                                            | Arterial supply         |
|---------------------|-----------------------------------------------------------------------------|-------------------------|
| Prearterial segment | Distal (3rd and 4th) part of duodenum, distal to the major duodenal papilla | Branches of SMA         |
|                     | Jejunum                                                                     | Jejunal branches of SMA |
|                     | Ileum, except its terminal part                                             | Ileal branches of SMA   |

| Segment              | Adult derivative                                  | Arterial supply                 |
|----------------------|---------------------------------------------------|---------------------------------|
| Postarterial segment | Terminal part of ileum                            | Ileal/ileocolic branches of SMA |
|                      | Cecum and vermiform appendix (from the cecal bud) | Ileocolic artery                |
|                      | Ascending colon                                   | Right colic artery              |
|                      | Proximal (right) two-thirds of transverse colon   | Middle colic artery             |

- All structures derived from the midgut are supplied by the **superior mesenteric artery** — this is a reliable rule for identifying midgut derivatives in the adult.
- The junction between foregut and midgut derivatives (anterior intestinal portal) corresponds in the adult to the opening of the bile duct in the second part of the duodenum; the junction between midgut and hindgut derivatives (posterior intestinal portal) corresponds to the junction of the proximal two-thirds and distal one-third of the transverse colon — the left one-third of the transverse colon is a hindgut derivative supplied by the inferior mesenteric artery.

## Applied / Clinical anatomy

- **Errors of rotation**
  - *Nonrotation*: the loop fails to rotate at all; the postarterial segment (large intestine) returns first and lies on the left, while the small intestine (prearterial derivative) lies on the right.
  - *Partial/incomplete rotation*: the first 180° occurs normally but the final 90° does not, leaving the cecum and appendix just below the pylorus instead of the right iliac fossa.
  - *Reversed rotation*: the loop rotates **clockwise**; the transverse colon then passes **behind** the duodenum and the SMA, instead of in front.
  - These rotational errors leave the small bowel mesentery abnormally narrow at its root, predisposing to **midgut volvulus** — twisting of the bowel around the SMA pedicle causing ischaemic obstruction, a paediatric surgical emergency.
- **Vitellointestinal duct anomalies** (failure of the duct to obliterate): **Meckel's diverticulum** is the commonest — a true diverticulum on the antimesenteric border of the ileum, classically described by the "rule of 2s": occurs in about 2% of people, situated about **2 feet (60 cm)** proximal to the ileocecal junction, about **2 inches (5 cm)** long; it may contain ectopic gastric or pancreatic mucosa and can mimic appendicitis if inflamed. Persistence of the whole duct produces a fecal/vitelline fistula at the umbilicus; persistence of only the umbilical end produces an umbilical sinus; persistence of the middle segment forms a vitelline (enterocystoma) cyst; a fibrous cord remnant can cause internal herniation and strangulation of bowel loops.
- **Nonreturn of the midgut loop (omphalocele/exomphalos)**: failure of the herniated loops to return to the abdomen; the sac is covered by peritoneum, Wharton's jelly and amnion, and is associated with cardiac and neural tube defects and chromosomal anomalies (poorer prognosis).
- **Gastroschisis**: a separate abdominal wall closure defect (not a failure of gut return), usually just to the right of the umbilicus; bowel loops herniate directly into the amniotic cavity with no covering membrane; it is not associated with chromosomal anomalies and has a better prognosis.

- ▶ **Congenital umbilical hernia:** herniation through a weak, imperfectly closed umbilical ring after the gut has already returned normally; covered by peritoneum, subcutaneous tissue and skin; usually resolves spontaneously by 2–3 years.
- ▶ **Subhepatic cecum/appendix:** failure of complete cecal descent leaves the cecum below the liver, which can make appendicitis mimic cholecystitis.
- ▶ **Congenital obstruction** of midgut-derived bowel may result from atresia, stenosis, external compression by peritoneal bands or an annular pancreas, or aganglioneosis (Hirschsprung's disease affecting the hindgut-derived colon).

### High-yield exam pointers

- ▶ Midgut = distal duodenum (beyond bile duct opening) + jejunum + ileum + cecum + appendix + ascending colon + proximal 2/3 transverse colon; artery = SMA.
- ▶ SMA is both the artery of the midgut **and** the fixed axis of rotation.
- ▶ Total rotation = **270° anticlockwise**, in three stages of 90° each — not 360°.
- ▶ 1st 90° occurs during physiological umbilical herniation (6th week, outside abdomen); the remaining 180° occurs during return to the abdomen (from the 10th week).
- ▶ Physiological umbilical hernia: herniation at 6th week, return begins 10th week, complete by ~12th week (end of 3rd month).
- ▶ Prearterial segment → duodenum (distal part), jejunum, most of ileum; postarterial segment → terminal ileum, cecum, appendix, ascending colon, right 2/3 transverse colon.
- ▶ Vitellointestinal duct persistence → Meckel's diverticulum (rule of 2s) and related sinus/fistula/cyst anomalies.
- ▶ Nonrotation, incomplete rotation and reversed rotation all predispose to midgut volvulus.
- ▶ Omphalocele (covered by amnion, gut-return failure) must be distinguished from gastroschisis (uncovered, body-wall defect) and congenital umbilical hernia (skin-covered, weak umbilical ring).

### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; Gray's Anatomy (Standring) 41e.



## Rotation of the Midgut and Anomalies of Rotation

Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The midgut is the segment of the primitive gut tube extending from just caudal to the developing liver bud (the future site of entry of the bile duct into the duodenum) to the junction of the right two-thirds and left one-third of the transverse colon; it is supplied throughout by the **superior mesenteric artery (SMA)**. Because the growing midgut loop temporarily outstrips the capacity of the embryonic abdomen, it herniates into the umbilical cord in the 6th week and undergoes a programmed **270° counter-clockwise rotation** around the axis of the SMA before returning to the abdomen. Errors at any stage of this rotation-and-fixation sequence produce the clinically important group of **malrotation anomalies**, several of which present as neonatal surgical emergencies (bilious vomiting, volvulus).

### Extent and derivatives of the midgut

- ▶ **Cranial (prearterial) limb**: distal duodenum (post-ampullary), jejunum, ileum.
- ▶ **Caudal (postarterial) limb**: caecum, appendix, ascending colon, proximal two-thirds of transverse colon.
- ▶ The **primary intestinal loop** has a proximal (prearterial) and distal (postarterial) segment joined at its apex by the **vitelline (yolk) duct**; the caecal bud appears on the postarterial limb in the 6th week.
- ▶ The whole loop rotates around a fixed axis — the **superior mesenteric artery** — which explains why the definitive relations of the gut to the SMA are the key to understanding every anomaly of rotation.

### Physiological (umbilical) herniation

- ▶ During the **6th week**, rapid elongation of the loop (especially the cranial limb) and the disproportionately large liver make the abdominal cavity too small to contain the intestines.
- ▶ The midgut loop herniates into the extra-embryonic coelom within the **umbilical cord** — physiological umbilical herniation.
- ▶ While herniated, the small-intestinal (prearterial) loop elongates greatly and coils; the large-intestinal (postarterial) loop elongates but does not coil.
- ▶ The **first 90° of rotation occurs during this herniated phase**.

### Stages of rotation of the midgut loop

Viewed from the front, the total rotation is **270° anticlockwise**, classically described in three 90° stages:

| Stage     | Timing                       | Event                                                                                | Resulting position                                                                                     |
|-----------|------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 1st stage | During herniation (6th week) | Loop, initially in the sagittal plane, rotates 90° anticlockwise around the SMA axis | Prearterial (small-gut) segment moves to the right; postarterial (large-gut) segment moves to the left |

| Stage                  | Timing                      | Event                                                                                                                                | Resulting position                                                                                                                                              |
|------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2nd stage              | Start of return, ~10th week | Prearterial segment (now coiled jejunum/ileum) re-enters first and rotates a further 90° anticlockwise as it slides into the abdomen | Jejunum-ileal coils pass <b>behind</b> the SMA and occupy the left and posterior part of the abdomen; caecum still extra-abdominal, in the right upper quadrant |
| 3rd stage (retraction) | Later in the 10th week      | Postarterial segment (caecal bud, ascending & transverse colon) returns last, rotating the final 90° anticlockwise                   | Transverse colon comes to lie <b>anterior</b> to the SMA; caecum descends progressively into the right iliac fossa                                              |

- Net result: **jejunum mainly left, ileum mainly right** of the midline; **duodenum** hooks behind the SMA; **transverse colon** crosses in front of it; **caecum and appendix** finally occupy the right iliac fossa.
- The **duodenum, ascending colon, descending colon** and rectum become secondarily retroperitoneal by fusion of their mesenteries with the posterior parietal peritoneum.

□ Fig 14.13 — *Herniation and Rotation of the Intestine (A, B) At the end of the* (Larsen — *Human Embryology* — 6e, p.868)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the primary intestinal loop as a loop straddling the SMA (drawn as a vertical axis) in three panels, labelling:

- **Superior mesenteric artery** (central vertical axis in every panel)
- **Prearterial (cranial) limb** — future jejunum/ileum
- **Postarterial (caudal) limb** — future caecum, ascending colon, proximal 2/3 transverse colon
- **Vitelline duct** at the apex of the loop
- **Caecal bud** on the postarterial limb
- Arrows showing the direction of rotation (anticlockwise) at each of the 3 stages
- Final panel: duodenum behind SMA, transverse colon in front of SMA, caecum in right iliac fossa

### Return of the herniated loops and final disposition

- Causes of return (10th week): regression of the mesonephros, reduced relative growth of the liver, and enlargement of the abdominal cavity.
- **Proximal jejunum** is the first part to re-enter and settles on the **left**; progressively later loops settle further to the **right**.
- The **caecal bud** is the **last** structure to return; it lies transiently in the right upper quadrant below the liver, then **descends into the right iliac fossa**, carrying the ascending colon and hepatic flexure to the right side.

- ▶ The distal, narrow part of the caecal bud forms the **vermiform appendix**; because it develops during descent of the caecum, its final position is frequently **retrocaecal/retrocolic** (in about 50% of cases).
- ▶ After rotation is complete, the **suspensory ligament of the duodenum (ligament of Treitz)** normally lies to the left of the L1/L2 vertebral body — its position is used radiologically to judge normal versus malrotated gut.

### Classification of anomalies of rotation

Malrotation may result in twisting of the gut (**volvulus**) with compromise of its blood supply because the SMA-dependent midgut then hangs from an abnormally narrow mesenteric pedicle.

| Anomaly                                                             | Defect in rotation                                                        | Resulting anatomy                                                                                                                                                   |
|---------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-rotation (left-sided colon)                                     | Only the first 90° occurs; the remaining 180° fails                       | Small intestine occupies the <b>right</b> half, large intestine (colon and caecum) the <b>left</b> half of the abdomen; caecum lies near the midline                |
| Malrotation / incomplete rotation (subhepatic or subpyloric caecum) | Rotation stops short of the full 270°                                     | Caecum remains high — subhepatic or subpyloric; more common in males (~6% of fetuses); prone to <b>Ladd's band</b> formation and volvulus                           |
| Reversed rotation                                                   | Loop rotates 90° <b>clockwise</b> instead of anticlockwise                | Transverse colon passes <b>behind</b> the SMA, duodenum lies <b>anterior</b> to it; transverse colon may be compressed/obstructed by the artery                     |
| Mixed rotation                                                      | Cranial and caudal limbs of the loop rotate independently/uncoordinatedly | Caecum comes to lie close to the duodenojejunal flexure, often just inferior to the pylorus, with a very short mesenteric attachment — high risk of midgut volvulus |

□ Fig 14.17 — Non-Rotation of the Gut (Also Called Left-Sided Colon) Arrows (Larsen — Human Embryology — 6e, p.874)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw four small schematic panels (stomach, duodenum, SMA axis, caecum/colon in each), labelling:

- ▶ **Panel A – Non-rotation:** small intestine on the right, colon + caecum on the left
- ▶ **Panel B – Malrotation/subhepatic caecum:** caecum fixed high under the liver, **Ladd's bands** crossing the duodenum
- ▶ **Panel C – Reversed rotation:** transverse colon **behind** SMA, duodenum **in front of** SMA
- ▶ **Panel D – Mixed rotation:** caecum just below the pylorus, narrow mesenteric pedicle → **volvulus**

**Related anomalies of fixation and return**

- ▶ **Ladd's bands** — abnormal peritoneal bands that fix a high (subhepatic) caecum to the posterolateral abdominal wall, crossing and compressing the second/third part of the duodenum → duodenal obstruction; classically dissected in **Ladd's procedure**.
- ▶ **Midgut volvulus** — twisting of the small gut around the narrow SMA-containing mesenteric stalk when fixation is incomplete; can infarct the entire SMA territory.
- ▶ **Mobile (undescended) caecum** — incomplete fixation of the ascending colon (~10% of individuals); predisposes to caecal volvulus and creates confusing appendix positions.
- ▶ **Internal hernia** — small intestine passes into the mesentery of the midgut loop during return, forming a hernial sac behind the peritoneum; usually asymptomatic, found incidentally.
- ▶ **Subhepatic/high-riding appendix** — consequence of arrested caecal descent; complicates the clinical diagnosis of appendicitis.
- ▶ **Failure of return of the herniated loops (exomphalos/omphalocele)** — loops remain outside the abdomen at the umbilicus, covered by peritoneum internally and amnion externally; must be distinguished from **gastroschisis**, a separate para-umbilical body-wall defect (not a rotation anomaly) in which uncovered bowel protrudes lateral to a normal umbilical cord.
- ▶ **Remnants of the vitelline duct** (Meckel's diverticulum, vitelline cyst, vitelline fistula/ligament) commonly co-exist with rotational anomalies and may themselves cause volvulus around a persistent fibrous band.

**Applied / Clinical anatomy**

- ▶ **Classical presentation:** bilious vomiting in the first days of life, or recurrent abdominal pain with bilious vomiting in an older infant/child — a surgical emergency because of the risk of midgut volvulus and gut infarction.
- ▶ **Imaging:** barium follow-through shows an abnormally placed duodenojejunal flexure (ligament of Treitz not to the left of the upper lumbar spine) and an "S-shaped" duodenum; ultrasound may show inversion of the normal relationship of the superior mesenteric vein (normally to the right of the artery) in volvulus, though normally related vessels do not exclude malrotation obstructed by Ladd's bands alone.



- ▶ **Ladd's procedure:** division of Ladd's bands, counter-clockwise reduction of any volvulus, broadening of the narrow mesenteric base (placing small bowel on the right and colon on the left) to reduce recurrence, and incidental appendectomy (since the appendix's position will be atypical after the repair).
- ▶ **Surgical relevance of caecal position:** a subhepatic or mobile caecum alters the site of the appendix and can mislead the diagnosis/approach to appendicitis.
- ▶ **CT/USG in adults:** incidental nonrotation may be discovered in adults presenting with chronic abdominal pain, showing the entire large intestine on the left and small bowel on the right.

### High-yield exam pointers

- ▶ Midgut = distal duodenum to junction of right 2/3 and left 1/3 of transverse colon; supplied by the SMA, the fixed axis of rotation.
- ▶ Physiological umbilical herniation occurs in the **6th week**; return to the abdomen begins in the **10th week**.
- ▶ Total rotation = **270° anticlockwise**, in **three stages of 90° each** — 1st during herniation, 2nd and 3rd during return.
- ▶ Final disposition: duodenum behind SMA, transverse colon in front of SMA, caecum in the right iliac fossa.
- ▶ Ligament of Treitz normally lies left of L1/L2 — displaced in malrotation.
- ▶ Four classical anomalies: **non-rotation (90° only)**, **malrotation/subhepatic caecum (incomplete 270°)**, **reversed rotation (90° clockwise)**, **mixed rotation** (uncoordinated limb rotation).
- ▶ **Ladd's bands** cause duodenal obstruction; **midgut volvulus** is the dangerous complication of a narrow mesenteric pedicle.
- ▶ Distinguish exomphalos (failure of return, covered by amnion+peritoneum, midline) from gastroschisis (lateral body-wall defect, uncovered bowel, not a rotation anomaly).
- ▶ Appendix position (retrocaecal in ~50%) and subhepatic/mobile caecum are direct consequences of the descent phase of rotation.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Moore The Developing Human 9e; Sontakke Textbook of Human Embryology; Brijesh Kumar Embryology Text & Atlas; Gray's Anatomy (Standring) 41e.



## Describe the rotation of the mid gut loop along with congenital malformations

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The midgut is the segment of the primitive gut tube extending from the entry of the bile duct into the duodenum to the junction of the proximal two-thirds and distal one-third of the transverse colon; it is

supplied throughout by the **superior mesenteric artery (SMA)**, which also forms the fixed axis around which the developing gut rotates. Because the midgut elongates far faster than the abdominal cavity can enlarge — a cavity further crowded by the disproportionately large liver and mesonephros — the primary intestinal loop is forced to herniate physiologically into the umbilical cord in the 6th week. Between the 6th and 12th weeks it undergoes a total **270° counter-clockwise rotation** around the SMA axis while it herniates, elongates, and then returns to and fixes within the abdominal cavity. Errors at any point of this rotation-and-fixation sequence produce a well-defined family of congenital malformations — nonrotation, malrotation, reversed rotation, mixed rotation and midgut volvulus — together with related ventral-wall and vitelline-duct anomalies such as omphalocele and Meckel's diverticulum.

## 1. Extent and Derivatives of the Midgut

| Feature                     | Detail                                                                                                                            |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Proximal limit              | Opening of the bile duct into the second part of the duodenum                                                                     |
| Distal limit                | Junction of proximal two-thirds and distal one-third of the transverse colon                                                      |
| Artery of the midgut        | Superior mesenteric artery (also the rotational axis)                                                                             |
| Derivatives                 | 3rd & 4th parts of duodenum, jejunum, ileum, caecum, vermiform appendix, ascending colon, proximal two-thirds of transverse colon |
| Communication with yolk sac | Via the vitello-intestinal (omphalomesenteric/vitelline) duct, obliterated by ~10th week                                          |

## 2. Physiological (Umbilical) Herniation — the First Phase

- ▶ The **primary intestinal loop** is first seen at stage 15 (~5th week) as a ventral bulge with a **cranial (proximal) limb** and a **caudal (distal) limb**; the vitelline duct arises from its apex.
- ▶ A **caecal bud/swelling** appears on the caudal limb — the primordium of the caecum and appendix; the caudal limb otherwise elongates very little.
- ▶ From the 6th week the loop outgrows the abdominal cavity (crowded by the large liver and mesonephros) and herniates into the extra-embryonic coelom of the umbilical cord — **physiological umbilical herniation**.
- ▶ The cranial limb elongates massively and coils to form the future jejunum and ileum; its mesentery becomes correspondingly pleated.

### 3. Rotation of the Midgut Loop (270° Counter-Clockwise)

| Phase      | Timing                                  | Degree of rotation                                      | Key events (viewed from the front)                                                                                                                                             |
|------------|-----------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Phase I    | During herniation, 6th week             | 90° anticlockwise/counter-clockwise around the SMA axis | Cranial (small-intestinal) limb swings to the <b>right</b> ; caudal (large-intestinal) limb swings to the <b>left</b> ; transverse colon comes to lie in front of the duodenum |
| Phase II   | During return/reduction, 10th–12th week | A further 180° counter-clockwise (total 270°)           | Proximal limb (future jejunum/ileum) returns first, passing <b>posterior</b> to the SMA, and occupies the central abdomen; the caecum is the <b>last</b> part to return        |
| Net result | —                                       | 270° counter-clockwise                                  | Duodenum lies posterior to the SMA; transverse colon lies anterior to the SMA and divides the peritoneal cavity into supra- and infracolic compartments                        |

- ▶ The caecum, on returning, at first lies transiently **subhepatic** (below the right lobe of the liver); it subsequently **descends into the right iliac fossa**, dragging out the ascending colon and hepatic flexure, while its distal end narrows to form the **appendix**.
- ▶ Consequences of completed, normal rotation: (1) duodenum passes posterior to the SMA; (2) transverse colon/mesocolon lies transversely, anterior to the SMA; (3) ascending and descending colon come to lie retroperitoneally on the right and left respectively; (4) jejunum occupies mainly the left, superolateral infracolic compartment; (5) ileum, caecum and appendix occupy mainly the right, inferolateral infracolic compartment.

### 4. Retraction of the Hernia and Fixation

- ▶ Enlargement of the abdominal cavity and relative shrinkage of the liver/mesonephros allow the herniated loops to re-enter the abdomen in a fixed sequence — jejunoileal loops first, caecum last.
- ▶ As the coils of jejunum/ileum re-enter, they slide over the right side of the descending mesocolon, displacing the **descending colon to the left**.
- ▶ The mesentery of the **ascending and descending colon fuses with the parietal peritoneum** and disappears, rendering these segments secondarily **retroperitoneal**; most of the **duodenal mesentery is likewise absorbed**, so the duodenum (except its first part) and the head of the pancreas become retroperitoneal.

- The jejunum and ileum retain a free mesentery whose root runs obliquely from the duodenojejunal flexure to the ileocaecal junction.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the classic three-panel scheme of midgut rotation: (1) the primary intestinal loop with its **cranial limb** and **caudal limb** straddling the SMA axis, with the **vitelline duct** at the apex, before rotation; (2) the loop after **90° counter-clockwise rotation** during physiological herniation into the **umbilical coelom**, labelling the cranial limb now to the right and the caecal bud/caudal limb to the left; (3) the loop after the further **180° rotation** during return to the abdomen, labelling the final positions of duodenum (posterior to SMA), jejunum (left, superolateral), ileum/caecum/appendix (right, inferolateral), transverse colon (anterior to SMA), and ascending/descending colon (retroperitoneal). Add direction arrows for each rotation step.

□ Fig 15.25 — A. Primary intestinal loop before rotation (lateral view). The superior mesenteric artery forms the axis of the loop. B. Primary intestinal loop after 90° counterclockwise rotation. (Langman's Medical Embryology — Sadler — 14e, p.265)

## 5. Congenital Malformations of Midgut Rotation

| Anomaly                           | Defect in the 270° rotation                                                   | Anatomical/clinical result                                                                                                                                                                                                                                                                                              |
|-----------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nonrotation (left-sided colon)    | Only the first 90° completes; the remaining 180° during return does not occur | Small intestine occupies the right half, entire large intestine (colon + caecum) the left half of the abdomen                                                                                                                                                                                                           |
| Malrotation (incomplete rotation) | Rotation arrests short of full 270°                                           | Caecum ends up <b>subhepatic or subpyloric</b> , fixed to the posterolateral wall by peritoneal <b>Ladd's bands</b> crossing over the duodenum → duodenal obstruction; only the duodenum and proximal colon are fixed to the posterior wall, so the small intestine hangs on a narrow SMA-containing mesenteric pedicle |
| Mixed rotation                    | Partial/combined derangement                                                  | Caecum comes to lie just inferior to the pylorus                                                                                                                                                                                                                                                                        |
| Reversed rotation                 | Loop rotates 90° <b>clockwise</b> instead of counter-clockwise                | Duodenum lies <b>anterior</b> to the SMA and transverse colon; transverse colon lies <b>posterior</b> to the SMA/duodenum and may be compressed by it                                                                                                                                                                   |
| Midgut volvulus                   | Consequence of the narrow-pedicle malrotation above                           | Twisting of the small bowel around its SMA-containing stalk → vascular compromise, infarction and gangrene                                                                                                                                                                                                              |

| Anomaly                                   | Defect in the 270° rotation                                    | Anatomical/clinical result                                                                         |
|-------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Internal (retrocolic/paraduodenal) hernia | Failure of fixation of the ascending or descending mesocolon   | A persistently mobile colon, or a retrocolic pocket, may entrap loops of small intestine behind it |
| Subhepatic caecum/appendix                | Caecum fails to descend from its transient subhepatic position | Caecum and appendix remain adherent to the inferior surface of the liver                           |

## 6. Malformations of Herniation, Ventral Wall and the Vitelline Duct

- **Omphalocele (exomphalos):** failure of the herniated midgut loop to return to the abdominal cavity between the 6th and 10th weeks; herniated viscera (intestine, and often liver, stomach, spleen) are covered internally by peritoneum and externally by amnion. High mortality (~25%) with strong association with cardiac anomalies (~50%), neural tube defects (~40%) and chromosomal abnormalities (~15% of live births).
- **Gastroschisis** (differential of omphalocele): a para-umbilical (usually right-sided) full-thickness body-wall defect, thought to follow periumbilical ischaemia/vascular compromise; viscera protrude **uncovered** by peritoneum or amnion directly into the amniotic cavity; unlike omphalocele it is *not* associated with chromosomal defects and carries a good prognosis.
- **Congenital umbilical hernia:** occurs *after* the midgut has already returned normally to the abdomen, through a persistently weak/imperfectly closed umbilical ring; unlike omphalocele the protruding bowel is covered by skin and subcutaneous tissue, and most resolve spontaneously.
- **Meckel's (ileal) diverticulum and vitelline-duct remnants:** incomplete obliteration of the vitello-intestinal duct leaves an outpouching (~2% of the population, ~2–5 cm long) on the antimesenteric border of the ileum, roughly 40–60 cm proximal to the ileocaecal junction; variants include a fibrous **vitelline ligament**, a **vitelline (entero-) cyst**, and a patent **vitelline fistula** discharging at the umbilicus — all of which can twist around a persistent fibrous band and cause volvulus/obstruction.

□ Fig 61.17 — A, A neonatal exomphalos. B, A persistent umbilical hernia in a child. (Gray's Anatomy — Standring — 41e, p.1502)

## Applied / Clinical anatomy

- Infants with malrotation classically present with **bilious vomiting**; midgut volvulus is a **surgical emergency** because SMA compromise leads rapidly to bowel infarction.
- Radiologically, the **duodenojejunal flexure (ligament of Treitz)** should lie to the left of the upper lumbar spine at the level of the pylorus on a barium study — any other position suggests malrotation; a barium/contrast study of a child in this scenario is the diagnostic figure shown above.
- On ultrasound, the superior mesenteric **vein** should lie to the right of the SMA; inversion of this relationship (the classic "whirlpool" appearance on Doppler as the mesentery twists) supports volvulus, though malrotation can occasionally occur with a normally related vessel pair.

- ▶ **Ladd's bands** (peritoneal bands fixing a malpositioned caecum to the right posterolateral wall) compress the second/third part of the duodenum and are divided surgically in **Ladd's procedure**, which also widens the mesenteric base to reduce recurrence of volvulus.
- ▶ Variable descent of the caecum explains the common surgical finding of a **retrocaecal or retrocolic appendix** (~50% of cases) and, less commonly, a subhepatic caecum/appendix mimicking cholecystitis.
- ▶ Retroperitonealization of the ascending/descending colon and most of the duodenum (secondary retroperitoneal viscera) is of direct surgical relevance in mobilising the colon and in the extent of the pancreatoduodenal (Kocher) manoeuvre.

### High-yield exam pointers

- ▶ Midgut = duodenum distal to the bile duct opening → proximal two-thirds of transverse colon; artery and rotational axis = SMA.
- ▶ Physiological umbilical herniation begins in the **6th week**; return begins in the **10th week**.
- ▶ Total rotation = **270° counter-clockwise** = 90° during herniation + a further 180° during return.
- ▶ Caecum is the **last** structure to re-enter the abdomen; it is transiently subhepatic before descending to the right iliac fossa.
- ▶ **Nonrotation** = only 90° complete (left-sided colon); **malrotation** = incomplete <270° with subhepatic/subpyloric caecum and Ladd's bands; **reversed rotation** = 90° clockwise (duodenum anterior to SMA); **mixed rotation** = caecum below the pylorus.
- ▶ Malrotation + narrow mesenteric pedicle → **midgut volvulus** → SMA compromise → gangrene; presents with bilious vomiting.
- ▶ **Omphalocele** = failure of return, covered by peritoneum + amnion, high association with cardiac/NTD/chromosomal anomalies; **gastroschisis** = uncovered, para-umbilical, no chromosomal association; **umbilical hernia** = post-return herniation, covered by skin.
- ▶ **Meckel's diverticulum** = persistent vitelline duct remnant on the antimesenteric border of the ileum (~2%, ~2–5 cm, ~40–60 cm from ileocaecal valve) — remember its variants (ligament, cyst, fistula).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Moore, Clinically Oriented Anatomy 9e; Larsen's Human Embryology 6e; Brijesh Kumar, Embryology Text & Atlas.



## Development of extrahepatic Biliary apparatus

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** The extrahepatic biliary apparatus — right and left hepatic ducts, common hepatic duct, cystic duct, gallbladder and bile duct (choledochus) — is wholly **endodermal** in origin. All of it arises from the **hepatic diverticulum (liver bud)**, a single outgrowth of the foregut endoderm that also gives rise to the liver parenchyma and the intrahepatic biliary tree. Understanding its development explains both the adult relations of the biliary passages and the common congenital anomalies (gallbladder shape/position variants, duct atresia, choledochal cyst) that are clinically important.

### Origin of the hepatic diverticulum (liver bud)

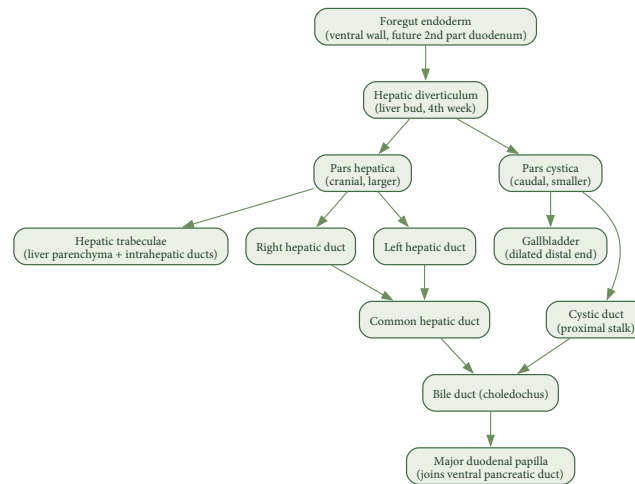
- ▶ In the **fourth week of intrauterine life** (proliferation begins from the middle of the third week), a rapidly proliferating **endodermal outgrowth** — the hepatic diverticulum (liver bud) — arises from the **ventral wall of the terminal part of the foregut**, the region that will become the **upper half of the second part of the duodenum**.
- ▶ The bud grows **ventrally and cranially** into the **ventral mesogastrium**, and through it penetrates the **septum transversum** (the unsplit mesoderm between the pericardial cavity and the yolk-sac stalk).
- ▶ Hepatic endoderm is induced to proliferate by adjacent **cardiac mesenchyme**; as the heart and foregut separate, this mesenchyme becomes the septum transversum.
- ▶ The diverticulum has two parts from the outset: a larger **cranial part** and a smaller **caudal part** — classically named, respectively, the **pars hepatica** and the **pars cystica**.

### Subdivision and fate-mapping of the hepatic diverticulum

The **pars hepatica** (cranial, larger) forms the liver and its intrahepatic/main extrahepatic ducts; the **pars cystica** (caudal, smaller) forms the gallbladder and cystic duct; the narrow connecting stalk between the diverticulum and the duodenum becomes the bile duct.

| Embryonic part                                                                                              | Adult derivative                                                                                                    |
|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Pars hepatica — right and left divisions (terminal parts, penetrating septum transversum)                   | Right and left hepatic ducts; hepatic trabeculae → liver parenchyma (hepatocytes) and intrahepatic biliary passages |
| Pars hepatica — undivided proximal segment (between the right/left division and the origin of pars cystica) | Common hepatic duct                                                                                                 |
| Pars cystica — dilated distal end                                                                           | Gallbladder                                                                                                         |
| Pars cystica — proximal stalk                                                                               | Cystic duct                                                                                                         |
| Narrow connecting stalk between diverticulum and duodenum, distal to the origin of pars cystica             | Bile duct (common bile duct, choledochus)                                                                           |
| Septum transversum mesenchyme surrounding the diverticulum                                                  | Kupffer cells, hematopoietic cells, connective tissue, fibrous (Glisson's) capsule                                  |
| Vitelline and umbilical veins, broken up within the septum transversum                                      | Hepatic sinusoids; portal and hepatic veins                                                                         |





Development of extrahepatic Biliary apparatus

□ Fig 15.1 — Development of the liver and gall bladder. The liver develops in ventr (Sontakke — Textbook of Human Embryology, p.150)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce a simple lateral schematic of the foregut at the level of the hepatic diverticulum, labelling exactly:

- ▶ Right hepatic bud and Left hepatic bud (terminal divisions of pars hepatica)
- ▶ Developing liver
- ▶ Cystic bud (pars cystica → gallbladder primordium)
- ▶ Stomach
- ▶ Dorsal pancreatic bud
- ▶ Ventral pancreatic bud
- ▶ Duodenum

Arrows should show the hepatic bud growing cranially into the septum transversum/ventral mesogastrium, and the cystic bud and ventral pancreatic bud both opening close together into the duodenum.

### Positional changes and union with the pancreatic duct system

- ▶ The bile duct initially opens on the ventral aspect of the developing duodenum.
- ▶ Owing to differential growth of the duodenal wall and rotation of the duodenal (stomach) loop, the opening progressively shifts to the dorsomedial aspect of the duodenum, migrating together with the ventral pancreatic bud.
- ▶ The ventral pancreatic duct and the bile duct come to share a common opening in the duodenum; as the pancreatic ducts fuse, this becomes the major duodenal papilla (bile duct opens here together with the main pancreatic duct; the accessory pancreatic duct opens separately at the minor duodenal papilla, about 2 cm proximal).
- ▶ Clinically, this explains why the bile duct lies posterior (dorsal) to the first part of the duodenum and the head of the pancreas in the adult.

## Molecular regulation of biliary induction

- ▶ Hepatic specification requires **fibroblast growth factor-2 (FGF2)** from cardiac mesoderm and **bone morphogenetic proteins (BMPs)** from septum-transversum mesoderm; these relieve inhibition of hepatic genes otherwise imposed by the notochord and non-cardiac mesoderm/ectoderm, "unmasking" the hepatic field.
- ▶ Once induced, liver-field cells differentiate along **hepatocyte or biliary (cholangiocyte)** lineages, a choice regulated in part by **hepatocyte nuclear transcription factors HNF3 and HNF4**.
- ▶ Intrahepatic duct patterning follows the **portal vein radicles**: peri-portal mesenchyme induces adjacent hepatoblasts to form a sleeve of cells, the **ductal plate**; ductal-plate cells (cholangiocytes) delineate a lumen, and development proceeds **from the hilum toward the periphery**. Angiogenic mesenchyme subsequently recruits the **hepatic artery** (from about 10 weeks), so the portal vein induces duct formation first, artery formation second — the basis of the mature **portal triad**.
- ▶ The **right and left hepatic ducts** are recognisable arising from the cranial end of the common hepatic duct from **12 weeks' gestation**.

## Recanalization of the biliary passages

- ▶ Classically (older embryology texts), the extrahepatic biliary apparatus is transiently **occluded by proliferating epithelial cells** (a "solid stage") and later **recanalized by vacuolation** consequent on degeneration of these cells; **failure of recanalization** is the traditional explanation for extrahepatic biliary atresia.
- ▶ Gray's Anatomy (41e) notes a revised view: developing bile ducts are now considered to **remain patent throughout development**, and the older "solid-stage" concept has been **refuted**; the cause of extrahepatic atresia is unclear and may instead involve an inflammatory process or a **ductal-plate malformation**. Candidates should know both accounts, as older-style questions still test the classical "solid stage → recanalization" description.

## Applied / Clinical anatomy

□ Fig 15.3 — Developmental anomalies of gallbladder (Sontakke — Textbook of Human Embryology, p.153)

| Category | Anomaly                            | Basis                                                                                    |
|----------|------------------------------------|------------------------------------------------------------------------------------------|
| Shape    | <b>Phrygian cap</b>                | Fundus folded on itself, cap-like                                                        |
| Shape    | <b>Hartmann's pouch</b>            | Infundibular wall pouches downward, may adhere to cystic/bile duct                       |
| Position | <b>Ectopic/transverse position</b> | Under right or left lobe of liver                                                        |
| Position | <b>Floating gallbladder</b>        | Completely peritonealized, attached only by a peritoneal fold or free — prone to torsion |
| Position | <b>Intrahepatic gallbladder</b>    | Embedded within liver substance                                                          |
| Number   | <b>Duplication</b>                 | Partial or complete septation of the lumen, may extend into the cystic duct              |

| Category           | Anomaly                                 | Basis                                                                                                                                                                                                                                                                                            |
|--------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number             | Agenesis                                | Absence of gallbladder                                                                                                                                                                                                                                                                           |
| Other              | Sessile gallbladder                     | Opens directly into the bile duct instead of via a cystic duct                                                                                                                                                                                                                                   |
| Other              | Diverticula                             | May arise from any part of the organ                                                                                                                                                                                                                                                             |
| Extrahepatic ducts | Abnormal length / abnormal termination  | Cystic duct may join the left side of the common hepatic duct (in front or behind it), end in the right hepatic duct, or pass anterior to the duodenum before joining                                                                                                                            |
| Extrahepatic ducts | Atresia                                 | Failure of recanalization of part/whole of the duct system; <b>extrahepatic biliary atresia occurs in ~1/15,000 live births</b> , often with other anomalies (e.g. situs inversus); ~15–20% have a patent proximal segment and a correctable defect, the remainder require liver transplantation |
| Extrahepatic ducts | Duplication / accessory ducts           | Partial or complete duplication of bile duct ± hepatic ducts; accessory ducts from the right lobe may drain directly into the right hepatic, cystic or bile duct                                                                                                                                 |
| Duct wall          | Choledochal cyst                        | Cystic dilatation of an area of weakness in the bile-duct wall, may hold up to ~2 L bile and compress the duct, producing obstructive jaundice                                                                                                                                                   |
| Intrahepatic       | Intrahepatic biliary atresia/hypoplasia | Rare (~1/100,000 live births), may follow fetal infection; usually runs a benign course, occasionally lethal                                                                                                                                                                                     |
| Intrahepatic       | Polycystic liver                        | Failure of union between intrahepatic biliary canaliculi/ductules and the extrahepatic ducts → intrahepatic cysts, often with renal/pancreatic cysts                                                                                                                                             |

- Surgically, awareness of cystic-duct/hepatic-duct variant anatomy is essential during laparoscopic cholecystectomy to avoid bile-duct injury ("Calot's triangle" dissection).

## High-yield exam pointers

- ▶ Entire extrahepatic biliary apparatus is **endodermal**, derived from the **caudal (pars cystica) and connecting-stalk parts** of the hepatic diverticulum, which buds from the ventral foregut wall (future 2nd part of duodenum) in the **4th week**.
- ▶ Diverticulum divides into **pars hepatica** (cranial → liver + hepatic ducts) and **pars cystica** (caudal → gallbladder + cystic duct); the connecting stalk to the duodenum → **bile duct**.
- ▶ **Right + left hepatic ducts → common hepatic duct; common hepatic duct + cystic duct → bile duct (choledochus)**.
- ▶ Right and left hepatic ducts are distinguishable from the common hepatic duct by **12 weeks' gestation**.
- ▶ **Bile secretion begins at ~12 weeks**, giving meconium its green colour.
- ▶ Positional shift: bile-duct opening migrates **ventral → dorsomedial**, finally sharing the **major duodenal papilla** with the ventral pancreatic duct.
- ▶ **Extrahepatic biliary atresia (~1/15,000 births)** — classically a recanalization failure; Gray's 41e now disputes the "solid stage" model.
- ▶ Common named anomalies to recall: **Phrygian cap, Hartmann's pouch, floating/intrahepatic gallbladder, sessile gallbladder, choledochal cyst**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology (figures).



## Development of Pancreas

Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy

### Definition / Introduction

The pancreas is a mixed exocrine–endocrine retroperitoneal gland that develops from **two endodermal outgrowths of the caudal foregut (duodenal) endoderm** — a **dorsal** and a **ventral pancreatic bud** — which appear in the 4th week of intra-uterine life. Differential growth of the duodenal wall, together with rotation of the stomach and duodenum, carries the ventral bud dorsally to fuse with the dorsal bud in the 5th–6th week, giving rise to the definitive gland and its duct system. Faults in bud formation, migration or fusion underlie the clinically important anomalies — annular pancreas, pancreas divisum and ectopic pancreatic tissue.

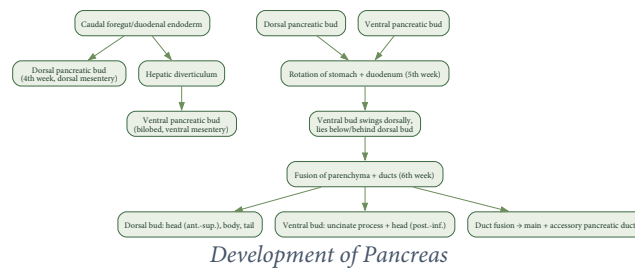
### 1. Origin of the two pancreatic buds

| Feature        | Dorsal pancreatic bud                                                                              | Ventral pancreatic bud                                                                             |
|----------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Site of origin | Endoderm of the <b>dorsal</b> wall of the duodenum, opposite (cranial to) the hepatic diverticulum | Endoderm at the base of the <b>hepatic diverticulum</b> , close to the primordium of the bile duct |

| Feature            | Dorsal pancreatic bud                  | Ventral pancreatic bud                                                                            |
|--------------------|----------------------------------------|---------------------------------------------------------------------------------------------------|
| Time of appearance | Earlier — about day 26 (4th week)      | Slightly later, late 4th–early 5th week                                                           |
| Mesentery entered  | Dorsal mesentery / dorsal mesogastrium | Ventral mesentery, alongside the bile duct                                                        |
| Relative size      | Larger — forms the bulk of the gland   | Smaller; frequently <b>bilobed</b> (right + left components) — the substrate for annular pancreas |

## 2. Rotation and fusion of the buds

- ▶ As the stomach rotates and the duodenum forms a C-shaped loop and rotates to the right, differential growth of the duodenal wall carries the **ventral bud, together with the bile duct, dorsally and to the right**.
- ▶ The ventral bud is swept posterior to the duodenum (5th week) and comes to lie **below and behind the dorsal bud**.
- ▶ By the **6th week** the two buds meet: their parenchyma fuses first, followed by anastomosis of their duct systems.



## 3. Fate of the two buds — adult derivatives

| Bud         | Adult part formed                                                                                                                                                      |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dorsal bud  | Antero-superior part of the head, the neck, body and tail — the <b>bulk</b> of the gland                                                                               |
| Ventral bud | Postero-inferior part of the head and the <b>uncinate process</b> (three-dimensional reconstructions show the dorsal bud also contributes part of the uncinat process) |

## 4. Development of the duct system

- ▶ The distal part of the dorsal duct anastomoses with the **entire ventral duct** to form the definitive **main pancreatic duct (of Wirsung)**, which opens with the bile duct at the **major duodenal papilla**.
- ▶ The **proximal part of the dorsal duct** usually regresses to a fine communicating channel, or persists as the **accessory pancreatic duct (of Santorini)**, opening independently at the **minor duodenal papilla** (~2 cm cranial to the major papilla).
- ▶ In roughly **9–10% of individuals** the two duct systems fail to anastomose and drain independently — the embryological basis of **pancreas divisum**.

□ Fig 15.4 — Successive stages of development of pancreas. Pancreas develops by fus (Sontakke — Textbook of Human Embryology, p.154)

## 5. Histogenesis — exocrine and endocrine differentiation

- ▶ **Pancreatic mesenchyme** (splanchnopleuric coelomic mesenchyme around the dorsal bud; septum-transversum-derived mesenchyme around the ventral bud) induces branching of the endodermal epithelium and forms the connective-tissue stroma, smooth muscle and, through invading angiogenic mesenchyme, blood and lymphatic vessels.
- ▶ The branching endodermal duct tree forms **acinar (exocrine) cells** by proliferation/reorganisation of cells at the tubule tips; zymogen granules and acinar markers are detectable at **12–16 weeks**, but exocrine secretion remains functionally quiescent until after birth.
- ▶ **Endocrine cells** delaminate from the duct epithelium and aggregate as clusters — the **Islets of Langerhans** — within the surrounding mesenchyme from the **3rd month** of fetal life.
- ▶ **Glucagon-secreting  $\alpha$  cells differentiate first** (~7th week; glucagon is detectable in fetal plasma by 15 weeks), followed by **insulin-secreting  $\beta$  cells** (~10th week); somatostatin-secreting  $\delta$  cells and pancreatic-polypeptide-secreting  $\gamma$  (PP) cells appear later. The **dorsal bud** gives rise mostly to  $\alpha$  cells and the **ventral bud** mostly to PP cells.

### Molecular regulation (brief):

- ▶ Notochord-derived **FGF2 + activin- $\beta$**  repress *Shh* in the dorsal foregut endoderm, thereby de-repressing **PDX1** (pancreatic and duodenal homeobox-1) and inducing the dorsal bud; retinoic acid sets the *Pdx1/Cdx* expression boundary.
- ▶ The ventral bud arises where locally **low FGF2** (from adjacent cardiogenic mesenchyme) permits *Pdx1* expression — the same signal at high concentration instead promotes hepatic fate in neighbouring endoderm.
- ▶ **PDX1** and **PTF1A** mark the common pancreatic progenitor epithelium. **Notch signalling** (via *Hes1*) suppresses *neurogenin-3* (*NGN3*) and keeps cells in the exocrine/ductal lineage; cells that escape Notch repression express *NGN3*, become endocrine progenitors, and differentiate under *NeuroD1* into hormone-secreting islet cells.
- ▶ **PAX6** alone specifies  **$\alpha$  (glucagon) cells**; **PAX4 + PAX6** together specify  **$\beta$ ,  $\delta$  and PP cells**.
- ▶ Mesenchymal **FGF10** and **ISL1** sustain bud growth and branching (knockouts give hypoplastic buds/near-absent mesenchyme); mesenchymal chemokine **SDF-1** regulates tubule branching.

## 6. Peritoneal fixation established by development

- ▶ Like the duodenum, the pancreas becomes **secondarily retroperitoneal** as its dorsal mesentery fuses with the parietal peritoneum of the posterior abdominal wall.
- ▶ The **tail** is the exception — it remains ensheathed within the two layers of the **lienorenal (splenorenal) ligament**, growing together with the spleen into the persisting free edge of the dorsal mesogastrium, reflecting the shared dorsal-mesogastrium origin of spleen and pancreatic tail.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label: stomach; hepatic diverticulum/bile duct; dorsal mesentery; **dorsal pancreatic bud** (in dorsal mesentery); **ventral pancreatic bud** (bilobed, near bile duct); direction-of-rotation arrow; duodenum (C-loop); fused pancreas — **head, uncinate process, body, tail**; **main pancreatic duct** (Wirsung); **accessory pancreatic duct** (Santorini); **major and minor duodenal papillae**.

**Applied / Clinical anatomy**

- ▶ **Annular pancreas** — a bilobed ventral bud has one lobe migrate along the normal route and the other in the reverse direction, so that a ring/collar of pancreatic tissue encircles the second (descending) part of the duodenum. Incidence  $\approx$  **1 in 12,000–15,000** births; more common in females; may coexist with **Down syndrome**, intestinal malrotation and cardiac defects. Produces duodenal obstruction  $\pm$  polyhydramnios in utero; postnatally, the "**double-bubble**" sign on plain film/ultrasound (distended stomach + proximal duodenum). Treated by surgical bypass (duodeno-duodenostomy/duodeno-jejunostomy) — the annular tissue itself is not resected, to avoid a pancreatic fistula.

□ Fig 15.7 — Formation of annular pancreas. There may be two ventral pancreatic bud (Sontakke — Textbook of Human Embryology, p.155)

- ▶ **Pancreas divisum** — failure of fusion of the dorsal and ventral duct systems; the bulk of the gland then drains through the narrow minor papilla via the accessory duct, predisposing to relative outflow obstruction and recurrent pancreatitis. The **commonest congenital ductal anomaly** of the pancreas ( $\approx$ 5–10%).
- ▶ **Ectopic (heterotopic) pancreatic tissue** — persistence of accessory endodermal outgrowths along the primitive foregut; found most often in the **stomach** (commonest site), duodenum, jejunum, Meckel diverticulum, gallbladder or spleen; may show full acinar/islet histology and rarely presents with obstruction, bleeding or malignant change.
- ▶ **Inversion of pancreatic ducts** — the embryonic, unfused arrangement persists so that the dorsal duct becomes the main drainage route via the minor papilla while the ventral duct joins the bile duct at the major papilla.
- ▶ **Accessory spleen at the tail of the pancreas** — failure of fusion of splenic buds (splenunculi) with the main splenic mass; surgically relevant during splenectomy, as a retained accessory spleen can cause relapse of haematological disease.
- ▶ **Dual arterial supply of the head** — because the developing head straddles the embryonic **foregut–midgut junction** (marked by entry of the bile duct into the duodenum), it receives both superior pancreaticoduodenal branches (coeliac trunk/foregut) and inferior pancreaticoduodenal branches (superior mesenteric artery/midgut); the body and tail (pure dorsal-bud/foregut derivatives) are supplied only by the splenic artery — relevant during pancreaticoduodenectomy.
- ▶ **Maternal diabetes mellitus** — chronic fetal hyperglycaemia causes hypertrophy/hyperplasia of fetal  $\beta$  cells with increased insulin secretion, contributing to fetal macrosomia and neonatal hypoglycaemia.
- ▶ **Duodenal atresia/stenosis** frequently coexists with (though is not caused by) annular pancreas, sharing the same "double-bubble" radiological sign.



## High-yield exam pointers

- ▶ Pancreas develops from **two** endodermal buds — **dorsal** (larger, appears first, 4th week) and **ventral** (smaller, often bifid) — both derivatives of the caudal **foregut**.
- ▶ Ventral bud rotates dorsally with the bile duct and fuses **below** the dorsal bud in the **6th week**.
- ▶ Dorsal bud → head (antero-superior), body, tail; **Ventral bud** → **uncinate process** + **postero-inferior head**.
- ▶ Main pancreatic duct (Wirsung) = distal dorsal duct + entire ventral duct → major papilla (with bile duct); accessory duct (Santorini) = proximal dorsal duct remnant → minor papilla.
- ▶ Islets of Langerhans differentiate from duct epithelium in the **3rd month**; **glucagon (α) cells precede insulin (β) cells**.
- ▶ **PDX1** is the master transcription factor of pancreatic specification; the **Notch–NGN3** axis decides endocrine vs exocrine/ductal fate.
- ▶ **Annular pancreas** = abnormal (reverse) migration of a bifid ventral bud around the duodenum → duodenal obstruction + double-bubble sign.
- ▶ **Pancreas divisum** = failure of duct fusion (~10%) — commonest pancreatic ductal anomaly, predisposes to pancreatitis.
- ▶ Only the **tail** of the pancreas lies in the lienorenal ligament with the spleen; the rest of the gland is secondarily retroperitoneal.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Moore The Developing Human 9e; IB Singh Human Embryology (CBME 2021); Sontakke Textbook of Human Embryology.



## Development of rectum and anal canal

*Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The rectum and the greater part of the anal canal are hindgut derivatives, formed by partitioning of the terminal cloaca by the **urorectal septum**. The rectum and the **upper two-thirds of the anal canal are endodermal** (hindgut) in origin, while the **lower one-third of the anal canal is ectodermal**, developing from the **proctodeum (anal pit)**. This dual embryological origin explains why the two parts of the anal canal differ in epithelium, arterial supply, venous and lymphatic drainage, and nerve supply — meeting at the **pectinate (dentate) line** — a point of major surgical and applied importance.

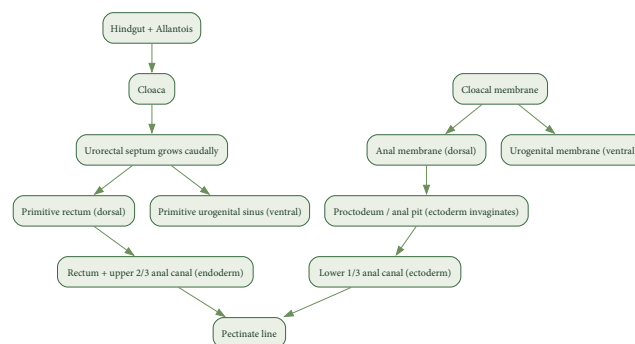
### 1. Origin: the hindgut and the cloaca

- ▶ The **hindgut** extends from the junction of the proximal two-thirds and the distal one-third of the transverse colon to the cloacal membrane; it gives rise to the descending colon, sigmoid colon, rectum, and the upper part of the anal canal.

- ▶ The most caudal (terminal) part of the hindgut, lying **caudal to the point where the allantois enters it**, is the **cloaca** — this is also termed the primitive anorectal canal region by some texts.
- ▶ The cloaca is an endoderm-lined cavity, closed caudally by the **cloacal membrane**, a bilaminar membrane formed by apposition of hindgut endoderm and overlying surface ectoderm, with no intervening mesenchyme.
- ▶ Even before septation, the cloaca shows an early subdivision into a larger **ventral part** (continuous with the allantois, the future urogenital sinus) and a narrower **dorsal part** (continuous with the hindgut proper, the future primitive rectum).

## 2. Partitioning of the cloaca by the urorectal septum

- ▶ Partitioning is effected by the **urorectal septum**, a wedge of splanchnic mesenchyme that first appears in the angle between the allantois (ventrally) and the hindgut (dorsally).
- ▶ The septum grows caudally in the coronal (frontal) plane between the two, its free edge advancing towards the cloacal membrane through successive stages (illustrated at about the 4th, 6th and 7th weeks).
- ▶ **At the end of the 7th week**, the tip of the septum fuses with the cloacal membrane, completing partition of the cloaca into:
  - a **dorsal primitive rectum** (anorectal canal) — continuous with the hindgut, and
  - a **ventral primitive urogenital sinus**.
- ▶ This fusion simultaneously divides the cloacal membrane into a **dorsal anal membrane** (overlying the primitive rectum) and a **ventral urogenital membrane** (overlying the urogenital sinus).
- ▶ The point where the septum fuses with the membrane becomes the **perineal body**, the fibromuscular node that permanently separates the anal canal from the urogenital tract in the adult perineum.
- ▶ A transient **postanal gut** — a caudal prolongation of the hindgut beyond the anal membrane — projects into the tail fold during the 4th–5th weeks and normally disappears before the end of the 5th week.
- ▶ Rupture of the cloacal (anal) membrane at the end of the 7th week creates the separate anal opening (dorsally) and urogenital opening (ventrally).



*Development of rectum and anal canal*

### 3. Development of the rectum

- ▶ The primitive rectum (dorsal cloacal compartment) differentiates into the definitive **rectum** and the **upper two-thirds of the anal canal**.
- ▶ Proximally it is continuous with the sigmoid colon; no distinct anatomical landmark separates the two until secondary peritoneal and skeletal relations mature.
- ▶ As the sacrum and coccyx develop and the pelvic cavity deepens, the rectum comes to lie against the sacrococcygeal concavity, acquiring its characteristic **anorectal (perineal) flexure** — a mechanical consequence of surrounding skeletal growth.
- ▶ Peritoneal covering matures secondarily: the **upper third** of the rectum retains ventrolateral peritoneum, the **middle third** only a ventral covering (forming the floor of the rectovesical/rectouterine pouch), while the **lower third of the rectum and the entire anal canal become extraperitoneal**.
- ▶ The mucosa differentiates from hindgut endoderm and the muscular/fibrous coats from the surrounding splanchnic mesenchyme, continuous with the rest of the colon.

### 4. Development of the anal canal: dual endodermal–ectodermal origin

- ▶ Surface ectoderm around the anal membrane proliferates and heaps up, producing a shallow depression — the **proctodeum (anal pit)** — at the bottom of which lies the anal membrane.
- ▶ At the end of the 7th week the **anal membrane ruptures**, establishing continuity between the endodermal (upper) and ectodermal (lower) parts of the anal canal and opening the hindgut to the exterior.
- ▶ The **upper two-thirds of the anal canal** is thus endodermal, derived from the primitive rectum (hindgut); the **lower one-third** is ectodermal, derived from the proctodeum.
- ▶ The junction of the two parts is represented in the adult by the **pectinate (dentate) line**, at the lower limit of the anal columns and anal valves; the epithelium changes here from simple columnar (upper part) to stratified squamous, keratinised close to the anal orifice and continuous with perianal skin.
- ▶ Because of their separate origins, the two parts differ in every point of applied importance, summarised below.

□ Fig 14.12 — Development of the anal canal. Urogenital septum divides cloaca into v (Sontakke — Textbook of Human Embryology, p.144)

| Feature         | Upper 2/3 of anal canal (endodermal)                            | Lower 1/3 of anal canal (ectodermal)                  |
|-----------------|-----------------------------------------------------------------|-------------------------------------------------------|
| Derived from    | Hindgut / primitive rectum                                      | Proctodeum (anal pit)                                 |
| Epithelium      | Columnar → transitional                                         | Stratified squamous (keratinised near anus)           |
| Arterial supply | Superior rectal artery (inferior mesenteric artery)             | Inferior rectal artery (internal pudendal artery)     |
| Venous drainage | Superior rectal vein → portal system (inferior mesenteric vein) | Inferior rectal vein → systemic (internal iliac vein) |

| Feature             | Upper 2/3 of anal canal (endodermal)                              | Lower 1/3 of anal canal (ectodermal)                              |
|---------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| Lymphatic drainage  | Inferior mesenteric (pararectal/superior rectal) nodes            | Superficial inguinal nodes                                        |
| Nerve supply        | Autonomic (inferior hypogastric plexus) — insensitive to pain     | Inferior rectal nerve (pudendal, S2–S4) — somatic, pain-sensitive |
| Junctional landmark | Pectinate line, at the lower ends of the anal columns/anal valves |                                                                   |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Longitudinal (sagittal) section through the cloacal region/developing anal canal, labelling: hindgut · allantois · cloaca · urorectal septum (with arrow showing caudal growth) · primitive rectum (dorsal) · primitive urogenital sinus (ventral) · cloacal membrane → anal membrane + urogenital membrane · perineal body · proctodeum (anal pit) · pectinate line · anal columns · **upper (endodermal) vs lower (ectodermal)** segments of the anal canal, each labelled with its artery/vein (superior rectal vs inferior rectal).

## 5. Molecular regulation of anorectal septation

- **Sonic hedgehog (Shh)**, secreted by hindgut endoderm, and **fibroblast growth factor-10 (Fgf10)** from the surrounding mesenchyme coordinate growth and fusion of the urorectal septum; disruption of Shh–Fgf signalling is implicated in anorectal birth defects.
- **HoxD** gene expression patterns the mesenchymal condensations that differentiate into the internal and external anal sphincters.
- Enteric neurons of the rectosigmoid arise from **vagal neural crest cells** that migrate craniocaudally and colonise the entire gut, under **RET proto-oncogene** signalling; failure of this colonisation produces congenital aganglionic megacolon (Hirschsprung disease), a related rectosigmoid neurocristopathy.

## Applied / Clinical anatomy

- Most **anorectal malformations** result from abnormal/incomplete growth of the urorectal septum (incomplete separation of the cloaca) or from failure of the anal membrane to rupture. Overall incidence of imperforate anus is about **1 in 5000 live births**, more common in males.

| Type           | Level (relative to puborectalis)            | Lesions                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Low anomalies  | Rectum ends <i>inferior</i> to puborectalis | Imperforate anus with an anoperineal/ectopic-anus fistula (>90% of low anomalies have an external fistula); <b>anal stenosis</b> (narrow anus/anal canal, from slight dorsal deviation of the urorectal septum); <b>membranous atresia</b> (anus in normal position but a thin epithelial-plug remnant occludes it, from failure of the plug to perforate)                                              |
| High anomalies | Rectum ends <i>superior</i> to puborectalis | <b>Anorectal agenesis with fistula</b> (commonest high anomaly) — rectovesical or rectourethral fistula in males, rectovaginal or rectovestibular fistula in females, from incomplete separation of the cloaca from the urogenital sinus; <b>rectal atresia</b> — anal canal and rectum both present but discontinuous (sometimes joined by a fibrous cord), attributed to defective local blood supply |

- Anorectal anomalies may occur as part of the VATER association (Vertebral, Anal, Tracheo-oesophageal, Renal anomalies).
- The dual blood/lymph/nerve supply across the pectinate line is of major surgical importance: **internal haemorrhoids** (above the line) are covered by mucosa, painless, and drain via the portal system (a site of porto-systemic anastomosis) to inferior mesenteric nodes; **external haemorrhoids** (below the line) are covered by skin, painful (somatic innervation), and drain to superficial inguinal nodes.
- Correspondingly, carcinoma arising **above** the pectinate line is an **adenocarcinoma** (columnar epithelium), typically painless, spreading to inferior mesenteric/para-aortic nodes; carcinoma **below** the line is a **squamous cell carcinoma**, painful, spreading to superficial inguinal nodes.
- Failure of neural-crest colonisation of the rectosigmoid (RET mutation) causes **Hirschsprung disease** — an aganglionic, non-relaxing distal bowel segment with proximal megacolon, classically presenting as delayed passage of meconium beyond 24 hours after birth.

### High-yield exam pointers

- Cloaca = terminal hindgut caudal to the allantoic attachment; endoderm-lined, closed by the bilaminar cloacal membrane.
- Urorectal septum = wedge of mesoderm that grows caudally between the allantois and hindgut and fuses with the cloacal membrane at the **end of the 7th week**.
- Cloaca divides into dorsal **primitive rectum** + ventral **primitive urogenital sinus**; cloacal membrane divides into dorsal **anal membrane** + ventral **urogenital membrane**.
- Tip of the urorectal septum forms the **perineal body**.

- ▶ **Rectum + upper 2/3 of anal canal = endoderm** (hindgut/primitive rectum); **lower 1/3 of anal canal = ectoderm** (proctodeum/anal pit).
- ▶ Anal membrane ruptures at the end of the 7th week, opening the hindgut to the exterior.
- ▶ Junction of the two parts = **pectinate line**; marks the change in epithelium, arterial supply, venous/lymphatic drainage and nerve supply.
- ▶ Imperforate anus (1:5000, ♂ > ♀) is classified as **low** (below puborectalis: anal stenosis, membranous atresia, anoperineal fistula) or **high** (above puborectalis: anorectal agenesis with recto-urethral/-vaginal/-vestibular/-vesical fistula, rectal atresia).
- ▶ Molecular regulators: **Shh/Fgf10** (septation), **HoxD** (sphincter patterning), **RET** (enteric neural-crest colonisation — Hirschsprung disease).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Sontakke, Textbook of Human Embryology; IB Singh, Human Embryology (CBME 2021); Vishram Singh, Textbook of Clinical Embryology; BD Chaurasia, Human Anatomy Vol 2 8e.



## Development of the spleen

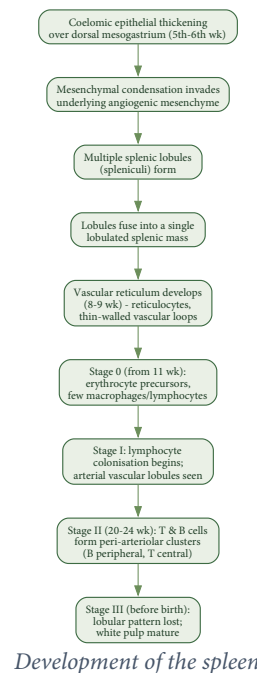
*Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The spleen is the largest lymphoid organ in the body and is unusual among the abdominal viscera in being **entirely mesodermal in origin** — unlike the liver, pancreas or gut, it has no endodermal contribution at all, even though it is described together with the alimentary system because of where it develops. It arises during the fifth–sixth week of intrauterine life as a mesenchymal condensation between the two layers of the **dorsal mesogastrium**, close to the developing stomach. Its adult shape, notched border, peritoneal ligaments and final position in the left hypochondrium are all secondary consequences of its multicentric (lobulated) origin and of the rotation of the stomach.

### 1. Site and mode of origin

- ▶ Develops from **mesenchymal cells condensed between the two layers of the dorsal mesogastrium**, near its cranial end, in close relation to the developing stomach.
- ▶ Gray's Anatomy describes the process as beginning with a **localized thickening of the coelomic epithelium** covering the dorsal mesogastrium; the proliferating epithelial cells invade the underlying angiogenic mesenchyme, which condenses and vascularises. The mature spleen is therefore of **dual origin** — a coelomic-epithelial covering plus a mesenchymal bulk (the future capsule, stroma and haemolymphoid tissue).
- ▶ Timing: **fifth week IUL** (Moore, Sontakke, IB Singh, Larsen); Gray's Anatomy (41e) states "about the sixth week" — both are acceptable in an exam answer.
- ▶ Condensation occurs **simultaneously in several adjoining foci**, which soon fuse — this multicentric (lobular) beginning is the embryological basis of the lobulated fetal spleen and of the notches seen on the adult organ.

## 2. Stages of development



- ▶ **Spleniculi (splenculi):** small mesenchymal masses/lobules of splenic tissue formed by proliferation in the 5th week.
- ▶ **Fusion:** the spleniculi fuse to form a single lobulated splenic mass, which bulges from beneath the left layer of the dorsal mesogastrium.
- ▶ **Vascularisation:** by 8–9 weeks a well-developed vascular reticulum is present, containing immature reticulocytes and numerous closely-spaced thin-walled vascular loops.
- ▶ **Lymphoid colonisation (Steiniger's four-stage scheme, from 11 weeks):** Stage 0 → erythrocyte precursors with few macrophages and fewer lymphocytes; Stage I → lymphocytes begin colonisation and arterial vascular lobules appear; Stage II → T- and B-lymphocytes form peri-arteriolar clusters, with B cells aggregating around peripheral arteriolar branches and T cells centrally; Stage III (before birth) → the lobular arrangement is no longer discernible.
- ▶ From week 17, **α-SMA-positive reticular cells** appear around arterioles and build a reticular framework by 20–23 weeks, when a **primitive white pulp** first becomes visible; by 24 weeks T- and B-cells are fully segregated, with B cells forming lymphoid follicles close to the peri-arteriolar lymphoid sheath.
- ▶ The splenic capsule is initially lined by **ciliated cuboidal cells bearing microvilli**.

## 3. Formation of the peritoneal ligaments

As the fused splenic mass enlarges and projects into the left layer of the dorsal mesogastrium, it divides that layer into an anterior and a posterior part, which become the two peritoneal ligaments of the adult spleen.



| Ligament                          | Part of dorsal mesogastrium | Extends between                                                              | Contents                                            |
|-----------------------------------|-----------------------------|------------------------------------------------------------------------------|-----------------------------------------------------|
| Gastrosplenic ligament            | Anterior (ventral) part     | Greater curvature of stomach ↔ hilum of spleen                               | Short gastric vessels, left gastro-epiploic vessels |
| Splenorenal (lienorenal) ligament | Posterior (dorsal) part     | Hilum of spleen ↔ anterior surface of left kidney / posterior abdominal wall | Splenic artery and vein, tail of pancreas           |

- ▶ The posterior layer of the dorsal mesogastrium fuses with the parietal peritoneum over the left kidney, but this fusion **stops short of the spleen itself**, so the spleen remains suspended from the posterior abdominal wall by the short splenorenal ligament.
- ▶ Its original attachment to the stomach persists unchanged as the gastrosplenic ligament.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 15.8 — *Developing spleen in dorsal mesogastrium* (Sontakke — *Textbook of Human Embryology*, p.156)

##### Sequential panels (transverse section through upper abdomen, cranial view):

- ▶ **Panel A:** Stomach; dorsal mesogastrium (left and right layers); mesenchymal splenic primordium within the left layer; posterior abdominal wall; lesser sac (omental bursa) forming to the right.
- ▶ **Panel B:** Splenic mass enlarging and bulging into the left layer of dorsal mesogastrium; division of dorsal mesogastrium into an anterior part (future gastrosplenic ligament) and a posterior part (future splenorenal/lienorenal ligament).
- ▶ **Panel C:** Posterior layer of dorsal mesogastrium fusing with parietal peritoneum over left kidney (fusion stopping short of the spleen).
- ▶ **Panel D (final position):** Spleen in the left hypochondrium; gastrosplenic ligament (short gastric vessels); splenorenal ligament (splenic artery and vein, tail of pancreas); left kidney; stomach; lesser sac bounded on the left by the spleen; splenic notches on the anterosuperior border.

## 5. Change in position and final relations

- ▶ Factors bringing the spleen to its adult position: (a) **rotation of the stomach** (~90° clockwise, viewed from below) and (b) **fusion of the posterior layer of the dorsal mesogastrium with the posterior parietal peritoneum**.
- ▶ As a consequence, the spleen is carried to the **left**, coming to lie against the left dome of the diaphragm superolaterally, and against the stomach, tail of pancreas, left kidney and splenic flexure of the colon inferomedially.
- ▶ The spleen thus forms part of the **left boundary of the lesser sac (omental bursa)**.

## 6. Histogenesis, molecular regulation and postnatal growth

- ▶ Mesoderm of the primordium differentiates into the **capsule, trabecular septa and the connective-tissue/reticular framework**; other mesenchymal cells differentiate into lymphoblasts and haemopoietic precursor cells.
- ▶ The spleen is an important **haemopoietic (chiefly erythropoietic) organ throughout fetal life**; this activity ceases at birth, but **lymphopoiesis continues into postnatal life**.
- ▶ Gene-targeting studies (Moore) show that the basic helix–loop–helix transcription factor **capsulin** and the homeobox genes **Nkx2-5, Hox11 and Bapx1** regulate spleen morphogenesis; disturbance of this laterality-related genetic programme underlies the asplenia/polysplenia syndromes described below.
- ▶ Postnatal growth: the spleen weighs about **13 g at birth, doubles** its weight in the first postnatal year, and **triples** it by the end of the third year.
- ▶ The lobulated fetal architecture normally disappears before birth, leaving one or more **notches on the anterosuperior border** as its only trace in the adult.

## Applied / Clinical anatomy

- ▶ **Accessory spleen (splenunculus/spleniculus)**: a splenic lobule that fails to fuse with the main splenic mass persists as a separate, fully functional island of splenic tissue. Found in **~10% of individuals** (Gray's Anatomy); classic sites are near the **splenic hilum**, within the **gastrosplenic** or **splenorenal (lienorenal) ligament**, the **tail of the pancreas**, along the **splenic artery**, and (rarely) in the **greater omentum** or the **left spermatic cord**.
- ▶ **Clinical importance of accessory spleens**: they must be actively searched for and removed at splenectomy for haematological disease (e.g., hereditary spherocytosis, ITP), because an overlooked accessory spleen can **hypertrophy after splenectomy** and cause recurrence of the very symptoms the operation was meant to cure.
- ▶ **Persistent lobulation**: incomplete fusion of spleniculi gives a **lobulated spleen**, seen as one or more notches on the anterosuperior border; this notch is not always present and so is **not a fully reliable landmark** for clinically identifying the spleen.
- ▶ **Agensis (asplenia) and polysplenia** are disorders of left–right patterning (laterality/isomerism): **right-sided isomerism** is characteristically associated with **asplenia** (or a hypoplastic spleen), and **left-sided isomerism** with **polysplenia**; both are associated with complex **cardiac and pulmonary anomalies**, making them clinically important beyond the spleen itself.
- ▶ **Situs inversus**: the spleen (with the liver and pancreas) may lie mirror-reversed, on the right side of the abdomen.
- ▶ **Wandering spleen**: deficient fixation by the splenorenal and gastrosplenic ligaments/an abnormally long "mesentery" allows excessive mobility of the spleen out of the left hypochondrium, predisposing to torsion of its vascular pedicle.
- ▶ **Surgical relevance of the ligaments**: the splenorenal ligament carries the splenic vessels close to the tail of pancreas (both structures are at risk during splenectomy or left nephrectomy); the short gastric vessels in the gastrosplenic ligament must not be ligated too close to the stomach wall during splenectomy, to avoid gastric ischaemia.

## High-yield exam pointers

- ▶ Spleen is **entirely mesodermal**, not endodermal — the only major "abdominal gland" without a gut-endoderm contribution.
- ▶ Develops in the **dorsal mesogastrium**, close to the stomach, in the 5th (–6th) week; of **dual origin** — coelomic epithelium + mesenchyme.
- ▶ Multicentric spleniculi fuse into one lobulated mass → adult **splenic notches** are the fossil trace of this lobulation.
- ▶ Dorsal mesogastrium is divided by the developing spleen into the **gastrosplenic ligament** (anterior) and **splenorenal/lienorenal ligament** (posterior, carries splenic vessels).
- ▶ Position change is driven by **stomach rotation** + fusion of dorsal mesogastrium to the posterior abdominal wall; spleen ends up forming part of the **left wall of the lesser sac**.
- ▶ Important fetal **haemopoietic organ**; this stops at birth, but lymphopoiesis continues.
- ▶ **Accessory spleen** in ~10% — commonest near the hilum/gastrosplenic ligament; must be sought at splenectomy to prevent disease recurrence.
- ▶ **Right isomerism** → **asplenia**; **left isomerism** → **polysplenia** — both linked with cardiopulmonary anomalies.
- ▶ Birth weight ≈13 g; doubles by 1 year, triples by 3 years.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Larsen — Human Embryology 6e.



## Developmental anomalies of pancreas

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The pancreas develops from a **dorsal pancreatic bud** and a **ventral pancreatic bud**, two endodermal evaginations of the caudal foregut, which grow, rotate and fuse to form a single gland with a single duct system draining into the second (descending) part of the duodenum. Developmental anomalies of the pancreas arise from faulty **migration/rotation of the ventral bud**, **failure of fusion of the two buds or their ducts**, or **persistence of embryonic (ectopic) pancreatic tissue**. The classical anomalies are annular pancreas, pancreas divisum, ectopic (accessory) pancreatic tissue, and inversion of the pancreatic ducts — of which annular pancreas and pancreas divisum are clinically the most important because of duodenal obstruction and recurrent pancreatitis respectively.

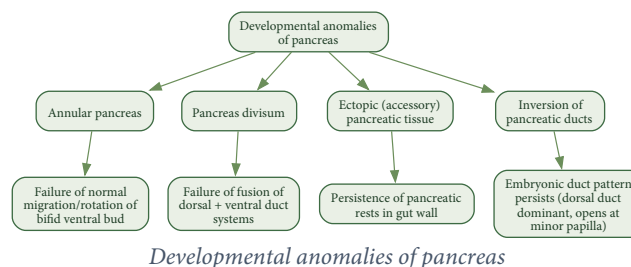
### Normal development of the pancreas (basis for the anomalies)

- ▶ The **dorsal pancreatic bud** appears first (Carnegie stage 13) as a thickening of the endodermal tube growing into the dorsal mesogastrium/dorsal mesoduodenum.

- ▶ The **ventral pancreatic bud** appears slightly later (stage 14) as an evagination of the bile duct itself, close to the hepatic diverticulum; it is therefore intimately related to the common bile duct from the outset.
- ▶ With differential growth of the duodenal wall (stage 16, ~5th week) and rotation of the duodenum/stomach, the ventral bud and bile duct swing to the right and then dorsally, coming to lie **below and behind** the dorsal bud.
- ▶ By stage 17 (~6th week) the two buds make contact and fuse; by the 7th week fusion of the parenchyma and duct systems is complete.
- ▶ Contribution of each bud to the adult gland:

| Adult part                                             | Embryological origin                                                                         |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Head (anterior/superior part) + neck, body, tail       | Dorsal pancreatic bud                                                                        |
| Uncinate process + posterior/inferior part of the head | Ventral pancreatic bud                                                                       |
| Main pancreatic duct (of Wirsung)                      | Entire ventral duct + distal part of dorsal duct                                             |
| Accessory pancreatic duct (of Santorini)               | Proximal part of dorsal duct (often persists; opens at the minor papilla)                    |
| Islets of Langerhans, acini, connective tissue         | Endodermal buds (acini/islets) + surrounding splanchnic mesenchyme (capsule, septa, vessels) |

- ▶ The main duct, together with the bile duct, opens at the **major duodenal papilla**; the accessory duct (when patent) opens just proximal to it at the **minor duodenal papilla**. A patent accessory duct is present in ~85% of infants but only ~40% of adults, reflecting progressive regression of the proximal dorsal duct with age.
- ▶ Along with the duodenum, the pancreas becomes secondarily retroperitoneal, except the tail, which remains within the lienorenal ligament.



## Annular pancreas

- ▶ **Definition:** a thin, flat ring of normal pancreatic tissue completely encircles the second (descending) part of the duodenum.
- ▶ **Incidence:** approximately 1 in 12,000–15,000 newborns; reported to be somewhat commoner in females.
- ▶ **Mechanism:** the ventral pancreatic bud is normally bifid (two components) that fuse with each other and then with the dorsal bud below it. In annular pancreas, one component of the bifid ventral bud migrates in the abnormal (anticlockwise) direction — or the bifid bud grows around

the duodenum on both sides — so that pancreatic tissue comes to completely surround the duodenum before fusing with the dorsal bud, forming a ring.

- **Associations:** Down syndrome, intestinal malrotation, and cardiac defects; it is also one of the recognised causes of extrinsic duodenal compression in duodenal atresia (compressing the duodenum externally in a proportion of atresia cases).

□ Fig 15.7 — Formation of annular pancreas. There may be two ventral pancreatic buds that fuse with dorsal pancreatic bud surrounding duodenum to form annular pancreas (Sontakke — Textbook of Human Embryology, p.155)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A two-panel schematic (as above) with these exact labels:

- Panel 1 (5th–6th week): **Stomach, Hepatic bud, Cystic bud, Two ventral pancreatic buds** (with curved arrows showing normal clockwise rotation of the right component and abnormal counter-rotation of the left component), **Dorsal pancreatic bud, Duodenum**.
- Panel 2 (after fusion): **Duodenum**, ring of pancreatic tissue labelled **Annular pancreas** encircling the second part of the duodenum, **bile duct** entering medially.
- **Clinical effects:** may cause partial or complete duodenal obstruction (from external compression, or if pancreatitis develops within the annular tissue); in intrauterine life, obstruction impedes normal swallowing/absorption of amniotic fluid and results in **polyhydramnios**.
- **Imaging:** plain abdominal radiograph or antenatal ultrasound shows the classical "**double bubble**" sign — a gas/fluid-filled distended stomach and proximal duodenum proximal to the site of obstruction.
- **Treatment:** surgical bypass of the obstructed duodenal segment by **duodenojejunostomy** (or duodenoduodenostomy); the annular tissue itself is not divided, as this risks pancreatic duct injury/fistula.

## Pancreas divisum

- **Definition:** the most common congenital anomaly of the pancreas, resulting from **failure of fusion of the dorsal and ventral pancreatic duct systems** — the parenchyma of the two buds may fuse normally, but their ducts remain separate.
- **Incidence:** duct fusion fails in about 5–10% of individuals (Gray's Anatomy); a comparable figure of ~9–10% is given by standard embryology texts.
- **Duct pattern:** the **accessory (dorsal) duct** drains the greater part of the gland — body, tail, and most of the head — via the **minor duodenal papilla**; the **ventral duct** drains only the uncinate process and the postero-inferior part of the head via the major papilla, together with the bile duct.
- **Clinical significance:** the minor papilla is relatively small/narrow, and if it is poorly developed it may inadequately drain the greater part of the pancreatic secretion, predisposing to elevated intraductal pressure and **recurrent (idiopathic) pancreatitis**.

## Ectopic (accessory) pancreatic tissue

- ▶ Islands of heterotopic pancreatic tissue, histologically identical to normal pancreas, may persist in the gut wall at sites away from the main gland — most often the **stomach**, and also the **duodenum**, **jejunum**, **Meckel's diverticulum**, and occasionally the **gallbladder**.
- ▶ Represents persistence/detachment of small outgrowths of the pancreatic buds during their extensive branching.
- ▶ Usually asymptomatic and an incidental finding, but can present with obstruction, bleeding, or (rarely) neoplastic change.

## Inversion of pancreatic ducts

- ▶ A rare anomaly in which the **embryonic (pre-fusion) duct pattern persists**: the main pancreatic duct is formed entirely by the dorsal pancreatic duct and drains the greater part of the gland through the **minor duodenal papilla**, while the duct of the ventral bud remains small and joins the bile duct to open at the major papilla.
- ▶ Represents an exaggerated/asymmetric form of failure of the normal duct-fusion pattern, differing from pancreas divisum mainly in the disproportionate size of the two ducts (accessory duct larger than the main duct).

## Applied / Clinical anatomy

- ▶ **Annular pancreas** in the neonate presents with bilious or non-bilious vomiting (depending on the level of obstruction relative to the bile duct opening) and epigastric distension; antenatal polyhydramnios is a clue. The "double bubble" sign on X-ray/ultrasound is a key radiological pointer shared with duodenal atresia, with which annular pancreas often coexists.
- ▶ **Pancreas divisum** is usually asymptomatic but is an important cause to consider in unexplained/recurrent acute pancreatitis in adults; endoscopic retrograde cholangiopancreatography (ERCP) demonstrates a short ventral duct and a dominant dorsal duct opening separately at the minor papilla — recognising this variant prevents misdiagnosis during ERCP/MRCP.
- ▶ **Ectopic pancreatic tissue** in the stomach, duodenum, or a Meckel's diverticulum can mimic a submucosal tumour endoscopically/radiologically, and may itself present with obstruction, bleeding, or (rarely) malignant change.
- ▶ Awareness of dorsal-vs-ventral bud contribution explains why **congenital pancreatic tumours/cysts and most duct anomalies cluster around the head/uncinate region** — the site of fusion of the two embryological components.
- ▶ A patent accessory duct (Santorini) is common and of no clinical significance by itself; only when it is the **SOLE** outflow (pancreas divisum) does it become clinically relevant.

## High-yield exam pointers

- ▶ Pancreas = **dorsal bud** (body, tail, upper head/neck) + **ventral bud** (uncinate process, lower head); ventral bud develops in continuity with the bile duct.
- ▶ Main duct (Wirsung) = ventral duct + distal dorsal duct → major papilla; accessory duct (Santorini) = proximal dorsal duct → minor papilla.



- ▶ **Annular pancreas** = failure of normal migration/rotation of the (bifid) ventral bud → ring around the 2nd part of duodenum → duodenal obstruction, "double bubble" sign, polyhydramnios; treated by bypass (duodenojejunostomy), never by dividing the ring.
- ▶ **Pancreas divisum** = commonest pancreatic anomaly = failure of dorsal-ventral duct fusion → dorsal duct drains via narrow minor papilla → risk of recurrent pancreatitis.
- ▶ **Ectopic pancreas** — commonest site is the **stomach**; also duodenum, jejunum, Meckel's diverticulum, gallbladder.
- ▶ **Inversion of pancreatic ducts** — embryonic pattern persists; main drainage through the minor papilla.
- ▶ Annular pancreas is associated with **Down syndrome, malrotation, and cardiac defects**.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); BD Chaurasia — Human Anatomy Vol 2 8e.



## Fate of septum transversum

*Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The septum transversum is a thick plate of splanchnopleuric mesenchyme that arises, as an unsplit condensation of intraembryonic mesoderm, cranial to the cardiogenic area during the third week — opposite the third to fifth cervical somites. With cephalocaudal folding of the embryo in the fourth week it is carried to a position caudal to the developing heart and pericardial cavity, where it forms an incomplete partition between the pericardial and peritoneal parts of the intraembryonic coelom, the paired pleuroperitoneal canals persisting dorsolateral to it. It is not a single simple membrane but a major organogenetic mesenchymal mass: its different parts go on to form the central tendon of the diaphragm, the non-parenchymal (mesenchymal) components of the liver, and the ventral mesentery, and it is also an active inductive signalling centre for hepatic differentiation. Its maldevelopment underlies several clinically important anomalies of the diaphragm, pericardium and anterior body wall.

### 1. Origin, position and relations

- ▶ **Origin:** proliferating coelomic (splanchnopleuric) epithelium of the caudal wall of the primitive pericardial cavity; appears as a mesenchymal condensation in the third week, opposite somites C3–C5.
- ▶ **Situation:** occupies the space between the primitive thoracic (pericardial/pleural) cavity above and the peritoneal cavity below, i.e., between the septum's cranial surface (pericardium) and caudal surface (peritoneal cavity/yolk-sac stalk region).
- ▶ **Relations:**
  - **Dorsal** — the terminal (pregastric) oesophagus with its dorsal mesentery, and the paired **pleuroperitoneal canals** (through which pleural and peritoneal cavities still communicate).



- **Dorsolateral edge** — continuous with the pulmonary ridge, which divides into the pleuropericardial membrane (carrying the common cardinal vein and phrenic nerve) and the pleuroperitoneal membrane.
- **Ventral/lateral** — continuous with the somatopleuric mesenchyme of the body wall.
- **Caudal (within it)** — invaded from the fourth week onward by the endodermal **hepatic diverticulum**, which grows in from the foregut.

## 2. Positional migration

As the embryo elongates and the heart enlarges, the septum transversum shifts progressively caudally, dragging its cervical myotome-derived innervation with it — the anatomical basis for the phrenic nerve's long thoraco-abdominal course.

| Stage    | Level of septum transversum                                                        |
|----------|------------------------------------------------------------------------------------|
| 4th week | Opposite cervical somites C3, C4, C5                                               |
| 6th week | Descended to the level of thoracic somites T7–T12 (definitive diaphragmatic level) |

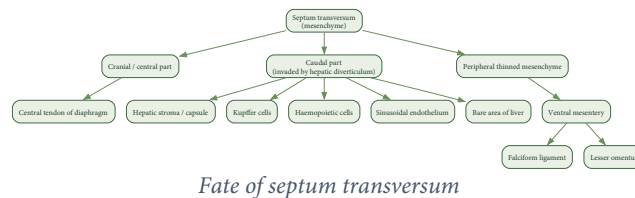
## 3. Fate / derivatives of the septum transversum

The septum transversum is one of **four embryonic components of the diaphragm** (the others being the paired pleuroperitoneal membranes, the dorsal mesentery of the oesophagus, and muscle ingrowth from the body wall), but it alone contributes to the liver and to the ventral mesentery as well.

| Part of septum transversum                                                                       | Fate / adult derivative                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cranial/central portion, later capped by the fused pleuroperitoneal membranes                    | Central tendon of the diaphragm                                                                                                                                                                                                                          |
| Caudal portion invaded by the hepatic diverticulum                                               | <b>Hepatic mesenchyme</b> → connective-tissue stroma/capsule of the liver, haemopoietic cells, Kupffer cells, and endothelium of the hepatic sinusoids                                                                                                   |
| Vitelline veins traversing the septum, broken up by growing liver cords                          | Hepatic sinusoidal (vascular) plexus, forerunner of the definitive hepatic sinusoids                                                                                                                                                                     |
| Thinned peripheral mesenchyme flanking the liver, not penetrated by liver cords                  | <b>Ventral mesentery</b> , subsequently divided by the growing liver into: (a) the <b>falciform ligament</b> (liver to ventral body wall/umbilicus) and (b) the <b>lesser omentum/ventral mesogastrium</b> (liver to stomach and first part of duodenum) |
| Loose areolar septal tissue persisting between liver and diaphragm, never invested by peritoneum | The " <b>bare area</b> " of the liver, bounded by the coronary ligament and right triangular ligament                                                                                                                                                    |
| Mesenchyme continuous with the lower ventral wall of the pericardioperitoneal canal              | Contributes to the connective-tissue investment of the <b>ventral pancreatic bud</b>                                                                                                                                                                     |
| Dorsolateral edge, continuous with the pulmonary ridge/pleuropericardial fold                    | Route by which the phrenic nerve and common cardinal vein are carried into the fibrous pericardium and diaphragm                                                                                                                                         |

**Important negative point (frequent exam trap):** the hepatocytes and biliary duct epithelium are **endodermal**, derived from the hepatic diverticulum of the foregut — NOT from the septum transversum. The septum transversum contributes only the *mesenchymal/stromal* elements of the liver.

**Inductive role:** the septum transversum is not a passive scaffold — it secretes **bone morphogenetic proteins (BMPs)** which, together with **fibroblast growth factor-2 (FGF2)** secreted by the adjacent cardiogenic mesoderm, induce the neighbouring foregut endoderm to differentiate into hepatic endoderm, initiating liver organogenesis.



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 17.5 — Development of abdominothoracic diaphragm: transverse sections through the septum transversum at 28 days, week 6, week 7 and week 16, showing its transformation into the central tendon (Sontakke — Textbook of Human Embryology, p.171)

Reproduce by hand as four labelled transverse sections (viewed from the cranial side), with these exact labels:

- ▶ **Embryo 28 days (inset):** plane of section passing through septum transversum, caudal to pericardial cavity.
- ▶ **Week 6:** aorta; dorsal mesentery of oesophagus; oesophagus; pleuroperitoneal canal; inferior vena cava; pleuroperitoneal fold; septum transversum.
- ▶ **Week 7:** muscular ingrowth from body wall; narrowing of pleuroperitoneal canal.
- ▶ **Week 16:** crura of diaphragm; small peripheral part; large peripheral part; central part (derived from septum transversum).

### Applied / Clinical anatomy

- ▶ **Congenital diaphragmatic hernia (CDH), Bochdalek type** — a posterolateral defect due to failure of the **pleuroperitoneal membrane** (not the septum transversum) to fuse and close the pleuroperitoneal canal; commoner on the left (the right canal closes earlier). Abdominal viscera (stomach, intestine, spleen, liver) herniate into the thorax, compressing the developing lung and causing pulmonary hypoplasia.
- ▶ **Morgagni (retrosternal/parasternal) hernia** — a rarer anterior defect at the sternocostal triangle, adjacent to where the septum-transversum-derived central tendon meets the costal muscle slips; usually right-sided.
- ▶ **Eventration of the diaphragm** — failure of muscularisation of one half of the septum-transversum-derived central portion, so that it remains thin and membranous and balloons into the thorax; clinically mimics CDH but is not a true defect/hernia.
- ▶ **Pentalogy of Cantrell** — a combined failure of anterior septum transversum/body-wall closure producing a defect of the anterior diaphragm, absence of pericardium, ectopia cordis, sternal

defect and an abdominal wall defect (omphalocele/gastroschisis) — reflects the septum transversum's shared contribution to diaphragm, pericardium and ventral body wall.

- ▶ **Phrenic nerve (C3, C4, C5)** — supplies the diaphragm's muscle and much of its peritoneal/pleural covering because the nerve is dragged caudally with the migrating septum transversum from its original cervical level ("C3, 4, 5 keep the diaphragm alive").
- ▶ **Bare area of the liver** — the septum-transversum-derived areolar tissue devoid of peritoneum is surgically important: it is a route for extraperitoneal spread of subphrenic collections and must be respected during liver mobilisation/transplantation dissection.
- ▶ **Falciform ligament and lesser omentum** — surgical landmarks (ligamentum teres in the free edge of the falciform ligament; lesser omentum as the anterior boundary of the epiploic foramen).

### High-yield exam pointers

- ▶ Septum transversum = **splanchnopleuric mesenchymal** partition between the pericardial and peritoneal coelom; appears in the **3rd week** opposite somites C3–C5.
- ▶ One of the **four embryonic components of the diaphragm**; it alone forms the **central tendon**.
- ▶ Caudal part invaded by the hepatic diverticulum gives the liver's **mesenchymal** elements — stroma/capsule, Kupffer cells, haemopoietic cells, sinusoidal endothelium — **hepatocytes and bile-duct epithelium are endodermal, not septal**.
- ▶ Peripheral thinned part forms the **ventral mesentery** → **falciform ligament + lesser omentum**; the liver is unique in retaining both a dorsal and a ventral mesentery.
- ▶ Persisting unperitonealised septal tissue on the posterior liver surface = the "**bare area**".
- ▶ Positional migration: **C3–C5 (4th week)** → **T7–T12 (6th week)** — basis of the phrenic nerve's cervical root value.
- ▶ Secretes **BMPs** (with FGF2 from cardiac mesoderm) to induce hepatic differentiation of foregut endoderm — an active inductive centre, not just a scaffold.
- ▶ **CDH (Bochdalek)** is a pleuroperitoneal-membrane defect, **not** a septum transversum defect — a common exam trap; anterior defects (Morgagni hernia, eventration, Pentalogy of Cantrell) are the ones genuinely linked to septum transversum maldevelopment.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Foregut

Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** The foregut is the cranial-most of the three subdivisions (foregut, midgut, hindgut) of the primitive gut tube formed when folding of the trilaminar embryo incorporates the dorsal yolk sac into the embryo in the fourth week. It extends from the **buccopharyngeal membrane** cranially to the **opening of the bile duct (major duodenal papilla)** in the second part of the duodenum, giving rise to the pharynx and its pouch derivatives, the respiratory tract, the oesophagus, the stomach, the proximal (pre-ampullary) duodenum, the liver with its extrahepatic biliary apparatus, and the pancreas. All abdominal foregut derivatives share a single arterial supply, the **coeliac trunk** — the anatomical basis of the region's applied importance.

### 1. Formation and general architecture of the foregut

- ▶ The primitive gut tube is divided into three regions by the **anterior (cranial) intestinal portal** (foregut–midgut junction) and the **posterior (caudal) intestinal portal** (midgut–hindgut junction); the midgut remains in wide communication with the yolk sac through the vitelline duct until this narrows and disappears by the fifth week.
- ▶ The **buccopharyngeal membrane** separates the stomodeum from the foregut; the **cloacal membrane** separates the hindgut from the proctodeum.
- ▶ The cranial (pharyngeal) part of the foregut is intimately tied to head-and-neck (branchial arch/pouch) development; the part passing dorsal to the pericardial cavity gives rise to the **respiratory diverticulum** and the **oesophagus** in the thorax; caudal to the developing diaphragm the foregut continues into the abdominal foregut (stomach, duodenum, liver, pancreas).
- ▶ There is no fundamental cytological difference between fore-, mid- and hindgut — all three tissue layers contribute identically throughout: the **endoderm** forms the epithelial lining and glandular derivatives; the **splanchnopleuric mesenchyme** forms the lamina propria, muscularis mucosae, submucosa and muscularis externa; and the **splanchnopleuric coelomic epithelium** forms the serosa. The gut is suspended from the posterior body wall by a **dorsal mesentery** throughout its length; a **ventral mesentery** exists only at the level of the foregut (from septum transversum mesenchyme), and this is why only foregut derivatives (stomach, first part of duodenum, liver) retain a ventral mesentery (falciform ligament, lesser omentum) in the adult.

### 2. Development of individual foregut derivatives

| Organ      | Key developmental events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oesophagus | Distinguishable from the stomach by stage 13 (~5 mm). The <b>tracheo-oesophageal septum</b> partitions the foregut caudal to the respiratory (laryngotracheal) diverticulum into a ventral trachea and dorsal oesophagus (4th week). It elongates rapidly with descent of the heart, lungs and diaphragm. Mucosal proliferation never fully occludes the lumen; the epithelium becomes ciliated columnar transiently and is stratified squamous by the end of the 5th month. Circular muscle appears by stage 15, longitudinal muscle by stage 21. |

| Organ                                  | Key developmental events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stomach                                | Recognisable as a fusiform dilatation of the foregut distal to the oesophagus at the end of the 4th/beginning of the 5th week. Faster growth of its dorsal border produces the <b>greater curvature and fundus</b> ; the <b>lesser curvature</b> forms ventrally. The stomach undergoes two ~90° "rotations": (i) about its <b>longitudinal axis</b> , so the original left surface becomes anterior (supplied by the <b>left vagus</b> ) and the original right surface becomes posterior (supplied by the <b>right vagus</b> ); (ii) about an <b>anteroposterior axis</b> , so the pyloric end moves right and cranially and the cardiac end moves left. These movements — plus growth of the liver — draw out the dorsal mesogastrium into the <b>greater omentum</b> and form the <b>lesser sac (omental bursa)</b> behind the stomach. |
| Duodenum                               | Formed from the <b>caudal foregut</b> (proximal to the bile-duct opening/major papilla) and the <b>cranial midgut</b> (distal to it) — hence its dual blood supply. Stomach rotation throws it into a right-directed C-loop; adherence/absorption of its serosa renders it secondarily retroperitoneal (except the first inch). The lumen, transiently obliterated by epithelial proliferation around week 8, recanalises by month 3 — failed recanalisation underlies duodenal stenosis/atresia.                                                                                                                                                                                                                                                                                                                                           |
| Liver & extrahepatic biliary apparatus | Arises as the <b>hepatic diverticulum</b> , an endodermal outgrowth from the ventral foregut wall at the foregut–midgut junction, growing into the <b>septum transversum</b> mesenchyme. Its larger cranial part forms hepatocyte cords and intrahepatic bile ducts; its smaller caudal part forms the <b>cystic duct and gallbladder</b> . Proliferating hepatic trabeculae break up the vitelline/umbilical veins to form the <b>hepatic sinusoids</b> .                                                                                                                                                                                                                                                                                                                                                                                  |
| Pancreas                               | Develops from <b>two endodermal buds</b> : a <b>dorsal bud</b> (stage 13, thickening of the foregut proliferating into the dorsal mesogastrium) and a <b>ventral bud</b> (stage 14, evaginating from the bile duct). Differential duodenal-wall growth (stage 16) rotates the ventral bud and bile duct right then dorsally; by stage 17 the buds fuse — dorsal bud → anterior head, body, tail; ventral bud → posterior head and (most of) the uncinate process.                                                                                                                                                                                                                                                                                                                                                                           |

### 3. Derivatives of the foregut



- **Pancreatic ducts:** the **main pancreatic duct** (duct of Wirsung) is formed by the **ventral pancreatic duct** joined to the **distal part of the dorsal duct**; the **accessory pancreatic duct** (duct of Santorini) is the persisting **proximal part of the dorsal duct** and remains patent in ~85% of infants versus ~40% of adults.
- **Islet histogenesis:** the dorsal bud gives rise mainly to  **$\alpha$  (glucagon) cells** and the ventral bud mainly to pancreatic-polypeptide cells;  **$\beta$  (insulin) cells** differentiate from duct epithelium throughout development, and  **$\delta$  (somatostatin) cells** appear after 30 weeks.
- **Note (exam trap):** the **spleen** is *not* a foregut (endodermal) derivative — it arises from mesenchymal condensations ("splenculi") in the **dorsal mesogastrium** from the 5th week onward — but it is included with the foregut viscera because it shares the **splenic artery**, a branch of the coeliac trunk (the artery of the foregut).

#### 4. Blood supply, venous drainage and nerve supply of the foregut

| Vessel                | Origin/course                                                                                                                                         | Structures supplied                                                                                                                                                                                                            |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Coeliac trunk         | Arises from the front of the abdominal aorta just below the aortic hiatus, at the level of T12; only ~1 cm long before it divides into three branches | The single artery of the entire foregut (abdominal oesophagus to major duodenal papilla), liver, pancreas and spleen                                                                                                           |
| Left gastric artery   | Passes upward/left, then turns onto the lesser curvature between the layers of the lesser omentum; anastomoses with the right gastric artery          | Abdominal oesophagus; both surfaces of the stomach along the lesser curvature                                                                                                                                                  |
| Splenic artery        | Runs a tortuous course along the superior border of the pancreas to the spleen                                                                        | Spleen; pancreas (body/tail, via pancreatic branches); stomach (via short gastric and left gastro-epiploic arteries)                                                                                                           |
| Common hepatic artery | Passes right, then divides into hepatic artery proper and gastroduodenal artery                                                                       | Hepatic artery proper → liver, cystic artery (gallbladder), right gastric artery; gastroduodenal artery → right gastro-epiploic + superior pancreaticoduodenal arteries (duodenum and pancreatic head up to the major papilla) |

□ Fig 14.2 — Blood supply of developing gut: the foregut and its derivatives are supplied by branches of the coeliac trunk; the midgut by the superior mesenteric artery; the hindgut by the inferior mesenteric artery (Sontakke — Textbook of Human Embryology, p.135)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A simplified anteroposterior scheme of the abdominal aorta at T12 giving off the coeliac trunk — label: **abdominal aorta**; **coeliac trunk** (~1 cm); its three terminal branches — **left gastric artery** (to oesophagus + lesser curvature), **splenic artery** (to spleen, pancreas, greater curvature via short gastrics/left gastro-epiploic) and **common hepatic artery** (→ hepatic artery proper to liver/gallbladder + gastroduodenal artery → right gastro-epiploic + superior pancreaticoduodenal arteries); outline the **stomach**, **liver**, **spleen**, **pancreas** and **duodenum** in situ around the trunk.

- ▶ **Venous drainage:** all foregut-derivative venous blood is portal — the splenic vein joins the superior mesenteric vein behind the neck of the pancreas to form the **portal vein**, which carries blood to the liver sinusoids before it reaches the **hepatic veins** and inferior vena cava; the left gastric (coronary) vein drains directly into the portal vein and communicates at the lower oesophagus with the azygos (systemic) system — the basis of oesophageal varices in portal hypertension.
- ▶ **Nerve supply:** parasympathetic supply to foregut derivatives is via the **vagus nerve** (right vagus → posterior/originally-right gastric surface; left vagus → anterior/originally-left surface), carrying secretomotor and motor fibres to smooth muscle and glands; sympathetic supply is via the **greater splanchnic nerve** (T5–T9), relaying in the **coeliac ganglia** and reaching the viscera along the coeliac plexus and the perivascular plexuses on the branches of the coeliac trunk (also the route for foregut visceral pain afferents, referred to the epigastrium).

### Applied / Clinical anatomy

- ▶ **Oesophageal atresia/tracheo-oesophageal fistula (TEF):** incomplete partitioning by the tracheo-oesophageal septum; incidence ~1 in 3000 births. Commonest variant (~90%) is a blind proximal pouch with a fistula from the distal segment into the trachea; isolated atresia and "H-type" fistula each ~4%. Presents with polyhydramnios and feeding-related choking; part of the **VACTERL** association.
- ▶ **Congenital hypertrophic pyloric stenosis:** hypertrophy of the pyloric circular muscle; incidence ~1:150 males, ~1:750 females; projectile non-bilious vomiting with a palpable "olive" mass.
- ▶ **Duodenal atresia/stenosis:** ~1:5000 live births, from failed recanalisation of the epithelial plug; ~20% associated with **annular pancreas** or bile-duct anomalies; strongly linked to **Down syndrome**; classic antenatal sign is the "**double bubble**" with polyhydramnios.
- ▶ **Annular pancreas:** failure of ventral-bud rotation/migration — a ring of pancreatic tissue encircles D2, causing obstruction; treated by duodeno-jejunostomy bypassing (not resecting) the ring.
- ▶ **Pancreas divisum:** commonest pancreatic ductal anomaly — failure of dorsal–ventral duct fusion (~10%), so most secretion drains via the minor papilla.
- ▶ **Ectopic pancreatic tissue** may occur in the stomach, duodenum, gallbladder or a Meckel's diverticulum wall.
- ▶ **Biliary atresia:** obliteration of extrahepatic bile ducts, linked to portal-vein branching anomalies; presents as neonatal cholestatic jaundice.



- **Surgical/radiological correlate:** a single coeliac axis supplies every foregut organ, so coeliac angiography maps them together, and coeliac compromise (e.g. median arcuate ligament syndrome) can jeopardise stomach, duodenum, liver, pancreas and spleen together.

### High-yield exam pointers

- Foregut = buccopharyngeal membrane → major duodenal papilla (opening of bile duct) in D2; artery of the foregut = **coeliac trunk** (from T12).
- Derivatives: pharynx + pouches, respiratory tree, oesophagus, stomach, proximal (pre-ampullary) duodenum, liver + extrahepatic biliary tree, pancreas. **Spleen is mesodermal, NOT endodermal** — grouped with foregut only by shared splenic-artery supply.
- Duodenum has a **dual origin** (foregut proximal to major papilla, midgut distal to it) and correspondingly dual arterial supply (coeliac + superior mesenteric).
- Pancreas = dorsal bud (body, tail, ant. head — mostly  $\alpha$  cells) + ventral bud (uncinate process, post. head — PP cells); main duct = ventral duct + distal dorsal duct; accessory duct = proximal dorsal duct (patent in 85% infants vs 40% adults).
- Liver arises from the hepatic diverticulum at the foregut–midgut junction, growing into the septum transversum; only foregut derivatives retain a ventral mesentery (falciform ligament, lesser omentum).
- Stomach undergoes two 90° rotations — explains left vagus → anterior wall, right vagus → posterior wall.
- Classic anomalies: TEF (90/4/4/1/1% pattern, VACTERL), congenital hypertrophic pyloric stenosis (1:150 M, 1:750 F), duodenal atresia (1:5000, "double bubble," Down syndrome, 20% with annular pancreas), pancreas divisum (~10%), annular pancreas.
- Portal venous drainage of all foregut derivatives passes first through the liver; portosystemic anastomosis at the lower oesophagus (left gastric ↔ azygos) explains oesophageal varices in portal hypertension.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; IB Singh — Textbook of Anatomy Vol 2 6e (coeliac trunk and branches).



## Formation of gut tube

*Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The primitive gut tube is the endoderm-lined tubular cavity that forms during the third and fourth weeks of intrauterine life when the flat trilaminar embryonic disc is converted into a cylindrical embryo by **cephalocaudal (head and tail) folding** and **lateral (horizontal) folding**. Before folding, the endoderm forms the roof of the yolk sac and is continuous with it over the whole ventral aspect of the disc; folding progressively pinches off a tubular portion of this endoderm into the body of the embryo, leaving only a narrow communication (the vitelline duct) with the yolk sac. The resulting tube is subdivided craniocaudally into **foregut, midgut and hindgut**, each with a distinct arterial supply, and each giving rise to defined derivatives of the alimentary tract.

### 1. Cause and mechanism of embryonic folding

- ▶ Folding results from **unequal growth rates**: the embryonic disc (particularly the neural tube and paraxial mesoderm/somites) grows very rapidly in length, while the yolk sac and the periphery of the disc do not keep pace — the disc is thereby forced to bulge and curl ventrally around the yolk sac.
- ▶ Folding occurs simultaneously in two perpendicular planes:
  - **Median (longitudinal) plane** — produces the **head fold** and the **tail fold**.
  - **Horizontal (transverse) plane** — produces paired **lateral folds** (right and left).
- ▶ The amnion is carried along passively as the folds move ventrally, so that the embryo comes to lie invaginated within the expanding amniotic cavity, attached to the chorion only by the narrowing connecting stalk (future umbilical cord).

### 2. Head fold (cephalic/cranial folding)

- ▶ Occurs first, at the beginning of the fourth week, driven mainly by the rapid growth of the developing brain (prosencephalon), which balloons cranially beyond the oropharyngeal membrane and overhangs the pericardial region.
- ▶ Consequences of the head fold:
  - The **oropharyngeal membrane, septum transversum, pericardial coelom and primitive heart tube** are carried from their original position (rostral, dorsal to the disc) onto the **ventral surface** of the embryo.
  - A part of the endoderm of the roof of the yolk sac is folded ventrally and incorporated into the embryo as the **foregut**, which now lies between the developing brain dorsally and the heart ventrally, and ends blindly at the oropharyngeal membrane.
  - The septum transversum comes to lie caudal to the heart (it later forms the central tendon of the diaphragm).

### 3. Tail fold (caudal folding)

- ▶ Occurs slightly later (about stage 10), driven by the rapid longitudinal growth of the caudal neural tube (future spinal cord) and the tail (caudal) eminence, which grows over the cloacal membrane.
- ▶ Consequences of the tail fold:

- The **cloacal membrane, allantois and connecting stalk** are carried onto the ventral surface of the embryo.
- A part of the endoderm caudal to this level is incorporated as the **hindgut**, which ends blindly at the cloacal membrane; its terminal part soon dilates to form the **cloaca**.
- The primitive streak, originally cranial to the cloacal membrane, now comes to lie caudal to it.

#### 4. Lateral folding

- ▶ Produced by the rapid growth of the somites and the lateral body wall on each side, which roll the edges of the disc ventrally toward the midline.
- ▶ As the two lateral folds meet and fuse in the ventral midline, the **ventral body wall closes** (except at the umbilical region), and the endoderm between them is drawn into the embryo to form the **midgut**.
- ▶ Before lateral folding the midgut is in wide, open communication with the yolk sac; as folding proceeds this broad connection is progressively narrowed into a slender tubular **vitelline (omphalomesenteric/yolk-stalk) duct**, which persists temporarily within the umbilical cord.

#### 5. Formation and fate of the intraembryonic coelom

- ▶ Before folding, the intraembryonic coelom is a flat, horseshoe-shaped cavity within the lateral plate mesoderm, its two limbs continuous across the midline cranial to the buccopharyngeal membrane and continuous laterally with the extraembryonic coelom.
- ▶ Head folding carries the midline (cranial) part of this horseshoe ventrally and caudally so that it comes to lie ventral to the foregut — this becomes the **pericardial cavity**; the two limbs, now lying alongside the foregut, become the **pericardioperitoneal (pleural) canals**; the rest of the coelom becomes the **peritoneal cavity**.
- ▶ Lateral and tail folding bring the two limbs of the coelom together in the midline ventral to the gut, converting the originally paired cavity into a single continuous peritoneal cavity, and the gut tube becomes suspended from the posterior body wall by a **dorsal mesentery** (the ventral mesentery persists only where the septum transversum/liver intervenes, in the foregut region).

#### 6. Subdivisions of the primitive gut tube and their boundaries

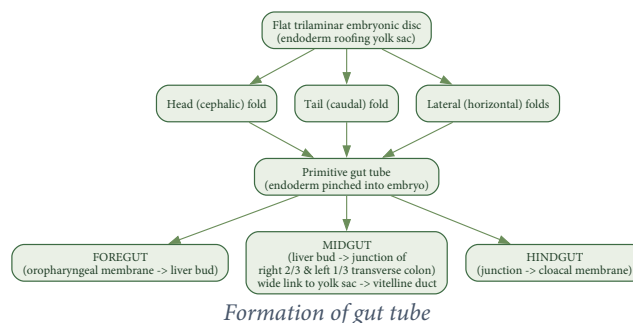
| Segment                               | Extent                                                                                                  | Chief derivatives                                                                                                                                                              |
|---------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharyngeal gut (cranial-most foregut) | Oropharyngeal membrane to the respiratory (laryngotracheal) diverticulum                                | Pharynx and its derivatives (tonsils, thyroid, parathyroids, thymus)                                                                                                           |
| Foregut (post-pharyngeal)             | Respiratory diverticulum to the liver bud (just distal to the entry of the bile duct into the duodenum) | Oesophagus, stomach, proximal half of duodenum, liver, biliary apparatus, ventral & dorsal pancreatic buds, and (via the respiratory diverticulum) the lower respiratory tract |

| Segment | Extent                                                                                       | Chief derivatives                                                                                                                                                                              |
|---------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Midgut  | Liver bud to the junction of the right two-thirds and left one-third of the transverse colon | Distal half of duodenum, jejunum, ileum, caecum, appendix, ascending colon, right two-thirds of transverse colon                                                                               |
| Hindgut | Left one-third of transverse colon to the cloacal membrane                                   | Left one-third of transverse colon, descending colon, sigmoid colon, rectum, upper anal canal; endodermal lining of urinary bladder and urethra (via the urorectal septum dividing the cloaca) |

- There is **no fundamental histological or morphological difference** between the three segments — the division is purely topographic/vascular, and the boundaries (liver bud, transverse-colon junction) mark where regional gene expression and blood supply change, not a change in tissue type.
- The gut wall everywhere has the same layered origin: **endoderm** forms the epithelial lining and glandular parenchyma (e.g. hepatocytes, pancreatic acinar/islet cells); the surrounding **splanchnopleuric mesenchyme** forms the lamina propria, muscularis mucosae, submucosa and muscularis externa; the outer **splanchnopleuric coelomic epithelium** forms the peritoneal (serosal) covering.

## 7. Molecular regulation

- Regional specification of the gut tube along its craniocaudal axis is initiated while the lateral folds are still bringing the two sides of the tube together.
- A gradient of **retinoic acid** acting through **Hox genes** patterns the gut tube, while the endodermal epithelium expresses **Sonic hedgehog (Shh)**, which signals to the surrounding splanchnic mesoderm to induce region-specific **Hox gene** expression (e.g. graded Cdx and Hox codes distinguish stomach, small intestine and colon); Shh/Ihh signal via **Patched receptors** to the transcription factor **Gli3**.
- Endoderm-specific transcription factors mark discrete gut regions, e.g. **Sox2** (oesophagus/stomach), **Pdx1** (duodenum, pancreas), **Cdxc/Cdx2** (small and large intestine).



□ Fig 14.2 — Gut Formation by Body Folding: the foregut, midgut and hindgut of the primary gut tube (Larsen — Human Embryology — 6e, p.835)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Median (sagittal) section through the embryo showing progressive cephalocaudal folding, at 2–3 successive stages, labelling:

- ▶ Neural tube / developing brain (dorsal)
- ▶ Oropharyngeal membrane and stomodeum
- ▶ Foregut, with the heart tube and pericardial cavity ventral to it
- ▶ Septum transversum
- ▶ Midgut, in wide communication with the yolk sac
- ▶ Vitelline (yolk sac) duct — shown narrowing across the stages
- ▶ Hindgut, with the cloacal membrane and allantois
- ▶ Connecting stalk / amnion

Also draw one transverse section at the level of the midgut to show the **lateral folds** meeting ventrally, the **gut tube** suspended by a **dorsal mesentery**, and the persisting connection to the **yolk sac** before the ventral body wall closes.

**8. Blood supply established with the subdivisions**

- ▶ **Coeliac trunk** — supplies the abdominal foregut (abdominal oesophagus, stomach, proximal half of duodenum, liver, pancreas, spleen).
- ▶ **Superior mesenteric artery** — supplies the midgut (distal duodenum to the right two-thirds of the transverse colon).
- ▶ **Inferior mesenteric artery** — supplies the hindgut (left one-third of transverse colon to the upper anal canal).
- ▶ These three ventral (splanchnic) branches of the abdominal aorta arise through consolidation and pruning of the vitelline (omphalomesenteric) arteries that originally supplied the yolk sac; their fixed craniocaudal order mirrors the foregut–midgut–hindgut boundaries exactly.

**Applied / Clinical anatomy**

- ▶ **Vitelline duct anomalies:** incomplete regression of the duct produces, depending on which portion persists — a **Meckel diverticulum** (in 2–4% of people, a true diverticulum of the ileum 40–60 cm proximal to the ileocaecal valve on its antimesenteric border, containing all layers of the bowel wall and sometimes ectopic gastric or pancreatic mucosa causing peptic ulceration/bleeding), a **vitelline (fibrous) cord/ligament** (fixed cord that can act as a point around which bowel volvulus/strangulation occurs), a **vitelline cyst** (enterocystoma, when both ends regress but the middle persists) or a **vitelline (umbilical) fistula** (the duct remains patent throughout, producing faecal discharge at the umbilicus).
- ▶ **Failure of lateral fold fusion** in the ventral body wall gives rise to **omphalocele** (herniation of gut loops into the base of the umbilical cord, covered by peritoneum and amnion, often with associated chromosomal anomalies) and **gastroschisis** (a paraumbilical defect through which uncovered bowel loops herniate directly into the amniotic cavity, not associated with chromosomal defects).

- ▶ **Persistence of the septum transversum/foregut relations** underlies developmental anomalies of the diaphragm and tracheo-oesophageal fistulae (division of the foregut by the tracheo-oesophageal septum).
- ▶ **Failure of the head or tail fold**, or of coelom formation, contributes to severe ventral wall defects (e.g. ectopia cordis when the pericardial coelom fails to be carried ventrally by the head fold).
- ▶ Knowledge of the fixed foregut/midgut/hindgut vascular territories underlies the surgical concept of **watershed zones** (e.g. splenic flexure at the SMA–IMA junction) vulnerable to ischaemia.

### High-yield exam pointers

- ▶ Folding = unequal growth of disc vs yolk sac; occurs in median plane (head + tail folds) and horizontal plane (lateral folds), simultaneously in the fourth week.
- ▶ Head fold carries oropharyngeal membrane, septum transversum, heart and pericardial coelom ventrally; forms the **foregut**.
- ▶ Tail fold carries cloacal membrane, allantois and connecting stalk ventrally; forms the **hindgut**.
- ▶ Lateral folds close the ventral body wall and form the **midgut**, narrowing the broad yolk-sac connection to a **vitelline duct**.
- ▶ Foregut extends oropharyngeal membrane → liver bud; midgut, liver bud → junction of right 2/3 and left 1/3 of transverse colon; hindgut, that junction → cloacal membrane.
- ▶ No true histological difference between the three segments — endoderm gives epithelium/glands, splanchnopleuric mesenchyme gives the wall, coelomic epithelium gives peritoneum.
- ▶ Blood supply mirrors the divisions: coeliac trunk (foregut), superior mesenteric artery (midgut), inferior mesenteric artery (hindgut).
- ▶ Molecular patterning: Shh from endoderm → mesodermal Hox code (retinoic-acid gradient); Sox2/Pdx1/Cdx2 mark region-specific endoderm.
- ▶ Clinically testable vitelline-duct remnants: Meckel diverticulum (2–4%, 40–60 cm from ileocaecal valve, antimesenteric border), vitelline cyst, vitelline fistula, vitelline (fibrous) cord.
- ▶ Ventral wall closure failure → omphalocele (covered, herniates through umbilical ring) vs gastroschisis (uncovered, paraumbilical defect).

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e — folding of the embryo and formation of the intraembryonic coelom (Ch. 10, Cell populations at gastrulation), postpharyngeal foregut/gut subdivisions and arterial territories (Ch. 60, Development of the peritoneal cavity, gastrointestinal tract and its adnexae). Langman's Medical Embryology (Sadler) 14e — divisions of the gut tube, cephalocaudal/lateral folding, molecular regulation, vitelline duct anomalies, omphalocele/gastroschisis (Ch. 6, Third to Eighth Weeks; Ch. 15, Digestive System). Moore, The Developing Human 9e — folding of the embryo in median and horizontal planes (Ch. 5). Larsen's Human Embryology 6e — gut tube formation by body folding, dorsal mesentery and vascular supply (Ch. 14, Development of the Gastrointestinal Tract). Sontakke, Textbook of Human Embryology and Brijesh Kumar, Embryology Text & Atlas — corroborating blood-supply and folding diagrams. Vishram Singh, Textbook of Clinical Embryology — folding of the embryo and formation of gut (Ch. 5).



## Mal formations of the esophagus and trachea

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The oesophagus (dorsal tube) and trachea (ventral tube) are both derivatives of the cranial foregut and are normally separated, in the 4th–5th week, by fusion of a pair of longitudinal **tracheoesophageal ridges (folds)** into the **tracheoesophageal septum**. Malformations of the oesophagus and trachea arise when this septation fails, is incomplete, or is malaligned, or when the subsequent recanalisation/maturation of either tube is defective. The most important and commonest group is **oesophageal atresia (EA) with or without tracheo-oesophageal fistula (TEF)**; less common are isolated oesophageal atresia, congenital oesophageal stenosis, tracheal agenesis/stenosis/atresia, tracheal bronchus, tracheomalacia, complete tracheal cartilage rings and the laryngo-tracheo-oesophageal cleft. Because they share a common developmental origin, these anomalies frequently coexist and are often linked to the **VACTERL** association.

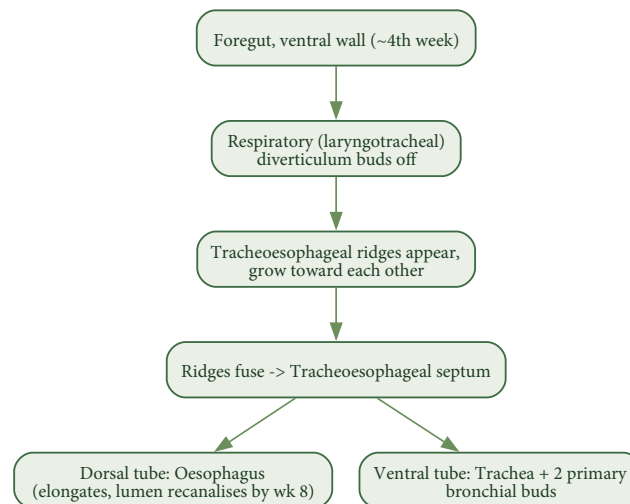
### 1. Normal septation of the foregut into oesophagus and trachea

- ▶ At approximately 4 weeks, the **respiratory (laryngotracheal) diverticulum** buds from the ventral wall of the foregut, induced by retinoic acid–driven up-regulation of the transcription factor **TBX4** in the foregut endoderm.
- ▶ Initially the diverticulum is in open communication with the foregut. As it grows caudally, two longitudinal **tracheoesophageal ridges** appear and approach each other.
- ▶ Fusion of the ridges forms the **tracheoesophageal septum**, dividing the foregut into a **dorsal oesophagus** and a **ventral trachea** (with its two primary bronchial buds); the respiratory primordium retains a cranial opening into the pharynx through the **laryngeal orifice**.
- ▶ The oesophagus is initially short; it elongates rapidly (mainly from growth/descent of the heart and lungs) and reaches its final relative length by the **7th week**. Rapid endodermal proliferation



transiently obliterates its lumen, and **recanalisation is normally complete by the end of the 8th week**.

- Muscle: the **striated muscle of the upper third** of the oesophagus is derived from mesenchyme of the 4th and 6th pharyngeal arches (innervated by the vagus — superior laryngeal nerve for the 4th-arch component, recurrent laryngeal nerve for the 6th-arch component); the **smooth muscle of the lower two-thirds** develops from the surrounding splanchnic mesenchyme.



*Mal formations of the esophagus and trachea*

## 2. Oesophageal atresia and tracheo-oesophageal fistula — classification

Failure of complete, correctly-aligned fusion of the tracheoesophageal ridges produces five recognised anatomical patterns (Gross-type classification):

| Type | Anatomy                                                                                                                                                            | Approx. incidence*                  |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| A    | Isolated oesophageal atresia — both proximal and distal segments end blindly; <b>no</b> fistula to the trachea                                                     | 8%                                  |
| B    | Proximal segment communicates with the trachea; distal segment ends blindly                                                                                        | 1%                                  |
| C    | Proximal segment ends blindly (atresia); <b>distal segment communicates with the trachea</b> near its bifurcation — the <b>commonest</b> pattern                   | 84% (cited as 85–90% in some texts) |
| D    | Both proximal and distal segments communicate separately with the trachea (double fistula)                                                                         | 3%                                  |
| E    | " <b>H-type</b> " fistula — trachea and oesophagus communicate through a fistulous tract <b>without</b> any atresia; both segments remain patent and in continuity | 4%                                  |

Percentages above follow Sontakke's Textbook of Human Embryology (matching the figure below); the letter assigned to each pattern varies between textbooks (e.g., Vishram Singh's Clinical Embryology numbers the same five patterns differently) — learn the anatomy and rough frequency\*, not the letter, as university-specific.

□ Fig 16.4 — Types of tracheoesophageal fistula (Sontakke — Textbook of Human Embryology, p.161)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the trachea (with its bifurcation) and the two oesophageal segments side by side for each type; label:

- ▶ **Trachea, Oesophagus, Proximal segment, Distal segment**
- ▶ Type A — both segments blind, **no** connecting arrow (8%)
- ▶ Type B — arrow: proximal segment → trachea; distal segment blind (1%)
- ▶ Type C — arrow: distal segment → trachea (near carina); proximal segment blind (84%, commonest — draw this one first)
- ▶ Type D — two arrows: both segments → trachea (3%)
- ▶ Type E — continuous oesophageal lumen with a side "H" bridge to the trachea, no atresia (4%)

## 3. Embryological basis and molecular control

- ▶ **Classical mechanism:** incomplete or malaligned fusion of the tracheoesophageal ridges leaves a persistent communication between the two tubes. The **direction of septal deviation determines the lesion** — posterior deviation of the tracheoesophageal septum narrows/obliterates the oesophagus (→ oesophageal atresia), whereas anterior (ventral) deviation narrows the trachea (→ tracheal stenosis).
- ▶ **Molecular mechanism** (from experimental/mouse studies): the dorsal (oesophagus/stomach) foregut endoderm expresses **Sox2**, while the ventral (trachea/lung) endoderm expresses **Nkx2.1**; these two transcription factors are reciprocally regulated and set up the dorsoventral boundary between the two tubes. **Sonic hedgehog (Shh)** signalling from the ventral endoderm, together with mesenchymal **Fgf** and **Bmp** signalling, maintains this boundary — loss of Sox2 lets Nkx2.1 expression expand into the presumptive oesophagus, and loss of Nkx2.1 lets Sox2 expand into the presumptive trachea, producing a fistulous connection.
- ▶ An alternative/complementary explanation for isolated oesophageal atresia is failure of the oesophageal endoderm to proliferate fast enough during the 5th week to keep pace with elongation of the embryo.

## 4. Other malformations of the oesophagus

- ▶ **Isolated oesophageal atresia (without TEF):** results from **failure of recanalisation** of the temporarily solid oesophageal lumen during the **8th week** — a mechanistically distinct process from tracheoesophageal-septum maldevelopment.

- ▶ **Congenital oesophageal stenosis:** narrowing anywhere along the oesophagus, most often in its **distal third**, as either a thin web or a longer thread-like segment; results from incomplete recanalisation at the 8th week, or from failure of the local oesophageal blood vessels to develop.

## 5. Other malformations of the trachea and larynx

- ▶ **Tracheal agenesis:** failure of formation of the laryngotracheal groove/tube — a rare, usually lethal anomaly.
- ▶ **Tracheal stenosis:** anterior (ventral) deviation of the tracheoesophageal septum encroaches on the tracheal lumen.
- ▶ **Tracheal atresia:** obstruction by a web of tissue within the tracheal lumen, derived from excess proliferation of endodermal cells that fails to recanalise.
- ▶ **Tracheal bronchus / tracheal lobe ("pig bronchus"):** an accessory diverticulum arising directly from the trachea that may end blindly (blind tracheal bronchus), supply an accessory lobe of lung (tracheal lobe), or replace the normal apical bronchus of the right upper lobe.
- ▶ **Tracheomalacia / bronchomalacia:** a defect of cartilage development leaving the airway wall floppy and liable to collapse — on inspiration if extrathoracic, on expiration if intrathoracic; may be localised or generalised (e.g. **Williams–Campbell syndrome**, diffuse cartilage deficiency from the 2nd to 7th bronchial generation), and may coexist with a TEF.
- ▶ **Complete tracheal cartilage rings:** the tracheal cartilages are normally horseshoe-shaped, bridged posteriorly by the membranous trachealis; when the rings are complete ("O"-shaped) over a segment, the posterior membranous wall is lost, producing long-segment tracheal stenosis, sometimes with an associated **pulmonary artery sling**.
- ▶ **Laryngo-tracheo-oesophageal cleft:** failure of fusion of the posterior cricoid lamina together with abnormal development of the tracheoesophageal septum, producing a posterior sagittal communication between the larynx/trachea and the pharynx/oesophagus.
- ▶ Other congenital laryngeal anomalies encountered in the same developmental field include laryngeal atresia, laryngeal web, laryngocele, saccular cysts, and aplasia/hypoplasia or bifid epiglottis.

## 6. Associated anomalies

- ▶ Oesophageal/tracheal septation defects are frequently part of the **VACTERL** (or VATER/VACTER) association: Vertebral defects, Anal atresia, Cardiac anomalies, Tracheo-oesophageal fistula, (o)Esophageal atresia, Renal anomalies and Limb defects (radial ray).
- ▶ Associated **cardiac anomalies** occur in roughly **30% (up to a third)** of cases (e.g. ventricular septal defect, tetralogy of Fallot); **anorectal anomalies** in ~15%; and **genitourinary anomalies** in ~15%.
- ▶ These associations occur together more often than chance alone predicts, but the underlying causation in most cases is unknown.

## Applied / Clinical anatomy

- ▶ **Antenatal:** an atresia that prevents fetal swallowing of amniotic fluid causes **polyhydramnios**; on antenatal ultrasound the fetal stomach (normally always visualised by the 20-week scan) may be small or absent, which should prompt further evaluation.
- ▶ **Neonatal presentation:** excessive drooling of saliva, choking, cyanosis and immediate regurgitation with the first feed; inability to pass a nasogastric/orogastric catheter into the stomach (the catheter coils in the blind proximal pouch — the classic "**coiled catheter**" sign on chest X-ray) is strongly suggestive.
- ▶ **Abdominal gas pattern:** when a **distal** fistula is present (types C and D), air enters the stomach and bowel with the baby's first breaths, producing a gas-filled abdomen; a **gasless abdomen** points to atresia without a distal fistula (types A and B).
- ▶ **H-type (type E) fistula** has no atresia and may escape detection at birth, presenting later in infancy or childhood with recurrent choking on feeds and recurrent aspiration/chest infections.
- ▶ Reflux of gastric and intestinal contents through a distal fistula into the trachea and lungs can cause chemical **pneumonitis** and respiratory compromise.
- ▶ **Management** is emergency surgical division/ligation of the fistula with primary end-to-end oesophageal anastomosis, usually via a right extrapleural thoracotomy; the **azygos vein**, which arches over the right main bronchus, and the **vagus and recurrent laryngeal nerves** lie close to the operative field and are at risk. Modern neonatal surgical repair achieves survival rates **above 85%**.
- ▶ Long-term sequelae include anastomotic stricture, gastro-oesophageal reflux, recurrent fistula and localised tracheomalacia at the level of the previously atretic segment.

## High-yield exam pointers

- ▶ TEF/EA result from faulty fusion (or malalignment) of the **tracheoesophageal ridges/septum** during foregut septation in the 4th–5th week.
- ▶ Overall incidence  $\approx$  **1 in 3000–4500** live births; **type C** (proximal atresia + distal fistula) is by far the commonest pattern ( $\approx$  84–90%).
- ▶ Learn the **5 anatomical patterns (A–E)** and their approximate frequencies, not the exact letters — these differ between textbooks.
- ▶ **H-type (type E)** has **no atresia** — it is a fistula with continuity, so it often presents **late**, not at birth.
- ▶ **Isolated oesophageal atresia** (no fistula) arises from failure of **recanalisation at week 8** — a different mechanism from the classic septal-fusion defect.
- ▶ Direction of septal deviation predicts the lesion: **posterior** deviation  $\rightarrow$  oesophageal atresia; **anterior/ventral** deviation  $\rightarrow$  tracheal stenosis.
- ▶ Antenatal clue: **polyhydramnios** + small/absent stomach bubble on USG. Postnatal clue: **failure to pass an NG tube**, coiled-catheter sign, and abnormal abdominal gas pattern.
- ▶ Strongly associated with the **VACTERL** association; screen for cardiac defects ( $\sim$ 30% of cases).
- ▶ Molecular boundary: **Sox2** (dorsal, oesophagus/stomach) vs **Nkx2.1** (ventral, trachea/lung), maintained by Shh–Bmp–Fgf signalling.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke, Textbook of Human Embryology; Vishram Singh, Textbook of Clinical Embryology; Brijesh Kumar, Embryology Text & Atlas.



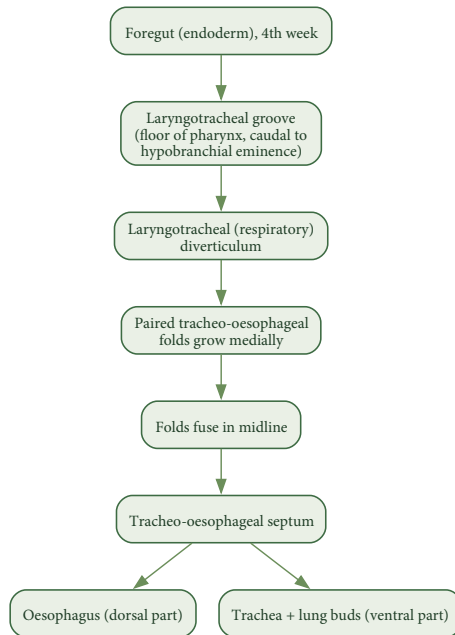
## Malformations of oesophagus and Trachea

*Asked in: Paper II May 2018 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The oesophagus and trachea both arise from the single tubular **foregut**, separated in the fourth week by the **tracheo-oesophageal septum**. Any defect in this septation process is the embryological basis of almost every malformation of the two organs — from the common oesophageal atresia/tracheo-oesophageal fistula (TEF) complex to isolated tracheal stenosis. TEF-with-atresia is the single commonest congenital anomaly of the oesophagus and one of the most important surgical emergencies of the newborn, with an incidence of about **1 in 3000–4500 live births**. This answer covers the developmental basis, classification, and the malformations of both organs together with their applied anatomy.

### 1. Developmental basis (how the septum forms and how it fails)

- ▶ In the **4th week**, a midline **laryngotracheal groove** appears in the floor of the primitive pharynx, just caudal to the hypobranchial eminence.
- ▶ The groove deepens into the **laryngotracheal (respiratory) diverticulum**, which stays in open communication with the foregut.
- ▶ Two longitudinal **tracheo-oesophageal folds/ridges** grow medially on either side of the diverticulum and **fuse in the midline** to form the **tracheo-oesophageal septum**.
- ▶ This septum divides the foregut into a **dorsal part (oesophagus)** and a **ventral part (trachea + lung buds)**.
- ▶ Cranial extension of the septum is arrested at the **laryngeal inlet (furcula of His)**, through which the larynx permanently communicates with the pharynx.
- ▶ The oesophagus is initially short; it **elongates** with (i) formation of the neck, (ii) descent of the diaphragm, and (iii) descent of the heart and lungs.
- ▶ Both organs pass through a **solid (occlusion) phase**, when endodermal cell proliferation obliterates the lumen, followed by **recanalisation**. Failure of recanalisation underlies atresia/stenosis in either tube.
- ▶ **Layers: lining epithelium and glands** — endoderm of the laryngotracheal tube/foregut; **musculature and connective tissue** — surrounding splanchnic mesenchyme. In the oesophagus this yields striated muscle in the upper third, mixed in the middle third, and smooth muscle in the lower third (as elsewhere in the gut tube).



*Malformations of oesophagus and Trachea*

## 2. Oesophageal atresia and tracheo-oesophageal fistula (TEF) — classification

- **Cause:** failure of the tracheo-oesophageal folds to fuse over a segment (leaves an abnormal communication = fistula), commonly compounded by **extreme posterior deviation of the septum** (which obliterates a segment of oesophagus = atresia).
- **Incidence:**  $\approx 1$  in 3000–4500 live births.
- Classified (Gross/Vogt classification) into five types by the pattern of atresia and fistula:

| Type       | Description                                                                                                                                                  | Approx. frequency* |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| A          | Isolated oesophageal atresia — both segments end blindly; <b>no</b> communication with the trachea                                                           | ~4%                |
| B          | Proximal oesophageal segment communicates with the trachea (proximal fistula); distal segment ends blindly                                                   | ~1%                |
| C          | Proximal segment ends blindly (atresia); distal segment communicates with the trachea (distal fistula) — <b>the classic and by far the commonest pattern</b> | ~90%               |
| D          | Both proximal and distal segments communicate separately with the trachea                                                                                    | ~1%                |
| E (H-type) | Oesophagus is continuous, with <b>no atresia</b> ; an abnormal fistulous canal connects the (otherwise patent) oesophagus and trachea                        | ~4%                |

Frequencies as given in the standard embryology figure legend (Langman 14e); some texts letter the same five anatomical patterns in frequency order rather than by pattern — the descriptions\*, not the letters, are what must be reproduced in the exam.

□ Fig 16.4 — Types of tracheoesophageal fistula (Sontakke — Textbook of Human Embryology, p.161)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw five labelled panels (A–E), each showing: **pharynx (top) → proximal oesophageal segment → distal oesophageal segment → stomach (bottom)**, with the **trachea and carina** alongside. In each panel label clearly: whether the proximal segment ends in a **blind pouch** or is **patent**; whether the distal segment ends **blind** or is **patent**; and the **fistulous communication** (if any) between oesophagus and trachea, with an arrow/asterisk marking the site of failed septal fusion. Panel C (proximal blind pouch + distal fistula) should be marked "commonest — ~90%".

### 3. Other malformations of the oesophagus

- ▶ **Isolated oesophageal stenosis**: narrowing of the lumen, usually in the **lower third**; caused by incomplete recanalisation and/or vascular insufficiency during development.
- ▶ **Short oesophagus**: failure of the oesophagus to elongate normally; the stomach is pulled up through the oesophageal hiatus, producing a **congenital hiatal hernia**.
- ▶ **Achalasia cardia**: failure of relaxation of the lower oesophageal musculature following **loss of ganglion cells of Auerbach's (myenteric) plexus**; presents with dysphagia and a "bird-beak"/pencil-shaped narrowing of the lower oesophagus on barium swallow.

### 4. Malformations of the trachea

- ▶ **Tracheal stenosis**: narrowing of the tracheal lumen due to **anterior (ventral) deviation** of the tracheo-oesophageal septum (the mirror-image defect of the posterior deviation that produces oesophageal atresia). Rare.
- ▶ **Tracheal atresia**: obstruction by a persistent **web of endodermal tissue** within the tracheal lumen, from failure of the normal recanalisation of the solid-phase trachea.
- ▶ **Tracheal bronchus / tracheal lobe**: an accessory bronchial diverticulum arising directly from the trachea (proximal to the carina) — it may end **blindly** (blind tracheal bronchus), may **supply an isolated tracheal lobe** of lung tissue, or may **replace** a normal bronchus (classically the apical bronchus of the upper lobe).

### Applied / Clinical anatomy

- ▶ **Antenatal**: the fetus with oesophageal atresia cannot swallow amniotic fluid, so amniotic fluid accumulates — **polyhydramnios** — a key antenatal ultrasound clue (often with a small/absent fetal stomach bubble).
- ▶ **Postnatal presentation**: the newborn tolerates the very first feed but then **regurgitates/vomits every subsequent feed**, with **coughing, choking and cyanosis** as milk enters the airway through the fistula; excess frothy saliva and inability to pass a nasogastric/feeding catheter into the stomach (it coils in the blind proximal pouch) are classic bedside signs.



- ▶ **Radiology:** a catheter coiled in the upper pouch on chest X-ray confirms proximal atresia; **air in the stomach** on an erect abdominal film indicates a **patent distal tracheo-oesophageal fistula** (as in type C), whereas a **gasless abdomen** suggests isolated atresia without a distal fistula (type A) — an important bedside distinguishing sign.
- ▶ **Associated anomalies — VACTERL association:** TEF/oesophageal atresia frequently co-exists with Vertebral, Anal, Cardiac, Tracheo-oesophageal, Renal, and Limb defects; their presence should always be actively screened for.
- ▶ **Vascular mimic:** an aberrant right subclavian artery crossing behind the oesophagus can form a vascular ring around the trachea/oesophagus and compress the oesophagus, producing **dysphagia lusoria** — an important differential for extrinsic (not intrinsic) oesophageal narrowing.
- ▶ **Management:** surgical division/ligation of the fistula with primary end-to-end oesophageal anastomosis is emergency treatment; reported survival with surgical correction is around 85%.

### High-yield exam pointers

- ▶ Both oesophagus and trachea are derivatives of the **foregut**, separated by the **tracheo-oesophageal septum** (formed by fusion of paired tracheo-oesophageal folds) in the **4th week**.
- ▶ **Posterior deviation** of the septum → oesophageal atresia/TEF; **anterior (ventral) deviation** → tracheal stenosis.
- ▶ Incidence of TEF/oesophageal atresia ≈ **1 in 3000–4500** live births; **Type C (proximal atresia + distal fistula) is commonest (~90%)**; H-type (E, no atresia) ~4%; isolated atresia (A) ~4%; types B and D are rarest (~1% each).
- ▶ Oesophageal atresia → fetus cannot swallow → **polyhydramnios**; postnatally choking/regurgitation with feeds.
- ▶ **Air in the stomach on X-ray = patent distal fistula**; gasless abdomen = isolated atresia.
- ▶ Screen for the **VACTERL association** whenever TEF/oesophageal atresia is diagnosed.
- ▶ Cranial limit of the tracheo-oesophageal septum is the **furcula of His** (laryngeal inlet).
- ▶ Other oesophageal anomalies: **stenosis** (lower third), **short oesophagus** (→ congenital hiatal hernia), **achalasia cardia** (loss of Auerbach's plexus ganglion cells).
- ▶ Other tracheal anomalies: **stenosis**, **atresia/web**, and **tracheal bronchus/lobe** (accessory bronchus arising directly from the trachea).

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke's Textbook of Human Embryology; Vishram Singh's Textbook of Clinical Embryology; Gray's Anatomy (Standring) 41e.



## Meckel's diverticulum

Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy

### Definition / Introduction

Meckel's diverticulum (diverticulum ilei) is a **true diverticulum** of the ileum formed by persistence of the proximal (intestinal) part of the vitellointestinal duct — also called the omphaloenteric, omphalomesenteric or vitelline duct — of the embryonic midgut. It is the **commonest congenital anomaly of the gastrointestinal tract**, and because its wall contains all four coats of the ileum it is a "true" diverticulum, unlike acquired (pulsion) diverticula of the colon. It is of major surgical importance because of the complications it can produce and the ectopic tissue it may harbour.

### 1. Embryological basis

- ▶ In the 3rd–4th week the primitive gut tube is in wide, open communication with the extra-embryonic yolk sac.
- ▶ As the embryo folds laterally and cranio-caudally, this communication is progressively narrowed to a slender **vitellointestinal (vitelline) duct** connecting the apex of the U-shaped midgut loop to the yolk sac; the duct runs within the connecting stalk (future umbilical cord), accompanied by the paired **vitelline arteries** and **vitelline veins**.
- ▶ The midgut loop herniates physiologically into the umbilical cord (6th–10th week), rotates 270° counter-clockwise around the axis of the superior mesenteric artery, and returns to the abdominal cavity by the 10th week.
- ▶ The vitellointestinal duct normally undergoes complete involution — obliterating and separating from the midgut — during this same window (usually described as complete by about the **6th week**, with obliteration of the intra-abdominal segment sometimes not finished before the **10th week**); the duct and its vessels are then shed with the yolk sac remnant as the umbilical cord forms.
- ▶ **Failure of obliteration of the vitellointestinal duct connecting the midgut to the yolk sac** is the basis of Meckel's diverticulum and the related spectrum of vitelline-duct anomalies described below.

### 2. Gross anatomical features — the "Rule of Twos"

| Feature                           | Description                                                                  |
|-----------------------------------|------------------------------------------------------------------------------|
| Incidence                         | ~2% of the population (quoted range 2–4% across texts)                       |
| Site                              | Antimesenteric border of the ileum                                           |
| Distance from ileocaecal junction | ≈2 feet (60 cm) proximal to the ileocaecal valve (reported range ~40–100 cm) |
| Length                            | ≈2 inches (5 cm) (reported range ~1–6 cm)                                    |
| Calibre                           | Same as that of the adjoining ileum                                          |
| Sex                               | More common in males (reported 2–5× male preponderance)                      |

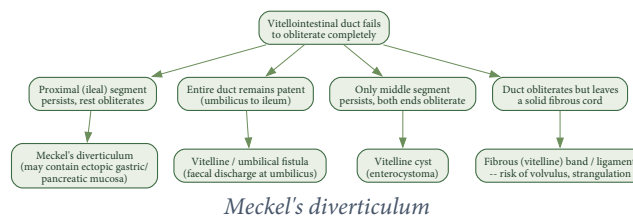
| Feature             | Description                                                                             |
|---------------------|-----------------------------------------------------------------------------------------|
| Tissue              | May contain 2 types of heterotopic epithelium — gastric mucosa and/or pancreatic tissue |
| Age at presentation | Most symptomatic cases present within the first 2 years of life                         |
| Wall                | Blind pouch with all 4 coats of ileum — serous, muscular, submucous, mucous             |

(The mnemonic "2s" — 2% incidence, 2 feet from the ileocaecal junction, 2 inches long, 2× commoner in males, 2 types of ectopic tissue — is the standard exam recall device for this anomaly.)

- It is a **blind-ended, finger-like pouch** projecting from the antimesenteric border of the ileum; its apex may be **free**, or attached by a fibrous cord (the obliterated remnant of the duct) to the umbilicus, the mesentery, or any other abdominal viscus.
- The fibrous cord, when present, may itself carry a **persistent vitelline artery** — a remnant of the vitelline vessels that originally carried blood to the yolk sac — running along it to the umbilicus; a diverticulum with its own such vessel effectively has an independent blood supply distinct from the main ileal mesenteric arcades, a point of surgical relevance during resection.

### 3. Spectrum of vitellointestinal duct anomalies

Persistence of different segments of the duct produces a family of related anomalies, all arising from the same embryological failure:



| Anomaly                           | Segment persisting               | Clinical consequence                                       |
|-----------------------------------|----------------------------------|------------------------------------------------------------|
| Meckel's diverticulum             | Proximal (ileal) part            | Ulceration, bleeding, diverticulitis, obstruction          |
| Vitelline (umbilical) fistula     | Entire duct, patent              | Faeculent discharge at the umbilicus                       |
| Vitelline cyst (enterocystoma)    | Middle part only                 | Cystic swelling deep to umbilicus; may twist               |
| Fibrous cord / vitelline ligament | Duct obliterates to a solid cord | Band around which bowel can twist → volvulus/strangulation |
| Umbilical sinus                   | Part of duct near umbilicus      | Blind sinus opening at the umbilicus                       |

□ Fig 10.6 — Meckel's diverticulum: (A) vitellointestinal duct connecting the midgut loop to the yolk sac in an early embryo; (B) schematic position of Meckel's diverticulum relative to the ileum, mesentery and umbilicus; (C) Meckel's diverticulum as seen at operation (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.450)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the ileum with its mesentery, and label:

- ▶ **Ileum** (with mesenteric border and antimesenteric border marked).
- ▶ **Meckel's diverticulum** — a blind pouch arising from the **antimesenteric border**, ≈60 cm proximal to the **ileocaecal junction**.
- ▶ Its **blind apex** — shown either free, or continued as a **fibrous cord** to the **umbilicus**.
- ▶ The fibrous cord carrying a **remnant of the vitelline artery** (if depicting the "own blood supply" variant).
- ▶ Inset/adjacent small panel: the embryonic stage showing the **vitellointestinal duct** joining the apex of the **midgut loop** to the **yolk sac**, to show the developmental origin.
- ▶ Optionally, a 3-panel row (as in the plate above) showing the three siblings of the same defect — **vitelline fistula** (patent duct opening at umbilicus) and **vitelline cyst** (isolated cystic segment) — to contrast with the diverticulum itself.

**Applied / Clinical anatomy**

- ▶ **Ectopic mucosa**: up to a large proportion of diverticula harbour heterotopic gastric or pancreatic tissue in the wall or at the tip; acid secretion from ectopic gastric mucosa causes **peptic ulceration** of the adjoining ileal mucosa, presenting as painless lower gastrointestinal bleeding — the commonest presentation in children.
- ▶ **Meckel's diverticulitis**: inflammation of the diverticulum produces periumbilical pain localising to the right iliac fossa, closely **mimicking acute appendicitis** — a classical differential diagnosis at laparotomy for a "normal appendix."
- ▶ **Intestinal obstruction**: a fibrous band (obliterated duct remnant) tethering the diverticulum to the umbilicus predisposes to volvulus of a loop of bowel around the band, with strangulation; the diverticulum itself may also intussuscept, acting as the lead point of an ileo-ileal or ileocolic intussusception.
- ▶ **Littre's hernia**: when a Meckel's diverticulum enters an inguinal (or femoral) hernial sac, the hernia is termed a **Littre's hernia**.
- ▶ **Perforation**: ulceration at the site of ectopic gastric mucosa may progress to perforation and peritonitis.
- ▶ **Associated anomalies**: roughly a third of symptomatic cases are associated with other congenital defects — intestinal atresia, imperforate anus, gastroschisis, or omphalocele — reflecting a shared window of vulnerability in midgut/ventral-wall development.
- ▶ **Related anomalies at the umbilicus** (vitelline fistula, vitelline cyst, fibrous band/ligament, umbilical sinus) arise from persistence of other segments of the same duct (see table above) and share the same surgical importance.
- ▶ **Investigation**: a symptomatic diverticulum with ectopic gastric mucosa can be localised clinically by a **technetium-99m pertechnetate scan** ("Meckel's scan"), which is taken up by gastric-type mucosa; surgical **diverticulectomy** (with ligation of its own persistent vessel when present) is curative.

- ▶ **Surface/operative note:** because the diverticulum arises well proximal to the ileocaecal junction on the antimesenteric border, it is readily missed unless the surgeon deliberately runs the terminal ileum for a defined length proximal to the caecum when appendicitis-like symptoms are found with a normal appendix.

### High-yield exam pointers

- ▶ Meckel's diverticulum = persistent **proximal part of the vitellointestinal (omphaloenteric) duct**; a **true diverticulum** (all 4 coats present).
- ▶ Recall via the "**Rule of Twos**": 2% incidence, 2 feet from ileocaecal junction, 2 inches long, 2× more common in males, 2 types of ectopic tissue (gastric/pancreatic), presents by age 2.
- ▶ Arises from the **antimesenteric border** of the ileum — the single most important localising fact distinguishing it from a duplication cyst (which lies on the mesenteric side).
- ▶ May carry its **own persistent blood vessel** (vitelline artery remnant) along the fibrous cord to the umbilicus — surgically relevant.
- ▶ The same embryological failure, at different points along the duct, produces **vitelline fistula**, **vitelline cyst (enterocystoma)**, and a **fibrous band/ligament** — know the whole family, not just the diverticulum.
- ▶ Complications to remember: **ulceration/bleeding** (ectopic gastric mucosa), **diverticulitis** (mimics appendicitis), **intestinal obstruction/volvulus** (around the fibrous band), **intussusception**, and **Littre's hernia** (in an inguinal/femoral sac).
- ▶ Named after **Johann Friedrich Meckel**, who correctly attributed it to persistence of the vitellointestinal duct.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2, 8e; AK Datta — Human Anatomy Vol 1 (Thorax & Abdomen); Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human, 9e; Larsen — Human Embryology, 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2, 4e (figure); Sontakke — Textbook of Human Embryology.



## Mid gut rotation and errors of rotation

Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **midgut** extends from the opening of the bile duct in the second part of the duodenum to the junction of the proximal two-thirds and distal one-third of the transverse colon, and is supplied throughout by the **superior mesenteric artery (SMA)**. Between the 6th and 12th weeks of intra-uterine life the rapidly elongating midgut loop herniates physiologically into the umbilical cord and, while herniated and while returning to the abdomen, undergoes a precisely orchestrated **270° counter-clockwise rotation** around the axis of the SMA. This rotation establishes the definitive adult arrangement of the small and large intestine. Any deviation in the amount or direction of this rotation — or in the subsequent fixation of the gut to the posterior abdominal wall — produces a spectrum of clinically important **errors of rotation** (nonrotation, incomplete/mixed rotation, reversed rotation) and related fixation anomalies (subhepatic caecum, mobile caecum, internal hernia, midgut volvulus).

### 1. Extent and derivatives of the midgut

| Segment (relative to SMA)   | Adult derivatives                                                                                                             |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Pre-arterial (cranial) limb | Lower half of 2nd, and the 3rd & 4th parts of duodenum; jejunum; ileum (except terminal part)                                 |
| Post-arterial (caudal) limb | Terminal ileum; caecum and vermiform appendix (from the caecal bud); ascending colon; proximal two-thirds of transverse colon |

- ▶ The SMA passes centrally between the two limbs and forms the fixed axis around which all subsequent rotation occurs.

### 2. Physiological umbilical herniation

- ▶ Begins in the **6th week**: the rapidly growing midgut loop, together with the disproportionately large liver and mesonephric kidneys, cannot be accommodated in the small embryonic abdominal cavity, so the loop herniates into the extra-embryonic coelom within the proximal umbilical cord.
- ▶ The loop communicates with the yolk sac through the narrow **vitello-intestinal (omphaloenteric) duct** at its apex.
- ▶ The pre-arterial limb elongates rapidly forming the jejuno-ileal coils; the post-arterial limb changes little apart from developing the **caecal bud** (primordium of caecum/appendix).
- ▶ Herniated loops begin to return to the enlarging abdominal cavity from the **10th week**, the herniation being fully reduced by about the 12th week.

### 3. Normal rotation of the midgut (270° counter-clockwise around the SMA axis)

| Stage   | When it occurs                               | Degree/net total | Result                                                                                                       |
|---------|----------------------------------------------|------------------|--------------------------------------------------------------------------------------------------------------|
| 1st 90° | Within the umbilical cord, during herniation | 90° (total 90°)  | Pre-arterial limb swings to the <b>right</b> , post-arterial limb to the <b>left</b> (viewed from the front) |

| Stage   | When it occurs                                             | Degree/net total      | Result                                                                                                                         |
|---------|------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------|
| 2nd 90° | During return of the small-intestinal coils to the abdomen | 90° more (total 180°) | Jejuno-ileal coils (pre-arterial limb) pass <b>behind</b> the SMA; the duodenum comes to lie <b>posterior</b> to the SMA       |
| 3rd 90° | During return of the post-arterial (caecal) limb           | 90° more (total 270°) | Caecum/appendix are carried to the <b>right</b> , transiently sub-hepatic; transverse colon crosses <b>anterior</b> to the SMA |

- The caecal bud finally descends from its sub-hepatic position into the **right iliac fossa**, defining the ascending colon and hepatic flexure.

□ Fig 14.13 — *Herniation and Rotation of the Intestine (A, B) At the end of the* (Larsen — *Human Embryology* — 6e, p.868)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A schematic lateral/oblique view of the abdomen at successive gestational stages, labelling: **Aorta**, **Superior mesenteric artery (axis)**, **Stomach**, **Primary intestinal loop**, **Pre-arterial (cranial) limb**, **Post-arterial (caudal) limb**, **Liver**, **Cecum**, **Vermiform appendix**, **Small intestine**, **Colon (ascending/transverse/descending)**, **Rectum**; mark the rotation arrows at 90° → 180° → 270° at each successive panel. For the **reversed-rotation** error, redraw the final panel with the labels **Duodenum (anterior to SMA)**, **Stomach**, **Small intestine**, **Cecum**, **Transverse colon (posterior to SMA)**, **Descending colon** to contrast with the normal (anterior transverse colon) arrangement.

### 4. Retraction and fixation of the midgut derivatives

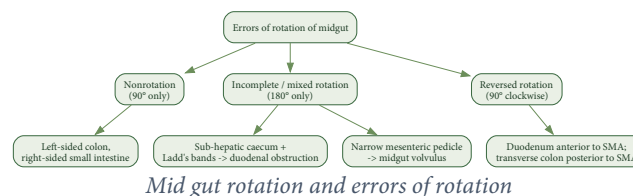
- As the gut returns and enlarges, its mesentery is pressed against the posterior abdominal wall; where this fuses with the parietal peritoneum (**zygosis**), the segment becomes secondarily **retroperitoneal**.
- Retroperitoneal by fusion: **duodenum** (except the proximal 1 inch, which is foregut-derived and retains a mesentery), **ascending colon**, and (hindgut-derived) **descending colon**.
- Free mesenteries that persist: **mesentery proper** (jejunum/ileum), **transverse mesocolon**, **sigmoid mesocolon**, **mesoappendix** — their oblique/transverse lines of attachment are a direct consequence of the rotation described above.
- The line of attachment of the mesentery proper runs obliquely from the **duodeno-jejunal flexure** to the **ileo-caecal junction**.



## 5. Errors of rotation

| Type                                             | Rotation actually completed                | Resulting anomaly                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nonrotation                                      | 90° only (or none)                         | Post-arterial (caecal) limb returns first, so the <b>entire large intestine lies on the left</b> and the <b>small intestine occupies the right side</b> of the abdomen; caecum lies close to the midline near the duodeno-jejunal flexure                                                                                                                           |
| Incomplete / mixed rotation ("partial rotation") | First 180° normal, final 90° fails         | Caecum and appendix fail to descend — they lie just <b>below the pylorus / sub-hepatic</b> ; the mal-positioned caecum is tethered to the posterior body wall by fibrous <b>peritoneal (Ladd's) bands</b> that cross the 2nd part of the duodenum, causing <b>duodenal obstruction</b> ; the resulting narrow-based mesentery predisposes to <b>midgut volvulus</b> |
| Reversed rotation                                | Net 90° clockwise (mirror-image of normal) | <b>Duodenum</b> lies <b>anterior</b> to the SMA (instead of posterior); the <b>transverse colon</b> lies <b>posterior</b> to the SMA/duodenum (instead of anterior) and may itself be obstructed by SMA compression                                                                                                                                                 |

□ Fig 14.18 — Reversed Rotation of the Gut The net rotation is 90 degree- clockwise, (Larsen — Human Embryology — 6e, p.875)



## 6. Fixation anomalies allied to malrotation

- ▶ **Sub-hepatic caecum and appendix** — if the ascending colon fails to elongate/descend, the caecum (which lies transiently below the liver during the third 90° of rotation) remains permanently sub-hepatic; occurs in about **6% of fetuses**, commoner in males, and may mimic cholecystitis when the appendix inflames.
- ▶ **Mobile caecum** — incomplete fixation of the ascending colon mesentery leaves the caecum abnormally free (about **10% of people**); predisposes to **caecal volvulus**.
- ▶ **Internal (para-duodenal) hernia** — a loop of small intestine becomes trapped within the mesentery of the midgut loop as it returns to the abdomen, creating a hernia-like sac; usually asymptomatic and often an incidental autopsy/surgical finding.
- ▶ **Midgut volvulus** — the hallmark surgical emergency of malrotation: the small intestine, suspended on an abnormally narrow stalk containing the SMA and its vein, twists on this

pedicle; the twist first obstructs venous return, then arterial inflow, producing **infarction and gangrene** of the entire SMA territory if not relieved promptly.

### Applied / Clinical anatomy

- ▶ **Neonatal bilious vomiting** is the classical presentation of malrotation with volvulus and is a surgical emergency until proved otherwise.
- ▶ **Ladd's bands**, running from the mal-positioned caecum across the duodenum to the posterior body wall, are the anatomical basis of the duodenal obstruction seen in incomplete rotation.
- ▶ The **suspensory ligament (of Treitz)**, which normally anchors the duodeno-jejunal flexure to the left of the body of the L1/L2 vertebra, is displaced in malrotation and its abnormal position is a key radiological sign.
- ▶ **Contrast (barium) studies** classically show an **"S"-shaped/mal-positioned duodenum** and an abnormally sited duodeno-jejunal junction; a corkscrew-shaped small bowel is the recognised sign of an established volvulus.
- ▶ Definitive treatment is the **Ladd's procedure** — surgical division of Ladd's bands, counter-clockwise de-rotation of the volvulus, broadening of the mesenteric base (to prevent recurrence), and appendicectomy (because the appendix's abnormal position would otherwise confound later diagnosis of appendicitis).
- ▶ Malrotation is frequently associated with other physiological-herniation-related defects (e.g., **omphalocele**, where the bowel simply fails to return, carrying an un-rotated gut with it) though these are distinct anomalies of *return*, not of rotation per se.
- ▶ A **sub-hepatic/high-riding appendix** can mimic acute cholecystitis clinically, an important differential in the right hypochondrium.

### High-yield exam pointers

- ▶ Midgut = 2nd part of duodenum (distal to bile-duct opening) to junction of proximal 2/3 and distal 1/3 of transverse colon; entirely supplied by the SMA.
- ▶ Physiological umbilical herniation: 6th–10th/12th week; caused by relative disproportion between rapidly growing gut/liver and the small embryonic abdominal cavity.
- ▶ Total rotation = **270° counter-clockwise** about the SMA axis, in **three successive 90° stages** — first 90° during herniation, remaining 180° during return.
- ▶ **Nonrotation** = only 90° completed → left-sided colon, right-sided small intestine.
- ▶ **Incomplete/mixed rotation** = 180° completed, final 90° fails → sub-hepatic caecum + Ladd's bands + duodenal obstruction + risk of volvulus.
- ▶ **Reversed rotation** = net 90° clockwise → duodenum anterior to SMA, transverse colon posterior to SMA.
- ▶ Retroperitoneal by fusion (zygosis): duodenum (except first inch), ascending colon, descending colon.
- ▶ Sub-hepatic caecum (~6%) and mobile caecum (~10%) are common incidental fixation variants; midgut volvulus is the life-threatening emergency of malrotation.
- ▶ Ladd's procedure = division of Ladd's bands + de-rotation + mesenteric broadening + appendicectomy.

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Larsen, Human Embryology 6e (figures); Vishram Singh, Textbook of Clinical Embryology; Sontakke, Textbook of Human Embryology; IB Singh, Human Embryology (CBME 2021).



## Midgut rotation

*Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The midgut extends from just distal to the opening of the common bile duct (mid-second part of duodenum) to the junction of the proximal two-thirds and distal one-third of the transverse colon; it is supplied throughout by the **superior mesenteric artery (SMA)**, which also forms the **axis of midgut rotation**. Rapid elongation of the midgut, combined with a temporarily small abdominal cavity (crowded by the enlarging liver and mesonephros), produces a **physiological umbilical herniation** of the midgut loop in the sixth week. As the herniated loop returns to the abdomen it undergoes a **total of 270° of anticlockwise rotation** around the SMA, carried out in three sequential 90° steps, which fixes the definitive relations of the small and large intestine. Errors at any step (non-rotation, reversed rotation, mixed rotation/malrotation) underlie important neonatal surgical emergencies such as midgut volvulus.

### 1. Formation of the primary intestinal (midgut) loop

- By the fifth week the midgut is thrown into a ventral, U-shaped **primary intestinal loop**, suspended by a short dorsal mesentery and connected at its apex to the yolk sac by the **vitello-intestinal (vitelline) duct**.
- The SMA runs through the mesentery along the long axis of the loop and divides it into two segments:

| Segment                    | Position        | Adult derivatives                                                                                                          |
|----------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| Prearterial (cranial) limb | Proximal to SMA | Distal half of duodenum, jejunum, ileum (except its terminal part)                                                         |
| Postarterial (caudal) limb | Distal to SMA   | Terminal ileum, caecum and appendix (via the <b>caecal bud</b> ), ascending colon, proximal two-thirds of transverse colon |

- The **caecal bud**, a small conical dilatation, appears on the antimesenteric border of the postarterial segment near the apex of the loop at about the sixth week; its proximal part enlarges to form the caecum, its narrow distal part forms the appendix.

! [Fig 15.25 — A. Primary intestinal loop before rotation [lateral view]. The superio (Langman's Medical Embryology — Sadler — 14e, p.265)](C:/Users/Harshad/Documents/anatomy-notes/references/figures/LangmansMedicalEEmbry/figp2652.png)

## 2. Physiological umbilical herniation

- ▶ During the third week the midgut loop (particularly its prearterial segment) elongates rapidly; simultaneous enlargement of the liver leaves the abdominal cavity too small to contain it.
- ▶ Consequently, from the **sixth week** the loops of midgut herniate through the umbilical opening into the extra-embryonic coelom within the proximal umbilical cord — the **physiological umbilical hernia**.
- ▶ The prearterial (jejuno-ileal) limb elongates extensively and coils while still outside the abdomen; the postarterial (colic) limb elongates far less and does not coil.
- ▶ Reduction begins as the abdominal cavity enlarges relative to the liver and mesonephros; return to the abdomen starts in the **tenth week** and is complete by about the **eleventh–twelfth week**.

## 3. Rotation of the midgut loop

Before any rotation, viewed from the front, the prearterial segment, the SMA, and the postarterial segment lie one below the other in a single vertical (sagittal) plane. Return of the loop to the abdomen is accompanied by a **total rotation of 270° in an anticlockwise direction (as seen from the front), occurring as three successive 90° steps** — the first while the loop is still within the umbilical cord, the remaining two as it re-enters the abdomen.

| Stage   | Timing                                                                 | What rotates                                   | Result                                                                                                                                                             |
|---------|------------------------------------------------------------------------|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st 90° | Within the umbilicus, during herniation (complete by ~8th week)        | Whole loop rotates around the SMA axis         | Prearterial segment swings to the embryo's right; postarterial segment swings to the left; jejuno-ileal coils now lie to the right of the SMA, outside the abdomen |
| 2nd 90° | As the jejuno-ileal coils re-enter the abdomen first (from ~10th week) | Prearterial-derived coils slide behind the SMA | Duodenum comes to lie <b>posterior/behind the SMA</b> ; jejunum settles mainly to the left, ileum mainly to the right, in the subhepatic space                     |
| 3rd 90° | As the postarterial segment (with the caecal bud) re-enters last       | Caecum and appendix rotate further             | Caecum and appendix come to lie on the <b>right side, just below the liver</b> (subhepatic); transverse colon passes anterior to the duodenum and SMA              |

- ▶ The caecum is the last part to return; it initially lies on coils of ileum in the subhepatic position and only later descends, with elongation of the ascending colon, to reach the right iliac fossa.
- ▶ The hepatic and splenic flexures are established once the colon has elongated after full return.

□ Fig 15.27 — A. Anterior view of the intestinal loops after 270° counterclockwise r (Langman's Medical Embryology — Sadler — 14e, p.266)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A left-lateral (or anterior cut-away) schematic of the midgut loop through the three stages, labelled:

- ▶ Stomach and duodenum
- ▶ Prearterial segment (future jejunum/ileum) and postarterial segment (future caecum–ascending colon–proximal transverse colon)
- ▶ Superior mesenteric artery — the axis of rotation
- ▶ Caecal bud / vitello-intestinal duct at the apex of the loop
- ▶ Umbilical ring / umbilical cord (site of herniation)
- ▶ Curved arrows showing each successive 90° anticlockwise rotation (× 3)
- ▶ Final adult disposition: duodenum behind SMA, caecum subhepatic → right iliac fossa, transverse colon anterior to SMA/duodenum
- ▶ Line of fixation of dorsal mesentery from duodenojejunal flexure to ileocaecal junction

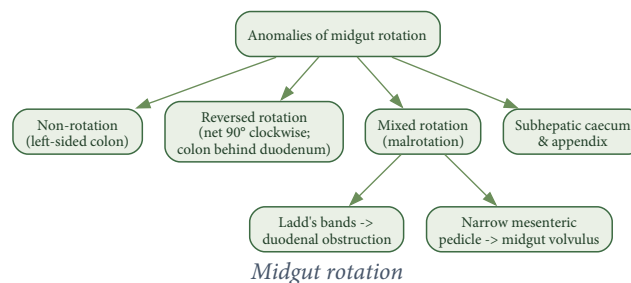
**4. Fixation (zygosis) of the midgut derivatives**

- ▶ The original dorsal mesentery is at first attached in the midline; after rotation its line of attachment runs obliquely from the duodenojejunal flexure to the ileocaecal junction.
- ▶ **Ascending colon** and the **duodenum** (distal to the first inch of its first part) develop only a short mesentery, which fuses with the parietal peritoneum of the posterior abdominal wall (**zygosis**) — both become **secondarily retroperitoneal**.
- ▶ **Transverse colon** retains a free mesentery (transverse mesocolon), running transversely — this orientation is a direct legacy of the third 90° rotation; it remains **intraperitoneal and mobile**.
- ▶ **Jejunum and ileum** retain the mesentery proper along the oblique fixation line; **sigmoid colon** also remains mobile on its mesentery.

**Applied / Clinical anatomy**

- ▶ **Non-rotation (left-sided colon)**: the loop fails to rotate; the postarterial (colonic) segment returns first and lies on the **left**, while small intestine occupies the **right** side of the abdomen.
- ▶ **Reversed rotation**: the first 90° occurs normally, but the subsequent 180° occurs **clockwise** instead of anticlockwise (net 90° clockwise); the **transverse colon comes to lie posterior to the duodenum and SMA** — the duodenum, not the colon, fails to become retroperitoneal.
- ▶ **Mixed rotation (malrotation)**: only the cephalic limb completes the initial 90°, and only the caudal limb completes the later 180°; the caecum becomes fixed near the midline just below the pylorus instead of the right iliac fossa. Abnormal peritoneal bands from this malpositioned caecum to the posterior body wall — **Ladd's bands** — cross and compress the duodenum, causing **neonatal duodenal obstruction with bilious vomiting**. The small intestine is left suspended from a narrow mesenteric pedicle, predisposing to **midgut volvulus** with vascular compromise — a surgical emergency treated by **Ladd's procedure**.

- **Subhepatic (undescended) caecum and appendix:** if the ascending colon fails to elongate, the caecum remains permanently below the liver; appendicitis then presents with right hypochondrial tenderness, mimicking cholecystitis.
- **Volvulus:** any segment that abnormally retains a mobile mesentery (instead of undergoing zygosis) can twist on its vascular pedicle, compromising blood supply and causing ischaemic obstruction.
- Distinguish rotation/return anomalies from related umbilical-region defects often asked together: **exomphalos (omphalocele)** — failure of the midgut to return by the tenth week, herniated loops covered by a membrane of peritoneum/amnion at the umbilical ring; **gastroschisis** — a para-umbilical body-wall defect (usually to the right of an intact umbilicus) through which uncovered bowel herniates directly into the amniotic cavity; **congenital umbilical hernia** — loops return normally but later protrude through an incompletely closed umbilical ring, covered by skin and subcutaneous tissue, and usually resolves spontaneously by 2–3 years.



## High-yield exam pointers

- SMA = artery **and** axis of rotation of the midgut.
- Total rotation = **270° anticlockwise**, as  $3 \times 90^\circ$  steps — 1st within the umbilical cord (herniation), remaining 2 during return to the abdomen.
- Prearterial segment → jejunum + ileum (except terminal part); postarterial segment → terminal ileum, caecum, appendix, ascending colon, proximal two-thirds transverse colon.
- Physiological umbilical herniation: begins 6th week; return begins 10th week; complete by ~11th–12th week.
- Caecal bud appears at ~6th week at the apex of the postarterial limb.
- After rotation: duodenum lies behind the SMA; transverse colon lies anterior to duodenum/SMA; caecum subhepatic before descending to the right iliac fossa.
- Ascending colon, descending colon and duodenum (beyond 1st inch) become secondarily retroperitoneal by **zygosis**; transverse colon and sigmoid colon remain mobile/intraperitoneal.
- Non-rotation = left-sided colon; reversed rotation = colon behind duodenum; mixed rotation/malrotation = Ladd's bands + risk of midgut volvulus.
- Malrotation with volvulus in a neonate presents with **bilious vomiting** — a surgical emergency.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Rotation of Gut

Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy

**Definition / Introduction** The midgut extends from the opening of the bile duct in the second part of the duodenum to the junction of the proximal two-thirds and distal one-third of the transverse colon, and is supplied throughout by the **superior mesenteric artery (SMA)**, which forms the fixed axis of rotation. Rapid elongation of the primary intestinal (midgut) loop, coupled with a transiently small abdominal cavity crowded by the enlarging liver and mesonephros, forces the loop to herniate physiologically into the umbilical coelom in the 6th week. While outside (and later while returning to) the abdominal cavity, the loop undergoes a total rotation of **270° in an anticlockwise (counterclockwise) direction**, viewed from the ventral aspect, around the SMA axis. This rotation is what converts a simple midline gut tube into the definitive, asymmetric adult disposition of small and large intestine, and its errors are the basis of clinically important anomalies (malrotation, volvulus, omphalocele).

### 1. Formation and extent of the primary intestinal (midgut) loop

- ▶ The midgut loop is first seen at Carnegie stage 15 (5th–6th week) as a ventral bulge of the gut tube, still widely continuous with the yolk sac through the **vitello-intestinal (vitelline) duct**, which arises at the apex/summit of the loop.
- ▶ The loop has two limbs, demarcated by the SMA which runs in the axis of the loop:
  - **Prearterial (cephalic/proximal) segment** — cranial and ventral to the artery.
  - **Postarterial (caudal/distal) segment** — caudal and dorsal to the artery.
- ▶ A small outpouching, the **caecal bud**, appears on the postarterial segment close to the yolk-sac attachment and marks the future caecum/appendix.

| Segment              | Derivatives                                                                                          |
|----------------------|------------------------------------------------------------------------------------------------------|
| Prearterial segment  | Distal (3rd & 4th) parts of duodenum, jejunum, and most of the ileum                                 |
| Postarterial segment | Terminal ileum, caecum, vermiform appendix, ascending colon, proximal two-thirds of transverse colon |

### 2. Physiological umbilical herniation

- ▶ During the 6th week, rapid elongation of the prearterial (small-intestinal) limb outstrips the growth of the abdominal cavity, which is further crowded by the bulky liver and mesonephros.



- ▶ The midgut loop therefore herniates into the **extra-embryonic coelom persisting within the umbilical cord** ("physiological umbilical hernia").
- ▶ Coiling of the jejunum and ileum, and the beginning of rotation, occur while the loop lies within this umbilical herniation.
- ▶ The large-intestinal (postarterial) limb also elongates during this period but does **not** coil.

### 3. Stages of rotation of the midgut (total 270°, anticlockwise, around the SMA axis)

The 270° rotation is conventionally described in three stages of 90° each — the first occurring during herniation, the remaining 180° during return of the loop to the abdominal cavity.

| Stage        | Timing                                             | Rotation (cumulative) | Key change                                                                                                                                                                                                                            |
|--------------|----------------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First stage  | During herniation (6th week)                       | 90° anticlockwise     | Loop turns from the sagittal into the horizontal plane; prearterial segment moves to the <b>right</b> , postarterial segment to the <b>left</b> of the SMA                                                                            |
| Second stage | During return of the prearterial limb (≈10th week) | +90° (180° total)     | Jejuno-ileal coils (prearterial segment) return first, pass <b>behind</b> the SMA, and come to occupy the left and lower part of the abdominal cavity; the postarterial segment is displaced further right/cranially                  |
| Third stage  | During return of the postarterial (caecal) limb    | +90° (270° total)     | Transverse colon comes to lie <b>anterior</b> to the SMA; caecum returns last, lying transiently subhepatic before descending to the right iliac fossa, at which point the ascending, transverse and descending colon become distinct |

□ Fig 14.9 — Rotation of gut: stages (A) 42 days to (E) 77 days, showing the prearterial segment, postarterial segment, caecal bud and superior mesenteric artery axis (Sontakke — *Textbook of Human Embryology*, p.141)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the sagittal-view embryo scheme (as above) with these exact labels:

- ▶ Dorsal aorta and **superior mesenteric artery** (axis of rotation, with rotation arrow)
- ▶ **Prearterial segment** (right after first 90°) and **postarterial segment** (left after first 90°)
- ▶ **Caecal bud, vitelline duct, umbilical vesicle** (yolk sac)
- ▶ Stomach, duodenum
- ▶ **Jejuno-ileal loops** (coiled, prearterial derivative)
- ▶ **Hepatic flexure, ascending colon, descending colon** (postarterial derivatives, uncoiled)
- ▶ Label each panel with the stage (90° / 180° / 270°) and approximate gestational timing

**4. Return of the midgut loop and final fixation**

- ▶ During the 10th week, reduction in the relative size of the liver, regression of the mesonephros, and enlargement of the abdominal cavity allow the herniated loop to return.
- ▶ The prearterial (jejuno-ileal) coils re-enter first, sliding medially over the right side of the developing descending mesocolon and displacing it to the left; the caecum, at the tip of the postarterial segment, re-enters last and lies transiently below the liver (subhepatic) before its final descent to the right iliac fossa.
- ▶ After rotation is complete, the **duodenum (2nd–4th parts), ascending colon and descending colon** become secondarily retroperitoneal by fusion of their mesenteries with the parietal peritoneum; the **jejunum, ileum, transverse colon and sigmoid colon** retain a free mesentery.
- ▶ The persisting root of the mesentery of the small intestine runs obliquely downward and to the right, from the duodeno-jejunal flexure (fixed to the left of the L1/L2 vertebral body by the suspensory ligament of the duodenum / ligament of Treitz) toward the right sacro-iliac region — a direct legacy of the rotation sequence.

**Applied / Clinical anatomy**

| Anomaly                          | Defect in rotation                                | Resulting anatomy/consequence                                                                                                                                                                                                                                                                      |
|----------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nonrotation ("left-sided colon") | Loop rotates only the first 90° (or not at all)   | Small intestine lies on the right, entire colon (including caecum) on the left of the abdomen                                                                                                                                                                                                      |
| Mixed/incomplete rotation        | Rotation arrested part-way through the second 90° | Caecum lies inferior to the pylorus/subhepatic instead of descending to the right iliac fossa; predisposes to <b>Ladd's bands</b> — peritoneal bands from the high caecum to the posterior abdominal wall crossing and compressing the second/third part of duodenum, causing duodenal obstruction |

| Anomaly                                    | Defect in rotation                                                                                                      | Resulting anatomy/consequence                                                                                                                             |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reversed rotation                          | Loop rotates 90° clockwise instead of anticlockwise                                                                     | Transverse colon passes <b>behind</b> the SMA and duodenum lies <b>in front</b> of it (mirror-image of normal)                                            |
| Subhepatic caecum/appendix                 | Failure of final descent of the caecum                                                                                  | Caecum and appendix remain high, close under the liver — a source of diagnostic confusion in appendicitis                                                 |
| Malrotation with volvulus                  | Any of the above, with an abnormally narrow, mobile mesenteric attachment (small intestine tethered at only two points) | Midgut twists around the SMA axis ( <b>volvulus</b> ), compromising the SMA and its branches → bowel ischaemia/gangrene — a paediatric surgical emergency |
| Failure of return (exomphalos/omphalocele) | Midgut loop fails to return from the physiological hernia                                                               | Loops of gut remain outside the abdomen at birth, covered by peritoneum and amnion, at the base of the umbilical cord                                     |
| Gastroschisis                              | Not a rotation defect — a para-umbilical body-wall defect (attributed to periumbilical vascular compromise)             | Loops of bowel lie free in the amniotic fluid, <b>not</b> covered by peritoneum/amnion — distinguishes it from omphalocele on antenatal ultrasound        |

- ▶ **Meckel's diverticulum:** persistence of the proximal vitello-intestinal duct on the antimesenteric border of the ileum — a remnant of the midgut loop's yolk-sac connection; may mimic appendicitis, and may contain ectopic gastric or pancreatic mucosa.
- ▶ **Imaging correlate:** on ultrasound/CT, the normal relation is superior mesenteric **vein to the right** of the artery; inversion of this relationship is a sign of volvulus, though malrotation with obstruction from Ladd's bands (without volvulus) can occur with an apparently normal vessel relationship.
- ▶ Radiologically, the duodeno-jejunal flexure (ligament of Treitz) should lie to the **left** of the upper lumbar vertebral bodies at the level of the pylorus on a barium study; any other position suggests malrotation.
- ▶ Clinically, malrotation classically presents in the neonate with **bilious vomiting**, reflecting either Ladd's-band duodenal compression or midgut volvulus.

### High-yield exam pointers

- ▶ Total rotation of the midgut = **270° anticlockwise** around the SMA axis, viewed from the front; occurs in three 90° stages (first during herniation, remaining two during return).
- ▶ Prearterial segment → duodenum (distal), jejunum, most of ileum; postarterial segment → terminal ileum, caecum, appendix, ascending colon, proximal 2/3 of transverse colon.
- ▶ Physiological umbilical herniation occurs in the **6th week**; return of the loop begins in the **10th week**.

- ▶ After rotation, transverse colon lies **anterior** to the SMA; in reversed rotation it lies **posterior** to it.
- ▶ Nonrotation → left-sided colon; reversed rotation → transverse colon behind SMA; incomplete rotation → subhepatic caecum + Ladd's bands + duodenal obstruction.
- ▶ Malrotation predisposes to **midgut volvulus** — a surgical emergency due to SMA compromise.
- ▶ Omphalocele = covered by peritoneum/amnion (failure of return); gastroschisis = uncovered (body-wall defect, not a rotation anomaly) — key differentiator.
- ▶ Meckel's diverticulum is a vitelline-duct remnant on the antimesenteric border of the ileum, not a rotation defect, but discussed alongside midgut-loop anomalies.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; IB Singh Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; IB Singh — Textbook of Anatomy Vol 2 (6e).



## Systemic embryology - urogenital



### Formation and fate of Paramesonephric duct

*Asked in: Paper II 14-Nov-2019 · Paper II Nov 2018 (2×) — RGUHS MD/MS Anatomy*

**Definition / Introduction** The paramesonephric (Müllerian) duct is one of the two paired genital ducts present in both sexes during the indifferent (ambisexual) stage of the urogenital system. It appears in the sixth week of intra-uterine life as an invagination of the coelomic epithelium lateral to the mesonephric (Wolffian) duct. In the female it is the primordium of virtually the entire genital tract — uterine tube, uterus, cervix and upper vagina — while in the male it regresses under the influence of a Sertoli-cell hormone, leaving only vestigial remnants. Its formation, sex-specific fate, and the anomalies that follow abnormal fusion or regression are recurring PG-embryology themes.

#### 1. Formation of the paramesonephric duct (indifferent stage)

- ▶ Develops in BOTH sexes, about 10 days later than the urinary system, appearing in the sixth week when the embryo is 10–12 mm crown–rump length (CRL).
- ▶ Arises as a longitudinal invagination of the coelomic (mesothelial) epithelium on the antero-lateral surface of the urogenital ridge, lateral to the mesonephros — the line of invagination is the **paramesonephric groove**.
- ▶ The invaginated epithelium canalises and elongates caudally as a solid rod of cells, using the already-formed mesonephric duct as a guide.
- ▶ **Cranial end** remains open into the coelomic (future peritoneal) cavity as a funnel-shaped abdominal ostium.

- **Course:** initially lies lateral to the mesonephric duct → on reaching the caudal end of the mesonephros (about the eighth week) it turns medially and crosses ventral to the mesonephric duct → enters the genital cord (tubal fold of the mesonephric ridge) → meets its fellow duct in the midline.
- The fused caudal tips project into the posterior wall of the urogenital sinus and raise a small elevation, the **Müllerian (sinus) tubercle**.

□ Fig 16.1 — Formation of the Genital Ridges and Paramesonephric Ducts (A, (Larsen — Human Embryology — 6e, p.957)

Three parts of the duct recognisable by the end of the indifferent stage:

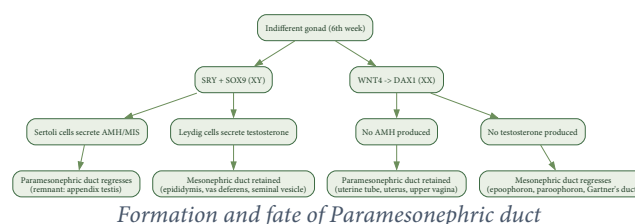
| Part                  | Position                                                  |
|-----------------------|-----------------------------------------------------------|
| Cranial vertical part | Opens into the coelomic cavity (future abdominal ostium)  |
| Horizontal part       | Crosses ventral to the mesonephric duct                   |
| Caudal vertical part  | Fuses with its fellow of the opposite side in the midline |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled cross-section/coronal schematic of the indifferent stage, and a paired composite showing final fate — label: **coelomic epithelium, paramesonephric groove/duct, mesonephric (Wolffian) duct, mesonephros, gonad, genital (tubal) fold, gonadal fold, urogenital sinus, Müllerian (sinus) tubercle**; and on the fate panel — Male side: **testis, appendix testis (hydatid of Morgagni), epididymis, vas deferens, prostatic utricle**; Female side: **infundibulum with fimbriae, ampulla, isthmus of uterine tube, fused uterovaginal canal → uterus/cervix, broad ligament, epoophoron, paroophoron, Gartner's duct, vagina, hymen**.

## 2. Molecular regulation of paramesonephric-duct fate

- The chromosomal sex (XY vs XX) of the indifferent gonad decides which duct system is retained, via a hormonal relay from the differentiated gonad, not from the duct itself.
- **SRY** (testis-determining factor on Yp) acts with the autosomal **SOX9** to commit the gonad to testis differentiation; Sertoli cells then secrete **anti-Müllerian hormone (AMH)**, also called **Müllerian-inhibiting substance (MIS)**, and Leydig cells secrete **testosterone**.
- **WNT4** is the ovary-determining gene; it upregulates **DAX1**, which inhibits **SOX9**, permitting ovarian differentiation and absence of AMH/testosterone.



### 3. Fate in the female (duct retained)

In the presence of oestrogen and the absence of testosterone/AMH, the paramesonephric duct becomes the main genital duct of the female.

| Part of paramesonephric duct                        | Adult female derivative                                                                              |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Cranial vertical (unfused) part + horizontal part   | Uterine (fallopian) tube — infundibulum, fimbriae, ampulla, isthmus                                  |
| Caudal vertical, fused part (uterovaginal canal)    | Body and fundus of uterus, cervix, and the upper part of the vagina                                  |
| Surrounding splanchnic mesenchyme                   | Myometrium and perimetrium of uterus                                                                 |
| Lateral extension of fused ducts to the pelvic wall | Broad ligament of the uterus (uterine tube lies in its upper border, ovary on its posterior surface) |
| Fused caudal tip at urogenital sinus                | Müllerian (sinus) tubercle                                                                           |

- ▶ With descent of the ovary the cranial two parts elongate into the uterine tube while the caudal parts fuse to form the uterine (uterovaginal) canal.
- ▶ The transverse pelvic fold created by this fusion divides the pelvic cavity into the **utero-vesical** and **utero-rectal (pouch of Douglas)** pouches.

□ Fig 31.30 — Remnants of the genital ducts (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.490)

Remnants in the female — do not confuse the two duct systems:

| Remnant                                                   | Origin                                                                    | Location                                                            |
|-----------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------|
| Vesicular appendix / paratubal cyst (hydatid of Morgagni) | Paramesonephric — cranial tip that did not contribute to the infundibulum | Near the fimbriated end of the tube                                 |
| Epoophoron                                                | Mesonephric tubules                                                       | Mesovarium, between ovary and tube                                  |
| Paroophoron                                               | Mesonephric tubules                                                       | Closer to the uterus, in the mesovarium                             |
| Gartner's duct (cyst)                                     | Mesonephric duct                                                          | Lateral wall of uterus/vagina, between layers of the broad ligament |

### 4. Development of the vagina (dual origin)

- ▶ Shortly after the solid tip of the fused paramesonephric ducts contacts the urogenital sinus, two solid endodermal outgrowths — the **sinovaginal bulbs** — proliferate from the pelvic urogenital sinus and fuse to form a solid **vaginal plate**.
- ▶ The vaginal plate canalises (largely complete by the fifth month); the vaginal fornices around the cervix are of paramesonephric origin, while the greater part of the vaginal canal derives from the sinovaginal bulbs — so the adult vagina has a **dual origin**: upper part from the uterovaginal canal (paramesonephric), remainder from the urogenital sinus (endoderm).

- ▶ The **hymen** is the thin residual tissue plate separating the vaginal lumen from the urogenital sinus, made up of sinus epithelium and a thin layer of vaginal tissue; it normally perforates perinatally.

## 5. Fate in the male (duct regresses)

- ▶ Sertoli cells of the fetal testis secrete AMH/MIS from about the sixth to seventh week; this diffuses locally (paracrine) and drives apoptosis of the paramesonephric-duct epithelium.
- ▶ The duct disappears almost completely except at its two ends, which persist as vestiges:

| Remnant                                            | Site                                                                                                          | Note                                                                                            |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Appendix testis (pedunculated hydatid of Morgagni) | Cranial end, attached to the upper pole of the testis                                                         | Classic paramesonephric remnant; may torsion clinically                                         |
| Prostatic utricle                                  | Caudal end, at the site of the Müllerian tubercle, opening on the seminal colliculus in the prostatic urethra | A vestige of the fused ducts; its epithelial lining is derived from urogenital sinus epithelium |

- ▶ Meanwhile testosterone from Leydig cells stimulates the adjacent mesonephric duct to differentiate into the epididymis, vas deferens, and seminal vesicle, and dihydrotestosterone masculinises the external genitalia.

## Applied / Clinical anatomy

- ▶ **Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome**: Müllerian agenesis/hypoplasia in a 46,XX individual with a normal ovary — presents as congenital absence of the uterus/upper vagina and primary amenorrhoea, with normal secondary sexual characters (ovarian function unaffected).
- ▶ **Uterine fusion/resorption anomalies** (failure of fusion of the caudal parts, or failure of resorption of the medial septum): uterus didelphys (complete non-fusion, double uterus ± double vagina), uterus bicornis bicollis/unicollis, septate/subseptate uterus, arcuate uterus, and unicornuate uterus (failure of one duct to develop) — all relevant to recurrent pregnancy loss and infertility work-up.
- ▶ **Vaginal anomalies**: failure of sinovaginal-bulb fusion/canalisation gives a double vagina or vaginal atresia; an imperforate hymen presents with cryptomenorrhoea/haematocolpos.
- ▶ **Persistent Müllerian duct syndrome (PMDS)**: 46,XY individuals with mutations in AMH or its receptor (AMHR2) fail to regress the paramesonephric duct — they retain a uterus, cervix and uterine tubes alongside normal male ducts and external genitalia; clinically presents as cryptorchidism or an inguinal hernia containing a uterus (hernia uteri inguinale).
- ▶ **Complete androgen insensitivity syndrome (CAIS)**: 46,XY with testes (so AMH is secreted and the paramesonephric duct still regresses) but a non-functional androgen receptor, so the mesonephric duct also fails to virilise — phenotypically female external genitalia with a blind vaginal pouch and no uterus.
- ▶ Broad-ligament cysts along the lateral uterine wall are classically Gartner's-duct (mesonephric) in origin, versus paratubal/hydatid cysts near the fimbriae, which are paramesonephric — a common viva distinction.



- ▶ The prostate arises from the urogenital sinus at the **Müllerian duct–urogenital sinus junction**, so paramesonephric-duct tissue contributes to the local mesenchymal environment patterning prostatic budding.

### High-yield exam pointers

- ▶ Paramesonephric duct = invagination of coelomic epithelium lateral to mesonephric duct, 6th week (10–12 mm CRL); crosses ventral to mesonephric duct at ~8th week.
- ▶ Three parts: cranial vertical (→ infundibulum), horizontal (→ ampulla/isthmus of tube), caudal vertical fused (→ uterovaginal canal).
- ▶ Female fate = uterine tube + uterus + cervix + upper vagina + broad ligament; vagina has dual origin (paramesonephric + sinovaginal bulbs of urogenital sinus).
- ▶ Male fate = regression by AMH/MIS (Sertoli cells, 6th–7th week); remnants = appendix testis (cranial) and prostatic utricle (caudal).
- ▶ Mesonephric duct remnants in the female (epoophoron, paroophoron, Gartner's duct) must not be confused with paramesonephric remnants (paratubal cyst/hydatid of Morgagni).
- ▶ MRKH = Müllerian agenesis (46,XX, ovaries normal); PMDS = failure of Müllerian regression (46,XY, AMH/AMHR2 mutation).
- ▶ Molecular axis: SRY–SOX9–AMH suppresses the duct; WNT4–DAX1–oestrogen preserves and differentiates it.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); BD Chaurasia Human Anatomy Vol 2 8e.



## Ascent of Testis

*Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The testis develops high on the posterior abdominal wall, in the upper lumbar region, medial to the mesonephros, and must be relocated to the scrotum — where the temperature is 2–3°C lower than the core — for normal spermatogenesis. This relocation is classically termed the **descent of testis**; because the gonad is tethered near-stationary to the anterior abdominal wall by the gubernaculum while the vertebral column and trunk elongate cranially above it, the same displacement is equally described as a relative **ascent of the trunk past a fixed testis**, which is why some question papers phrase this topic as "Ascent of Testis." It occurs in two hormonally distinct phases — **transabdominal** and **inguinoscrotal** — guided by the gubernaculum testis and processus vaginalis, and is complete in over 95% of full-term male neonates by birth.

### Site of origin and primary position

- ▶ The testis develops from the **genital ridge** on the medial side of the mesonephros, at the level of the upper lumbar (T10) segments.

- ▶ The **indifferent gonad** differentiates into a testis under the influence of the **SRY** gene (~7th week); fetal **Leydig cells** appear soon after and secrete **testosterone** and **insulin-like factor 3 (Insl3)**; Sertoli cells secrete **anti-Müllerian hormone (AMH)**.
- ▶ A **cranial suspensory ligament**, from the upper pole of the gonad to the diaphragmatic region of the urogenital ridge, tethers the gonad cranially in both sexes. In the male, it **regresses under androgen action**, freeing the testis to descend; in the female it persists as part of the ovarian suspensory mechanism.
- ▶ A **gubernaculum** condenses from mesenchyme at the caudal pole of the gonad in both sexes, connecting the mesonephric duct/lower pole of the testis to the anterior abdominal wall and, later, to the floor of the scrotum.

### Mechanism of descent — two phases (Gray's Anatomy, Standring 41e)

| Phase          | Timing                                  | Key events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Transabdominal | Up to ~15 weeks (4th month)             | Insl3 from Leydig cells produces a " <b>swelling reaction</b> " that enlarges the gubernaculum, anchoring the testis near the future deep inguinal ring as the abdominal cavity enlarges; the cranial suspensory ligament regresses under androgens; testis remains apposed to the deep inguinal ring through the 4th–6th month                                                                                                                                                                                                                                                            |
| Inguinoscrotal | ~25–35 weeks, rapid about the 7th month | The gubernaculum bulges out through the abdominal wall muscles and elongates 3–5 cm across the pubis into the scrotum; the <b>processus vaginalis</b> (a peritoneal outpocketing) hollows out the gubernaculum ahead of the testis; elongation is androgen-dependent and mediated via the genital branch of the <b>genitofemoral nerve</b> , which releases <b>calcitonin gene-related peptide (CGRP)</b> , driving chemotactic growth of the gubernacular tip toward the scrotum; rising intra-abdominal pressure acting through the patent processus vaginalis assists the rapid transit |

The left testis usually descends slightly ahead of the right. Moore additionally notes that enlargement of the testis with atrophy of the mesonephros permits its caudal movement along the posterior abdominal wall during the transabdominal stage.

## Structures and factors guiding descent

| Structure/factor              | Role                                                                                                                                                                                                                                                                                                                                |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gubernaculum testis           | Mesenchymal band from lower pole of testis (and mesonephric duct) to the base of scrotum; because the posterior body wall grows rapidly while the gubernaculum does not lengthen correspondingly, the testis is progressively drawn to a lower position; it also dilates the inguinal bursa/canal and lays down the path of descent |
| Inguinal bursa                | An outpouching of the layers of the anterior abdominal wall that precedes the testis; its cavity forms the inguinal canal                                                                                                                                                                                                           |
| Processus vaginalis           | Diverticulum of peritoneum that precedes and accompanies the testis through the inguinal canal into the scrotum; later forms the tunica vaginalis                                                                                                                                                                                   |
| Testicular hormones           | Testosterone and Insl3 from fetal Leydig cells are obligatory for both phases; CGRP from the genitofemoral nerve mediates gubernacular growth                                                                                                                                                                                       |
| Intra-abdominal pressure      | Growing abdominal viscera raise intra-abdominal pressure, helping push the testis through the canal                                                                                                                                                                                                                                 |
| Differential body-wall growth | Relative "ascent" of the trunk past the gubernaculum-fixed testis                                                                                                                                                                                                                                                                   |
| Temperature gradient          | Higher intra-abdominal than scrotal temperature is a contributory factor                                                                                                                                                                                                                                                            |

## Timeline of descent

| Time (intrauterine life) | Position of testis                                                                              |
|--------------------------|-------------------------------------------------------------------------------------------------|
| 3rd–4th month            | Testis reaches the <b>iliac fossa</b> , near the abdominal end of the inguinal canal            |
| 4th–6th month            | Held apposed to the <b>deep inguinal ring</b> (transabdominal phase complete)                   |
| 7th month                | Rapid transit through the <b>inguinal canal</b> (inguinoscrotal phase); left side usually leads |
| 8th month                | Reaches the <b>superficial inguinal ring</b> /upper scrotum                                     |
| 9th month (by birth)     | Testis lies in the <b>scrotum</b>                                                               |

Over 95–97% of full-term male neonates have both testes descended at birth; in most of the remainder, descent is completed within the first 3 postnatal months.

 Fig 72.17 — The descent of the testis. The testis is retroperitoneal throughout development. It beco (Gray's Anatomy — Standring — 41e, p.1687)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

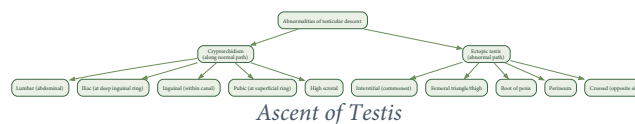
Sagittal section of the posterior abdominal wall and developing inguinal canal, showing progressive descent (label each stage): **testis** (with epididymis) → **mesonephric duct/ductus deferens** → **gubernaculum testis** (abdominal, interstitial, and subcutaneous parts) → **processus vaginalis** (crescentic parietal layer + column around epididymis) → **deep inguinal ring** → **inguinal canal** → **superficial inguinal ring** → **scrotum with tunica vaginalis** (parietal and visceral layers) and **remains of processus vaginalis**. Show the testis as retroperitoneal throughout, and mark the **genitofemoral nerve** alongside the gubernaculum.

### Fate of the gubernaculum and processus vaginalis

- **Gubernaculum:** from ~35 weeks its gelatinous extracellular matrix is resorbed; the remnant becomes a short fibrous band — the **ligament of the scrotum** — anchoring the tail of the epididymis/lower pole of testis to the scrotal floor.
- **Processus vaginalis:** the distal part persists around the testis as the **tunica vaginalis** (parietal and visceral layers). The proximal part normally obliterates — patent in ~70% of infants at 2 weeks, at least partially closed in ~80% by 3 weeks (left side before right); classically described as closing by the end of the first year.
- **Persistent patency** of the proximal processus vaginalis is the embryological basis of **congenital indirect inguinal hernia** (wide patency, bowel prolapse) or **congenital hydrocele** (narrow patency, fluid trickle only).
- Because the testis carries the ductus deferens and its vessels with it during descent, the **ductus deferens crosses anterior to the ureter** near the bladder — a direct embryological consequence of descent.

### Applied / Clinical anatomy

- **Cryptorchidism (undescended testis):** failure of one or both testes to reach the scrotum; affects ~2–3% of term male infants (25% of these bilateral), more common in preterm infants. In many, descent completes by 1 year; if not, hormonal therapy (hCG/testosterone) or surgical **orchidopexy** is undertaken. Classified by the level of arrest:



- Consequences of (especially bilateral) cryptorchidism: impaired spermatogenesis/infertility (higher intra-abdominal temperature), increased risk of germ cell tumour, greater vulnerability to torsion and trauma, and frequent association with a co-existing indirect inguinal hernia.
- **Ectopic testis:** the testis deviates from the normal path of descent, most often lodging superficial to the external oblique aponeurosis (interstitial — commonest), or in the femoral triangle, root of the penis, perineum, or opposite scrotal compartment (crossed ectopia); attributed to the gubernaculum following an aberrant band (of Lockwood) to the wrong site.

- ▶ **Congenital indirect inguinal hernia:** persistence of a wide processus vaginalis allows bowel to herniate through the deep inguinal ring into the scrotum alongside the spermatic cord.
- ▶ **Congenital/infantile hydrocele and hydrocele of the cord:** incomplete obliteration of a narrow segment of the processus vaginalis permits peritoneal fluid, but not bowel, to accumulate around the testis or along the cord.
- ▶ **Surface/clinical correlation:** an empty scrotal sac with a swelling along the line of descent (groin) should be evaluated for cryptorchidism versus an inguinal hernia/ectopic testis.

### High-yield exam pointers

- ▶ Testis develops in the **upper lumbar region** and must relocate to the scrotum; process = descent (or, viewed relatively, "ascent" of the growing trunk past a fixed testis).
- ▶ Two phases: **transabdominal** (Insl3/Leydig-cell driven, up to ~4th month) and **inguinoscrotal** (androgen + CGRP/genitofemoral-nerve driven, rapid ~7th month).
- ▶ Key structures: **gubernaculum testis** (guides/pulls) and **processus vaginalis** (precedes testis, becomes tunica vaginalis).
- ▶ Classic timeline: iliac fossa (3rd–4th month) → deep inguinal ring (4th–6th month) → inguinal canal (7th month) → superficial ring (8th month) → scrotum (9th month/birth).
- ▶ >95% of term neonates have descended testes at birth; most remaining complete descent within 3 postnatal months.
- ▶ Gubernaculum remnant = ligament of scrotum; processus vaginalis remnant around testis = tunica vaginalis.
- ▶ Persistent processus vaginalis → indirect inguinal hernia (wide) or hydrocele (narrow).
- ▶ Cryptorchidism (2–3% term infants) vs ectopic testis (abnormal path) — know the distinction and the sites/complications of each.
- ▶ Descent explains why the ductus deferens crosses anterior to the ureter.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2 8e; IB Singh — Textbook of Anatomy Vol 2 6e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Cryptorchidism

Asked in: Paper II May 2018 — RGUHS MD/MS Anatomy

**Definition / Introduction** Cryptorchidism (Greek *kryptos* = hidden, *orchis* = testis), also called undescended testis, is failure of one or both testes to reach the scrotum, the descent being arrested at some point along the normal transabdominal–inguinoscrotal pathway. It is the commonest anomaly of the male genital tract in neonates and is of major clinical importance because the scrotal position is essential for normal spermatogenesis, which requires a temperature 3–5°C below core body temperature. The condition must be distinguished from **ectopic testis** (a fully descended testis that has strayed off its normal path) and from a **retractile testis** (a normally descended testis that intermittently withdraws into the groin), both common differentials in the anatomy viva and in clinical practice.

### Embryological basis — normal descent of the testis (brief recap)

- ▶ The testis develops from the **genital ridge**, medial to the mesonephros, at the upper lumbar level; the indifferent gonad differentiates into a testis under the **SRY** gene on Yp11, after which fetal **Leydig cells** secrete testosterone and **insulin-like factor 3 (Insl3)**, and **Sertoli cells** secrete anti-Müllerian hormone.
- ▶ Descent occurs in two phases guided by the **gubernaculum testis** (a mesenchymal band from the lower pole of the testis to the scrotal floor) and the **processus vaginalis** (a peritoneal diverticulum that precedes the testis into the scrotum):

| Phase          | Timing               | Driving factors                                                                                                                                                                                                     |
|----------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Transabdominal | Up to ~3rd–4th month | Insl3-driven gubernacular "swelling reaction" holds the testis near the deep inguinal ring as the abdomen enlarges; the cranial suspensory ligament regresses under androgen                                        |
| Inguinoscrotal | Rapid, ~7th month    | Androgen-dependent gubernacular elongation through the inguinal canal, mediated by <b>CGRP</b> released from the genital branch of the <b>genitofemoral nerve</b> ; rising intra-abdominal pressure assists transit |

- ▶ Normal timeline: iliac fossa (3rd month) → apposed to deep inguinal ring (up to 6th month) → traverses inguinal canal (7th month) → superficial inguinal ring (8th month) → scrotum (9th month/birth). About 97% of term neonates have both testes descended at birth; most of the remainder complete descent within the first few postnatal months.

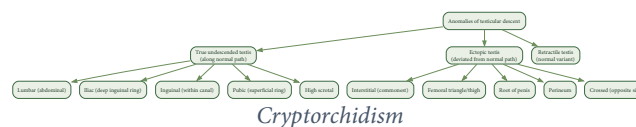
### Classification of testicular maldescent

Failure of descent is classified by whether the testis lies **along** the normal path (true cryptorchidism) or has **deviated from** it (ectopic testis), with **anorchism/monorchism** (absent gonad) and **retractile testis** (a normal variant) as important differentials.

□ Fig 17.13 — Bilateral undescended testis (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.294)

| Category                              | Site                              | Notes                                                                           |
|---------------------------------------|-----------------------------------|---------------------------------------------------------------------------------|
| True undescended (cryptorchid) testis | Lumbar (posterior abdominal wall) | Arrest early in transabdominal phase                                            |
|                                       | Iliac                             | At/near the deep inguinal ring                                                  |
|                                       | Inguinal                          | Within the inguinal canal                                                       |
|                                       | Pubic                             | At the superficial inguinal ring                                                |
|                                       | High scrotal                      | Has entered the scrotum but not reached its floor                               |
| Ectopic testis (deviated off path)    | Interstitial                      | Superficial to the external oblique aponeurosis — <b>commonest ectopic site</b> |
|                                       | Femoral                           | Anteromedial thigh/femoral triangle                                             |
|                                       | Penile                            | Root of the penis                                                               |
|                                       | Perineal                          | Superficial perineal pouch                                                      |
|                                       | Crossed                           | Opposite scrotal compartment                                                    |

□ Fig 17.14 — Positions of ectopic testis: (1) lower abdomen, (2) front of thigh, (3) femoral canal, (4) skin of penis, (5) behind scrotum (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.294)



Two features help separate the true undescended testis from the ectopic testis on table and in the exam: an ectopic testis, having already traversed the canal, is **usually fully developed**, whereas a true undescended testis is more often **hypoplastic/immature** and may show **testis-epididymis non-fusion**; a true undescended testis is also frequently accompanied by a co-existing indirect inguinal hernia.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A sagittal/coronal schematic of the trunk from posterior abdominal wall to scrotum, marking (label each): **kidney** and **deep inguinal ring** as fixed references → the five sites of arrest of a true undescended testis along the normal path — **lumbar, iliac, inguinal, pubic, high scrotal** → the gubernaculum and processus vaginalis as the guiding structures. On a second, separate figure of the front of the trunk and thigh, mark the five ectopic sites — **interstitial (over external oblique), femoral triangle, root of penis, perineum, and crossed (opposite scrotum)** — each as a labelled dot away from the normal inguinoscrotal line.

### Etiology, incidence and natural history

- **Hormonal**: deficient prenatal/postnatal androgen (testosterone) secretion is the commonest attributed cause; deficient **Ins13** signalling or a mutation of its receptor (LGR8/RXFP2) has been identified in experimental and human cryptorchidism.



- ▶ **Neural:** injury to, or inadequate CGRP release from, the **genitofemoral nerve** impairs gubernacular migration.
- ▶ **Mechanical/associated anomalies:** persistence of the cranial suspensory ligament, a narrow inguinal canal, and abdominal-wall defects — cryptorchidism is common with **bladder exstrophy**, **exomphalos** (~30% affected), and **gastroschisis**; the incidence of cryptorchidism is increased about ten-fold with **epispadias**; it is also frequent in **myelomeningocele** affecting the upper lumbar cord.
- ▶ Cryptorchidism is now regarded as one manifestation of the **testicular dysgenesis syndrome** spectrum, which also includes hypospadias, impaired semen quality, and testicular germ-cell cancer.
- ▶ **Incidence:** about 3% of full-term male neonates (up to 30% of preterm infants) have an undescended testis at birth; roughly one-quarter of cases are bilateral. Spontaneous descent occurs in the large majority during the first year of life, and the incidence falls to under 1% by about 6 months of age.

### Pathophysiology and complications

- ▶ The scrotal environment is normally 3–5°C cooler than the abdomen; the higher temperature to which an undescended testis is exposed impairs spermatogenesis by depleting adult-type A spermatogonia, with germ-cell loss becoming progressive if descent is delayed beyond 1–2 years.
- ▶ The undescended testis is often histologically normal at birth, but atrophy and failure of tubular development become detectable by the end of the first year; **Leydig cell (endocrine) function is usually preserved**, so serum testosterone typically remains normal even though exocrine (spermatogenic) function is compromised.
- ▶ **Infertility:** unilateral disease reduces fertility potential; bilateral cryptorchidism causes sterility, and even after early orchidopexy men with bilateral undescended testes remain about six times more likely to be infertile.
- ▶ **Malignancy:** an undescended testis carries a substantially higher risk of germ-cell tumour than a normally descended one; orchidopexy improves the ability to palpate/monitor the gonad but does **not** by itself eliminate this cancer risk.
- ▶ **Vulnerability to injury and torsion:** an undescended testis, lying against bone (pelvic brim/pubis) and often lacking normal gubernacular fixation, is more exposed to trauma and to torsion.
- ▶ **Associated indirect inguinal hernia/hydrocele:** a patent processus vaginalis commonly co-exists, since the same developmental step (gubernaculo-vaginal descent) is shared.

### Diagnosis and management

- ▶ Clinical palpation localises most (~80–90%) undescended testes to a low inguinal or high-scrotal position; an impalpable testis suggests an intra-abdominal or absent gonad and is further evaluated by ultrasonography, MRI, or diagnostic laparoscopy.
- ▶ **Watchful waiting** is appropriate up to about 6 months of age, since most testes descend spontaneously in this period.
- ▶ **Hormonal therapy** (hCG/testosterone) has been used to promote descent, with modest efficacy.

- **Orchidopexy** (surgical mobilisation of the testis and fixation to the scrotal floor) is the definitive treatment, now recommended between about 6 and 18 months of age — earlier than in the past — because germ-cell numbers fall rapidly in the undescended testis and delayed correction impairs testicular catch-up growth.

## Applied / Clinical anatomy

- At **laparoscopic orchidopexy for an intra-abdominal (impalpable) testis**, the surgeon must recognise a "looping vas deferens" that enters the inguinal canal and loops back into the abdomen before reaching the testis — failure to identify this anomalous course risks inadvertent division of the vas.
- A **retractile testis** — one that moves freely between groin and scrotum and can be manipulated down to the scrotal floor on examination, unlike a true undescended testis — must be excluded before a child is labelled cryptorchid and subjected to unnecessary intervention; retractile testes are typically smaller in volume than normal.
- Because the descending testis carries the ductus deferens, its vessels and its investing peritoneal fold with it, disorders of descent are anatomically linked to the **inguinal canal contents, the processus vaginalis (tunica vaginalis), and the position of the ductus deferens anterior to the ureter** near the bladder — the same embryological step that produces this crossing also explains why a patent processus vaginalis at any level along the path predisposes to congenital indirect inguinal hernia or hydrocele.
- Surface and radiological correlation: an empty hemi-scrotum with a swelling somewhere along the groin/lower abdomen should raise suspicion of cryptorchidism, ectopic testis, or an inguinal hernia, and should be differentiated clinically and, if needed, sonographically.

## High-yield exam pointers

- Cryptorchidism = failure of testicular descent arrested **along the normal path**; ectopic testis = testis has **deviated off** the normal path — know the sites of each.
- Guiding structures of descent: **gubernaculum testis** and **processus vaginalis**, driven by InsI3/androgen (transabdominal phase) and androgen + genitofemoral-nerve CGRP (inguinoscrotal phase).
- Incidence: ~3% of term male neonates (up to 30% preterm); most descend spontaneously by 6–12 months; ~25% of cases bilateral.
- Complications: **infertility** (temperature effect on spermatogenesis; Leydig/endocrine function usually preserved), **malignancy** (risk not abolished by orchidopexy), **torsion/trauma**, and associated **indirect inguinal hernia/hydrocele**.
- Ectopic testis is usually fully developed (it completed transit through the canal); true undescended testis is more often hypoplastic and may show testis–epididymis non-fusion.
- Retractable testis (normal, manipulable into the scrotum) must be distinguished from true cryptorchidism.
- Management ladder: watchful waiting ( $\leq 6$  months)  $\rightarrow$  hormonal therapy (hCG/testosterone)  $\rightarrow$  orchidopexy (recommended by 6–18 months); "looping vas deferens" is a recognised pitfall at laparoscopic orchidopexy.

- Associated with abdominal-wall defects (exomphalos, gastroschisis, bladder exstrophy), epispadias, and myelomeningocele; regarded as part of the testicular dysgenesis syndrome.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2 8e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e.



## Derivatives of Cloaca

Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **cloaca** is the common endoderm-lined terminal chamber of the hindgut, present from the 4th week of intrauterine life, into which the hindgut opens dorsally, the **allantois** opens ventrally, and the paired **mesonephric ducts** enter laterally. It is closed externally by the **cloacal membrane** (endoderm apposed to proctodeal ectoderm, with no intervening mesenchyme). Between the 4th and 7th weeks a mesenchymal **urorectal septum** grows caudally and fuses with the cloacal membrane, dividing the cloaca into a dorsal **anorectal canal** and a ventral **urogenital sinus** — the source of most of the lower urinary tract, the vestibule/prostatic urethra region, and their associated glands. This single event therefore underlies the anatomy of both the hindgut outlet and the lower urogenital tract, and its disturbance produces a well-defined family of anorectal and urogenital malformations.

### 1. Formation and Partitioning of the Cloaca

- The **endodermal cloaca** is formed where the tubular hindgut widens just before the cloacal membrane; it is encased in splanchnopleuric mesenchyme.
- Proliferation of mesenchyme and endoderm in the **angle between the hindgut and the allantois** produces the **urorectal septum** (its mesenchyme is also termed *intercloacal mesenchyme*; molecular markers *Six1* and *Six2* have been identified in it).
- The septum elongates caudally and its endodermal epithelium approaches — and fuses with — the cloacal membrane, thereby dividing the cloacal cavity into a **dorsal part (future rectum/anorectal canal)** and a **ventral part (urogenital sinus)**.
- The point of fusion of the septum tip with the cloacal membrane becomes the **perineal body**.
- The cloacal membrane is correspondingly split into a dorsal **anal membrane** and a ventral **urogenital membrane**; at the end of the **7th week** the cloacal membrane ruptures, creating a separate anal opening for the hindgut and a separate ventral opening for the urogenital sinus.
- The mesonephric ducts, which originally opened into the cloaca, come to open into the urogenital sinus after partitioning.

□ Fig 15.36 — Cloacal region in embryos at successive stages of development, showing progressive growth of the urorectal septum toward the cloacal membrane (Langman's Medical Embryology — Sadler — 14e, p.272)

## 2. Derivatives of the Dorsal Part — Anorectal Canal

- ▶ The dorsal part of the cloaca gives rise to the **rectum and the upper part of the anal canal** — identical in both sexes, since this region is not influenced by gonadal sex.
- ▶ The **anal canal has a dual embryological origin**: its upper part is derived from **hindgut endoderm**, while its lower part is formed by an invaginating ectodermal pit, the **proctodeum**, that develops around the anal membrane.
- ▶ The endodermal–ectodermal junction is marked by the **pectinate (dentate) line**, at which the epithelium changes from columnar (endodermal) above to stratified squamous (ectodermal) below.
- ▶ This dual origin explains the differing blood supply (superior rectal artery above vs inferior rectal/pudendal branches below), venous drainage (portal vs systemic — the site of porto-systemic anastomosis), nerve supply (autonomic/visceral above, insensate to pain vs somatic pudendal below, pain-sensitive), and lymphatic drainage (internal iliac nodes above vs superficial inguinal nodes below) across the pectinate line.

## 3. Derivatives of the Ventral Part — Urogenital Sinus

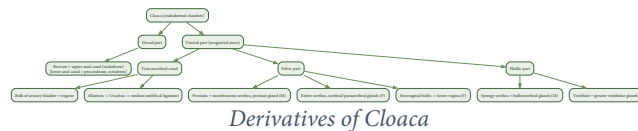
- ▶ The ventral part of the cloaca becomes the **urogenital sinus**, continuous cranially with the allantois. It is conventionally described in **three craniocaudal parts**:
- ▶ **Vesicourethral canal** (cranial-most, continuous above with the allantoic duct) — forms the bulk of the **urinary bladder**.
- ▶ **Pelvic part** (narrow, intermediate) — forms the urethra at the bladder neck, and in the male the **prostatic and membranous urethra**; in the female, virtually the **entire urethra**.
- ▶ **Phallic part** (caudal, flattened side-to-side, growing toward the genital tubercle) — its later fate diverges sharply between the sexes under androgen influence.
- ▶ The **allantoic duct** narrows to become the **urachus**, which in the adult persists as the fibrous **median umbilical ligament** running from the bladder apex to the umbilicus.
- ▶ **Trigone of the bladder**: the caudal (mesonephric-duct-bearing) ends of the vesicourethral canal absorb the mesonephric ducts into its dorsal wall, so that the ureter and mesonephric duct come to open separately; this absorbed area forms the trigone. Older teaching held the trigone epithelium was partly mesodermal (from the absorbed duct), but molecular fate-mapping now shows the entire trigone epithelium is **endodermal**, derived from the urogenital sinus, with the incorporated duct segment (the "common nephric duct") undergoing apoptosis during normal development.

## 4. Sex-Differentiated Derivatives of the Urogenital Sinus

| Subdivision of urogenital sinus | Male derivative                                                 | Female derivative |
|---------------------------------|-----------------------------------------------------------------|-------------------|
| Vesicourethral canal            | Bulk of urinary bladder; urachus<br>→ median umbilical ligament | Same as male      |

| Subdivision of urogenital sinus | Male derivative                                                                                                                                                                  | Female derivative                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pelvic part                     | Prostatic urethra (proximal to opening of ejaculatory ducts) and membranous urethra; endodermal buds from this part form the <b>prostate gland</b>                               | Entire urethra; endodermal buds from the cranial urethra form the <b>urethral and paraurethral glands</b> ; paired evaginations ( <b>sinovaginal bulbs</b> ) from this part form a solid vaginal plate that canalises to give the <b>lower part of the vagina</b> (the upper vagina/fornices are of paramesonephric-duct origin — the vagina thus has a dual origin) |
| Phallic part                    | Contributes, together with growth of the genital tubercle, to the <b>spongy (penile) urethra</b> ; its endoderm buds also form the paired <b>bulbourethral (Cowper's) glands</b> | Persists relatively unelongated as the <b>vestibule of the vagina</b> (into which the urethra, vagina, and paired <b>greater vestibular [Bartholin's] glands</b> open)                                                                                                                                                                                               |

## 5. Summary of Cloacal Derivatives



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A midsagittal schematic of the caudal embryo showing progressive division of the cloaca (label, in sequence, left to right as three successive stages):

- ▶ **Hindgut** entering dorsally; **Allantois** entering ventrally; **Mesonephric duct** opening laterally into the cloaca
- ▶ **Cloaca** (single endodermal chamber) with **Cloacal membrane** closing it externally
- ▶ **Urorectal septum** growing caudally in the angle between hindgut and allantois
- ▶ Septum tip approaching and fusing with the cloacal membrane at the site of the future **Perineal body**
- ▶ Final stage: **Anal membrane** (dorsal) and **Urogenital membrane** (ventral) as separate membranes; **Rectum/anorectal canal** (dorsal compartment) and **Urogenital sinus** (ventral compartment) as separate cavities

## Applied / Clinical anatomy

- ▶ **Anorectal malformations**: a dorsally-deviated or maldeveloped urorectal septum produces the spectrum from **anal stenosis** and **membranous atresia** to **anorectal agenesis**, often with a **rectourethral or rectovaginal fistula** where the rectum communicates abnormally with the persisting urogenital tract; meconium in the urine of a male neonate suggests a rectourethral fistula.

- ▶ **Persistent cloaca:** incomplete partitioning in a female results in the rectum, vagina and urethra all draining into a single perineal channel — a severe anorectal malformation frequently associated with the **VACTERL** association.
- ▶ **Bladder and cloacal exstrophy:** failure of ventral body-wall/septum development leaves the posterior bladder wall (and, in the more severe cloacal exstrophy, the rectum and anal canal too) exposed on the abdominal surface; cloacal exstrophy is often accompanied by epispadias and widely separated pubic bones.
- ▶ **Urachal anomalies:** incomplete obliteration of the allantois-derived urachus gives a **patent urachus** (urine leak at the umbilicus), **urachal cyst**, or **urachal sinus**.
- ▶ **Pectinate line:** its position marks the clinically vital transition in blood supply, innervation, venous and lymphatic drainage of the anal canal — the basis for distinguishing **internal** (above, painless, portal drainage) from **external** (below, painful, systemic drainage) **haemorrhoids**, and for planning anorectal surgery.
- ▶ **Vaginal anomalies:** failure of sinovaginal-bulb canalisation/fusion underlies **vaginal atresia** and a **transverse vaginal septum**.
- ▶ **Ectopic ureteric orifice:** anomalous absorption of the mesonephric duct into the trigone can displace the ureteric orifice into the urethra, vas deferens, or (in females) the vestibule/vagina.

### High-yield exam pointers

- ▶ Cloaca = common endodermal chamber for hindgut + allantois, closed by the cloacal membrane; divided by the **urorectal septum** (weeks 4–7).
- ▶ Septum fuses with cloacal membrane at the future **perineal body**; membrane ruptures at the end of week 7.
- ▶ **Dorsal part** → **rectum + upper anal canal** (endoderm); lower anal canal is **ectodermal** (proctodeum) — junction = **pectinate line**.
- ▶ **Ventral part** = urogenital sinus, in 3 parts: vesicourethral canal → **bladder**; pelvic part → **prostatic/membranous urethra (M) or entire urethra (F) + prostate/urethral-paraurethral glands**; phallic part → **spongy urethra + bulbourethral glands (M) or vestibule + greater vestibular glands (F)**.
- ▶ **Allantois** → **urachus** → **median umbilical ligament**.
- ▶ Trigone of bladder is entirely **endodermal** (urogenital-sinus derived), despite historically being taught as part-mesodermal.
- ▶ **Vagina has dual origin:** upper part from paramesonephric (uterovaginal) tissue, lower part from urogenital-sinus sinovaginal bulbs.
- ▶ Clinical spectrum of septal maldevelopment: anal stenosis → membranous atresia → anorectal agenesis with fistula → persistent cloaca → cloacal exstrophy.



**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Derivatives of Cloacae

*Asked in: Paper II May 2018 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **cloaca** is the common endoderm-lined terminal chamber of the hindgut, present from the 4th week of intrauterine life, into which the hindgut opens dorsally, the **allantois** opens ventrally, and the paired **mesonephric ducts** enter laterally. It is closed externally by the **cloacal membrane** (apposed ectoderm and endoderm, with no intervening mesenchyme). Between the 4th and 7th weeks a mesenchymal **urorectal septum** grows caudally between the hindgut and the allantois and comes to lie against the cloacal membrane, dividing the cloaca into a dorsal **anorectal canal** and a ventral **urogenital sinus** — the source of most of the lower urinary tract, the vestibule/prostatic urethra region, and their associated glands. This single partitioning event therefore underlies the anatomy of both the hindgut outlet and the lower urogenital tract, and its disturbance produces a well-defined family of anorectal and urogenital malformations.

### 1. Formation and Partitioning of the Cloaca

- ▶ The **endodermal cloaca** is the dilated terminal part of the hindgut just proximal to the cloacal membrane; it is invested by splanchnopleuric mesenchyme.
- ▶ Proliferation of mesenchyme and endoderm in the **angle between the hindgut and the allantois** forms the **urorectal septum** (its mesenchyme is also called the *intercloacal* or *pericloacal mesenchyme*; molecular markers **Six1** and **Six2** have been identified in it — Gray's Anatomy 41e).
- ▶ The septum grows caudally so that its endodermal epithelium comes to lie against — and, by traditional teaching, fuses with — the cloacal membrane, dividing the cloacal cavity into a **dorsal part (future rectum/anorectal canal)** and a **ventral part (urogenital sinus)**. (Note: some modern accounts hold the septum approaches but does not truly fuse with the membrane, dividing the cloaca functionally rather than by fusion — the net anatomical result, a separated dorsal and ventral compartment, is the same and is what matters for gross/clinical anatomy.)
- ▶ The site where the septum tip meets the cloacal membrane becomes the **perineal body**.
- ▶ The cloacal membrane is correspondingly divided into a dorsal **anal membrane** and a ventral **urogenital membrane**; at the end of the **7th week** the cloacal membrane breaks down, creating a separate anal opening for the hindgut and a separate ventral opening for the urogenital sinus.
- ▶ The mesonephric ducts, which originally opened into the cloaca, come to open into the urogenital sinus after partitioning.

□ Fig 15.36 — Cloacal region in embryos at successive stages of development, showing progressive growth of the urorectal septum toward the cloacal membrane (Langman's Medical Embryology — Sadler — 14e, p.272)



## 2. Derivatives of the Dorsal Part — Anorectal Canal

- ▶ The dorsal part of the cloaca gives rise to the **rectum and the upper (two-thirds) part of the anal canal** — identical in both sexes, since this region is not influenced by gonadal sex.
- ▶ The **anal canal has a dual embryological origin**: its upper part is derived from **hindgut endoderm**, while its lower part is formed by an invaginating ectodermal pit, the **proctodeum**, that develops around the anal membrane.
- ▶ The endodermal–ectodermal junction is marked by the **pectinate (dentate) line**, at which the epithelium changes from columnar (endodermal) above to stratified squamous (ectodermal) below.
- ▶ This dual origin explains the differing blood supply (superior rectal artery above vs inferior rectal/pudendal branches below), venous drainage (portal vs systemic — the site of a porto-systemic anastomosis), nerve supply (autonomic/visceral above, insensate to pain vs somatic pudendal below, pain-sensitive), and lymphatic drainage (internal iliac nodes above vs superficial inguinal nodes below) across the pectinate line.

## 3. Derivatives of the Ventral Part — Urogenital Sinus

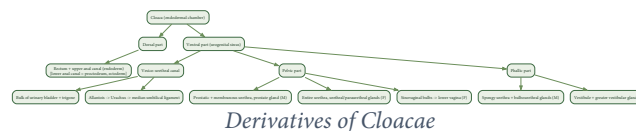
- ▶ The ventral part of the cloaca becomes the **urogenital sinus**, continuous cranially with the allantois. It is conventionally described in **three craniocaudal parts**:
- ▶ **Vesico-urethral canal** (cranial-most, continuous above with the allantoic duct) — forms the bulk of the **urinary bladder**.
- ▶ **Pelvic part** (narrow, intermediate) — forms the urethra at the bladder neck, and in the male the **prostatic and membranous urethra**; in the female, virtually the **entire urethra**.
- ▶ **Phallic part** (caudal, flattened side-to-side, growing toward the genital tubercle) — its later fate diverges sharply between the sexes under androgen influence.
- ▶ The **allantoic duct** narrows to become the **urachus**, which in the adult persists as the fibrous **median umbilical ligament** running from the bladder apex to the umbilicus.
- ▶ **Trigone of the bladder**: the caudal (mesonephric-duct-bearing) ends of the vesico-urethral canal absorb the mesonephric ducts into its dorsal wall, so the ureter and mesonephric duct come to open separately; this absorbed area forms the trigone. Classical teaching held the trigone epithelium was part-mesodermal (from the absorbed duct); current teaching (Moore's Developing Human 9e) is that the connective tissue of the trigone incorporates mesonephric-duct-derived tissue, while molecular fate-mapping has shown the trigone **epithelium** is in fact **endodermal**, derived from the urogenital sinus.

## 4. Sex-Differentiated Derivatives of the Urogenital Sinus

| Subdivision of urogenital sinus | Male derivative                                                 | Female derivative |
|---------------------------------|-----------------------------------------------------------------|-------------------|
| Vesico-urethral canal           | Bulk of urinary bladder; urachus<br>→ median umbilical ligament | Same as male      |

| Subdivision of urogenital sinus | Male derivative                                                                                                                                                                          | Female derivative                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pelvic part                     | Prostatic urethra (proximal to opening of the ejaculatory ducts) and membranous urethra; endodermal outgrowths from this part form the <b>prostate gland</b>                             | Entire urethra; endodermal outgrowths from the cranial urethra form the <b>urethral and paraurethral glands</b> ; paired outgrowths ( <b>sinovaginal bulbs</b> ) from this part fuse to form a solid vaginal plate that canalises to give the <b>lower part of the vagina</b> (the upper vagina/fornices are of paramesonephric-duct origin — the vagina thus has a dual origin) |
| Phallic part                    | Contributes, together with growth of the genital tubercle, to the <b>spongy (penile) urethra</b> ; its endodermal outgrowths also form the paired <b>bulbourethral (Cowper's) glands</b> | Persists relatively unelongated as the <b>vestibule of the vagina</b> (into which the urethra, vagina, and paired <b>greater vestibular [Bartholin's] glands</b> open)                                                                                                                                                                                                           |

## 5. Summary of Cloacal Derivatives



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A midsagittal schematic of the caudal embryo showing progressive division of the cloaca (label, in sequence, left to right as three successive stages):

- ▶ **Hindgut** entering dorsally; **Allantois** entering ventrally; **Mesonephric duct** opening laterally into the cloaca
- ▶ **Cloaca** (single endodermal chamber) with **Cloacal membrane** closing it externally
- ▶ **Urorectal septum** growing caudally in the angle between hindgut and allantois
- ▶ Septum tip approaching the cloacal membrane at the site of the future **Perineal body**
- ▶ Final stage: **Anal membrane** (dorsal) and **Urogenital membrane** (ventral) as separate membranes; **Rectum/anorectal canal** (dorsal compartment) and **Urogenital sinus** (ventral compartment) as separate cavities

## Applied / Clinical anatomy

- ▶ **Anorectal malformations:** a maldeveloped urorectal septum or too-small cloaca produces the spectrum from **anal stenosis** and **membranous atresia** to **anorectal agenesis**, often with a **rectourethral** or **rectovaginal fistula** where the rectum communicates abnormally with the persisting urogenital tract; meconium in the urine of a male neonate suggests a rectourethral fistula.

- ▶ **Persistent cloaca:** incomplete partitioning in a female results in the rectum, vagina and urethra all draining into a single perineal channel — a severe anorectal malformation frequently associated with the **VACTERL** association.
- ▶ **Bladder and cloacal exstrophy:** failure of ventral body-wall/septum development leaves the posterior bladder wall (and, in the more severe cloacal exstrophy, the rectum and anal canal too) exposed on the abdominal surface; cloacal exstrophy is often accompanied by epispadias and widely separated pubic bones.
- ▶ **Urachal anomalies:** incomplete obliteration of the allantois-derived urachus gives a **patent urachus** (urine leak at the umbilicus), **urachal cyst**, or **urachal sinus**.
- ▶ **Pectinate line:** its position marks the clinically vital transition in blood supply, innervation, venous and lymphatic drainage of the anal canal — the basis for distinguishing **internal** (above, painless, portal drainage) from **external** (below, painful, systemic drainage) **haemorrhoids**, and for planning anorectal surgery.
- ▶ **Vaginal anomalies:** failure of sinovaginal-bulb canalisation/fusion underlies **vaginal atresia** and a **transverse vaginal septum**.
- ▶ **Ectopic ureteric orifice:** when the ureter is not incorporated into the trigone (remaining attached to the mesonephric duct instead), it is carried caudally and may open ectopically into the urethra, vas deferens, or (in females) the vestibule/vagina.

### High-yield exam pointers

- ▶ Cloaca = common endodermal chamber for hindgut + allantois, closed by the cloacal membrane; divided by the **urorectal septum** (weeks 4–7).
- ▶ Septum tip meets the cloacal membrane at the future **perineal body**; the membrane breaks down at the end of week 7, creating separate anal and urogenital openings.
- ▶ **Dorsal part** → **rectum + upper anal canal** (endoderm); lower anal canal is **ectodermal** (proctodeum) — junction = **pectinate line**.
- ▶ **Ventral part** = **urogenital sinus**, in 3 parts: **vesico-urethral canal** → **bladder**; **pelvic part** → **prostatic/membranous urethra (M) or entire urethra (F) + prostate/urethral-paraurethral glands**; **phallic part** → **spongy urethra + bulbourethral glands (M) or vestibule + greater vestibular glands (F)**.
- ▶ **Allantois** → **urachus** → **median umbilical ligament**.
- ▶ Trigone of bladder epithelium is **endodermal** (urogenital-sinus derived); mesonephric-duct remnants contribute only connective tissue.
- ▶ **Vagina has dual origin:** upper part from paramesonephric (uterovaginal) tissue, lower part from urogenital-sinus sinovaginal bulbs.
- ▶ Clinical spectrum of septal maldevelopment: anal stenosis → membranous atresia → anorectal agenesis with fistula → persistent cloaca → cloacal exstrophy.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e.



## Derivatives of Mesonephric duct in Males and Females

*Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **mesonephric (Wolffian) duct** is the duct of the mesonephros, the second, transient excretory organ of the embryo. It first drains the mesonephric tubules into the cloaca and, from the 5th week, gives off the **ureteric bud** which forms the entire metanephric collecting system. In the male, under the influence of **testosterone** from the Leydig cells, the duct itself and its associated tubules persist and differentiate into the greater part of the male genital duct system. In the female, in the absence of testosterone, the duct and tubules largely regress, leaving only inconstant vestiges in the broad ligament. This "one duct, two fates" pattern is a classic, oft-repeated (NEET/PG) embryology question because it neatly links the indifferent stage to the adult male and female genital anatomy.

### Origin and early relations of the mesonephric duct

- Develops in week 4 from the **nephrogenic cord** (intermediate mesoderm) as the **primary/pronephric duct**; once mesonephric tubules connect to it (~stage 12), it is renamed the **mesonephric duct**.
- Runs caudally in the urogenital ridge, lateral to the mesonephros, and opens into the **cloaca**.
- Near its caudal end it gives off the **ureteric bud** (an evagination), which penetrates the metanephric blastema to form the ureter, renal pelvis, calyces and collecting tubules — **this part is common to both sexes and is retained irrespective of gonadal sex**.
- With cloacal division, the caudal (common) segment of the duct is absorbed into the wall of the developing bladder, forming the **trigone**; the ureter thus gains a separate opening, lateral to (and above) the mesonephric duct orifice.
- The **paramesonephric (Müllerian) duct** develops just lateral to it in both sexes during the indifferent stage; the mesonephric duct then acts as a "guide" along which the paramesonephric duct grows caudally.

### Hormonal control of duct fate

| Hormone                                                       | Source                        | Action                                                                                                                                         |
|---------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Testosterone                                                  | Leydig cells of fetal testis  | Stimulates ipsilateral mesonephric duct to differentiate (paracrine, locally acting — unilateral castration causes only unilateral regression) |
| Anti-Müllerian hormone (AMH / Müllerian-inhibiting substance) | Sertoli cells of fetal testis | Causes regression of the paramesonephric duct in the male                                                                                      |

| Hormone                          | Source         | Action                                                                                                                |
|----------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------|
| Absence of testosterone (female) | —              | Mesonephric duct fails to be maintained and regresses, leaving only vestiges                                          |
| Oestrogen (female)               | Ovary/placenta | Supports paramesonephric duct development (uterine tube, uterus, upper vagina) — does not rescue the mesonephric duct |

## Derivatives in the male

Under testosterone, the mesonephric duct and closely related mesonephric tubules form the entire excretory duct system of the testis, cranial to caudal:

| Structure                                                                        | Origin                                                                                          |
|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Vasa efferentia (efferent ductules)                                              | Persisting cranial group of <b>mesonephric tubules</b> that join the rete testis                |
| Duct of epididymis                                                               | Cranial part of the mesonephric duct — elongates and becomes highly coiled                      |
| Vas (ductus) deferens                                                            | Middle part of the mesonephric duct — develops a thick muscular coat                            |
| Seminal vesicle                                                                  | A diverticulum from the duct just proximal to its termination                                   |
| Ejaculatory duct                                                                 | Part of the duct distal to the seminal-vesicle outgrowth, opening into the prostatic urethra    |
| Trigone of bladder + posterior wall of prostatic urethra proximal to the utricle | Caudal (common) part of the duct incorporated into the urogenital sinus wall                    |
| Mesodermal stroma/smooth muscle of prostate & bulbourethral glands               | Surrounding mesenchyme of the duct (glands themselves are endodermal outgrowths of the urethra) |

**Vestigial mesonephric remnants in the male** (clinically important as cyst-forming rests):

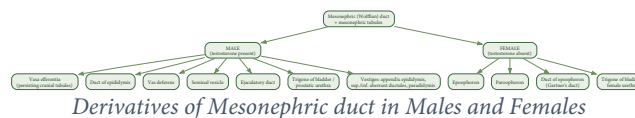
- **Appendix of the epididymis** — cranial-most tip of the mesonephric duct, persisting as a small pedunculated body on the head of the epididymis (do **not** confuse with the appendix testis, which is a paramesonephric remnant).
- **Superior aberrant ductules (epigenital tubules)** — mesonephric tubules cranial to the vasa efferentia; connected to the rete testis but not to the epididymis.
- **Inferior aberrant ductules** — mesonephric tubules caudal to the vasa efferentia; connected only to the epididymis, not the testis.
- **Paradidymis** — a cluster of unconnected ("paragenital") mesonephric tubules lying between testis and epididymis.

## Derivatives in the female

The mesonephric duct is not maintained (no testosterone) and largely disappears, but three inconstant vestiges persist in the mesovarium/broad ligament, parallel to the (dominant) paramesonephric-duct-derived genital tract:

| Vestige                                               | Nature                                                                                                                                                         | Location                                                                                               |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Epoophoron                                            | Cranial mesonephric tubules + the cranial-most segment of the duct (longitudinal duct with transverse ductules); homologue of the epididymis + vasa efferentia | Mesosalpinx, lateral to the ovary, between ovary and uterine tube                                      |
| Paroophoron                                           | Caudal mesonephric tubules persisting as small blind tubules; homologue of the paradidymis                                                                     | Broad ligament, between ovary and uterus                                                               |
| Duct of epoophoron / Gartner's duct                   | Persisting part of the mesonephric duct itself; homologue of the ductus deferens                                                                               | Runs in the broad ligament alongside the uterus, may extend into the lateral wall of the cervix/vagina |
| Trigone of bladder + posterior wall of female urethra | Caudal (common) part of the duct, as in the male                                                                                                               | —                                                                                                      |

- These structures have **no functional significance** and are found incidentally; their principal clinical relevance is as sites of **Gartner's duct cysts** in the lateral vaginal/cervical wall.
- The mesonephric duct makes **no connection** with the developing ovary at any stage (unlike in the male, where efferent ductules link it to the rete testis).



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a coronal schematic of the mesonephros/gonad with the mesonephric duct running caudally:

- ▶ Testis with **rete testis** and **vasa efferentia** entering the coiled **epididymis** (head, body, tail).
- ▶ **Appendix of epididymis** at the head; **superior aberrant ductules** above and **inferior aberrant ductules** below the vasa efferentia; **paradidymis** between testis and epididymis.
- ▶ **Vas deferens** continuing from the tail of epididymis; **seminal vesicle** as a lateral diverticulum near its termination; **ejaculatory duct** opening into the **prostatic urethra**.
- ▶ On the female side (mirror panel): **Ovary**, with **epoophoron** (longitudinal + transverse ductules) and **paroophoron** in the mesosalpinx/broad ligament; **Gartner's duct** running down alongside the **uterus**, **cervix** and lateral vaginal wall; **uterine tube**, **uterus**, **vagina** (paramesonephric derivatives, labelled but not detailed).
- ▶ Mark the **ureter** arising from the ureteric bud on the mesonephric duct in both panels, entering the **trigone** of the bladder.

Real reference plate — Sontakke, *Textbook of Human Embryology*, Fig 21.8 (p.231):

□ Fig 21.8 — Derivatives of mesonephric duct in genital system (Sontakke — *Textbook of Human Embryology*, p.231)

**Applied / Clinical anatomy**

- ▶ **Gartner's duct cyst** — a smooth, submucosal cyst in the anterolateral wall of the vagina/cervix arising from a persistent duct-of-epoophoron remnant; usually asymptomatic and found incidentally, occasionally causing dyspareunia or presenting as a bulge.
- ▶ **Appendix-of-epididymis cyst/torsion** — the pedunculated mesonephric-duct remnant on the epididymal head can twist, mimicking testicular torsion clinically ("blue dot sign").
- ▶ Because the **ureteric bud is a mesonephric-duct derivative common to both sexes**, mesonephric duct anomalies and urinary-tract anomalies (renal agenesis, ectopic ureter) frequently coexist — the embryological basis for combined uro-genital anomaly syndromes.
- ▶ **Persistence/failure of regression** of the female mesonephric duct underlies **Gartner's duct anomalies**; conversely, failure of the male mesonephric duct to differentiate (e.g. androgen-insensitivity or absent Leydig-cell testosterone) leads to **absent/atretic epididymis, vas deferens and seminal vesicle** — a cause of obstructive azoospermia and congenital bilateral absence of vas deferens (CBAVD, associated with CFTR mutations).
- ▶ The **appendix testis** (paramesonephric remnant) and **appendix of epididymis** (mesonephric remnant) are both surgically relevant scrotal "hydatids" that must be distinguished from testicular torsion during acute-scrotum evaluation.
- ▶ Since the epoophoron, paroophoron and Gartner's duct all lie in the **mesosalpinx/broad ligament**, they are the embryological explanation for **paratubal/paraovarian cysts** encountered incidentally at laparotomy or laparoscopy.



## High-yield exam pointers

- ▶ Mesonephric duct = **Wolffian duct**; paramesonephric duct = **Müllerian duct** — never interchange the male/female-forming duct in an answer.
- ▶ **Testosterone (paracrine, Leydig cells)** maintains the mesonephric duct in the male; **AMH (Sertoli cells)** regresses the paramesonephric duct in the male — two separate hormones, two separate ducts.
- ▶ Male mesonephric-duct derivatives, cranial to caudal: **vasa efferentia** → **epididymis** → **vas deferens** → **seminal vesicle** → **ejaculatory duct**.
- ▶ Female mesonephric vestiges (all in the broad ligament/mesovarium): **epoophoron**, **paroophoron**, **Gartner's duct** — remember by their male homologues (vasa efferentia/epididymis, paradidymis, vas deferens respectively).
- ▶ **Appendix of epididymis = mesonephric**; **appendix of testis = paramesonephric** — a classic distractor pair.
- ▶ **Ureteric bud, trigone of bladder, and posterior urethral wall are mesonephric-duct derivatives common to BOTH sexes** — do not omit these when the question says "in males and females."
- ▶ The mesonephric duct never connects with the ovary — no female equivalent of the "vasa efferentia-to-rete-testis" link exists.
- ▶ Clinically: Gartner's duct cyst (female) and appendix-of-epididymis cyst/torsion (male) are the two commonest vestige-related lesions.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology.



## Derivatives of the Cloacae

Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **cloaca** is the common endoderm-lined terminal chamber of the caudal embryo, present from the 4th week of intra-uterine life, into which the tubular **hindgut** opens dorsally, the ventral diverticulum **allantois** opens ventrally, and the paired **mesonephric ducts** enter laterally. It is closed externally by the bilaminar **cloacal membrane** (apposed ectoderm and endoderm, with no intervening mesenchyme). Between the 4th and 7th weeks, a mesenchymal **urorectal septum** grows caudally in the angle between the hindgut and the allantois and comes to lie against the cloacal membrane, partitioning the single cloacal chamber into a dorsal **anorectal canal** and a ventral **urogenital sinus**. This one partitioning event is therefore the developmental source of the rectum and upper anal canal, the entire urinary bladder and much of the urethra, the prostate/para-urethral, bulbourethral/greater-vestibular glands, part of the vagina, and the urachus — and its disturbance produces a well-defined family of anorectal and urogenital malformations.

### 1. Formation and Partitioning of the Cloaca

- ▶ The **endodermal cloaca** is the dilated terminal expansion of the hindgut immediately proximal to the cloacal membrane, invested by splanchnopleuric mesenchyme; it receives the hindgut dorsally, the allantois ventrally and, later, the mesonephric ducts laterally.
- ▶ Mesenchymal and endodermal proliferation at the **hindgut–allantois angle** forms the **urorectal septum** (its mesenchyme is also termed *intercloacal/pericloacal mesenchyme*; the molecular markers **Six1** and **Six2** have been localised to it — Gray's Anatomy 41e).
- ▶ The septum elongates caudally so that its tip **approaches** the cloacal membrane at the site of the future **perineal body**; Gray's Anatomy 41e is explicit that true fusion of septum and membrane does not occur — the septum merely comes to lie against it — though many standard texts still describe this step loosely as "fusion." Either way, the net anatomical result is the same: the cloacal chamber is divided into a **dorsal part (future rectum/anorectal canal)** and a **ventral part (urogenital sinus)**.
- ▶ The **cloacal membrane** is correspondingly split into a dorsal **anal membrane** and a ventral **urogenital membrane**. During the **7th week**, both membranes rupture, creating a separate posterior (anal) opening for the hindgut and a separate anterior (urogenital) opening for the urogenital sinus onto the body surface.
- ▶ The **mesonephric ducts**, which originally opened directly into the cloaca, now open into the urogenital sinus following partitioning.

□ Fig 14.12 — Development of the anal canal. Urogenital septum divides cloaca into v (Sontakke — Textbook of Human Embryology, p.144)

### 2. Derivatives of the Dorsal Part — Rectum and Anal Canal

- ▶ The dorsal compartment gives rise to the **rectum** and the **upper (approximately two-thirds) of the anal canal**, identical in both sexes as this region is not influenced by gonadal hormones.
- ▶ The **anal canal has a dual embryological origin**: its upper part is **endodermal**, derived directly from the hindgut/cloaca, while its lower part is formed by an ingrowing ectodermal pit, the **proctodeum (anal pit)**, that invaginates around the ruptured anal membrane.

- The endodermal–ectodermal junction is marked by the **pectinate (dentate) line**, where columnar (endodermal) epithelium above gives way to stratified squamous (ectodermal) epithelium below.

| Feature            | Above pectinate line (endodermal)                                                | Below pectinate line (ectodermal)                          |
|--------------------|----------------------------------------------------------------------------------|------------------------------------------------------------|
| Arterial supply    | Superior rectal artery                                                           | Inferior rectal artery                                     |
| Venous drainage    | Superior rectal vein → portal system                                             | Inferior rectal vein → systemic (caval) system             |
| Nerve supply       | Autonomic (sympathetic + pelvic splanchnic parasympathetic); insensitive to pain | Somatic — inferior rectal (pudendal) nerve; pain-sensitive |
| Lymphatic drainage | Internal iliac nodes                                                             | Superficial inguinal nodes                                 |

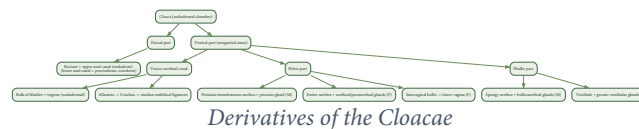
### 3. Derivatives of the Ventral Part — the Urogenital Sinus

- The ventral compartment becomes the **urogenital sinus**, continuous cranially with the allantois. It is conventionally described in **three craniocaudal parts**:
- **Vesico-urethral canal** (cranial-most, continuous above with the allantoic duct) — forms the bulk of the **urinary bladder**, the urethra as far as the bladder neck, and (in the male) the prostatic urethra proximal to the opening of the prostatic utricle.
- **Pelvic part** (narrow, intermediate segment) — forms the more distal urethra: the remainder of the prostatic and the membranous urethra in the male, and virtually the entire urethra in the female.
- **Phallic part** (caudal-most, flattened side to side, growing toward the genital tubercle, closed externally by the urogenital membrane) — its fate diverges sharply between the sexes under androgen influence.
- The apex of the vesico-urethral canal is prolonged toward the umbilicus as the **allantoic duct**, which narrows to become the **urachus**; in the adult this persists as the fibrous **median umbilical ligament** running from the bladder apex to the umbilicus.
- **Trigone of the bladder**: the paired mesonephric ducts are absorbed into the dorsal wall of the vesico-urethral canal, so that the ureter and mesonephric duct come to open separately, the ureteric orifice migrating cranially and the mesonephric-duct orifice moving caudally. The incorporated "common nephric duct" segment undergoes local **apoptosis** as part of this process. Older teaching held that this absorbed segment contributed a patch of mesodermal epithelium to the trigone; current evidence (antibody labelling and transgenic fate-mapping, cited in Gray's Anatomy 41e) shows the **trigone epithelium is entirely endodermal**, of urogenital-sinus origin, differentiating like the rest of the bladder/prostatic epithelium — the mesonephric-duct remnant contributes no epithelium, and even the trigonal smooth muscle is now shown to arise predominantly from detrusor (bladder) muscle rather than from the ureter.

#### 4. Sex-Differentiated Derivatives of the Urogenital Sinus

| Subdivision of urogenital sinus | Male derivative                                                                                                                                                                                                                 | Female derivative                                                                                                                                                                                                                                                                                                                          |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vesico-urethral canal           | Bulk of urinary bladder + trigone; prostatic urethra above the seminal colliculus; urachus → median umbilical ligament                                                                                                          | Same as male                                                                                                                                                                                                                                                                                                                               |
| Pelvic part                     | Remainder of prostatic urethra + membranous urethra; endodermal outgrowths form the <b>prostate gland</b>                                                                                                                       | Entire urethra; endodermal outgrowths form the <b>urethral and para-urethral (Skene's) glands</b> ; paired outgrowths ( <b>sinovaginal bulbs</b> ) fuse into a solid vaginal plate that canalises to form the <b>lower part of the vagina</b> (upper vagina/fornices are paramesonephric-duct derived — the vagina thus has a dual origin) |
| Phallic part                    | Contributes, with growth of the genital tubercle, to the <b>spongy (penile) urethra</b> (except the terminal glandular part, which is ectodermal); endodermal outgrowths form the paired <b>bulbourethral (Cowper's) glands</b> | Persists relatively un-elongated as the <b>vestibule of the vagina</b> , into which the urethra, vagina and paired <b>greater vestibular (Bartholin's) glands</b> open                                                                                                                                                                     |

#### 5. Summary of Cloacal Derivatives



#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A midsagittal schematic of the caudal embryo in three successive stages, labelling:

- **Hindgut** entering dorsally; **Allantois** entering ventrally; **Mesonephric duct** opening laterally into the single **cloaca**, closed by the **cloacal membrane**
- **Urorectal septum** growing caudally in the hindgut–allantois angle, its tip approaching the cloacal membrane at the site of the future **perineal body**
- Final stage: separate **anal membrane** (dorsal) and **urogenital membrane** (ventral); separate **rectum/anorectal canal** (dorsal) and **urogenital sinus**, subdivided into **vesico-urethral canal**, **pelvic part** and **phallic part** (ventral)

#### Applied / Clinical anatomy

- **Anorectal malformations**: a maldeveloped or dorsally-deviated urorectal septum produces a spectrum from **anal stenosis** and **membranous anal atresia** to **anal/rectal agenesis** (the commonest form of imperforate anus), often with a **rectourethral** or **rectovesical fistula** in the male or a **rectovaginal/rectovestibular fistula** in the female; meconium in the neonatal urine

points to a rectourinary fistula. Anomalies are broadly grouped as **low** (rectum ends below the puborectalis sling — good continence prognosis) or **high** (rectum ends above puborectalis, usually with a fistula — poorer prognosis), a distinction that guides surgical approach.

- ▶ **Persistent cloaca:** incomplete partitioning in a female leaves the rectum, vagina and urethra draining into one common perineal channel — a severe anorectal malformation often part of the VACTERL association.
- ▶ **Bladder and cloacal exstrophy:** failure of urorectal septum/ventral-body-wall development leaves the posterior bladder wall (and, in the more severe cloacal exstrophy, the rectum and anal canal too) exposed on the abdominal surface, typically with epispadias and diastasis of the pubic symphysis.
- ▶ **Urachal anomalies:** incomplete obliteration of the allantois-derived urachus produces a **patent urachus** (urinary leak at the umbilicus), **urachal cyst**, or **urachal sinus**.
- ▶ **Pectinate line:** this embryological boundary is the basis for distinguishing **internal haemorrhoids** (above, painless, portal drainage) from **external haemorrhoids** (below, painful, systemic drainage), and for staging the differing lymphatic spread of tumours above versus below the line.
- ▶ **Vaginal anomalies:** failure of sinovaginal-bulb canalisation or fusion underlies **vaginal atresia** and **transverse vaginal septum**.
- ▶ **Ectopic ureteric orifice:** aberrant absorption of the mesonephric duct into the trigone can carry the ureteric orifice caudally, causing it to open ectopically into the urethra, vas deferens, or (in females) the vestibule/vagina — with associated incontinence.

## High-yield exam pointers

- ▶ Cloaca = common endodermal chamber receiving hindgut (dorsal), allantois (ventral) and mesonephric ducts (lateral); closed externally by the **cloacal membrane**.
- ▶ Partitioned by the **urorectal septum** (weeks 4–7); septum tip approaches the membrane at the future **perineal body** (Gray's 41e: true fusion does not occur, though many texts describe it as "fusion").
- ▶ Cloacal membrane splits into **anal membrane** + **urogenital membrane**, both rupturing during the 7th week.
- ▶ **Dorsal part** → **rectum** + **upper anal canal** (endoderm); lower anal canal is **ectodermal** (proctodeum); junction = **pectinate line**, with differing blood/nerve/lymphatic drainage on each side.
- ▶ **Ventral part** = **urogenital sinus**, in three parts: **vesico-urethral canal** → **bladder** + **trigone**; **pelvic part** → **prostatic/membranous urethra** (M) or **entire urethra** (F) + **prostate/urethral-paraurethral glands**; **phallic part** → **spongy urethra** + **bulbourethral glands** (M) or **vestibule** + **greater vestibular glands** (F).
- ▶ **Allantois** → **urachus** → **median umbilical ligament**.
- ▶ **Trigone epithelium** is **entirely endodermal** (modern fate-mapping); the absorbed "common nephric duct" undergoes apoptosis and contributes no epithelium.
- ▶ **Vagina** has a **dual origin**: upper part paramesonephric, lower part from urogenital-sinus sinovaginal bulbs.

- Clinical spectrum of septal maldevelopment: anal stenosis → anorectal agenesis with fistula → persistent cloaca → cloacal exstrophy; low vs high anorectal anomalies are defined relative to puborectalis.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); BD Chaurasia — Human Anatomy Vol 2 8e (anal canal applied anatomy).



## Descent of Testis

Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy

### Definition / Introduction

The testis develops from the genital (gonadal) ridge on the **posterior abdominal wall**, medial to the mesonephros, in the upper lumbar region, and remains **retroperitoneal** throughout its migration. Between roughly the 3rd fetal month and birth it relocates caudally to occupy the scrotum, a process now understood as **two sequential, distinctly-regulated phases** — a hormone-independent-of-androgen **transabdominal phase** that brings the testis to the deep inguinal ring, followed by an androgen-dependent **inguinoscrotal phase** that carries it through the inguinal canal into the scrotum (Barteczko and Jacob 2000, cited in Gray's 41e). Descent is guided throughout by the **gubernaculum testis** and preceded by the **processus vaginalis**, a peritoneal diverticulum. Normal descent is essential because spermatogenesis requires the lower, scrotal temperature; disorders of descent (cryptorchidism, ectopic testis) and of processus vaginalis closure (congenital hernia, hydrocele) are major clinical correlates of this process.

### 1. Site of origin and structures guiding descent

| Structure           | Description                                                                                                                                                  | Fate                                                                                                                                                                            |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gubernaculum testis | A mesenchymal cord (the genito-inguinal ligament) extending from the lower pole of the testis/mesonephric duct to the labioscrotal (future scrotal) swelling | Its extracellular matrix is resorbed after descent; the residue condenses into the <b>scrotal ligament (ligament of the testis)</b> , anchoring the testis to the scrotal floor |
| Processus vaginalis | A peritoneal diverticulum that hollows out the gubernaculum and precedes the testis, which invaginates it from behind as it enters the scrotum               | Distal part persists as the <b>tunica vaginalis</b> (parietal + visceral layers); proximal stalk normally obliterates by about 3 weeks after birth                              |

| Structure                   | Description                                                                                               | Fate                                                                                                                           |
|-----------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Cranial suspensory ligament | The cranial attachment of the urogenital ridge (to the diaphragm)                                         | Regresses under androgen action in the male, permitting caudal relocation; persists in the female, restraining ovarian descent |
| Mesorchium                  | A peritoneal fold carrying the testicular vessels and nerves                                              | Persists — accounts for the long lumbar course of the testicular vessels down to the scrotum                                   |
| Inguinal bursa              | An outpouching of the abdominal-wall layers toward the scrotum, formed <i>before</i> the testis enters it | Its cavity becomes the <b>inguinal canal</b>                                                                                   |

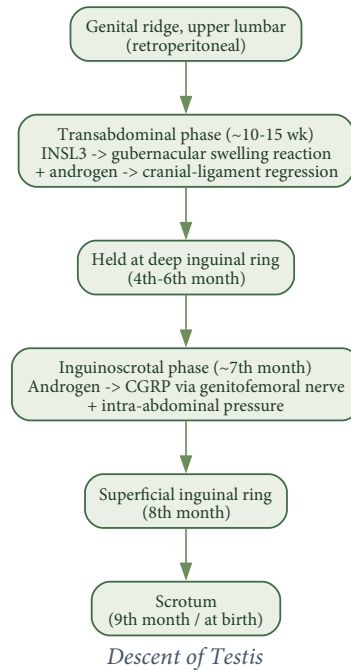
## 2. Two-phase mechanism and month-wise timeline of descent

| Phase          | Timing                   | Position / event                                                                                                                                                                                                            | Directing mechanism                                                                                                          |
|----------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Transabdominal | up to 10 weeks           | Gubernaculum is identical in the two sexes                                                                                                                                                                                  | —                                                                                                                            |
| Transabdominal | 10–15 weeks (≈3rd month) | Gubernaculum undergoes a " <b>swelling reaction</b> ", anchoring the testis near the future deep inguinal ring as the trunk elongates around it (largely a <i>relative</i> movement); testis reaches the <b>iliac fossa</b> | INSL3 secreted by fetal Leydig cells                                                                                         |
| Transabdominal | 4th–6th month            | Testis remains apposed to the <b>deep inguinal ring</b> , held there by the gubernaculum; cranial suspensory ligament regresses                                                                                             | Androgens                                                                                                                    |
| Inguinoscrotal | 7th month                | Gubernaculum bulges out of the abdominal-wall muscles and elongates rapidly across the pubis into the scrotum; testis <b>traverses the inguinal canal</b> relatively quickly (left usually before right)                    | Androgen-driven CGRP release from the genital branch of the genitofemoral nerve; assisted by rising intra-abdominal pressure |
| Inguinoscrotal | 8th month                | Testis reaches the <b>superficial inguinal ring</b>                                                                                                                                                                         | —                                                                                                                            |



| Phase          | Timing                             | Position / event                                                                                           | Directing mechanism |
|----------------|------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------|
| Inguinoscrotal | 9th month / at or soon after birth | Testis reaches the <b>floor of the scrotum</b> ; over 95% of full-term neonates have both testes descended | —                   |

□ Fig 72.17 — The descent of the testis. The testis is retroperitoneal throughout development. It becomes obliquely orientated during abdominal descent (Gray's Anatomy — Standring — 41e, p.1687)



### 3. Fate of the gubernaculum and processus vaginalis

- ▶ At birth the proximal processus vaginalis is narrowed and collapsed but **not necessarily fully obliterated**: it remains patent in nearly 70% of male infants at 2 weeks, and is at least partially obliterated in 80% by 3 weeks (left before right).
- ▶ The **distal** processus persists as a small satellite peritoneal cavity, the **tunica vaginalis**, which becomes firmly attached to the scrotum within a few weeks.
- ▶ Obliteration of the proximal stalk is itself androgen-dependent, mediated indirectly via CGRP from the genitofemoral nerve.
- ▶ Because the testis carries the **ductus deferens and testicular vessels** with it from their original high lumbar position, this explains why the ductus deferens comes to cross **anterior to the ureter** near the bladder, and why the testicular vessels have such a long course from the L2 level down to the scrotum.

### 4. Fascial coverings acquired during descent

As the testis and gubernaculum traverse the anterior abdominal wall, each musculo-fascial layer contributes a corresponding covering to the spermatic cord and testis:

| Abdominal-wall layer             | Covering of spermatic cord/testis                                                                    |
|----------------------------------|------------------------------------------------------------------------------------------------------|
| Transversalis fascia             | Internal spermatic fascia                                                                            |
| Internal oblique muscle + fascia | Cremasteric muscle and fascia                                                                        |
| External oblique aponeurosis     | External spermatic fascia                                                                            |
| Transversus abdominis            | <b>No contribution</b> — it arches over the inguinal region and does not cover the path of migration |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Four-panel sagittal/coronal schematic of the posterior and anterior abdominal wall (label as A→D):

- ▶ **Panel A** — testis and mesonephric duct high on the posterior abdominal wall; gubernaculum testis running from the lower pole of the testis to the base of the future scrotum; peritoneum draped over the testis.
- ▶ **Panel B** — gubernaculum swollen to the width of the testis; testis apposed to the deep inguinal ring; a crescentic column of peritoneum (processus vaginalis) beginning to hollow out the gubernaculum.
- ▶ **Panel C** — testis traversing the inguinal canal, gubernaculum's distal end bulging over the pubic ramus into the scrotal swelling; ductus deferens and testicular vessels descending alongside.
- ▶ **Panel D** — testis in the floor of the scrotum; parietal and visceral layers of tunica vaginalis labelled; obliterated proximal processus vaginalis; ductus deferens crossing anterior to the ureter (inset); scrotal ligament (gubernacular remnant).

Label throughout: testis, mesonephric duct/ductus deferens, gubernaculum testis, processus vaginalis, deep inguinal ring, superficial inguinal ring, base of scrotum, tunica vaginalis (parietal/visceral).

## Applied / Clinical anatomy

**Cryptorchidism (undescended testis):** failure of one or both testes to descend; classified by the level at which descent is arrested:

| Type           | Location                         |
|----------------|----------------------------------|
| Lumbar         | Lumbar region of the abdomen     |
| Iliac          | At the deep inguinal ring        |
| Inguinal       | Within the inguinal canal        |
| Pubic          | At the superficial inguinal ring |
| Scrotal (high) | High up in the scrotum           |

Occurs in ~30% of premature and 3–5% of full-term male neonates; most complete descent within the first 3 postnatal months, and spontaneous descent essentially does not occur after one year of age. Cause

is usually deficient fetal androgen (transabdominal-phase failure is uncommon since that phase is hormonally simple; inguinoscrotal-phase failure — deficient androgen/CGRP action — is far commoner and leaves the testis in the inguinal or pubic region in 2–5% of neonates). Cryptorchidism is now regarded as one feature of the **testicular dysgenesis syndrome** (with hypospadias, impaired semen quality and germ-cell cancer risk) rather than a trivial birth defect; because germ-cell numbers fall rapidly in an undescended testis, **orchidopexy** is now recommended at 6–9 months of postnatal life, and even with early surgery bilateral cryptorchidism carries a roughly six-fold higher risk of infertility.

- ▶ **Ectopic testis:** the testis deviates from the normal path of descent to lie in the superficial fascia of the anterior abdominal wall (**interstitial type — commonest site**), the femoral triangle, the root of the penis, the perineum, or rarely the opposite side (crossed ectopia); attributed to hypothetical fibrous **bands of Lockwood** diverting the gubernacular tract, possibly via a mislocated genitofemoral nerve.
- ▶ **Congenital indirect inguinal hernia and hydrocele:** both follow failure of the proximal processus vaginalis to obliterate — wide patency allows bowel to herniate into the scrotum (congenital indirect inguinal hernia); narrow patency permits only peritoneal fluid to trickle down (congenital/communicating hydrocele); partial, segmental obliteration traps fluid mid-canal as an **encysted hydrocele of the cord**.
- ▶ **Crossing of vas deferens over the ureter:** a direct embryological consequence of testicular descent, since the ductus deferens and vessels are dragged down from their high lumbar origin.
- ▶ **Acquired ("ascending") undescended testis:** a previously scrotal testis may re-ascend if the spermatic cord fails to double in length between birth and puberty, linked to the same deficient androgen/CGRP axis as hernia and hydrocele.
- ▶ **Associated anomalies:** cryptorchidism is commoner with abdominal-wall defects (bladder exstrophy, exomphalos ~30%, gastroschisis ~15%) and with upper-lumbar myelomeningocele (>30%), reflecting shared abdominal-pressure and genitofemoral-innervation mechanisms.

## High-yield exam pointers

- ▶ Descent occurs in **two phases**: transabdominal (INSL3-driven gubernacular "swelling reaction," ~10–15 weeks) and inguinoscrotal (androgen → CGRP via genitofemoral nerve, ~7th month).
- ▶ Classical month-wise landmarks: **3rd month** — iliac fossa; **4th–6th month** — held at deep inguinal ring; **7th month** — traverses inguinal canal; **8th month** — superficial inguinal ring; **9th month** — scrotum.
- ▶ **Gubernaculum** anchors/guides the path; **processus vaginalis** precedes the testis and is invaginated by it from behind.
- ▶ Distal processus vaginalis → **tunica vaginalis**; proximal stalk obliterates (~3 weeks postnatal); residual gubernaculum → **scrotal ligament**.
- ▶ Coverings: transversalis fascia → internal spermatic fascia; internal oblique → cremaster; external oblique aponeurosis → external spermatic fascia; transversus abdominis contributes nothing.
- ▶ >95% of full-term neonates have descended testes; most residual cases complete descent within 3 postnatal months; virtually none after 1 year without intervention.
- ▶ Persistent processus vaginalis → congenital indirect inguinal hernia (wide) / congenital hydrocele (narrow) / encysted hydrocele of the cord (segmental).

- ▶ Cryptorchidism = part of testicular dysgenesis syndrome; orchidopexy now recommended at 6–9 months postnatal.
- ▶ Descent explains the ductus deferens crossing anterior to the ureter and the long lumbar course of the testicular vessels.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; BD Chaurasia Human Anatomy Vol 2 8e; Vishram Singh Textbook of Clinical Embryology; IB Singh Textbook of Anatomy Vol 2 6e — for the embedded plate, Gray's Anatomy (Standring) 41e, Fig 72.17.



## Describe in Detail "Derivatives of Paramesonephric duct". Mention about the Anomalies Resulting

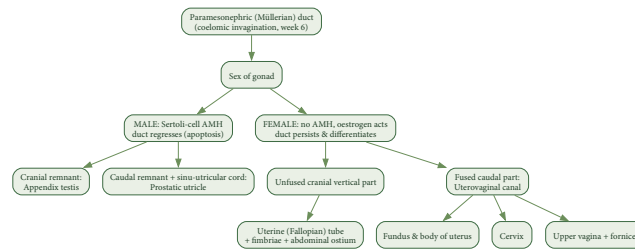
*Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The paramesonephric (Müllerian) duct is one of the two paired genital ducts present in the bipotential ("indifferent") embryo of both sexes, arising in the sixth week as a longitudinal invagination of the coelomic epithelium on the anterolateral surface of the urogenital ridge, lateral to the mesonephric (Wolffian) duct. Its fate is governed entirely by the gonad: in the female (no anti-Müllerian hormone) it persists and forms virtually the whole genital duct system — uterine tube, uterus, cervix and upper vagina — whereas in the male, Sertoli-cell anti-Müllerian hormone (AMH) causes it to regress almost completely, leaving only two small remnants. Because nearly every congenital anomaly of the female genital tract is a fault of fusion, canalisation or regression of this duct, its derivatives and defects form a single, linked exam topic.

### 1. Origin and sex-dependent fate of the duct

- ▶ **Week 6 (10–12 mm embryo):** each paramesonephric duct begins as a funnel-shaped invagination of coelomic epithelium — the **paramesonephric groove** — on the lateral aspect of the mesonephric ridge, near its cranial end; the blind caudal end grows as a solid rod, canalising as it lengthens, always **lateral** to the mesonephric duct, which acts as its guide.
- ▶ **Week 8:** on reaching the caudal end of the mesonephros the duct turns medially and crosses **ventral** to the mesonephric duct to enter the genital cord, coming into contact with its fellow of the opposite side in the midline.
- ▶ **Third month:** the two ducts reach the dorsal wall of the urogenital sinus; their caudal, fused ends raise an elevation on the sinus wall, the **Müllerian (sinus) tubercle**.
- ▶ Each duct wall has three layers, all reflected in the adult derivatives: an outer **serosa** (coelomic epithelium), a **muscularis** (surrounding mesenchyme) and an inner **mucosa** (the duct/coelomic epithelium itself).
- ▶ **Molecular control:** SRY on the Y chromosome upregulates SOX9 in pre-Sertoli cells; SF1 with SOX9 raises AMH secretion, which acts on an AMH-receptor-II-bearing peri-ductal mesenchyme to trigger apoptosis of the duct epithelium (with MMP2-mediated basement-

membrane degradation) — the mechanism of male duct regression. In the female, absence of SRY/AMH and testosterone leaves the duct unopposed to differentiate under oestrogen.



Describe in Detail "Derivatives of Paramesonephric duct". Mention about the Anomalies Resulting

## 2. Derivatives in the female

| Part of paramesonephric duct                                      | Adult derivative                                                                                                                                                                                       |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cranial vertical (unfused) part + original coelomic opening       | <b>Uterine (Fallopian) tube</b> — infundibulum with fimbriae opening at the pelvic/abdominal ostium, ampulla, isthmus                                                                                  |
| Horizontal part, taken up as the ovary descends                   | Incorporated into the <b>fundus and most of the body of the uterus</b>                                                                                                                                 |
| Caudal fused part (uterovaginal canal/primordium)                 | <b>Body and cervix of the uterus; upper (paramesonephric) part of the vagina and the vaginal fornices</b>                                                                                              |
| Surrounding mesenchyme of the genital cord                        | <b>Myometrium and perimetrium</b> ; muscular coat of the vagina; stroma of the endometrium                                                                                                             |
| Fused ducts pulling a peritoneal fold as they meet in the midline | <b>Broad ligament of the uterus</b> — uterine tube in its upper (mesosalpinx) border, ovary attached to its posterior layer (mesovarium); divides the pelvis into uterovesical and uterorectal pouches |

□ Fig 21.9 — Development of uterus and vagina. Paramesonephric ducts (Müllerian ducts) grow caudally, fuse and form the uterovaginal canal; sinovaginal bulbs from the urogenital sinus form the vaginal plate, which canalises to complete the vagina. (Sontakke — Textbook of Human Embryology, p.232)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label: paired paramesonephric ducts (unfused cranial part) → point of crossing ventral to the mesonephric duct → fused caudal part (uterovaginal canal) → Müllerian/sinus tubercle on the urogenital sinus wall → sinovaginal bulbs → vaginal plate → canalised vagina and fornices → hymen; separately label the uterine tube (fimbriated infundibulum, ampulla, isthmus), fundus/body/cervix of uterus, and the broad ligament with ovary and uterine tube in its free border.

## 3. Development of the vagina — a dual origin

- The uterovaginal canal meets the dorsal wall of the urogenital sinus at the Müllerian tubercle; this induces the sinus epithelium to proliferate as two solid endodermal outgrowths, the **sinovaginal bulbs**, which fuse to form a solid **vaginal plate**.

- ▶ The plate canalises **from caudal to cranial**; by about 170 mm crown–rump length the fornices, initially solid, become hollow, and the genital canal is continuous with the exterior by roughly mid-gestation ( $\approx 180$  mm).
- ▶ Consequently the vagina has a **dual embryological origin**: the **upper vagina and fornices** are conventionally ascribed to paramesonephric (mesenchymal) tissue, while the **lower vagina** derives from the urogenital-sinus-derived sinovaginal bulbs; the exact cranio-caudal boundary of the epithelial contribution has only been precisely mapped in the mouse and remains debated in humans.
- ▶ The **hymen**, a thin membrane at the introitus, marks the junction of the sinus-derived vaginal wall and the vestibule; a complete diaphragm across the lumen gives an **imperforate hymen**.

#### 4. Derivatives in the male, and the mesonephric/paramesonephric homologies

- ▶ Under AMH, the paramesonephric duct atrophies almost completely in the male. Only two vestiges persist: a small **cranial remnant** — the **appendix testis** — attached near the upper pole of the testis, and a **caudal remnant** that fuses with a proliferation of urogenital-sinus epithelium (the sinu-utricular cord) to form the **prostatic utricle**, a blind pouch opening on the colliculus seminalis beside the ejaculatory ducts — the male homologue of the uterus and vagina.
- ▶ The main male reproductive ducts (epididymis, vas deferens, ejaculatory duct, seminal vesicle) are, in fact, **mesonephric**, not paramesonephric, derivatives; their appearance coincides with, but is not caused by, paramesonephric regression.
- ▶ Table of parallel homologies across the two duct systems and the gonad, useful for a comparative exam answer:

| Embryonic structure              | Male derivative                                              | Female derivative                                                  |
|----------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------|
| Gubernacular cord                | Gubernaculum testis                                          | Ovarian ligament + round ligament of the uterus                    |
| Mesonephric tubules              | Efferent ductules, lobules of epididymis                     | Epoophoron, paroophoron, aberrant ductules                         |
| Mesonephric (Wolffian) duct      | Duct of epididymis, vas deferens, ejaculatory duct           | Duct of epoophoron ( <b>Gartner's duct</b> , $\pm$ Gartner's cyst) |
| Paramesonephric (Müllerian) duct | <b>Appendix testis (cranial); prostatic utricle (caudal)</b> | <b>Uterine tube; uterus and cervix; upper vagina/fornices</b>      |

#### 5. Anomalies resulting from paramesonephric duct defects

All uterovaginal anomalies stem from **failure of fusion** of the two ducts, **failure of canalisation/resorption** of the fused septum, or **unilateral agenesis/atresia** of one duct.

| Anomaly                                        | Mechanism                                                             | Salient feature                                           |
|------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Uterus didelphys</b> ( $\pm$ double vagina) | Complete failure of fusion of both ducts (and both sinovaginal bulbs) | Two separate uteri and cervixes, each with its own vagina |

| Anomaly                                                | Mechanism                                                                                                             | Salient feature                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bicornuate uterus</b> (bicollis or unicollis)       | Partial failure of fusion of the caudal ducts                                                                         | Two uterine horns opening into one or two cervixes; if one horn is rudimentary and non-communicating it can fill with retained blood                                                                                                                                                  |
| <b>Septate uterus</b>                                  | Ducts fuse normally, but the <b>uterovaginal septum fails to resorb</b>                                               | Normal external contour, midline septum inside the cavity — accounts for <b>≈55% of paramesonephric duct anomalies</b>                                                                                                                                                                |
| <b>Arcuate uterus</b>                                  | Minor, near-complete septal resorption                                                                                | Slight fundal indentation only — the mildest anomaly                                                                                                                                                                                                                                  |
| <b>Unicornuate uterus</b>                              | One duct fails to develop or elongate                                                                                 | Single horn with a single uterine tube — accounts for <b>≈20% of paramesonephric duct anomalies</b>                                                                                                                                                                                   |
| <b>Cervical atresia</b>                                | Bilateral partial atresia at the fused caudal duct ends                                                               | Obstructed outflow; risk of haematometra                                                                                                                                                                                                                                              |
| <b>Vaginal atresia / agenesis</b> (Müllerian agenesis) | Sinovaginal bulbs fail to canalise, or fail to develop at all; the uterus may be absent too                           | Congenital absence of the vagina occurs in about <b>1 in 4000–5000 female births</b> ; complete uterovaginal agenesis with normal ovaries, karyotype and secondary sexual characters, presenting as primary amenorrhoea, is the <b>Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome</b> |
| <b>Persistent Müllerian duct syndrome (PMDS)</b>       | Mutation of the <b>AMH gene</b> or <b>AMH-receptor II gene</b> in a 46,XY individual                                  | The duct fails to regress: uterus, cervix and uterine tubes coexist with vasa deferentia and male external genitalia; the testes may lie in the normal "ovarian" position within a persistent broad ligament (≈60–70%) or descend into an inguinal hernial sac (≈20–30%)              |
| <b>Diethylstilbestrol (DES)-related anomalies</b>      | Prenatal DES exposure represses <i>Hoxa10</i> , <i>Hoxa11</i> and <i>Wnt7a</i> signalling during duct differentiation | Uterine anomalies (classically a hypoplastic "T-shaped" cavity) and vaginal adenosis in the daughter, with an increased risk of <b>clear-cell adenocarcinoma of the vagina</b>                                                                                                        |

□ Fig 21.10 — Congenital anomalies of uterus. (Sontakke — *Textbook of Human Embryology*, p.233)



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a row of uterine outlines labelled: (1) normal uterus and single vagina, (2) uterus didelphys with double vagina, (3) bicornuate uterus (bicollis and unicollis variants; mark a blind, non-communicating rudimentary horn), (4) septate uterus, (5) arcuate uterus, (6) unicornuate uterus with a single tube; add a small inset showing cervical atresia and vaginal atresia/agenesis.

**Applied / Clinical anatomy**

- ▶ Uterovaginal anomalies are worked up by **hysterosalpingography, 3-D transvaginal ultrasound and MRI**, all of which directly demonstrate the fused/unfused duct pattern described above, and matter for infertility and recurrent pregnancy loss.
- ▶ Because the mesonephric (ureteric) and paramesonephric ducts develop side by side in the same urogenital ridge, a Müllerian duct anomaly is frequently accompanied by an **ipsilateral renal anomaly** (agenesis or ectopia) — the kidneys must always be imaged when a uterine anomaly is found.
- ▶ A **non-communicating rudimentary horn** (uterus bicornis unicollis) accumulates menstrual blood and presents with cyclical pain despite a normal external cycle — a recognised surgical emergency (haematometra, risk of rupture or of an ectopic pregnancy within the horn).
- ▶ **Imperforate hymen** presents at puberty with cyclical abdominal pain and primary amenorrhoea, with a bulging bluish membrane from retained blood (haematocolpos/haematometra); treated by simple cruciate incision.
- ▶ **Gartner's duct cysts**, arising from the mesonephric remnant along the anterolateral vaginal wall, must be distinguished from paramesonephric-derived cystic remnants such as the epoophoron/paroophoron in the broad ligament.
- ▶ Because the broad ligament is formed by the fusing paramesonephric ducts dragging a peritoneal fold with them, the **ureter passes close beneath the uterine artery** at its base — the surgical "water under the bridge" relation, critical during hysterectomy.
- ▶ At birth the cervix is about two-thirds or more of total uterine length (the isthmus is not yet formed); the adult body-to-cervix ratio is established only after puberty under oestrogen, relevant to interpreting paediatric pelvic imaging.

**High-yield exam pointers**

- ▶ Paramesonephric duct = coelomic epithelial invagination, week 6, **lateral** to the mesonephric duct; crosses it **ventrally** in week 8; fuses caudally in the third month.
- ▶ **Female**: unfused cranial part → uterine tube; fused caudal part (uterovaginal canal) → uterus, cervix, upper vagina/fornices; surrounding mesenchyme → myometrium and broad ligament.
- ▶ **Male**: duct regresses under Sertoli-cell AMH; only remnants are the **appendix testis** (cranial) and **prostatic utricle** (caudal) — the main male ducts are mesonephric, not paramesonephric.
- ▶ Vagina has a **dual origin**: upper vagina/fornices from paramesonephric tissue, lower vagina from urogenital-sinus sinovaginal bulbs.
- ▶ Commonest paramesonephric anomalies: **septate uterus** (~55%) and **unicornuate uterus** (~20%); congenital vaginal absence ≈ **1 in 4000–5000** births.

- ▶ **PMDS** = AMH/AMH-receptor-II mutation in a 46,XY male → paramesonephric derivatives persist alongside normal male ducts.
- ▶ **MRKH syndrome** = complete Müllerian agenesis with normal ovaries, karyotype and secondary sexual characters (ovary is never a paramesonephric derivative — it arises from coelomic epithelium/genital ridge).
- ▶ Mesonephric-duct remnants in the female (epoophoron, paroophoron, Gartner's duct) lie in the broad ligament — do not confuse them with paramesonephric derivatives.

### SOURCE & COVERAGE

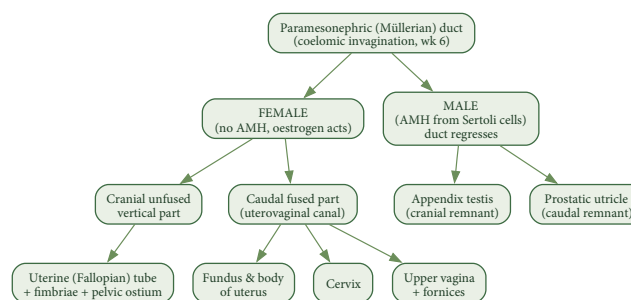
Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology.



## Describe in detail about the Derivatives of Paramesonephric duct. Add a note on its developmental defects

Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy

**Definition / Introduction** The paramesonephric (Müllerian) duct is one of the two paired genital ducts of the bipotential ("indifferent") embryo, arising in the 6th week as a longitudinal invagination of the coelomic epithelium on the anterolateral surface of the urogenital ridge, lateral to the mesonephric (Wolffian) duct. Its fate is strictly sex-dependent: in the presence of anti-Müllerian hormone (AMH) from fetal Sertoli cells it regresses almost completely in the male, whereas in its absence — and under oestrogen — it persists and differentiates into virtually the entire female genital duct system (uterine tube, uterus, cervix and upper vagina). It is therefore the embryological basis of most congenital anomalies of the female genital tract.



*Describe in detail about the Derivatives of Paramesonephric duct. Add a note on its developmental defects*

### 1. Formation and sex determination of the duct

- ▶ **Week 6:** paired paramesonephric ducts appear lateral to the mesonephric ducts; each has a funnel-shaped cranial opening into the coelomic (peritoneal) cavity.
- ▶ **Week 8:** the caudal end of each duct runs lateral to, then crosses **ventral** to, the mesonephric duct to grow caudomedially, meeting its fellow in the midline.

- ▶ **~9th week:** the caudal ends of the two ducts **fuse** to form a single-lumen **uterovaginal canal/primordium**; the fused tip projects into the dorsal wall of the urogenital sinus, raising the **Müllerian (sinus) tubercle**.
- ▶ **Molecular control:** SRY + SOX9 drive testis formation; Sertoli cells then secrete **AMH**, which binds AMH-receptor II on the peri-ductal mesenchyme and triggers apoptosis of the duct epithelium together with **Mmp2**-mediated basement-membrane degradation — the mechanism of duct regression. In the female, absence of SRY lets **WNT4** (via DAX1 inhibition of SOX9) permit ovarian differentiation; without testosterone and AMH the paramesonephric duct is left unopposed and differentiates under oestrogen.
- ▶ Each duct wall has three coats, all present in the adult derivatives: an outer **serosa** (coelomic epithelium), a **muscularis** (surrounding mesenchyme) and an inner **mucosa** (duct/coelomic epithelium).

## 2. Derivatives in the female

| Part of paramesonephric duct                           | Adult derivative                                                                                                                                                      |
|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cranial vertical (unfused) part + its coelomic opening | <b>Uterine (Fallopian) tube</b> ; fimbriae; abdominal/pelvic ostium                                                                                                   |
| Horizontal part                                        | Incorporated into the <b>fundus</b> and most of the <b>body of the uterus</b> as the ovary descends                                                                   |
| Caudal fused part (uterovaginal canal)                 | <b>Body and cervix of the uterus</b> ; <b>upper (paramesonephric) part of the vagina and the vaginal fornices</b>                                                     |
| Surrounding mesenchyme                                 | <b>Myometrium and perimetrium</b> ; muscular coat of the vagina                                                                                                       |
| Fused ducts approaching the pelvic wall                | <b>Broad ligament of the uterus</b> (uterine tube in its upper border, ovary on its posterior surface, dividing the pelvis into uterovesical and uterorectal pouches) |

□ Fig 21.9 — Development of uterus and vagina. Paramesonephric ducts (müllerian ducts) grow caudally, fuse and form the uterovaginal canal; sinovaginal bulbs form the vaginal plate, which canalises to complete the vagina. (Sontakke — Textbook of Human Embryology, p.232)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label: paired paramesonephric ducts (unfused cranial part) → fused caudal part (uterovaginal canal) → Müllerian/sinus tubercle → sinovaginal bulbs (from urogenital sinus) → vaginal plate → vaginal fornices → hymen; also label uterine tube with fimbriated end, body & cervix of uterus, and broad ligament fold.

## 3. Development of the vagina (dual origin)

- ▶ The uterovaginal canal contacts the dorsal wall of the urogenital sinus at the sinus tubercle; the sinus responds by growing two solid endodermal evaginations, the **sinovaginal bulbs**, which fuse to form a solid **vaginal plate**.

- ▶ The vaginal plate canalises from caudal to cranial and is complete by the **5th month**, giving the definitive vaginal lumen.
- ▶ The **lower vagina** is conventionally ascribed to the urogenital sinus (sinovaginal bulb) endoderm; the **vaginal fornices**, which cap the cervix, and the muscular coat of the vagina are of **paramesonephric (mesenchymal)** origin — the precise cranio-caudal boundary of the mucosal contribution is still debated and has only been mapped in the mouse.
- ▶ The **hymen** is a thin membrane at the vaginal introitus formed where the urogenital-sinus epithelium meets the thin overlying vaginal wall; failure to canalise it centrally gives an **imperforate hymen**.

#### 4. Derivatives in the male (and homologues)

- ▶ Under AMH, the paramesonephric duct atrophies almost completely; the only persisting parts are a small **cranial remnant** — the **appendix testis** — and a **caudal remnant** that, together with a proliferation of urogenital-sinus epithelium (the sinu-utricular cord), forms the **prostatic utricle** opening on the colliculus seminalis (utriculus masculinus, a rudimentary "male uterus/vagina" analogue).
- ▶ For exam completeness, the reciprocal mesonephric-duct fate and the shared gubernacular homologue are:

| Embryonic structure              | Male derivative                                    | Female derivative                                 |
|----------------------------------|----------------------------------------------------|---------------------------------------------------|
| Gubernacular cord                | Gubernaculum testis                                | Ovarian ligament + round ligament of uterus       |
| Mesonephric tubules              | Efferent ductules                                  | Epoophoron, paroophoron, aberrant ductules        |
| Mesonephric (Wolffian) duct      | Duct of epididymis, vas deferens, ejaculatory duct | Duct of epoophoron ( <b>Gartner's duct</b> )      |
| Paramesonephric (Müllerian) duct | <b>Appendix testis; prostatic utricle</b>          | <b>Uterine tube, uterus, cervix, upper vagina</b> |

#### 5. Developmental defects of the paramesonephric duct

All uterovaginal anomalies arise from a **failure of fusion**, a **failure of canalisation/resorption** of the fused septum, or **unilateral atresia/agenesis** of the ducts.

| Anomaly                                       | Mechanism                                                         | Feature                                                                                                                        |
|-----------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <b>Uterus didelphys</b> (with double vagina)  | Complete failure of fusion of both ducts + both sinovaginal bulbs | Two separate uteri, cervixes, and vaginas                                                                                      |
| <b>Bicornuate uterus</b> (bicollis/unicollis) | Partial failure of fusion of the caudal ducts                     | Two uterine horns, single or double cervix; if one horn is rudimentary and non-communicating it may fill with blood/secretions |

| Anomaly                                    | Mechanism                                                                                                                     | Feature                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Septate uterus                             | Ducts fuse but the <b>uterovaginal septum fails to resorb</b>                                                                 | Single external contour, midline septum inside the cavity — <b>≈55% of paramesonephric anomalies</b>                                                                                                                                                                                                        |
| Arcuate uterus                             | Minor, incomplete septal resorption                                                                                           | Slight fundal indentation only — mildest form                                                                                                                                                                                                                                                               |
| Unicornuate uterus                         | One duct fails to develop/elongate                                                                                            | Single horn + single tube; <b>≈20% of paramesonephric anomalies</b>                                                                                                                                                                                                                                         |
| Cervical atresia                           | Bilateral partial atresia at the fused caudal ends                                                                            | Obstructed outflow, haematometra                                                                                                                                                                                                                                                                            |
| Vaginal atresia / agenesis                 | Sinovaginal bulbs fail to canalise or form at all                                                                             | Blind vaginal pouch; uterus may also be absent — <b>congenital absence of the vagina occurs in ~1 in 4000–5000 female births</b> (complete uterovaginal agenesis = Müllerian agenesis, Mayer–Rokitansky–Küster–Hauser syndrome: 46,XX, normal ovaries and secondary sexual characters, primary amenorrhoea) |
| Persistent Müllerian duct syndrome (PMDS)  | Mutation of AMH or AMH-receptor II gene in a 46,XY individual                                                                 | Duct fails to regress: a vagina, cervix, uterus and uterine tubes coexist with vasa deferentia and male external genitalia; testes may lie in the normal "ovarian" position within a persistent broad ligament, or in an inguinal hernial sac                                                               |
| Diethylstilbestrol (DES)-related anomalies | In-utero exposure to the synthetic oestrogen DES suppresses <i>HOXA10/HOXA11/WNT7A</i> signalling during duct differentiation | Uterine anomalies (classically a hypoplastic, "T-shaped" cavity), vaginal adenosis, and increased risk of <b>clear-cell adenocarcinoma of the vagina</b> in the daughter                                                                                                                                    |

□ Fig 21.10 — Congenital anomalies of uterus. (Sontakke — *Textbook of Human Embryology*, p.233)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label a row of six uterine outlines: (1) normal uterus, (2) uterus didelphys with double vagina, (3) bicornuate uterus (bicollis and unicollis variants — mark a blind rudimentary horn), (4) septate uterus, (5) arcuate uterus, (6) unicornuate uterus; add a second small panel showing cervical atresia and vaginal atresia/agenesis.

## Applied / Clinical anatomy

- **Infertility / recurrent pregnancy loss work-up:** uterovaginal anomalies are screened by hysterosalpingography, 3-D transvaginal ultrasound and MRI, all of which directly image the fused/unfused duct pattern described above.

- ▶ Because the mesonephric (ureteric) and paramesonephric systems develop in the same urogenital ridge, a Müllerian duct anomaly is frequently associated with **ipsilateral renal anomalies** (agenesis, ectopia) — always image the kidneys when a uterine anomaly is found.
- ▶ A **non-communicating rudimentary horn** (uterus bicornis unicollis) accumulates menstrual blood and presents as cyclical pain with a normal external cycle — a classic surgical emergency (haematometra, risk of rupture/ectopic implantation).
- ▶ **Imperforate hymen** presents at puberty as cyclical abdominal pain with primary amenorrhoea and a bulging bluish membrane (haematocolpos/haematometra) — treated by simple cruciate incision.
- ▶ **Gartner's duct cysts** (mesonephric remnant) are found along the anterolateral vaginal wall and must be distinguished clinically from paramesonephric-derived cysts.
- ▶ The **broad ligament**, being formed by the fusing paramesonephric ducts pulling a peritoneal fold with them, explains why the ureter runs close to the uterine artery at the base of this ligament ("water under the bridge") — a key point in hysterectomy.
- ▶ At birth the uterine cervix is about twice the length of the body of the uterus (the isthmus is not yet formed); this ratio reverses only after puberty under oestrogen — relevant to interpreting neonatal/paediatric pelvic ultrasound.

### High-yield exam pointers

- ▶ Paramesonephric duct = coelomic epithelial invagination, week 6, **lateral** to the mesonephric duct; crosses it **ventrally** in week 8.
- ▶ **Female** derivatives: unfused cranial part → uterine tube; fused caudal part (uterovaginal canal) → uterus, cervix, upper vagina + fornices; surrounding mesenchyme → myometrium/broad ligament.
- ▶ **Male**: duct regresses under Sertoli-cell AMH; only remnants are the **appendix testis** (cranial) and **prostatic utricle** (caudal).
- ▶ Vagina has a **dual origin**: upper part/fornices from paramesonephric tissue, lower part from urogenital sinus (sinovaginal bulbs).
- ▶ Septate uterus (~55%) and unicornuate uterus (~20%) are the commonest paramesonephric anomalies; congenital vaginal absence ≈ 1:4000–5000.
- ▶ **PMDS** = AMH/AMH-receptor mutation in a 46,XY male → paramesonephric derivatives persist alongside normal male ducts.
- ▶ **MRKH syndrome** = complete Müllerian agenesis with normal ovaries/karyotype/secondary sexual characters (ovary is NOT a paramesonephric derivative).
- ▶ Mesonephric-duct remnants in the female (epoophoron, paroophoron, Gartner's duct) sit in the broad ligament — do not confuse with paramesonephric derivatives.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e.



## Describe in detail the development of the testis and its congenital anomalies

Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy

### Definition / Introduction

The testis develops from the **medulla of the indifferent gonad**, itself derived from the **gonadal (genital) ridge** — a mesothelial thickening on the medial aspect of the mesonephros, colonised by migrating **primordial germ cells**. Differentiation into a testis (rather than an ovary) is switched on by the **SRY/testis-determining factor (TDF)** on the Y chromosome, after which the fetal testis drives masculinisation of the ducts and external genitalia and, through the gubernaculum and processus vaginalis, its own **descent** into the scrotum. Because this is a long, hormonally-choreographed journey, the testis is prone to a wide range of **congenital anomalies of number, position and fusion**.

### 1. Origin of the gonad — genital ridge and primordial germ cells

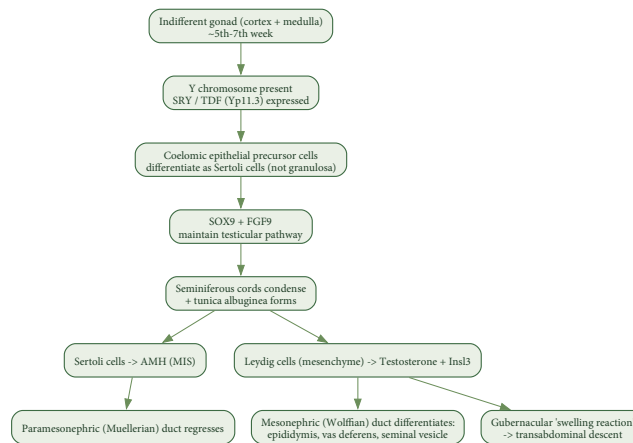
- ▶ In the **5th week**, proliferation of the coelomic epithelium and underlying mesenchyme on the medial side of the mesonephros produces the **gonadal (genital) ridge**.
- ▶ Finger-like **gonadal (sex) cords** grow into the mesenchyme, giving the gonad an outer **cortex** and inner **medulla** — the **indifferent gonad**, identical in both sexes up to about the 7th week.
- ▶ **Primordial germ cells (PGCs)**, large spherical cells, are first recognisable at about **24 days** post-fertilisation among the endodermal cells of the umbilical vesicle (yolk sac), near the origin of the allantois.
- ▶ During embryonic folding they migrate along the dorsal mesentery of the hindgut and, in the **6th week**, enter the gonadal ridge mesenchyme and are incorporated into the gonadal cords (migration regulated by genes including *stella*, *fragilis* and *BMP-4*).
- ▶ PGCs are not essential for testis determination (testes can form without them) but are required for orderly ovarian differentiation.

### 2. Chromosomal and molecular basis of sex determination

- ▶ Chromosomal sex is fixed at fertilisation, but the gonad stays **indifferent (bipotential)** until about the 7th week.
- ▶ The default ("set-up") pathway is female. Testicular development is switched on by the **Y chromosome**, whose testis-determining region carries the **SRY gene** (sex-determining region Y), functionally equivalent to the classical testis-determining factor (TDF).



- **SRY** acts within the coelomic epithelial cords, directing bipotential supporting-cell precursors to become **Sertoli cells** rather than granulosa cells — this commitment triggers the whole testicular pathway; **SOX9** and **FGF9** then maintain and amplify it.
- The differentiated testis produces three masculinising hormones: **testosterone** and **insulin-like factor 3 (Insl3)** from Leydig cells, and **anti-Müllerian hormone (AMH/MIS)** from Sertoli cells.



*Describe in detail the development of the testis and its congenital anomalies*

### 3. Differentiation of the indifferent gonad into the testis

- Under **SRY/TDF**, the gonadal cords condense and extend into the medulla, branching and anastomosing to form the **rete testis** (a network of canals).
- Connection of the cords with the surface epithelium is lost as a thick fibrous capsule, the **tunica albuginea**, develops beneath it — the single most characteristic histological marker distinguishing an early testis from an early ovary.
- The enlarging testis separates from the degenerating mesonephros and hangs from its own mesentery, the **mesorchium**.
- The gonadal cords become **seminiferous cords** (primordia of seminiferous tubules, tubuli recti and rete testis); they remain solid, acquiring a lumen only by about the **7th month** of gestation (the rete testis canalises somewhat earlier).
- Seminiferous cords contain two cell lines: **Sertoli cells** (from the surface coelomic epithelium) and **spermatogonia** (from the incorporated primordial germ cells).
- Mesenchyme between the cords differentiates into **interstitial cells of Leydig**, which begin secreting **testosterone** and **androstenedione** from about the **8th week**, driven by rising **hCG** that peaks at 8–12 weeks.
- The rete testis joins the 5–12 most cranial persisting **mesonephric tubules**, which become the highly convoluted **efferent ductules** (lobules of the **epididymal head**), opening into the mesonephric duct.

### 4. Fate of the ducts under testicular hormones

| Hormone                          | Source        | Action                                                                                 |
|----------------------------------|---------------|----------------------------------------------------------------------------------------|
| Anti-Müllerian hormone (AMH/MIS) | Sertoli cells | Causes regression of the <b>paramesonephric (Müllerian) duct</b> (future uterus/tubes) |

| Hormone                     | Source       | Action                                                                                                                        |
|-----------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------|
| Testosterone                | Leydig cells | Stabilises and differentiates the <b>mesonephric (Wolffian) duct</b> into epididymis, vas deferens and seminal vesicle        |
| Insl3 (relaxin-like factor) | Leydig cells | Produces the gubernacular "swelling reaction" that anchors the testis near the future inguinal canal (transabdominal descent) |

- Distal to the epididymis, the mesonephric duct acquires a thick smooth-muscle coat to become the **ductus (vas) deferens**; its caudal outgrowth forms the **seminal vesicle**, and the part between vesicle and urethra becomes the **ejaculatory duct**.

## 5. Descent of the testis

Descent occurs in two overlapping phases, regulated by distinct endocrine and mechanical factors.

| Phase                  | Approx. timing                                                            | Principal driving factors                                                                                                                                                                                                                    | Result                                                                                    |
|------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Transabdominal         | Up to ~15 weeks; held at the deep inguinal ring through the 4th–6th month | Insl3 from Leydig cells causes gubernacular "swelling reaction"; androgen-mediated regression of the cranial suspensory ligament; relative cranial abdominal growth away from the pelvis                                                     | Testis moves from the dorsal lumbar region to the <b>deep inguinal ring</b>               |
| Inguinoscrotal         | ~25–35 weeks; rapid transit around the 7th month                          | <b>Androgens</b> act on the genitofemoral nerve, whose genital branch releases <b>calcitonin gene-related peptide (CGRP)</b> , driving gubernacular elongation/migration; rising intra-abdominal pressure via the patent processus vaginalis | Testis traverses the inguinal canal into the <b>scrotum</b> (left usually precedes right) |
| Postnatal obliteration | Perinatal period to ~18–24 months                                         | CGRP (via genitofemoral nerve) and hepatocyte growth factor mediate closure of the <b>proximal processus vaginalis</b>                                                                                                                       | Distal processus persists as the <b>tunica vaginalis</b> around the testis                |

- The **gubernaculum** (genito-inguinale ligament) connects the caudal pole of the testis to the labioscrotal swelling and forms the guiding track for descent; the **processus vaginalis**, a peritoneal diverticulum, precedes the testis and carries with it the layers of the abdominal wall that become the spermatic-cord coverings (transversalis fascia → internal spermatic fascia; internal oblique → cremaster; external oblique aponeurosis → external spermatic fascia).

- Quick-recall timetable: **3rd month** – iliac fossa; **6th month** – deep inguinal ring; **7th month** – traversing the inguinal canal; **8th month** – superficial inguinal ring; **9th month** – scrotum. Over **95–97% of full-term neonates** have fully descended testes.

□ Fig 72.17 — The descent of the testis. The testis is retroperitoneal throughout development (Gray's Anatomy — Standring — 41e, p.1687)

## 6. Congenital anomalies of the testis

| Category          | Anomaly                             | Description                                                                                                                                                                                                                                                                                                                                           |
|-------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number            | Anorchism                           | Both testes absent, or represented only by rudimentary/streak intra-abdominal gonads                                                                                                                                                                                                                                                                  |
| Number            | Monorchism                          | Only one testis descends/is present; the other is absent or intra-abdominal                                                                                                                                                                                                                                                                           |
| Number            | Polyorchidism                       | Rare anomaly with two or more (commonly three, occasionally four) testes; the supernumerary testis may or may not connect to a vas deferens                                                                                                                                                                                                           |
| Descent/position  | Cryptorchidism (undescended testis) | Descent arrested anywhere along the normal path — abdomen, deep inguinal ring, inguinal canal, or just proximal to the superficial ring; ~3–5% full-term, ~30% preterm; ~95% unilateral                                                                                                                                                               |
| Descent/position  | Ectopic testis                      | Deviates from the normal path <i>after</i> traversing the inguinal canal; commonest site is <b>interstitial</b> (superficial inguinal pouch, external to the external oblique aponeurosis); also femoral, penile, perineal, and <b>transverse/crossed ectopia</b> (both testes in one hemiscrotum, sometimes with persistent Müllerian duct syndrome) |
| Retractile testis | —                                   | A normally descended testis pulled up by an overactive cremaster reflex; unlike cryptorchidism it can be manipulated down into the scrotum                                                                                                                                                                                                            |
| Fusion anomaly    | Splenogonadal fusion                | Rare, almost always left-sided; splenic tissue connected to the gonad continuously (to the main spleen) or discontinuously (to ectopic splenic nodules)                                                                                                                                                                                               |

| Category                     | Anomaly                              | Description                                                                                                                                                                              |
|------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Duct-fusion anomaly          | Testis–epididymis non-fusion         | Failure of fusion between testis and epididymal head/tail (or the whole epididymis); associated with cryptorchidism                                                                      |
| Processus vaginalis — wide   | Congenital inguinal hernia           | A patent, wide processus vaginalis allows a loop of bowel to herniate into the scrotum/labium majus; commoner with undescended or ectopic testes                                         |
| Processus vaginalis — narrow | Congenital (communicating) hydrocele | A patent but narrow processus vaginalis permits only peritoneal fluid, not bowel, to track into the tunica vaginalis                                                                     |
| Positional/vascular          | Testicular torsion                   | Twisting of the spermatic cord — <b>extravaginal</b> (perinatal, involves the tunica vaginalis) or <b>intravaginal</b> (older child/adult, testis alone rotates within an intact tunica) |

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Differentiation of the indifferent gonad into the testis** (transverse section) — label: coelomic epithelium, gonadal (sex) cords, mesonephros, mesonephric duct, paramesonephric duct, medulla → seminiferous cords, tunica albuginea, rete testis, primordial germ cells.
- **Descent of the testis** (sagittal section series) — label: testis (lumbar position → deep inguinal ring → scrotum), gubernaculum, processus vaginalis, deep and superficial inguinal rings, ductus deferens, testicular vessels, degenerating mesonephros, tunica vaginalis in the scrotum.

#### Applied / Clinical anatomy

- **Infertility:** higher intra-abdominal temperature (2–4°C above scrotal) impairs spermatogenesis in an undescended testis; histology is often normal at birth but atrophy becomes evident by the end of the first year if uncorrected.
- **Malignancy risk:** cryptorchid (especially intra-abdominal) testes carry a markedly higher risk of germ-cell tumours, thought to arise from persisting fetal gonocytes/carcinoma-in-situ cells; orchidopexy does **not** eliminate this risk but allows earlier detection.
- **Timing of orchidopexy:** watchful waiting up to 6 months (most spontaneous descent occurs in this window); surgical correction between 6 and 18 months to maximise later spermatogenic potential.
- **Leydig cell (endocrine) function is usually preserved** in simple maldescent, so serum testosterone and virilisation are typically normal even when spermatogenesis fails.

- ▶ **Hydrocele vs hernia:** a hydrocele transilluminates and lacks a cough impulse; a congenital inguinal hernia is reducible, may show bowel sounds, and does not transilluminate.
- ▶ **Testicular torsion** is a surgical emergency — detorsion within 4–6 hours for salvage; clues are sudden severe scrotal pain, a high-riding testis and loss of the cremasteric reflex. **Spermatic cord coverings** used at surgery trace directly to the abdominal-wall layers carried down during descent, and **crossed testicular ectopia** should prompt a search for persistent Müllerian duct syndrome.

### High-yield exam pointers

- ▶ Testis = **medulla** of the genital ridge; ovary = **cortex** — reciprocal fate of the same indifferent gonad.
- ▶ **SRY (Yp11.3)** = testis-determining factor → Sertoli-cell differentiation from coelomic epithelium; **SOX9/FGF9** maintain the pathway. Earliest histological hallmark of the testis = early, dense **tunica albuginea**.
- ▶ Three fetal testicular hormones: **testosterone** (Wolffian duct + virilisation), **AMH/MIS** (Müllerian duct regression), **Ins13** (gubernacular swelling reaction).
- ▶ Descent = **two phases** — transabdominal (Ins13-driven, to ~15 weeks) and inguinoscrotal (androgen + CGRP via genitofemoral nerve, ~25–35 weeks, rapid transit ~7th month); >95% of full-term neonates have descended testes.
- ▶ **Cryptorchidism:** 3–5% full-term, ~30% preterm; most descend spontaneously by 1 year; orchidopexy by 6–18 months.
- ▶ Anomalies of **number** (anorchism, monorchism, polyorchidism) ≠ anomalies of **position** (cryptorchidism, ectopic testis) ≠ anomalies of **fusion** (splenogonadal fusion, testis–epididymis non-fusion).
- ▶ Processus vaginalis spectrum: **wide** → **congenital inguinal hernia**; **narrow** → **congenital hydrocele**; closure is androgen/CGRP/HGF-mediated. Undescended/ectopic testis carries increased risk of **infertility** and **germ-cell malignancy**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore The Developing Human 9e; Larsen Human Embryology 6e; Sontakke Textbook of Human Embryology; Vishram Singh Textbook of Clinical Embryology; Moore's Clinically Oriented Anatomy 9e. Embedded plate: Gray's Anatomy (Standring) 41e, Fig 72.17 (p.1687).



## Describe the development and descent of Testis

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The testis develops from the medial (gonadal) part of the urogenital ridge, passing through a sexually indifferent (ambisexual) stage that is converted to a testis by the Y-linked **SRY** gene. Testicular **descent** is the process by which the developing gonad migrates from its site of origin on the posterior abdominal wall (upper lumbar level) to the scrotum, in two mechanistically distinct phases — **transabdominal** and **inguinoscrotal** — guided by the **gubernaculum** and accompanied by an evagination of peritoneum, the **processus vaginalis**. Descent is essentially complete by the ninth month; its arrest produces the commonly examined anomaly of **cryptorchidism**.

### 1. Origin of the gonad — the indifferent (ambisexual) stage

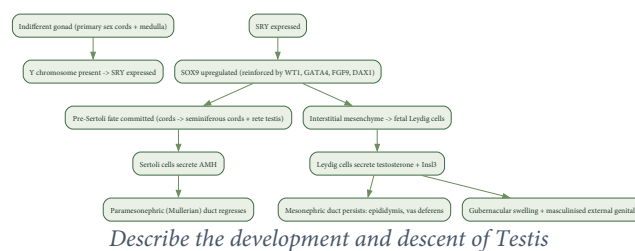
- ▶ Four cell lineages contribute to the gonad: proliferating **coelomic epithelium** on the medial side of the mesonephros; underlying **mesonephric mesenchyme**; invading **angiogenic mesenchyme**; and **primordial germ cells**.
- ▶ Primordial germ cells arise extragonadally in the wall of the yolk sac near the allantois and migrate, in the 5th–6th week, along the dorsal mesentery of the hindgut to reach the **genital (gonadal) ridge**.
- ▶ In the 5th week (stage 16), thickened coelomic epithelium on the medial aspect of the mesonephric ridge proliferates to form the **gonadal ridge**, connected to the mesonephros by a mesentery, the **mesogenitale** (which later becomes the **mesorchium** in the male).
- ▶ The proliferating epithelium forms cellular **primary sex cords** peripherally (future cortex), while proliferation of mesonephric/angiogenic mesenchyme forms a central **medulla**.
- ▶ Up to the 7th week the gonad shows **no sexually differentiating feature** — it is truly ambisexual, with both the mesonephric (Wolffian) and paramesonephric (Müllerian) ducts present in every embryo.

### 2. Sex determination and differentiation into a testis

- ▶ The default ("set-up") pathway is female; testis formation requires a positive trigger — the **SRY gene** (sex-determining region, Y chromosome; equivalent to the testis-determining factor, TDF), acting within the coelomic epithelial cords.
- ▶ SRY directs these bipotential supporting-cell precursors to become **Sertoli cells** rather than granulosa cells, by up-regulating **SOX9**; the male pathway is then reinforced by **WT1**, **GATA4**, **FGF9** and **DAX-1**, which simultaneously repress the female-promoting genes **RSPO1**, **WNT4** and **FOXL2**.
- ▶ Primary sex cords lengthen, encroach on the medulla, and unite with mesonephric-mesenchyme-derived cords to form the **rete testis**; primordial germ cells become incorporated within them and are enclosed by Sertoli cells — they do **not** enter meiosis but continue to proliferate (unlike the ovary).
- ▶ Interstitial mesenchyme differentiates into fetal **Leydig cells** slightly later than the Sertoli lineage is committed; a further wave of subepithelial mesenchyme forms the **tunica albuginea**.
- ▶ The differentiated testis secretes **three key hormones** that drive masculinisation:

| Hormone                          | Source        | Principal action                                                                   |
|----------------------------------|---------------|------------------------------------------------------------------------------------|
| Anti-Müllerian hormone (AMH/MIS) | Sertoli cells | Regression of the paramesonephric (Müllerian) duct                                 |
| Testosterone                     | Leydig cells  | Stabilises the mesonephric duct; masculinises external genitalia and other tissues |
| Insulin-like factor 3 (Insl3)    | Leydig cells  | Triggers gubernacular "swelling reaction" for transabdominal descent               |

- Seminiferous tubules do not acquire a lumen until the 7th month, although the rete testis canalises somewhat earlier.



### 3. Development of the genital ducts and rete system

- The **mesonephric (Wolffian) duct** persists under testosterone: its 5–12 most cranial surviving mesonephric tubules become highly convoluted **efferent ductules**, and the duct itself becomes the **epididymis, vas deferens** and **ejaculatory duct**.
- The **paramesonephric (Müllerian) duct** regresses under AMH, leaving only vestiges — the **appendix testis** (cranial remnant, attached to the upper pole) and the **prostatic utricle** (caudal remnant).
- The rete testis cords connect the seminiferous cords to glomerular capsules of the persisting cranial mesonephric tubules, completing the excurrent duct system.

### 4. Descent of the testis — mechanism and phases

- The testis develops in relation to the mesonephros at an upper lumbar (roughly T10–T12/L2) level and remains **retroperitoneal throughout its descent**; its blood supply is retained from the aorta, so in the adult the testicular artery still arises from the aorta just below the renal artery, and the testicular vein still drains to the IVC/left renal vein — a direct legacy of the site of origin.
- **Transabdominal phase**: as the abdominal cavity enlarges, the testis is held close to the future deep inguinal ring by (i) the **gubernaculum**, whose caudal genito-inguinal cord undergoes an Insl3-driven "swelling reaction" from about 10 weeks, and (ii) regression of the **cranial suspensory ligament** under androgen. This phase occupies roughly the 4th–6th months.
- **Inguinoscrotal phase**: between the 25th and 35th weeks the gubernaculum bulges out of the abdominal wall and elongates across the pubis into the scrotal swelling; growth of its gelatinous (hyaluronic-acid-rich), androgen-controlled tip is guided along a chemotactic gradient by calcitonin-gene-related peptide (CGRP) released from the genitofemoral nerve. An outpocketing of peritoneum, the **processus vaginalis**, extends into the gubernaculum ahead of the testis. Rapid



transit through the inguinal canal occurs around the 7th month, assisted by rising intra-abdominal pressure acting through the patent processus vaginalis; the left testis usually descends slightly ahead of the right.

- **Time-table of descent** (classical teaching, BD Chaurasia, cross-checked against Langman/Gray's):

| Intrauterine period          | Event                                                      |
|------------------------------|------------------------------------------------------------|
| 2nd month                    | Testis begins to descend from the posterior abdominal wall |
| 3rd month (~12 weeks)        | Reaches the iliac fossa / future deep inguinal ring        |
| 4th–6th month                | Rests at the deep inguinal ring (transabdominal phase)     |
| 7th month                    | Traverses the inguinal canal (~28 weeks, Langman)          |
| 8th month                    | Reaches the superficial inguinal ring                      |
| 9th month (~33 weeks onward) | Reaches the bottom of the scrotum                          |

- By full term, over 95% of male neonates have fully descended testes; descent may remain incomplete in premature infants, and rarely completes spontaneously up to one year of age.

## 5. Gubernaculum and processus vaginalis

- The **gubernaculum** is a mesenchymal cord that extends, via the mesorchium, from the caudal pole of the testis/epididymis to the anterior abdominal wall and, later, the floor of the scrotum. Up to 10 weeks it is identical in both sexes; Ins13 from fetal Leydig cells then causes it to swell in the male (in the female it stays thin and becomes the round ligament/ovarian ligament).
- Descriptively it is divided into **abdominal**, **interstitial** (within the developing inguinal canal) and **subcutaneous/scrotal** parts; it dilates the path ahead of the testis ("inguinal bursa") and anchors/guides it.
- From about 35 weeks its gelatinous extracellular matrix is resorbed and it forms a short fibrous attachment to the scrotum — the postnatal remnant is the **ligament of the testis (scrotal ligament)**.
- The **processus vaginalis** is a tubular diverticulum of peritoneum that grows into the gubernacular mesenchyme, preceding/accompanying the testis into the scrotum and forming the parietal (cremasteric) layer around the developing cremaster muscle. After descent, its distal part persists as the **tunica vaginalis** (visceral layer on the testis, parietal layer lining the scrotal sac), while its proximal part normally **obliterates** around birth — a process also indirectly androgen/CGRP-dependent. Persistent patency underlies several common clinical anomalies (below).

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Sagittal schematic of testicular descent through the inguinal canal into the scrotum (based on Fig 21.26, Vishram Singh — Textbook of Clinical Embryology). Label:

- ▶ Testis (retroperitoneal, intra-abdominal position)
- ▶ Mesorchium
- ▶ Gubernaculum — abdominal part, interstitial part, subcutaneous (scrotal) part
- ▶ Cranial suspensory ligament (regressing)
- ▶ Processus vaginalis (peritoneal diverticulum within the gubernaculum)
- ▶ Deep inguinal ring
- ▶ Inguinal canal
- ▶ Superficial inguinal ring
- ▶ Scrotal swelling / scrotum
- ▶ Tunica vaginalis (visceral + parietal layers) after proximal processus vaginalis obliterates
- ▶ Ligament of the testis (remnant of gubernaculum)

□ Fig 21.26 — Descent of testis. (Vishram Singh — Textbook of Clinical Embryology, p.273)

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- ▶ **Cryptorchidism (undescended testis):** present in about 3% of full-term male infants at birth (descent is frequently incomplete in premature infants); falls to under 1% by 6 months as many descend spontaneously. About 25% of cases are bilateral. Arrest can occur at any point along the path — lumbar, iliac, inguinal (commonest) or upper scrotal — and is frequently associated with a **patent processus vaginalis and an indirect inguinal hernia**. Consequences include impaired spermatogenesis (Sertoli cell degeneration if maldescent persists beyond infancy), sub/infertility (especially if bilateral), and a several-fold increased risk of testicular germ-cell tumour; Leydig-cell (endocrine) function is usually preserved. Orchidopexy is recommended between 6 and 18 months of age.
- ▶ **Retractile testis:** an exaggerated cremasteric reflex pulls an otherwise normally descended testis intermittently out of the scrotum; unlike a true undescended testis it can be manipulated back into the scrotal fundus and needs no surgery.
- ▶ **Ectopic testis:** the gubernaculum tracks to an abnormal site so the testis, having passed the superficial inguinal ring, comes to lie in the superficial inguinal pouch, the thigh, the penile skin, or the perineum (or, rarely, crosses to the opposite hemiscrotum — transverse ectopia). The testis is usually otherwise fully developed.
- ▶ **Congenital indirect inguinal hernia and congenital/communicating hydrocele:** both result from failure of the proximal processus vaginalis to obliterate, allowing peritoneal fluid or bowel to track down toward the tunica vaginalis; an **encysted hydrocele of the cord** results if only an isolated distal segment remains patent.
- ▶ **Varicocele:** an anatomical consequence of the descent-related, asymmetric venous drainage — the longer left testicular vein enters the left renal vein at a right angle (and may be compressed by

the loaded sigmoid colon), predisposing to left-sided dilatation of the pampiniform plexus far more often than on the right.

- ▶ Because the testis retains its original arterial supply, the **testicular artery** arises from the aorta just below the renal artery (vertebral level L2) — the anatomical basis for the long, oblique course of the spermatic vessels and the classical "loin-to-groin/scrotum" pattern of testicular referred pain (T10–T11 sympathetic supply follows the vessels back to their origin).

### High-yield exam pointers

- ▶ Indifferent gonad differentiates from 5th week (stage 16) coelomic epithelium + mesonephric mesenchyme; ambisexual until the 7th week.
- ▶ SRY (Yp) → SOX9 → Sertoli cell commitment is the master switch; AMH, testosterone and *Ins3* are the three effector hormones of masculinisation.
- ▶ Mesonephric duct persists (testosterone) → epididymis/vas deferens/ejaculatory duct; paramesonephric duct regresses (AMH) → appendix testis + prostatic utricle only.
- ▶ Descent has two phases: transabdominal (gubernacular "swelling reaction," *Ins3*-driven, ~months 4–6) and inguinoscrotal (gubernacular elongation, androgen/CGRP-driven, weeks 25–35).
- ▶ Classical time-table: iliac fossa by 3rd month → deep inguinal ring 4th–6th month → inguinal canal 7th month → scrotum by 9th month.
- ▶ Gubernaculum guides/anchors the testis and leaves the scrotal (testicular) ligament; processus vaginalis precedes it and gives the tunica vaginalis after proximal obliteration.
- ▶ Testis is retroperitoneal throughout descent — vessels, lymphatics (para-aortic nodes) and nerve supply retain their original lumbar origin.
- ▶ Cryptorchidism: ~3% at birth, ~1% by 6 months, 25% bilateral; risks are infertility and germ-cell tumour, not endocrine failure.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2 8e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Describe the development of external genitalia. Add a note on their congenital anomalies

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The external genitalia — penis and scrotum in the male; clitoris, labia minora, labia majora and vestibule in the female — develop from a common set of mesenchymal primordia that surround the cloacal membrane: the **genital tubercle**, a pair of **genital (urethral) folds** and a pair of **genital (labioscrotal) swellings**. These primordia are morphologically identical in both sexes up to about the 6th–8th week (the **indifferent stage**). Thereafter, divergence into the male or female pattern is driven principally by fetal **androgens** (acting through 5 $\alpha$ -dihydrotestosterone), the female pathway being the constitutive "default" in their absence. Because both sexes use the same three primordia, most congenital anomalies of the external genitalia (hypospadias, epispadias, ambiguous genitalia) represent failure or aberration of the same fusion events.

### 1. Indifferent stage of the external genitalia (3rd–6th week)

- ▶ In the **3rd week**, mesenchyme from the primitive streak migrates around the cloacal membrane to raise a pair of **cloacal folds**.
- ▶ **Cranial** to the cloacal membrane the two cloacal folds unite in the midline to form a single midline elevation, the **genital tubercle** (~4th week).
- ▶ By the **6th week**, the urorectal septum has divided the cloacal membrane into a cranial **urogenital membrane** and a caudal **anal membrane**; correspondingly the cloacal folds are subdivided into **urethral (genital) folds** anteriorly and **anal folds** posteriorly.
- ▶ A second, more lateral pair of elevations — the **genital (labioscrotal) swellings** — appears on each side of the urethral folds at this stage.
- ▶ At the end of the 6th week the external genitalia of the two sexes are **indistinguishable** — the indifferent stage.
- ▶ The urogenital membrane breaks down, and its attenuated endodermal floor within the phallus becomes the **urethral plate**; proliferation of mesenchyme around it produces the primary **urethral groove**.

□ Fig 21.12 — Development of external genitalia: Indefinitive stage (Sontakke — *Textbook of Human Embryology*, p.234)

### 2. Hormonal control of sexual differentiation

- ▶ Differentiation of the indifferent primordia is **not** determined by chromosomal sex directly but by the **hormonal milieu** the tissues are exposed to.
- ▶ Fetal **Leydig cells** of the testis secrete **testosterone**; in the genital tubercle, urethral folds and labioscrotal swellings, testosterone is converted by **5 $\alpha$ -reductase** to **dihydrotestosterone (DHT)**, which is the active androgen driving masculinisation of the external genitalia (elongation of the phallus, fusion of folds/swellings).
- ▶ In the absence of androgen (as in the normal female, or in an androgen-insensitive/DHT-deficient XY fetus), the primordia follow the **default feminising pathway** regardless of genetic sex — estrogen further promotes but is not obligatory for this pathway.
- ▶ The female external genitalia remain responsive to virilising androgen only up to about the **4th month**; beyond this point they can no longer be masculinised.

### 3. Development of male external genitalia

- ▶ Under androgen influence the genital tubercle elongates rapidly to form the **phallus**, pulling the urethral folds forward so that they flank a deep **urethral groove** on the ventral aspect of the phallus (this groove does not extend to the glans).
- ▶ By the **end of the 3rd month**, the two urethral folds fuse over the urethral plate, **caudocranially** (base → tip), converting the groove into the **penile (spongy) urethra**; the line of fusion is marked postnatally by the **penile (median) raphe**.
- ▶ The **glandular part** of the urethra forms separately in the **4th month**: ectodermal cells at the tip of the glans invaginate to form a solid epithelial cord, which later canalises to complete the urethra and create the **external urethral meatus**.
- ▶ The **genital (labioscrotal) swellings**, now called **scrotal swellings**, migrate caudally from the inguinal region and fuse in the midline (from behind forward) to form the **scrotum**; the line of fusion persists as the **scrotal septum/raphe**.
- ▶ The **corpora cavernosa** and **corpus spongiosum** differentiate from the mesenchymal core of the phallus (defined by the 3rd month); nerves appear in the mesenchyme from the 7th week onward.
- ▶ The **prepuce** develops in the 3rd–5th month as a proliferating epithelial ridge that grows forward over the glans and later separates from it (may remain incompletely separated up to 6–12 months postnatally).
- ▶ Testicular descent into the scrotum occurs prenatally (usually complete by 33 weeks), guided by the **gubernaculum**.

### 4. Development of female external genitalia

- ▶ In the absence of significant androgen, the genital tubercle elongates only **slightly** to form the **clitoris** (it is actually larger than the male tubercle in the early stages — a pitfall in ultrasound sexing).
- ▶ The **urethral folds do not fuse** — they remain separate and form the **labia minora**.
- ▶ The **genital (labioscrotal) swellings** likewise remain unfused and enlarge to form the **labia majora**, which unite posteriorly as the **posterior labial commissure** and anteriorly to help form the **mons pubis**.
- ▶ The urogenital groove stays open and widens to form the **vestibule of the vagina**, into which the urethra and vagina open; the perineal orifice of the urogenital sinus persists as the cleft between the labia minora.
- ▶ The clitoral prepuce develops the same way as its male homologue.

### 5. Homologues of the external genitalia

| Indifferent primordium | Male derivative                                                          | Female derivative                  |
|------------------------|--------------------------------------------------------------------------|------------------------------------|
| Genital tubercle       | Glans penis (glans of phallus); corpora cavernosa/spongiosum of the body | Glans clitoridis; body of clitoris |

| Indifferent primordium           | Male derivative                                                           | Female derivative             |
|----------------------------------|---------------------------------------------------------------------------|-------------------------------|
| Genital (urethral) folds         | Fuse → floor of the penile (spongy) urethra + ventral skin (penile raphe) | Remain unfused → labia minora |
| Genital (labioscrotal) swellings | Fuse in the midline → scrotum (scrotal septum = fusion line)              | Remain unfused → labia majora |
| Urogenital sinus (phallic part)  | Penile urethra                                                            | Vestibule of the vagina       |
| Urogenital groove                | Closed over (obliterated)                                                 | Open — forms the vestibule    |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the **definitive (10-week) male and female external genitalia in parallel**, from the same indifferent-stage template, and label:

- **Male:** glans penis; deep urethral groove flanked by urethral folds; line of fusion of urethral folds (ventral raphe); penile urethra; scrotal swellings; line of fusion of scrotal swellings (scrotal septum); perineum; anus.
- **Female:** glans clitoridis; unfused urethral folds = labia minora; unfused genital swellings = labia majora; urogenital (vestibular) orifice; urethral orifice; vaginal orifice; perineum; anus.
- Use one colour for genital-tubercle derivatives, one for urethral-fold derivatives and one for labioscrotal-swellings derivatives in both sexes, so the homology is visually obvious to the examiner.

## 6. Congenital anomalies — hypospadias and epispadias

### Hypospadias

- Definition: a congenital anomaly in which the **external urethral orifice opens on the ventral (under) surface of the penis** instead of at the tip of the glans.
- Incidence: ~1 in 300 male births (~3–5/1000); the rate has roughly doubled over recent decades, possibly linked to environmental oestrogenic/endocrine-disrupting exposure.
- Embryological basis: (i) **incomplete fusion of the urethral folds**, and/or (ii) **failure of canalisation of the solid ectodermal cord** that forms the glandular urethra.
- Classified by the site of the abnormal opening (mildest → most severe):

| Type              | Site of external urethral opening                             |
|-------------------|---------------------------------------------------------------|
| Glandular         | Ventral surface of the glans penis                            |
| Balanic (coronal) | At the base of the glans                                      |
| Penile            | Ventral shaft, between glans and scrotum                      |
| Penoscrotal       | Junction of penis and scrotum                                 |
| Perineal          | On the unfused scrotum (failed labioscrotal-swellings fusion) |

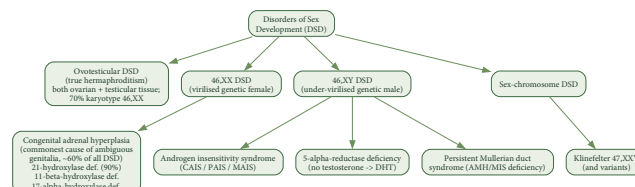
- ▶ In the most severe (perineal) form, the scrotum remains divided and, especially with associated undescended testes, closely resembles the labia majora — a cause of **genital ambiguity**.
- ▶ Often associated with **chordee** (ventral curvature of the penis on erection) and, in more severe grades, with cryptorchidism.
- ▶ Treatment: surgical urethroplasty; the foreskin is frequently used as flap tissue for repair, so **circumcision must be deferred** until hypospadias has been excluded/repaired.

### Epispadias

- ▶ Definition: the external urethral orifice opens on the **dorsal (upper) surface** of the penis.
- ▶ Incidence: rare, ~1 in 30,000 births.
- ▶ Embryological basis: probably an **abnormally caudal/dorsal position of the genital tubercle** relative to the urogenital membrane, so that the urogenital sinus opens onto the dorsum rather than the ventral aspect.
- ▶ Strongly associated with — and considered a milder form of the same spectrum as — **exstrophy of the urinary bladder** (misalignment of the genital tubercle and labioscrotal swellings with the urogenital membrane); isolated epispadias also occurs.
- ▶ Treatment: comprehensive surgical reconstruction.

## 7. Congenital anomalies — ambiguous genitalia (Disorders of Sex Development)

- ▶ Because both sexes share the same primordia, errors of hormonal signalling produce **ambiguous genitalia** — a phenotype spanning from clitoromegaly to an incompletely virilised, hypospadiac "micropenis," with variable labioscrotal fusion.
- ▶ Modern nomenclature groups these as **Disorders/Differences of Sex Development (DSD)**:



*Describe the development of external genitalia. Add a note on their congenital anomalies*

- ▶ **46,XX DSD**: a genetically female fetus is masculinised by excess androgen. **Congenital adrenal hyperplasia (CAH)** is the commonest cause of ambiguous genitalia overall (~60% of all DSD); ~90% of CAH is due to **21-hydroxylase deficiency** (autosomal recessive), with rarer 11 $\beta$ -hydroxylase and 17 $\alpha$ -hydroxylase deficiencies. The internal genital tract is normally female; only the external genitalia are virilised (spectrum from mild clitoromegaly to a fully fused labioscrotal fold).
- ▶ **46,XY DSD**: a genetically male fetus is inadequately virilised.
  - **Persistent Müllerian duct syndrome** — isolated deficiency of anti-Müllerian hormone (AMH/MIS); external genitalia are normally male, but Müllerian remnants (uterus, tubes) persist.
  - **Androgen insensitivity syndrome (AIS)** — absent/defective androgen receptors; testes and AMH are present (so Müllerian structures regress), but tissues fail to respond to androgen. **Complete AIS** gives a phenotypic female with a short vagina and intra-abdominal/inguinal



testes (increased risk of testicular malignancy); partial/mild forms give ambiguous genitalia, e.g. clitoromegaly or a small hypospadiac penis.

- **5 $\alpha$ -reductase deficiency** — testosterone cannot be converted to DHT, so external genitalia (which need DHT) fail to virilise even though internal (testosterone-dependent) Wolffian structures develop normally; the child may appear female with clitoromegaly, virilising further at puberty.
- ▶ **Ovotesticular DSD** (formerly "true hermaphroditism"): both ovarian and testicular tissue are present (as separate gonads or combined as an ovotestis); genitalia are always ambiguous with a tendency to masculinisation; karyotype is 46,XX in ~70% of cases.
- ▶ **Sex-chromosome DSD**: e.g. Klinefelter syndrome (47,XXY and variants) — external genitalia are usually unambiguously (if hypoplastic) male.

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- ▶ **Sex assignment in ambiguous genitalia** requires urgent determination of karyotype, internal duct anatomy (uterus/tubes present or absent) and endocrine status before a decision on rearing sex is made.
- ▶ **Hypospadias repair before circumcision**: the foreskin is used as vascularised flap tissue for urethroplasty, so routine circumcision must be withheld until hypospadias is excluded.
- ▶ **Hypospadias–cryptorchidism association** falls within the concept of "testicular dysgenesis syndrome," reflecting a shared insult to fetal Leydig/Sertoli cell function.
- ▶ **Exstrophy–epispadias complex**: antenatal ultrasound absence of a normal bladder shadow with a low-set umbilicus should prompt a search for associated epispadias.
- ▶ **Chordee** frequently accompanies hypospadias and must be corrected (release of fibrous ventral tissue) at the same sitting as urethroplasty to allow normal erection/intercourse later.
- ▶ **Micropenis** (stretched length >2.5 SD below mean) reflects inadequate androgen stimulation (primary hypogonadism or hypothalamic-pituitary dysfunction), not a fusion defect — distinguishing it from hypospadias is clinically important.
- ▶ Because the genital tubercle is **larger in the female than the male** in the early second trimester, tubercle length alone is an unreliable sonographic sex marker in early pregnancy.

## High-yield exam pointers

- ▶ Three primordia — **genital tubercle, genital (urethral) folds, genital (labioscrotal) swellings** — are common to both sexes; indifferent until week 6–8.
- ▶ Male pathway = **androgen (DHT via 5 $\alpha$ -reductase)-driven fusion**: tubercle → glans penis; folds fuse → spongy urethra; swellings fuse → scrotum.
- ▶ Female pathway = **default, unfused**: tubercle → clitoris; folds unfused → labia minora; swellings unfused → labia majora.
- ▶ Penile urethra completed by **end of 3rd month** (fold fusion); glandular urethra by **4th month** (ectodermal canalisation).
- ▶ Female genitalia can be masculinised by androgen only **up to the 4th month**.
- ▶ **Hypospadias** = ventral urethral meatus (fold-fusion/canalisation failure), incidence ~1/300 males, 5 types glandular → perineal.

- **Epispadias** = dorsal urethral meatus, rare (1/30,000), linked to bladder exstrophy.
- **DSD** = ovotesticular / 46,XX (CAH — 21-OHase 90%) / 46,XY (AIS, 5-ARD, persistent Müllerian duct syndrome) / sex-chromosome (Klinefelter).
- Karyotype + internal duct + hormonal work-up must precede sex assignment in any ambiguous-genitalia case.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke's Textbook of Human Embryology.



## Describe the development of human kidney and the developmental anomalies

Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** The human kidney passes through three successive, cranio-caudally overlapping excretory systems derived from intermediate mesoderm — the **pronephros**, **mesonephros**, and **metanephros**. Only the metanephros, appearing in the fifth week, persists as the **permanent (definitive) kidney**; it has a dual embryological origin — the ureteric bud (collecting system) and the metanephric mesenchyme/blastema (nephrons) — under tight reciprocal molecular induction. Congenital anomalies of the kidney and urinary tract are among the commonest human malformations (3–6% of live births) and reflect disturbances at specific steps of this sequence — failure of induction (agenesis), abnormal ascent (ectopia), abnormal fusion (horseshoe kidney), abnormal rotation, abnormal ureteric-bud branching (duplications), or defective epithelial/ciliary differentiation (cystic disease).

### 1. The three embryonic kidney systems (pronephros → mesonephros → metanephros)

| Feature                      | Pronephros                                                                       | Mesonephros                                                                                                                                                                                    | Metanephros                                                                                           |
|------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Appears                      | Beginning of 4th week                                                            | 4th week, as pronephros regresses                                                                                                                                                              | 5th week                                                                                              |
| Site (intermediate mesoderm) | Cervical region                                                                  | Upper thoracic to upper lumbar (L3) segments                                                                                                                                                   | Sacral intermediate mesoderm / metanephric (nephrogenic) blastema                                     |
| Structure formed             | 7–10 solid cell groups (nephrotomes) — vestigial, non-functional excretory units | S-shaped tubules acquiring a glomerular tuft → renal corpuscle (Bowman capsule + glomerulus); duct = <b>mesonephric (Wolffian) duct</b> ; gonad + mesonephros form the <b>urogenital ridge</b> | <b>Ureteric bud</b> (outgrowth of the mesonephric duct near the cloaca) + <b>metanephric mesoderm</b> |

| Feature  | Pronephros                              | Mesonephros                                                                                                                                        | Metanephros                                                 |
|----------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Function | None                                    | Functions briefly in the early fetal period                                                                                                        | Becomes the permanent kidney; functional near the 12th week |
| Fate     | Regresses completely by end of 4th week | Degenerates by end of 2nd month (in the male, caudal tubules + duct persist to form part of the genital duct system; in the female they disappear) | Persists as the adult kidney                                |

□ Fig 20.3 — A 28-day foetus showing pronephros, mesonephros and metanephros (Sontakke — Textbook of Human Embryology, p.212)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Longitudinal scheme of the intermediate mesoderm, 4–5 weeks, labelled: **cervical pronephric nephrotomes** (regressing) — **thoraco-lumbar mesonephros** (S-shaped tubules, glomerulus, mesonephric/Wolffian duct, urogenital ridge) — **metanephric blastema** (caudal) with the **ureteric bud** from the mesonephric duct, near the cloaca, penetrating the blastema.

## 2. Development of the metanephros: dual origin and the collecting system

- ▶ The metanephros has **two embryological sources**: (i) the **ureteric bud**, which gives rise entirely to the collecting/excretory duct system, and (ii) the **metanephric mesoderm**, which gives rise to the nephrons (excretory units).
- ▶ **Ureteric bud sequence**:
  - Arises as an outgrowth of the mesonephric duct close to its entry into the cloaca; penetrates the metanephric tissue, which caps its growing tip.
  - The bud **dilates** to form the **primitive renal pelvis** and splits into cranial and caudal parts — the future **major calyces**.
  - Each major calyx sends out two new buds while penetrating the metanephric tissue; repeated dichotomous branching continues until **12 or more generations of tubules** have formed.
  - The 2nd-order collecting tubules enlarge and absorb the 3rd and 4th generations, forming the **minor calyces**; the 5th and subsequent generations elongate and converge on a minor calyx to form a **renal pyramid**.
  - Overall, the ureteric bud gives rise to the **ureter, renal pelvis, major and minor calyces**, and 1–3 million **collecting tubules**.

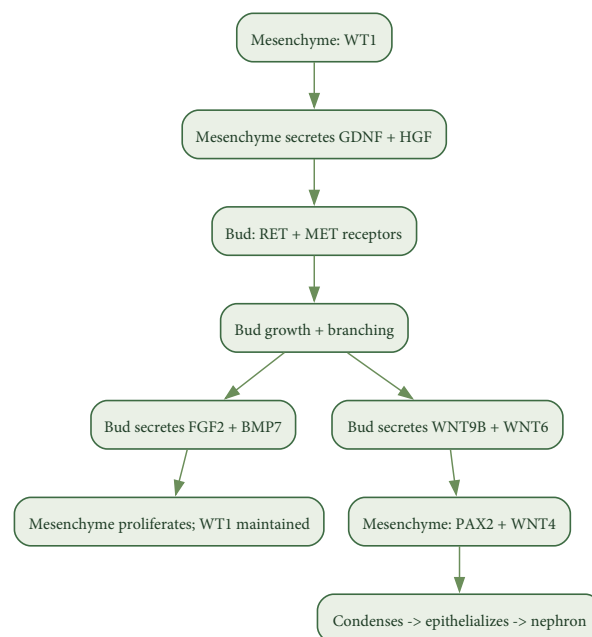
## 3. Nephron (excretory unit) formation and onset of function

- ▶ Each collecting tubule is capped distally by a mass of metanephric tissue; cells of this cap form small vesicles (**renal vesicles**), which elongate into **S-shaped tubules**.

- ▶ Capillaries grow into the pocket at one end of the S and differentiate into a **glomerulus**; the surrounding cells form **Bowman capsule** — together, the **renal corpuscle**, at the proximal end of the nephron.
- ▶ The distal end of the S-shaped tubule opens into a collecting tubule, establishing continuity for urine flow from glomerulus to collecting duct.
- ▶ Continued elongation of the tubule differentiates the **proximal convoluted tubule**, **loop of Henle**, and **distal convoluted tubule**.
- ▶ **Nephrons form continuously until birth** — approximately **1 million nephrons per kidney** are present at birth; no new nephrons form thereafter (further growth is by lengthening of existing tubules, not by an increase in number).
- ▶ **Glomerular capillaries differentiate from the 10th week**; **urine formation begins by the 12th week** and is voided into the amniotic cavity, contributing to and recycling with amniotic fluid. The fetal kidney is **not** responsible for excretion of waste products — this is a placental function.
- ▶ At birth the kidney surface is **lobulated** (fetal lobulation); lobulation disappears during infancy as existing nephrons grow, not as new ones are added.

#### 4. Molecular regulation of metanephric induction

Kidney differentiation is a classic example of reciprocal epithelial–mesenchymal induction between the ureteric bud epithelium and the metanephric mesenchyme.



*Describe the development of human kidney and the developmental anomalies*

- ▶ Conversion of mesenchyme to epithelium is accompanied by matrix remodelling: fibronectin, collagen I and collagen III (mesenchymal) are replaced by **laminin and type IV collagen** (epithelial basal lamina), with expression of the adhesion molecules **syndecan** and **E-cadherin**.
- ▶ Clinical relevance of this pathway: mutations affecting **GDNF–RET–WT1** signalling, or of **PAX2**, **SALL1**, **EYA1**, underlie syndromic forms of renal agenesis/dysplasia (see anomalies below); **WT1** mutation is also the basis of **Wilms tumour**.

## 5. Position and ascent of the kidney

- ▶ The metanephros initially lies in the **pelvis**; it later ascends to a more cranial (lumbar) position because of (a) diminishing curvature of the body and (b) differential growth of the lumbar and sacral regions.
- ▶ During ascent, the kidney is revascularised in succession by arteries arising from the aorta at progressively higher levels; the lower (transient) vessels usually degenerate but may persist as **accessory renal arteries** — a common finding.
- ▶ During ascent the kidney passes through the arterial "fork" formed by the two umbilical arteries and undergoes concurrent rotation about its long axis, so that the hilum (renal pelvis), initially facing ventrally, comes to face medially.
- ▶ The definitive kidney becomes functional (urine formation) near the **12th week**, well before its ascent is complete.

## 6. Developmental anomalies of the kidney and ureter

| Anomaly                                         | Embryological basis                                                                                      | Incidence        | Key feature                                                                          |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------------|
| Unilateral renal agenesis                       | Ureteric bud degenerates before reaching the metanephric mesenchyme on one side                          | ~1/1000          | Asymptomatic; compensatory hypertrophy of the other kidney; single umbilical artery  |
| Bilateral renal agenesis                        | Same defect bilaterally; GDNF-RET-WT1/PAX2/SALL1/EYA1 mutations                                          | ~1/3000          | <b>Potter sequence</b> — oligohydramnios, pulmonary hypoplasia, limb defects; lethal |
| Renal dysplasia / multicystic dysplastic kidney | Ureteric bud fails to branch/undergoes atresia — nephrons never induced                                  | —                | Non-functional, cystic; may progress to agenesis                                     |
| ARPKD (autosomal recessive polycystic kidney)   | Ciliopathy; cysts from collecting ducts                                                                  | ~1/5000          | Kidneys markedly enlarged; renal failure in infancy                                  |
| ADPKD (autosomal dominant polycystic kidney)    | Ciliopathy; cysts from all nephron segments                                                              | ~1/500–1000      | Commoner, less aggressive; renal failure delayed to adulthood                        |
| Pelvic/ectopic kidney                           | Fails to ascend beyond the arterial fork of the umbilical arteries                                       | ~1/2500 (pelvic) | Blood supply from nearby iliac vessels; may fuse (discooid kidney) or cross midline  |
| Horseshoe kidney                                | Lower poles fuse in the arterial fork; ascent then arrested by root of <b>inferior mesenteric artery</b> | ~1/500–600       | Ureters cross anterior to isthmus; UPJ obstruction up to 30%; ~7% of Turner syndrome |

| Anomaly                                          | Embryological basis                                                                                                                                               | Incidence                      | Key feature                                                                   |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------|
| Malrotated kidney                                | Failure/excess/reversed rotation about the long axis                                                                                                              | —                              | Hilum anterior (no rotation), posterior (over-rotated), or lateral (reversed) |
| Duplex kidney / bifid pelvis / duplicated ureter | Early splitting of the ureteric bud (partial or complete)                                                                                                         | Bilateral duplex ureter ~1/800 | Partial → bifid pelvis/ureter; complete → two separate ureters                |
| Ectopic ureter                                   | An extra caudal ureteric bud descends with the mesonephric duct, opening outside the trigone (urethra/vagina/vestibule; or prostatic urethra/vas/seminal vesicle) | Rare                           | Continuous incontinence — orifice distal to the sphincter                     |
| Supernumerary kidney                             | Two separate ureteric buds, each inducing its own metanephric mass                                                                                                | Rare                           | Extra kidney with its own ureter                                              |

□ Fig 11.19 — Horseshoe kidney (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.517)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Horseshoe kidney in situ, labelled: fused **lower poles/isthmus** anterior to the aorta and vertebral column, **inferior mesenteric artery** at the root of the isthmus arresting ascent, both **ureters crossing anterior to the isthmus**, and anteriorly-facing renal pelvis (malrotation).

## Applied / Clinical anatomy

- ▶ **Potter sequence** (bilateral agenesis): oligohydramnios compresses the fetus, producing **Potter facies** (widely spaced eyes, epicanthic folds, low-set ears, flat nose, receding chin), club foot, and pulmonary hypoplasia; usually fatal soon after birth.
- ▶ Antenatal ultrasonography detects renal agenesis, cystic dysplastic kidneys, hydronephrosis, and oligohydramnios early.
- ▶ **Horseshoe kidney**: anteriorly crossing ureters and the abnormal course over the isthmus predispose to stasis, UPJ obstruction, stones, and infection; variable arterial supply (one vessel/moiety in only ~30%) makes CT/angiographic mapping essential before renal or aortic surgery, and its fixed midline position increases trauma risk.
- ▶ **ARPKD vs ADPKD** differ chiefly in age at renal failure and inheritance; both are **ciliopathies**, alongside Bardet–Biedl (renal cysts, obesity, intellectual disability, limb defects) and Meckel–Gruber syndrome (renal cysts, hydrocephalus, microphthalmia, polydactyly).
- ▶ **Wilms tumour** (nephroblastoma), from persisting metanephric blastema, follows WT1 mutation (11p13); WT1 + PAX6 microdeletion gives **WAGR syndrome** (Wilms, Aniridia, GU anomalies,

mental Retardation); WT1 mutation also underlies **Denys–Drash syndrome** (renal failure, ambiguous genitalia, Wilms tumour).

- ▶ Syndromic agenesis/dysplasia genes: **SALL1** (Townes–Brocks), **PAX2** (renal-coloboma syndrome), **EYA1** (branchio-oto-renal syndrome).
- ▶ **Ectopic ureter**: continuous dribbling incontinence, as the orifice lies beyond the urethral sphincter.

### High-yield exam pointers

- ▶ Three overlapping systems, cranial to caudal: **pronephros** (cervical, 4th week, vestigial) → **mesonephros** (thoraco-lumbar, transient, forms the Wolffian duct) → **metanephros** (5th week, permanent kidney).
- ▶ Metanephros has a **dual origin** — ureteric bud (collecting system: ureter, pelvis, calyces, collecting tubules) + metanephric mesenchyme (nephrons).
- ▶ Reciprocal induction cascade: **WT1** → **GDNF/HGF–RET/MET** → bud branching → **FGF2/BMP7** and **WNT9B/WNT6** → **PAX2/WNT4** → nephron formation.
- ▶ ~1 **million nephrons/kidney** at birth; number is fixed at birth — subsequent growth is by tubular lengthening only.
- ▶ Urine formation begins by the **12th week**; the fetal kidney does not excrete waste (the placenta does).
- ▶ Kidney ascends from pelvis to lumbar level with sequential revascularisation from higher aortic levels; persisting lower vessels = **accessory renal arteries**.
- ▶ **Horseshoe kidney**: fused lower poles, ascent arrested by the root of the **inferior mesenteric artery**; ureters cross anterior to the isthmus.
- ▶ **Bilateral renal agenesis** → **Potter sequence** (oligohydramnios + pulmonary hypoplasia + Potter facies), incompatible with life.
- ▶ **WT1** mutation → Wilms tumour/WAGR/Denys–Drash; **PAX2/SALL1/EYA1** mutations → syndromic renal agenesis.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Anatomy Vol 2 4e; Sontakke — Textbook of Human Embryology (figures).





## Describe the development of kidney and discuss adult polycystic renal disease and infantile cystic renal disease

Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The definitive human kidney (metanephros) develops from intermediate mesoderm through three successive, overlapping excretory systems — pronephros, mesonephros and metanephros — an example of ontogeny recapitulating phylogeny. The metanephros forms from an interaction between the **ureteric bud** (which forms the collecting system) and the **metanephric blastema** (which forms the nephron). Adult polycystic kidney disease (ADPKD) and infantile/childhood polycystic kidney disease (ARPKD) are the two classical hereditary cystic nephropathies in which this developmental programme goes awry, producing progressive dilatation of nephron or collecting-duct segments; they differ fundamentally in inheritance, gene, age of onset and prognosis.

### 1. Origin — intermediate mesoderm and the nephrogenic cord

- ▶ The urinary system develops from **intermediate mesoderm**, a longitudinal strip lying between the paraxial mesoderm and the lateral plate mesoderm; it develops *before* the genital system.
- ▶ After lateral folding of the embryo, intermediate mesoderm forms a longitudinal elevation, the **urogenital ridge**, on each side of the dorsal aorta.
- ▶ The urogenital ridge differentiates into a medial **genital ridge** (→ gonad) and a lateral **nephrogenic cord** (→ urinary system).
- ▶ The nephrogenic cord extends from the cervical to the sacral region and successively forms three kidneys — pronephros, mesonephros, metanephros — such that the last to appear is retained as the permanent kidney.

### 2. Pronephros and mesonephros

| Feature      | Pronephros                                                                                                                                                                 | Mesonephros                                                                                                                                                                                         |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Location     | Cervical region                                                                                                                                                            | Thoracolumbar region (somites 8–20)                                                                                                                                                                 |
| Appearance   | Beginning of 4th week (stage 11, ~14 somites)                                                                                                                              | End of 4th week                                                                                                                                                                                     |
| Segmentation | Segmented                                                                                                                                                                  | Segmented, non-metameric tubules                                                                                                                                                                    |
| Function     | Non-functional; no glomeruli form in humans                                                                                                                                | Functional for a short period (excretes urine)                                                                                                                                                      |
| Fate         | Completely regresses; its duct (the <b>primary excretory/pronephric duct</b> ) persists and is annexed by the mesonephros to become the <b>mesonephric (Wolffian) duct</b> | Cranial tubules degenerate; a few caudal tubules/duct persist — in the male they form the vasa efferentia, epididymis and vas deferens; the mesonephric duct also gives off the <b>ureteric bud</b> |

- ▶ Each mesonephric tubule condenses from mesenchyme, epithelializes into a vesicle, and forms an S-shaped tubule; one end forms a glomerular (Bowman's-like) capsule invaginated by

capillaries, the other joins the mesonephric duct — structurally similar to the future metanephric nephron but arranged as a *linear* series of tubules (hence hypotonic urine), unlike the concentric metanephric arrangement.

### 3. Metanephros — the definitive kidney

- ▶ The metanephros appears at the **beginning of the third month** in the **sacral region** and persists permanently, draining eventually into the ureter.
- ▶ It develops from **three sources**:
- ▶ **Ureteric bud** — an evagination of the mesonephric duct close to the cloaca → gives rise to the **collecting system**.
- ▶ **Metanephric blastema/mesenchyme** — a local condensation of nephrogenic mesenchyme capping the ureteric bud tip → gives rise to the **excretory (nephron) system**.
- ▶ **Angiogenic mesenchyme** — invades later → forms the glomerular capillary tuft, mesangial cells and vasa recta.

**Development of the collecting system:** the ureteric bud grows cranially, its blind end dilates to form the renal pelvis, and it undergoes repeated (about 13 generations of) dichotomous branching — the first few generations dilate/coalesce to form the **major and minor calyces**, and later generations form the **collecting ducts and collecting tubules** (1–3 million). Branching requires chondroitin-sulphate-mediated epithelial–mesenchymal signalling between the bud and blastema.

**Development of the nephron (excretory system):** at each branch tip, metanephric blastema condenses into a **metanephric cap**, which converts into a **metanephric (renal) vesicle** → a **comma-shaped**, then **S-shaped** primitive renal tubule. The tubule's proximal narrow end joins a collecting tubule; its distal dilated end invaginates around a capillary tuft to form the **Bowman's capsule + glomerulus**. The rest of the S-shaped tubule differentiates into the **proximal convoluted tubule, loop of Henle and distal convoluted tubule**, which opens into the collecting tubule to complete a **uriniferous tubule**. Nephrogenesis proceeds centrifugally — the earliest (juxtamedullary) nephrons form first and the most recent nephrons lie in the outer cortex, so that all stages of differentiation are present simultaneously in the fetal kidney. The fetal kidney remains **lobulated** until the first year of life.

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros. Pron (Sontakke — *Textbook of Human Embryology*, p.212)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the metanephric nephron-induction sequence in four panels with labels:

- ▶ Ureteric bud (from mesonephric duct) tipped by condensed **metanephric blastema/cap**
- ▶ Metanephric (renal) vesicle — pear-shaped
- ▶ Comma-shaped body → S-shaped body, showing junction with the **collecting tubule**
- ▶ Fully formed **nephron**: Bowman's capsule + **glomerulus** → **proximal convoluted tubule** → **loop of Henle** → **distal convoluted tubule**, opening into the **collecting duct** → **minor calyx** → **major calyx** → **renal pelvis** → **ureter**

**4. Ascent, rotation and blood supply of the kidney**

- ▶ The metanephros is initially **sacral**; as the ureteric outgrowth elongates and the posterior abdominal wall/lumbosacral region grows disproportionately (with reduction of the body's caudal curvature), the kidney **ascends** to reach the level of the **2nd lumbar vertebra**.
- ▶ During ascent the kidney **rotates 90° medially**, so that the hilum, initially facing ventrally, comes to face **medially**.
- ▶ Blood supply changes sequentially as the kidney ascends — first the **median sacral artery**, then the **common iliac arteries**, and successively higher **lateral splanchnic (mesonephric) branches of the aorta** — until the **definitive renal artery** (the most caudal of the three primitive suprarenal arteries) is established at the L2 level by the beginning of the third month. Persisting embryonic lateral splanchnic vessels account for **accessory/aberrant renal arteries**, a common anatomical variant.

**5. Adult (autosomal dominant) polycystic kidney disease — ADPKD**

- ▶ The **most common inherited kidney disease**, transmitted as an **autosomal dominant** trait, with a prevalence of about **1 in 500–1,000 births**.
- ▶ **Genetics**: ~85% of cases result from mutation of **\_PKD1\_** (chromosome 16), encoding **polycystin-1**, a transmembrane receptor-like protein; the remainder are due to **\_PKD2\_** (chromosome 4), encoding **polycystin-2**, a calcium-channel protein homologous to voltage-gated cation channels. Both proteins localise to the **primary cilium** of tubular epithelial cells, where they interact in a mechanosensory complex that senses luminal fluid flow.
- ▶ **Pathogenesis**: **PKD1/PKD2** are expressed in the embryo from **5–6 weeks**, first in the mesonephros and later the metanephros. Cyst formation follows a **"two-hit" mechanism** — a somatic second mutation must inactivate the remaining normal allele (as in tumour-suppressor genes) before a cell forms a cyst. Loss of polycystin function is followed by cyst formation, previously thought to reflect failure of fusion between excretory and collecting tubules but now understood as **focal cystic dilatation of an otherwise-continuous nephron**, potentially affecting **any segment from Bowman's capsule to the collecting duct**.
- ▶ **Clinical features**: usually manifests in the **3rd–4th decade**. Presents with flank pain from the mass effect of enlarging kidneys, haematuria, recurrent urinary infection, nephrolithiasis and **hypertension** (affecting ~75% of adults, from intrarenal ischaemia activating the renin–

angiotensin system). Renal cysts are detectable by ultrasound in 80–90% by age 20 and nearly 100% by age 30. End-stage renal disease develops in roughly half of patients by 60 years of age.

- ▶ **Extra-renal manifestations:** hepatic cysts (the commonest extrarenal finding), pancreatic, splenic and ovarian cysts; **intracranial (berry) saccular aneurysms** in 5–10% (risk of subarachnoid haemorrhage); **mitral valve prolapse** (~25%) and aortic/tricuspid regurgitation; **colonic diverticula** (more prone to perforation than in the general population).
- ▶ **Management:** aggressive blood-pressure control and treatment of infection to preserve renal function, drainage/sclerosis of symptomatic cysts, and ultimately **dialysis or renal transplantation** for end-stage disease.

□ Fig 24.17 — Polycystic kidney (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.402)

## 6. Infantile (autosomal recessive) polycystic kidney disease — ARPKD

- ▶ Inherited as an **autosomal recessive** trait; considerably **less common** than ADPKD, with a prevalence of about **1 in 5,000 births**.
- ▶ **Genetics:** caused by mutation of **\_PKHD1\_** on chromosome 6, encoding **fibrocystin (polyductin)**, a protein required for normal assembly and function of the primary cilium.
- ▶ **Pathogenesis:** cysts arise predominantly from **dilatation of the collecting ducts** (in contrast to ADPKD's involvement of all nephron segments); both are now classed as **ciliopathies**, since the affected gene products are cilia-associated.
- ▶ **Clinical features:** diagnosed **at birth or even in utero by ultrasonography**; both kidneys are grossly enlarged with innumerable small cysts, producing **renal insufficiency from infancy**. Severe bilateral disease reduces fetal urine output and contributes to **oligohydramnios and secondary pulmonary hypoplasia**; many affected infants die shortly after birth, though improving neonatal dialysis and transplantation are increasing survival. ARPKD is also associated with **hepatic and biliary ductal anomalies (congenital hepatic fibrosis)**.
- ▶ **Course/prognosis:** rapidly progressive; renal failure and death occur at an **early age**, in marked contrast to the slowly progressive course and later mortality (occasionally to 60 years) seen in ADPKD.

## 7. ADPKD vs ARPKD — comparative summary

| Feature               | Infantile/childhood type (ARPKD)                 | Adult type (ADPKD)                                                                  |
|-----------------------|--------------------------------------------------|-------------------------------------------------------------------------------------|
| Inheritance           | Autosomal recessive                              | Autosomal dominant                                                                  |
| Gene (protein)        | <b>_PKHD1_</b> , chr. 6 (fibrocystin/polyductin) | <b>_PKD1_</b> ~85% chr. 16 (polycystin-1); <b>_PKD2_</b> ~15% chr. 4 (polycystin-2) |
| Incidence             | ~1 in 5,000 births                               | ~1 in 500–1,000 births                                                              |
| Predominant cyst site | Collecting ducts                                 | All nephron segments, Bowman's capsule to collecting duct                           |
| Age of onset          | Birth / in utero                                 | 3rd–4th decade                                                                      |
| Progression           | Rapid                                            | Slow                                                                                |

| Feature                     | Infantile/childhood type (ARPKD)                               | Adult type (ADPKD)                                                                    |
|-----------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Renal failure               | Infancy/childhood                                              | Adulthood (~50% ESRD by 60 yr)                                                        |
| Key extra-renal association | Hepatic/biliary fibrosis, oligohydramnios/pulmonary hypoplasia | Hepatic/pancreatic cysts, berry aneurysms, mitral valve prolapse, colonic diverticula |
| Prognosis                   | Poor; early death                                              | Long survival; death at a later age                                                   |

### Applied / Clinical anatomy

- ▶ **Cyst origin controversy:** older teaching held that renal cysts arose from failed fusion of the ureteric-bud-derived tips with the metanephrogenic cap; current understanding is that they represent **wide dilatations of otherwise-continuous nephron/collecting-duct segments** — relevant to both ADPKD and ARPKD.
- ▶ **Radiological correlate:** bilaterally enlarged, irregularly studded kidneys on ultrasound/CT are the imaging hallmark of both diseases; antenatal ultrasound may detect severe ARPKD in utero.
- ▶ **Genetic counselling:** ADPKD carries a **50% risk** to offspring of an affected parent (only ~10% are de-novo); ARPKD parents are usually asymptomatic heterozygous carriers with a **25% recurrence risk** per pregnancy, per their respective Mendelian patterns.
- ▶ **Complication awareness:** unexplained hypertension, flank pain or haematuria in a young adult with a positive family history should prompt renal ultrasound; a family history of intracranial haemorrhage warrants cerebral angiographic screening for berry aneurysm.
- ▶ Severe ARPKD-related oligohydramnios reproduces the deformation sequence classically described with renal agenesis, underscoring the shared dependence of amniotic fluid volume on fetal urine output.

### High-yield exam pointers

- ▶ Three successive kidneys: **pronephros (cervical, 4th week, non-functional)** → **mesonephros (thoracolumbar, functional briefly)** → **metanephros (sacral, 3rd month, permanent)**.
- ▶ Metanephros has a **dual origin**: ureteric bud → collecting system; metanephric blastema → nephron (excretory system).
- ▶ Ureteric bud undergoes ~13 generations of dichotomous branching; comma- and S-shaped bodies are the key induction stages of the nephron.
- ▶ Kidney ascends from **sacral to L2 level** and **rotates 90° medially** (hilum anterior → medial); blood supply shifts from median sacral → common iliac → serial lateral splanchnic branches → definitive renal artery.
- ▶ **ADPKD** = autosomal dominant, *PKD1/PKD2*, polycystin-1/-2, presents in adulthood, ~1:500–1,000, associated with hepatic cysts and **berry aneurysms**.
- ▶ **ARPKD** = autosomal recessive, *PKHD1*, fibrocystin/polyductin, presents at birth/infancy, ~1:5,000, associated with **congenital hepatic fibrosis**.
- ▶ Cyst pathogenesis in ADPKD follows a **"two-hit" mechanism**; both diseases are **ciliopathies**.

- ▶ ADPKD: 50% inheritance risk to offspring; ARPKD: 25% recurrence risk (autosomal recessive).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Thompson & Thompson — Genetics in Medicine 8e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Brijesh Kumar — Embryology Text & Atlas; BD Chaurasia — Human Anatomy Vol 2 8e (figure).



## Development of the Male Urethra and its Congenital Anomalies

*Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The adult male urethra has four parts — **prostatic, membranous, spongy (bulbar + penile)** and **glandular** (in the glands, ending at the navicular fossa and external urethral meatus). These parts arise from **three different embryonic tissues**: the endoderm of the urogenital sinus forms the prostatic, membranous and most of the spongy urethra; the surface ectoderm forms the terminal glandular part; and splanchnic mesenchyme forms the surrounding connective tissue and smooth muscle of all parts. Development of the urethra is inseparable from development of the external genitalia, which is itself driven by fetal androgens (testosterone and its active metabolite dihydrotestosterone, DHT) — hence anomalies of the urethra and external genitalia commonly occur together.

### 1. Division of the cloaca and formation of the urogenital sinus (weeks 4–7)

- ▶ The **cloaca**, the common terminal chamber of the hindgut, is closed externally by the bilaminar **cloacal membrane** (ectoderm + endoderm, no intervening mesenchyme).
- ▶ The **urorectal septum** (mesenchyme between allantois and hindgut) grows caudally and approaches the cloacal membrane by the **7th week**, dividing the cloaca into a dorsal **anorectal canal** and a ventral **primitive urogenital sinus (UGS)**; the point of contact becomes the **perineal body**, and the cloacal membrane is correspondingly split into a dorsal **anal membrane** and ventral **urogenital membrane**.
- ▶ The primitive UGS differentiates into **three parts**:
- ▶ **Vesical part** — the upper, largest part, continuous cranially with the allantois; forms the **urinary bladder** (its apex continues as the urachus).
- ▶ **Pelvic part** — a narrow canal; in the male, gives rise to the **prostatic urethra (below the ejaculatory duct openings)** and the **membranous urethra**.
- ▶ **Phallic part** — flattened side-to-side; as the genital tubercle grows, this part is pulled ventrally and, in the male, forms the **spongy (penile) urethra**.



## 2. Development of the prostatic and membranous urethra

- ▶ **Prostatic urethra**, dual source: segment **above** the ejaculatory duct openings develops from the **caudal part of the vesicourethral canal**; segment **below** these openings develops from the **pelvic part of the definitive urogenital sinus**.
- ▶ The paired **mesonephric ducts**, opening into the posterior UGS wall at a raised **sinus (Müllerian) tubercle**, are drawn medially/caudally to open on this mound as the **ejaculatory ducts**.
- ▶ The fused caudal tip of the **paramesonephric (Müllerian) ducts** regresses under fetal **anti-Müllerian hormone (AMH)** from Sertoli cells, leaving only a small posterior-wall outpocketing — the **prostatic utricle** (male homologue of the uterovaginal canal).
- ▶ **Prostate**: multiple **endodermal buds** grow from the prostatic urethra into surrounding **splanchnic mesenchyme**, forming glandular acini/ducts, while the mesenchyme becomes the fibromuscular stroma and capsule.
- ▶ **Membranous urethra**: formed entirely from the **pelvic part of the UGS**; pierces the developing perineal membrane, whose surrounding mesenchyme forms the **external urethral sphincter**.
- ▶ All these segments carry an **endodermal, transitional-to-columnar epithelium**, continuous with that of the bladder, prostatic ducts, seminal vesicles and vasa deferentia.

## 3. Development of the external genitalia and the spongy (penile) urethra (weeks 7–14)

- ▶ Up to the 7th week the genitalia pass through an **indifferent stage** (identical in both sexes): a midline **genital tubercle** (cranial to the cloacal membrane, from fusion of the paired cloacal folds), paired **urethral folds** flanking the urogenital membrane, and paired **genital swellings** lateral to these folds.
- ▶ From about the 9th week, masculinisation is driven by **testosterone from fetal Leydig cells**, converted locally in genital skin to the more potent **dihydrotestosterone (DHT)** by 5 $\alpha$ -reductase — DHT is the principal androgen for external-genital virilisation.
- ▶ The genital tubercle **elongates to form the phallus**, pulling the urethral folds forward to become the **lateral walls of a urethral groove** on the ventral phallic surface (stopping short of the glans); the floor of this groove, continuous with the phallic UGS, is the endodermal **urethral plate**.
- ▶ By the **end of the 3rd month**, the urethral folds progressively fuse over the plate (proximodistally, not reaching the glans), converting the groove into the **penile (spongy) urethra**; the line of fusion becomes the **penile raphe**.
- ▶ The genital swellings enlarge, migrate caudally and fuse in the midline as the **scrotum** (separated internally by the **scrotal septum**); their line of fusion, the **scrotal raphe**, is continuous with the penile raphe.

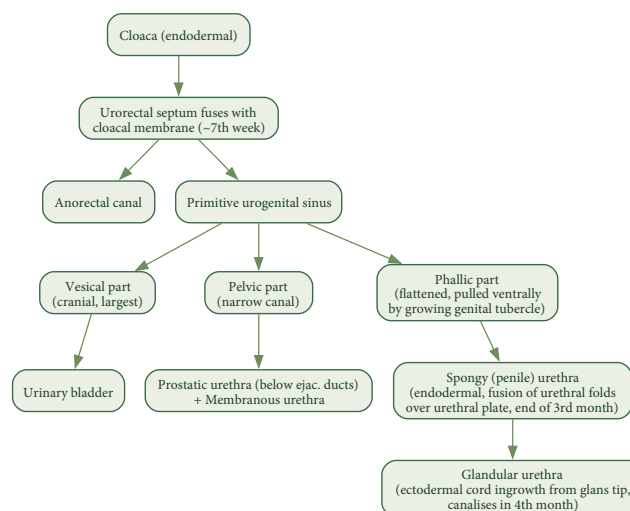
## 4. Development of the glandular urethra and prepuce (4th month)

- ▶ The most distal segment of the urethra — the **glandular (balanic) urethra**, within the glans penis — is **not** formed by folding of the urethral plate/folds.
- ▶ During the **fourth month**, **ectodermal cells from the tip of the glans** penetrate inward as a short, **solid epithelial cord**.



- This cord later **canalises** (acquires a lumen) and joins the already-canalised, more proximal spongy urethra, thereby establishing the definitive **external urethral meatus** at the tip of the glans.
- Because this terminal segment is **ectodermal** in origin, its lining epithelium is **stratified squamous**, unlike the endodermal (stratified/pseudostratified columnar) epithelium of the rest of the urethra.
- The **prepuce (foreskin)** develops in parallel: surface ectoderm covering the glans proliferates and grows inward circumferentially as a double-layered epithelial fold; the two ectodermal layers later separate to free the prepuce as a retractile skin fold over the glans.

| Part of male urethra                           | Embryonic source                                                                 | Epithelium                           |
|------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------|
| Prostatic — above ejaculatory duct openings    | Caudal part of vesicourethral canal (endoderm)                                   | Transitional                         |
| Prostatic — below ejaculatory duct openings    | Pelvic part of definitive urogenital sinus (endoderm)                            | Transitional                         |
| Membranous                                     | Pelvic part of definitive urogenital sinus (endoderm)                            | Stratified/pseudostratified columnar |
| Spongy — bulbar + penile (except tip)          | Phallic part of definitive urogenital sinus (endoderm)                           | Stratified/pseudostratified columnar |
| Glandular (terminal, in glans)                 | Surface ectoderm — solid cord ingrowth from tip of glans, canalises in 4th month | Stratified squamous                  |
| Connective tissue and smooth muscle, all parts | Splanchnic (lateral plate) mesenchyme                                            | —                                    |



Development of the Male Urethra and its Congenital Anomalies

□ Fig 21.13 — Development of male external genitalia (Sontakke — Textbook of Human Embryology, p.235)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Ventral view of the developing phallus at the 10th week and at birth, with the transverse-section inset of the urethral plate/groove-to-urethra sequence. Label:

- ▶ Phallus (primitive penis)
- ▶ Urethral groove (ventral, flanked by urethral folds)
- ▶ Scrotal swelling (paired, lateral)
- ▶ Anal opening
- ▶ Transverse-section inset: **urethral plate** → **urethral groove** → **urethra** (progressive canalisation)
- ▶ Newborn panel: glans penis, external urethral meatus, median (penile) raphe continuous with scrotal raphe

**5. Congenital anomalies of the urethra — Hypospadias**

- ▶ **Definition:** the **commonest congenital anomaly of the urethra** — the external urethral orifice opens on the **ventral aspect of the penis**, proximal to its normal site at the tip of the glans.
- ▶ **Incidence:** about **1 in 300 male births** (3–5 per 1000); the rate has roughly doubled over the last 15–20 years, possibly linked to a rise in environmental oestrogens (endocrine disruptors).
- ▶ **Embryological basis:** (i) failure of fusion of the urethral folds (affects the spongy/penile urethra), and/or (ii) failure of canalisation of the solid ectodermal cord in the glans (affects the glandular urethra) — both ultimately due to **inadequate androgen (testosterone/DHT) production or action** by the fetal testis during the critical window of external genital differentiation.
- ▶ **Associated features:** **chordee** (ventral curvature of the penis, from persistent fibrous tissue distal to the abnormal meatus); an abnormal **prepuce**, longer dorsally and deficient ventrally ("hooded prepuce"), because preputial fusion fails ventrally wherever urethral closure is incomplete; reduced anogenital distance.

| Type (proximal severity increases downward) | Site of external urethral orifice                                                                                                                |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Glandular (commonest)                       | Ventral aspect of the glans                                                                                                                      |
| Coronal / balanic                           | Base of the glans, at the corona; glans often grooved ventrally                                                                                  |
| Penile                                      | Anywhere on the shaft, between the glans and the scrotum                                                                                         |
| Penoscrotal                                 | At the junction of penis and scrotum                                                                                                             |
| Perineal                                    | Wide sagittal slit along the entire length of penis and scrotum; the two scrotal swellings resemble labia majora (may mimic ambiguous genitalia) |

□ Fig 16.17 — Types of hypospadias (Vishram Singh — *Textbook of Anatomy Vol 2 — 4e*, p.713)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Ventral view of the penis, scrotum and perineum with dots marking each abnormal meatal position; label, from tip to perineum: **Glandular** → **Balanic/coronal** → **Penile** → **Penoscrotal** → **Perineal**, and finally the **anal orifice** for reference.

**6. Congenital anomalies of the urethra — Epispadias**

- ▶ **Definition:** a rare anomaly in which the external urethral meatus opens on the **dorsal aspect of the penis**.
- ▶ **Incidence:** rare — quoted as **1 in 30,000 births** (Langman) to **1 in 100,000 boys** (Gray's Anatomy); either way, far less common than hypospadias.
- ▶ **Embryological basis:** not fully established; the accepted explanation is that the **genital tubercle forms abnormally dorsally**, so part of the urogenital membrane lies cranial to it rather than the tubercle being entirely cranial to the membrane — when this malpositioned membrane ruptures, the urogenital sinus and urethral groove open dorsally instead of ventrally.
- ▶ **Associations:** usually **not isolated** — most often part of the **exstrophy–epispadias complex** with **exstrophy of the bladder (ectopia vesicae)**, a ventral abdominal-wall defect with exposed bladder mucosa, from failed mesenchymal reinforcement of an abnormally large, prematurely-ruptured cloacal membrane; also a shortened **dorsal chordee** and a ten-fold increased incidence of cryptorchidism.

**7. Other congenital anomalies related to the urethra**

- ▶ **Posterior urethral valves** — commonest cause of urinary outflow obstruction in male infants (1 in 5000–8000 males); thick mucosal cusps extend caudally from the verumontanum, from abnormally anterior migration of the mesonephric (Wolffian) ducts onto the primitive prostatic urethra. **Megalourethra** (dilated penile urethra) may coexist.
- ▶ **Urethral duplication** — very rare; the two channels usually lie one above the other, the more dorsal one often blind-ending.
- ▶ **Micropenis** (length >2.5 SD below mean, from insufficient androgen stimulation) and **bifid/double penis** (splitting of the genital tubercle) are related genital-tubercle anomalies, not strictly urethral, but classically grouped with these.

**Applied / Clinical anatomy**

- ▶ The **hooded, asymmetric prepuce** (dorsal excess, ventral deficiency) is itself a clinical clue to underlying hypospadias — the foreskin should be examined before circumcision, since it may be needed as flap tissue for surgical repair, and **chordee** must be released before urethroplasty or the penis stays curved despite a well-sited meatus.
- ▶ Because the glandular urethra alone is **ectodermal**, surgeons respect this different embryological plane when mobilising the glans for tension-free meatal advancement.
- ▶ An **enlarged/persistent prostatic utricle** (a Müllerian-duct remnant) can mimic a rudimentary vagina on retrograde urethrography and cause catheterisation difficulty or recurrent infection.

- ▶ **Bladder exstrophy–epispadias complex** needs early multidisciplinary (urological + orthopaedic, for pubic diastasis) reconstruction — the triad of exposed bladder mucosa, dorsal epispadias and pubic diastasis all trace to the same abnormally persistent, prematurely ruptured cloacal membrane.
- ▶ **Posterior urethral valves** are the classic cause of antenatal megacystis/hydronephrosis in a male fetus and the key differential when discussing male urethral anomalies clinically.

### High-yield exam pointers

- ▶ Urethra develops from **three tissues**: endoderm of urogenital sinus (prostatic, membranous, most of spongy), surface ectoderm (glandular part, canalises in the 4th month), splanchnic mesenchyme (surrounding muscle/connective tissue).
- ▶ Primitive UGS has **3 parts**: vesical (→ bladder), pelvic (→ prostatic below ejaculatory ducts + membranous urethra), phallic (→ spongy/penile urethra).
- ▶ **Prostatic utricle** = Müllerian-tubercle/paramesonephric-duct remnant opening on the posterior wall of the prostatic urethra.
- ▶ Penile (spongy) urethra forms by **fusion of urethral folds over the urethral plate** by the **end of the 3rd month**; glandular urethra forms separately by **ectodermal cord canalisation in the 4th month**.
- ▶ **Hypospadias**: commonest urethral anomaly, ~1/300 births, ventral meatus, 5 types (glandular > coronal/balanic > penile > penoscrotal > perineal), often with chordee and hooded prepuce.
- ▶ **Epispadias**: rare (1/30,000–1/100,000), dorsal meatus, usually part of the **exstrophy–epispadias complex**, associated with dorsal chordee and ↑cryptorchidism.
- ▶ Both anomalies trace to the **androgen-dependent** (testosterone → DHT) masculinisation window of the indifferent external genitalia (7th–14th week).
- ▶ Remember: **female urethra** develops entirely from the **narrow pelvic (caudal) part of the urogenital sinus** — unlike the male, it has no ectodermal terminal segment, which is why this contrast is a favourite short-note pairing.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2, 4e; IB Singh — Human Embryology (CBME 2021); Brijesh Kumar — Embryology Text & Atlas.



## Describe the development of the female genital system

Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy

**Definition / Introduction** The female genital system develops from three separate embryonic sources that mature independently under a common hormonal theme — the "default" or **unopposed pathway** of development in the absence of the testis-determining factor (SRY), anti-Müllerian hormone (AMH/MIS) and testosterone. The **genital ridge + primordial germ cells** form the ovary; the **paramesonephric (Müllerian) ducts** form the uterine tubes, uterus and upper vagina; the **urogenital sinus** forms the lower vagina; and the **indifferent external genitalia** (genital tubercle, urethral folds, genital swellings) form the clitoris, labia minora and labia majora under oestrogen influence. Because male and female genital primordia are initially identical, errors at any step produce a well-recognised spectrum of Müllerian and vaginal anomalies.

### 1. Indifferent (ambisexual) stage

- ▶ **Genital (gonadal) ridge:** appears in the 5th week (stage 16) as a thickening of coelomic epithelium on the medial side of the mesonephros, with underlying mesenchymal condensation; it projects into the coelom, connected to the mesonephros by the mesonephros.
- ▶ **Primordial germ cells (PGCs):** arise in the epiblast, pass through the primitive streak, and by the 3rd week lie in the wall of the yolk sac near the allantois. During the 4th week they migrate by amoeboid movement along the dorsal mesentery of the hindgut, arriving at the genital ridges by the end of the 5th week and invading them in the 6th week. PGCs exert an **inductive influence** — if they fail to arrive, the gonad does not develop.
- ▶ **Primary (primitive) sex cords:** proliferating coelomic epithelium forms irregular cords that surround the incoming germ cells; up to the 7th week the gonad shows no sexual differentiation and is termed the **indifferent gonad**.
- ▶ **Genital ducts (both present in both sexes):** the **mesonephric (Wolffian) duct** already exists; the **paramesonephric (Müllerian) duct** arises about the 6th week as a longitudinal invagination of coelomic epithelium on the antero-lateral surface of the urogenital ridge, lateral to the mesonephric duct. It grows caudally, crosses ventral to the mesonephric duct, and meets its fellow of the opposite side in the midline; the fused caudal tip projects into the posterior wall of the urogenital sinus, raising the **sinus (Müllerian) tubercle**.

### 2. Molecular control — why the default pathway runs to female

| Step          | With SRY (male)                                                                                     | Without SRY (female)                                                        |
|---------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Gonadal ridge | SRY → SOX9 → SF1 → testis differentiation                                                           | SRY absent; WNT4 (unopposed) → DAX1 → inhibits SOX9 → ovary differentiation |
| Sertoli cells | Secrete AMH (MIS) → paramesonephric ducts regress (leaving only appendix testis)                    | No AMH → paramesonephric ducts <b>persist and differentiate</b>             |
| Leydig cells  | Secrete <b>testosterone</b> → mesonephric duct persists (epididymis, vas deferens, seminal vesicle) | No testosterone → mesonephric duct <b>regresses</b> (remnants only)         |

| Step               | With SRY (male)                      | Without SRY (female)                                                                                |
|--------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------|
| External genitalia | Dihydrotestosterone → penis, scrotum | Oestrogen → clitoris, labia minora/majora, lower vagina (default, does not require ovarian hormone) |

This scheme (Sadler/Langman) is the standard exam diagram of testis- versus ovary-determining gene cascades and should be reproduced as a two-column flow (see Diagram to draw).

### 3. Development of the ovary

- ▶ **Medullary cords** (1st-generation cords) dissociate into cell clusters in the medulla and later degenerate, being replaced by vascular stroma that forms the **ovarian medulla**.
- ▶ **Cortical cords** (2nd generation) arise from continued proliferation of the surface epithelium in the 7th week, penetrate the mesenchyme but stay near the surface; in the 3rd month they break up into isolated clusters, and cells surround each oogonium with a layer of follicular cells to form the **primordial follicle**.
- ▶ **Descent of the ovary**: less extensive than testicular descent and **not hormonally regulated**. A fibrous **gubernaculum** runs from the ovary (via the mesovarium) to the abdominal wall, acquiring a secondary attachment to the lateral uterine wall near the entering uterine tube. The part **caudal** to this becomes the **round ligament of the uterus**; the part **cranial** to it becomes the **ligament of the ovary proper** — together homologous with the gubernaculum testis. This uterine attachment restricts descent, so the ovary settles in the pelvis and never enters the inguinal canal (except in rare anomalies).

### 4. Fate of the genital ducts in the female

- ▶ In the presence of **oestrogen** and the absence of testosterone/AMH, the **paramesonephric ducts** become the **main genital ducts**. Each duct initially has three parts: a cranial vertical part opening into the abdominal cavity, a horizontal part crossing the mesonephric duct, and a caudal vertical part that fuses with its partner.
- ▶ With descent of the ovary, the **cranial + horizontal parts** become the **uterine tube** (the original coelomic opening persists as the abdominal ostium/fimbriae); the **fused caudal parts** form the **uterovaginal canal/primordium**, giving rise to the **corpus and cervix of the uterus** and, together with tissue derived from the urogenital sinus, the **upper vagina**. Surrounding mesenchyme forms the myometrium and perimetrium.
- ▶ As the fused ducts approach in the midline, a transverse peritoneal fold is thrown up on each side — the **broad ligament of the uterus** — with the uterine tube in its upper border and the ovary on its posterior surface; the broad ligament divides the pelvis into the **utero-vesical pouch** and **utero-rectal pouch (of Douglas)**.
- ▶ The **mesonephric duct** is vestigial in the female: its cranial remnant becomes the **duct of the epoophoron**, a caudal remnant may persist as **Gartner's duct**, and remaining mesonephric tubules persist as the **epoophoron** (cranial tubules) and **paroophoron** (caudal tubules) in the mesovarium/broad ligament.

| Male structure      | Common precursor                          | Female structure                               |
|---------------------|-------------------------------------------|------------------------------------------------|
| Appendix testis     | Paramesonephric duct (cranial remnant)    | Uterine tube                                   |
| —                   | Paramesonephric duct (fused caudal parts) | Uterus, upper vagina                           |
| Duct of epididymis  | Mesonephric duct                          | Duct of epoophoron (→ Gartner's duct caudally) |
| Efferent ductules   | Mesonephric tubules                       | Epoophoron                                     |
| Paradidymis         | Mesonephric tubules (caudal)              | Paroophoron                                    |
| Gubernaculum testis | Gubernacular cord                         | Ovarian ligament + round ligament of uterus    |

## 5. Formation of the uterus and vagina

- ▶ A **uterine septum** transiently separates the lumens of the two fused paramesonephric ducts; it disappears by about the **9th week**, producing a single-lumen uterine canal.
- ▶ The **vagina has a dual origin**. Shortly after the solid tip of the fused paramesonephric ducts contacts the urogenital sinus, two solid endodermal evaginations — the **sinovaginal (sinuvaginal) bulbs** — grow out from the pelvic urogenital sinus at the site of the sinus tubercle and fuse to form a solid **vaginal plate**. Proliferation at the cranial end of the plate progressively increases the distance between uterus and urogenital sinus.
- ▶ The plate canalises from caudal to cranial, being **entirely canalised by the 5th month**; its upper expanded end grows around the cervix to form the **vaginal fornices** (of paramesonephric origin). Thus the **upper part of the vagina (and fornices) is derived from the uterovaginal/paramesonephric canal, and the lower part from the sinovaginal bulbs of the urogenital sinus**.
- ▶ The **hymen**, a thin tissue plate at the vaginal–sinus junction, is composed of urogenital sinus epithelium and a thin layer of vaginal tissue; it usually perforates centrally during the perinatal period.

□ Fig 21.9 — Development of the uterus and vagina at 9, 10 and 20 weeks, showing the urogenital sinus, paramesonephric duct, uterovaginal canal, sinovaginal bulb, fallopian tube, vagina and hymen (Sontakke — Textbook of Human Embryology, p.232)

## 6. Development of the external genitalia

- ▶ **Indifferent stage (~4th week)**: mesenchyme migrating around the cloacal membrane raises paired **cloacal folds**, which unite cranially as the **genital tubercle**; caudally they subdivide into **urethral folds** (anterior) and **anal folds** (posterior). A further pair of **genital (labioscrotal) swellings** appears lateral to the urethral folds. Up to the 6th week the two sexes are indistinguishable.
- ▶ **Female (default, oestrogen-driven) differentiation**:
  - **Genital tubercle** elongates only slightly → **clitoris** (it is briefly larger than the male phallus in early development, a point of note on ultrasound sexing).



- **Urethral folds** do NOT fuse (unlike the male) → remain as the **labia minora**; the open urogenital groove between them becomes the **vestibule**.
- **Genital swellings** enlarge without fusing → **labia majora**, joined posteriorly by the labial commissure.
- The (unfused) perineal opening of the urogenital sinus persists as the vestibular cleft into which the urethra and vagina open.
- By the 4th month the female external genitalia can no longer be virilised by androgens.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled transverse/schematic diagram of the **genital ducts at the end of the indifferent stage** (6th–8th week), male side vs female side, showing:

- ▶ **Gonad** (indifferent) with **mesonephros** and **mesonephric ridge**
- ▶ **Mesonephric (Wolffian) duct** — full length, both sides
- ▶ **Paramesonephric (Müllerian) duct** — lateral to the mesonephric duct, its caudal tip crossing ventral to it and fusing in the midline
- ▶ **Sinus (Müllerian) tubercle** at the point where the fused paramesonephric ducts meet the **urogenital sinus**
- ▶ On the female side: label the **fused caudal parts** → **uterovaginal canal**, the **broad ligament** forming as a transverse peritoneal fold, **uterine tube** in its upper border, **ovary** on its posterior surface, and the **utero-vesical/utero-rectal pouches** it creates.

## Applied / Clinical anatomy

| Anomaly                   | Embryological basis                                      | Feature                                                 |
|---------------------------|----------------------------------------------------------|---------------------------------------------------------|
| Uterus didelphys          | Complete failure of fusion of the paramesonephric ducts  | Two uteri, two cervices ± double vagina                 |
| Bicornuate uterus         | Partial failure of fusion of the upper (fundal) segments | One cervix, one vagina; two horns/cornua, one tube each |
| Unicornuate uterus        | One paramesonephric duct fails to develop/degenerates    | Half the uterus with one uterine tube                   |
| Septate uterus            | Ducts fuse but the uterine septum fails to resorb        | Vertical intracavitary septum                           |
| Arcuate uterus            | Minimal residual fundal indentation                      | Least severe fusion anomaly                             |
| Cervical/uterine agenesis | Failure of paramesonephric ducts to develop (bilateral)  | Absent uterus/cervix                                    |

□ Fig 21.10 — Congenital anomalies of the uterus: A. Bicornuate, B. Unicornuate, C. Septate, D. Uterus didelphys (Sontakke — Textbook of Human Embryology, p.233)

- ▶ **Vaginal anomalies (Gray's)**: vaginal agenesis, absent hymen, transverse vaginal septum, and persistent cloaca. Vaginal agenesis occurring with other Müllerian duct anomalies and renal agenesis is termed **Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome** — a 46,XX individual with normal ovaries/secondary sexual characters but an absent/rudimentary uterus

and upper vagina, reflecting the shared developmental field of the paramesonephric duct and the (adjacent, mesonephric-duct-dependent) metanephric/ureteric bud.

- ▶ **Imperforate hymen / transverse vaginal septum:** failure of central canalisation of sinovaginal tissue → obstructed outflow presenting at puberty as **primary amenorrhoea with cyclical pain and haematocolpos** (retained menstrual blood).
- ▶ **Mesonephric remnant cysts:** persistence of tubules/duct gives **epoophoron and paroophoron cysts** in the mesosalpinx, and a **Gartner's duct cyst** in the lateral wall of the vagina/cervix — both classic broad-ligament/vaginal-wall swellings on clinical and radiological examination.
- ▶ **Ipsilateral renal agenesis** commonly accompanies unilateral Müllerian duct anomalies (e.g., unicornuate uterus, obstructed hemivagina) because the paramesonephric duct develops using the mesonephric duct as a guide — a key point linking gross, radiological and embryological anatomy.

### High-yield exam pointers

- ▶ Female pathway = **default/unopposed** pathway: no SRY → no AMH, no testosterone → paramesonephric ducts persist, mesonephric ducts regress, oestrogen drives external genitalia.
- ▶ **Paramesonephric duct → uterine tube (unfused cranial/horizontal parts) + uterus and upper vagina (fused caudal parts = uterovaginal canal).**
- ▶ **Vagina has a DUAL origin:** upper part/fornices from the uterovaginal (paramesonephric) canal; lower part from the sinovaginal bulbs of the urogenital sinus; canalisation complete by the 5th month.
- ▶ **Mesonephric duct remnants in the female:** epoophoron, paroophoron, Gartner's duct — all classic viva/short-note items.
- ▶ **Gubernaculum in the female** stays thin (no *Ins13*-driven bulging as in the male) and gives the **ovarian ligament (cranial part) + round ligament of the uterus (caudal part).**
- ▶ **Broad ligament** = transverse peritoneal fold formed as the fused paramesonephric ducts pull the mesonephric ridges medially; divides the pelvis into uterovesical and uterorectal (Douglas) pouches.
- ▶ **Uterine anomalies (didelphys > bicornuate > septate > arcuate)** all trace to a single defect — failure of paramesonephric duct fusion/septal resorption; **vaginal agenesis + renal agenesis = MRKH syndrome.**
- ▶ External genitalia in the female = **non-fusion** default: genital tubercle → clitoris; urethral folds unfused → labia minora; genital swellings unfused → labia majora.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



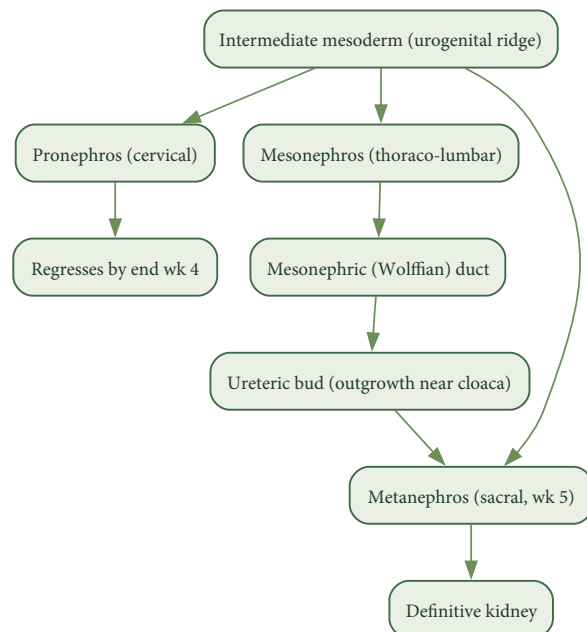
## Describe the development of urinary system

Asked in: Paper II Nov 2018 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The urinary system develops from two germ-layer sources: the **intermediate mesoderm** (paired urogenital ridge, running from cervical to sacral levels) gives rise to three successive, cranio-caudally overlapping excretory organs — the **pronephros**, **mesonephros** and **metanephros** — of which only the metanephros persists as the definitive kidney; and the **cloaca** (endoderm), which is divided by the urorectal septum into the urogenital sinus that forms the bladder and urethra. The kidney thus has a dual origin — **ureteric bud** (collecting system) and **metanephric mesenchyme/blastema** (nephrons) — joined by reciprocal induction.

### 1. The three kidney systems (cranio-caudal sequence)

| System      | Level / segments                   | Structure formed                                                                                     | Fate                                                                                                                                                                                                                                        |
|-------------|------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pronephros  | Cervical region                    | 7–10 solid cell groups = vestigial nephrotomes                                                       | Non-functional; regresses completely by end of 4th week                                                                                                                                                                                     |
| Mesonephros | Upper thoracic → upper lumbar (L3) | S-shaped tubules + glomerulus + Bowman capsule, draining into the <b>mesonephric (Wolffian) duct</b> | Functions transiently in early fetal period; most tubules degenerate by end of 2nd month; in the <b>male</b> , caudal tubules and the mesonephric duct persist to form part of the genital duct system; in the <b>female</b> they disappear |
| Metanephros | Sacral (from 5th week)             | Ureteric bud + metanephric mesenchyme                                                                | <b>Permanent kidney</b>                                                                                                                                                                                                                     |



*Describe the development of urinary system*

## 2. Development of the metanephros — the definitive kidney

The metanephros appears in the **5th week** and, unlike the earlier two systems, develops from **two separate sources** that induce each other:

- ▶ **Ureteric bud** — an outgrowth of the mesonephric duct close to its entry into the cloaca — penetrates the metanephric mesenchyme (which caps its tip) and gives rise to the entire **collecting system**: it dilates to form the primitive renal pelvis, splits into cranial and caudal major calyces, and each calyx throws off further generations of branching tubules (12 or more) — the first few generations enlarge and are absorbed to form the **minor calyces**, later generations elongate and converge on a minor calyx to form the **renal pyramid**. The ureteric bud thus gives rise to the **ureter, renal pelvis, major and minor calyces, and collecting ducts** (1–3 million of them).
- ▶ **Metanephric mesenchyme (blastema)** — under inductive influence of each collecting tubule, forms a cap of cells that condense into renal vesicles → S-shaped tubules → **nephrons**. Capillaries invaginate one end of the S to form the glomerulus; the proximal end expands as **Bowman capsule**; the tubule elongates into **proximal convoluted tubule, loop of Henle and distal convoluted tubule**, and opens into a collecting tubule so that urine can flow from glomerulus to collecting duct.

``markdown embed: ![Fig 20.5 — Development of kidney: the ureteric bud divides dichotomously to form the renal pelvis, major and minor calyces and collecting tubules (Sontakke — Textbook of Human Embryology, p.214)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/f4d496e809ac7e6a.jpg) ``

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label: Ureteric bud → Renal pelvis → Major calyx → Minor calyx → Collecting tubule; Metanephric blastema (cap) around each tubule end; a nephron (glomerulus + Bowman capsule + PCT + loop of Henle + DCT) opening into the collecting tubule; mark the two embryological sources with different shading (ureteric-bud derivatives vs metanephric-mesenchyme derivatives).

Nephrons continue to form until birth ( $\approx 1$  million per kidney); no new nephrons form thereafter — postnatal growth is by elongation/hypertrophy of existing tubules, which is why the lobulated fetal/neonatal kidney surface smooths out in infancy. Glomerular capillaries differentiate from the 10th week and **urine formation begins by the 12th week**, contributing to amniotic fluid; the fetal kidney is not an excretory organ (the placenta performs that role).

### 3. Molecular regulation (reciprocal induction)

- ▶ Metanephric mesenchyme expresses **WT1**, which makes it competent to respond to the ureteric bud and drives production of **GDNF** and **HGF**.
- ▶ **GDNF/RET** and **HGF/MET** signalling (receptors on the ureteric-bud epithelium) stimulate **branching and growth of the bud**.
- ▶ The bud in turn induces the mesenchyme via **FGF2** and **BMP7** (block apoptosis, maintain WT1) and via **WNT9B/WNT6**, which upregulate **PAX2** (condensation → epithelialisation) and **WNT4** (tubule formation) in the mesenchyme.
- ▶ Failure of this reciprocal induction (e.g., mutated GDNF signalling, *SALL1* in Townes-Brocks syndrome, *PAX2* in renal-coloboma syndrome, *EYA1* in branchio-oto-renal syndrome) causes **renal agenesis**.

### 4. Development of the ureter and ascent of the kidney

- ▶ The **ureter** is a direct derivative of the stalk of the ureteric bud; its epithelium is therefore of mesodermal (Wolffian-duct) lineage.
- ▶ **Position/ascent**: the metanephros first lies in the pelvis; as the body straightens (diminishing curvature) and the lumbar/sacral region grows disproportionately, the kidney appears to "ascend" into the abdomen. During this ascent its arterial supply is renewed at successively higher levels from the aorta; lower vessels usually degenerate (persistence of these gives **accessory renal arteries**).

### 5. Development of the urinary bladder and urethra

Between the 4th and 7th weeks, the **urorectal septum** divides the cloaca into a dorsal anorectal canal and a ventral **urogenital sinus**; the tip of the septum forms the **perineal body**. The urogenital sinus has three parts:

| Part of urogenital sinus                                     | Adult derivative                                                                                                       |
|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Vesical part (upper, largest; continuous with the allantois) | Most of the <b>urinary bladder</b> ; allantois becomes fibrous <b>urachus</b> → adult <b>median umbilical ligament</b> |

| Part of urogenital sinus   | Adult derivative                                                                 |
|----------------------------|----------------------------------------------------------------------------------|
| Pelvic part (narrow canal) | Prostatic + membranous urethra (male); the whole urethra (female)                |
| Phallic part               | Penile urethra (male only; pulled ventrally with growth of the genital tubercle) |

During this division, the caudal (common) segments of the mesonephric ducts are absorbed into the posterior wall of the bladder, so the **ureters come to open separately** into the bladder; because of the kidneys' ascent, the ureteric orifices migrate cranially while the mesonephric-duct orifices move together and enter the prostatic urethra as the **ejaculatory ducts** (male) or degenerate (female). Classical teaching (Langman, Moore) holds that this incorporation gives the **trigone** a transient mesodermal epithelium later replaced by endoderm; Standring's *Gray's Anatomy* (41e) notes that current cell-lineage/knockout studies instead show the common nephric duct undergoes local **apoptosis**, with **no mesodermal epithelial contribution** — the trigone epithelium is endodermal throughout, and the bulk of its muscle derives from **detrusor (bladder) smooth muscle** rather than from the ureter. The entire epithelium of the bladder and urethra is endodermal in both sexes; surrounding connective tissue and smooth muscle are of splanchnic-mesoderm origin. From the 3rd month, epithelial outgrowths of the prostatic urethra penetrate the mesenchyme to form the **prostate** (male); in the female the cranial urethral epithelium forms the **urethral and paraurethral (Skene) glands**.

``markdown embed: ![Fig 16.13 — Development of the urogenital sinus into the urinary bladder and definitive urogenital sinus; in the male it develops into the penile urethra, the prostate forms by budding from the urethra, and seminal vesicles bud from the ductus deferens (Langman's Medical Embryology — Sadler — 14e, p.284)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/61ed174ea3fd3b0e.jpg) ``

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Label: Urogenital sinus subdivided into vesical, pelvic and phallic parts; urinary bladder with **urachus** running to the umbilicus; **mesonephric duct** and **ureter** entering separately with the **trigone** shaded at their common base; **prostatic + membranous urethra** and **penile urethra** (male) / **single female urethra**.

### Applied / Clinical anatomy

- **Bilateral renal agenesis** (1/10,000 births) → **Potter sequence**: anuria, oligohydramnios, pulmonary hypoplasia, "Potter facies," club feet; unilateral agenesis is compensated by hypertrophy of the remaining kidney.
- **Pelvic kidney** — failure of ascent past the aortic bifurcation; **horseshoe kidney** (~1/600) — lower poles fuse and ascent is arrested by the root of the inferior mesenteric artery; ureters descend ventral to the isthmus.
- **Duplex kidney/ureter and ectopic ureter** — early or complete splitting of the ureteric bud; an abnormally-positioned second bud may drag down with the mesonephric duct and open ectopically into the bladder neck, urethra, vagina or vestibule.

- ▶ **Multicystic dysplastic kidney** — failure of ureteric-bud branching/induction so nephrons and collecting ducts fail to form.
- ▶ **Polycystic kidney disease** — autosomal recessive (ARPKD, ~1/5,000; cysts from collecting ducts; renal failure in infancy) vs autosomal dominant (ADPKD, 1/500–1/1,000; cysts from all nephron segments; a ciliopathy presenting in adulthood, though the abnormality is already demonstrable in the mesonephros/early metanephros by 5–6 weeks).
- ▶ **Wilms tumour** — *WT1* mutation (11p13); **WAGR syndrome** (Wilms tumour, aniridia, gonadal tumours, intellectual disability — contiguous *PAX6+WT1* deletion) and **Denys–Drash syndrome** (renal failure, ambiguous genitalia, Wilms tumour).
- ▶ **Urachal anomalies** — patent urachus (urachal fistula), urachal cyst, urachal sinus — from incomplete obliteration of the allantoic lumen.
- ▶ **Bladder/cloacal exstrophy** — failure of lateral body-wall-fold fusion exposes the bladder mucosa (with epispadias); rare (Langman: ~2/10,000; Moore: 1/10,000–1/40,000); cloacal exstrophy is a more severe variant with associated anorectal malformation.
- ▶ **Posterior urethral valves** — an obstructing membrane in the posterior (prostatic) urethra causing megacystis, hydronephrosis and, if severe, pulmonary hypoplasia.
- ▶ **Antenatal ultrasound**: fetal bladder visible from 9–11 weeks (absence beyond 13 weeks is abnormal); fetal renal pelvis AP diameter  $\leq 7$  mm is normal at mid-gestation; genitourinary anomalies are detectable from 12–15 weeks.
- ▶ **Neonatal points**: kidneys are lobulated at birth (lobulation disappears in infancy); combined neonatal renal weight  $\approx 23$  g; GFR at birth is  $\sim 30\%$  of adult value, reaching adult levels by 3–5 months; the neonatal bladder is an abdominal organ whose apex may reach the umbilicus when full (basis of suprapubic bladder aspiration), attaining the adult pelvic position only by  $\sim 6$  years of age.

## High-yield exam pointers

- ▶ Three kidney systems in strict cranio-caudal, overlapping sequence: **pronephros** (cervical, regresses)  $\rightarrow$  **mesonephros** (thoraco-lumbar, transient)  $\rightarrow$  **metanephros** (sacral, permanent).
- ▶ Metanephros = **dual origin**: ureteric bud (ureter, pelvis, calyces, collecting ducts) + metanephric mesenchyme (nephrons) — reciprocal induction (GDNF-RET, WT1, PAX2/WNT4).
- ▶ Nephron count fixed at birth ( $\sim 1$  million/kidney); urine formation begins in the 12th week.
- ▶ Kidney "ascent" = differential body growth + straightening, not true migration; explains variable/accessory renal arteries and ectopic kidneys.
- ▶ Urorectal septum (wk 4–7) splits cloaca  $\rightarrow$  urogenital sinus (vesical/pelvic/phallic parts) + anorectal canal.
- ▶ Trigone: classical teaching = mesodermal (mesonephric-duct) origin later replaced by endoderm; modern evidence (Gray's 41e) = endodermal throughout, muscle from detrusor.
- ▶ Ureteric-bud anomalies (agenesis, duplication, ectopia) explain most congenital urinary-tract malformations.
- ▶ Know the syndromic associations of Wilms tumour (WAGR, Denys–Drash) and of ciliopathic PKD (Bardet–Biedl, Meckel–Gruber).



- Potter sequence is the classic "connect the dots" applied question linking bilateral renal agenesis to pulmonary hypoplasia via oligohydramnios.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology.



## Describe the development of urinary system. Add a note on the related anomalies

Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The urinary and genital systems arise from a common mesodermal ridge, the **intermediate mesoderm**, along the posterior abdominal wall; the two remain intimately linked throughout development because they share the mesonephric duct and the cloaca. Three successive, cranio-caudally overlapping "kidneys" develop — the **pronephros**, **mesonephros** and **metanephros** — recapitulating phylogeny, of which only the metanephros persists as the definitive kidney. The lower urinary tract (bladder, urethra) develops separately, from partitioning of the cloaca into the **urogenital sinus**. Because several inductive tissues (ureteric bud, metanephric mesenchyme, cloaca, mesonephric duct) must interact correctly, the urinary tract is one of the most common sites of congenital malformation.

### 1. The three kidney systems

| Feature                      | Pronephros                                             | Mesonephros                                                                                          | Metanephros                                          |
|------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Site (intermediate mesoderm) | Cervical region                                        | Thoraco-lumbar region (upper thoracic–L3)                                                            | Sacral region                                        |
| Segmentation                 | Segmented (7–10 solid cell groups/nephrotomes)         | Segmented                                                                                            | Unsegmented (metanephric blastema)                   |
| Time of appearance           | Beginning of 4th week                                  | End of 4th week                                                                                      | 5th week                                             |
| Functional status            | Non-functional; regresses by end of 4th week           | Functions briefly in early fetal life; degenerates by end of 2nd month (caudal tubules/duct persist) | Becomes the permanent, functioning kidney            |
| Duct                         | Gives rise to the primary excretory (mesonephric) duct | Mesonephric (Wolffian) duct persists                                                                 | Drains via the <b>ureter</b> (from the ureteric bud) |

Each mesonephric tubule forms an S-shaped loop, acquires a glomerular tuft (Bowman capsule + glomerulus = renal corpuscle) and opens laterally into the mesonephric duct. In the male, a few caudal mesonephric tubules and the duct persist to form the male genital duct system (epididymis, vas deferens); in the female, both regress almost completely.

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros. Pron (Sontakke — Textbook of Human Embryology, p.212)

## 2. Development of the metanephros (definitive kidney)

The metanephros develops from **two sources** that must induce one another:

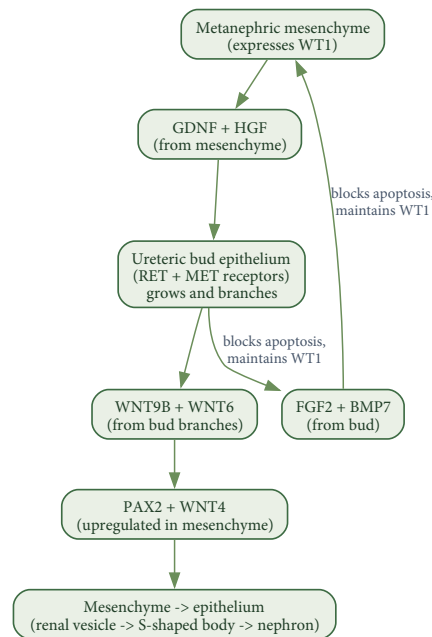
- ▶ **Ureteric bud (metanephric diverticulum)** — an outgrowth of the mesonephric duct close to its entry into the cloaca (end of 4th/5th week) — gives rise to the **collecting system**: ureter → renal pelvis → major calyces → minor calyces → collecting ducts/tubules (ductogenesis).
- ▶ **Metanephric mesenchyme (blastema)** — caudal, unsegmented intermediate mesoderm in the sacral region that caps the growing tip of the bud — gives rise to the **nephron** (nephrogenesis).

**Ductogenesis**: the bud penetrates the metanephric blastema; its growing end dilates into an ampulla that forms the primitive **renal pelvis**, then divides dichotomously — the first 3–5 generations of branches fuse to form the pelvis, further generations become **major then minor calyces**, and later generations (up to ~12 or more) form the **collecting ducts/tubules** (1–3 million in number). Fetal kidney lobulation reflects this branching (2 lobes at 6th week → 14–16 lobes by the 16th week); lobulation is normally lost in infancy as nephrons enlarge, without any increase in their number.

**Nephrogenesis**: metanephric mesenchymal cells that cap each new collecting tubule condense into a **renal (metanephric) vesicle**, which elongates into an **S-shaped tubule**. Capillaries invade the deeper end and differentiate into a **glomerulus**, invaginating the cupped end into **Bowman capsule**; the rest of the S-tubule differentiates into the proximal convoluted tubule, loop of Henle and distal convoluted tubule. The distal end fuses with a collecting tubule, establishing an open passage from glomerulus to collecting duct — i.e., the **nephron (mesodermal) + collecting duct (ureteric-bud derived)** together constitute the definitive uriniferous tubule. Nephron formation continues until birth, giving ~1 million nephrons/kidney; no new nephrons form thereafter.

□ Fig 20.5 — Development of kidney. Ureteric bud divides dichotomously to form rena (Sontakke — Textbook of Human Embryology, p.214)

**Molecular regulation** (epithelial–mesenchymal reciprocal induction):



*Describe the development of urinary system. Add a note on the related anomalies*

WT1 makes the mesenchyme competent to respond to the bud and drives GDNF/HGF production; GDNF–RET and HGF–MET signalling stimulate ureteric-bud growth and branching; the bud reciprocates via FGF2/BMP7 (anti-apoptotic, proliferative) and via WNT9B/WNT6, which upregulate PAX2 (mesenchymal condensation) and WNT4 (mesenchyme-to-epithelium conversion) — with the extracellular matrix switching from fibronectin/collagen I & III to laminin/type-IV collagen as the epithelial basal lamina forms. Failure at any node (e.g., GDNF/RET mutation) causes **renal agenesis or dysplasia**.

Urine formation begins around the **12th week** (glomerular capillaries differentiate from the 10th week), contributing to amniotic fluid from the second trimester onward; the placenta, not the fetal kidney, remains the principal excretory organ in utero.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled schematic (lateral view of a 5th-week embryo) reproducing the two embedded plates above, with these exact labels: **pronephros (degenerating) — mesonephros — mesonephric (Wolffian) duct — metanephric blastema (metanephros) — ureteric bud — cloaca/urogenital sinus — hindgut/allantois**; then, as an inset, the ureteric-bud branching sequence: **ureteric bud → renal pelvis → major calyx → minor calyx → collecting tubule**, capped at each tip by a **metanephric tissue cap → renal vesicle → S-shaped body → nephron (Bowman capsule + PCT + loop of Henle + DCT)** opening into the collecting tubule.

### 3. Ascent and rotation of the kidney

- ▶ The metanephros initially lies in the **sacral/pelvic region** with its hilum facing **ventrally**.
- ▶ **Ascent** into the abdomen results from diminishing embryonic body curvature and disproportionate growth of the lumbosacral region (not active migration); the kidney simultaneously **rotates ~90° medially** so the hilum comes to face medially.

- ▶ During ascent the kidney passes through the fork formed by the **umbilical arteries**; failure to do so leaves it as a **pelvic kidney**.
- ▶ **Blood supply changes serially** with ascent — initially from pelvic/lateral sacral branches of the aorta, then successively higher lateral splanchnic branches take over; the definitive renal artery corresponds to the branch at the L2 level. Lower vessels usually degenerate but persisting ones become **accessory/aberrant renal arteries**.

#### 4. Development of the ureter and the bladder trigone

The **ureter** is derived from the stalk of the ureteric bud lying between the renal pelvis and the cloaca. As the cloaca differentiates, the **mesonephric duct** caudal to the origin of the ureteric bud is progressively **absorbed** into the dorsal wall of the vesico-urethral canal, so the ureter and the mesonephric duct come to open **separately**. With continued absorption, the ureteric orifice migrates **cranio-laterally** (following renal ascent) while the mesonephric duct orifices move **caudo-medially** toward the (future) prostatic urethra, becoming the ejaculatory ducts in the male. The triangular area between these two pairs of openings forms the **trigone of the bladder** — mesodermal in origin (from the absorbed mesonephric duct) but subsequently overgrown/replaced by endoderm, so the adult bladder mucosa is uniformly of endodermal (urothelial) origin.

#### 5. Development of the urinary bladder and urethra

- ▶ Between the 4th and 7th weeks, the **urorectal septum** partitions the cloaca into a ventral **urogenital sinus** and a dorsal **anorectal canal**; the septum's tip forms the **perineal body**.
- ▶ The urogenital sinus has three parts: (i) the upper, largest **vesico-urethral canal** → **urinary bladder**; its apex continues into the allantois as the **urachus**, which obliterates to form the **median umbilical ligament**; (ii) the narrow **pelvic part** → prostatic and membranous urethra in the male, most of the female urethra; (iii) the **phallic part**, pulled ventrally by growth of the genital tubercle → penile urethra in the male, vestibule in the female.
- ▶ Bladder/urethral **epithelium is endodermal** (trigone transiently mesodermal, as above); the surrounding connective tissue and detrusor smooth muscle are derived from **splanchnic mesoderm**. In the male, prostatic buds arise from the endodermal prostatic urethral epithelium at the end of the third month.

#### Applied / Clinical anatomy — congenital anomalies of the urinary system

Congenital anomalies of the kidney and urinary tract are among the **commonest congenital malformations** (~3–6% of live births).

| Site   | Anomaly                                                                       | Basis / feature                                                                                                                                                                                                                                                                                     |
|--------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kidney | <b>Renal agenesis</b><br>(unilateral/bilateral)                               | Ureteric bud fails to induce/contact metanephric mesenchyme; bilateral (~1/10,000 births) → <b>Potter sequence</b> — oligohydramnios, pulmonary hypoplasia, flattened facies, limb deformities; genes: <i>SALL1</i> (Townes–Brocks), <i>PAX2</i> (renal-coloboma), <i>EYA1</i> (branchio-oto-renal) |
| Kidney | <b>Multicystic dysplastic kidney</b>                                          | Ureteric bud fails to branch/ureteric atresia — nephrons fail to form                                                                                                                                                                                                                               |
| Kidney | <b>Polycystic kidney disease</b>                                              | <b>ARPKD</b> (autosomal recessive, ~1/5,000, collecting-duct cysts, presents in infancy) vs <b>ADPKD</b> (autosomal dominant, ~1/500–1,000, cysts in all nephron segments — <i>PKD1/PKD2</i> mutations, presents in adulthood); both are <b>ciliopathies</b>                                        |
| Kidney | <b>Ectopic/pelvic kidney</b>                                                  | Fails to pass through the umbilical-artery fork during ascent                                                                                                                                                                                                                                       |
| Kidney | <b>Horseshoe kidney</b>                                                       | Lower (rarely upper) poles fuse; ascent arrested at the level of the <b>inferior mesenteric artery</b> (~1/600 births)                                                                                                                                                                              |
| Kidney | <b>Pancake kidney; malrotation</b><br>(non-, incomplete- or reverse-rotation) | Fused single mass in the midline; hilum abnormally directed (forward/anteromedial/anterolateral)                                                                                                                                                                                                    |
| Kidney | <b>Duplex kidney/ureter</b>                                                   | Early splitting of the ureteric bud — partial or complete duplication, each with its own pelvicalyceal system; associated with <b>ureterocele</b> , ectopic ureteric insertion and vesico-ureteric reflux                                                                                           |
| Kidney | <b>Wilms tumour</b>                                                           | <i>WT1</i> mutation (11p13); <b>WAGR</b> (Wilms, aniridia, gonadoblastoma, mental retardation) and <b>Denys–Drash</b> (renal failure, ambiguous genitalia, Wilms tumour) syndromes                                                                                                                  |

| Site    | Anomaly                               | Basis / feature                                                                                                                                                                                           |
|---------|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ureter  | Ectopic ureteric orifice              | A second, low-migrating ureteric bud opens abnormally — vagina/urethra/vestibule (female) or seminal vesicle/vas/prostatic urethra (male)                                                                 |
| Ureter  | Retrocaval ureter, hydroureter        | Anomaly of IVC development causing kinking; or obstruction (e.g., aberrant renal artery, posterior urethral valve)                                                                                        |
| Bladder | Urachal fistula / cyst / sinus        | Persistence of the allantoic lumen — full-length / mid-segment / upper-segment respectively                                                                                                               |
| Bladder | Exstrophy of the bladder ± epispadias | Failure of infra-umbilical mesenchyme to migrate between the two halves of the cloacal membrane → bladder mucosa exposed on the abdominal wall (~2/10,000); epispadias is a constant accompanying feature |
| Bladder | Cloacal exstrophy                     | More severe body-wall/urorectal-septum defect (~1/30,000) with associated anorectal malformation                                                                                                          |
| Bladder | Hourglass bladder                     | Median constriction dividing the lumen into two compartments                                                                                                                                              |
| Urethra | Hypospadias                           | Incomplete fusion of urethral folds — abnormal ventral urethral opening (glans/shaft/base of penis); relatively common (~3–5/1,000 births)                                                                |
| Urethra | Epispadias                            | Rare dorsal urethral opening (~1/30,000), usually with bladder exstrophy                                                                                                                                  |

### High-yield exam pointers

- ▶ Three kidney systems in cranio-caudal sequence: **pronephros** (cervical, non-functional) → **mesonephros** (thoraco-lumbar, transiently functional) → **metanephros** (sacral, permanent).
- ▶ Kidney has a **dual origin**: ureteric bud → collecting system (pelvis, calyces, collecting ducts); metanephric mesenchyme → nephron (Bowman capsule to DCT).
- ▶ Key inductive genes: **WT1**, **GDNF/RET**, **HGF/MET**, **FGF2/BMP7**, **WNT9B/WNT6** → **PAX2/WNT4**.
- ▶ ~1 million nephrons/kidney at birth; urine formation from the **12th week**; nephrons never increase in number after birth.

- ▶ Kidney ascends and rotates 90° medially; blood supply changes serially (persistence of lower vessels = accessory renal arteries).
- ▶ **Trigone of the bladder is mesodermal** (absorbed mesonephric duct) though the adult mucosa is endodermal throughout.
- ▶ Urorectal septum divides cloaca into urogenital sinus (bladder + urethra) and anorectal canal; urachus = obliterated allantois → median umbilical ligament.
- ▶ Bilateral renal agenesis → **Potter sequence**; horseshoe kidney is arrested by the **inferior mesenteric artery**; ADPKD/ARPKD are **ciliopathies**.
- ▶ Bladder exstrophy = failure of infra-umbilical mesenchymal migration; always check for accompanying **epispadias**.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; BD Chaurasia — Human Anatomy Vol 2, 8e.



## Describe the microscopic structure of endometrium of uterus at different phases of menstrual cycle, co-relate the changes with hormones involved?

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The endometrium is the mucosal (innermost) coat of the uterine wall, lying internal to the myometrium and composed of a simple columnar surface epithelium, simple tubular uterine glands, and a highly cellular vascular stroma. Unlike any other mucosa in the body, it undergoes a reproducible cycle of proliferation, secretory transformation and partial shedding roughly every 28 days from menarche to menopause. This cyclicity is not autonomous — it is driven, phase by phase, by the sequential output of the hypothalamo-pituitary-ovarian (HPO) axis: rising **oestrogen** from the growing follicle rebuilds the endometrium (proliferative phase), **progesterone** from the corpus luteum matures it for implantation (secretory phase), and withdrawal of both hormones on corpus luteal regression causes it to break down and slough (menstrual phase).

### 1. General microscopic architecture of the endometrium

- ▶ **Surface epithelium:** simple columnar; in the reproductive years it comprises a mixture of ciliated cells and non-ciliated secretory ("peg") cells (before puberty the epithelium is ciliated and cuboidal).
- ▶ **Uterine glands:** simple tubular glands that invaginate from the surface, run perpendicular to it, and penetrate the full thickness of the endometrium down to the myometrium; lined by the same columnar cell types, secreting glycoproteins and glycogen.
- ▶ **Endometrial stroma (lamina propria):** a highly cellular, mesenchyme-like connective tissue rich in ground substance and fine (type III) collagen, with abundant fibroblast-like stromal cells,

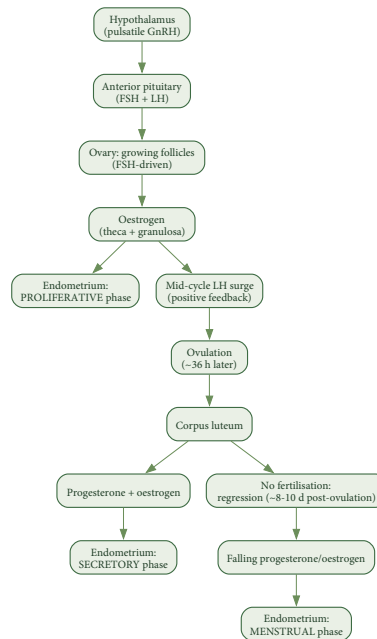


blood vessels, lymphatics and nerves; there is **no submucosa or muscularis mucosae** separating endometrium from myometrium.

- ▶ **Two functional zones**, present from puberty onward:
  - **Stratum basale** — deep, adjacent to the myometrium; contains the basal ends of the glands; hormonally quiescent and **not shed**; the regenerative reservoir for each new cycle.
  - **Stratum functionale** — superficial, hormone-responsive layer that thickens, secretes and is shed each cycle. Just before menstruation it can itself be resolved into an outer **stratum compactum** (gland necks, decidualised stroma) and an inner **stratum spongiosum** (dilated, tortuous gland bodies with scanty interglandular stroma).
- ▶ **Vascular supply** (basis of cyclical change): uterine artery → **arcuate arteries** (myometrium) → **radial arteries** → two terminal sets — **straight (basal) arteries**, short and hormone-insensitive, supplying only the stratum basale; and **spiral arteries**, long, coiled and highly sensitive to oestrogen/progesterone, supplying the stratum functionale.

## 2. Hypothalamo-pituitary-ovarian axis — the hormonal driver

- ▶ **Hypothalamus** secretes **GnRH** in a pulsatile fashion, stimulating the anterior pituitary.
- ▶ **Anterior pituitary** gonadotropins: **FSH** drives growth of a cohort of ovarian follicles and stimulates oestrogen synthesis (theca interna produces androstenedione, aromatised to oestradiol by granulosa cells); **LH** converts the dominant follicle into the corpus luteum after ovulation and drives its progesterone secretion.
- ▶ Rising oestrogen from the maturing follicle exerts positive feedback on the pituitary/hypothalamus around mid-cycle, producing the **LH surge**; ovulation follows about **36 hours** after this surge.
- ▶ After ovulation, the corpus luteum secretes **progesterone and oestrogen**; if fertilisation does not occur it regresses (beginning ~8–10 days after ovulation, ceasing to function by ~12–14 days), and falling steroid levels precipitate menstruation. If implantation occurs, trophoblastic hCG rescues the corpus luteum.



Describe the microscopic structure of endometrium of uterus at different phases of menstrual cycle, co-relate the changes with hormones involved?

### 3. Proliferative phase (days ~5–14) — oestrogen-driven

- ▶ Begins even before menstrual flow has fully ceased: epithelium surviving in the basal stumps of glands spreads to re-cover the denuded surface, complete by 5–6 days after the onset of bleeding.
- ▶ **Glands:** straight, narrow, tubular, with scanty or absent secretion; lining cells short columnar, mitotically active.
- ▶ **Stroma:** dense, highly cellular, spindle-shaped fibroblasts with frequent mitoses; scattered lymphocytes; minimal oedema.
- ▶ **Spiral arteries:** lengthen in parallel with the growing endometrium but remain only slightly coiled, confined to the basal two-thirds of the functionalis.
- ▶ **Thickness:** increases from ~1–2 mm just after menstruation to ~2–3 mm by the end of the phase (around ovulation).
- ▶ **Hormone correlation:** driven entirely by **oestrogen** from the cohort of growing follicles (FSH-dependent); oestrogen acts on both epithelial and stromal receptors to stimulate mitosis and gland/stromal regeneration.

### 4. Secretory phase (days ~15–28) — progesterone-driven

- ▶ Begins after ovulation under the influence of **progesterone** (with continuing oestrogen) from the corpus luteum; the first morphological effects appear 24–36 hours after ovulation.
- ▶ **Early secretory:** glycogen accumulates as sub-nuclear vacuoles in the basal cytoplasm of glandular epithelial cells, with nuclei displaced centrally.
- ▶ **Mid-secretory** (peak ~6 days post-ovulation): glycogen/mucus is transferred to the apical cytoplasm and released into gland lumina; glands become tortuous, dilated and closely packed, giving the classic **corkscrew/"saw-tooth"** profile in section. Endometrial thickness reaches its **maximum** (~5–6 mm).

- ▶ **Stroma:** progressively oedematous; in the late secretory phase peri-vascular stromal cells enlarge, accumulate glycogen/lipid and round up — the **decidual (pseudodecidual) reaction**.
- ▶ **Spiral arteries:** continue to coil and now extend almost to the surface epithelium, developing superficial dilated, thin-walled vascular lacunae.
- ▶ **Implantation:** if fertilisation has occurred, the blastocyst reaches the uterine cavity by ~5 days and begins attaching/invading the endometrium by ~7 days after fertilisation, when secretory transformation is optimal for nutrition and implantation.
- ▶ **Hormone correlation:** progesterone (LH/corpus-luteum dependent) is the dominant driver, converting the oestrogen-primed proliferative endometrium into a secretory, implantation-ready tissue; progesterone also suppresses strong myometrial contractions that could dislodge an implanting blastocyst.

## 5. Menstrual phase (days ~1–4/5) — hormone withdrawal

- ▶ Triggered by regression of the corpus luteum in the absence of fertilisation, with falling **progesterone and oestrogen**.
- ▶ Just before flow begins, three layers are still distinguishable — stratum compactum (superficial, gland necks, decidualised), stratum spongiosum (tortuous glands, scant stroma) and stratum basale (deep, unaltered).
- ▶ **Vascular event:** intermittent then sustained constriction of the spiral arteries produces ischaemia of the functionalis; local prostaglandin release intensifies vasoconstriction; hypoxic cells release cytokines that recruit leukocytes bearing collagenase/matrix metalloproteinases, degrading the stromal matrix.
- ▶ **Shedding:** the surface epithelium, most of each gland, the stroma and blood-filled lacunae of the stratum functionale detach piecemeal — typically **65–75% of endometrial thickness** — and pass with escaping blood as the **menstrual flow**, usually lasting **3–6 days** (commonly quoted as 3–5 days), with an average blood loss of about **35–50 mL**.
- ▶ The **stratum basale**, supplied by the hormone-insensitive straight arteries, is unaffected and immediately begins re-epithelialising the surface, initiating the next proliferative phase.
- ▶ **Hormone correlation:** this is purely a consequence of steroid **withdrawal** — no new hormone acts here; it is the fall in progesterone (and oestrogen) that removes the trophic/anti-contractile support of the functionalis.

## 6. Comparative summary — phase-wise correlation with hormones

| Feature                     | Proliferative           | Secretory                  | Menstrual                     |
|-----------------------------|-------------------------|----------------------------|-------------------------------|
| Approx. cycle days          | 5–14                    | 15–28                      | 1–4/5                         |
| Driving ovarian hormone     | Oestrogen               | Progesterone (+ oestrogen) | Withdrawal of both            |
| Pituitary/ovarian correlate | FSH → growing follicles | LH → corpus luteum         | Corpus luteal regression      |
| Endometrial thickness       | ~1–2 → 2–3 mm           | ~5–6 mm (maximum)          | Reduced to thin basal remnant |

| Feature         | Proliferative                      | Secretory                                              | Menstrual                             |
|-----------------|------------------------------------|--------------------------------------------------------|---------------------------------------|
| Glands          | Straight, narrow, scanty secretion | Coiled, "saw-tooth"/corkscrew, glycogen-rich secretion | Disintegrating, collapsing            |
| Stroma          | Compact, highly cellular, mitotic  | Oedematous → decidual reaction                         | Necrotic, leukocyte-infiltrated       |
| Spiral arteries | Slightly coiled, basal two-thirds  | Markedly coiled, near surface                          | Intermittent constriction → ischaemia |
| Key event       | Re-epithelialisation & growth      | Implantation-readiness                                 | Piecemeal shedding of functionalis    |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a vertical block schematic of the endometrium (uterine cavity above, myometrium below) and label:

- ▶ Surface (luminal) simple columnar epithelium
- ▶ Uterine gland (straight in proliferative / coiled "saw-tooth" in secretory / disintegrating in menstrual — draw as three side-by-side panels)
- ▶ Endometrial stroma
- ▶ Stratum compactum (superficial) and stratum spongiosum (middle) — together forming the stratum functionale
- ▶ Stratum basale (deep, adjoining myometrium)
- ▶ Myometrium
- ▶ Uterine artery → arcuate artery → radial artery
- ▶ Straight (basal) artery — ends in stratum basale
- ▶ Spiral (coiled) artery — extends through stratum functionale, nearly to the surface in the secretory phase

□ Fig 23.17 — Photomicrographs of the uterine lining in proliferative, secretory, and menstrual phases of the menstrual cycle (Ross Histology — A Text and Atlas — 7e, p.871)

### Applied / Clinical anatomy

- ▶ **Endometrial biopsy/dating:** the day-specific gland and stromal appearance (gland shape, secretory content, degree of decidual change) allows histological "dating" of a biopsy against the expected cycle day — used in infertility work-up to assess ovulation and luteal-phase adequacy.
- ▶ **Anovulatory cycles/dysfunctional uterine bleeding:** without ovulation no corpus luteum forms; the endometrium remains under unopposed, persistent oestrogenic drive, staying in a proliferative pattern that eventually breaks down irregularly, producing dysfunctional uterine bleeding.

- ▶ **Unopposed oestrogen and hyperplasia:** prolonged oestrogenic stimulation unbalanced by progesterone (anovulation, oestrogen-secreting tumours, oestrogen-only replacement therapy) predisposes to endometrial hyperplasia, a recognised precursor of endometrioid carcinoma.
- ▶ **Asherman syndrome:** aggressive curettage or post-partum infection destroying the stratum basale abolishes the regenerative reservoir, causing intrauterine adhesions/synechiae and secondary amenorrhoea or infertility.
- ▶ **Endometriosis:** retrograde menstrual reflux can implant endometrial glands and stroma ectopically (ovary, pouch of Douglas, tubes); these deposits continue to respond cyclically to oestrogen/progesterone, producing cyclical pain, adhesions and infertility.
- ▶ **Ectopic (tubal) pregnancy:** the tubal lamina propria can mount a decidual-type reaction similar to the endometrium, but the tube cannot expand to accommodate a growing embryo and ruptures, causing haemorrhage.
- ▶ **Imaging correlate:** transvaginal ultrasound/MRI shows a "triple-line" endometrium (echogenic mid-line, hypoechoic functionalis, echogenic basalis) in the late proliferative phase, becoming uniformly hyperechoic in the secretory phase — used to estimate cycle day and assess endometrial receptivity before assisted reproduction.
- ▶ **Hormonal contraception:** exogenous progestogens keep the endometrium thin and non-proliferative (decidualised/atrophic glands), while combined pills suppress the natural FSH/LH-driven cyclicity described above.

### High-yield exam pointers

- ▶ Endometrium = surface columnar epithelium + tubular uterine glands + cellular vascular stroma; no submucosa separates it from the myometrium.
- ▶ Two functional zones: **stratum functionale** (shed each cycle; further split premenstrually into compactum + spongiosum) and **stratum basale** (permanent, regenerative).
- ▶ Vascular basis of cyclicity: straight arteries → basale (hormone-insensitive); spiral arteries → functionale (oestrogen/progesterone-sensitive; their constriction triggers menstruation).
- ▶ **Proliferative phase** (day 5–14): oestrogen from growing follicles (FSH-driven); straight narrow glands; ~2–3 mm thick by ovulation.
- ▶ **Secretory phase** (day 15–28): progesterone from corpus luteum (LH-driven); coiled/"saw-tooth" secretory glands, decidual reaction; maximum thickness ~5–6 mm; optimal window for implantation.
- ▶ **Menstrual phase:** withdrawal of progesterone/oestrogen on corpus luteal regression → spiral artery vasoconstriction → ischaemia → shedding of ~65–75% of endometrial thickness over 3–6 days (~35–50 mL blood loss).
- ▶ **Mid-cycle LH surge** (positive-feedback response to peak oestrogen) triggers ovulation ~36 hours later — the pivot between proliferative and secretory phases.
- ▶ Classic applied correlates: endometrial dating biopsy, anovulatory DUB, Asherman syndrome, endometriosis, unopposed-oestrogen hyperplasia.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Junqueira's Basic Histology (Text & Atlas) 17e; Ross Histology — A Text and Atlas 7e; IB Singh Textbook of Human Histology 9e; Sontakke Textbook of Human Histology 2e.



## Describe urachal fistula, cyst & sinus

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The urachus is the fibrous, obliterated remnant of the intra-embryonic allantois that runs from the apex of the urinary bladder to the umbilicus, deep to the linea alba; in the adult it is renamed the **median umbilical ligament** and raises the median umbilical peritoneal fold. When the lumen of the allantois/urachus fails to obliterate completely — at one end, in the middle, or throughout — a urine-filled or mucus-filled tract or cyst results. Depending on the level at which patency persists, four **urachal anomalies** are described: patent urachus (**urachal fistula**), **urachal sinus**, **vesicourachal diverticulum**, and **urachal cyst**. They present with umbilical urine leakage, recurrent umbilical discharge/infection, or a peri-umbilical/suprapubic mass, and are important because a retained epithelial lumen can rarely undergo malignant change.

### 1. Embryological development of the urachus

- ▶ The **allantois** (allantoenteric diverticulum) appears around the **16th day** of development as a small endodermal diverticulum from the posterior/caudal wall of the yolk sac (primitive hindgut), extending into the connecting stalk; in humans it is vestigial and does not function as an excretory reservoir as it does in lower vertebrates.
- ▶ The **cloaca** is the expanded terminal part of the hindgut that receives the allantois ventrally and is closed externally by the cloacal membrane.
- ▶ Mesenchyme proliferating at the angle between the hindgut and the allantois forms the **urorectal septum** (intercloacal mesenchyme), which grows caudally between the fourth and sixth weeks and partitions the cloaca into a dorsal **anorectal canal** and a ventral **urogenital sinus**; simultaneously the allantois and the presumptive bladder apex regress.
- ▶ The cranial (vesical) part of the urogenital sinus becomes the **vesico-urethral canal**, which forms the bulk of the bladder and (proximal) urethra; its apex is drawn out into a narrow tube — the **urachus** — that connects the bladder apex to the umbilicus.
- ▶ The **extra-embryonic** portion of the allantois degenerates by the second month of intra-uterine life; the **intra-embryonic** portion is progressively incorporated into the apex of the enlarging bladder, while the remaining distal segment condenses into a solid fibromuscular cord.
- ▶ Normally the lumen obliterates (closure is usually complete by about 32 weeks of gestation) so that, after birth, the urachus persists only as the **median umbilical ligament** — a fibrous band about 5 cm long and 1 cm wide, ascending in the extraperitoneal (subperitoneal) fat from the bladder dome to the umbilicus, covered by peritoneum as the median umbilical fold.

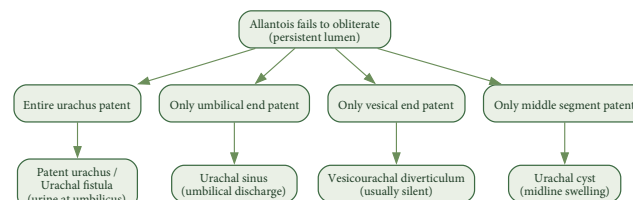
- A remnant of the urachal lumen, however, may persist into infancy/adult life; in roughly half of such cases the residual lumen still communicates with the bladder cavity — the substrate for the anomalies described below.

## 2. Classification of urachal anomalies

Failure of obliteration at different levels of the urachus produces four distinct lesions:

| Type                                    | Segment that remains patent                       | Communication                                                         | Typical presentation                                                                                              |
|-----------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Patent urachus / urachal fistula        | Entire length (umbilicus to bladder)              | Umbilicus and bladder both open                                       | Continuous or intermittent <b>dribbling of urine from the umbilicus</b> , worse on crying/straining               |
| Urachal sinus (umbilical urachal sinus) | Proximal (umbilical) end only                     | Open at umbilicus; blind superiorly, may or may not reach the bladder | Chronic mucoid/serous <b>umbilical discharge</b> , recurrent peri-umbilical infection/granuloma                   |
| Vesicourachal diverticulum              | Distal (vesical) end only                         | Open into the bladder lumen; blind superiorly                         | Usually <b>asymptomatic</b> ; occasionally urinary stasis, infection or stone formation in the diverticulum       |
| Urachal cyst                            | Intermediate segment only (both ends obliterated) | No communication with either umbilicus or bladder                     | Clinically silent <b>midline infra-umbilical cystic swelling</b> until it becomes infected, enlarges, or ruptures |

- The **urachal cyst** is the most common of the four anomalies; the classical site is the **upper (umbilical) end** of the urachus, just inferior to the umbilicus.
- Because the residual lumen is lined by transitional/glandular epithelium capable of secretory activity, an isolated patent segment distends into a cystic cavity — this is the mechanism of both the sinus and the cyst.
- All four lesions lie in the midline, deep to the linea alba, in the properitoneal/subperitoneal fat between the transversalis fascia and the parietal peritoneum, in the line of the median umbilical fold.



Describe urachal fistula, cyst & sinus

□ Fig 15.15 — Fate of the Allantois Normally, the allantois becomes occluded to form (Larsen — Human Embryology — 6e, p.943)



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A midline sagittal schematic of the anterior abdominal wall, umbilicus, and bladder, drawn four times side by side (A–D), labelling:

- ▶ **Umbilicus** (superior end) and **apex of urinary bladder** (inferior end), joined by the **urachus**
- ▶ **A — Patent urachus/urachal fistula:** entire tract shown open, with an arrow showing urine flow from bladder to umbilicus
- ▶ **B — Urachal sinus:** only the upper (umbilical) segment shown as a blind, open pouch at the umbilicus; rest of the tract solid/fibrosed
- ▶ **C — Vesicourachal diverticulum:** only the lower (vesical) segment shown as a blind outpouching from the bladder dome; rest of the tract solid
- ▶ **D — Urachal cyst:** only the middle segment shown as an isolated fluid-filled cavity, with both the umbilical and vesical ends fibrosed
- ▶ Label the fibrosed (obliterated) urachus in the normal adult as the **median umbilical ligament**, and show the **median umbilical peritoneal fold** raised over it

**3. Histological basis**

- ▶ The urachal lumen, where it persists, is lined predominantly by **transitional epithelium (urothelium)** near the bladder end, which may show columnar/glandular metaplasia more distally.
- ▶ The wall contains longitudinal smooth muscle fibres continuous with the detrusor of the bladder, becoming progressively more fibrous towards the umbilical end — this is why the normal adult ligament is a solid fibromuscular cord rather than a patent tube.
- ▶ Persistent secretory (glandular) epithelium in an isolated cystic or sinus segment accounts for the mucoid/serous discharge and cystic distension seen clinically.

**Applied / Clinical anatomy**

- ▶ **Surface marking:** the median umbilical ligament (obliterated urachus) lies in the midline of the anterior abdominal wall, deep to the linea alba, extending from the umbilicus to the pubic symphysis/bladder apex; it raises the **median umbilical fold** of peritoneum, flanked laterally by the two medial umbilical folds (over the obliterated umbilical arteries).
- ▶ **Patent urachus:** presents in the neonatal period as continuous wetness/urine leakage from the umbilical stump, accentuated by crying or straining (raised intra-abdominal pressure); confirmed by sinography/fistulogram, voiding cystourethrogram, or instillation of methylene blue into the bladder with appearance at the umbilicus.
- ▶ **Urachal sinus and urachal cyst:** often present later in childhood or adult life with recurrent peri-umbilical discharge/infection (sinus) or a tender midline infra-umbilical/suprapubic mass if the cyst becomes infected; an inflamed low-lying urachal cyst can mimic acute appendicitis.
- ▶ **Imaging:** ultrasonography or CT shows a midline cystic or tubular tract between the umbilicus and the bladder dome; a urachal cyst may calcify and be mistaken for a neoplasm.

- ▶ **Malignant potential:** chronic irritation of retained, glandular-metaplastic urachal epithelium is a recognised (though rare) source of **urachal adenocarcinoma**, typically a mucinous adenocarcinoma arising at the bladder dome in adults — hence the surgical principle of excising the entire tract.
- ▶ **Fetal physiological role:** rarely, in fetal urethral atresia causing complete lower urinary tract obstruction, a patent urachus can act as a "pop-off" fistula decompressing the obstructed bladder into the amniotic cavity, preserving amniotic fluid volume and thereby normal pulmonary and renal development — an unusual life-saving natural anomaly.
- ▶ **Associated anomalies:** severe failure of closure/partitioning in this region (abnormal cloacal membrane breakdown, deficient lateral body-wall fold fusion) underlies the related spectrum of **exstrophy of the bladder** and **exstrophy of the cloaca**, in which the urachal defect coexists with epispadias and, in cloacal exstrophy, ano-rectal malformation.
- ▶ **Treatment principle:** symptomatic anomalies (fistula, infected sinus/cyst, diverticulum with stasis or calculus) require complete surgical excision of the urachal tract together with a cuff of the bladder dome, to relieve symptoms and eliminate the risk of later malignant transformation; small, asymptomatic remnants discovered incidentally may simply be observed.

### High-yield exam pointers

- ▶ Urachus = obliterated remnant of the **intra-embryonic allantois**, connecting bladder apex to umbilicus; adult name = **median umbilical ligament**; raises the median umbilical peritoneal fold.
- ▶ Allantois appears at ~day 16 from the caudal wall of the yolk sac/hindgut, extending into the connecting stalk; vestigial in humans.
- ▶ Urorectal septum partitions the cloaca into urogenital sinus + anorectal canal between the 4th and 6th weeks; the vesico-urethral canal's tapering apex becomes the urachus.
- ▶ **Four anomalies**, by level of persistent patency: **fistula** (entire tract), **sinus** (umbilical end only), **vesicourachal diverticulum** (vesical end only), **cyst** (middle segment only).
- ▶ Urachal cyst is the commonest anomaly; classic site is just below the umbilicus.
- ▶ Urachal fistula = classic sign is **urine dribbling from the umbilicus**, worsened by straining.
- ▶ ~50% of persistent infantile urachal remnants communicate with the bladder.
- ▶ Retained glandular urachal epithelium can (rarely) transform into **urachal adenocarcinoma** at the bladder dome — hence complete surgical excision is preferred over simple drainage.
- ▶ Related developmental spectrum: bladder/cloacal exstrophy, epispadias (failure of lateral body-wall fold fusion/cloacal membrane breakdown).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Larsen Human Embryology 6e; Vishram Singh Textbook of Anatomy Vol 2 4e; Vishram Singh Textbook of Clinical Embryology; BD Chaurasia Human Anatomy Vol 2 8e.



## Development and anomalies of Vagina

*Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The vagina is the fibromuscular birth canal connecting the cervix to the vestibule. It has a classical **dual embryological origin**: the upper part develops from the fused caudal ends of the **paramesonephric (Müllerian) ducts** (uterovaginal canal/primordium), while the lower part and the hymen develop from an endodermal outgrowth of the **urogenital sinus**, the **sinovaginal bulbs**, which proliferate to form the solid **vaginal plate** that later canalises. Because vaginal development is intimately linked to fusion of the paramesonephric ducts, most congenital vaginal anomalies occur together with uterine anomalies.

### 1. Normal development — sequence of events

- ▶ **5th–6th week:** Paramesonephric (Müllerian) ducts arise as longitudinal invaginations of the coelomic epithelium lateral to the mesonephric ridge, guided medially by the mesonephric duct.
- ▶ **8th week onward:** Each paramesonephric duct grows caudally, crosses ventral to the mesonephric duct, and meets its fellow in the midline in the genital cord.
- ▶ **3rd month:** The two ducts fuse in a cranio-caudal ("zippering") direction; their fused caudal (vertical) parts form the **uterovaginal primordium/canal**, which gives rise to the fundus and body of the uterus and the upper vagina. The unfused cranial parts remain as the two uterine tubes.
- ▶ The fused ducts meet the dorsal wall of the urogenital sinus and produce a midline endodermal elevation, the **Müllerian (sinus) tubercle**.
- ▶ **~60 mm CRL (~9th week):** The endoderm on either side of the sinus tubercle proliferates as paired **sinovaginal bulbs**, which fuse and grow cranially as a solid, antero-posteriorly flattened **vaginal plate**, lying within the fibromuscular condensation of the uterovaginal primordium.
- ▶ **3rd–5th month:** The vaginal plate elongates cranially, pushing the uterus further from the urogenital sinus; canalisation proceeds caudo-cranially as the central cells desquamate, establishing the vaginal lumen. By the 5th month canalisation is essentially complete.
- ▶ The cranial end of the canalised plate expands around the cervix and is excavated to form the **vaginal fornices** (of paramesonephric origin).
- ▶ The junction between the vagina and the urogenital sinus is marked by a thin endodermal/vaginal membrane, the **hymen**, which usually perforates centrally in the perinatal period.
- ▶ **Tissue contribution (classical view; texts vary on the exact fraction — BD Chaurasia gives upper one-third: uterovaginal canal, lower two-thirds + fornices: sinovaginal bulb/vaginal plate):** fibromuscular wall — mesenchyme around the paramesonephric ducts; vaginal epithelium — largely the sinovaginal-bulb-derived vaginal plate (endoderm), with the paramesonephric contribution restricted to the fornices. Newer studies (Kurita 2010, 2011, cited in Gray's) suggest the entire adult vaginal epithelium may in fact derive from the endodermal vaginal plate, the paramesonephric mesenchyme contributing only to the muscular coat — the precise epithelial fusion boundary is still debated.

- Hormonal control: **oestrogen** drives paramesonephric duct differentiation into uterine tubes, uterus, cervix and upper vagina, and also promotes formation of the lower vagina and external genitalia from the urogenital sinus/genital folds.
- **Neonate:** vagina is 2.5–3.5 cm long, 1.5 cm wide at the fornices; the cervix projects about 1 cm into it; the posterior wall is longer than the anterior, giving the vagina its characteristic curve.

□ Fig 21.9 — Development of uterus and vagina. Paramesonephric ducts (müllerian ducts) grow caudally, fuse and form uterus and part of vagina; sinovaginal bulbs proliferate from the urogenital sinus to form the vaginal plate, which canalises to form the lower vagina (Sontakke — Textbook of Human Embryology, p.232)

## 2. Related structures and homologues

| Embryonic structure                                                          | Female derivative                                                              |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Paramesonephric (Müllerian) duct — cranial vertical part                     | Uterine tube (fimbriae = coelomic opening)                                     |
| Paramesonephric duct — fused caudal vertical parts (uterovaginal primordium) | Body/fundus of uterus, upper vagina, fornices                                  |
| Sinovaginal bulbs / vaginal plate (urogenital sinus endoderm)                | Lower vagina, hymen                                                            |
| Mesonephric duct — cranial remnant                                           | Epoophoron                                                                     |
| Mesonephric duct — caudal remnant                                            | Duct of Gartner (may form Gartner's cyst in the lateral vaginal/cervical wall) |
| Genital tubercle, urogenital folds/swellings                                 | Clitoris, labia minora/majora, vestibule (definitive urogenital sinus)         |

## 3. Congenital anomalies of the vagina

(a) **Vaginal agenesis** — absence of the vagina, due to failure of the sinovaginal bulbs to form/fuse into a vaginal plate; almost always accompanied by absence/hypoplasia of the uterus and uterine tubes because the developing uterovaginal primordium normally induces sinovaginal bulb formation.

- When associated with other Müllerian duct anomalies, rudimentary uterine cornua, and **renal agenesis**, with morphologically normal ovaries and Fallopian tubes lying on the pelvic side wall, this constitutes the **Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome** — presents with primary amenorrhoea in an otherwise normally virilised female (normal secondary sexual characters, 46,XX karyotype).

(b) **Vaginal atresia (imperforate vagina)** — failure of canalisation of the vaginal plate; a fibrous cord replaces the lumen.

- **Transverse vaginal septum** — partial failure of canalisation, typically at the junction of the middle and upper thirds of the vagina; presents at puberty with primary amenorrhoea and cyclical pain from retained menstrual blood (**haematocolpos**, and if the uterus also distends, **haematometocolpos**).

(c) **Imperforate hymen** — failure of the central cells of the hymenal membrane (junction of vaginal plate and urogenital sinus) to break down/perforate; obstructs menstrual outflow at puberty, causing haematocolpos, and may distend as a bluish bulging membrane at the introitus.

(d) **Septate (double) vagina** — incomplete fusion, or persistence of the septum between, the caudal paramesonephric ducts/sinovaginal bulbs; produces a longitudinal (sagittal) septum dividing the vagina partially or completely into two canals. Usually associated with duplication of the uterus (**uterus didelphys with double vagina**) as both ductal systems fail to fuse throughout their length.

(e) **Anomalies secondary to paramesonephric duct fusion defects** (Fig. 72.15 of Gray's Anatomy) — because the vagina develops in continuity with the fused ducts, uterine fusion anomalies commonly carry a vaginal component:

- ▶ **Uterus didelphys with double vagina** — complete failure of fusion of both ducts and their vaginal contributions.
- ▶ **Bicornuate uterus (bicornis unicollis)** — two uterine horns, one cervix, one vagina.
- ▶ **Uterus bicornis unicollis with rudimentary horn** — unilateral atresia; the rudimentary horn's lumen usually does not communicate with the vagina, so menstrual blood/pregnancy products may become trapped (haematometra in the blind horn).
- ▶ **Septate uterus (arcuatus/septus)** with septate vagina — failure of resorption of the uterovaginal septum after the ducts have fused.

(f) **Fistulae** — abnormal communication of the vaginal canal with adjacent structures: **recto-vaginal fistula** (posterior wall, related to abnormal cloacal partitioning) and **vesico-vaginal fistula** (anterior wall).

(g) **Persistent cloaca** — failure of normal urorectal septation so that the rectum, vagina and urethra open into a single common perineal channel (length 1–7 cm); a severe anorectal/urogenital malformation, usually detected at birth.

(h) **Duct remnant lesions** — **Gartner's duct cyst** in the antero-lateral vaginal wall from a persistent mesonephric duct remnant.



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw the coronal/sagittal scheme of uterovaginal development with labels: **mesonephric duct**, **paramesonephric (Müllerian) duct**, **fused caudal ducts (uterovaginal primordium/canal)**, **Müllerian (sinus) tubercle**, **urogenital sinus**, **sinovaginal bulbs**, **solid vaginal plate**, **canalised vaginal lumen**, **vaginal fornices**, **hymen**. Alongside, sketch the standard anomaly panel (as in Fig. 72.15, Gray's Anatomy): normal uterus/vagina; uterus didelphys with double vagina; bicornuate uterus with single vagina; septate uterus; unicornuate uterus with rudimentary horn; septate vagina.

□ Fig 21.10 — Congenital anomalies of uterus (illustrating didelphys, bicornuate, septate and unicornuate patterns, the classical anomaly spectrum that carries vaginal fusion/septation defects) (Sontakke — Textbook of Human Embryology, p.233)

**Applied / Clinical anatomy**

- ▶ **Primary amenorrhoea work-up:** vaginal agenesis (MRKH), imperforate hymen and transverse vaginal septum are the classical anatomical causes of primary amenorrhoea with normal secondary sexual characters; distinguished clinically by whether a bulging haematocolpos mass is palpable/visible at the introitus (imperforate hymen/low septum) or not (high septum/agenesis).
- ▶ **MRKH syndrome** — because the Müllerian ducts and metanephric (renal) system develop in close spatiotemporal relation, screen for associated **renal agenesis/ectopia** and skeletal (vertebral) anomalies; ovaries are normal (of separate, non-Müllerian origin), so secondary sexual characters and hormonal function are normal.
- ▶ **Uterus didelphys with double vagina / septate vagina:** may present with dyspareunia, obstructed hemivagina (if one side is also atretic — obstructed hemivagina with ipsilateral renal anomaly), or be an incidental finding on speculum/imaging; often coexists with a longitudinal vaginal septum that can be surgically excised.
- ▶ **Imaging:** transvaginal/transabdominal ultrasound and MRI are used to define the uterovaginal anomaly (fundal contour, septum, cervix number) before surgical correction; MRI is the gold standard for complex Müllerian anomalies.
- ▶ **Gartner's duct cyst** — an anterolateral vaginal wall swelling from mesonephric remnants; must be differentiated from a cystocele or urethral diverticulum on examination.
- ▶ **Surgical correlation:** knowledge of the sinovaginal (endodermal, lower) versus paramesonephric (mesodermal, upper) contribution guides reconstructive vaginoplasty (e.g., McIndoe vaginoplasty for agenesis) and septum resection.
- ▶ **Persistent cloaca and recto-/vesico-vaginal fistula** are managed by paediatric surgeons; anatomical severity (common channel length) determines surgical approach.

**High-yield exam pointers**

- ▶ Vagina has a **dual origin**: upper part from the fused **paramesonephric ducts** (uterovaginal canal/primordium — mesodermal contribution + fornices), lower part from the **sinovaginal bulbs** of the **urogenital sinus** (endodermal vaginal plate).
- ▶ **Sinus/Müllerian tubercle** = site of union of paramesonephric ducts with the urogenital sinus and origin of the sinovaginal bulbs; marks the future hymen.

- ▶ **Vaginal plate** is initially solid; canalises caudo-cranially by desquamation of central cells, essentially complete by the 5th month.
- ▶ **Vaginal agenesis** = failed sinovaginal bulb formation → also absent uterus (uterus induces the bulbs); with renal agenesis + rudimentary cornua = **MRKH syndrome**.
- ▶ **Vaginal atresia** = failed canalisation of the vaginal plate; **transverse vaginal septum** = partial atresia, classically at junction of middle and upper thirds.
- ▶ **Imperforate hymen** = failure of the hymenal membrane to perforate → haematocolpos at puberty.
- ▶ **Septate/double vagina** = failure of fusion of paired sinovaginal bulbs/caudal ducts → usually with uterus didelphys.
- ▶ **Persistent cloaca** = failure of urorectal septation → single common perineal channel for rectum, vagina, urethra.
- ▶ **Gartner's cyst** arises from mesonephric (Wolffian) duct remnants in the antero-lateral vaginal wall — NOT of paramesonephric origin.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; BD Chaurasia Human Anatomy Vol 2 8e; AK Datta Human Anatomy Vol 1 (Thorax & Abdomen); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; Moore The Developing Human 9e. Coverage note: Textbooks disagree on the exact fractional split of the vagina between paramesonephric and urogenital-sinus contribution (BD Chaurasia: upper one-third/lower two-thirds; Sontakke: lower one-fourth from sinus; AK Datta: lower one-sixth from sinus) — the qualitative dual-origin scheme and the evolving evidence for an entirely sinus-derived epithelium (Gray's, citing Kurita 2010/2011) are presented in preference to any single disputed fraction.





## Development of Adrenal Gland

Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The adrenal (suprarenal) gland is embryologically a composite organ formed by the fusion of **two tissues of entirely different origin** that come together within a single mesenchymal capsule: an outer **cortex**, derived from the mesodermal coelomic epithelium, and an inner **medulla**, derived from neuroectodermal neural crest cells. Development begins in the 5th week of intrauterine life in the posterior abdominal wall, opposite the 6th–12th thoracic segments, at the root of the dorsal mesentery — the same region from which the gonad and mesonephros arise. Because cortex and medulla differentiate independently before merging, the adrenal gland is a favourite RGUHS question linking embryology to endocrinology, histology and applied anatomy.

### 1. Dual Embryological Origin — Overview

| Component       | Germ-layer origin | Precursor tissue                                                                                                                  | Structure formed                                                                            |
|-----------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Adrenal cortex  | Mesoderm          | Coelomic (mesothelial) epithelium between the root of the dorsal mesogastrium/mesenter y and the mesonephros ("suprarenal ridge") | Fetal (provisional) cortex → definitive cortex → zona glomerulosa, fasciculata, reticularis |
| Adrenal medulla | Neuroectoderm     | Neural crest cells (from somite levels 18–24, alongside cells forming the adjacent sympathetic ganglia)                           | Chromaffin cells of the medulla                                                             |

Both components arise close together in the 5th week and become invested by a common mesenchymal capsule derived from the mesonephros — hence "one gland, two origins."

### 2. Development of the Adrenal Cortex (Mesodermal Component)

- ▶ In the **5th week**, mesothelial cells of the coelomic epithelium between the root of the dorsal mesentery and the developing gonad/mesonephros proliferate to form a thickening, the **suprarenal ridge**, extending from the 6th to the 12th thoracic segment level.
- ▶ **First wave of proliferation**: large, acidophilic cells detach from the coelomic epithelium and penetrate the underlying mesenchyme, forming the **fetal (provisional) cortex**.
- ▶ **Second wave of proliferation**: shortly afterwards, a further group of smaller cells from the coelomic epithelium surrounds the fetal cortex from outside to form the **definitive (permanent) cortex**. Subcapsular nests of these cells are the rudiment of the **zona glomerulosa**, which sends cords of cells inward between developing capillaries and venous sinusoids.
- ▶ The mesenchymal **capsule** enclosing the cortex (first ventrally, then dorsally) is derived from the adjoining mesonephros; capillaries penetrating the cortex radially arise from adjacent mesonephric arteries.
- ▶ The **fetal cortex** is large and endocrinologically active: from the **second trimester** it secretes **dehydroepiandrosterone (DHEA)**, which is aromatised by the placenta to oestrogen — essential for maintaining pregnancy.

- ▶ **Postnatal zonation:** the **zona fasciculata** differentiates from the definitive (glomerular) cortex around the time of birth; the **zona reticularis** becomes histologically identifiable only in the **third year of life**.
- ▶ **Involution of the fetal cortex:** this begins at birth and is rapid — combined gland weight falls from ~9 g (both glands, term) to ~5 g by 2 weeks and ~4 g by 3 months, with full histological involution of fetal-zone remnants over roughly the first two postnatal years; birth weight is not regained until puberty.

### 3. Development of the Adrenal Medulla (Neuroectodermal Component)

- ▶ Neural crest cells migrating from **somite levels 18–24** (the same population contributing to the neighbouring sympathetic ganglia) invade the **medial aspect of the fetal cortex** during the 5th–6th week, disorganising it dorsomedially.
- ▶ Migration and specification of these cells towards a medullary (chromaffin) fate are directed by signals from the **dorsal aorta**, including BMPs.
- ▶ The invading cells differentiate into **chromaffin cells** — so called because they stain yellow-brown with chrome salts — arranged in cords and clusters that come to lie centrally, surrounded almost completely by the definitive cortex.
- ▶ Functionally, chromaffin cells are **modified postganglionic sympathetic neurons**: unlike ordinary postganglionic neurons, they are innervated directly by **preganglionic sympathetic fibres** (splanchnic nerves) and, on stimulation, release **adrenaline and noradrenaline** directly into the bloodstream rather than at a synapse.
- ▶ During embryonic life chromaffin cells are widely scattered (para-aortic bodies, organ of Zuckerkandl); in the adult, the principal persisting mass is confined to the adrenal medulla.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

embed: ![Fig 25.4 — Development of the adrenal gland: Day 45 (migrating chromaffin cells invading the fetal cortex derived from coelomic epithelium), Day 60 (medulla surrounded by developing definitive cortex), Month 4 (definitive cortex encircling the medulla) (Sontakke — Textbook of Human Embryology, p.285)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/1523e8bf286666b6.jpg)

For hand reproduction, draw the three-stage sequence with these exact labels:

- ▶ **Day 45:** Coelomic epithelium → Foetal cortex → Migrating chromaffin cells
- ▶ **Day 60:** Developing definitive cortex (outer) → Medulla (central, chromaffin cells)
- ▶ **Month 4:** Definitive cortex (encircling) → Medulla (centre)
- ▶ **Final postnatal cross-section** (label outer to inner): Capsule → Zona glomerulosa → Zona fasciculata → Zona reticularis → (degenerating fetal cortex remnant) → Adrenal medulla (chromaffin cells)

**4. Applied / Clinical Anatomy**

- ▶ **Congenital adrenal hyperplasia (CAH):** the commonest developmental anomaly (incidence 1:5000–1:15,000 births); an autosomal recessive deficiency of an adrenocortical steroidogenic enzyme, in **90% of cases 21-hydroxylase**, causes accumulation of 17-hydroxyprogesterone diverted to androgen synthesis. Resulting androgen excess produces external genital masculinisation (clitoral hypertrophy to a phallus/scrotum) in female fetuses — the basis of the **adrenogenital syndrome**; male external genitalia are unaffected in utero, though precocious puberty and accelerated growth may follow.
- ▶ **Adrenal hypoplasia congenita:** an X-linked disorder due to mutation of **DAX1 (NR0B1)**; **SF1 (NR5A1)**, expressed in the common adrenogonadal primordium, similarly regulates adrenocortical and gonadal differentiation — the molecular basis linking adrenal and gonadal development from adjacent coelomic epithelium.
- ▶ **Ectopic/accessory adrenal (cortical) tissue:** rests of cortical tissue may be found fused deep to the kidney capsule, in the right lobe of the liver, or along the line of gonadal descent (near the testis, epididymis, ovary or broad ligament) — a direct consequence of the close embryological proximity of the suprarenal ridge to the developing gonad.
- ▶ **Pheochromocytoma:** a chromaffin-cell tumour causing paroxysmal hypertension, tachycardia and headache from excess catecholamine release; most arise in the adrenal medulla, ~10% at extra-adrenal chromaffin sites; ~25% are familial, including **RET** gene mutations that also govern neural crest cell migration (MEN 2 syndromes).
- ▶ **Neonatal gland size:** relative to body weight the neonatal gland is disproportionately large — 0.2% of body weight versus 0.01% in the adult (a ~20-fold relative difference) — because of the bulky fetal cortex; this underlies the rapid postnatal weight fall described above and is relevant to neonatal adrenal ultrasound and adrenal haemorrhage.

- ▶ **Basis of adult arterial supply:** unlike the kidney, the suprarenal gland develops largely **in place** in the posterior abdominal wall and does not migrate. It is therefore vascularised locally by three separate lateral branches acquired in situ — from the inferior phrenic artery (superior suprarenal), the aorta directly (middle suprarenal), and the renal artery (inferior suprarenal) — explaining the classical triple arterial supply taught in gross anatomy.
- ▶ The gland remains a **retroperitoneal** structure capping the upper pole of the kidney within the renal fascia, consistent with its coelomic-epithelial/mesonephric-mesenchyme origin described above.

### High-yield exam pointers

- ▶ Adrenal gland = **two embryologically distinct tissues** fused within one capsule: cortex (mesoderm) + medulla (neuroectoderm/neural crest).
- ▶ Development starts **5th week**, opposite T6–T12, from coelomic epithelium at the root of the dorsal mesentery near the mesonephros/gonad.
- ▶ **Two waves** of coelomic-epithelial proliferation: 1st → fetal cortex; 2nd → definitive cortex (zona glomerulosa rudiment).
- ▶ Neural crest cells (somite levels 18–24) invade the fetal cortex medially, under dorsal-aortic BMP signalling, to form chromaffin cells of the medulla.
- ▶ Postnatal cortical zonation sequence: zona glomerulosa earliest → zona fasciculata at birth → zona reticularis by the **3rd year**.
- ▶ Fetal cortex secretes **DHEA** (2nd trimester) for placental oestrogen synthesis, then undergoes rapid postnatal involution (~9 g → ~5 g by 2 weeks → ~4 g by 3 months).
- ▶ Chromaffin cells are unique — directly innervated by **preganglionic** sympathetic fibres (no synaptic ganglion relay).
- ▶ Clinical correlates: **CAH/21-hydroxylase deficiency** (adrenogenital syndrome), **pheochromocytoma** (RET mutation), **ectopic adrenal tissue**, **DAX1/SF1** gene disorders.
- ▶ Because the gland develops in situ (unlike the ascending kidney), it retains three separate embryonic arterial sources — the basis of the adult superior/middle/inferior suprarenal arteries.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Ross Histology — A Text and Atlas 7e.



## Development of female external genital organs

*Asked in: Paper II Nov 2017 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The external genitalia of both sexes arise from a common set of mesenchymal primordia — the **genital tubercle**, paired **urethral (genital) folds** and paired **genital (labioscrotal) swellings** — that surround the cloacal membrane and are morphologically identical up to about the 7th week (the "indifferent stage"). Female differentiation is the **passive/default pathway**: in the absence of fetal testicular androgen (testosterone/dihydrotestosterone), the same primordia develop with minimal virilising change into the clitoris, labia minora, vestibule and labia majora. Differentiation begins around the 9th week and is complete by the 12th week of gestation.

### Indifferent stage of the external genitalia (weeks 3–7)

- ▶ In the **3rd week**, mesenchyme from the primitive streak migrates around the cloacal membrane to raise a pair of low **cloacal folds**.
- ▶ Cranial to the cloacal membrane the two folds unite in the midline to form the **genital tubercle**.
- ▶ With formation of the **urorectal septum**, the cloacal membrane is subdivided (by the 6th–7th week) into a ventral **urogenital membrane** and a dorsal **anal membrane**; correspondingly, the cloacal folds are subdivided into anterior **urethral (genital) folds** and posterior **anal folds**.
- ▶ A second, more lateral pair of elevations — the **genital (labioscrotal) swellings** — appears on either side of the urethral folds.
- ▶ The urogenital membrane breaks down, opening the urogenital sinus to the exterior and forming a median **urethral groove** flanked by the urethral folds.
- ▶ Up to the 7th week the genitalia of the two sexes are indistinguishable; sex-specific features begin to appear from the **9th week**, and full differentiation is achieved by the **12th week**.

### Hormonal basis of female differentiation

- ▶ Female external genital development does **not require ovarian hormones** — it is the constitutive, default pathway that unfolds whenever the tissues are **not exposed to testicular androgen**. Direct evidence: in **5 $\alpha$ -reductase deficiency** (an XY fetus that cannot convert testosterone to dihydrotestosterone), the external genitalia develop with a female phenotype (enlarged clitoris, small vaginal pouch) despite functioning testes — proving that **5 $\alpha$ -dihydrotestosterone (DHT)**, not testosterone itself, drives masculinisation of the genital tubercle, folds and swellings.
- ▶ (Some texts, e.g. Langman, additionally describe maternal/fetal **oestrogen** as promoting growth of the female primordia; the current consensus, however, is that female differentiation is essentially hormone-independent/"default" rather than oestrogen-driven.)
- ▶ By the **4th month (12th week)**, the female external genitalia become **refractory to androgen** — exogenous or endogenous androgen exposure after this point (e.g. from a virilising maternal tumour) no longer produces labioscrotal fusion, only clitoromegaly.
- ▶ Because the clitoris (**genital tubercle**) is **relatively larger than the male phallus in the early second trimester (and remains conspicuous as late as 18 weeks)**, tubercle length/angle is an unreliable criterion for foetal sexing on early ultrasound and has been a recognised source of sex-misassignment during the third and fourth months of gestation.

### Development of the clitoris (from the genital tubercle)

- ▶ The genital tubercle **elongates only slightly** (unlike the marked elongation that forms the male phallus/penis) and bends caudally to form the **clitoris**.
- ▶ Its mesenchymal core differentiates into the **glans clitoridis** and paired **corpora cavernosa clitoridis** — homologous to the glans penis and corpora cavernosa penis.
- ▶ Because the urethral folds do not fuse over it, the **clitoris does not incorporate a urethra** (unlike the penis).
- ▶ A **prepuce of the clitoris** develops around the glans in the same way as the male foreskin.

### Development of the labia minora, vestibule and vestibular structures (from the urethral folds + urogenital sinus)

- ▶ The paired **urethral folds fail to fuse** across the midline (as they do in the male to enclose the penile urethra); they persist as the **labia minora**, joining only at their posterior ends to form the **frenulum of the labia minora**.
- ▶ The unfused urogenital groove between the labia minora remains open as the **vestibule of the vagina**, into which the urethra and vagina both open — the vestibule itself represents the caudally shortened phallic/pelvic part of the **urogenital sinus**.
- ▶ The paired **bulbs of the vestibule** (erectile tissue flanking the vaginal orifice) develop from the same mesenchyme that forms the **corpus spongiosum/bulb of the penis** in the male.
- ▶ **Greater vestibular (Bartholin's) glands**, opening into the groove between the hymen and labia minora, are the homologues of the male **bulbourethral (Cowper's) glands**.
- ▶ **Para-urethral (Skene's) glands** are the female homologues of the prostatic urethral glands.
- ▶ The **hymen** forms at the junction where the caudal end of the vaginal plate (sinovaginal bulbs) meets the urogenital sinus/vestibule; it is a thin fold that usually perforates partially before birth.

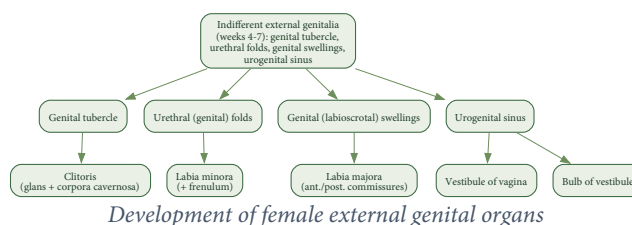
### Development of the labia majora (from the genital/labioscrotal swellings)

- ▶ The paired genital swellings, which in the male fuse in the midline to form the scrotum, **remain unfused** in the female and simply enlarge to form the two **labia majora**.
- ▶ Their anterior ends fuse to form the **anterior labial commissure and mons pubis**; their posterior ends fuse to form the **posterior labial commissure**.
- ▶ The labia majora are the female homologue of the scrotum and, like it, receive the distal end of the **gubernaculum** — here the **round ligament of the uterus (gubernaculum ovarii)** — which terminates just outside the superficial inguinal ring (the potential site of a **canal of Nuck hernia/hydrocele**).

### Homologues of the external genitalia — male vs female

| Indifferent primordium | Male derivative            | Female derivative                              |
|------------------------|----------------------------|------------------------------------------------|
| Genital tubercle       | Glans penis, body of penis | Glans clitoridis, corpora cavernosa clitoridis |

| Indifferent primordium           | Male derivative                         | Female derivative                       |
|----------------------------------|-----------------------------------------|-----------------------------------------|
| Urethral (genital) folds         | Ventral penis (encloses spongy urethra) | Labia minora (unfused)                  |
| Genital (labioscrotal) swellings | Scrotum                                 | Labia majora (unfused)                  |
| Urogenital sinus (phallic part)  | Corpus spongiosum / bulb of penis       | Bulb of vestibule                       |
| Urogenital sinus (pelvic part)   | Prostatic + membranous urethra          | Vestibule of vagina                     |
| Bulbourethral (Cowper's) glands  | Bulbourethral glands                    | Greater vestibular (Bartholin's) glands |
| Urethral/para-urethral glands    | Prostate                                | Para-urethral (Skene's) glands          |
| Sinus (Müllerian) tubercle       | Seminal colliculus                      | Hymen                                   |



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw two panels side by side, labelled "5 months" and "Newborn" (indifferent-to-female transition):

- ▶ Panel 1 (5 months): **genital tubercle, genital swelling, urethral fold, perineum, anal opening.**
- ▶ Panel 2 (newborn): **glans clitoridis (genital tubercle), labia majora (labioscrotal folds), labia minora (urogenital folds), urethral orifice, vaginal orifice, hymen.**
- ▶ Draw arrows from each indifferent-stage label to its corresponding definitive-stage label to show the homology explicitly (this is the exact examiner expectation).

□ Fig 21.16 — Development of female external genitalia (Sontakke — Textbook of Human Embryology, p.236)

### Applied / Clinical anatomy

- ▶ **Disorders of sex development (DSD) / ambiguous genitalia:** because male and female external genitalia arise from identical primordia, errors of hormone exposure produce a spectrum from mild clitoromegaly to a fully male-appearing phallus with labioscrotal fusion.
- ▶ **46,XX DSD:** genetically female infants virilised by excess androgen. **Congenital adrenal hyperplasia (CAH)** is the single commonest cause of ambiguous genitalia overall (~60% of all DSDs); ~90% of CAH is due to **21-hydroxylase deficiency** (autosomal recessive), with excess adrenal androstenedione causing variable clitoromegaly and labioscrotal fold fusion while internal Müllerian structures (uterus, tubes) remain normally female, since the ovaries do not secrete anti-Müllerian hormone.



- ▶ **Ovotesticular DSD** (formerly "true hermaphroditism"): both ovarian and testicular tissue present; genitalia are always ambiguous with a tendency to masculinisation; ~70% have a 46,XX karyotype.
- ▶ **5 $\alpha$ -reductase deficiency** and **androgen insensitivity syndrome** in 46,XY individuals both give female-looking or ambiguous external genitalia despite testes, underscoring that **DHT action**, not chromosomal or gonadal sex, is what drives masculinisation of these primordia.
- ▶ **Female-specific anomalies** described in the corpus: clitoris may be absent, bifid or abnormally enlarged; the labia minora may show partial fusion; the urethra may open onto the anterior vaginal wall — the female equivalent of hypospadias.
- ▶ **Imperforate hymen**: failure of the hymen to perforate causes retention of menstrual blood (haematocolpos) presenting at puberty with cyclical pelvic pain and primary amenorrhoea despite normal secondary sexual characters.
- ▶ **Clinical/surgical landmarks**: the vestibule is the site of Bartholin's gland cyst/abscess (posterolateral to the vaginal orifice); the labia majora carry the terminal round ligament and are the site of a canal-of-Nuck hydrocele; episiotomy and perineal tear classification are described with reference to the fused genital-fold/genital-swelling derivatives.
- ▶ **Antenatal sexing**: because the clitoris is relatively large before mid-gestation, tubercle morphology on early ultrasound can be misleading, and definitive sexing is more reliable only after full differentiation (12th week) is complete.

### High-yield exam pointers

- ▶ Female external genitalia development is the **default/passive pathway**, occurring in the **absence** of testicular androgen (DHT) rather than requiring active hormonal induction.
- ▶ Genital tubercle → **clitoris**; urethral folds → **labia minora**; genital (labioscrotal) swellings → **labia majora**; urogenital sinus → **vestibule + bulb of vestibule**.
- ▶ Unlike the male, the **urethral folds and genital swellings remain unfused** in the female — this single fact explains almost every anatomical difference from the male pattern.
- ▶ The clitoris has **no urethra** running through it (unlike the penis), because the urethral folds never close over the urogenital groove.
- ▶ **Greater vestibular (Bartholin's) glands** = homologue of bulbourethral glands; **para-urethral (Skene's) glands** = homologue of prostate; **hymen** = homologue of the sinus (Müllerian) tubercle.
- ▶ Indifferent stage: weeks 4–7; sex-specific change begins week 9; full differentiation by **week 12**.
- ▶ **CAH (21-hydroxylase deficiency)** is the most common cause of ambiguous genitalia in a genetic female (46,XX DSD).
- ▶ By the 4th month, female external genitalia can **no longer be virilised** by androgen exposure.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021).



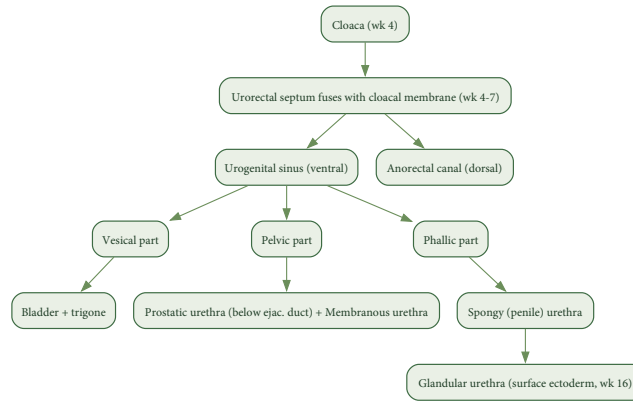
## Development of male urethra

*Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The male urethra develops largely from the endoderm of the **urogenital sinus** (UGS), the ventral compartment left after the cloaca is partitioned by the urorectal septum, together with a small terminal ectodermal contribution at the glans. Its four named parts — prostatic, membranous, spongy (penile) and glandular — each trace to a different embryonic source, and masculinisation of the urethral groove into a closed tube is driven by fetal androgen (dihydrotestosterone). Faulty fusion or canalisation at any step produces the common anomalies hypospadias, epispadias and posterior urethral valves.

### Partitioning of the cloaca and formation of the urogenital sinus

- ▶ In the 4th–7th weeks, the **urorectal septum** (a wedge of mesoderm between the allantois and the hindgut) grows caudally and fuses with the cloacal membrane, dividing the cloaca into a **ventral urogenital sinus** and a **dorsal anorectal canal**; the tip of the septum forms the **perineal body**.
- ▶ The urogenital membrane (ventral part of the cloacal membrane) ruptures around the 7th week, opening the UGS to the amniotic cavity.
- ▶ The definitive urogenital sinus is described in **three parts**, cranial to caudal:
- ▶ **Vesical part** — the upper, largest part; becomes the **urinary bladder**. It is continuous with the allantois, which later obliterates to form the fibrous **urachus** (median umbilical ligament).
- ▶ **Pelvic part** — a narrow canal; in the male it gives rise to the **prostatic urethra** (below the ejaculatory duct openings) and the **membranous urethra**.
- ▶ **Phallic part** — flattened side to side; as the genital tubercle enlarges it is drawn ventrally and, in the male, becomes the **spongy (penile) urethra**.
- ▶ The caudal ends of the **mesonephric ducts** are progressively absorbed into the dorsal wall of the sinus; this incorporated tissue forms the **trigone of the bladder** (mesodermal at first, later replaced by endodermal epithelium) and carries the mesonephric-duct openings (future **ejaculatory ducts**) down to open into the prostatic urethra flanking the seminal colliculus.
- ▶ Epithelium of the urethra throughout is **endodermal**; the surrounding connective tissue and smooth muscle differentiate from **splanchnic (visceral) mesoderm**.



*Development of male urethra*

## Development of the prostatic urethra and associated glands

- ▶ From the **end of the 3rd month**, the epithelium of the prostatic urethra proliferates into **five solid epithelial buds** — one anterior, two posterior, two lateral — that grow into the surrounding mesenchyme to form the **prostate gland**.
- ▶ Buds arising from the **mesodermal posterior wall above the level of the ejaculatory duct openings** form the prostate's **inner (mesodermal) glandular zone** — the zone prone to **benign hyperplasia** later in life.
- ▶ Buds from the rest of the (endodermal) prostatic urethra form the **outer (endodermal) glandular zone** — the zone prone to **carcinoma of the prostate**.
- ▶ Surrounding mesenchyme condenses into the fibromuscular stroma and capsule of the gland.
- ▶ The **prostatic utricle** develops from the fused caudal ends of the regressing **paramesonephric (Müllerian) ducts**: a solid **utricular cord** links them to the sinus wall and merges with a proliferation of sinus epithelium (**sinu-utricular cord**); in the second half of fetal life this composite cord canalises to form the utricle, lined by stratified squamous epithelium. The site of union, the **sinus tubercle**, becomes the **seminal colliculus (colliculus seminalis / verumontanum)** on which the utricle and the two ejaculatory ducts open.
- ▶ **Bulbourethral (Cowper's) glands** arise as paired outgrowths of endoderm from the **spongy part of the urethra**; surrounding mesenchyme forms their smooth muscle and stroma.

## Development of the external genitalia and the penile urethra

- ▶ **Indifferent stage (3rd–6th week)**: mesenchyme migrates around the cloacal membrane to raise a pair of **cloacal folds**. Cranial to the membrane these folds unite to form the **genital tubercle**; caudally (after the urorectal septum reaches the membrane) they are named **urethral folds** anteriorly and **anal folds** posteriorly. A further pair of swellings lateral to the urethral folds — the **genital swellings** — appears. Male and female are indistinguishable until about the end of the 6th week.
- ▶ **Masculinisation** is driven by androgens (testosterone, converted locally to **dihydrotestosterone (DHT)** by **5 $\alpha$ -reductase**) secreted by fetal Leydig cells:
  - The genital tubercle elongates rapidly into the **phallus**.
  - Elongation pulls the urethral folds forward so they form the lateral walls of a deep **urethral groove** on the ventral aspect of the phallus; the groove does not extend to the glans.

- The endodermal epithelial floor of the groove proliferates to form the **urethral plate**.
- By the **end of the 3rd month**, the two urethral folds fuse over the urethral plate from base towards the glans ("zipper" fusion), converting the groove into the tubular **penile (spongy) urethra**; surrounding mesenchyme forms the **corpus spongiosum**. This tube still falls short of the tip of the glans.
- During the **4th month**, the terminal (**glandular/navicular**) segment is completed by an inward growth of **surface ectoderm** at the tip of the glans, forming a short solid epithelial cord that subsequently canalises to create the **external urethral meatus** at the glans tip. (Some modern studies, e.g. Larsen, describe this step instead as canalisation of a solid distal "glans plate" that joins the penile urethra — the practical outcome, an ectoderm-derived terminal urethra, is the same.)
- The **genital swellings** become the **scrotal swellings**; they migrate caudally from the inguinal region and fuse in the midline, forming the two halves of the scrotum separated by the **scrotal septum**, continuous with the **penile (median) raphe** that marks the line of fusion of the urethral folds.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 21.13 — Development of male external genitalia (Sontakke — Textbook of Human Embryology, p.235)

Reproduce a labelled sequence (indifferent stage → 10-week phallus → newborn) with: **genital tubercle/phallus**, **urethral folds**, **genital (scrotal) swellings**, **urethral groove**, **urethral plate** (endodermal floor), **line of fusion of urethral folds (penile raphe)**, **glans penis**, **glandular part of urethra** (ectodermal ingrowth), **external urethral meatus**, **scrotal septum**.

**Table — parts of the male urethra and their embryonic source**

| Part of urethra                                | Embryonic source                                     |
|------------------------------------------------|------------------------------------------------------|
| Prostatic — above opening of ejaculatory ducts | Caudal (vesicourethral) part of the urogenital sinus |
| Prostatic — below opening of ejaculatory ducts | Pelvic part of the definitive urogenital sinus       |
| Membranous                                     | Pelvic part of the definitive urogenital sinus       |
| Spongy (penile), except terminal part          | Phallic part of the definitive urogenital sinus      |
| Glandular (terminal, in the glans)             | Surface ectoderm (invagination that canalises)       |

#### Applied / Clinical anatomy

- **Hypospadias** — the commonest anomaly of the male urethra; the external urethral meatus opens on the **ventral** aspect of the penis (or scrotum/perineum) instead of at the tip, from **incomplete fusion of the urethral folds** (the glandular variant instead reflects defective canalisation of the distal glans plate). Graded by site: **glandular** (ventral surface of glans — commonest, mildest), **coronal/balanic** (at the corona), **penile** (along the shaft), **penoscrotal** (junction of penis and scrotum — folds and genital swellings both fail to fuse), and **perineal** (most severe — urethra opens through the unfused scrotal swellings, which then resemble labia majora; often with ambiguous genitalia and ventral penile curvature, **chordee**).

- ▶ Incidence is about **3–5 per 1000 live births**, having roughly doubled over the last 15–20 years — postulated (not proven) to relate to rising environmental (endocrine-disrupting) estrogens.
- ▶ **5 $\alpha$ -reductase deficiency** prevents conversion of testosterone to DHT: external genitalia are under-masculinised, ranging from isolated hypospadias to a female-appearing perineum at birth that virilises at puberty when the testosterone surge acts directly (without needing DHT) on some target tissues.
- ▶ **Epispadias** is rare (~1 in 30,000 births); the meatus opens on the **dorsum** of the penis. It is strongly associated with **exstrophy of the bladder**, both arising from failure of mesoderm to reinforce the infra-umbilical body wall so that the cloacal membrane is malpositioned too far cranially.
- ▶ **Posterior urethral valves** (persistent mucosal folds in the prostatic/membranous urethra) are the commonest cause of congenital lower urinary tract obstruction in male infants and may coexist with **megalourethra** (a urethra deficient in erectile/spongy tissue support).
- ▶ The **seminal colliculus (verumontanum)** — bearing the openings of the prostatic utricle and the two ejaculatory ducts — is an important **surgical landmark** during transurethral prostatic surgery, marking the limit proximal to which resection risks injuring the external urethral sphincter and ejaculatory ducts.
- ▶ A persistently dilated **prostatic utricle** (Müllerian remnant) is a recognised cystic anomaly that may be found incidentally or in association with hypospadias/disorders of sex development.

### High-yield exam pointers

- ▶ Male urethra = **prostatic + membranous + spongy (penile, incl. glandular) parts**; epithelium is endodermal throughout except the terminal glandular part (ectodermal).
- ▶ Cloaca → urorectal septum divides it (wk 4–7) → urogenital sinus (vesical, pelvic, phallic parts) + anorectal canal.
- ▶ Pelvic part of UGS → membranous urethra + prostatic urethra below ejaculatory ducts; caudal vesicourethral canal → prostatic urethra above ejaculatory ducts; phallic part of UGS → spongy urethra.
- ▶ Prostate = 5 epithelial buds from prostatic urethra (inner mesodermal zone → BPH; outer endodermal zone → carcinoma).
- ▶ Penile urethra forms by **fusion of urethral folds over the urethral plate** (end of 3rd month); glandular/navicular part by **ectodermal ingrowth** (4th month).
- ▶ Masculinisation of external genitalia is **androgen (DHT)-dependent**; absence/deficiency → hypospadias-spectrum anomalies.
- ▶ **Hypospadias** = ventral meatus, folds fail to fuse, ~3–5/1000 births; **epispadias** = dorsal meatus, rare, linked to bladder exstrophy.
- ▶ **Prostatic utricle** = Müllerian vestige opening on the **seminal colliculus (verumontanum)**, alongside the ejaculatory ducts.
- ▶ Bulbourethral glands bud off the **spongy urethra**; corresponds developmentally to the female's greater vestibular (Bartholin's) glands.

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Larsen — Human Embryology 6e; Brijesh Kumar — Embryology Text & Atlas; Gray's Anatomy (Standring) 41e.



## Development of supra renal gland

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The suprarenal (adrenal) gland is unique among endocrine organs in possessing a **dual embryological origin**: the outer **cortex** is **mesodermal**, arising from the coelomic epithelium of the urogenital ridge, while the inner **medulla** is **neuroectodermal**, arising from neural crest cells. The two primordia develop independently but in close topographical association on the posterior abdominal wall, close to the developing gonad and kidney, and fuse into one encapsulated organ by about the 9th week of intrauterine life (IUL). This dual origin explains the gland's distinctive histology, its two functionally separate secretions, and several of its congenital anomalies.

### 1. Site of origin — the suprarenal ridge

- ▶ In the 5th week of IUL, mesothelial cells of the **coelomic epithelium**, situated in the angle between the **root of the dorsal mesentery** and the **developing gonad** on the posterior abdominal wall, proliferate.
- ▶ This proliferation raises a longitudinal thickening, the **suprarenal ridge**, closely related to the adjacent **gonadal ridge** and **nephrogenic cord** (together constituting the urogenital ridge).
- ▶ Formation of the suprarenal, gonadal and renal primordia is governed by a shared set of transcription factors expressed in the intermediate mesoderm — **WT1** (Wilms tumour-suppressor 1), **steroidogenic factor-1 (SF-1)** and the **DAX1** gene.
- ▶ The suprarenal and gonadal primordia segregate once primordial germ cells colonise the gonadal ridge; by the 9th week the suprarenal primordium is fully enclosed by its own capsule, separating it from the gonad and kidney.

### 2. Development of the adrenal cortex (mesodermal component)

Two successive waves of proliferation arise from the same coelomic epithelium:

| Wave       | Timing       | Cell character                 | Fate                                                                                                                              |
|------------|--------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| First wave | 5th–6th week | Large <b>acidophilic</b> cells | Migrate into the underlying mesenchyme and surround the invading neural crest cells to form the <b>fetal (provisional) cortex</b> |

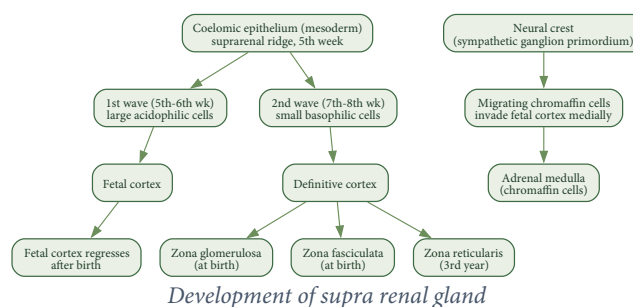


| Wave        | Timing       | Cell character                  | Fate                                                                                                                                 |
|-------------|--------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Second wave | 7th–8th week | Smaller <b>basophilic</b> cells | Proliferate from the coelomic epithelium and surround the fetal cortex from outside to form the <b>definitive (permanent) cortex</b> |

- ▶ The **fetal cortex** is by far the larger component of the gland in utero. From the second trimester it secretes **dehydroepiandrosterone (DHEA)**, which the placenta aromatises to **oestrogen** — essential for maintaining pregnancy; fetal-cortical products also influence maturation of the fetal lung, liver and gut.
- ▶ The **definitive cortex** differentiates centripetally into the three adult zones:
  - **Zona glomerulosa** and **zona fasciculata** — differentiated and present at birth.
  - **Zona reticularis** — the last to appear, identifiable only towards the **end of the 3rd postnatal year**.
- ▶ An intermediate "**transitional zone**", lying between the regressing fetal cortex and the maturing definitive cortex, has been described; the zona fasciculata is thought to be derived from this layer.

### 3. Development of the adrenal medulla (neuroectodermal component)

- ▶ **Neural crest cells**, from an adjacent primordial **sympathetic ganglion**, migrate ventrally soon after the fetal cortex is laid down.
- ▶ Around the 6th–7th week these cells invade the fetal cortex from its **medial aspect** and become progressively cordoned off as the surrounding cortex (and later its capsule) forms.
- ▶ Migration and specification of these cells towards a chromaffin fate are directed by signals arising from the **dorsal aorta**, including **bone morphogenetic proteins (BMPs)**.
- ▶ The cells differentiate into **sympathochromaffin (chromaffin) cells** — essentially **modified postganglionic sympathetic neurons** that have lost their axons/dendrites. They are innervated directly by **preganglionic sympathetic fibres** (an unusual "single-neuron" arrangement) and, on stimulation, release **adrenaline** and **noradrenaline** directly into the bloodstream rather than at a synapse.
- ▶ The name "chromaffin" derives from their brown-black staining reaction with chromium salts (e.g., potassium dichromate).
- ▶ Unlike the cortex, the medulla remains relatively small throughout fetal life and grows mainly after birth.





#### 4. Molecular regulation (brief)

- ▶ **WT1, SF-1 (NR5A1) and DAX1 (NR0B1)** — the same factors patterning the urogenital ridge — govern suprarenal cortical specification, reflecting the common intermediate-mesodermal origin shared with the kidney and gonad.
- ▶ Neural-crest-to-chromaffin specification is driven by **BMP signalling from the dorsal aorta** together with local sympathetic-ganglion cues.

#### 5. Postnatal changes in size

- ▶ At birth the gland is disproportionately large: relative to body weight, the **fetal gland is 10–20 times larger than the adult gland**, and each gland is roughly one-third the size of the ipsilateral kidney — due to the bulk of the fetal cortex.
- ▶ After birth the fetal cortex regresses rapidly; **by the end of the second postnatal month the gland has lost more than half its weight**.
- ▶ The gland begins to enlarge again from the end of the second year and **regains its birth weight only by puberty**; there is little further increase thereafter.
- ▶ The **zona reticularis** becomes histologically distinct only by the **end of the 3rd year**, completing the adult cortical pattern.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Real reference plate (reproduce by hand with these labels):

□ Fig 25.4 — Development of adrenal gland (Sontakke — Textbook of Human Embryology, p.285)

Labels/stages to reproduce (three panels, left to right):

- ▶ **Day 45** — Coelomic epithelium; Foetal cortex; Migrating chromaffin cells (approaching from lateral/superficial aspect).
- ▶ **Day 60** — Developing definitive cortex (outer rim); Medulla (chromaffin cells now central); Foetal cortex (between the two).
- ▶ **Month 4** — Definitive cortex (fully encircling); Medulla (central, chromaffin cells).
- ▶ Arrows showing progression left → right (time axis).

#### Applied / Clinical anatomy

- ▶ **Congenital adrenal hyperplasia (CAH)**: the classic applied correlate of cortical development. Caused most commonly by **21-hydroxylase deficiency (CYP21A2 gene)**, incidence **≈ 1 in 15,000 live births**. Enzyme deficiency → reduced cortisol → ACTH-driven hyperplasia of the cortex → excess androgen production (**adrenogenital syndrome**): in females this causes virilisation of the external genitalia (clitoral enlargement, **pseudohermaphroditism**); in males it causes precocious development of secondary sexual characters. The **salt-wasting form** additionally has deficient aldosterone, producing life-threatening hyponatraemia.
- ▶ **DAX1 (NR0B1) mutations**: produce suprarenal insufficiency with skin hyperpigmentation and delayed puberty (X-linked adrenal hypoplasia), reflecting DAX1's shared role in cortical and gonadal specification.

- ▶ **Accessory/ectopic suprarenal tissue ("adrenal rests")**: small yellow-orange nodules composed of **cortex only, without medulla** (because they are left behind by the migrating mesodermal wave, not accompanied by neural crest cells). Found in the areolar tissue around the gland, and — because of the shared origin/descent pathway with the gonad — in the **spermatic cord, epididymis, testis** (up to 2% of boys at inguinal surgery) or in the **ovary/broad ligament** in girls.
- ▶ **Ectopic complete suprarenal gland**: rarely, the whole gland may be found fused to the kidney or to the right lobe of the liver, from failure of separation of the suprarenal primordium from adjacent organs.
- ▶ **Independence from renal descent**: because the suprarenal primordium develops and fixes its position independently of the kidney, it remains in its **normal suprarenal position even when the kidney fails to ascend** (e.g., a pelvic kidney) — a useful point in antenatal/postnatal ultrasound interpretation.
- ▶ **Persistent extra-adrenal chromaffin tissue**: neural crest cells of the same migratory wave that do not reach the cortex persist as chromaffin tissue along the **sympathetic chain/ganglia and plexuses**, and at the **para-aortic bodies (organs of Zuckerkandl)** near the origin of the inferior mesenteric artery.
- ▶ **Phaeochromocytoma**: a tumour of chromaffin cells, arising in the adrenal medulla or in extra-adrenal chromaffin tissue ( $\approx 10\%$ , chiefly Zuckerkandl bodies); causes paroxysmal hypertension, palpitation and headache from catecholamine excess; about 25% are familial, some linked to RET mutations — again reflecting the neural-crest lineage of these cells.

### High-yield exam pointers

- ▶ Dual origin: **cortex = mesoderm** (coelomic epithelium of the suprarenal ridge); **medulla = neuroectoderm** (neural crest).
- ▶ Cortex forms in **two waves**: fetal cortex (large acidophilic cells, 5th–6th week) → definitive cortex (small basophilic cells, 7th–8th week) surrounding it.
- ▶ Fetal cortex secretes **DHEA** → **placental oestrogen**, essential for maintaining pregnancy.
- ▶ Adult cortical zones appear in sequence: glomerulosa & fasciculata at birth; **reticularis only by the 3rd year**.
- ▶ Medulla cells are chromaffin cells = modified postganglionic sympathetic neurons directly innervated by preganglionic fibres.
- ▶ **WT1 / SF-1 / DAX1** link suprarenal, gonadal and renal specification in the common urogenital ridge.
- ▶ Fetal gland is **10–20× the (relative) adult size**; loses over half its weight by the end of the 2nd postnatal month as the fetal cortex regresses.
- ▶ **CAH (21-hydroxylase/CYP21A2 deficiency)** is the classic clinical correlate — adrenogenital syndrome,  $\sim 1:15,000$  live births.
- ▶ Accessory suprarenal tissue contains **cortex only (no medulla)** — high-yield discriminator in vivas.
- ▶ Suprarenal gland position is **independent of kidney position** (helps distinguish a pelvic kidney from other causes on imaging).

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Moore's The Developing Human 9e; Sontakke's Textbook of Human Embryology; Vishram Singh's Textbook of Clinical Embryology; Vishram Singh's Textbook of Anatomy Vol 2 4e; IB Singh's Textbook of Anatomy Vol 2 6e.



## Development of suprarenal gland

*Asked in: Paper II Nov 2017 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The suprarenal (adrenal) gland is unique among the major endocrine organs in having a **dual embryological origin**: the **cortex** is **mesodermal**, derived from proliferating coelomic epithelium overlying the urogenital ridge, while the **medulla** is **neuroectodermal**, derived from migrating neural crest cells that behave as a modified sympathetic ganglion. The two primordia appear side by side from the fifth week of intrauterine life and fuse into a single encapsulated organ by the second month. The gland then continues to remodel well into postnatal life — a bulky "fetal cortex" dominates the prenatal and neonatal gland and regresses rapidly after birth, while the three-layered definitive cortex differentiates in its place.

### 1. Origin and site of the primordium

- ▶ Bilateral thickenings of the **coelomic epithelium** (mesothelium of the posterior abdominal wall), situated **medial to the developing gonad**, between the root of the **dorsal mesentery** (**mesogastrium**) and the **mesonephros**, begin to proliferate in the **5th week**.
- ▶ This proliferating mesothelial tissue extends longitudinally from the level of the **6th to the 12th thoracic segments**, forming the **suprarenal ridge** — essentially a cranial extension of the same coelomic-epithelial ridge that gives rise to the gonadal primordium. This shared origin explains the close anatomical and clinical association between suprarenal cortex and gonad (e.g., ectopic cortical tissue found along the line of gonadal descent).

### 2. Development of the cortex (mesodermal component)

- ▶ **Wave 1 (5th–6th week)**: cells of the coelomic epithelium detach and invade the underlying mesenchyme, enlarging into acidophilic cells that constitute the **fetal (provisional) cortex** — the bulk of the prenatal gland.
- ▶ **Wave 2 (2nd month onward)**: a second, smaller wave of mesothelial cells proliferates and surrounds the fetal cortical mass; these cells later differentiate into the **definitive (permanent) cortex**.
- ▶ The subcapsular cells of this second wave are the rudiment of the **zona glomerulosa**; they proliferate cords of cells that pass centripetally between the developing capillaries and venous sinusoids toward the medulla, laying down the future **zona fasciculata** and, still later, the **zona reticularis**.

- ▶ **Fate of the fetal cortex:** its cords degenerate progressively as they approach the medulla — the cells become granular, eosinophilic, and finally autolysed. This fetal cortex undergoes **rapid involution in the first two years after birth**.
- ▶ **Encapsulation:** once coelomic-epithelial proliferation ceases, a **mesenchymal capsule derived from the mesonephros** grows around the cortex, first ventrally and then dorsally.
- ▶ **Vascularisation:** venous sinusoids develop within the cortical mass and are joined by capillaries derived from adjacent **mesonephric arteries**, which penetrate the gland radially — the developmental basis of the adult gland's dense subcapsular arterial supply.
- ▶ The fetal cortex is functionally active, not vestigial: it secretes **dehydroepiandrosterone (DHEA)**, which the placenta aromatises to oestrogen — an important contribution to maintaining the fetoplacental unit and pregnancy.

### 3. Development of the medulla (neuroectodermal component)

- ▶ While the fetal cortex is being laid down, **neural crest cells** (arising, per Gray's, from somite levels 18–24) migrate ventrally alongside the cells forming the dorsal root ganglia and sympathetic chain, and invade the **medial aspect** of the fetal cortex.
- ▶ These cells arrange themselves as cords and clusters within the cortical mass and progressively differentiate into the **medulla**. Migration and lineage specification of these cells are directed by signals — including BMPs — arising from the adjacent dorsal aorta.
- ▶ Differentiated medullary cells stain yellow-brown with chromium salts and are therefore termed **chromaffin cells (pheochromocytes)**. Functionally they are **modified postganglionic sympathetic neurons**: they lack long axons, are innervated directly by **preganglionic sympathetic fibres**, and on stimulation release **adrenaline and noradrenaline** straight into the bloodstream rather than across a synapse.
- ▶ As the definitive cortex enlarges circumferentially, the medulla comes to lie centrally, almost completely surrounded by cortex — the mature cortex-around-medulla arrangement.
- ▶ During embryonic life chromaffin tissue is widely scattered along the sympathetic chain and around the aorta (the **para-aortic bodies of Zuckerkandl**); in the adult, the only large persisting mass of chromaffin tissue is within the suprarenal medulla.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 25.4 — Development of adrenal gland (Sontakke — *Textbook of Human Embryology*, p.285)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A three-panel time-course (mirror the plate above), each panel a wedge of posterior abdominal wall with the coelomic epithelium as the continuous surface layer; label exactly:

- ▶ **Day 45:** Coelomic epithelium (surface layer) · Foetal cortex (acidophilic mass just deep to it) · Migrating chromaffin cells (small circles, neural crest, invading the mass)
- ▶ **Day 60:** Foetal cortex (centre) · Medulla (chromaffin-cell cluster, now central within the mass) · Developing definitive cortex (thin cellular rim appearing around the mass)
- ▶ **Month 4:** Medulla (central) · Definitive cortex (complete outer rim, fetal cortex regressing/absent)
- ▶ Arrows Day 45 → Day 60 → Month 4 showing progressive circumferential encirclement of the medulla by the definitive cortex.

**Postnatal changes**

- ▶ At birth, the gland is proportionately huge — about **one-third the size of the ipsilateral kidney** — very largely because of the bulky fetal cortex; the medulla, by contrast, grows comparatively little in this period.
- ▶ Only the **zona glomerulosa** and **zona fasciculata** are differentiated at birth; the **zona reticularis** appears only by the **end of the third postnatal year**.
- ▶ The fetal zone regresses rapidly after birth: the gland loses **more than half its weight by the end of the second postnatal month**, and fetal-cortex involution is essentially complete by the **end of the second year**.
- ▶ The gland begins to enlarge again from the end of the second year and regains its birth weight only around puberty; there is little further weight gain thereafter in adult life.

| Feature        | Cortex                                                                                  | Medulla                                                        |
|----------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Germ layer     | Mesoderm (coelomic epithelium)                                                          | Neuroectoderm (neural crest)                                   |
| Primordium     | Suprarenal ridge, medial to gonad                                                       | Neural crest cells, somite levels 18–24                        |
| Cell type      | Steroidogenic epithelial cells                                                          | Chromaffin cells (modified postganglionic sympathetic neurons) |
| Secretion      | Cortisol, aldosterone, androgens (fetal cortex: DHEA)                                   | Adrenaline, noradrenaline                                      |
| Innervation    | —                                                                                       | Preganglionic sympathetic fibres                               |
| Postnatal fate | Fetal cortex involutes by 2nd year; 3 definitive zones mature (reticularis by 3rd year) | Persists, encircled by definitive cortex                       |

**Applied / Clinical anatomy**

- ▶ **Accessory suprarenal tissue ("adrenal rests"):** small nodules of cortical tissue (occasionally with medullary tissue) persist near the main gland or migrate with the gonad along its line of descent

— found in the spermatic cord, epididymis, testis, or the ovary/broad ligament of the uterus. This reflects the shared coelomic-epithelial origin of gonad and suprarenal cortex, and such rests may occasionally cause diagnostic confusion or, rarely, undergo neoplastic change.

- ▶ **Ectopic suprarenal tissue** may also be found deep to the renal capsule, or fused to the kidney or liver.
- ▶ **Congenital adrenal hyperplasia (CAH)**: autosomal recessive enzyme defects of cortical steroidogenesis — commonly **21-hydroxylase** deficiency, and less commonly 11 $\beta$ -hydroxylase or 3 $\beta$ -hydroxysteroid dehydrogenase deficiency — cause glucocorticoid deficiency with compensatory ACTH-driven cortical hyperplasia and androgen excess: virilisation in genetic females (**female pseudohermaphroditism**) and precocious sexual development in males (**adrenogenital syndrome**).
- ▶ **Pheochromocytoma**: a tumour of chromaffin cells, mostly arising in the medulla (~10% extra-adrenal, along the sympathetic chain/organ of Zuckerkandl), causing paroxysmal catecholamine excess; a familial subset is linked to mutations affecting the RET gene involved in neural crest cell migration.
- ▶ **Neuroblastoma**: a malignant embryonal tumour of primitive sympathetic/chromaffin (neural-crest-derived) cells, arising in the adrenal medulla or elsewhere along the sympathetic chain in infants and young children; behaviour ranges from spontaneous regression to aggressive metastasis.
- ▶ Failure of the normal encirclement of medulla by definitive cortex, or persistence of fetal-cortical nests, underlies patterns of adrenal cytomegaly occasionally noted in neonatal/perinatal specimens.

### High-yield exam pointers

- ▶ Suprarenal gland has a **dual origin**: cortex = mesoderm (coelomic epithelium); medulla = neuroectoderm (neural crest) — always state both together.
- ▶ Cortex primordium = **suprarenal ridge**, medial to the developing gonad, 6th–12th thoracic level, arising in the **5th week**.
- ▶ Cortex develops in **two waves**: fetal cortex (wave 1, dominant prenatally) → definitive cortex (wave 2, subcapsular, becomes zona glomerulosa).
- ▶ Medulla = neural crest cells (somite levels 18–24) invading the medial aspect of the fetal cortex → differentiate into **chromaffin cells**, which are modified postganglionic sympathetic neurons.
- ▶ At birth: only **zona glomerulosa + zona fasciculata** present; **zona reticularis** appears only by end of 3rd year.
- ▶ **Fetal cortex** secretes DHEA (→ placental oestrogen); it involutes by the end of the 2nd postnatal year, with >50% weight loss by the 2nd postnatal month.
- ▶ Gonad and suprarenal cortex share a **common coelomic-epithelial origin** — the anatomical basis for accessory suprarenal (cortical) tissue found near the gonads.
- ▶ Clinical correlates by component: cortex → CAH/adrenogenital syndrome; medulla → pheochromocytoma, neuroblastoma; shared origin → accessory suprarenal tissue.



**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Larsen — Human Embryology 6e; BD Chaurasia — Human Anatomy Vol 2 8e; Vishram Singh — General Anatomy 4e; Vishram Singh — Textbook of Clinical Embryology.



## Development of urethra in male and female

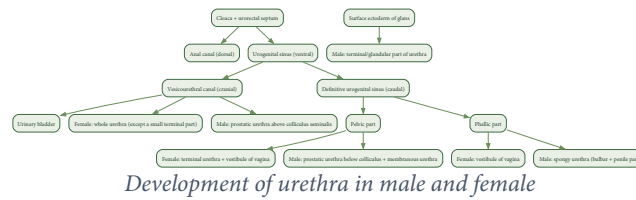
*Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The urethra is the endodermal derivative of the divided cloaca that conveys urine (and, in the male, semen) from the bladder to the exterior. Its development is inseparable from the subdivision of the cloaca into the urogenital sinus and, distally, from the development of the external genitalia. The **female urethra is short and its development simple**, being entirely a passive derivative of the urogenital sinus, whereas the **male urethra is long and its development complex**, intimately bound up with elongation of the phallus and fusion of the genital folds. Except for a short ectodermal segment within the glans penis, the lining epithelium of the urethra in both sexes is endodermal; its connective tissue and smooth muscle are derived from surrounding splanchnopleuric mesoderm.

### 1. Division of the cloaca and formation of the urogenital sinus

- ▶ Between the 4th and 7th weeks, the **urorectal septum** (mesenchyme growing between the allantois and hindgut) fuses with the cloacal membrane, dividing the cloaca into a dorsal **primitive rectum** and a ventral **urogenital sinus**. The tip of the septum forms the **perineal body**; the cloacal membrane is correspondingly split into a dorsal **anal membrane** and a ventral **urogenital membrane**.
- ▶ The **mesonephric (Wolffian) ducts** open into the primitive urogenital sinus, and their point of entry subdivides it further into:
  - a cranial, dilated **vesicourethral canal**, continuous above with the allantois; and
  - the **definitive urogenital sinus**, below the level of the mesonephric duct openings, itself subdivided into a narrow **pelvic part** and a flattened **phallic part** (closed externally by the urogenital membrane).
- ▶ The vesicourethral canal expands to form the **urinary bladder** and continues as urachus (→ median umbilical ligament); its lower, narrow part forms the **primitive urethra**.
- ▶ The terminal parts of the mesonephric ducts are absorbed into the dorsal wall of the vesicourethral canal, so the ureters and mesonephric ducts come to open separately — the absorbed area becomes the **trigone of the bladder**, giving the trigone (and dorsal wall of the adjoining urethra) a **mesodermal lining**, in contrast with the endodermal lining elsewhere.





## 2. Development of the female urethra

- ▶ The whole of the female urethra develops from the narrow caudal part of the **vesicourethral canal**, *except* a small terminal part, which develops from the **pelvic part of the definitive urogenital sinus**.
- ▶ The **phallic part of the definitive urogenital sinus** does not form urethra in the female — it expands to form the **vestibule of the vagina**, into which both the urethra and vagina open.
- ▶ The female urethra is the **developmental homologue of the male prostatic urethra proximal to the colliculus seminalis** (i.e., proximal to the openings of the ejaculatory ducts and prostatic utricle).
- ▶ Epithelial lining: **endodermal** (from the urogenital sinus) throughout, *except* its **dorsal wall**, which is **mesodermal**, derived from the absorbed terminal parts of the mesonephric ducts (as with the bladder trigone).
- ▶ The cranial part of the urethra buds off outgrowths that form the **urethral and paraurethral (Skene's) glands** — the female homologue of the prostate gland; these remain rudimentary without androgenic stimulation.
- ▶ The adult female urethra is short (~4 cm) — a direct reflection of the simple embryological derivation described above, unlike the long, segmented male urethra.

## 3. Development of the male urethra

The male urethra develops as **three parts**, and its distal development is inseparable from that of the external genitalia (Section 5):

| Part of male urethra                                                                 | Embryonic source                                                                                                                             |
|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Prostatic urethra, above the opening of the ejaculatory ducts (colliculus seminalis) | Caudal part of <b>vesicourethral canal</b> ; its posterior wall from absorbed mesonephric ducts                                              |
| Prostatic urethra, below the ejaculatory duct openings                               | Upper <b>pelvic part</b> of definitive urogenital sinus                                                                                      |
| Membranous urethra (in the deep perineal pouch)                                      | Lower <b>pelvic part</b> of definitive urogenital sinus                                                                                      |
| Spongy (penile) urethra — bulbar part and shaft (penile) part                        | <b>Phallic part</b> of definitive urogenital sinus, by canalisation of the urethral plate and fusion of the genital (urethral) folds over it |
| Terminal/glandular part, within the glans penis                                      | <b>Surface ectoderm</b> , which invaginates from the tip of the glans and later canalises to join the penile urethra                         |

- ▶ Outgrowths from the endoderm around the prostatic urethra (14–20 buds) invade the surrounding mesenchyme to form the **prostate gland**; the corresponding rudiments in the female remain vestigial as the paraurethral glands.

- The **bulbourethral (Cowper's) glands** arise as diverticula of the epithelial lining of the (phallic) urogenital sinus — these are the male homologue of the female **greater vestibular (Bartholin's) glands**.

#### 4. Homologies between male and female derivatives of the cloaca

| Embryonic structure                    | Male derivative                                          | Female derivative                                    |
|----------------------------------------|----------------------------------------------------------|------------------------------------------------------|
| Vesicourethral canal                   | Bladder + prostatic urethra above utricle                | Bladder + whole urethra (except small terminal part) |
| Pelvic part of urogenital sinus        | Prostatic urethra (below utricle) + membranous urethra   | Terminal urethra + part of vestibule                 |
| Phallic part of urogenital sinus       | Bulb of urethra + spongy urethra                         | Vestibule of vagina                                  |
| Urogenital sinus epithelial outgrowths | Prostate gland                                           | Urethral and paraurethral (Skene's) glands           |
| Urogenital sinus diverticula           | Bulbourethral (Cowper's) glands                          | Greater vestibular (Bartholin's) glands              |
| Genital tubercle                       | Glans penis / body of penis                              | Clitoris                                             |
| Genital (urethral) folds               | Fuse → ventral aspect of penis, enclosing spongy urethra | Remain unfused → labia minora                        |
| Genital (labioscrotal) swellings       | Fuse → scrotum                                           | Remain unfused → labia majora                        |

#### 5. Development of the external genitalia — hormonal control of urethral fate

□ Fig 72.20 — The development of the external genitalia from the indifferent stage to the definitive male and female states. (Gray's Anatomy — Standring — 41e, p.1690)

- Around the urogenital membrane, an **indifferent stage** is common to both sexes: a midline **genital tubercle**, paired **genital (urethral) folds**, and paired **labioscrotal (genital) swellings** appear by the 4th–6th week; the sexes are indistinguishable up to the end of the 6th week.
- The urogenital membrane breaks down (~7th week), and the exposed endoderm on the caudal aspect of the phallus becomes the **urethral plate**; as mesenchyme proliferates in the genital folds, this plate sinks in to form the **urethral groove**.
- **Male pathway** (androgen/dihydrotestosterone-dependent): the genital tubercle elongates rapidly into the **phallus**, pulling the urethral folds forward as the lateral walls of the urethral groove. By the end of the 3rd month, the folds **fuse from behind forward** over the urethral plate, converting the groove into the **penile (spongy) urethra**, and leaving a **median raphe**. Fusion of the labioscrotal swellings in the midline forms the **scrotum**. The **glandular urethra** forms later (4th month) by ingrowth of ectoderm from the tip of the glans, which canalises to join the penile urethra and complete the **external urethral meatus**. Testosterone (via 5 $\alpha$ -dihydrotestosterone) drives this masculinisation.
- **Female pathway** (default, oestrogen-associated): in the absence of androgen, the genital tubercle elongates only slightly to form the **clitoris**; the urethral folds do **not** fuse and persist as the **labia minora**; the labioscrotal swellings enlarge unfused as the **labia majora**. The urethral groove remains open as the **vestibule**, into which the urethra and vagina open separately.

- ▶ **Sensitivity window:** the female external genitalia cannot be masculinised by androgen after about the 4th month, which is clinically important in disorders of sexual differentiation.

## Applied / Clinical anatomy

- ▶ **Hypospadias** — incomplete fusion of the urethral folds; the urethral meatus opens on the ventral aspect of the penis (glandular, penile, penoscrotal or perineal types depending on severity). Incidence  $\approx$  3–5/1000 male births. Severe forms with failure of labioscrotal fusion mimic labia majora and cause **genital ambiguity**, mandating urgent karyotype and internal genital tract assessment for sex assignment.
- ▶ **Epispadias** — rarer ( $\approx$  1/30,000 births); urethral meatus opens on the dorsum of the penis/clitoris; almost always associated with **exstrophy of the bladder** (failure of mesoderm migration into the infra-umbilical anterior abdominal wall, exposing the posterior bladder mucosa).
- ▶ **Persistent urogenital sinus** — seen in virilised females (e.g. congenital adrenal hyperplasia), where excess fetal androgen fuses the urethral folds and labioscrotal swellings, producing a single perineal orifice and clitoromegaly instead of separate urethral, vaginal and vestibular openings.
- ▶ **5 $\alpha$ -reductase deficiency** (46,XY DSD) — failure to convert testosterone to dihydrotestosterone leaves the external genitalia female-like (enlarged clitoris, blind vaginal pouch, persistent urogenital sinus) despite functioning testes; virilisation occurs at puberty.
- ▶ **Skene's (paraurethral) gland cyst/abscess** and **Bartholin's gland cyst** reflect the prostate/bulbourethral-gland homology described above.
- ▶ **Prostatic utricle cyst / Müllerian remnant cysts** and **Gartner's duct cyst** (mesonephric duct remnant) relate to incomplete regression of the "wrong-sex" duct system that runs alongside urethral development.
- ▶ **Posterior urethral valves** — a congenital obstructing membrane in the prostatic/membranous urethra in males, causing hydronephrosis and a thick-walled bladder.
- ▶ **Urethral duplication** and **ectopic ureteric openings** (into prostatic urethra in males; into urethra or vagina in females) arise from anomalies of mesonephric duct absorption into the vesicourethral canal.

## High-yield exam pointers

- ▶ Cloaca is divided by the urorectal septum (weeks 4–7) into urogenital sinus (ventral) + rectum (dorsal); urogenital sinus = vesicourethral canal (cranial) + definitive urogenital sinus (pelvic + phallic parts, caudal).
- ▶ **Female urethra** = caudal vesicourethral canal + small terminal part from pelvic urogenital sinus; homologous to male prostatic urethra **above** the colliculus seminalis.
- ▶ **Male urethra** has three parts — prostatic, membranous, spongy — plus a terminal ectodermal segment in the glans; only the glandular urethra is ectodermal, the rest is endodermal.
- ▶ Phallic part of urogenital sinus  $\rightarrow$  vestibule of vagina (female) vs spongy urethra (male).
- ▶ Urethral epithelium is endodermal in both sexes except: (a) the dorsal wall of the female urethra/bladder trigone (mesodermal, from absorbed mesonephric duct), and (b) the glandular urethra in the male (ectodermal).

- ▶ Homologous glands: prostate ↔ paraurethral (Skene's) glands; bulbourethral (Cowper's) ↔ greater vestibular (Bartholin's) glands.
- ▶ External genitalia: genital tubercle → glans penis/clitoris; genital folds → fuse (penile urethra, male) or stay open (labia minora, female); labioscrotal swellings → scrotum (male) or labia majora (female).
- ▶ Male external genital differentiation is dihydrotestosterone-dependent; the female pattern is the constitutive "default" in the absence of androgen.
- ▶ Hypospadias (failure of urethral fold fusion) and epispadias (with bladder exstrophy) are the classic clinical correlates.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e.



## Development of urinary bladder

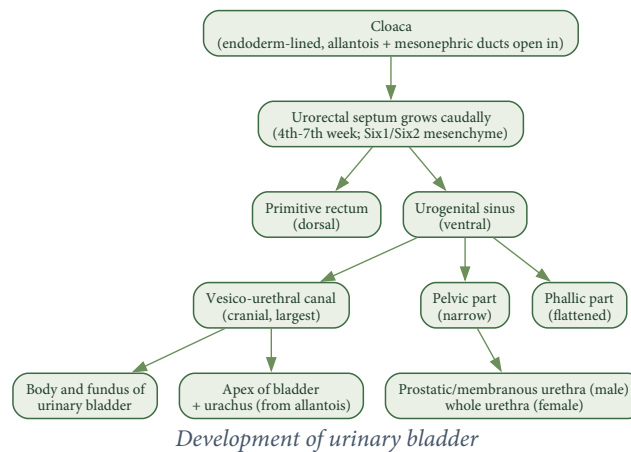
*Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The urinary bladder is a derivative of the **cloaca**, the common terminal chamber into which the hindgut, allantois and mesonephric ducts all open in the early embryo. Between the **4th and 7th weeks**, the cloaca is divided by the urorectal septum into a dorsal anorectal canal and a ventral urogenital sinus, whose largest cranial part — the **vesico-urethral canal** — forms the bulk of the bladder. The bladder therefore has a composite origin: **endoderm** (epithelium of the body and fundus), **mesoderm** (detrusor muscle, connective tissue, and — classically — the trigonal epithelium via incorporated mesonephric ducts), and the **allantois** (apex and urachus). Its development is inseparable from that of the ureter, mesonephric duct and urorectal septum, and several clinically important anomalies (urachal remnants, exstrophy) trace directly to faults at specific steps of this sequence.

### 1. Division of the cloaca and origin of the urogenital sinus (weeks 4–7)

- ▶ The primitive hindgut ends in the **cloaca**, an endoderm-lined cavity closed externally by the bilaminar **cloacal membrane** (ectoderm apposed to endoderm, with no intervening mesenchyme).
- ▶ Ventrally the cloaca is continuous with a blind diverticulum, the **allantois**, which extends into the connecting stalk; posterolaterally, the paired **mesonephric ducts** open into it.
- ▶ A wedge of mesenchyme, the **urorectal septum** (also termed the intercloacal mesenchyme; molecular markers **Six1** and **Six2**), proliferates in the angle between the hindgut and the allantois and grows caudally toward the cloacal membrane, which it approaches but does not fuse with.
- ▶ This subdivides the cloacal region into a dorsal **primitive rectum** and a ventral **urogenital sinus** (UGS), and correspondingly splits the cloacal membrane into a dorsal **anal membrane** and a ventral **urogenital membrane**; the point of contact of the septum with the membrane forms the **perineal body**.

- The urogenital sinus itself has three parts: a cranial, largest part — the **vesico-urethral canal**, continuous above with the allantoic duct; a narrow **pelvic part**; and a flattened **phallic part**, closed externally by the urogenital membrane.
- **The urinary bladder develops from the cranial vesico-urethral canal**; its apex remains continuous with the allantois.



## 2. Embryological sources of the urinary bladder wall

| Part of the bladder                                                         | Embryonic source                                                               | Germ layer                                     |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|
| Lining (transitional) epithelium of the body and fundus, except the trigone | Cranial, dilated part of the vesico-urethral canal                             | Endoderm                                       |
| Lining epithelium of the trigone (classical description)                    | Incorporated terminal (common) segments of the mesonephric ducts               | Mesoderm, later replaced by ingrowing endoderm |
| Detrusor muscle, submucous connective tissue, serosa/adventitia             | Splanchnopleuric intraembryonic mesoderm surrounding the vesico-urethral canal | Mesoderm                                       |
| Apex of bladder and urachus (median umbilical ligament)                     | Allantois                                                                      | Endoderm-lined; lumen obliterates              |

## 3. Incorporation of the mesonephric ducts and formation of the trigone

- The **ureteric bud** arises, in the 5th week, as an outgrowth from the mesonephric duct close to its entry into the vesico-urethral canal; initially, therefore, the mesonephric duct and the ureteric bud share a **common opening**.
- With growth, the terminal (common) segment of the mesonephric duct is progressively **absorbed (incorporated) into the dorsal wall** of the vesico-urethral canal; this steadily separates the two orifices — the ureteric orifice migrates **cranio-laterally**, while the mesonephric-duct orifice migrates **caudo-medially**.
- The triangular zone of dorsal bladder wall bounded above by the (now separate) ureteric orifices and below by the mesonephric-duct orifices is the **trigone of the bladder**.

- ▶ The fate of the terminal mesonephric duct at this site is sex-dependent: it **degenerates in the female**, but in the **male** it persists and opens as the **ejaculatory duct** on the developing prostatic urethra.
- ▶ **Current concept (Gray's Anatomy, 41st ed.):** antibody-labelling and transgenic-mouse studies show that this terminal "common nephric duct" segment actually undergoes local, **retinoic-acid-dependent apoptosis** — rather than being incorporated as living epithelium — to establish separate ureteric and mesonephric-duct openings. Tissue-recombination experiments confirm that trigonal epithelium differentiates as prostatic-type epithelium, i.e. it is of **endodermal**, not mesodermal, lineage throughout. Likewise, the bulk of trigonal smooth muscle — including the eponymous **Mercier's bar** and **Bell's muscle** — is now shown to derive mainly from **detrusor (bladder) muscle**, with only a limited contribution from the ureter itself.

□ Fig 20.16 — Development of urinary bladder. A–C: Side view of developing urinary bladder; D–F: Dorsal view of the developing bladder showing changing relationship of ureter and mesonephric duct (Sontakke — Textbook of Human Embryology, p.220)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Dorsal-view sequence (four panels, A→D) of the developing bladder showing the changing relationship of the ureter and mesonephric duct. Label in each panel:

- ▶ **Panel A** — mesonephric duct and ureteric bud sharing a common opening into the vesico-urethral canal.
- ▶ **Panel B** — ureteric orifice beginning to separate, migrating cranio-laterally.
- ▶ **Panel C** — terminal mesonephric duct incorporated into the dorsal wall; a triangular field (developing trigone) appears between the two pairs of orifices.
- ▶ **Panel D** — definitive pattern: ureteric orifices at the two superolateral angles of the trigone; mesonephric-duct orifices (→ ejaculatory ducts in the male) at the inferior angle/bladder neck.
- ▶ Also label: allantois/urachus at the apex, body of bladder, and the vesico-urethral canal.

#### 4. Fate of the allantois — the urachus

- ▶ The intraembryonic part of the allantois remains continuous with the apex of the bladder as a narrow tube.
- ▶ Its lumen normally obliterates progressively; per Gray's Anatomy, closure is complete only by about the **32nd week**, converting the allantois into a fibrous cord, the **urachus**.
- ▶ In the adult, the obliterated urachus persists as the **median umbilical ligament**, raising the median umbilical fold on the internal aspect of the anterior abdominal wall between the apex of the bladder and the umbilicus.

#### 5. Congenital anomalies of the bladder and urachus

| Anomaly                          | Part of allantois/urachus that persists | Result                                       |
|----------------------------------|-----------------------------------------|----------------------------------------------|
| Patent urachus (urachal fistula) | Entire lumen                            | Urine drains continuously from the umbilicus |



| Anomaly                    | Part of allantois/urachus that persists | Result                                                                |
|----------------------------|-----------------------------------------|-----------------------------------------------------------------------|
| Urachal sinus              | Proximal (umbilical) part only          | Blind sinus opening at the umbilicus                                  |
| Urachal cyst               | Intermediate segment only               | Palpable midline infra-umbilical cystic swelling; may become infected |
| Vesicourachal diverticulum | Distal (vesical) part only              | Diverticulum continuous with the apex of the bladder                  |

- **Exstrophy of the bladder (ectopia vesicae):** results from **failure of migration of lateral-plate mesoderm** into the infra-umbilical (hypogastric) region during lateral body-wall folding. The abnormally large cloacal membrane in this region ruptures prematurely, so the anterior abdominal wall and anterior bladder wall fail to form; the mucosa of the posterior bladder wall, with the ureteric orifices visible and urine dribbling from them, is exposed on the surface. **Epispadias is a constant accompanying feature.** Incidence is quoted as roughly **1–2 per 10,000 live births**.
- **Exstrophy of the cloaca:** a more severe defect in which the **urorectal septum** also fails to develop normally in addition to the body-wall defect, so anorectal malformations (imperforate anus) and widely separated, malformed external genitalia accompany the exposed bladder and hindgut; this is much rarer (about **1 in 30,000** births).
- **Congenital rectovesical / vesicovaginal fistula:** results from an incompletely formed urorectal septum, allowing an abnormal communication between the developing bladder and the adjoining rectum or vagina.

## Applied / Clinical anatomy

- The **neonatal bladder is an abdominal organ** — egg-shaped, with its larger end directed downward, and nearly half of it still lying above the pelvic inlet; it does not descend into the true pelvis until about the **6th year** of life.
- Because the bladder remains tethered to the umbilicus by the obliterated urachus, stimulation of the umbilical stump can trigger the micturition reflex in an infant, and conversely gentle suprapubic pressure can express urine from a full infant bladder.
- This high, anterior position, with the apex reaching toward the umbilicus when full, is the anatomical basis for **suprapubic aspiration** of urine in infants — best performed after ultrasound confirmation that the bladder is full.
- On **antenatal ultrasound**, the fetal bladder is normally identifiable by **9–11 weeks**; its absence at 13 weeks or beyond is abnormal, and cyclical filling/emptying can be demonstrated over a 30–45-minute cycle. Persistent distension (megacystis) suggests lower urinary tract obstruction, most often from **posterior urethral valves**, and affects about 2.2 per 10,000 births, more commonly in males.
- The distinct developmental history of the trigone — its separate incorporation of the mesonephric-duct territory and the oblique submucosal course the ureter takes through the detrusor tunnel — underlies the **valve-like, anti-reflux mechanism** of the ureterovesical



junction; disturbance of this mechanism (short intramural tunnel) is the basis of **vesicoureteric reflux**, and restoring an adequate tunnel length is the surgical principle of ureteric reimplantation.

### High-yield exam pointers

- ▶ Bladder derives from the **cranial vesico-urethral canal**, the largest part of the urogenital sinus formed once the urorectal septum divides the cloaca (**4th–7th week**).
- ▶ Bladder epithelium (except trigone, classically) = **endoderm**; detrusor muscle and connective tissue = **splanchnopleuric mesoderm**; apex and urachus = **allantois**.
- ▶ Trigone forms by incorporation of the terminal (common) segment of the **mesonephric ducts** into the dorsal bladder wall, separating the ureteric and mesonephric-duct orifices.
- ▶ **Current molecular evidence** (Gray's 41e) shows trigonal epithelium is wholly **endodermal** — the mesonephric-duct remnant undergoes **apoptosis** (retinoic-acid dependent), not epithelial incorporation; trigonal muscle (including Mercier's bar/Bell's muscle) is mainly **detrusor**-derived, not ureteric.
- ▶ Mesonephric-duct fate at the trigone is sex-dependent: **degenerates in the female**; forms the **ejaculatory duct** in the male.
- ▶ Urachus = obliterated allantois → **median umbilical ligament**; closure completes by about the **32nd week**.
- ▶ Patent or partial urachal remnants give, respectively, a **urachal fistula, sinus, cyst, or vesicourachal diverticulum**.
- ▶ **Exstrophy of the bladder** = failure of hypogastric mesoderm migration → premature rupture of an over-sized cloacal membrane → exposed posterior bladder wall with a **constant epispadias**.
- ▶ Neonatal bladder is abdominal until about the **6th year** — the basis for suprapubic aspiration and umbilical-stimulation of micturition.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Brijesh Kumar — Embryology Text & Atlas.



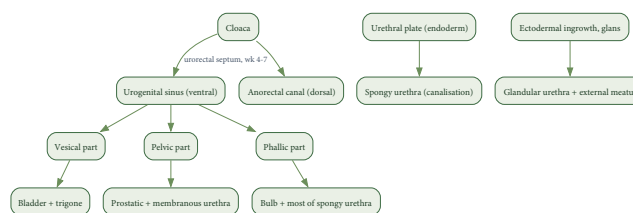
## Discuss the development of male urethra with different congenital anomalies

Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The male urethra is a composite structure: its proximal (prostatic + membranous) part and most of the spongy part are **endodermal**, derived from the **urogenital sinus** (itself formed by cloacal partitioning), while its terminal glandular segment is formed secondarily by an **ectodermal ingrowth** from the tip of the glans. Because each urethral segment has a distinct embryological source, a defect at any one step produces a characteristic congenital anomaly — hypospadias, epispadias, bladder exstrophy, posterior urethral valves and rarer variants — each explainable directly from the developmental sequence.

### 1. Partitioning of the cloaca and formation of the urogenital sinus

- ▶ Between the 4th and 7th weeks, the **urorectal septum** (a wedge of mesoderm) grows caudally between the hindgut and allantois and divides the endodermal cloaca into a ventral **urogenital sinus** and a dorsal **anorectal canal**; its tip fuses with the cloacal membrane to form the **perineal body**.
- ▶ The urogenital sinus has **three parts**:
- ▶ **Vesical (upper) part** — largest; becomes the **urinary bladder**. It is continuous with the allantois, which later obliterates to the fibrous **urachus** (adult median umbilical ligament).
- ▶ **Pelvic (narrow) part** — becomes the **prostatic and membranous urethra**.
- ▶ **Phallic (flattened) part** — pulled ventrally as the genital tubercle grows; forms most of the **penile (spongy) urethra**.
- ▶ The caudal ends of the **mesonephric (Wolffian) ducts** are absorbed into the posterior bladder wall, so the ureters come to open separately into the bladder; this incorporated segment becomes the **trigone** — initially mesodermal, later replaced by ingrowing endothelium so the adult bladder lining is uniformly endodermal.
- ▶ The urethral **epithelium** is endodermal in both sexes; the surrounding connective tissue and smooth muscle are derived from **visceral (splanchnic) mesoderm**.



Discuss the development of male urethra with different congenital anomalies

### 2. Development of external genitalia and the spongy (anterior) urethra

- ▶ **Indifferent stage (up to 6th week):** mesenchyme around the cloacal membrane raises paired **cloacal folds**; cranially these unite to form the **genital tubercle**; caudally they are named **urethral (genital) folds** flanking the urogenital membrane, with **genital (labioscrotal) swellings** lateral to the folds. The two sexes are indistinguishable at this stage.
- ▶ **Masculinisation (from ~9th week, testosterone/DHT-driven):** the genital tubercle elongates rapidly into the **phallus**, dragging the urethral folds forward to form the lateral walls of a deep

**urethral groove**; the floor of this groove is the **urethral plate**, the exposed endodermal lining of the attenuated phallic urogenital sinus.

- ▶ The urethral folds **fuse from behind forwards** over the plate, enclosing the phallic urogenital sinus proximally to form the **bulb of the urethra** and closing the groove distally to form the greater part of the **spongy urethra**; the fusion line is marked by the **median raphe**.
- ▶ The **glandular urethra** (the segment normally within the glans) is completed differently: an **ectodermal ingrowth from the tip of the glans** canalises and joins the penile urethra, carrying the external urethral meatus to the tip of the glans — completed by the end of the 4th month.
- ▶ The genital (labioscrotal) swellings meet in the midline ventral to the anus and fuse to form the **scrotum**; the persisting midline mesenchyme forms the **scrotal septum**.
- ▶ The **prostate** develops as multiple **endodermal buds from the prostatic urethra** (from the end of the 3rd month) that penetrate the surrounding mesenchyme; the **bulbourethral (Cowper's) glands** arise similarly from the phallic urethra/bulb.

| Adult urethral segment                                                      | Embryological origin                                                                       |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Prostatic urethra proximal to the prostatic utricle                         | Vesico-urethral part of cloaca + incorporated caudal ends of mesonephric ducts             |
| Remainder of prostatic urethra, membranous urethra, urethra within the bulb | Pelvic + phallic parts of the definitive urogenital sinus                                  |
| Spongy (penile) urethra up to the glans                                     | Canalisation of the endodermal urethral plate; folds fused over it by ingrowing mesenchyme |
| Glandular urethra + external meatus                                         | Secondary ectodermal ingrowth from the tip of the glans, later canalised                   |

□ Fig 21.13 — Development of male external genitalia (Sontakke — Textbook of Human Embryology, p.235)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Indifferent stage → male stage, labelling: genital tubercle → phallus, urethral (genital) folds → fused forming spongy urethra/median raphe, genital (labioscrotal) swellings → scrotum, urethral groove, urethral plate, glans penis with ingrowing ectodermal cord, external urethral meatus at tip, anal fold/anus.

### 3. Congenital anomalies of the male urethra

| Anomaly                             | Embryological basis                                                                                                                                                                                | Key features                                                                                                                                                                                                                                                                              | Incidence                                                                          |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Hypospadias                         | Incomplete/failed fusion of the urethral folds; or failure of canalisation of the ectodermal glandular cord                                                                                        | Urethra opens on the <b>ventral</b> aspect; classified <b>glandular</b> (commonest), <b>balanic</b> , <b>penile</b> , <b>penoscrotal</b> , <b>perineal</b> (unfused labioscrotal folds); often with <b>chordee</b> (ventral curvature) and a dorsally-hooded, ventrally-deficient prepuce | ~1 in 300 male births (Gray's/Sontakke); Langman quotes 3–5/1000                   |
| Epispadias                          | Genital tubercle develops too far caudally/dorsally relative to the urogenital membrane; regarded as a <b>milder form of bladder exstrophy</b>                                                     | Urethra opens on the <b>dorsal</b> aspect of the penis, up to the pubic symphysis in severe forms; <b>dorsal chordee</b> , short broad penis; usually part of the <b>exstrophy–epispadias complex</b> ; cryptorchidism risk increased ~10-fold                                            | Rare — quoted from ~1 in 30,000 (older texts) to ~1 in 100,000 (Gray's 41e) births |
| Bladder exstrophy (ectopia vesicae) | Misalignment of the genital tubercle and urogenital swellings relative to the urogenital membrane → premature membrane breakdown before mesenchymal reinforcement → posterior bladder wall exposed | Lower abdominal wall defect with everted bladder mucosa, visible ureteric orifices; <b>constantly associated with epispadias</b>                                                                                                                                                          | ~1 in 10,000 births                                                                |

| Anomaly                              | Embryological basis                                                                                                                                                      | Key features                                                                                                                                                   | Incidence                         |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Posterior urethral valves (PUV)      | Type I (commonest): Wolffian ducts open too far anteriorly onto the primitive prostatic urethra, leaving thick vestigial ridges (valve cusps) caudal to the verumontanum | <b>Commonest cause of urinary outflow obstruction in male infants</b> ; antenatal hydronephrosis/megacystis, oligohydramnios, pulmonary hypoplasia when severe | 1 in 5000–8000 males              |
| Megalourethra                        | Deficient development of corpus spongiosum (and/or cavernosa)                                                                                                            | Dilated, redundant anterior urethra; may coexist with PUV                                                                                                      | Rare                              |
| Congenital anterior urethral valve   | Rare mucosal fold in the anterior (bulbar/penile) urethra                                                                                                                | Urethral obstruction; may coexist with PUV, hypospadias                                                                                                        | Rare                              |
| Urethral duplication                 | Errant splitting of the urethral plate/genital tubercle                                                                                                                  | Two urethrae, almost always one above the other (dorsal channel often blind-ending)                                                                            | Very rare                         |
| Congenital urethrocuteaneous fistula | Localised failure of ventral fold fusion without chordee                                                                                                                 | Ventral urethral opening without hypospadias/chordee                                                                                                           | Very rare                         |
| Congenital rectourethral fistula     | Incomplete separation of hindgut from urogenital sinus (with anorectal malformation)                                                                                     | Shared wall between rectum and prostatic/bulbar urethra                                                                                                        | Seen with anorectal malformations |
| Micropenis                           | Insufficient fetal androgen stimulation (hypogonadism or hypothalamic–pituitary dysfunction)                                                                             | Stretched penile length > 2.5 SD below mean, normally formed urethra                                                                                           | Uncommon                          |
| Bifid/double penis                   | Splitting of the genital tubercle                                                                                                                                        | Duplicated phallic structures, often duplicated urethra                                                                                                        | Very rare                         |

□ Fig 16.17 — Types of hypospadias (Vishram Singh — Textbook of Anatomy Vol 2 4e, p.713)

## Applied / Clinical anatomy

- **Hypospadias surgery:** urethroplasty is corrective; circumcision is deliberately withheld before repair because the abnormal, vascularised prepuce is used as flap tissue for reconstruction.
- **Chordee** must be released (fibrous tissue excised) at the same sitting as urethroplasty to correct the ventral (hypospadias) or dorsal (epispadias) penile curvature.
- **Exstrophy–epispadias complex** needs staged multidisciplinary reconstruction (bladder closure, epispadias repair, bladder-neck reconstruction); associated pubic diastasis and abnormally sited neurovascular bundles of the corpora make surgery technically demanding.

- ▶ **Posterior urethral valves** are diagnosed antenatally by oligohydramnios/megacystis on ultrasound and confirmed postnatally by micturating cystourethrogram (VCUG); managed by early catheterisation and endoscopic valve ablation to prevent renal damage.
- ▶ **Straddle (fall-astride) injury** or pelvic fracture ruptures the urethra typically at the **bulbomembranous junction**; because Buck's fascia and Colles' (superficial perineal) fascia are continuous with the anterior abdominal wall fascia, extravasated urine tracks into the scrotum, penis and anterior abdominal wall but not into the thigh or posteriorly into the ischiorectal region.
- ▶ Catheterisation is more difficult in hypospadias/epispadias because the meatus is displaced from its normal apical position.

### High-yield exam pointers

- ▶ Urethral **epithelium is endodermal** (both sexes); surrounding stroma/muscle is **visceral mesoderm**; the terminal glandular segment alone is **ectodermal**.
- ▶ Urogenital sinus has **3 parts**: vesical → bladder; pelvic → prostatic + membranous urethra; phallic → most of spongy urethra.
- ▶ **Hypospadias** = **ventral meatus**, failure of urethral fold fusion/glandular canalisation, ~1 in 300; **epispadias** = **dorsal meatus**, milder form of bladder exstrophy, much rarer.
- ▶ Bladder exstrophy is **constantly associated with epispadias** — both arise from abnormal genital tubercle/urogenital membrane relationships.
- ▶ **Posterior urethral valves** are the commonest cause of male infant urinary outflow obstruction — remember Type I, arising caudal to the verumontanum.
- ▶ Chordee = ventral (hypospadias) or dorsal (epispadias) penile curvature from a fibrous remnant.
- ▶ Prostate buds off the **prostatic urethra** (endoderm); bulbourethral glands bud from the **phallic urethra/bulb**.
- ▶ Classify hypospadias by meatal site: glandular, balanic, penile, penoscrotal, perineal (proximal → distal severity reversed, i.e. perineal is most severe).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2 4e.



## Discuss the fate of cloaca

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The **cloaca** is the common terminal chamber of the embryonic hindgut, formed in the fourth week when the caudal end of the hindgut expands to receive the **allantois** ventrally; it is an endoderm-lined cavity closed externally by the bilaminar **cloacal membrane** (apposed endoderm and ectoderm, with no

intervening mesoderm). Between the fourth and seventh weeks a wedge of mesenchyme, the **urorectal septum**, grows caudally between the hindgut and the allantois and subdivides the cloaca into a dorsal **anorectal canal** and a ventral **urogenital sinus**, simultaneously splitting the cloacal membrane into an **anal membrane** and a **urogenital membrane**. "The fate of the cloaca" is essentially the fate of these two derivative compartments, of the cloacal membrane, and of the malformations that follow incomplete partitioning.

## 1. Partitioning of the cloaca — the urorectal septum

- ▶ The urorectal septum is derived from a wedge of mesenchyme (the **intercloacal mesenchyme**, marked by *Six1/Six2* expression) lying in the angle between the hindgut dorsally and the allantois ventrally.
- ▶ As caudal folding of the embryo proceeds, the septum does **not literally fuse** with the cloacal membrane; rather, it approaches it and comes to lie close against its inner surface, effectively dividing the cloacal region into a dorsal (rectal) and a ventral (urogenital) part, and the cloacal membrane into anal (dorsal) and urogenital (ventral) membranes.
- ▶ The **ventral pericloacal mesenchyme** contributes to the **genital tubercle**.
- ▶ By the **end of the 7th week** the cloacal membrane breaks down, creating a separate anal opening for the hindgut and a separate ventral opening for the urogenital sinus.
- ▶ The point where the tip of the urorectal septum meets the former cloacal membrane becomes the **perineal body** — described as the "nodal centre" of the whole partitioning process.

## 2. Fate of the dorsal compartment — rectum and anal canal

- ▶ The dorsal part of the divided cloaca (the primitive **anorectal canal**) forms the **rectum** and the **upper part of the anal canal** — both of hindgut endodermal origin.
- ▶ Around the anal (dorsal) membrane, the surrounding mesenchyme proliferates and the surface ectoderm invaginates to form the **proctodeum (anal pit)**.
- ▶ The anal membrane ruptures (~8th week), establishing continuity between the endodermal upper anal canal and the ectodermal lower anal canal derived from the proctodeum.
- ▶ The junction of the two embryological territories is the **pectinate (dentate) line**, marked by a change from columnar to stratified squamous epithelium.

| Feature              | Upper ~2/3 of anal canal                                                   | Lower ~1/3 of anal canal                                           |
|----------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------|
| Embryological origin | Hindgut endoderm (dorsal cloaca)                                           | Ectoderm of the proctodeum (anal pit)                              |
| Epithelium           | Columnar → transitional                                                    | Stratified squamous                                                |
| Arterial supply      | <b>Superior rectal artery</b> (continuation of inferior mesenteric artery) | <b>Inferior rectal artery</b> (branch of internal pudendal artery) |
| Venous drainage      | Superior rectal vein → portal system                                       | Inferior rectal vein → internal pudendal vein → systemic           |
| Lymphatic drainage   | Inferior mesenteric / internal iliac nodes                                 | Superficial inguinal nodes                                         |



| Feature      | Upper ~2/3 of anal canal                                                                           | Lower ~1/3 of anal canal                                                                     |
|--------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Nerve supply | Autonomic (inferior hypogastric plexus) — insensitive to touch/pinprick, sensitive only to stretch | Somatic — <b>inferior rectal nerve</b> (pudendal) — sensitive to pain, touch and temperature |
| Landmark     | —                                                                                                  | Pectinate line marks the boundary                                                            |

### 3. Fate of the ventral compartment — the urogenital sinus

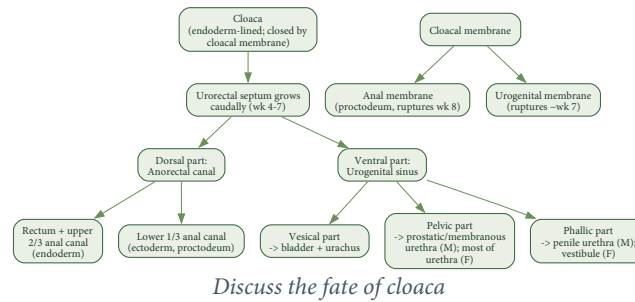
The ventral (urogenital) part of the divided cloaca is subdivided, for descriptive purposes, into three continuous parts:

| Part of urogenital sinus                                                                                 | Fate in the male                                                                                                                   | Fate in the female                                              |
|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Vesical part</b> (cranial, continuous above with the allantois)                                       | Epithelium of most of the <b>urinary bladder</b> ; allantois obliterates to the fibrous <b>urachus</b> (median umbilical ligament) | Same                                                            |
| <b>Pelvic part</b> (narrow middle segment)                                                               | <b>Prostatic and membranous urethra</b>                                                                                            | Almost the <b>entire female urethra</b>                         |
| <b>Phallic part</b> (caudal, in contact with the urogenital membrane, grows toward the genital tubercle) | <b>Penile (spongy) urethra</b>                                                                                                     | <b>Vestibule of the vagina</b> (lower vagina/vestibular region) |

- ▶ The **trigone of the bladder** is *not* derived from the urogenital sinus — it is mesodermal, formed from the absorbed caudal ends of the **mesonephric ducts**, which is why the ureteric orifices come to open separately and obliquely into the bladder base.
- ▶ In the male, the terminal (caudal) ends of the mesonephric ducts become the **ejaculatory ducts** opening into the prostatic urethra; in the female these distal duct remnants degenerate.

### 4. Fate of the cloacal membrane

- ▶ **Anal (dorsal) membrane** → ruptures around the 8th week (after proctodeal invagination) to open the anal canal to the exterior; occasional epithelial remnants persist as **anal papillae**.
- ▶ **Urogenital (ventral) membrane** → ruptures a little earlier, opening the urogenital sinus onto the surface and permitting the definitive external urethral (and, in the female, vaginal) orifice to form.
- ▶ The mesenchymal tip that separates the two membranes at the moment of rupture forms the **perineal body**, the central fibromuscular node of the perineum onto which the bulbospongiosus, external anal sphincter, superficial transverse perineal and levator ani fibres later insert.



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 14.12 — Development of the anal canal. Urogenital septum divides cloaca into ventral primitive urogenital sinus and dorsal primitive rectum; proctodeum invaginates around the anal membrane; rupture of the anal membrane produces the definitive anal canal with the pectinate line marking the endoderm–ectoderm junction (Sontakke — *Textbook of Human Embryology*, p.144)

Reproduce a 3-panel schema (as above) with these exact labels:

- ▶ **Panel A (~4th week):** Genital tubercle, Allantois, Urogenital septum (urorectal septum), Cloaca, Cloacal membrane.
- ▶ **Panel B (~6th week):** Urorectal septum descending, Proctodeum (proctodeum), Anal membrane.
- ▶ **Panel C (after rupture):** Endoderm (above) / Ectoderm (below), Pectinate line, Anal sinuses, Anal columns, Anal canal after rupture of anal membrane.
- ▶ Also sketch, alongside, a coronal schema of the ventral compartment labelling: Vesico-urethral canal (vesical part), Pelvic part, Phallic part, Genital tubercle, Mesonephric duct openings, Perineal body.

### Applied / Clinical anatomy

- ▶ **Anorectal malformations** (incidence  $\approx$  1 in 5000 live births) result from a deficient or mal-directed urorectal septum and are classified as *high* or *low* according to whether the rectal pouch ends above or below the puborectalis sling — this determines continence prognosis and surgical approach.
- ▶ **Rectourethral and rectovesical fistulae** (males) and **rectovaginal / rectovestibular fistulae** (females) occur when the septum fails to reach far enough caudally, so the hindgut opening shifts anteriorly into the urogenital tract; **rectovestibular fistula is the commonest anorectal malformation in girls**.
- ▶ **Persistent cloaca:** a female anomaly in which the rectum, vagina and urethra fail to separate and open through a **single common perineal channel**, 1–7 cm long — the classic "fate-of-cloaca-gone-wrong" lesion.
- ▶ **Imperforate anus:** failure of the anal membrane to rupture (membranous form) or failure of proctodeal development (agenesis form); presents as absence of a patent anal orifice in the neonate.
- ▶ **Cloacal exstrophy:** the most severe ventral body-wall defect — a very early (pre-migration) failure that leaves the bladder split into two exstrophied halves with the exposed rectum/ileum

between them, associated with omphalocele; rare (~1 in 200,000–400,000 pregnancies), with the intussuscepted ileum giving the "elephant-trunk" sign.

- ▶ **Urachal anomalies** (patent urachus, urachal cyst, urachal sinus) follow incomplete obliteration of the allantois arising from the vesical part of the urogenital sinus.
- ▶ **Surgical/clinical landmark:** the pectinate line demarcates differing blood supply, venous drainage (portal vs systemic — the anorectal watershed for portosystemic anastomosis and internal vs external haemorrhoids), lymphatic drainage and pain sensitivity above versus below it — all a direct consequence of the dual (endodermal/ectodermal) origin of the anal canal.

### High-yield exam pointers

- ▶ Cloaca = common endodermal chamber receiving hindgut (dorsally) and allantois (ventrally); closed by the bilaminar cloacal membrane.
- ▶ Urorectal septum (mesenchymal wedge, Six1/Six2<sup>+</sup>) divides the cloaca into dorsal anorectal canal and ventral urogenital sinus by the end of the 7th week; its tip becomes the perineal body.
- ▶ Anal canal: upper 2/3 endoderm (superior rectal vessels, autonomic nerve, portal drainage), lower 1/3 ectoderm/proctodeum (inferior rectal vessels, pudendal nerve, systemic drainage); junction = pectinate line.
- ▶ Urogenital sinus has 3 parts — vesical (→ bladder + urachus), pelvic (→ prostatic/membranous urethra in male, most of female urethra), phallic (→ penile urethra in male, vestibule in female).
- ▶ Bladder trigone is mesodermal (absorbed mesonephric duct), NOT from the urogenital sinus endoderm.
- ▶ Cloacal membrane divides into anal membrane (ruptures ~8th week) and urogenital membrane; remnants of anal membrane = anal papillae.
- ▶ Persistent cloaca (single perineal channel, 1–7 cm) and cloacal exstrophy are the two classic named anomalies of failed cloacal partitioning.
- ▶ Anorectal malformations ≈ 1:5000; rectovestibular fistula is commonest in females.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; BD Chaurasia — Human Anatomy Vol 2 8e and Moore's Clinically Oriented Anatomy 9e (gross/applied anatomy of the anal canal).



## Ectopia Vesicae

*Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Ectopia vesicae (exstrophy of the urinary bladder) is a rare congenital anomaly in which the median infraumbilical part of the anterior abdominal wall and the anterior wall of the urinary bladder both fail to develop, so that the mucosal posterior wall of the bladder — with the trigone and the two ureteric orifices — lies exposed on the surface of the body. It is not an isolated malformation but the mid-point of a spectrum of ventral midline closure defects that runs from simple epispadias at the mild end to exstrophy of the cloaca (the OEIS complex) at the severe end. Epispadias is a constant accompaniment of classic bladder exstrophy.

### Normal development relevant to the defect

- ▶ The **cloaca** is the common endodermal chamber into which the hindgut and the allantois open; ventrally it is closed by the **cloacal membrane**, a bilaminar plate of surface ectoderm fused to cloacal endoderm with no intervening mesoderm.
- ▶ The **urorectal septum** (a wedge of intercloacal mesenchyme at the hindgut–allantois angle) grows caudally and, without actually fusing with it, pushes the endodermal epithelium toward the cloacal membrane — dividing the cloaca into a dorsal anorectal canal and a ventral urogenital sinus, and correspondingly splitting the cloacal membrane into a cranial **urogenital membrane** and a caudal **anal membrane**.
- ▶ During **lateral body-wall folding**, paired lateral folds grow ventromedially and fuse in the midline; the mesoderm carried in these folds migrates into the **infraumbilical region** (between the umbilicus and the genital tubercle) to form the muscles of the lower anterior abdominal wall, ventral to the developing bladder (vesicourethral canal).
- ▶ Only after this mesoderm has migrated in does the urogenital membrane normally rupture, so that the pre-formed muscular abdominal wall already separates the ectoderm from the bladder lumen.

### Aetiopathogenesis

Two complementary explanations are offered in the literature for the same underlying event — a failure to interpose mesoderm between ectoderm and bladder endoderm in the infraumbilical region before breakdown of the membrane:

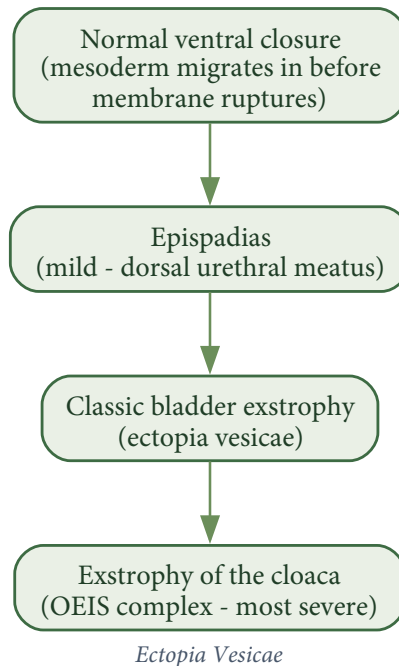
- ▶ **Failure of mesodermal migration:** the lateral folds fail to bring mesoderm into the hypogastric region between the umbilicus and genital tubercle, so no abdominal-wall musculature forms there. Surface ectoderm consequently lies directly against the endoderm of the vesicourethral canal; this thin ectoderm–endoderm bilayer breaks down, exposing the posterior bladder wall.
- ▶ **Cloacal-membrane / genital-tubercle malposition theory:** anomalies of the ventral body wall caudal to the umbilicus, with inappropriate siting of the genital tubercle, cause the urorectal septum (internal) to become associated with the genital tubercle (external); this widely separates the urogenital and anal membranes. An abnormally large or persistent urogenital membrane then ruptures too early — before adjacent mesenchyme can proliferate and migrate in — so that when it involutes, the posterior surface of the bladder is exposed to the anterior abdominal wall

as an irregularly oval, mucosa-covered area on which the two ureteric orifices open; the periphery of this area (covered by urothelium) becomes continuous with the surrounding skin.

- Because the genital tubercle is directly implicated, **epispadias is an obligatory associated defect**, not a coincidental one.

### Spectrum of the exstrophy–epispadias complex

| Grade        | Defect                                                             | Extent of failure                                                                                                                           |
|--------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Mildest      | Epispadias                                                         | Urethral opening displaced to the dorsum of the genital tubercle; abdominal wall and bladder otherwise intact                               |
| Intermediate | Exstrophy of the bladder (ectopia vesicae)                         | + absent anterior bladder wall and infraumbilical abdominal wall; posterior bladder mucosa exposed                                          |
| Most severe  | Exstrophy of the cloaca (vesico-intestinal fissure / OEIS complex) | + failure of urorectal-septum development; both bladder and anorectal lumen are exposed, with a strip of hindgut between two bladder halves |



### Morphological and clinical features

- **Deficient infraumbilical anterior abdominal wall**, with the umbilicus low-set close to the upper margin of the defect.
- **Absent anterior wall of the bladder**; the exposed posterior wall shows the trigone and both ureteric orifices, from which urine dribbles intermittently onto the surface (no storage of urine is possible).

- ▶ **Epispadias** (constant): the urethra opens on the dorsal aspect of a short, broad phallus with widely separated corpora cavernosa.
- ▶ **Genital anomalies** reported with the more severe forms include a buried/absent-appearing phallus, bifid scrotum, undescended testis, and — in the cloacal variant — continuity of the urethral opening with the anal opening and prolapse of bowel through the exposed segment.
- ▶ **Incidence:** reported figures vary between sources — approximately 1 in 10,000 live births in some texts, and about 1 in 40,000–50,000 in others; all agree on a **male preponderance** (about 2:1 to 3:1). Exstrophy of the cloaca is much rarer (~1 in 200,000 births).

### OEIS complex and prenatal diagnosis

When the defect is severe enough to involve the urorectal septum itself, it presents as part of the **OEIS complex**:

- ▶ **O** — Omphalocele
- ▶ **E** — Exstrophy of the bladder or cloaca
- ▶ **I** — Imperforate anus
- ▶ **S** — Skeletal (spinal) anomalies

Prenatal detection:

- ▶ **Biochemical:** raised maternal serum and amniotic-fluid **alpha-fetoprotein (AFP)**, as with other open ventral-wall defects (omphalocele, gastroschisis).
- ▶ **Ultrasound:** non-visualization of a normally filled fetal urinary bladder, an infraumbilical anterior-abdominal-wall defect (with or without omphalocele), and a low-set umbilicus.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 20.18 — *Ectopia vesicae* (exstrophy of urinary bladder). A. Line diagram. B. Actual clinical photograph. (Vishram Singh — *Textbook of Clinical Embryology*, p.256)

Reproduce a simple line diagram of the lower abdomen/perineum labelling:

- ▶ Low-set **umbilicus**
- ▶ Deficient **infraumbilical anterior abdominal wall** (skin merging directly with mucosa at the margins of the defect)
- ▶ Exposed **posterior wall / mucosa of the bladder** as an oval area
- ▶ **Trigone** and both **ureteric orifices**, with drops indicating dribbling urine
- ▶ Dorsally-placed urethral opening — **epispadias**, on a short phallus with separated corpora cavernosa
- ▶ Widely separated **pubic bones** underlying the defect

### Applied / Clinical anatomy

- ▶ Because the bladder cannot store urine and the ureteric orifices are directly exposed, patients present at birth with continuous urinary leakage and are at risk of ascending infection.
- ▶ Epispadias, being constant, must always be assessed and repaired alongside the bladder defect.

- ▶ **Management is by staged surgical bladder reconstruction** — closure of the exposed bladder plate and abdominal wall, followed by epispadias repair and later bladder-neck/continence reconstruction.
- ▶ Differentiate from **prune-belly (Eagle–Barrett) syndrome**, another anterior-wall anomaly in which the abdominal wall itself closes but its musculature fails to develop, producing a wrinkled, distended abdomen with undescended testes and urinary-tract malformations — the bladder mucosa is not exposed, unlike in ectopia vesicae.
- ▶ Complete failure of the urorectal septum with a widened, prematurely ruptured cloacal membrane produces the more severe **exstrophy of the cloaca (ectopia cloacae)**, in which bladder and hindgut both lie exposed with bilateral bladder halves flanking the exposed hindgut — this is managed as a multidisciplinary neonatal surgical emergency.

### High-yield exam pointers

- ▶ Ectopia vesicae = absent anterior wall of bladder + absent infraumbilical anterior abdominal wall; posterior bladder mucosa (trigone, ureteric orifices) exposed on the surface.
- ▶ Cause: failure of mesoderm to migrate into the infraumbilical region during lateral body-wall folding, so ectoderm and bladder endoderm remain apposed and later break down; genital-tubercle malposition/abnormal cloacal-membrane behaviour is the complementary mechanistic explanation.
- ▶ **Epispadias is a constant associated feature.**
- ▶ Spectrum: epispadias → classic bladder exstrophy → exstrophy of the cloaca (most severe).
- ▶ Cloacal exstrophy = OEIS complex (Omphalocele, Exstrophy of bladder/cloaca, Imperforate anus, Skeletal defects).
- ▶ Reported incidence varies by source (roughly 1:10,000 to 1:50,000), with a consistent male preponderance; cloacal exstrophy is far rarer (~1:200,000).
- ▶ Antenatal clues: raised AFP; USG shows a non-visualized fetal bladder and an infraumbilical wall defect.
- ▶ Treated by staged surgical bladder/abdominal-wall reconstruction with later epispadias and continence repair.
- ▶ Differentiate from prune-belly syndrome (abdominal wall closes but its muscle fails to form; bladder mucosa is not exposed).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Moore The Developing Human 9e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; Brijesh Kumar Embryology Text & Atlas.





## Fate of mesonephric ducts and tubules in males

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

### Definition / Introduction

The **mesonephric (Wolffian) duct** is the primary excretory duct of the mesonephros, the second (transient) excretory organ of intermediate mesoderm origin. In both sexes it first gives rise to the **ureteric bud**, from which the definitive urinary collecting system develops, and its caudal end is absorbed into the developing bladder to form the **trigone**. Thereafter its fate diverges: in the male, **testosterone** secreted locally by fetal Leydig cells causes the duct and a subset of its associated tubules to **persist and differentiate into the main genital duct system** — efferent ductules, epididymis, vas deferens, seminal vesicle and ejaculatory duct — while in the female, in the absence of testosterone, the duct largely degenerates. Understanding this fate requires tracing (1) the mesonephric **tubules** and (2) the mesonephric **duct** itself, each of which contributes both functional derivatives and inconstant vestiges in the adult male.

### 1. The mesonephros and mesonephric duct in the indifferent stage

- ▶ The **mesonephros (Wolffian body)** develops from intermediate mesoderm caudal to the pronephros, extending initially from about the upper thoracic to upper lumbar somites; it develops as many as **70–80 mesonephric tubules**, each acquiring a glomerulus (Bowman capsule) at its medial end and draining laterally into a longitudinal **primary excretory duct**.
- ▶ Once the tubules connect to this duct, it is renamed the **mesonephric (Wolffian) duct**; it runs caudally in the nephric ridge and opens into the **cloaca** (later the urogenital sinus).
- ▶ The **gonad** develops as a thickening on the **medial** aspect of the mesonephric (urogenital) ridge; primordial germ cells populate the gonadal ridge from the yolk-sac endoderm during the 5th–6th week.
- ▶ Around the **5th week**, near its caudal/cloacal end, the mesonephric duct gives off a diverticulum, the **ureteric bud (metanephric diverticulum)**, which penetrates the metanephrogenic mesenchyme and induces the **metanephros** (definitive kidney) — this event and its derivatives are **common to both sexes** and precede gonadal differentiation.
- ▶ Most cranial mesonephric tubules degenerate early; by stage 19, tubules persist mainly over the first three lumbar segments (up to ~26 tubules), positioned to be recruited by the developing gonad.

### 2. Hormonal control — why the duct persists only in the male

- ▶ From about the **8th week**, fetal **Leydig cells** (stimulated first by placental hCG, later fetal LH) secrete **testosterone**, which acts **locally (paracrine, ipsilaterally)** on the adjoining mesonephric duct, stimulating its **persistence and differentiation** into the epididymis, vas deferens, seminal vesicle and ejaculatory duct.
- ▶ Simultaneously, **Sertoli cells** secrete **anti-Müllerian hormone (AMH/Müllerian-inhibiting substance)**, which causes regression of the **paramesonephric (Müllerian) duct** on the same side (it persists only as the vestigial **appendix testis**, and contributes with the urogenital sinus to the **prostatic utricle**).

- ▶ Because testosterone acts locally, mesonephric-duct persistence and paramesonephric regression each occur **only on the side of a functioning testis** — the embryological basis of asymmetric internal genitalia when a testis is absent, dysgenetic or produces AMH but not androgen (or vice versa).

### 3. Fate of the mesonephric tubules in the male

| Group of tubules                                                        | Fate in the male                                                                                                                                                       |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rostral-most 1–2 tubules (cranial to the testis)                        | Regress to vestigial <b>superior (rostral) aberrant ductules</b>                                                                                                       |
| <b>Epigenital tubules</b> — next 5–6 tubules, lying opposite the testis | Establish contact with cords of the <b>rete testis</b> ; become the <b>efferent ductules (ductuli efferentes)</b> and the <b>lobules of the head of the epididymis</b> |
| <b>Paragenital tubules</b> — caudal tubules, caudal to the testis       | Do <b>not</b> join the rete testis; regress to the vestigial <b>paradidymis (of Giralde's)</b> and <b>inferior (caudal) aberrant ductules</b>                          |

### 4. Fate of the mesonephric duct itself in the male

- ▶ The **most cranial part** of the duct, above the level where the efferent ductules enter it, degenerates and persists only as the vestigial **appendix of the epididymis**.
- ▶ The segment of duct **receiving the efferent ductules** elongates enormously and becomes highly convoluted, forming the **duct (canal) of the epididymis** (head, body and tail).
- ▶ From the **tail of the epididymis** to the point where the seminal vesicle buds off, the duct acquires a **thick muscular coat** and becomes the **ductus (vas) deferens**.
- ▶ Near the end of the 3rd into the 4th month, a **common swelling** appears at the caudal end of the duct; this separates into two rudiments — the **ampulla of the vas deferens** and the outgrowing, diverticulated **seminal vesicle** — with a marked growth spurt of both around the 6th month, roughly coincident with (but not proven to cause) paramesonephric-duct regression.
- ▶ The segment of duct **distal to the seminal-vesicle outgrowth** becomes the **ejaculatory duct**, which pierces the prostate to open on the seminal colliculus into the prostatic urethra, flanking the (paramesonephric-derived) prostatic utricle.
- ▶ The **caudal-most part of the duct**, together with the ureter, is absorbed into the posterior wall of the urogenital sinus as the bladder develops: this mesodermal tissue forms the **trigone of the bladder** and, more distally, the **posterior wall of the prostatic urethra** cranial to the openings of the ejaculatory ducts.

Summary table — mesonephric system to adult male derivative

| Embryonic structure                             | Adult male derivative                                |
|-------------------------------------------------|------------------------------------------------------|
| Rostral 1–2 mesonephric tubules                 | Superior aberrant ductules (vestigial)               |
| Epigenital tubules (opposite testis)            | Efferent ductules + lobules of head of epididymis    |
| Paragenital (caudal) tubules                    | Paradidymis + inferior aberrant ductules (vestigial) |
| Mesonephric duct — cranial to efferent ductules | Appendix of epididymis (vestigial)                   |

| Embryonic structure                                          | Adult male derivative                                   |
|--------------------------------------------------------------|---------------------------------------------------------|
| Mesonephric duct — receiving efferent ductules               | Duct (canal) of epididymis                              |
| Mesonephric duct — tail of epididymis to seminal-vesicle bud | Ductus (vas) deferens                                   |
| Common caudal swelling of duct                               | Seminal vesicle + ampulla of vas deferens               |
| Duct segment distal to seminal vesicle                       | Ejaculatory duct                                        |
| Caudal-most duct absorbed into urogenital sinus              | Trigone of bladder; posterior wall of prostatic urethra |
| Ureteric bud (diverticulum of mesonephric duct)              | Ureter, renal pelvis, calyces, collecting tubules/ducts |

□ Fig 21.8 — Derivatives of mesonephric duct in genital system (Sontakke — Textbook of Human Embryology, p.231)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled longitudinal schematic of the male genital duct system, showing (top to bottom): **testis** with seminiferous tubules → **rete testis** → **efferent ductules (ductuli efferentes)** entering the **head of epididymis** → **body and tail of epididymis** → **ductus (vas) deferens** ascending in the spermatic cord → **ampulla of vas deferens** joined by the duct of the **seminal vesicle** → combined **ejaculatory duct** opening into the **prostatic urethra** at the seminal colliculus (beside the prostatic utricle). Mark the vestigial structures separately alongside: **appendix of epididymis** (cranial duct remnant), **superior aberrant ductules** and **inferior aberrant ductules/paradidymis** (tubule remnants). Add, as a side inset, the **ureteric bud** arising from the caudal mesonephric duct with an arrow to the **ureter** → **renal pelvis** → **calyces**, and label the **trigone of the bladder** at the duct's absorbed caudal end.

### Applied / Clinical anatomy

- **Congenital bilateral absence of the vas deferens (CBAVD)**: absence of the body/tail of the epididymis, vas deferens and seminal vesicle; ~80% of cases carry **CFTR** gene mutations (the cystic fibrosis gene), reflecting the CFTR ion channel's requirement for normal mesonephric-duct differentiation. CBAVD accounts for 1–2% of male infertility and ~10% of obstructive azoospermia; a man with CBAVD but no lung disease may still be a CFTR-mutation carrier.
- **Ectopic ureteric opening**: because the ureteric bud is itself a mesonephric-duct outgrowth, an abnormally caudal or duplicated bud can retain a low entrance into the **epididymal region**, vas deferens, seminal vesicle or urethra instead of the bladder — a recognised anomaly of shared embryological origin.
- **Appendix of the epididymis** (a mesonephric-duct vestige) can undergo **torsion**, producing acute scrotal pain in a boy that must be distinguished clinically from testicular torsion.
- **Vasectomy**: elective division/ligation of the vas deferens — a direct mesonephric-duct derivative — in the spermatic cord is the standard surgical method of male sterilisation.
- **Aberrant ductules and the paradidymis** (vestigial tubule remnants) are potential sites for small paratesticular/epididymal cysts.

- ▶ **Prostatic utricle**, though paramesonephric/sinus in origin, sits immediately between the two ejaculatory duct (mesonephric-derived) openings on the seminal colliculus and can rarely be enlarged enough to cause outflow obstruction — of surgical relevance during transurethral instrumentation.

### High-yield exam pointers

- ▶ Mesonephric duct → **efferent ductules** are NOT from the duct — they are from the **epigenital tubules**; the duct itself gives **epididymis (duct)** → **vas deferens** → **ejaculatory duct**.
- ▶ **Testosterone (Leydig cells)**, acting locally/ipsilaterally, is what makes the mesonephric duct persist in the male; **AMH (Sertoli cells)** independently suppresses the paramesonephric duct on the same side.
- ▶ Three tubule fates: rostral tubules → **superior aberrant ductules**; middle (epigenital) tubules → **efferent ductules + epididymal head lobules**; caudal (paragenital) tubules → **paradidymis + inferior aberrant ductules**.
- ▶ Duct vestige cranial to efferent-ductule entry = **appendix of epididymis** (mesonephric); do not confuse with **appendix testis** (paramesonephric vestige).
- ▶ **Seminal vesicle and ampulla of vas deferens** arise from a **common swelling** at the caudal end of the mesonephric duct (end of 3rd/4th month), later separating into two.
- ▶ **Ureteric bud** (→ ureter, pelvis, calyces, collecting tubules) and the **trigone of the bladder** are mesonephric-duct derivatives common to **both sexes**, formed before gonadal differentiation.
- ▶ Clinical hook: **CBAVD ↔ CFTR mutation** — high-yield genetics–embryology correlation.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Sontakke Textbook of Human Embryology (for the embedded plate, Fig 21.8, p.231).



## Formation and fate of mesonephric ducts in male and female

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **mesonephric (Wolffian) duct** — also called Leydig's duct, archinephric duct or nephric duct — is the paired excretory duct of the intermediate mesoderm that first drains the mesonephric ("second") kidney and later becomes the genital duct system of the male. It arises in the fourth week as a continuation of the pronephric duct, gives off the ureteric bud that induces the metanephros, and opens into the cloaca. Its ultimate fate diverges sharply between the sexes: under testosterone it differentiates into the epididymis, vas deferens, seminal vesicle and ejaculatory duct in the male, whereas in the absence of local androgen it degenerates in the female, leaving only vestigial remnants (epoophoron, paroophoron, Gartner's duct). This duality — one primordium, two very different fates — is a favourite PG viva and theory topic because it links embryology directly to congenital anomalies of the urogenital tract.

### 1. Formation of the mesonephric duct and the mesonephros

- ▶ In the fourth week, the **nephrogenic cord** (intermediate mesoderm extending from cervical to sacral levels) gives rise cranially to the transitory **pronephros**, whose duct grows caudally as the **primary excretory (pronephric) duct**.
- ▶ From **stage 12** (mesonephric tubules developing from intermediate mesenchyme between somite levels 8–20) onward, mesonephric tubules connect to this duct, which is now renamed the **mesonephric (Wolffian) duct**.
- ▶ The duct runs caudally within a **mesonephric (tubal) fold** and opens into the cloaca by the end of the fourth week.
- ▶ The **mesonephros (Wolffian body)** is a bulky ridge extending from the septum transversum to the third lumbar segment; roughly **70–80 mesonephric tubules**, each S-shaped with its own glomerulus and Bowman's capsule, develop opposite the thoracolumbar somites and briefly function as an excretory (nephron-like) unit.
- ▶ Development proceeds **cranio-caudally** — cranial tubules degenerate as caudal ones are still forming — so by the time the metanephros (definitive kidney) takes over, most mesonephric tubules have disappeared; only tubules at the **cranial (epigenital)** and **caudal (paragenital)** ends persist as vestiges (fate below).
- ▶ The mesonephric duct also gives off the **ureteric bud** from its caudal part (a little cranial to the cloaca), which grows into the metanephric blastema to form the ureter, pelvis, calyces and collecting duct system of the definitive kidney — a derivative common to **both sexes**.
- ▶ As the ureteric bud's connection shifts, the caudal segment of each mesonephric duct (between the ureteric bud origin and the cloaca) is **absorbed** into the wall of the developing vesicourethral canal, forming the **trigone of the urinary bladder** and part of the posterior wall of the prostatic/female urethra — again common to both sexes.

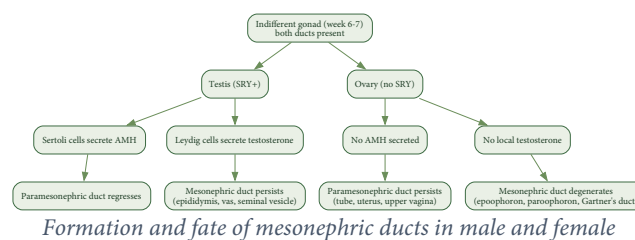
### 2. Formation of the paramesonephric duct and the indifferent stage

- ▶ In the fifth–sixth week (10–12 mm embryo), a second, paired duct — the **paramesonephric (Müllerian) duct** — develops lateral to the mesonephric duct as a linear invagination of coelomic epithelium on the mesonephric ridge.

- ▶ Each paramesonephric duct grows caudally, guided by the mesonephric duct, then in the eighth week turns medially, crosses **ventral** to the mesonephric duct, and fuses with its fellow in the midline to form the **uterovaginal canal**, whose blind tip abuts the dorsal wall of the urogenital sinus, raising the **sinus (Müllerian) tubercle** around the ninth week.
- ▶ Until about the seventh week, **both duct systems (mesonephric and paramesonephric) coexist side by side in both sexes** — the "indifferent" or ambisexual stage of the genital ducts.
- ▶ Thereafter one system is retained and differentiates while the other regresses, under the control of testicular hormones (see below).

### 3. Hormonal control of duct-fate divergence

- ▶ The gonad differentiates first (testis under SRY, ~week 6–7); the duct fate then follows the gonad, not the chromosomal sex directly.
- ▶ **Sertoli cells** of the fetal testis secrete **anti-Müllerian hormone (AMH / Müllerian-inhibiting substance)**, which acts locally (paracrine, via the mesonephric duct as a conduit) to cause the **paramesonephric ducts to regress rapidly between the 8th and 10th weeks**.
- ▶ **Leydig cells** of the fetal testis secrete **testosterone** from about the eighth week; this acts **locally and unilaterally** (the mesonephric duct is retained only on the side where testosterone is present — classically shown by unilateral castration experiments) to stabilise and differentiate the mesonephric duct into the male genital duct system.
- ▶ In the female, the absence of a testis means no AMH is secreted, so the **paramesonephric ducts persist and differentiate** into the genital tract; and the absence of local testosterone means the **mesonephric ducts degenerate**, leaving only vestiges.
- ▶ Clinically, this explains **persistent Müllerian duct syndrome** (deficient AMH/AMH-receptor signalling — an XY individual retains a uterus and tubes alongside normal male mesonephric derivatives) and **complete androgen insensitivity syndrome** (normal AMH causes Müllerian regression, but the androgen receptor defect prevents mesonephric duct differentiation despite adequate testosterone, so the mesonephric ducts also fail to develop).



□ Fig 21.8 — Derivatives of mesonephric duct in genital system (Sontakke — Textbook of Human Embryology, p.231)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A bilateral labelled scheme (as in the plate above), male and female side by side:

- ▶ **Male:** Testis → Rete testis → Efferent ductules → Canal of epididymis → Vas deferens → Seminal vesicle → Ejaculatory duct.
- ▶ **Female:** Ovary/Fallopian tube for orientation → **Epoophoron** (in the mesosalpinx) → **Paroophoron** (between ovary and uterus) → **Gartner's duct** (along the uterus/cervix into the vaginal wall).
- ▶ Mark the **broad ligament/mesovarium** as the site of all female vestiges.

## 4. Fate of the mesonephric duct and tubules in the male

| Mesonephric structure                                                            | Male derivative                                                                                                                                               |
|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cranial (epigenital) mesonephric tubules                                         | <b>Efferent ductules (vasa efferentia / ductuli efferentes)</b> — join the rete testis to the mesonephric duct                                                |
| Caudal (paragenital) mesonephric tubules                                         | Mostly degenerate; a few persist as the <b>paradidymis</b> (unconnected to testis or epididymis)                                                              |
| Epigenital tubules cranial to the efferent ductules, not reaching the epididymis | <b>Superior aberrant ductules</b> (connected to testis, not epididymis)                                                                                       |
| Tubules caudal to the efferent ductules                                          | <b>Inferior aberrant ductules</b> (connected to epididymis, not testis)                                                                                       |
| Cranial blind end of mesonephric duct                                            | <b>Appendix of the epididymis</b> (vestigial; not to be confused with the appendix of the testis, a paramesonephric remnant)                                  |
| Mesonephric duct — cranial part, becomes highly coiled                           | <b>Canal (duct) of the epididymis</b>                                                                                                                         |
| Mesonephric duct — distal/mid part                                               | <b>Vas (ductus) deferens</b>                                                                                                                                  |
| Mesonephric duct — diverticulum near its lower end                               | <b>Seminal vesicle</b>                                                                                                                                        |
| Mesonephric duct — part between seminal vesicle and urethra                      | <b>Ejaculatory duct</b>                                                                                                                                       |
| Mesonephric duct — caudal-most part absorbed into vesicourethral canal           | <b>Trigone of the bladder</b> ; posterior wall of prostatic urethra above the ejaculatory-duct openings; contributes mesodermal tissue to the <b>prostate</b> |
| Ureteric bud (from mesonephric duct)                                             | <b>Ureter, renal pelvis, calyces, collecting tubules</b> of the definitive kidney                                                                             |

- ▶ Because the mesonephric duct becomes the entire excurrent duct system caudal to the rete testis, a single embryological error here (e.g. failure of testosterone action, or CFTR-related agenesis) can produce **congenital absence of the vas deferens and/or seminal vesicle**, often with an associated ipsilateral renal anomaly since both derive from the same duct.



## 5. Fate of the mesonephric duct and tubules in the female

| Mesonephric structure                                                                                                                                              | Female derivative                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Ureteric bud (from mesonephric duct)                                                                                                                               | Ureter, renal pelvis, calyces, collecting tubules — same as in the male                                                                       |
| Caudal-most part of mesonephric duct absorbed into vesicourethral canal                                                                                            | Trigone of the bladder; posterior wall of the female urethra                                                                                  |
| Rest of the mesonephric duct and tubules                                                                                                                           | Do <b>not</b> connect to the developing ovary; the great majority <b>degenerate</b> (no local testosterone)                                   |
| Cranial persisting duct + transverse tubules, in the mesosalpinx                                                                                                   | <b>Epoophoron</b> — a longitudinal duct with transverse ductules opening into it; the female equivalent of the epididymis + efferent ductules |
| Caudal (paragenital) tubule remnants, between ovary and uterus                                                                                                     | <b>Paroophoron</b> — the female equivalent of the paradidymis                                                                                 |
| Persisting caudal segment of the longitudinal duct, running along the side of the uterus and embedding in the cervical wall (never opening into the uterine lumen) | <b>Duct of the epoophoron / Gartner's duct</b> (or <b>Gartner's cyst</b> , if it dilates) — the female equivalent of the vas deferens         |

- ▶ The mesonephric duct and its remnants never make functional contact with the ovary in the female — this is a key point that distinguishes the female pathway from the male, where the mesonephric duct's efferent ductules physically connect to the rete testis.
- ▶ These vestiges are of no functional importance in the adult except as a source of **paraovarian/broad-ligament (Gartner's duct) cysts**.

## Applied / Clinical anatomy

- ▶ **Gartner's duct cyst:** the commonest cystic remnant along the anterolateral vaginal wall/broad ligament; usually asymptomatic, found incidentally on pelvic examination or imaging, and enucleated if symptomatic or enlarging.
- ▶ **Persistent Müllerian duct syndrome (PMDS):** deficient AMH synthesis or AMH-receptor mutation in a 46,XY individual — normal male mesonephric (Wolffian) derivatives develop under testosterone, but a uterus, tubes and upper vagina also persist because the paramesonephric ducts were never suppressed; often discovered incidentally during herniorrhaphy/orchidopexy for cryptorchidism.
- ▶ **Complete androgen insensitivity syndrome (CAIS):** AMH acts normally (Müllerian ducts regress), but end-organ resistance to testosterone means the mesonephric ducts also fail to differentiate — the phenotype is a female with testes, absent uterus/tubes, and a blind vaginal pouch.
- ▶ **Ectopic ureteric opening:** since the ureteric bud is itself a mesonephric-duct derivative, an anomalous bud origin can make the ureter open ectopically into other mesonephric derivatives — the vas deferens, seminal vesicle or prostatic urethra in the male, or the vestibule/vagina in the female (continuous incontinence if distal to the sphincter).

- ▶ **Congenital unilateral absence of vas deferens/seminal vesicle with ipsilateral renal agenesis:** both share the same mesonephric-duct origin, so one early insult explains the combined urinary + genital anomaly — a classic exam correlation.
- ▶ **Mesonephric duct tumours:** rare clear-cell adenocarcinomas can arise from persisting female mesonephric remnants (epoophoron/Gartner's duct) in the broad ligament or lateral vaginal/cervical wall.
- ▶ **Appendix of epididymis vs appendix of testis:** the appendix of the epididymis (mesonephric remnant) and the appendix of the testis/hydatid of Morgagni (paramesonephric remnant) are the two vestigial appendages on the testis that may undergo **torsion** — a frequently tested clinical distinction that hinges directly on their differing embryological origin.

### High-yield exam pointers

- ▶ Mesonephric duct = **Wolffian duct** = **Leydig's duct** = **archinephric/nephric duct**; mesonephros first described by Caspar Friedrich Wolff (1759).
- ▶ Gives off the **ureteric bud** and forms the **bladder trigone** in **both** sexes — this part of the fate is sex-independent.
- ▶ Male fate (testosterone-dependent): **efferent ductules, epididymis, vas deferens, seminal vesicle, ejaculatory duct**; plus vestiges — appendix of epididymis, paradidymis, superior/inferior aberrant ductules.
- ▶ Female fate (default, no local testosterone): duct degenerates; vestiges only — **epoophoron, paroophoron, Gartner's duct/cyst**; never connects to the ovary.
- ▶ Divergence is hormone-driven: **AMH from Sertoli cells** suppresses the paramesonephric duct; **testosterone from Leydig cells** rescues/differentiates the mesonephric duct — action is **local and unilateral**, not systemic.
- ▶ Paramesonephric duct develops **lateral to**, then crosses **ventral to**, the mesonephric duct before fusing in the midline (uterovaginal canal).
- ▶ Appendix of epididymis (mesonephric) vs appendix of testis (paramesonephric) — do not confuse in torsion questions.
- ▶ Clinical triad to remember: Gartner's duct cyst, persistent Müllerian duct syndrome, and the combined vas deferens/renal agenesis anomaly.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Hamilton, Boyd & Mossman — Human Embryology.



# Formation of kidney and related anomalies

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** The kidney develops from intermediate mesoderm through three successive, overlapping excretory organs — **pronephros**, **mesonephros** and **metanephros** — recapitulating vertebrate phylogeny. Only the **metanephros** persists as the permanent kidney, formed by reciprocal induction between the **ureteric bud** (an outgrowth of the caudal mesonephric duct) and the **metanephric blastema** (a condensation of sacral intermediate mesoderm). Because this induction, the subsequent ascent/rotation, and the kidney's sequential vascular supply are all tightly choreographed, congenital anomalies of the kidney and urinary tract (**CAKUT**) are relatively common — affecting 3–6% of live births — ranging from agenesis and ectopia to fusion and cystic malformations.

## 1. Embryological origin and the three succeeding kidneys

- ▶ The **intermediate mesoderm** is a longitudinal strip lying between the paraxial and lateral plate mesoderm; after lateral folding of the embryo it forms the **urogenital ridge** on the posterior wall, flanking the dorsal aorta.
- ▶ The urogenital ridge differentiates into a medial **genital ridge** (gonad) and a lateral **nephrogenic cord** (urinary system); the nephrogenic cord extends from cervical to sacral levels.
- ▶ Three excretory organs arise in **craniocaudal succession** from the nephrogenic cord, each overlapping in time with the next:

| Organ       | Location      | Segmentation  | Time of appearance     | Functional status                                                  | Fate of its duct                                    |
|-------------|---------------|---------------|------------------------|--------------------------------------------------------------------|-----------------------------------------------------|
| Pronephros  | Cervical      | Segmented     | Beginning of 4th week  | Non-functional; completely regresses                               | Pronephric duct persists → becomes mesonephric duct |
| Mesonephros | Thoracolumbar | Segmented     | End of 4th week        | Functional briefly (produces dilute urine), then largely regresses | Mesonephric (Wolffian) duct persists                |
| Metanephros | Sacral        | Non-segmented | Beginning of 3rd month | Functional; persists permanently                                   | Drains via the ureter                               |

- ▶ A few caudal mesonephric tubules persist in the male as the **vasa efferentia** of the testis; the mesonephric duct itself becomes the epididymis, vas deferens and ejaculatory duct.

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros. Pronephric tubules appear cranially, mesonephros in the thoracolumbar region, and the metanephros with its ureteric bud caudally (Sontakke — Textbook of Human Embryology, p.212)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Lateral view of a 4th–5th week embryo — label: **degenerating pronephros** (cervical) with pronephric duct; **mesonephros** (thoracolumbar) with mesonephric tubules opening into the **mesonephric duct**; **metanephros** (sacral) capped by the **ureteric bud**; **cloaca**; vertebral levels (cervical/thoracic/lumbar/sacral) marked alongside.

## 2. Development of the metanephros (permanent kidney)

The permanent kidney has a **dual embryological origin**, and each part gives rise to a distinct component of the adult kidney:

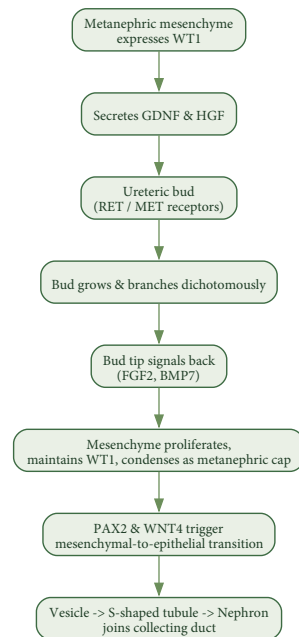
- ▶ **Ureteric bud** (diverticulum of the mesonephric duct, arising just before the duct opens into the cloaca) → grows dorsocranially and forms the **collecting system**:
  - Its stalk elongates into the **ureter**; its dilating cranial end forms the **renal pelvis**.
  - The bud undergoes ~13 generations of **dichotomous branching**, producing the **major calyces** (first few generations, by confluence), **minor calyces**, and **collecting ducts/tubules** (1–3 million in number).
- ▶ **Metanephric blastema** (metanephrogenic mesenchyme) → forms the **excretory system (nephron)**:
  - Mesenchyme condenses around each new ureteric-bud tip as a **metanephric cap** → **metanephric vesicle** → comma-shaped → **S-shaped tubule** (primitive renal tubule).
  - The tubule's proximal end opens into the collecting tubule; its distal end dilates and is invaginated by a capillary tuft (from angiogenic mesenchyme) to form the **glomerulus** and **Bowman's (glomerular) capsule**.
  - The intervening tubule differentiates into the **proximal convoluted tubule**, **loop of Henle** and **distal convoluted tubule**, which joins the collecting tubule to complete the **uriniferous tubule**.

| Embryonic structure  | Adult derivative                                                      |
|----------------------|-----------------------------------------------------------------------|
| Ureteric bud         | Ureter, renal pelvis, major & minor calyces, collecting ducts/tubules |
| Metanephric blastema | Glomerulus, Bowman's capsule, PCT, loop of Henle, DCT                 |

- ▶ Nephron formation proceeds **centrifugally** — the outermost cortical nephrons are the last to form; all stages of differentiation coexist concurrently in the growing kidney, which remains visibly **lobulated throughout fetal life**, the lobulation normally effacing during the **first year after birth**.

## 3. Molecular regulation of nephrogenesis

Reciprocal epithelial–mesenchymal induction between the ureteric bud and metanephric blastema is driven by a defined set of signalling molecules:



*Formation of kidney and related anomalies*

- ▶ **WT1**, expressed by the mesenchyme, confers competence to respond to bud induction and regulates its own **GDNF/HGF** output; **GDNF–RET** and **HGF–MET** then drive bud outgrowth and dichotomous branching.
- ▶ **FGF2/BMP7** (from the bud) sustain mesenchymal proliferation and **WT1** expression; **PAX2/WNT4** (from the bud) trigger mesenchymal-to-epithelial transition into vesicles and S-shaped tubules.
- ▶ **Clinical link:** **WT1** mutation (chromosome 11p13) underlies **Wilms' tumour (nephroblastoma)**, the commonest primary renal tumour of childhood.

#### 4. Ascent, rotation and blood supply of the kidney

- ▶ The metanephros initially lies in the **sacral region**. As the caudal trunk grows disproportionately and embryonic curvature straightens, the kidney comes to occupy a progressively more cranial level — its so-called "**ascent**."
- ▶ By the time the embryo is ~13 mm long, the metanephric pelvis already lies opposite **L2**; the kidney finally settles at the **T12–L3** vertebral span.
- ▶ **Rotation:** the hilum initially faces **ventrally**; during ascent the kidney rotates **90° medially**, so the hilum comes to face medially in its final position.
- ▶ **Sequential blood supply:** as the kidney ascends it is supplied successively by nearby vessels at each level — first the **median sacral artery** (pelvic continuation of the aorta), then successively higher **lateral splanchnic (mesonephric) branches of the aorta**, including a transient supply from the **common iliac artery**. The **definitive renal artery** is not recognizable until the **beginning of the third month**; it arises as the most caudal of three transient suprarenal/lateral-splanchnic arteries.
- ▶ Persistence of any of these transient vessels produces a **supernumerary/aberrant renal artery** — common, and clinically important because such a vessel may cross the **pelviureteric junction (PUJ)** and obstruct urine outflow, causing hydronephrosis.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Three superimposed outlines of the kidney at successive levels during ascent — label: **pelvic (sacral) position** with median sacral artery; **intermediate (abdominal) position** with common iliac artery; **final lumbar position (L2)** with the definitive renal artery from the aorta; mark the **inferior mesenteric artery** origin at L3 (site of horseshoe-kidney entrapment); show the hilum rotating from anterior to medial.

## 5. Congenital anomalies of the kidney

| Anomaly                                               | Embryological basis                                                                                                                                                                                                                              | Key features                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unilateral renal agenesis                             | Ureteric bud fails to reach/induce the blastema on one side                                                                                                                                                                                      | Relatively common, more common in males; compatible with life due to compensatory hypertrophy of the other kidney; often an incidental finding                                                                                                                                            |
| Bilateral renal agenesis                              | Both ureteric buds fail                                                                                                                                                                                                                          | Rare; incompatible with life; causes <b>oligohydramnios</b> → <b>Potter sequence</b> (flattened facies, low-set ears, limb deformities, pulmonary hypoplasia)                                                                                                                             |
| Pelvic (ectopic) kidney                               | Failure of ascent, classically due to a sickle-shaped peritoneal fold (containing the umbilical artery) blocking the pathway                                                                                                                     | ~1 in 2500 live births; associated malrotation of the hilum; may mimic a pelvic mass                                                                                                                                                                                                      |
| Crossed renal ectopia                                 | Kidney and ureter cross to the opposite side                                                                                                                                                                                                     | Ureter still opens on the original side                                                                                                                                                                                                                                                   |
| Horseshoe kidney                                      | Lower poles fuse while the kidneys are still close together passing through the arterial fork of the umbilical arteries; the fused mass is then arrested in ascent when the isthmus catches beneath the origin of the inferior mesenteric artery | Commonest fusion anomaly of the kidney, ~1 in 400 individuals; lies at lower lumbar level; ureters pass <b>anterior</b> to the isthmus with a high insertion into the pelvis; associated congenital <b>UPJ obstruction in up to 30%</b> and a <b>chromosomal anomaly in ~56%</b> of cases |
| Pancake kidney                                        | Complete fusion of both kidneys into a single midline or unilateral mass                                                                                                                                                                         | Rare                                                                                                                                                                                                                                                                                      |
| Lobulated (fetal) kidney                              | Persistence of the normal fetal lobulation                                                                                                                                                                                                       | Normally effaces by the end of the first year; if not, persists as lobulation                                                                                                                                                                                                             |
| Congenital (childhood-type) polycystic kidney disease | Abnormal dilatation of collecting tubules/loops of Henle (previously attributed to failure of union between excretory and collecting tubules)                                                                                                    | Autosomal recessive; prevalence ~1:5000; usually bilateral; presents early, often with renal/pulmonary failure                                                                                                                                                                            |

| Anomaly                              | Embryological basis                                                                 | Key features                                                                                                                              |
|--------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Adult-type polycystic kidney disease | As above, dilatation affecting nephron segments more widely                         | Autosomal dominant, delayed onset; prevalence ~1:600; bilateral; associated cysts in liver, pancreas; managed by dialysis/transplantation |
| Multicystic dysplastic kidney        | Atresia/obstruction of the ureter in utero while nephron induction is still ongoing | Non-functional, dysplastic, cyst-replaced kidney                                                                                          |
| Supernumerary/aberrant renal artery  | Persistence of a transient fetal renal artery as the kidney ascends                 | Common; may cross the pelviureteric junction and obstruct urine flow → hydronephrosis                                                     |

□ Fig 11.19 — Horseshoe kidney: the lower poles are fused across the midline by an isthmus lying anterior to the aorta and inferior vena cava, trapped below the origin of the inferior mesenteric artery (Vishram Singh — *Textbook of Anatomy Vol 2* — 4e, p.517)

## 6. Congenital anomalies of the ureter and pelvicalyceal system

These arise from variations in ureteric-bud division and are closely linked to kidney formation:

- ▶ **Double (bifid) renal pelvis:** premature division of the ureteric bud near its termination — an upper pelvis drains the upper group of calyces, a lower pelvis drains the middle and lower groups.
- ▶ **Bifid ureter:** the upper ureter divides early, but the two limbs reunite in its lower third to open into the bladder by a single, common orifice.
- ▶ **Duplex (complete double) ureter:** two entirely separate ureteric buds arise from the mesonephric duct, giving two ureters that drain independently into the bladder — occurs in about **1 in 125 individuals** (unilateral); bilateral duplex ureters occur in about **1 in 800**.
- ▶ **Ectopic ureter:** the ureter fails to be incorporated into the trigone; in males it may open into the bladder neck or prostatic urethra, in females into the bladder neck, urethra or vagina — a common cause of continuous urinary incontinence, since urine bypasses the sphincteric control normally provided by oblique passage through the detrusor.

## Applied / Clinical anatomy

- ▶ **Unilateral renal agenesis** is asymptomatic and often an incidental finding — clinicians must never assume two kidneys are present before nephrectomy or contrast studies.
- ▶ **Bilateral renal agenesis** with oligohydramnios/Potter sequence is a key antenatal-ultrasound diagnosis; the neonate rarely survives.
- ▶ **Horseshoe kidney** is fixed at L3–L5 under the inferior mesenteric artery — more vulnerable to blunt trauma; its variable blood supply mandates preoperative CT angiography before renal surgery.
- ▶ **Aberrant/supernumerary renal arteries** crossing the pelviureteric junction are a classical surgical cause of hydronephrosis, to be identified before pyeloplasty.



- ▶ **Adult-type (autosomal dominant) polycystic kidney disease** presents in adulthood with hypertension, haematuria and progressive renal failure; associated with hepatic/pancreatic cysts and berry aneurysms of the circle of Willis.
- ▶ **Duplex/ectopic ureters** predispose to vesico-ureteric reflux or obstruction depending on which moiety's ureter is involved — a common cause of paediatric urinary tract infection and incontinence.

### High-yield exam pointers

- ▶ Three successive kidneys — **pronephros (cervical)** → **mesonephros (thoracolumbar)** → **metanephros (sacral)** — only the metanephros persists.
- ▶ Metanephros has a **dual origin**: ureteric bud → collecting system; metanephric blastema → excretory system (nephron).
- ▶ Ureteric bud divides dichotomously through ~13 **generations**; **WT1**, **GDNF/RET**, **HGF/MET**, **FGF2/BMP7**, **PAX2/WNT4** regulate reciprocal induction.
- ▶ Kidney **ascends** from sacral to T12–L3 level and **rotates 90° medially** (hilum anterior → medial); blood supply changes sequentially, ending in the definitive renal artery from the aorta at L2.
- ▶ **Unilateral renal agenesis** = common, compatible with life; **bilateral** = rare, fatal, causes **Potter sequence**.
- ▶ **Horseshoe kidney** (~1:400) — commonest fusion anomaly; trapped below the inferior mesenteric artery; ureters pass **anterior** to the isthmus.
- ▶ **Childhood (ARPKD, ~1:5000)** vs **adult (ADPKD, ~1:600)** polycystic kidney disease — inheritance, onset and prognosis differ sharply.
- ▶ **Duplex ureter** (~1:125) results from early/complete division of the ureteric bud; ectopic ureteric openings cause incontinence.
- ▶ **CAKUT** overall affects **3–6% of live births** — the commonest congenital anomalies of the urinary tract are those of shape and position.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 2 (4e); BD Chaurasia — Human Anatomy Vol 2 (8e); Sontakke — Textbook of Human Embryology; Moore — The Developing Human (9e); Moore — Clinically Oriented Anatomy (9e); Brijesh Kumar — Embryology Text & Atlas; IB Singh — Human Embryology (CBME 2021).



## Mesonephric duct

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **mesonephric (Wolffian) duct** — also called the **archinephric** or **nephric duct** (first described by Caspar Friedrich Wolff, 1759) — is the **primary excretory duct of the mesonephros**, the transient "second kidney" of intermediate-mesoderm origin. It is a paired longitudinal duct present in the indifferent embryo of both sexes, running caudally to open into the cloaca/urogenital sinus. It is developmentally pivotal to **three separate systems**: it gives rise to the **ureteric bud** that induces and drains the definitive (metanephric) kidney; under the local, paracrine action of fetal testicular testosterone it becomes the **principal genital duct of the male** (epididymis, vas deferens, seminal vesicle, ejaculatory duct); and, in the absence of that stimulus, it **regresses in the female**, leaving only inconstant vestiges (epoophoron, paroophoron, Gartner's duct).

### 1. Origin and early development

- ▶ Intermediate mesoderm gives rise to three successive, cranio-caudally overlapping excretory organs: **pronephros** → **mesonephros** → **metanephros**.
- ▶ The **pronephros** (7–10 solid cell groups, cervical region) is vestigial and has disappeared by the end of the 4th week.
- ▶ The **mesonephros** develops from intermediate mesoderm extending from the **upper thoracic to the 3rd lumbar (L3) segment**; by the 7th week its cranial part has atrophied and it is confined to the **upper three lumbar segments**.
- ▶ Early in the 4th week, mesonephric tubules appear, elongate into an **S-shaped loop**, and acquire a glomerular tuft (Bowman capsule + glomerulus = renal corpuscle) at their medial end; laterally each tubule opens into the **primary excretory duct**, which is renamed the **mesonephric (Wolffian) duct** once this connection is made.
- ▶ An estimated **70–80 mesonephric tubules** develop in all, but because cranial tubules degenerate before caudal ones form, **no more than 30–40** are present at any one time.
- ▶ By the middle of the 2nd month the mesonephros is a large, ovoid, coelom-projecting organ with the gonad on its medial surface — together the two form the **urogenital ridge**. The mesonephros functions as a temporary excretory organ (urine formation demonstrated from about the 6th week) before undergoing regression from the end of the 2nd month onward.

### 2. Course, relations and termination

- ▶ The duct runs caudally in the lateral part of the nephric (urogenital) ridge and, at the ridge's caudal end, projects into the coelom within a **mesonephric fold**.
- ▶ The two mesonephric folds fuse in the pelvis, between bladder (ventral) and rectum (dorsal), forming the **genital cord**; the intervening peritoneal fossa is obliterated in the male but persists in the female as the **uterovesical pouch**.
- ▶ The duct opens into the **cloaca** (later the dorsal wall of the definitive urogenital sinus) flanking the **sinus (Müllerian) tubercle** — the elevation raised by the fused paramesonephric ducts.
- ▶ The **paramesonephric (Müllerian) duct**, present alongside it in the indifferent embryo, uses the mesonephric duct as a lateral guide during its own caudal growth, crossing ventral to it before reaching the urogenital sinus.

### 3. Relation to the metanephros and the bladder trigone

- ▶ Early in the 5th week, the **ureteric bud** arises as an outgrowth of the mesonephric duct **close to its entry into the cloaca**; it penetrates the metanephric (metanephrogenic) mesenchyme and undergoes reciprocal induction (GDNF–RET, WT1, PAX2/WNT4 signalling) to form the **ureter, renal pelvis, calyces and collecting ducts** of the definitive kidney.
- ▶ As the cloaca is partitioned and the bladder enlarges, the **caudal segments of the mesonephric ducts are absorbed into the bladder wall**; consequently the ureters, initially outgrowths of the mesonephric duct, come to open **separately** and progressively more cranially, while the mesonephric duct orifices move together and descend toward the (prospective) prostatic urethra.
- ▶ This incorporated mesodermal tissue forms the **trigone of the bladder** — mesodermal at first, later re-covered by ingrowing endodermal epithelium so that the mature bladder mucosa is uniformly endodermal.

### 4. Fate of the mesonephric duct in the male (testosterone-driven)

Fetal Leydig-cell **testosterone** acts locally (paracrine, ipsilateral) to maintain the duct; **AMH/Müllerian-inhibiting substance** from Sertoli cells acts on the *other* duct (paramesonephric), not on this one.

| Region of the mesonephric duct                                    | Male adult derivative                                          |
|-------------------------------------------------------------------|----------------------------------------------------------------|
| Cranial-most tip (fails to join efferent ductules)                | <b>Appendix of the epididymis</b> (vestige)                    |
| Body, immediately below entry of efferent ductules                | <b>Duct of the epididymis</b> (becomes highly convoluted)      |
| From tail of epididymis to point of outbudding of seminal vesicle | <b>Ductus (vas) deferens</b> (acquires a thick muscular coat)  |
| Segment beyond the seminal-vesicle outbudding                     | <b>Ejaculatory duct</b>                                        |
| Caudal end, absorbed into bladder wall                            | Contributes to the <b>trigone</b> and <b>prostatic urethra</b> |

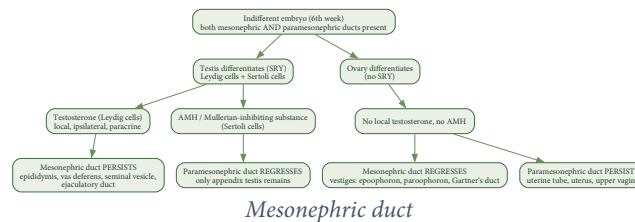
- ▶ The **seminal vesicles** arise as a *bud from the ductus deferens* — they are a derivative of, but not literally continuous with, the main duct lumen.
- ▶ The **prostate** develops separately, from **endodermal buds of the urogenital sinus/urethra**, not from the mesonephric duct — a common exam trap.
- ▶ The associated mesonephric **tubules**: the cranial 1–2 (rostral) tubules become vestigial **rostral aberrant ductules**; the next 5–12 (epigenital) tubules join cords of the rete testis to form the **efferent ductules** and lobules of the **head of the epididymis**; the caudal (paragenital) tubules fail to join the rete and persist as the vestigial **paradidymis** (organ of Giraldu).

### 5. Fate of the mesonephric duct in the female (regression)

In the absence of local testosterone, regression of the mesonephric duct is the **default fate**; only inconstant vestiges remain.

| Region of the mesonephric duct/tubules | Female vestige                             |
|----------------------------------------|--------------------------------------------|
| Cranial-most part of the duct          | <b>Longitudinal duct of the epoophoron</b> |

| Region of the mesonephric duct/tubules                                       | Female vestige                             |
|------------------------------------------------------------------------------|--------------------------------------------|
| Caudal part of the duct (occasionally persists in the wall of uterus/vagina) | Gartner's duct → may form a Gartner's cyst |
| Cranial (epigenital) tubules                                                 | Tubules of the <b>epoophoron</b>           |
| Caudal (paragenital) tubules                                                 | <b>Paroophoron</b>                         |
| Rest of the duct and tubules                                                 | Regress completely                         |



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 72.13 — A, The indifferent or ambisexual stage of development. B, Male: the mesonephric ducts are retained (left) and the paramesonephric ducts involute (right). C, Female: the paramesonephric ducts are retained (right) and the mesonephric ducts involute (left) (Gray's Anatomy — Standring — 41e, p.1681)

Reproduce three panels (indifferent → male → female), labelling in each:

- ▶ Gonad (indifferent gonad → testis / ovary)
- ▶ Mesonephric (Wolffian) duct and mesonephros
- ▶ Paramesonephric (Müllerian) duct
- ▶ Urogenital sinus / bladder
- ▶ Male panel: appendix testis, epididymis, vas deferens, seminal vesicle, gubernaculum testis, utricle of prostate
- ▶ Female panel: epoophoron, Gartner's duct, gubernaculum ovarii, uterine tube, uterus

### Applied / Clinical anatomy

- ▶ **Gartner's cyst**: a persistent caudal remnant of the mesonephric duct in the female, seen protruding through the **lateral fornix/anterolateral wall of the vagina**; usually asymptomatic, discovered incidentally.
- ▶ **Epoophoron/paroophoron (paratubal/paraovarian) cysts** arise from vestigial mesonephric tubules in the broad ligament/mesovarium.
- ▶ **Duplex ureter** (about 1 in 125 individuals; bilateral in ~1 in 800) results from **two ureteric buds arising off the same mesonephric duct**. By the **Weigert–Meyer rule**, the ureter from the **upper renal pole** (the one whose bud arose more distally on the mesonephric duct, giving it a longer time to migrate) inserts **more caudally and medially** in the bladder — often ectopically; the ureter from the **lower pole** inserts **more cranially and laterally** with a shorter intramural tunnel and is prone to **vesico-ureteric reflux**.

- ▶ **Congenital bilateral absence of the vas deferens (CBAVD)**: incidence 1:1000–1:10,000; accounts for 1–2% of male infertility and ~10% of obstructive azoospermia; absent body/tail of epididymis, vas deferens and seminal vesicle. CFTR mutations (the cystic-fibrosis gene) are found in ~80% of cases — CFTR is required for normal mesonephric-duct-derived vas deferens development.
- ▶ **Renal agenesis–genital tract association**: because the **ureteric bud** and the **vas deferens/seminal vesicle** share a **common origin** from the mesonephric duct, failure of the duct to develop on one side produces **ipsilateral absence of both the kidney and the vas deferens/seminal vesicle** — a key reason to image the kidneys in men with unilateral CBAVD or seminal-vesicle agenesis, and vice versa.
- ▶ **Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome**: vaginal (Müllerian) agenesis with other paramesonephric duct anomalies is characteristically associated with **renal agenesis**, reflecting the paramesonephric duct's dependence on the mesonephric duct as a caudal growth-guide and the shared origin of the kidney (via the ureteric bud) from the same duct.
- ▶ The **bladder trigone**, though ultimately endoderm-lined, is embryologically mesodermal (incorporated mesonephric duct tissue) — it is smooth and non-rugose, and behaves differently from the rest of the bladder in some pathological and cystoscopic contexts.

### High-yield exam pointers

- ▶ Mesonephric (Wolffian) duct = primary excretory duct of the **mesonephros**; synonyms — archinephric duct, nephric duct.
- ▶ Sequence of excretory organs: **pronephros (vestigial)** → **mesonephros (transient)** → **metanephros (permanent)**.
- ▶ Mesonephros: intermediate mesoderm, upper thoracic–L3 level; ~70–80 tubules form but never >30–40 present simultaneously; functional urine-forming organ transiently before regressing after the 2nd month.
- ▶ Gives origin to the **ureteric bud** (early 5th week, near duct's entry into cloaca) → ureter, pelvis, calyces, collecting ducts of the metanephros.
- ▶ Caudal ends absorbed into the bladder wall → separate ureteric orifices + formation of the **trigone**.
- ▶ Male fate governed by **testosterone** (Leydig cells, local/paracrine) → epididymis, vas deferens, seminal vesicle (buds off vas), ejaculatory duct; **AMH acts on the paramesonephric duct, not this one**.
- ▶ Female fate = **default regression** (no local testosterone) → vestiges only: epoophoron, paroophoron, Gartner's duct.
- ▶ **Prostate is NOT a mesonephric duct derivative** — it arises from urogenital sinus/urethral endoderm.
- ▶ Clinical entities all traceable to this one duct: **Gartner's cyst, duplex ureter/Weigert–Meyer rule, CBAVD–CFTR, and the renal-agenesis/genital-tract & MRKH associations**.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; BD Chaurasia — Human Anatomy Vol 2 8e.



## Mesonephros

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The mesonephros ("middle kidney") is the second of the three successive excretory organs of intrauterine life — pronephros, mesonephros, metanephros — that arise in cranio-caudal sequence from the intermediate mesoderm. It develops from the upper thoracic to upper lumbar (L3) segments during the fourth week, functions transiently as an excretory organ in the early fetal period, and then largely regresses; its duct and a few tubules, however, are re-purposed to build the definitive male genital duct system and give minor vestiges in the female. It is thus of major applied importance because the ureteric bud (the primordium of the entire collecting system of the permanent kidney) also buds from the mesonephric duct.

### 1. Origin and Development

- ▶ Arises from **intermediate mesoderm** (nephrogenic cord), which in the upper thoracic region lies as a segmented mass but becomes an unsegmented, continuous ridge more caudally.
- ▶ The **primary excretory duct** first appears (stage 11 embryo, ~14 somites) as a solid rod in the nephrogenic cord opposite the ninth somite; it grows caudally independent of the cord, canalises progressively from its caudal end, and opens into the cloaca by stage 12.
- ▶ From **stage 12** onward, mesonephric tubules develop from intermediate mesenchyme between somite levels 8–20 (a continuous nephrogenic ridge extends to somite 24) and connect to this duct, which is now renamed the **mesonephric (Wolffian) duct**.
- ▶ Early in the fourth week, during regression of the pronephric system, the first mesonephric tubules appear; they **lengthen rapidly, form an S-shaped loop**, and acquire a capillary tuft at their medial end.
- ▶ By the **middle of the second month**, each mesonephros is a large ovoid organ on either side of the midline; because the developing gonad lies on its medial aspect, the combined swelling is called the **urogenital ridge**.

### 2. Structure of the Mesonephric Nephron

- ▶ Each tubule is a condensation of mesenchyme that epithelialises into a vesicle; one end grows towards and opens into the mesonephric duct, the other dilates and invaginates around a capillary tuft.
- ▶ The **outer stratum** of the invaginated end forms the **glomerular (Bowman) capsule**; the **inner cells** differentiate into **mesonephric podocytes** clothing the capillaries to form a **glomerulus** — together these constitute a **renal (mesonephric) corpuscle**.



- ▶ Capillaries of the glomerulus are supplied by lateral branches of the dorsal aorta.
- ▶ Laterally, the tubule drains into the longitudinal **mesonephric (Wolffian) duct**.
- ▶ The mesonephric nephron closely resembles the metanephric (permanent) nephron in plan but **lacks a segment corresponding to the descending limb of the loop of Henle** — it is a simpler, non-concentrating nephron.

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros. Pronephric tubules appear as vestigial groups; the mesonephric tubules and duct dominate the mid-trunk. (Sontakke — Textbook of Human Embryology, p.212)

### 3. Extent, Numbers and Function

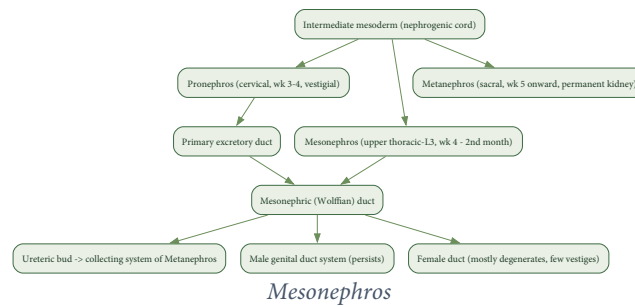
- ▶ By the end of the sixth week each mesonephros is an elongated, spindle-shaped organ — the **mesonephric ridge / Wolffian body** — projecting into the coelom from the level of the septum transversum to the third lumbar segment.
- ▶ An estimated **70–80 mesonephric tubules** (and a corresponding number of glomeruli) form in all, but they are **not all present simultaneously**: rarely more than **30–40** coexist in one embryo, because cranial tubules and glomeruli atrophy before the caudal ones have finished forming.
- ▶ The mesonephros is believed to **produce urine by about stage 17 (~5 weeks)** — it is a genuinely, if transiently, functional excretory organ before the metanephros takes over.

### 4. Regression and Comparison of the Three Kidney Systems

- ▶ In stage 18 embryos (13–17 mm) the mesonephric ridge has already shrunk cranially to about the level of rib 9 — the cranial end atrophies in both sexes.
- ▶ By stage 19 (~20 mm), the mesonephros is confined to the first three lumbar segments, though it may still contain up to 26 tubules.
- ▶ Of the surviving tubules: the most cranial one or two persist only as **rostral aberrant ductules**; the next five or six become either the **efferent ductules of the testis** (male) or the tubules of the **epoophoron** (female); the caudal tubules form the **caudal aberrant ductules and paradidymis** (male) or the **paroophoron** (female).
- ▶ By the end of the second month the majority of tubules have disappeared in both sexes; in the **male** a few caudal tubules and the whole duct persist to build the genital duct system; in the **female** almost all tubules and most of the duct disappear.

| Feature    | Pronephros                        | Mesonephros                                        | Metanephros                                      |
|------------|-----------------------------------|----------------------------------------------------|--------------------------------------------------|
| Site       | Cervical (7–10 solid cell groups) | Upper thoracic–L3                                  | Sacral, ascending to L1/L2                       |
| Onset      | Start of 4th week                 | Early 4th week                                     | 5th week                                         |
| Duration   | Regresses by end of 4th week      | Functions till ~2nd month, vestiges persist longer | Permanent                                        |
| Glomerulus | Absent/doubtful in humans         | Present — true renal corpuscle                     | Present — mature nephron with full loop of Henle |
| Fate       | Totally vestigial, non-functional | Duct + a few tubules re-used in genital system     | Becomes the adult kidney                         |





## 5. Derivatives of the Mesonephric Duct and Tubules

- The **mesonephric duct** also sprouts the **ureteric bud** near its junction with the cloaca — the primordium of the ureter, pelvicalyceal system and collecting ducts of the metanephros — and its caudal end is absorbed into the posterior wall of the urogenital sinus to help form the **trigone of the bladder**.
- Under testosterone (Leydig cells) the duct persists in the male; under oestrogen and absence of anti-Müllerian hormone/testosterone it degenerates in the female, leaving only vestiges.

| Structure                                           | Male derivative (duct persists)                  | Female derivative (duct degenerates)                      |
|-----------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------|
| Cranial tip of duct                                 | Appendix of epididymis                           | —                                                         |
| Cranial mesonephric tubules                         | Efferent ductules (ductuli efferentes) of testis | Epoophoron (in mesosalpinx, near ovary)                   |
| Duct just below efferent ductules                   | Duct of the epididymis (convoluted)              | —                                                         |
| Duct from tail of epididymis to seminal-vesicle bud | Vas (ductus) deferens (thick muscular coat)      | —                                                         |
| Duct outgrowth                                      | Seminal vesicle                                  | —                                                         |
| Duct beyond seminal vesicle                         | Ejaculatory duct                                 | —                                                         |
| Caudal mesonephric tubules                          | Paradidymis (organ of Giralde's)                 | Paroophoron (nearer uterus)                               |
| Caudal part of duct                                 | (continuous with vas/ejaculatory duct)           | Gartner's duct (in broad ligament / lateral vaginal wall) |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Transverse section through the urogenital ridge (5th–6th week) — label: coelomic (peritoneal) cavity, urogenital mesentery, gonad, mesonephros with an excretory tubule, glomerulus, Bowman (glomerular) capsule, mesonephric (Wolffian) duct, paramesonephric (Müllerian) duct, dorsal aorta, hindgut/cloaca.

## Applied / Clinical anatomy

- **Gartner's duct cyst** — cystic dilatation of the persisting caudal mesonephric duct remnant in the broad ligament or antero-lateral vaginal wall; a common incidental gynaecological cyst.

- ▶ **Paradidymis and appendix-epididymis cysts** — vestigial-tubule/duct remnants near the epididymal head that may enlarge into palpable, clinically benign paratesticular cysts; the appendix epididymis (duct-derived) must be distinguished from the appendix testis (Müllerian-derived), which is important in the differential of acute scrotal pain (torsion of either appendage).
- ▶ **Renal agenesis and genital-duct anomalies go together** — because the ureteric bud and the vas deferens both derive from the mesonephric duct, failure of the duct to develop on one side causes **ipsilateral absence of both the kidney and the vas deferens**; this embryological link explains why unilateral renal agenesis is often found with an ipsilateral genital duct defect, and vice versa.
- ▶ **Epoophoron/paroophoron cysts** are the tubal (mesonephric-tubule) counterpart of Gartner's cysts and lie in the mesosalpinx/broad ligament.
- ▶ The **mesonephric duct's absorption into the urogenital sinus** to form the bladder trigone explains why the trigone is mesodermal (mesonephric-duct derived) in origin, unlike the rest of the bladder, which is endodermal.

### High-yield exam pointers

- ▶ Mesonephros = second of three kidney generations; from intermediate mesoderm, upper thoracic to L3.
- ▶ Nephron unit = S-shaped tubule + glomerulus + Bowman capsule = **renal corpuscle**; drains into the **mesonephric (Wolffian) duct**.
- ▶ ~70–80 tubules form in all; rarely >30–40 present at once (cranio-caudal sequential formation and atrophy).
- ▶ Mesonephros forms urine transiently by ~stage 17; degenerates for the most part by end of 2nd month.
- ▶ Duct **persists in male** (testosterone) → epididymis, vas deferens, seminal vesicle, ejaculatory duct; efferent ductules and paradidymis from tubules.
- ▶ Duct **regresses in female** (no testosterone) → epoophoron, paroophoron, Gartner's duct as vestiges.
- ▶ Ureteric bud (→ permanent kidney's collecting system) buds from the mesonephric duct — key link to metanephric development and to the bladder trigone.
- ▶ Clinically: Gartner's cyst, paradidymis/appendix-epididymis cysts, and the renal-agenesis/vas-deferens-agenesis association.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology.



# Sinuvaginal bulb

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The sinuvaginal bulbs (sinovaginal bulbs) are a pair of solid endodermal outgrowths that arise from the dorsal (pelvic) wall of the definitive urogenital sinus, at the site where the fused, solid caudal tip of the uterovaginal primordium (paramesonephric ducts) meets the sinus and raises the sinus (Müllerian) tubercle. They proliferate cranially, fuse in the midline, and combine with the caudal solid tip of the uterovaginal canal to form the solid vaginal plate — the primordium that subsequently canalizes to form the vagina. Because the sinuvaginal bulb is the key structure whose failure of formation, fusion or canalization underlies almost every congenital anomaly of the vagina, it is a compact but high-yield embryological landmark for the PG exam.

## 1. Site and time of origin

- ▶ The vagina develops in relation to the **uterovaginal primordium** (the fused caudal, vertical parts of the two **paramesonephric/Müllerian ducts**) and the **definitive urogenital sinus**.
- ▶ At approximately **60 mm crown–rump (CR) length** (early fetal period), the solid caudal tip of the uterovaginal primordium comes into contact with the dorsal wall of the pelvic part of the urogenital sinus, at the region of the **sinus tubercle (Müllerian tubercle/eminence)**.
- ▶ This contact **induces an epithelial proliferation of the urogenital sinus endoderm** — two solid evaginations growing out from the dorsal wall of the sinus — the **sinuvaginal (sinovaginal) bulbs**.
- ▶ The bulbs are paired at first and **soon fuse with each other in the midline** to form a single solid mass.
- ▶ Their point of origin marks the future site of the **hymen**.

## 2. Formation of the vaginal plate — composite origin

- ▶ The fused sinuvaginal bulbs **proliferate rapidly** and, together with proliferating mesodermal cells at the tip of the uterovaginal canal, form a **solid, anteroposteriorly flattened plate of cells** — the **vaginal plate** — interposed between the uterovaginal canal above and the urogenital sinus below.

| Contribution                           | Origin                                               | Part of vaginal plate formed                                 |
|----------------------------------------|------------------------------------------------------|--------------------------------------------------------------|
| Sinuvaginal bulbs                      | Endoderm of urogenital sinus                         | Bulk of the plate, especially its caudal/lower part          |
| Solid caudal tip of uterovaginal canal | Mesoderm surrounding the fused paramesonephric ducts | Cranial/upper part of the plate, adjoining the future cervix |

- ▶ **Proliferation continues at the cranial end of the plate**, progressively increasing the distance between the developing uterus and the urogenital sinus — this is the mechanism by which the vagina elongates.
- ▶ By about **140 mm CR length**, the junction between the paramesonephric-duct epithelium and the sinus-derived proliferation has receded until it lies within the **cervical canal**.
- ▶ **Controversy on origin:** classical teaching (as above) holds the vaginal plate to be of dual/composite origin. Gray's Anatomy notes that mouse studies (Kurita 2010, 2011) have

mapped the precise boundary between paramesonephric- and sinus-derived epithelium; Larsen similarly records evidence, from marker-expression studies in mouse and human embryos, favouring the view that the **entire adult vaginal epithelial lining is derived from the endodermal sinuvaginal bulb/vaginal plate**, with the paramesonephric ducts contributing mainly connective tissue/muscle rather than epithelium. Both versions should be known; the composite-origin scheme remains the standard exam answer.

### 3. Canalization — formation of the vaginal lumen, fornices and hymen

- ▶ Canalization proceeds **from the caudal end cranially**: the solid, cylindrical vaginal plate enlarges, and its **central cells desquamate (break down)** to hollow out the definitive vaginal lumen.
- ▶ This process is **complete by about the 5th month** of intrauterine life.
- ▶ As the **cranial (upper) end of the vaginal plate enlarges**, it grows up around the cervix and is excavated to produce the **vaginal fornices** — these are therefore of **paramesonephric (mesodermal-canal)** origin.
- ▶ The vaginal lumen remains separated from the lumen of the urogenital sinus by a thin membrane — the **hymen** — composed of the epithelial lining of the sinus together with a thin layer of vaginal cells; **both surfaces of the hymen are endoderm-lined**.
- ▶ The hymen normally develops a small central opening (perforates partially) during the **perinatal period**.

### 4. Fate — embryonic structure to adult derivative

| Embryonic structure                                                          | Adult derivative                                                                    |
|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Sinuvaginal bulbs (endodermal, from urogenital sinus)                        | Lower part of the vaginal mucosa (classical teaching: roughly the lower quarter)    |
| Solid tip of uterovaginal canal (mesodermal, paramesonephric)                | Upper part of the vaginal mucosa, <b>including the vaginal fornices</b>             |
| Fused vaginal plate (composite)                                              | Body of the vagina, after canalization (complete ~5th month)                        |
| Central, desquamated cells of the vaginal plate                              | Vaginal lumen                                                                       |
| Residual thin tissue plate at junction of vaginal plate and urogenital sinus | <b>Hymen</b>                                                                        |
| Sinus (Müllerian) tubercle                                                   | Site marking the future hymen; central part degenerates to form the hymenal orifice |
| Phallic part of the definitive urogenital sinus                              | <b>Vestibule of the vagina</b> , into which the vagina and urethra both open        |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 21.9 — Development of uterus and vagina. Paramesonephric ducts (müllerian ducts) grow caudally, fuse and form uterovaginal canal. The uterovaginal canal forms solid vaginal cord. Endodermal urogenital sinus develops two sinovaginal bulbs that later fuse and form vaginal plate. By the 5th month, vaginal cord and vaginal plate get canalised to form vaginal canal. (Sontakke — Textbook of Human Embryology, p.232)

Reproduce a stepwise (4-panel) diagram of the developing female genital tract in coronal/sagittal section, labelling in sequence:

- ▶ Fused paramesonephric ducts → **uterovaginal canal/primordium**, its solid caudal tip against the **urogenital sinus**
- ▶ **Sinus (Müllerian) tubercle** at the point of contact
- ▶ Paired **sinuvaginal (sinovaginal) bulbs** proliferating from the sinus wall, then fusing in the midline
- ▶ The composite **vaginal plate** (upper mesodermal part + lower endodermal part), still solid
- ▶ Progressive **canalization from below upward**, forming the vaginal lumen
- ▶ Expanded cranial end of the plate embracing the cervix — the **vaginal fornices**
- ▶ The thin residual **hymen** at the vaginal–vestibular junction, with its small perinatal opening
- ▶ Final labelled panel: **uterus, cervix, vaginal fornices, vagina, hymen, vestibule of vagina**

### Applied / Clinical anatomy

| Anomaly                                               | Embryological basis                                                                                                | Clinical presentation                                                                                                                                                   |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Vaginal agenesis</b> (~1 in 5000 births)           | Urogenital sinus fails to form the sinuvaginal bulbs, so the vaginal plate never forms                             | Vagina absent; because the developing uterus normally induces sinuvaginal bulb formation, the <b>uterus is usually absent too</b> (combined Müllerian/vaginal agenesis) |
| <b>Vaginal atresia</b>                                | Failure of canalization of the (formed) vaginal plate                                                              | Blind, non-canalized vagina; primary amenorrhoea                                                                                                                        |
| <b>Transverse vaginal septum</b> (~1 in 80,000 women) | Localized failure of canalization, classically at the <b>junction of the middle and upper thirds</b> of the vagina | If imperforate — cyclical pain, <b>haematocolpos</b> , delayed presentation at menarche                                                                                 |
| <b>Imperforate hymen</b>                              | Central part of the sinus/hymenal membrane fails to break down/perforate                                           | Bulging membrane at introitus at puberty; <b>haematocolpos</b> , cyclical pelvic pain with primary amenorrhoea                                                          |
| <b>Septate vagina</b>                                 | Patchy/incomplete disintegration of the central fused sinuvaginal bulb mass, or incomplete fusion of the two bulbs | Longitudinal vaginal septum; often coexists with a septate/didelphys uterus                                                                                             |

| Anomaly                                | Embryological basis                                                                                     | Clinical presentation                                                                        |
|----------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Double (duplex) vagina                 | Failure of fusion of the right and left sinuvaginal bulbs (with failure of paramesonephric duct fusion) | Usually associated with <b>uterus didelphys</b> ; may also occur with a single, fused uterus |
| Recto-vaginal / vesico-vaginal fistula | Aberrant relation of the sinus (Müllerian) tubercle to the developing rectum or bladder neck            | Abnormal communication of the vagina with rectum or bladder                                  |

- ▶ Clinically, because sinuvaginal-bulb–derived vaginal tissue and the hymen are both endoderm-lined, **imperforate hymen is examined and managed as a membranous, not a solid, obstruction** — a cruciate hymenotomy relieves the retained menstrual flow.
- ▶ The dependence of sinuvaginal bulb induction on a normally developed uterovaginal primordium explains why **uterine and vaginal agenesis so often occur together** — a key applied-anatomy/viva point.

### High-yield exam pointers

- ▶ Sinuvaginal (sinovaginal) bulbs = **paired solid endodermal outgrowths of the urogenital sinus**, arising at ~60 mm CR (9th week) at the site of the **sinus/Müllerian tubercle**.
- ▶ They **fuse in the midline** and, with the mesodermal tip of the uterovaginal canal, form the solid vaginal plate — of composite (dual) origin.
- ▶ **Canalization** proceeds caudocranially by desquamation of central plate cells; **complete by the 5th month**.
- ▶ **Vaginal fornices** are paramesonephric (mesodermal) in origin, not sinus-derived.
- ▶ **Hymen** = residual tissue at the vaginal–sinus junction; both surfaces endoderm-lined; perforates partially perinatally.
- ▶ Newer evidence (Kurita, mouse/human marker studies — cited in Gray's/Larsen) suggests the **entire vaginal epithelium may be sinus (endodermal) derived**, revising the classical dual-origin teaching.
- ▶ **Failure of sinuvaginal bulb formation** → **vaginal agenesis**, usually with uterine agenesis (~1 in 5000 births); **failure of canalization** → **vaginal atresia/transverse septum** (~1 in 80,000); **failure of central breakdown of the hymenal membrane** → **imperforate hymen/haematocolpos**.
- ▶ **Failure of bulb fusion** → **septate or double vagina**, typically with a septate/didelphys uterus.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas.



## Write about the development, derivatives and anomalies of endodermal cloaca?

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The **cloaca** is the endoderm-lined, slightly dilated terminal expansion of the hindgut into which the **allantois** opens ventrally; it is closed caudally by the bilaminar **cloacal membrane** (endoderm apposed to proctodeal ectoderm, no intervening mesoderm). Between the 4th and 7th weeks it is partitioned by the mesodermal **urorectal septum** into a dorsal **anorectal canal** and a ventral **urogenital sinus**, giving rise to the lower gastrointestinal, urinary and (in part) reproductive outlets. Faulty septation or faulty ventral body-wall closure produces a well-recognised spectrum of anomalies — from simple imperforate anus to lethal cloacal exstrophy.

### 1. Formation of the endodermal cloaca

- ▶ Appears in the **4th week** as the hindgut, extending from the caudal intestinal portal to the cloacal membrane, receives the **allantois** (a ventral endodermal diverticulum) into its connecting stalk.
- ▶ The cloaca is thus a common chamber shared by the **hindgut** (dorsally) and **allantois** (ventrally), encased in splanchnopleuric mesenchyme.
- ▶ It is closed externally by the **cloacal membrane** — endoderm of the cloaca fused with the surface ectoderm, with no mesoderm between them.
- ▶ A small, transient **postanal gut** projects caudally beyond the cloacal membrane in the 4th–5th week and normally disappears by the end of the 5th week.
- ▶ The **mesonephric ducts** open into the cloaca (at Carnegie stage 12), and the later **ureteric buds** arise from their caudal ends close to this point — this relation dictates the derivatives described below.

### 2. Partitioning of the cloaca — the urorectal septum

- ▶ Mesenchyme (with overlying endoderm) proliferates at the angle between the hindgut and the allantois to form the **urorectal septum**, also called the **intercloacal mesenchyme**; its molecular markers include *\*Six1 and Six2\**.
- ▶ The septum grows caudally during the 4th–7th weeks, carrying its endodermal epithelium towards the cloacal membrane and meeting it in the midline.
- ▶ This divides:
  - the cloaca into a dorsal **primitive rectum/anorectal canal** and a ventral **urogenital sinus**;
  - the **cloacal membrane** into a dorsal **anal membrane** and a ventral **urogenital membrane**.
- ▶ The **tip of the urorectal septum** forms the **perineal body** — the nodal site of attachment of the perineal muscles.
- ▶ The **anal membrane** ruptures at the **end of the 8th week**, opening the anal canal to the exterior; the **urogenital membrane** breaks down slightly earlier, opening the urogenital sinus.

□ Fig 15.36 — Cloacal region in embryos at successive stages of development. A. The (Langman's Medical Embryology — Sadler — 14e, p.272)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal schematic through the caudal embryo, three stages side by side:

- ▶ **Early cloaca** — Hindgut, Allantois, Cloaca, Cloacal membrane, Postanal gut, Notochord.
- ▶ **Urorectal septum growing caudally** — same labels + Urorectal septum (intercloacal mesenchyme) shown as a wedge between hindgut and allantois.
- ▶ **Complete separation** — label Rectum/anorectal canal (dorsal), Urogenital sinus/developing bladder (ventral), Anal membrane, Urogenital membrane, Perineal body (tip of septum).

### 3. Derivatives of the cloaca

| Part of cloaca                  | Subdivision                                                | Adult derivative                                                                                                                                       |
|---------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dorsal part (anorectal canal)   | —                                                          | Rectum + <b>upper two-thirds of the anal canal</b>                                                                                                     |
| Ventral part (urogenital sinus) | Vesico-urethral canal (cranial, continuous with allantois) | <b>Urinary bladder</b> (trigone excepted — from absorbed mesonephric duct tissue) + <b>urachus</b> (obliterated allantois → median umbilical ligament) |
|                                 | Pelvic part (narrow)                                       | <b>Prostatic + membranous urethra</b> (male); homologous part of female urethra                                                                        |
|                                 | Phallic part (deep, closed by urogenital membrane)         | <b>Penile urethra</b> up to the glans (male, via urethral plate canalisation); <b>vestibule of the vagina</b> (female)                                 |
| Cloacal membrane                | Anal membrane (dorsal)                                     | Ruptures → lower limit of upper (endodermal) anal canal                                                                                                |
|                                 | Urogenital membrane (ventral)                              | Ruptures → external urogenital orifice                                                                                                                 |

- ▶ In the **male**, the prostatic urethra proximal to the prostatic utricle is derived from the vesico-urethral part of the cloaca together with the incorporated caudal ends of the mesonephric ducts; the rest of the prostatic urethra, the membranous urethra and the bulbar urethra are from the urogenital sinus proper.
- ▶ In the **female**, the entire urethra is derived from the vesico-urethral region of the cloaca (including the mesonephric-duct contribution dorsally) and is homologous with the male prostatic urethra proximal to the utricle; the remaining (pelvic + phallic) part persists as the **vestibule**, into which both urethra and vagina open.
- ▶ The **mesonephric ducts** are progressively absorbed into the expanding bladder wall, so the **ureters** come to open separately into the bladder.
- ▶ **Genital tubercle, urogenital folds and labioscrotal swellings** arise from pericloacal mesenchyme around the divided cloacal membrane and go on to form the external genitalia.

#### 4. Development of the anal canal (dual origin)

- ▶ **Upper two-thirds** — endodermal, from the hindgut (dorsal cloaca).
- ▶ **Lower one-third** — ectodermal, from the invaginating **proctodeum**.
- ▶ The junction is the **pectinate (dentate) line**, at the level of the anal valves — epithelium changes from columnar to stratified squamous here.

| Feature            | Upper 2/3 (endoderm)                      | Lower 1/3 (ectoderm)                                         |
|--------------------|-------------------------------------------|--------------------------------------------------------------|
| Arterial supply    | Superior rectal artery                    | Inferior rectal artery                                       |
| Venous drainage    | Superior rectal vein → portal             | Inferior rectal vein → systemic (porto-systemic anastomosis) |
| Nerve supply       | Autonomic (visceral, insensitive to pain) | Somatic, pudendal (sensitive)                                |
| Lymphatic drainage | Internal iliac nodes                      | Superficial inguinal nodes                                   |

#### 5. Anomalies of cloacal development

- ▶ **Persistent cloaca**: incomplete septation leaves rectum, vagina and urethra opening into a **single common perineal channel, 1–7 cm long** — the most severe congenital anomaly of the female urogenital tract; usually associated with other Müllerian anomalies.
- ▶ **Extroversion/exstrophy of the cloaca** (ectopia cloacae): the urorectal septum fails to develop, together with failure of mesenchymal migration around the ventral body wall; produces a large infra-umbilical defect with an exposed central colonic/hindgut remnant flanked by **bilateral halves of an exstrophied bladder**; anal musculature is present but not connected to a canal. Incidence ≈ 1/30,000 births.
  - When combined with **omphalocele** and vertebral/spinal defects it constitutes the **OEIS complex** — Omphalocele, Exstrophy of bladder/cloaca, Imperforate anus, Spinal/skeletal defects (e.g. lumbosacral meningocele, scoliosis). Antenatal clues: raised maternal serum alpha-fetoprotein; ultrasound shows a non-visualised fetal bladder with an infra-umbilical wall defect.
- ▶ **Bladder exstrophy** (milder, isolated): failure of the lateral body-wall folds to close in the midline pelvic region without urorectal septum failure — exposed bladder mucosa with constant epispadias; incidence ≈ 2/10,000 live births.
- ▶ **Anorectal malformations** — most result from abnormal/incomplete development of the urorectal septum (genes implicated: *Shh*, *Fgf-10*); classified as **low** or **high** relative to puborectalis:

| Class                                  | Lesion                                                 | Basis                                                               |
|----------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------|
| <b>Low</b> (rectum below puborectalis) | Imperforate anus / anal agenesis ± anoperineal fistula | Ectopic anus; >90% of low anomalies have an external fistula        |
|                                        | Anal stenosis                                          | Slight dorsal deviation of urorectal septum                         |
|                                        | Membranous atresia                                     | Failure of the epithelial anal plug to perforate by end of 8th week |

| Class                            | Lesion                                                                                                             | Basis                                                                                    |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| High (rectum above puborectalis) | Anorectal agenesis with rectovesical/rectourethral fistula (male) or rectovaginal/rectovestibular fistula (female) | Incomplete separation of cloaca from urogenital sinus by septum — commonest high anomaly |
|                                  | Rectal atresia                                                                                                     | Discontinuous anal canal and rectum, joined by a fibrous cord; likely vascular in origin |

· Overall incidence of imperforate anus  $\approx$  1:5000 live births, more common in males.

- **Urachal anomalies** (persistence of parts of the allantoic/vesico-urethral remnant): **urachal fistula** (patent throughout — urine leaks from umbilicus), **urachal cyst** (mid-segment persists, secretes and dilates), **urachal sinus** (upper segment persists, opens into bladder).

□ Fig 15.16 — *Anomalies of the Urogenital and Anorectal Tracts Insufficient formatio* (Larsen — *Human Embryology* — 6e, p.944)

## Applied / Clinical anatomy

- **Persistent cloaca and cloacal exstrophy** are neonatal surgical emergencies requiring staged reconstruction (colostomy/vesicostomy followed by definitive posterior sagittal anorectoplasty or cloacal repair); pre-operative MRI/cloacagram defines the length of the common channel and confluence of the three tracts.
- **Pectinate line** is the single most tested clinical landmark of this topic: it explains why internal haemorrhoids (above the line) are painless and drain via the portal system, while external haemorrhoids (below the line) are painful and drain systemically; it also marks the transition in lymphatic drainage relevant to staging of anal carcinoma.
- **Anorectal malformations** frequently co-exist with the **VACTERL** spectrum (Vertebral, Anorectal, Cardiac, Tracheo-oEsophageal, Renal, Limb anomalies) — any child with imperforate anus needs a spinal and renal ultrasound screen.
- **Meconuria** (meconium in urine) in a male neonate, or meconium at the vaginal vestibule in a female neonate, signals a high anorectal malformation with a recto-urinary or recto-vaginal fistula.
- Failure of anal canal recanalisation/ganglion cell migration in this region is the embryological substrate discussed alongside **Hirschsprung's disease**, though the aganglionosis itself is a neural-crest migration defect, not a cloacal septation defect.

## High-yield exam pointers

- Cloaca = endoderm-lined caudal hindgut dilation, ventrally continuous with allantois, closed by the cloacal membrane.
- Urorectal septum (intercloacal mesenchyme, *Six1/Six2*) divides cloaca (weeks 4–7) into dorsal anorectal canal + ventral urogenital sinus; its tip forms the perineal body.
- Cloacal membrane divides into anal membrane (ruptures end of week 8) and urogenital membrane.

- ▶ Urogenital sinus has 3 parts: vesico-urethral canal (bladder + urachus), pelvic part (prostatic/membranous urethra), phallic part (penile urethra/vestibule).
- ▶ Anal canal has dual origin: upper 2/3 endoderm, lower 1/3 ectoderm; junction = pectinate line, with differing blood/nerve/lymphatic drainage on either side.
- ▶ Persistent cloaca = single 1–7 cm perineal channel for GI, urinary and genital tracts in females.
- ▶ OEIS complex = Omphalocele + Exstrophy (bladder/cloaca) + Imperforate anus + Spinal defects; cloacal exstrophy  $\approx 1/30,000$ , isolated bladder exstrophy  $\approx 2/10,000$ .
- ▶ Anorectal malformations classified low/high relative to puborectalis; overall imperforate anus incidence  $\approx 1:5000$ .
- ▶ Urachal remnants give fistula, cyst or sinus depending on which segment of the allantoic duct persists.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Systemic embryology - head, neck & pharyngeal apparatus



### Age changes in mandible

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The mandible is often called the most dynamic bone of the skeleton because its size, shape, gonial angle, and complement of teeth change continuously and predictably from intrauterine life through old age. It develops from the first pharyngeal (mandibular) arch by membranous ossification around Meckel's cartilage, and thereafter undergoes lifelong remodelling driven first by tooth eruption and functional loading of the temporomandibular joint, and later — in old age — by tooth loss and alveolar resorption. Three life-stages are classically described in the RGUHS exam: infancy/childhood, adulthood, and old age, each with reproducible changes in the gonial angle, mental foramen position, mandibular canal course, and coronoid–condylar relationship.

#### 1. Development and ossification of the mandible

- ▶ Develops from the **first pharyngeal (mandibular) arch**; its embryonic cartilaginous core is **Meckel's cartilage**, which forms the mandibular process of the first arch.
- ▶ Each half ossifies from a **single centre** that appears near the site of the future mental foramen at about the **6th week of intrauterine life**, in the mesenchymal sheath lateral to Meckel's cartilage — almost the whole bone forms by **intramembranous ossification**.

- ▶ Ossification spreads medially (towards the symphysis) and posterosuperiorly (into the ramus), first below and then around the inferior alveolar nerve and its incisive branch; by the **10th week**, Meckel's cartilage deep to the incisor rudiments is invaded and surrounded by bone.
- ▶ The **condylar and coronoid processes ossify from independent secondary cartilages**, not from Meckel's cartilage itself. The condylar cartilage persists as a proliferating growth site until about the third decade; the coronoid secondary cartilage ossifies and disappears before birth.
- ▶ **Mental ossicles** — small cartilaginous nodules at the symphysis menti — appear about the 7th month in utero and unite with the adjacent bone before the end of the first postnatal year.
- ▶ Most of Meckel's cartilage degenerates; only its dorsal end persists to form the **malleus and incus** of the middle ear and the sphenomandibular/anterior malleolar ligament.
- ▶ At birth the two halves of the mandible are still separate, united only by the fibrous **symphysis menti**.

## 2. Postnatal growth mechanism

- ▶ **Union of the two halves**: begins in the first postnatal year and is essentially complete by the end of the second year, though separation near the alveolar margin may occasionally persist a little longer.
- ▶ **Growth in height** of the body occurs mainly by deposition of alveolar bone accompanying developing and erupting teeth, with some deposition also on the lower border.
- ▶ **Growth in length** is achieved by bone deposition on the posterior border of the ramus with compensatory resorption on the anterior border, so that part of the ramus is progressively remodelled into an addition to the body.
- ▶ **Growth in width** occurs by apposition on the outer surface with resorption on the inner surface.
- ▶ The **ramus enlarges disproportionately more than the body** during postnatal growth and tooth eruption.
- ▶ The **condylar cartilage** is now regarded as growing largely as an adaptive response to functional loading and movement at the temporomandibular joint, rather than as an autonomous primary growth centre — but it remains the chief site responsible for the increase in ramus height and mandibular length.

## 3. Age changes in infancy and childhood

- ▶ Body of the mandible is almost entirely made up of the **alveolar part**, containing sockets for the deciduous teeth in each half.
- ▶ **Mental foramen** opens close to the **lower border** of the body (in the neonate it also faces forwards; it turns to face backwards, as in the adult, by about the 2nd year as the chin develops).
- ▶ **Mandibular canal** runs close to the lower border.
- ▶ **Gonial (mandibular) angle** is obtuse, about **140° or more**, because the head/condyle lies almost in line with the body.
- ▶ The **coronoid process projects above** the level of the condylar process.
- ▶ Deciduous teeth begin to erupt at about 6 months of age; permanent teeth begin erupting from the 6th year and eruption is not complete until early adulthood.

#### 4. Age changes in adulthood

- ▶ The alveolar and sub-alveolar parts of the body become approximately equally developed.
- ▶ The mental foramen lies midway between the upper and lower borders of the body.
- ▶ The mandibular canal runs roughly parallel to the mylohyoid line.
- ▶ The gonial angle reduces to about 110–120° as the ramus becomes almost vertical.
- ▶ The relationship at the mandibular notch reverses: the condylar process now projects above the coronoid process.

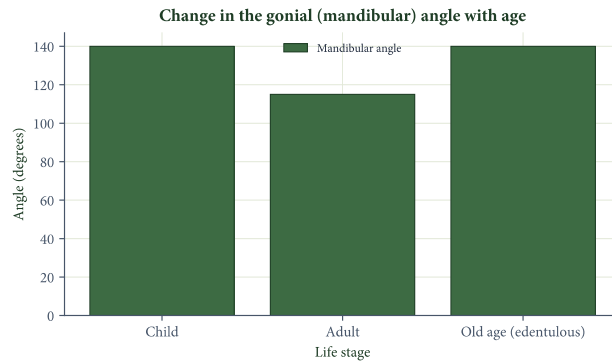
#### 5. Age changes in old age (the edentulous mandible)

- ▶ Progressive loss of teeth leads to resorption of the alveolar process, so that the height of the body is markedly reduced — sometimes to little more than a thin bar of bone.
- ▶ The mental foramen and mandibular canal come to lie close to the (former) alveolar/superior border; because the foramen sits higher than the canal behind it, resorption typically exposes the mental nerve at the foramen before it exposes the nerve within the canal — a hazard for denture-bearing patients and for surgery in this region.
- ▶ The gonial angle again becomes obtuse, about 140°, because the ramus becomes oblique.
- ▶ The coronoid process again projects above the condylar process, recreating the childhood relationship.
- ▶ Net effect: reduced vertical facial height, mandibular over-closure with relative prognathism, and deepening of skin creases running back from the corners of the mouth.

#### 6. Comparative summary

| Feature                      | Children                                     | Adult                                     | Old age                                                |
|------------------------------|----------------------------------------------|-------------------------------------------|--------------------------------------------------------|
| Body composition             | Almost all alveolar bone (deciduous sockets) | Alveolar + sub-alveolar equally developed | Alveolar border resorbed; body height markedly reduced |
| Mental foramen               | Close to lower border                        | Midway between upper and lower borders    | Close to upper/alveolar border (may disappear)         |
| Mandibular canal             | Near the lower border                        | Parallel to the mylohyoid line            | Close to the upper border                              |
| Gonial (mandibular) angle    | ~140° (obtuse)                               | ~110–120°                                 | ~140° (obtuse)                                         |
| Coronoid vs condylar process | Coronoid projects above condyle              | Condyle projects above coronoid           | Coronoid projects above condyle                        |
| Ramus orientation            | Oblique                                      | Near-vertical                             | Oblique                                                |

□ Fig 2.18 — ■ Age-related changes in the mandible. (Vishram Singh — Textbook of Anatomy Vol 3 — 4e, p.141)



*The gonial angle is obtuse in children and in the edentulous elderly, and most acute in the dentate adult (BD Chaurasia; Vishram Singh).*

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw three lateral profile outlines of the mandible side by side, labelled **Child** → **Adult** → **Old age**, and mark on each:

- ▶ The **gonial angle** with its value —  $140^\circ$  /  $110-120^\circ$  /  $140^\circ$ .
- ▶ The **mental foramen** position — near lower border / midway / near upper (alveolar) border.
- ▶ The **mandibular canal** course — near lower border / parallel to mylohyoid line / near upper border.
- ▶ The **coronoid process vs condylar process** relative height — coronoid above condyle / condyle above coronoid / coronoid above condyle.
- ▶ The **teeth and alveolar bone** — deciduous sockets and full alveolar body (child) → complete permanent dentition (adult) → edentulous, resorbed alveolar ridge and reduced body height (old age).
- ▶ The **ramus orientation** — oblique / near-vertical / oblique.

### Applied / Clinical anatomy

- ▶ **Age-related fracture pattern:** in children the condylar neck is the weakest point (thin cortex, active cartilage) and fractures there predominate; in adults, fractures cluster at the angle (abrupt curvature), body/canine region (long canine root weakens bone), and parasymphysis; in the edentulous elderly, the atrophic, thinned body fractures easily, is often comminuted, and heals poorly because of reduced medullary blood supply and bone stock.
- ▶ Overall site distribution of mandibular fractures: condyle/neck ~36% (commonest site), angle ~21%, body ~25%, canine/parasymphyseal region ~14–15%, symphysis ~10%; occurs about 4.5 times more often in males.
- ▶ In the **edentulous mandible**, alveolar resorption exposes the mental nerve at the foramen, producing pain from a denture flange resting over it; the landmarks for an inferior alveolar nerve block (lingula, occlusal plane) shift as the ramus and canal change position with age.
- ▶ Age changes in the gonial angle, mental foramen position, and dental status are used in **forensic and skeletal age estimation**.



- ▶ Failure of normal first-arch (Meckel's cartilage) development underlies **micrognathia** seen in Treacher Collins syndrome and Pierre Robin sequence, linking the embryological origin of the mandible to a real clinical anomaly.
- ▶ Panoramic (OPG) radiographic interpretation differs by age: unerupted tooth crypts and thin cortex in children versus a resorbed alveolar ridge and superiorly displaced canal in the edentulous elderly — directly relevant to dental implant planning.

### High-yield exam pointers

- ▶ Mandible = most dynamic bone of the body; develops from the **1st pharyngeal arch/Meckel's cartilage**; ossifies mainly by the membranous route from a centre appearing at the **6th week IU**; it is the **second bone (after the clavicle) to ossify** in the body.
- ▶ At birth the two halves are joined at the symphysis menti by fibrocartilage; they fuse by the end of the 1st–2nd year, aided by transient mental ossicles.
- ▶ **Gonial angle is the single most tested number**: Child 140° → Adult 110–120° → Old age 140° again (a "U-shaped" change).
- ▶ **Mental foramen migrates**: low in the child → midway in the adult → high (near-absorbed alveolar border) in old age.
- ▶ **Coronoid–condyle relationship flips twice**: coronoid above condyle (child) → condyle above coronoid (adult) → coronoid above condyle again (old age).
- ▶ Condylar and coronoid processes ossify from **secondary cartilages**, NOT from Meckel's cartilage.
- ▶ The old-age "edentulous mandible" is a classic viva/OSPE specimen: thin body, everted-then-oblique angle, superiorly placed mental foramen and canal.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia's Human Anatomy Vol 3–4 8e; Vishram Singh — Textbook of Anatomy Vol 3 4e; Moore's Clinically Oriented Anatomy 9e; Langman's Medical Embryology (Sadler) 14e.



## Branchial apparatus

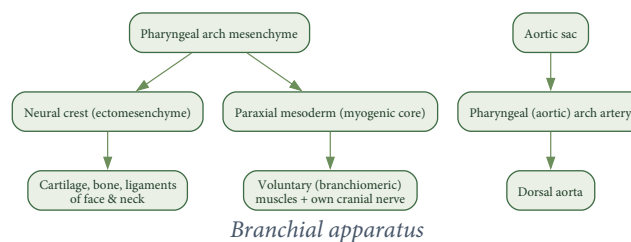
Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **branchial (pharyngeal) apparatus** is the set of paired mesodermal, ectodermal and endodermal structures — **pharyngeal arches**, **pharyngeal clefts (grooves)** and **pharyngeal pouches**, together with the **pharyngeal membranes** formed where a cleft and pouch meet — that appear on the lateral wall of the primitive pharynx during the 4th–5th weeks of intrauterine life. It is the embryological homologue of the gill (branchial) apparatus of fish, and in the human it fashions almost the entire skeleton, musculature, nerve supply and vasculature of the face, jaws, and neck. Six pharyngeal arches form, but the 5th is rudimentary and regresses without a trace, so only arches 1, 2, 3, 4 and 6 contribute definitive structures. Faulty development of this apparatus underlies a large group of clinically important congenital anomalies of the head and neck.

### 1. Formation and basic plan

- ▶ Intermittent mesodermal thickenings appear in the floor and lateral wall of the primitive pharynx and fuse in the midline with their opposite fellow to form horseshoe-shaped **pharyngeal (branchial) arches** — six in number, the 5th being small and rudimentary.
- ▶ Between consecutive arches, the **surface ectoderm** invaginates to form four **pharyngeal clefts (grooves)**; simultaneously the **endoderm** of the foregut evaginates opposite each cleft to form the **pharyngeal pouches**.
- ▶ Where an ectodermal cleft and endodermal pouch come into direct apposition (with an intervening thin mesenchymal layer), a **pharyngeal membrane** is formed.
- ▶ Each arch has four basic components (Flowchart 11.1, Sontakke): a **cartilaginous skeletal bar** derived from **neural-crest-derived ectomesenchyme**; **voluntary (branchiomeric) muscle** derived from **paraxial/somitic mesoderm**, which carries its own **cranial nerve**; and an **aortic (pharyngeal) arch artery** connecting the aortic sac to the dorsal aorta.
- ▶ By day 22 the first and second arches are visible; by day 29 (5th week) four arches are present externally — the 6th does not form a visible external elevation.

□ Fig 11.2 — (A) Section of the embryo showing the foregut and pharyngeal pouches; (B) Section through the arches showing the numbered arches, pouches and clefts (Sontakke — *Textbook of Human Embryology*, p.105)



## 2. Derivatives of the pharyngeal arches

| Arch                                | Cartilage (skeletal element)                                                                                                                                                                                                       | Muscles                                                                                                                                                 | Nerve                                                                                                                | Aortic arch artery                                                                                                   |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| I — Mandibular (Meckel's cartilage) | Malleus, incus; anterior ligament of malleus and sphenomandibular ligament (from perichondrium); body of mandible ossifies membranously around the ventral cartilage (Meckel's cartilage itself does <b>not</b> form the mandible) | Muscles of mastication (temporalis, masseter, medial & lateral pterygoid), mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini | Mandibular nerve (V3) — post-trematic; <b>chorda tympani</b> (facial n.) — the only pre-trematic nerve that persists | Part of the maxillary artery                                                                                         |
| II — Hyoid (Reichert's cartilage)   | Stapes, styloid process; stylohyoid ligament (from perichondrium); lesser (short) cornu and upper part of body of hyoid                                                                                                            | Muscles of facial expression, stapedius, stylohyoid, posterior belly of digastric                                                                       | Facial nerve (VII)                                                                                                   | Stapedial and hyoid arteries                                                                                         |
| III                                 | Greater cornu and lower part of body of hyoid                                                                                                                                                                                      | Stylopharyngeus                                                                                                                                         | Glossopharyngeal nerve (IX)                                                                                          | Common carotid artery + proximal (stem) part of internal carotid artery                                              |
| IV                                  | Thyroid cartilage (+ epiglottic and cuneiform cartilages via the hypobranchial eminence)                                                                                                                                           | Cricothyroid, constrictors of pharynx, muscles of the soft palate except tensor veli palatini                                                           | Superior laryngeal branch of vagus (X)                                                                               | Right — proximal right subclavian artery; Left — arch of aorta                                                       |
| V                                   | Rudimentary — regresses completely, no derivative                                                                                                                                                                                  | —                                                                                                                                                       | —                                                                                                                    | Disappears completely                                                                                                |
| VI                                  | Cricoid, arytenoid and corniculate cartilages                                                                                                                                                                                      | All intrinsic muscles of the larynx <b>except</b> cricothyroid                                                                                          | Recurrent laryngeal branch of vagus (X)                                                                              | Right — right pulmonary artery; Left — left pulmonary artery + ductus arteriosus (ligamentum arteriosum after birth) |

- ▶ Mnemonic detail: the **carotid body** is a derivative of the 3rd arch, the **aortic (para-aortic) body** of the 4th arch.
- ▶ Epiglottic cartilage is **not** a true arch-cartilage derivative — it develops from the **hypobranchial eminence** (a midline proliferation of 3rd/4th arch mesenchyme), not from an arch bar itself.

### 3. Derivatives of the pharyngeal pouches

There are classically four functional pouches (a rudimentary 5th fuses with the 4th).

| Pouch                                                   | Derivatives                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First                                                   | Dorsal part + dorsal part of 2nd pouch → <b>tubotympanic recess</b> ; proximal part becomes the <b>auditory (Eustachian) tube</b> ; distal part expands into the <b>middle-ear (tympanic) cavity</b> , <b>mastoid antrum</b> and <b>mastoid air cells</b> , and forms the inner (mucosal) lining of the tympanic membrane                                          |
| Second                                                  | Ventral part → epithelial lining of the <b>palatine tonsil</b> and tonsillar crypts (lymphoid follicles are of mesodermal origin); the <b>intratonsillar cleft</b> is the unobliterated remnant of the pouch                                                                                                                                                       |
| Third                                                   | Ventral wing → <b>thymus</b> (endoderm forms the cytotreticulum and Hassall's corpuscles; thymocytes are of mesodermal/bone-marrow origin); dorsal wing → <b>inferior parathyroid gland (parathyroid III)</b> — migrates furthest caudally with the descending thymus, so the inferior parathyroid ends up more variable in final position than the superior gland |
| Fourth                                                  | Dorsal wing → <b>superior parathyroid gland (parathyroid IV)</b> , which attaches to the posterior border of the thyroid lobe; ventral part fuses with the rudimentary 5th pouch to form the <b>caudal pharyngeal (ultimobranchial) complex</b>                                                                                                                    |
| Caudal pharyngeal complex (4th + rudimentary 5th pouch) | <b>Ultimobranchial body</b> → parafollicular (C) cells of the thyroid gland (these are neural-crest derived, reaching the thyroid via the ultimobranchial body); thymic element and lateral thyroid element also contribute here                                                                                                                                   |

- ▶ Thymus continues to grow from birth until puberty, then undergoes gradual **thymic involution**.
- ▶ Thyroid gland itself develops from **two** sources — median thyroid follicular tissue from the thyroglossal duct (floor of pharynx, at the tuberculum impar/foramen caecum) and parafollicular cells from the ultimobranchial body — and is the **first endocrine gland to develop**, with follicular cells beginning hormone synthesis by the 12th week.

### 4. Fate of the pharyngeal clefts and membranes

- ▶ Only the **dorsal part of the 1st cleft** persists, forming the epithelial lining of the **external acoustic meatus** (and the outer/cuticular layer of the tympanic membrane).

- ▶ The mesenchyme of the rapidly growing **2nd arch** overgrows and buries the 2nd, 3rd and 4th clefts, fusing with the epicardial ridge caudally; the buried, ectoderm-lined space so created is the **cervical sinus**, which normally disappears completely, leaving a smooth neck contour.
- ▶ Of the pharyngeal membranes, only the **1st** persists — as the **tympanic membrane**, uniquely composed of all three germ layers (ectoderm of the 1st cleft, mesenchyme, endoderm of the 1st pouch).
- ▶ Persistence of the cervical sinus or a cleft remnant is the embryological basis of **branchial cysts, sinuses and fistulae** (see below).

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

**A. Sagittal section through a 5th-week embryo** — Labels: forebrain, hindbrain/neural tube, notochord, stomodeum, buccopharyngeal membrane (ruptured), septum transversum, pericardial bulge, foregut/primitive pharynx, pharyngeal pouches (numbered 1–4), yolk sac. **B. Coronal/frontal section through the pharyngeal arches** — Labels: 1st (mandibular), 2nd (hyoid), 3rd, 4th and 6th arches (mark the 5th as "disappears"); 1st–4th pharyngeal clefts (ectodermal, between arches); 1st–4th pharyngeal pouches (endodermal, opposite each cleft); site of the pharyngeal membrane (cleft–pouch apposition); cervical sinus (2nd arch overgrowth burying clefts 2–4).

### Applied / Clinical anatomy

- ▶ **Branchial (cervical) cyst** — congenital cyst along the **anterior border of sternocleidomastoid**, typically at the junction of its upper one-third and lower two-thirds, from failure of obliteration of the cervical sinus/2nd cleft; lined by stratified squamous or simple columnar epithelium; usually absent at birth, presenting later as a slowly enlarging, painless neck swelling that enlarges further with upper respiratory infection.
- ▶ **Branchial fistula/sinus** — persistent communication along the cleft/pouch tract: an **external** branchial sinus opens only on the skin of the neck; an **internal** branchial sinus opens only into the pharynx (near the tonsillar fossa); a **complete branchial fistula** communicates both externally on the skin and internally with the pharynx.
- ▶ **DiGeorge syndrome (22q11.2 deletion / velocardiofacial / Shprintzen syndrome)** — a microdeletion of chromosome 22 causing failure of development of 3rd and 4th pouch derivatives together with neural-crest-dependent cardiac outflow structures: thymic hypoplasia/aplasia (T-cell immunodeficiency, recurrent infections), parathyroid hypoplasia (hypocalcaemia/tetany), conotruncal cardiac defects, short philtrum ("fish-mouth" facies), low-set malformed ears and micrognathia; incidence  $\approx 1$  in 2000–4000 live births.
- ▶ **First arch syndromes** — failure of neural-crest cell migration into the 1st pharyngeal arch: **Treacher Collins syndrome** (mandibulofacial dysostosis; autosomal dominant, *TCOF1* gene, chromosome 5; mandibular and malar hypoplasia, down-slanting palpebral fissures, external ear malformations;  $\approx 1:50,000$  births) and **Pierre Robin syndrome** (cleft palate + retrognathia/micrognathia + glossoptosis, linked to the *SOX9* gene region on chromosome 17;  $\approx 1:10,000$  births).

- ▶ **Goldenhar syndrome (oculo-auriculo-vertebral spectrum)** — hemifacial microsomia with anotia/microtia, ocular anomalies, and hemivertebrae/spina bifida ± cardiac defects; incidence ≈1 in 5600 births.
- ▶ **Thyroglossal cyst/fistula** — persistence of a segment of the thyroglossal duct anywhere along its path from the foramen caecum to the normal thyroid position; presents as a midline neck swelling that moves upward on tongue protrusion (given its attachment via the duct tract); may rupture to form a draining thyroglossal fistula.
- ▶ **Ectopic thyroid** — thyroid tissue arrested anywhere along the thyroglossal tract; **lingual thyroid** (under the mucosa of the tongue dorsum) is the commonest ectopic site; thyroid tissue may also be found intralingually, suprahyoid, infrahyoid, or intrathoracically.
- ▶ **Surgical relevance** — branchial cysts/fistulae and thyroglossal cysts are important differentials for a lateral vs midline neck swelling respectively in clinical/viva examination.

### High-yield exam pointers

- ▶ Branchial apparatus = pharyngeal **arches** (mesoderm + neural crest) + **clefts** (ectoderm) + **pouches** (endoderm) + **membranes** (cleft–pouch junction).
- ▶ Six arches form; the **5th is rudimentary** and disappears completely — only 1, 2, 3, 4, 6 give derivatives.
- ▶ Each arch = one cartilage bar + muscle group + its own cranial nerve + its own aortic arch artery.
- ▶ **Meckel's cartilage** (1st arch) → malleus, incus; **Reichert's cartilage** (2nd arch) → stapes, styloid process, lesser cornu/upper body of hyoid.
- ▶ Nerves of arches, cranial to caudal: V3 → VII → IX → X(**superior laryngeal**) → X(**recurrent laryngeal**) for arches 1, 2, 3, 4, 6.
- ▶ Only the **1st cleft** persists (external acoustic meatus); 2nd–4th clefts are buried by 2nd-arch overgrowth to form the **cervical sinus**, which normally obliterates.
- ▶ Only the **1st membrane** persists, as the **tympanic membrane** (all three germ layers).
- ▶ Pouch derivatives: 1st = tubotympanic recess/middle ear; 2nd = palatine tonsil; 3rd = thymus + inferior parathyroid; 4th = superior parathyroid + ultimobranchial body (parafollicular C-cells).
- ▶ Persistent cervical sinus/cleft → **branchial cyst/fistula**; failed 3rd/4th pouch development + neural crest cardiac defect → **DiGeorge syndrome**; failed 1st-arch neural crest migration → **Treacher Collins/Pierre Robin syndromes**.

### SOURCE & COVERAGE

Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Gray's Anatomy (Standring) 41e.



## Cervical sinus

Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **cervical sinus** (sinus cervicalis; **cervical sinus of His**) is a transient, ectoderm-lined, slit-like cavity that appears in the lateral neck of the 4–5 week embryo. It is formed when the rapidly proliferating **second (hyoid) pharyngeal arch** grows caudally as an "operculum," overlapping and burying the second, third, and fourth pharyngeal clefts, and fuses with the epicardial ridge below. Normally it is obliterated completely, giving the neck its smooth external contour; its abnormal persistence is the embryological basis of **lateral cervical (branchial) cysts, sinuses, and fistulae** — collectively the second commonest congenital malformation of the head and neck in children.

### 1. Developmental background — the pharyngeal apparatus

- ▶ The **pharyngeal (branchial) apparatus** of the 4th–5th week embryo consists of paired **pharyngeal arches** (mesenchyme cores containing an aortic arch artery, a cartilage bar, a cranial nerve, and eventual muscle), separated externally by **ectoderm-lined pharyngeal clefts (grooves)** and internally by **endoderm-lined pharyngeal pouches**, with a two-layered **pharyngeal membrane** where cleft and pouch ectoderm/endoderm appose.
- ▶ Four pharyngeal clefts are recognised externally (between arches 1–2, 2–3, 3–4, 4–6); of these, only the **first cleft** persists as a permanent adult structure — it becomes the **external acoustic meatus**.
- ▶ The **second, third, and fourth clefts** are the ones concerned in cervical-sinus formation; they never form gill slits (unlike fish) because they never perforate — mesenchyme always keeps ectoderm and endoderm apart.

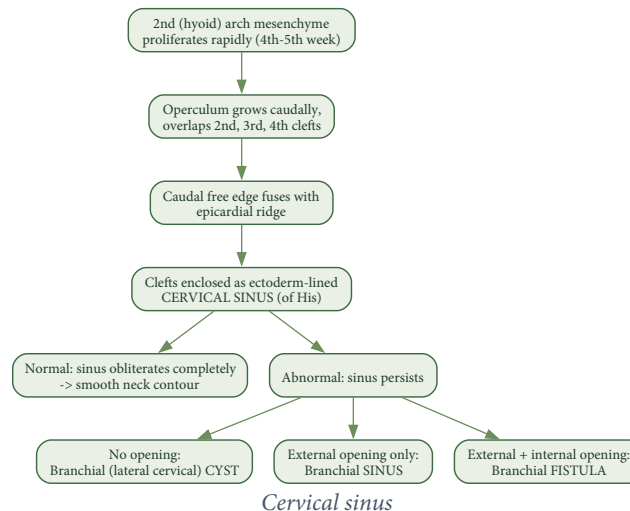
| Structure                       | Fate                                                                         |
|---------------------------------|------------------------------------------------------------------------------|
| 1st pharyngeal cleft            | External acoustic meatus (persists)                                          |
| 2nd, 3rd, 4th pharyngeal clefts | Overgrown and buried → form the <b>cervical sinus</b> → normally obliterated |
| 1st pharyngeal pouch            | Tubotympanic recess → middle-ear cavity + auditory (Eustachian) tube         |
| 2nd pharyngeal pouch            | Palatine tonsil, intratonsillar cleft                                        |
| 3rd pharyngeal pouch            | Inferior parathyroid, thymus                                                 |
| 4th pharyngeal pouch            | Superior parathyroid, ultimobranchial body (caudal pharyngeal complex)       |

### 2. Formation of the cervical sinus (mechanism)

- ▶ During the **4th and 5th weeks**, the mesenchyme of the **second pharyngeal arch** proliferates rapidly and expands caudally as a fold called the **operculum**, overhanging the third and fourth arches like a hood.
- ▶ This overgrowth progressively buries the second, third, and fourth **pharyngeal clefts**, so that a slit-like potential space is enclosed between the operculum superficially and the third, fourth (and sixth) arches deeply.



- ▶ The free caudal edge of the operculum fuses with the **epicardial ridge** (the swelling produced by the developing pericardium/heart in the lower neck), sealing the enclosed space off from the exterior.
- ▶ This transient, ectoderm-lined cavity is the **cervical sinus (of His)**. Its floor and walls are lined entirely by **ectoderm** derived from the buried clefts and the deep surface of the operculum.
- ▶ Deep structures belonging to the buried arches (great vessels, cranial nerves IX, X, XI, XII and their branches) come to lie **beneath** the smooth skin surface of the developing neck as a result of this process.



### 3. Normal fate — obliteration

- ▶ The walls of the enclosed sinus normally appose and fuse, and the cavity is **obliterated rapidly and completely** before the end of the embryonic period.
- ▶ This obliteration converts the previously grooved lateral profile of the pharyngeal-arch stage into the **smooth, uninterrupted contour** of the definitive neck.
- ▶ No trace of the sinus, and no communication with the skin surface or the pharynx, should remain in the normal fetus/neonate.

□ Fig 11.7 — Development of pharyngeal clefts and pouches. The second arch grows to cover the second, third and fourth clefts, finally fusing with the epicardial ridge; the trapped part of the second, third, and fourth clefts forms the cervical sinus that later gets obliterated (Sontakke — Textbook of Human Embryology, p.111)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A coronal/schematic section through the developing neck at the pharyngeal-arch stage, labelled with:

- ▶ **First, second, third, fourth pharyngeal arches** (numbered 1–4)
- ▶ **Operculum** of the second arch, shown growing caudally as an overhanging fold
- ▶ **Second, third, fourth pharyngeal clefts**, shown being buried beneath the operculum
- ▶ **Epicardial ridge**, with the caudal edge of the operculum fusing onto it
- ▶ **Cervical sinus** — the enclosed, ectoderm-lined slit-like cavity, labelled clearly
- ▶ A second panel showing the **normal obliterated state** (smooth neck contour) versus the **persistent sinus** with possible external opening (onto the neck skin, anterior border of sternocleidomastoid) and/or internal opening (into the tonsillar fossa)

**4. Abnormal persistence — classification of anomalies**

If the cervical sinus fails to obliterate, three related anomalies can result depending on whether an opening remains, and where:

| Anomaly                           | Basis                                                                                                                                                                                 | Opening(s)                                                   | Typical site                                                                                                                   |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Branchial (lateral cervical) cyst | Sinus persists as a closed, epithelium-lined cavity with no opening                                                                                                                   | None                                                         | Anterior border of sternocleidomastoid, at the junction of its upper 1/3 and lower 2/3, below/behind the angle of the mandible |
| Branchial sinus                   | Persistent connection of the sinus with the skin surface only                                                                                                                         | External opening only                                        | Along the anterior border of sternocleidomastoid, lower third of the neck                                                      |
| Branchial fistula                 | Sinus connects both to the skin and, via a small canal, to the pharynx (tonsillar fossa) — classically follows rupture of a cyst, or failure of the operculum to grow caudally at all | Both external (neck) and internal (tonsillar fossa) openings | External opening on neck (anterior border of SCM); internal opening in the tonsillar sinus/fossa                               |
| Internal branchial fistula (rare) | Cervical sinus connects to the pharyngeal lumen by a small canal only                                                                                                                 | Internal opening only                                        | Tonsillar fossa                                                                                                                |

- ▶ All these lesions are lined by **ectoderm** (stratified squamous epithelium), often with lymphoid tissue in the wall, reflecting their origin from the ectoderm-lined cervical sinus/clefts.
- ▶ A branchial fistula, when present, ascends from its cervical opening through subcutaneous tissue, platysma and cervical fascia, enters the **carotid sheath**, and passes **between the internal and external carotid arteries** on its way to the tonsillar fossa.

- ▶ A cyst may not be clinically evident at birth; it frequently enlarges and presents only in **childhood or early adulthood** as the epithelial lining accumulates desquamated debris and fluid.
- ▶ (For completeness: an anomaly of the **first** pharyngeal cleft — not the cervical sinus — produces a preauricular sinus/cyst anterior to the external ear; this is a separate entity and is not asked here.)

### Applied / Clinical anatomy

- ▶ **Incidence:** branchial cysts/sinuses/fistulae together form the **second most common congenital lesion of the head and neck in children**.
- ▶ **Presentation:** a painless, fluctuant, slowly enlarging swelling along the anterior border of sternocleidomastoid; a sinus/fistula opening may discharge mucus or saliva intermittently, and become infected, producing an inflamed, tender neck swelling with discharge.
- ▶ **Surgical relations:** during excision, the tract/cyst wall lies close to the **hypoglossal (XII)**, **glossopharyngeal (IX)** and **spinal accessory (XI) nerves**, and passes between the internal and external carotid arteries — these structures must be identified and preserved.
- ▶ **Investigations:** a fistulous tract can be outlined by **sinography/fistulography** (radio-opaque dye injection) to delineate its course pre-operatively.
- ▶ **Treatment:** complete surgical **excision** of the cyst/sinus/fistula tract is required, particularly if infected, to prevent recurrence; the whole tract up to its pharyngeal opening (if present) must be removed.
- ▶ **Differential diagnosis:** distinguished from a **thyroglossal cyst** (midline, moves upward on tongue protrusion/swallowing because of its attachment to the foramen caecum) and from **cystic hygroma** (multiloculated lymphatic malformation, usually in the posterior triangle) — the branchial cyst is classically lateral, at the anterior border of SCM, and does not move with swallowing or tongue protrusion.
- ▶ **Evolutionary correlate:** the transient pharyngeal clefts/cervical sinus recapitulate the gill-slit stage of lower vertebrates, though in humans the clefts never perforate to communicate with the pharyngeal pouches.

### High-yield exam pointers

- ▶ Cervical sinus = **cervical sinus of His**; transient ectoderm-lined cavity of the 4th–5th week neck.
- ▶ Formed by caudal overgrowth of the **second (hyoid) arch operculum** burying the **2nd, 3rd, and 4th pharyngeal clefts**, fusing with the **epicardial ridge**.
- ▶ Only the **1st cleft** normally persists (→ external acoustic meatus); the 2nd–4th clefts are buried in the sinus and then obliterated.
- ▶ Normal fate: **complete obliteration** → smooth neck contour.
- ▶ Persistence → **branchial cyst** (no opening, at ant. border of SCM, junction of upper 1/3–lower 2/3), **branchial sinus** (external opening only), or **branchial fistula** (both external and internal openings, tract passing between internal and external carotid arteries to the tonsillar fossa).
- ▶ Second most common congenital head-and-neck anomaly in children.
- ▶ Key differential: thyroglossal cyst (midline, moves with tongue protrusion) vs branchial cyst (lateral, at SCM, does not move).

- Nerves at surgical risk during excision: hypoglossal (XII), glossopharyngeal (IX), spinal accessory (XI).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Moore — The Developing Human 9e; Moore's Clinically Oriented Anatomy 9e; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Congenital anomalies of face and palate

Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy

**Definition / Introduction** Congenital anomalies of the face and palate are structural malformations arising from failure of normal proliferation, growth or fusion of the facial processes (frontonasal, paired maxillary, paired mandibular) and of the palatine shelves during the fourth to twelfth week of intra-uterine life. Clefts of the lip and palate are the commonest craniofacial birth defects and form the core of this group, while oblique facial cleft, macro-/microstomia, proboscis, agnathia, hypertelorism and the Robin sequence arise from disturbances of the same developmental events. The large majority (non-syndromic) show multifactorial inheritance; the remainder are syndromic, resulting from single-gene mutations, chromosomal aberrations or teratogen exposure.

### 1. Development of the face — the five facial processes

At the end of the fourth week the primitive mouth (**stomodeum**) is bounded by five mesenchymal (neural-crest-derived) elevations that surround it:

| Process                                               | Origin                                                    | Chief derivatives                                                                                                                                                                                                                        | Sensory nerve         |
|-------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Frontonasal process (single)                          | Mesenchyme proliferating ventral to the forebrain vesicle | Forehead; external nose (bridge from the process itself, dorsum/tip from fused <b>medial nasal processes</b> , alae from <b>lateral nasal processes</b> ); nasal septum; <b>philtrum</b> of upper lip; <b>premaxilla</b> /primary palate | Ophthalmic nerve (V1) |
| Maxillary process (paired, dorsal part of 1st arch)   | 1st pharyngeal arch                                       | Lateral part of upper lip, upper cheek, <b>secondary palate</b> (palatine shelves); skin overgrowing the philtrum                                                                                                                        | Maxillary nerve (V2)  |
| Mandibular process (paired, ventral part of 1st arch) | 1st pharyngeal arch                                       | Chin, lower lip, lower cheek                                                                                                                                                                                                             | Mandibular nerve (V3) |

Key sequential events:

- ▶ Bilateral ectodermal thickenings on the frontonasal process — **olfactory (nasal) placodes** — invaginate into **nasal pits**; their raised margins form the **medial** and **lateral nasal processes**.
- ▶ The maxillary process grows medially, fusing first with the **lateral** nasal process (the intervening nasolacrimal groove later canalises into the **nasolacrimal duct**), then, by the 7th–10th week, with the **medial** nasal process — converting the nasal pit into the primitive anterior naris.
- ▶ The two medial nasal (globular) processes fuse in the midline as the **intermaxillary segment** — labial component (**philtrum**), upper-jaw component (4 incisors) and palatal component (triangular **primary palate/premaxilla**).
- ▶ **Enigma of the upper lip:** the philtrum's mesoderm is frontonasal, but maxillary-process ectoderm overgrows it to form its skin — hence philtrum skin is supplied by the **maxillary nerve**, not the ophthalmic nerve.
- ▶ Lateral fusion of maxillary and mandibular processes forms the cheeks and the definitive angle of the mouth.

□ Fig 12.1 — Development of the face: the five facial primordia (single frontonasal process, paired maxillary processes, paired mandibular processes) around the stomodeum, with formation of the medial and lateral nasal processes from the nasal placode/pit (Sontakke — Textbook of Human Embryology, p.118)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw four sequential panels (A→D) of the developing face, each with these exact labels:

- ▶ Stomodeum (primitive mouth), lens placode, eye
- ▶ Frontonasal process (cranial border) with olfactory/nasal placode → nasal pit
- ▶ Medial nasal process and lateral nasal process flanking the nasal pit
- ▶ Maxillary process (paired) growing medially — mark its **line of fusion with the lateral nasal process** and, later, **with the medial nasal process**
- ▶ Mandibular process (paired) forming the lower border, with **fusion in the midline**
- ▶ Final panel: narrowed **oral fissure**, fused **cheek**, and labelled **philtrum**

## 2. Development of the palate

The palate develops in two parts between the 5th/6th and 12th weeks; the **critical period** during which interruption produces a cleft is from the **end of the 6th week to the beginning of the 9th week**.

| Component                                       | Source                                                                                                       | Forms                                                                                               |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Primary palate</b> (median palatine process) | Intermaxillary segment (frontonasal process)                                                                 | Wedge-shaped premaxilla bearing the four incisor teeth; triangular anterior part of the hard palate |
| <b>Secondary palate</b>                         | Paired <b>palatine shelves</b> (lateral palatine processes) from the inner aspect of the maxillary processes | Remainder of the hard palate + whole of the soft palate, including the <b>uvula</b>                 |

Sequence: the palatine shelves appear in the 6th week and initially grow **vertically downward** alongside the tongue; during the 7th–8th weeks, as the mandible enlarges and the tongue drops, the shelves reorient to a **horizontal position above the tongue** and fuse — (i) with each other in the midline, (ii) with the nasal septum above, and (iii) with the posterior margin of the primary palate anteriorly, by a **Y-shaped suture** whose limbs pass between the lateral incisor and canine. Ossification then extends from the maxilla and palatine bones into the anterior three-fourths (**hard palate**); the posterior one-fourth remains unossified, forming the **soft palate and uvula**. The adult junction of primary and secondary palate is marked by the **incisive fossa**, into which the incisive canals open.

### 3. Cleft lip — types, embryological basis, epidemiology

| Type                                   | Embryological basis                                                                                               |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Unilateral cleft lip (commonest)       | Failure of fusion of the maxillary process with the medial nasal process of the <b>same side</b>                  |
| Bilateral cleft lip                    | Bilateral failure of the same fusion                                                                              |
| Median cleft lip ("hare-lip") — rarest | Failure of merging of the two medial nasal processes / failure of philtrum formation from the frontonasal process |
| Cleft of the lower lip — very rare     | Failure of the two mandibular processes to fuse in the midline                                                    |

- Incidence of cleft lip (with or without cleft palate) is **≈1.4 per 1000 births worldwide**; isolated cleft lip alone is quoted as **≈1 in 1000 births**, arising around the **35th day** of gestation.
- **60–80% of affected infants are male.**
- **Unilateral cleft of the upper lip is the commonest congenital anomaly of the face.**

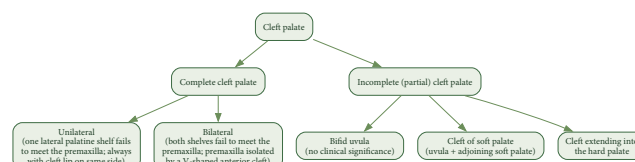
□ Fig 12.5 — Cleft lip and cleft palate: non-fusion of the maxillary process with the medial nasal process produces cleft lip; non-fusion of the median and lateral palatine processes produces cleft palate, which may be complete (unilateral/bilateral) or incomplete (Sontakke — *Textbook of Human Embryology*, p.123)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the four clinical types of cleft upper lip side by side, labelling in each: **philtrum**, **lateral part of upper lip (maxillary-process derivative)**, and the **defective line of fusion** — (A) unilateral cleft, (B) bilateral cleft, (C) median cleft ("hare-lip"), (D) cleft of the lower lip.

### 4. Cleft palate — types, embryological basis, epidemiology

Defective fusion of the palatal segments produces clefts of varying degree:



*Congenital anomalies of face and palate*

- **Embryological basis:** non-fusion of the median palatine process (primary palate) with the lateral palatine processes (secondary palate), or non-fusion of the two lateral palatine processes with each other and with the nasal septum.

- **Incidence:** isolated cleft palate  $\approx$  1 in 2500 births; it is **more common in females** ( $\approx$ 67%) and, unlike cleft lip, its incidence is **not related to maternal age**. It is **etiologically distinct** from cleft lip with/without cleft palate — CL(P) and isolated cleft palate are separate entities with different embryological timing and sex predilection.

## 5. Other congenital anomalies of the face

- **Oblique facial cleft (naso-ocular/orbito-facial fissure):** failure of fusion of the maxillary process with the lateral nasal process; the fissure runs from the medial angle of the eye to the upper lip, exposing the nasolacrimal duct; usually **bilateral**.
- **Macrostomia:** abnormally wide mouth from **incomplete** lateral fusion of the maxillary and mandibular processes.
- **Microstomia:** abnormally small mouth from **excessive** fusion of the same processes.
- **Proboscis:** an elongated cylindrical nasal appendage from failed nasal-process development; in severe midline defects it may coexist with **cyclopia** (fused eyes), part of the holoprosencephaly spectrum.
- **Agnathia:** absence of the mandible due to failure of mandibular-process development.
- **Retrognathia:** an abnormally small, set-back mandible/chin.
- **Hypertelorism:** widely spaced orbits resulting from an abnormally broad frontonasal process.
- **Robin sequence:** primary hypoplasia of the mandible **before the 9th week** displaces the tongue posteriorly (glossoptosis), which mechanically obstructs the palatal shelves from closing — producing a secondary, **U-shaped** cleft palate with micrognathia. This differs from a true **primary** cleft palate (failure of shelf fusion itself), which begins anteriorly and is typically **V-shaped**. Robin sequence may be isolated or occur as one feature of **Stickler syndrome** (a type-II-collagen gene defect also affecting the eye, joints and stature).

## 6. Genetic basis and etiology

- The great majority of both cleft lip ( $\pm$  palate) and isolated cleft palate are **non-syndromic**, showing **multifactorial (polygenic + environmental threshold) inheritance** — the commonest cause overall.
- **Syndromic** cleft lip/palate may instead follow a **mendelian single-gene** pattern, or result from **chromosomal disorders** — notably **trisomy 13 (Patau syndrome)** and the **4p- deletion (Wolf-Hirschhorn) syndrome** — or from **teratogenic exposure** (rubella embryopathy, thalidomide, anticonvulsants such as **phenytoin**, which raises the risk two- to three-fold).
- **Recurrence risk for CL(P)** rises steeply with the number of affected relatives and affected parents:

| Affected relatives (besides parents) | 0 parents affected | 1 parent affected | 2 parents affected |
|--------------------------------------|--------------------|-------------------|--------------------|
| None                                 | 0.1%               | 3%                | 34%                |
| One sibling                          | 3%                 | 11%               | 40%                |
| Two siblings                         | 8%                 | 19%               | 45%                |



- ▶ For **isolated cleft palate**, if a couple already has one affected child the recurrence risk for a subsequent pregnancy is about **2%** — a separate figure from the CL(P) table above, consistent with its distinct etiology.
- ▶ Midline SHH (sonic hedgehog) gene mutations produce the **holoprosencephaly spectrum**, in which midline cleft lip/palate can accompany hypotelorism/cyclopia and microcephaly, with markedly variable expressivity even within one family.

### Applied / Clinical anatomy

- ▶ **Feeding:** the infant cannot generate adequate negative intra-oral pressure for suckling; special long-teat feeders or palatal obturators are required until surgical repair.
- ▶ **Speech:** nasal air escape through the unrepaired cleft causes hypernasality and defective articulation of plosive consonants (D, T, G).
- ▶ **Hearing:** abnormal insertion/action of the tensor veli palatini (and levator veli palatini) around the Eustachian tube predisposes to recurrent secretory otitis media and conductive hearing loss in cleft palate.
- ▶ **Dental:** the lateral incisor near the cleft is commonly missing, malformed or supernumerary, with alveolar arch collapse.
- ▶ **Antenatal diagnosis:** facial clefts become sonographically recognisable from the beginning of the second trimester once fetal facial features are formed.
- ▶ **Surgical timing:** cleft lip is classically repaired around the "**rule of 10s**" (age  $\approx$  10 weeks, weight  $\approx$  10 lb, haemoglobin  $\approx$  10 g/dL); cleft palate repair follows at  $\approx$  9–12 months, before speech develops, to optimise later articulation.
- ▶ **Submucous cleft palate:** an occult muscular cleft beneath intact oral mucosa — suspected clinically by a **bifid uvula**, a palpable notch in the posterior hard palate, and a translucent **zona pellucida** in the midline soft palate.
- ▶ The **incisive foramen/fossa**, the adult marker of the primary–secondary palate junction, is an important surgical landmark during palatoplasty.

### High-yield exam pointers

- ▶ Five facial processes surround the stomodeum by the end of the 4th week: 1 frontonasal + 2 maxillary + 2 mandibular.
- ▶ Upper lip = lateral parts from **maxillary processes** + midline **philtrum** from fused medial nasal processes, but philtrum **skin** is supplied by the **maxillary nerve** (overgrowth phenomenon).
- ▶ **Primary palate**  $\leftarrow$  frontonasal process (premaxilla, 4 incisors); **Secondary palate**  $\leftarrow$  maxillary processes (palatine shelves); they meet at the **incisive fossa** by a Y-shaped suture.
- ▶ Critical period for palate closure: **end of 6th week to beginning of 9th week**.
- ▶ **Unilateral cleft lip** is the commonest congenital facial anomaly; CL(P)  $\approx$  1.4/1000 births, **male-predominant** (60–80%).
- ▶ Isolated **cleft palate**  $\approx$  1/2500 births, **female-predominant** (67%), unrelated to maternal age, and etiologically **distinct** from CL(P).
- ▶ **Commonest cause** of both CL(P) and isolated cleft palate is **multifactorial inheritance**.

- ▶ **Robin sequence** (U-shaped cleft, 2° to mandibular hypoplasia + glossoptosis) must be distinguished from primary (V-shaped) cleft palate.
- ▶ Oblique facial cleft = failure of maxillary–lateral nasal process fusion; macrostomia/microstomia = incomplete/excessive maxillo-mandibular fusion respectively.

### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; BD Chaurasia — Human Anatomy Vol 3–4, 8e; Thompson & Thompson — Genetics in Medicine, 8e; Gray's Anatomy (Standing) 41e.



## Derivatives of Pharyngeal pouches

*Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy*

**Definition/Introduction** — The **pharyngeal (branchial) pouches** are four paired, endoderm-lined outpocketings of the lateral wall of the primitive pharynx (cranial foregut) that appear during the 4th–5th week of intrauterine life, interposed between successive pharyngeal arches. Each pouch meets the corresponding ectoderm-lined **pharyngeal cleft** externally, separated only by a thin mesenchymal **closing membrane**. A rudimentary 5th pouch is transient and, in humans, is incorporated into the 4th pouch. Because their endodermal epithelium gives rise to major endocrine and lymphoid organs of the head, neck and thorax, the fate of each pouch is described separately.

### 1. General plan and mechanism

- ▶ Pouches form under reciprocal **endoderm–ectoderm–neural crest** signalling; FGF8 from the pouch endoderm patterns the neural-crest-derived arch mesenchyme.
- ▶ The two most anterior (1st, 2nd) pouches form together early; the more posterior (3rd, 4th) pouches form **sequentially** and require the T-box transcription factor **Tbx1** for their development — the same gene deleted in the 22q11.2 region implicated in DiGeorge syndrome.
- ▶ Unlike the pharyngeal clefts (of which only the 1st persists as a definitive adult structure; 2nd–4th are normally obliterated), **all four pharyngeal pouches contribute a definite adult derivative** — this is a key point of distinction asked in viva.
- ▶ Only the pouches (3rd and 4th, aided by neural crest and the 5th-pouch remnant) give rise to **discrete endocrine organs** (parathyroids, thymus, C cells) — the pouches are therefore far more clinically important than the clefts.

## 2. Summary table — derivatives of the pharyngeal pouches

| Pouch             | Part                                                           | Primordium                                     | Adult derivative                                                                                                                        |
|-------------------|----------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 1st               | Tubotympanic recess                                            | Diverticulum contacting 1st cleft              | Tympanic (middle ear) cavity;<br>pharyngotympanic (auditory/eustachian) tube; inner (endodermal/mucosal) layer of the tympanic membrane |
| 2nd               | Tonsillar buds                                                 | Endodermal buds invaded by lymphoid mesenchyme | Palatine tonsil (crypts + lining epithelium); tonsillar (intratonsillar) fossa persists in the adult                                    |
| 3rd               | Dorsal wing                                                    | Parathyroid primordium                         | Inferior parathyroid gland                                                                                                              |
| 3rd               | Ventral wing                                                   | Thymic primordium                              | Thymus (bilateral lobes descend and fuse in the anterior mediastinum)                                                                   |
| 4th               | Dorsal wing                                                    | Parathyroid primordium                         | Superior parathyroid gland                                                                                                              |
| 4th               | Ventral wing (+ 5th-pouch remnant = caudal pharyngeal complex) | Ultimobranchial body                           | Parafollicular (C) cells of the thyroid (secrete calcitonin), via neural-crest cells incorporated into the ultimobranchial body         |
| 5th (rudimentary) | —                                                              | Fuses with 4th pouch                           | No independent human derivative; forms the caudal pharyngeal complex with the 4th pouch                                                 |

□ Fig 17.31 — Development of the Pharyngeal Pouch Derivatives (Larsen — Human Embryology — 6e, p.1100)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a coronal/sagittal schematic of the pharynx at 5–6 weeks showing the four pouches in series, and label:

- ▶ Pharyngeal pouches 1–4 (and vestigial 5th) opening into the primitive pharynx
- ▶ **1st pouch** → tubotympanic recess → tympanic cavity + auditory tube
- ▶ **2nd pouch** → tonsillar bud → palatine tonsil + tonsillar fossa
- ▶ **3rd pouch**: dorsal wing → inferior parathyroid; ventral wing → thymus (with arrow showing its caudal descent into the thorax)
- ▶ **4th pouch**: dorsal wing → superior parathyroid; ventral wing → ultimobranchial body → C cells of thyroid
- ▶ The **thyroid gland** in the midline (from the foramen cecum), receiving the migrating parathyroids and ultimobranchial body
- ▶ Common carotid artery bifurcation as a landmark for the final position of the inferior parathyroid

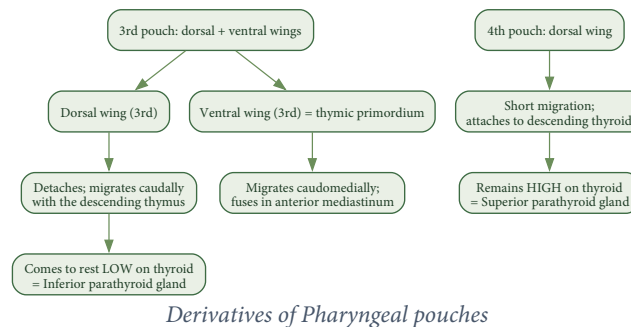
**3. First and second pharyngeal pouches**

- ▶ **First pouch**: forms a stalk-like diverticulum, the **tubotympanic recess** — its distal end widens into the **primitive tympanic (middle ear) cavity** and mastoid antrum, while its narrow proximal part becomes the **pharyngotympanic (auditory/eustachian) tube**. Its endodermal lining contributes the inner mucosal layer of the trilaminar **tympanic membrane** (outer ectoderm from the 1st cleft, middle mesenchyme, inner endoderm from the 1st pouch).
- ▶ **Second pouch**: its epithelial lining proliferates into solid buds that invade the surrounding mesenchyme; these are secondarily infiltrated by lymphoid tissue during the 3rd–5th months to form the **palatine tonsil**. Part of the pouch cavity persists as the **tonsillar (intratonsillar) fossa/crypt** in the adult.

**4. Third and fourth pharyngeal pouches — parathyroids and thymus**

- ▶ At the 5th week, the 3rd and 4th pouches each develop a **dorsal wing** and a **ventral wing** at their distal ends.
- ▶ **Third pouch**: the **dorsal wing** differentiates into the **inferior parathyroid gland**; the **ventral wing** forms the **thymus**. Both primordia detach from the pharyngeal wall, and the thymus then migrates **caudally and medially**, dragging the inferior parathyroid with it, before fusing in the midline with its contralateral partner in the **anterior mediastinum**.
- ▶ **Fourth pouch**: its **dorsal wing** forms the **superior parathyroid gland**, which attaches to the dorsal surface of the caudally-descending thyroid gland. Its **ventral wing** forms the **ultimobranchial body**, which becomes incorporated into the thyroid gland substance.
- ▶ **Positional inversion (classic exam point)**: because the parathyroid of the 3rd pouch travels the longer distance (together with the descending thymus), it finally comes to lie **inferior** on the thyroid, becoming the **inferior parathyroid** — even though the 3rd pouch is cranial to the 4th. Conversely, the 4th-pouch parathyroid migrates only a short distance and remains **superior**. This explains why the "inferior" parathyroid is embryologically the more cranial of the two.

- Growth of the thymus continues until puberty; its "tail" of tissue may persist as isolated **accessory thymic nests** along the line of descent, sometimes embedded within the thyroid gland.



## 5. Fifth pouch, caudal pharyngeal complex, and neural crest contribution

- A **fifth pharyngeal pouch** is seen only transiently; in humans its fate is debated and it is generally regarded as being **incorporated into the 4th pouch**, the two together forming the **caudal pharyngeal complex**.
- Strictly, the term "ultimobranchial body" (which in lower vertebrates arises from a discrete 5th pouch) is applied loosely in humans to this caudal pharyngeal complex.
- **Neural crest cells** migrate into the caudal pharyngeal complex and give rise to the **parafollicular (C) cells** of the thyroid, which secrete **calcitonin**; the endodermal component of the complex merely provides the epithelial vesicle into which these neural-crest cells are incorporated before fusing with the median thyroid primordium (derived from the thyroglossal duct).
- Fusion of the lateral (ultimobranchial/4th–5th pouch) thyroid component with the median (thyroglossal-duct) component also **arrests further caudal migration of the developing thyroid gland**.

## Applied / Clinical anatomy

- **DiGeorge syndrome (22q11.2 deletion syndrome)**: failure of the 3rd and 4th pharyngeal pouches to differentiate, due to disrupted endoderm–neural crest signalling (with **TBX1** as the key gene in the deleted 22q11.2 region). Results in **thymic aplasia/hypoplasia** (defective T-cell-mediated immunity, recurrent infections) and **parathyroid aplasia** (congenital hypoparathyroidism → neonatal hypocalcaemic tetany), together with **cardiac outflow-tract anomalies** (aortic arch defects) and craniofacial anomalies (low-set notched ears, short philtrum/"fish-mouth" upper lip, micrognathia) from associated 1st-arch neural-crest disruption.
- **Ectopic parathyroid glands**: because of variable migration, parathyroid tissue (especially the inferior gland, which travels farthest with the thymus) may be found anywhere from the angle of the mandible down to the mediastinum — including within the thymus or embedded in the thyroid capsule. This variability is the leading cause of a "missing gland" at parathyroidectomy for hyperparathyroidism.
- **Accessory/ectopic thymic tissue**: isolated nests of thymic tissue may persist along the cervical path of thymic descent, often close to an inferior parathyroid gland — relevant to neck masses in children and to incomplete resection during transcervical thymectomy for myasthenia gravis.

- ▶ **Supernumerary or absent parathyroid glands:** extra glands arise from splitting of a primordium; absence results from failure of a primordium to differentiate or its early atrophy — both are surgically relevant causes of persistent/recurrent hyperparathyroidism or unexpected hypoparathyroidism.
- ▶ **Medullary carcinoma of the thyroid** arises from the neural-crest-derived parafollicular (C) cells of the caudal pharyngeal complex; serum **calcitonin** is its tumour marker, and it may occur as part of MEN 2A/2B syndromes.
- ▶ **Internal branchial fistula:** rupture of the membrane between the 2nd pharyngeal cleft and 2nd pouch allows a persistent cervical sinus remnant to open internally into the **tonsillar fossa**, linking the pouch anatomy to the clinically important branchial-cleft anomaly group (though the primary lesion there is cleft-, not pouch-, derived).
- ▶ Knowledge of pouch derivatives underpins the surgical anatomy of **thyroidectomy/parathyroidectomy** (identifying and preserving all four parathyroids and recognising ectopic sites) and of **tonsillectomy** (the tonsillar fossa marking the 2nd-pouch remnant).

### High-yield exam pointers

- ▶ Four pairs of pharyngeal pouches (endodermal); a rudimentary 5th is incorporated into the 4th, forming the **caudal pharyngeal complex**.
- ▶ 1st pouch → tubotympanic recess → **tympanic cavity + auditory (eustachian) tube** (+ inner layer of tympanic membrane).
- ▶ 2nd pouch → tonsillar buds → **palatine tonsil + tonsillar fossa**.
- ▶ 3rd pouch: dorsal wing → **inferior parathyroid**; ventral wing → **thymus**.
- ▶ 4th pouch: dorsal wing → **superior parathyroid**; ventral wing → **ultimobranchial body** → **parafollicular (C) cells** of thyroid (calcitonin).
- ▶ **Positional inversion:** the 3rd-pouch parathyroid migrates farther (with the thymus) and ends up **inferior**; the 4th-pouch parathyroid migrates less and stays **superior**.
- ▶ Unlike the pharyngeal clefts (only the 1st persists), **all four pharyngeal pouches** form definite adult structures.
- ▶ Tbx1 gene governs posterior (3rd/4th) pouch development; its deletion (22q11.2) underlies **DiGeorge syndrome** — thymic + parathyroid aplasia with cardiac and facial anomalies.
- ▶ Parafollicular C cells are of **neural crest** origin, not endodermal, despite arising within an endodermally-derived pouch complex.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; Gray's Anatomy (Standring) 41e.



## Describe the development of face

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The face develops around the primitive mouth (**stomodeum**) from **five facial primordia (prominences)** that appear at the end of the fourth week of intrauterine life — a single **frontonasal process** and paired **maxillary** and **mandibular processes** of the first pharyngeal arch. Each primordium consists of neural-crest-derived mesenchyme (ectomesenchyme) covered by surface ectoderm. Growth, medial migration and progressive fusion of these processes between the 4th and 12th weeks convert the primitive facial pattern into the recognisably human face; failure of fusion at specific lines is the embryological basis of the common facial clefts.

### 1. Facial primordia — appearance and boundaries of the stomodeum

- ▶ At the end of the 4th week, the stomodeum is bounded:
  - **Cranially** — by the **frontonasal process**, formed by proliferation of mesenchyme ventral to the forebrain vesicle.
  - **Laterally** — by the paired **maxillary processes** (dorsal part of the 1st arch).
  - **Caudally** — by the paired **mandibular processes** (ventral part of the 1st arch), which meet and fuse in the midline.
- ▶ The mesenchyme of all five processes is largely derived from **neural crest cells** migrating from the mesencephalic and rostral rhombencephalic neural folds; this ectomesenchyme forms the connective tissue, cartilage and bone of the face.
- ▶ The **mandibular processes fuse first** (by the end of the 4th week) to form the chin and lower lip — the first parts of the face to be completed.
- ▶ Overall facial development occurs mainly **between the 4th and 8th weeks**; by the end of the embryonic period the face has an unmistakably human appearance, and facial proportions mature further through the fetal period.

### 2. Nasal placodes, nasal pits and the medial/lateral nasal processes

- ▶ In the **4th–5th week**, bilateral thickenings of surface ectoderm — the **nasal (olfactory) placodes** — appear on the inferolateral parts of the frontonasal process, induced by the underlying forebrain.
- ▶ The placodes **invaginate** to form **nasal (olfactory) pits**, which are continuous with the roof of the stomodeum.
- ▶ Mesenchyme proliferating around the margin of each pit raises a horseshoe-shaped ridge:
  - **Medial nasal process** — the inner limb of the ridge.
  - **Lateral nasal process** — the outer limb of the ridge.
- ▶ Lateral and cranial to the nasal placodes, a pair of **lens placodes** mark the sites of the developing eyes.
- ▶ Each lateral nasal process is separated from the maxillary process by a deep furrow — the **nasolacrimal groove**.



### 3. Formation of the upper lip, cheek and intermaxillary segment

| Component of face   | Develops from                                                     | Sensory nerve   |
|---------------------|-------------------------------------------------------------------|-----------------|
| Forehead            | Frontonasal process                                               | Ophthalmic (V1) |
| External nose       | Frontonasal process                                               | Ophthalmic (V1) |
| Upper part of cheek | Maxillary process                                                 | Maxillary (V2)  |
| Lower part of cheek | Mandibular process                                                | Mandibular (V3) |
| Upper lip           | Two maxillary processes + fused medial nasal processes (philtrum) | Maxillary (V2)  |
| Lower lip, chin     | Fusion of two mandibular processes                                | Mandibular (V3) |

- ▶ Between the **7th and 10th weeks**, the maxillary processes enlarge and grow medially below the developing eyes, compressing the medial nasal processes toward the midline and fusing with them; this separates the nasal pit from the stomodeum and converts it into the primitive anterior naris.
- ▶ The **two medial nasal processes fuse with each other** (at a deeper as well as surface level) to form the **intermaxillary segment**, which has three parts:
  - ▶ **Labial component** → philtrum of the upper lip.
  - ▶ **Upper-jaw component** → alveolar process bearing the **four incisor teeth**.
  - ▶ **Palatal component** → the triangular **primary palate (premaxilla)**.
- ▶ The **lateral part of the upper lip and cheek** is formed entirely by the two maxillary processes; the lateral nasal processes take **no part** in forming the upper lip.
- ▶ **Lateral angles of the mouth (oral fissure)** are formed where the maxillary and mandibular processes fuse on each side; continued fusion here narrows the stomodeum and forms the cheeks.
- ▶ **Developmental enigma of the upper lip**: though the philtrum is genetically derived from the fused medial nasal processes, maxillary-process ectoderm overgrows it to form its skin — so, despite a triple origin, the **entire upper lip is supplied by the maxillary nerve (V2)**.
- ▶ The **nasolacrimal groove** floor ectoderm proliferates into a solid cord that detaches and canalises to form the **nasolacrimal duct**, its upper end widening into the **lacrimal sac**; the duct runs from the medial canthus to the inferior meatus and becomes fully patent only after birth.

### 4. Development of the external nose and nasal cavity

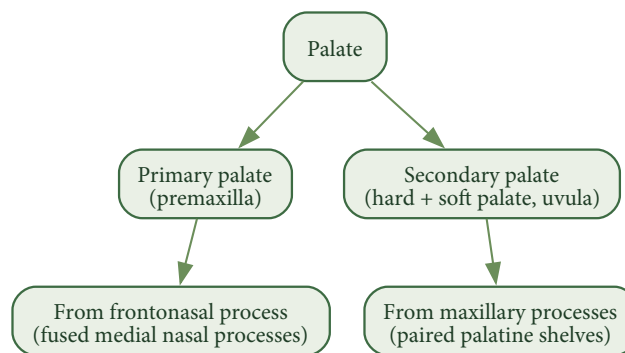
| Part of nose           | Source                           |
|------------------------|----------------------------------|
| Bridge of nose         | Frontonasal process              |
| Dorsum and tip of nose | Fused medial nasal processes     |
| Sides and alae of nose | Lateral nasal processes          |
| Nasal septum           | Frontonasal process (downgrowth) |

| Part of nose              | Source                                |
|---------------------------|---------------------------------------|
| Nasal cavities            | Nasal sacs (elongation of nasal pits) |
| Anterior nares (nostrils) | Nasal pits                            |
| Choanae (posterior nares) | Rupture of the oronasal membrane      |

- ▶ During the **6th week**, the nasal pits deepen dorsally to form **nasal sacs**, growing toward the forebrain to form the **primitive nasal cavity**, separated from the oral cavity by the **ornasal membrane**.
- ▶ At the **end of the 6th week** this membrane ruptures, forming the **primitive choanae**, lying just behind the primary palate; once the secondary palate forms, the **definitive choanae** come to lie at the junction of nasal cavity and nasopharynx.
- ▶ The **superior, middle and inferior conchae** develop as curved elevations from the lateral nasal wall; the roof epithelium differentiates into **olfactory epithelium**, giving rise to the olfactory nerve fibres.
- ▶ **Paranasal air sinuses** arise as diverticula from the nasal cavity walls, invading the maxilla, ethmoid, frontal and sphenoid bones (named accordingly). **Maxillary sinus** appears first (3rd intrauterine month); **frontal sinus** only postnatally (5th–6th year). All reach maximum size at puberty, shaping the face, lightening the skull, and adding vocal resonance.

## 5. Development of the palate

- ▶ The palate has two embryologically distinct parts:



*Describe the development of face*

- ▶ **Primary palate:** formed by deep fusion of the two medial nasal processes — a wedge-shaped mesenchymal mass opposite the incisor-bearing jaw, which ossifies to form the **premaxilla**.
- ▶ **Secondary palate:** the main part of the definitive palate, formed from two shelf-like outgrowths — **palatine shelves** — from the medial aspect of the maxillary processes.
  - Palatine shelves appear in the **6th week**, initially growing **downward, vertically** on either side of the tongue.
  - In the **7th–8th week**, as the mandible grows and the tongue moves down, the shelves reorient to a **horizontal position above the tongue** and fuse with each other in the midline.
  - Anteriorly they fuse with the triangular primary palate by a **Y-shaped suture**; the **incisive fossa/foramen** marks the junction of primary and secondary palate in the adult.

- The **nasal septum** (a downgrowth of the frontonasal process) grows down and fuses with the superior aspect of the fused shelves — beginning anteriorly in the **9th week** and completed posteriorly by the **12th week**.
- ▶ **Ossification:** anterior three-fourths ossifies in membrane → **hard palate**; posterior one-fourth (beyond the nasal septum) stays unossified → **soft palate** and **uvula**.
- ▶ Palatal development begins in the 6th week and is **complete by the 12th week**; the **critical period** is **end-6th to beginning-9th week**.

## 6. Development of facial musculature (a distinct source)

- ▶ Unlike the facial skeleton and dermis (neural-crest ectomesenchyme), the **muscles of facial expression** develop from the **paraxial mesoderm of the second pharyngeal arch**. Myoblasts migrate as a continuous sheet into the face and scalp but retain the nerve of their arch of origin — hence **all muscles of facial expression, wherever finally located, are supplied by the facial nerve (CN VII)**.

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences around the stomodeum (frontonasal, paired maxillary, paired mandibular processes); nasal placode/pit gives rise to medial and lateral nasal processes (Sontakke — Textbook of Human Embryology, p.118)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a frontal view of the developing face at three successive stages (5th, 6th–7th, and 10th week) and label:

- ▶ Stomodeum (primitive mouth)
- ▶ Frontonasal process
- ▶ Nasal (olfactory) placode → Nasal pit
- ▶ Medial nasal process
- ▶ Lateral nasal process
- ▶ Nasolacrimal groove
- ▶ Maxillary process (both sides)
- ▶ Mandibular process (both sides)
- ▶ Eye (with lens placode)
- ▶ Philtrum (final stage) and fused upper lip
- ▶ Line of fusion: maxillary process with medial nasal process, and maxillary with lateral nasal process

## Applied / Clinical anatomy

- ▶ **Cleft lip** (incidence ≈ 1 in 1000 births; 60–80% males):
  - **Unilateral cleft lip** (commonest) — failure of fusion of the maxillary process with the medial nasal process of the same side.
  - **Bilateral cleft lip** — failure of fusion of both maxillary processes with the frontonasal (medial nasal) processes.

- **Median cleft lip ("hare-lip")** — very rare; failure of development/fusion of the philtrum from the frontonasal process; a feature of **Mohr syndrome** (autosomal recessive).
  - **Median cleft of the lower lip** — extremely rare; failure of the two mandibular processes to fuse in the midline.
  - ▶ **Oblique facial cleft (orbitofacial fissure)** — rare; maxillary process fails to fuse with the lateral nasal process; the fissure runs from the medial angle of the eye to the upper lip, exposing the nasolacrimal duct; usually bilateral.
  - ▶ **Microstomia / macrostomia** — excessive or deficient fusion of maxillary and mandibular processes at the angle of the mouth.
  - ▶ **Cleft palate** (incidence  $\approx$  1 in 2500 births; more common in females):
    - **Complete cleft palate** — unilateral (one maxillary process fails to fuse with the premaxilla, always with cleft lip on that side) or bilateral (both fail to fuse, premaxilla separated by a median cleft).
    - **Incomplete/partial cleft palate** — bifid uvula (clinically unimportant)  $\rightarrow$  cleft of soft palate  $\rightarrow$  cleft extending into the hard palate.
    - Clefts are classified relative to the **incisive fossa/foramen** into anterior (primary palate/lip) and posterior (secondary palate) types.
  - ▶ Cleft lip is often associated with cleft palate because both share a common developmental source (frontonasal/maxillary processes and their palatine derivatives).
- Fig 12.5 — Cleft lip and cleft palate: non-fusion of the median and lateral palatine processes (Sontakke — *Textbook of Human Embryology*, p.123)
- ▶ **Aetiology:** mostly **multifactorial** (genetic + environmental); the **IRF6 gene** is implicated in isolated clefts; some cases occur with **trisomy 13** or single-gene syndromes. **Phenytoin** in pregnancy increases incidence 2–3-fold. Genetic factors weigh more in cleft lip ( $\pm$  palate) than isolated cleft palate.
  - ▶ **Clinical consequences:** disfigurement, difficulty suckling, speech defects (consonants D, T, G need an intact lip/palate seal), dental malalignment. Diagnosable antenatally by ultrasonography from the second trimester onward.

## High-yield exam pointers

- ▶ Face develops from **5 primordia** around the stomodeum at the **end of the 4th week**: 1 frontonasal + 2 maxillary + 2 mandibular (all neural-crest mesenchyme).
- ▶ **Mandibular processes fuse first** (chin, lower lip) — by end of 4th week; overall facial development spans the **4th–8th week**.
- ▶ Frontonasal process  $\rightarrow$  forehead, external nose (bridge, dorsum, tip via fused medial nasal processes), nasal septum, and **philtrum**.
- ▶ Upper lip = 2 maxillary processes + fused medial nasal processes; but **whole upper lip is supplied by maxillary nerve (V2)** because maxillary ectoderm overgrows the philtrum.
- ▶ **Intermaxillary segment** = philtrum + 4-incisor premaxilla + primary palate — all from fused medial nasal processes.

- ▶ **Primary palate** (frontonasal) vs **secondary palate** (paired palatine shelves of maxillary processes); critical period **6th–9th week**; complete by **12th week**.
- ▶ Nasolacrimal duct develops from a solid ectodermal cord buried along the nasolacrimal groove (maxillary/lateral nasal process junction).
- ▶ Commonest facial cleft: **unilateral cleft lip** (maxillary process fails to fuse with medial nasal process of the same side).
- ▶ Cleft lip 1:1000 (male-predominant); cleft palate 1:2500 (female-predominant); both show multifactorial inheritance.
- ▶ Muscles of facial expression are **2nd-arch mesoderm**, supplied by the **facial nerve (VII)** — distinct from the neural-crest-derived facial skeleton/dermis.

#### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Gray's Anatomy (Standring) 41e (neural crest contribution to the frontonasal process).



## Development of the Hyoid Bone

*Asked in: Paper II 31-Jul-2021 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The hyoid bone is a single, mobile, U-shaped bone lying in the anterior midline of the neck, suspended from the two styloid processes by the stylohyoid ligaments and giving attachment to the supra- and infrahyoid muscle groups, the tongue and the pharynx. Unlike every other bone in the skeleton, it does not articulate directly with any adjacent bone — it is held purely by ligaments and muscles. Its embryology is equally distinctive: the whole bone is built from the cartilaginous bars of the **second and third pharyngeal (branchial) arches**, with the intervening cartilage of the second arch persisting only as the stylohyoid ligament. This arch-by-arch derivation is one of the most repeatedly asked correlates in pharyngeal-apparatus embryology.

### 1. Pharyngeal arch cartilages and their skeletal fate — where the hyoid fits

Each pharyngeal arch contains a cartilaginous rod (in addition to an artery, a muscle mass and a nerve). Only the cartilages of arches I, II and III form recognisable named bones/ligaments; IV and VI fuse to give the laryngeal skeleton. Knowing the full scheme prevents the common exam error of crediting the wrong arch for the hyoid.

| Arch                | Cartilage (eponym)           | Skeletal / ligamentous derivative                                                                                                                                             |
|---------------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I — mandibular arch | Meckel's cartilage           | Malleus and incus (dorsal tip); mandible ossifies membranously around the cartilage, which itself regresses except for a remnant forming the <b>sphenomandibular ligament</b> |
| II — hyoid arch     | Reichert's cartilage         | Stapes and styloid process (dorsal end); <b>stylohyoid ligament</b> (intervening perichondrial sheath); <b>lesser cornu + upper part of body of hyoid bone</b> (ventral end)  |
| III                 | (unnamed 3rd-arch cartilage) | <b>Greater cornu + lower part of body of hyoid bone</b> (ventral end; fuses in the midline with the 2nd-arch ventral end)                                                     |
| IV & VI             | (unnamed)                    | Laryngeal cartilages — thyroid, cricoid, arytenoid, corniculate, cuneiform                                                                                                    |

Note that the hyoid receives **no contribution from the first arch** and **none from the fourth/sixth arches** — a frequent point of confusion candidates must state explicitly.

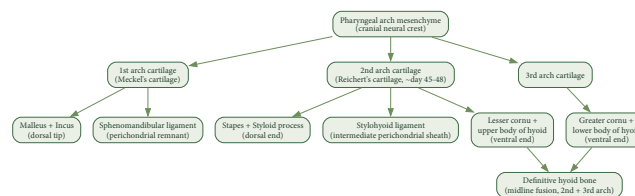
## 2. Second arch (hyoid arch) cartilage — Reichert's cartilage

- ▶ Chondrifies within the mesenchymal core of the second pharyngeal arch at about 45–48 days of gestation; the mesenchyme of the arch is itself derived from neural-crest cells that migrate in from the hindbrain.
- ▶ **Dorsal end:** lies close to the developing otic capsule. A separate nodule near its tip forms the **stapes**; the segment immediately below the stapes fuses with the otic capsule and later ossifies to form the **styloid process** of the temporal bone.
- ▶ **Intermediate segment** (between the styloid process and the hyoid bone): this part of the cartilage itself regresses, but its perichondrial sheath persists as the fibrous **stylohyoid ligament** — it normally never ossifies.
- ▶ **Ventral end:** ossifies to form the **lesser cornu** and the **upper part of the body** of the hyoid bone, and fuses in the midline with its fellow of the opposite side.
- ▶ High-yield mnemonic: every named second-arch skeletal derivative begins with "S" — Stapes, Styloid process, Stylohyoid ligament, (smaller) lesser cornu, Superior part of body of hyoid.

## 3. Third pharyngeal arch cartilage

- ▶ Chondrifies from neural-crest cells that migrate in from the caudal hindbrain (myelencephalon) — a slightly more caudal crest stream than that of the second arch.
- ▶ Ossifies endochondrally in its ventral part to form the **greater cornu** and the **lower part of the body** of the hyoid bone.

- ▶ The ventral extremity of the third-arch cartilage fuses with the ventral extremity of the corresponding second-arch cartilage on the same side, and across the midline with the cartilages of the opposite side, completing the U-shaped body of the definitive bone.
- ▶ The fourth and fifth/sixth arch cartilages do **not** chondrify dorsally at all; their ventral remnants fuse instead to form the laryngeal cartilages, remaining entirely separate from the hyoid.



Development of the Hyoid Bone

#### 4. Diagram of the hyoid bone

□ Fig 2.31 — Hyoid bone (anterior view). Parts of (Vishram Singh — Textbook of Anatomy Vol 3 — 4e, p.176)

##### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

On an anterior-view outline of the hyoid, label:

- ▶ **Body** — central quadrilateral part; convex anterior surface, concave posterior surface.
- ▶ **Greater cornu** (right and left) — projecting posterolaterally from the lateral part of the body; tip gives attachment to the lateral thyrohyoid ligament.
- ▶ **Lesser cornu** (right and left) — small conical projections at the junction of body and greater cornu; apex gives attachment to the stylohyoid ligament.
- ▶ **Lesser cornu–body junction** — mark as fibrous (occasionally synovial).
- ▶ **Greater cornu–body junction** — mark as a synchondrosis/synovial joint that may ankylose with age.
- ▶ Shade/annotate the **upper body + lesser cornu in one colour** (2nd-arch/Reichert's cartilage origin) and the **lower body + greater cornu in a second colour** (3rd-arch origin) to reinforce the developmental boundary.

#### 5. Molecular control of arch identity

- ▶ The neural-crest mesenchyme of the second (hyoid) arch expresses the homeobox gene **Hoxa2**, which specifies "hyoid-arch" identity on its skeletal derivatives.
- ▶ In **Hoxa2** loss-of-function mice, the normal second-arch skeleton (stapes, styloid process, lesser horn of hyoid) fails to form, and is replaced by **duplicated first-arch elements** (an extra malleus, incus and tympanic ring) — a homeotic transformation. This demonstrates that arch-specific Hox expression, not the local mesenchyme alone, dictates which skeletal fate a given pharyngeal arch cartilage adopts, and is a favourite "recent advances/molecular embryology" correlate for this topic.

#### 6. Postnatal ossification and fusion

- ▶ Chondrification (as above) is followed by endochondral ossification of the arch cartilages; ossification of the third-arch-derived greater cornu and body proceeds first, with the second-arch-derived lesser cornu ossifying later from its own separate centre.



- ▶ The **lesser cornu–body** junction usually remains fibrous throughout life (occasionally becomes a synovial joint).
- ▶ The **greater cornu–body** junction is typically a synchondrosis/synovial-type joint that persists throughout adult life in most people but may become ankylosed (fused) with advancing age.
- ▶ Because the cartilage between the styloid process and the lesser cornu never ossifies (it stays ligamentous as the stylohyoid ligament), the hyoid remains a floating bone — the only bone in the body that forms no joint with any other bone of the skeleton.

## Applied / Clinical anatomy

- ▶ **Forensic significance:** fracture of the hyoid bone (usually of the greater cornu) in a death investigation strongly indicates throttling or manual/ligature strangulation, because the bone is otherwise well protected and mobile.
- ▶ **Eagle syndrome:** the stylohyoid ligament is embryologically the persistent perichondrial sheath of the second-arch cartilage between the styloid process and the lesser cornu, and normally stays fibrous. Abnormal ossification of this ligament, or an elongated styloid process, can compress cranial nerve XII and adjacent structures during head rotation, producing dysphagia, facial/throat pain and tongue weakness with atrophy.
- ▶ **Thyroglossal cyst/fistula:** the thyroid gland descends from the tongue base to the neck along the thyroglossal tract, which passes close to and often just behind/inferior to the body of the hyoid; roughly half of thyroglossal duct cysts lie at or just inferior to the hyoid body. Surgical excision of the tract must remove the central segment of the hyoid body en bloc with it, or recurrence is common — a direct clinical consequence of the intimate developmental relationship between the descending thyroid primordium and the ossifying hyoid body.
- ▶ **Surface anatomy:** the body of the hyoid is palpable in the midline a few centimetres below the chin, at the level of the C4 vertebra in adults (range C3–C5/6), and lies higher in children; it is an important landmark for tracheostomy, cricothyroidotomy and neck-space localisation (infrahyoid vs suprahyoid deep cervical fascial spaces).
- ▶ **Mobility without a joint:** because it is suspended only by muscles and ligaments and forms no bony articulation, the hyoid moves freely with swallowing and phonation but is also vulnerable to displacement/fracture in blunt neck trauma and strangulation.

## High-yield exam pointers

- ▶ Hyoid develops **only from the 2nd (Reichert's) and 3rd arch cartilages** — never the 1st or the 4th/6th arch.
- ▶ 2nd arch → lesser cornu + upper body ("S" mnemonic: Stapes, Styloid process, Stylohyoid ligament, (S)maller cornu, Superior body).
- ▶ 3rd arch → greater cornu + lower body; the two arches' ventral ends fuse in the midline.
- ▶ Intervening 2nd-arch cartilage between styloid process and hyoid → stylohyoid ligament (does not ossify normally).
- ▶ Hoxa2 patterns 2nd-arch identity; its loss duplicates 1st-arch skeletal elements (homeotic transformation).

- ▶ Lesser cornu–body junction: fibrous (occasionally synovial); greater cornu–body junction: synchondrosis/synovial joint, may ankylose with age.
- ▶ Hyoid is the only bone in the body that does not form a joint with any other bone.
- ▶ Fracture of hyoid = classic forensic sign of strangulation/throttling.
- ▶ Ossified stylohyoid ligament + elongated styloid process = Eagle syndrome.
- ▶ Thyroglossal cyst is closely, and often intimately, related to the body of the hyoid.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology; BD Chaurasia — Human Anatomy Vol 3-4 8e; AK Datta — Human Anatomy Vol 2 (Head & Neck); IB Singh — Textbook of Anatomy Vol 3 6e; Vishram Singh — General Anatomy 4e; Vishram Singh — Textbook of Anatomy Vol 3 4e; Moore's Clinically Oriented Anatomy 9e; Gray's Anatomy (Standring) 41e.

Coverage note: the retrieved corpus confirms the qualitative cartilage-to-bone derivation, the Hoxa2 molecular correlate, and the fibrous/synovial nature of the two hyoid joints, but does not give precise gestational/postnatal ages for the appearance of the individual hyoid ossification centres; the general sequence given above (prenatal ossification of the 3rd-arch-derived greater cornu/body, later ossification of the 2nd-arch-derived lesser cornu) reflects standard, universally taught anatomy rather than a specific cited figure.



## Describe the development of tongue and correlate it with its nerve supply

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The tongue is a muscular organ of deglutition, taste and speech that develops in the floor of the primitive pharynx from **five embryonic sources**: three swellings of the first pharyngeal arch, a hypobranchial eminence contributed by the second, third and fourth arches, and occipital myotomes that supply its musculature. Because each mucosal territory and the musculature are derived from a different pharyngeal arch (or somite), the tongue's mature nerve supply is a direct embryological fossil of these multiple origins — the single most important "correlation" concept tested in this question.

### Embryonic primordia of the tongue

| Primordium                    | Pharyngeal-arch contribution | Adult part formed                       |
|-------------------------------|------------------------------|-----------------------------------------|
| Two lateral lingual swellings | 1st arch (mandibular)        | Bulk of anterior two-thirds (oral part) |

| Primordium                                                            | Pharyngeal-arch contribution                          | Adult part formed                                                                                                  |
|-----------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Tuberculum impar (median swelling between the mandibular prominences) | 1st arch                                              | Overgrown and buried by the lingual swellings; forms no recognisable adult part (site marked by the median sulcus) |
| Hypobranchial eminence (copula of His) — cranial part                 | Mainly 3rd arch (2nd arch mesoderm buried beneath it) | Posterior one-third (pharyngeal part), including the circumvallate papillae                                        |
| Hypobranchial eminence — caudal part                                  | 4th arch                                              | Posteriormost part of tongue + epiglottis                                                                          |
| Occipital myotomes (occipital somites)                                | —                                                     | All musculature (intrinsic + extrinsic) of the tongue                                                              |

The mucosa (epithelium + lamina propria) of the tongue is derived from **endoderm of the primitive foregut**; the fibroareolar stroma binding the muscles is derived from **pharyngeal-arch mesenchyme**.

### Stepwise development (with timeline)

- **4th week of IUL**: on the floor of the primitive pharynx, the mandibular (1st) arch mesenchyme proliferates to form **two lateral lingual swellings** and a smaller midline **tuberculum impar**.
- Immediately caudal to the tuberculum impar, mesenchyme of the **2nd, 3rd and part of the 4th arches** proliferates to form a large median swelling, the **hypobranchial eminence (copula of His)** — visible by the **5th week**; it soon subdivides into a larger cranial part and a smaller caudal part.
- The two lateral lingual swellings enlarge rapidly, **overgrow the tuberculum impar**, and **fuse with each other in the midline** — this line of fusion becomes the **median sulcus** on the dorsum. Together they form the **anterior two-thirds (oral part)** of the tongue.
- As the hypobranchial eminence grows, mesoderm of the **3rd arch overgrows and buries the 2nd-arch component** underneath it, so the **cranial part of the hypobranchial eminence is contributed mainly by the 3rd arch** — this becomes the **posterior one-third (pharyngeal part)**, carrying the circumvallate papillae.
- The junction between the anterior two-thirds and posterior one-third is marked by a V-shaped groove, the **sulcus terminalis**, whose apex is the **foramen caecum** — the site of origin of the thyroid diverticulum (thyroglossal duct).
- The **caudal part of the hypobranchial eminence (4th arch)** forms the **posteriormost part of the tongue and the epiglottis**.
- **Musculature**: myoblasts derived from the **occipital myotomes** migrate anteroinferiorly around the pharynx and invade the tongue primordium (a few muscle fibres may differentiate in situ). The **hypoglossal nerve (XII)**, the nerve of the occipital myotomes, accompanies this migration — this explains the long, curved peripheral course of the hypoglossal nerve as it crosses superficial to both the internal and external carotid arteries.
- Epithelium is at first a single layer, later becoming stratified squamous; **papillae** develop, and **taste buds form in relation to the terminal branches of the nerve supplying that region** — this is the embryological basis for the arch-wise correlation of taste.

- By **6 months**, formation of the tongue is essentially complete. At birth, both anterior and posterior parts still lie within the oral cavity; the **posterior third subsequently descends into the oropharynx by about 4 years of age**, becoming the anterior wall of the oropharynx — explaining why, in the adult, the anterior two-thirds lies in the oral cavity while the posterior third lies in the oropharynx.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 17.11 — Development of tongue (BD Chaurasia — Human Anatomy Vol 3-4 — 8e, p.324)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

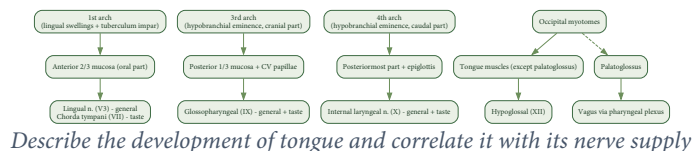
Draw the dorsum of the adult tongue with its developmental map superimposed, labelling:

- Tuberculum impar and the two lateral lingual swellings (1st arch) — anterior two-thirds
- Median sulcus (line of fusion of the lingual swellings)
- Sulcus terminalis (V-shaped) and foramen caecum at its apex
- Cranial part of hypobranchial eminence (3rd arch) — posterior one-third with circumvallate papillae
- Caudal part of hypobranchial eminence (4th arch) — posteriormost part
- Epiglottis
- An inset showing the buried 2nd-arch component beneath the overgrowing 3rd arch

## Correlation of nerve supply with development

| Part of tongue                                                 | Embryonic origin (arch)              | General sensation                                                 | Taste sensation                                               | Motor supply                 |
|----------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------|------------------------------|
| Anterior two-thirds (oral part)                                | 1st arch                             | Lingual nerve (V <sub>3</sub> ) — post-trematic nerve of 1st arch | Chorda tympani (facial, VII) — pre-trematic nerve of 1st arch | —                            |
| Posterior one-third + circumvallate papillae (pharyngeal part) | 3rd arch (2nd arch buried)           | Glossopharyngeal nerve (IX)                                       | Glossopharyngeal nerve (IX)                                   | —                            |
| Posteriormost part + epiglottis                                | 4th arch                             | Internal laryngeal nerve (branch of superior laryngeal, vagus X)  | Internal laryngeal nerve (X)                                  | —                            |
| All tongue muscles except palatoglossus                        | Occipital myotomes                   | —                                                                 | —                                                             | Hypoglossal nerve (XII)      |
| Palatoglossus                                                  | Pharyngeal-arch (palatal) mesenchyme | —                                                                 | —                                                             | Vagus, via pharyngeal plexus |

| Part of tongue                              | Embryonic origin (arch) | General sensation | Taste sensation       | Motor supply |
|---------------------------------------------|-------------------------|-------------------|-----------------------|--------------|
| Fungiform & filiform papillae/taste buds    | 1st arch                | —                 | VII (chorda tympani)  | —            |
| Circumvallate & foliate papillae/taste buds | 3rd arch                | —                 | IX (glossopharyngeal) | —            |



## Applied / Clinical anatomy

- **Ankyloglossia (tongue-tie):** the lingual frenulum extends too far towards the tip of the tongue instead of being resorbed, restricting protrusion and interfering with speech; occasionally the tongue is adherent to the palate (**ankyloglossia superior**).
- **Bifid tongue:** failure of fusion of the two lateral lingual swellings in the midline.
- **Aglossia, hemiglossia, micro-/macroglossia:** complete agenesis of the tongue primordia, failure of one lingual swelling, or abnormal size of the swellings, respectively.
- **Median rhomboid glossitis:** a smooth, red, rhomboid zone just anterior to the foramen caecum, attributed to persistence of the tuberculum impar.
- **Lingual thyroid / thyroglossal duct cyst or fistula:** because the thyroid diverticulum arises at the foramen caecum (apex of the sulcus terminalis) and normally migrates away down the thyroglossal duct, failure of descent leaves ectopic thyroid tissue at the tongue base, while persistence of duct remnants anywhere along its course produces a midline thyroglossal cyst/fistula.
- **Dissociated sensory testing** exploits the embryological split of the anterior two-thirds: a facial nerve lesion proximal to the chorda tympani (e.g. in the middle ear) abolishes **taste** on the anterior two-thirds while general sensation (lingual nerve, V<sub>3</sub>) remains intact, and vice versa for isolated lingual nerve injury.
- **"Beer drinker's nerve":** the internal laryngeal nerve (branch of the vagus, nerve of the 4th arch) carries taste/general sensation from the posteriormost tongue/vallecula/epiglottis — classically said to mediate the taste of beer.
- **Glossopharyngeal nerve palsy:** loss of general sensation, taste, and the afferent limb of the gag reflex over the posterior one-third — consistent with its being the nerve of the 3rd arch that forms this part.
- **Hypoglossal nerve (LMN) palsy:** because the muscles (and genioglossus in particular) are derived from the migrated occipital myotomes supplied by XII, a lower motor neurone lesion causes ipsilateral wasting/fasciculation and deviation of the protruded tongue **towards** the paralysed side.

- ▶ The tongue's nerve supply follows its **embryonic arch of origin, not its adult topographic position** — the single unifying principle behind every one of the correlations above.

### High-yield exam pointers

- ▶ Five sources: 2 lateral lingual swellings + tuberculum impar (1st arch) → anterior 2/3; cranial hypobranchial eminence (3rd arch) → posterior 1/3; caudal hypobranchial eminence (4th arch) → posteriormost part + epiglottis; occipital myotomes → muscle.
- ▶ The **2nd arch is buried by overgrowth of the 3rd arch** — this is why the posterior one-third is supplied by IX (3rd arch), not VII (2nd arch).
- ▶ **Foramen caecum** = apex of sulcus terminalis = origin site of the thyroglossal duct — key link to lingual thyroid/thyroglossal cyst.
- ▶ Anterior 2/3: **lingual nerve (V<sub>3</sub>, post-trematic of 1st arch)** = general sensation; **chorda tympani (VII, pre-trematic of 1st arch)** = taste.
- ▶ Posterior 1/3: **glossopharyngeal (IX)** carries both general sensation and taste.
- ▶ Posteriormost part + epiglottis: **internal laryngeal nerve (X)** carries both general sensation and taste ("beer drinker's nerve").
- ▶ Motor supply to all tongue muscles is by **hypoglossal (XII)** except **palatoglossus**, supplied by the **vagus via the pharyngeal plexus**.
- ▶ Hypoglossal nerve's long peripheral course (crossing superficial to the internal and external carotid arteries) is explained by the migratory path of the occipital myotomes into the developing tongue.
- ▶ Nerve supply always follows **embryonic arch of origin**, not adult surface topography — the master key to every applied question on this topic.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 3-4, 8e; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 3, 4e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler), 14e.



## Describe the development, fate and anomalies of endodermal pouches of pharyngeal arches

Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** Pharyngeal (branchial) pouches are paired, endoderm-lined outpocketings of the primitive pharynx that develop between successive pharyngeal arches during the 4th–5th weeks of intra-uterine life. There are four well-defined pairs, craniocaudally numbered I–IV; a fifth pair is rudimentary and fuses with the fourth. Pouch endoderm meets the ectoderm of the corresponding external pharyngeal groove to form a bilaminar pharyngeal membrane. Unlike the pharyngeal clefts (which mostly disappear), pouch endoderm gives rise to major glandular and lymphoid organs of the head, neck and superior mediastinum — the auditory tube/middle ear, palatine tonsil, thymus, and parathyroid glands.

### General development of the pouches

- ▶ Pouches appear in craniocaudal sequence as lateral diverticula of the foregut endoderm, growing into the mesenchyme of the adjacent arches.
- ▶ Each pouch (except the rudimentary 5th) develops a **dorsal (bulbar)** and a **ventral (elongate)** part; the connection of the pouch with the pharyngeal lumen narrows to a duct that soon degenerates.
- ▶ Differentiation of the pouch endoderm into glandular tissue requires local **cranial (vagal) neural-crest mesenchyme**; without this epithelial–mesenchymal interaction the derivatives fail to form (the basis of DiGeorge syndrome, below).
- ▶ As the pharynx and heart migrate caudally while the brain expands rostrally, derivatives of pouches II–IV are carried progressively caudally into the neck and superior mediastinum.

### Fate of individual pouches

| Pouch  | Site of proliferation                                            | Adult derivative                                                                                                                                                                                                               |
|--------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First  | Elongates as the <b>tubotympanic recess</b>                      | Tympanic (middle ear) cavity and mastoid antrum; proximal part narrows to form the <b>pharyngotympanic (auditory/eustachian) tube</b> ; distal expanded part contributes the inner (endodermal) layer of the tympanic membrane |
| Second | Endoderm proliferates into buds that canalise (tonsillar crypts) | Epithelium and crypt lining of the <b>palatine tonsil</b> (lymphoid stroma is mesodermal); residual cavity persists as the <b>tonsillar fossa/sinus</b> ; an unobliterated remnant is the <b>intratonsillar cleft</b>          |



| Pouch               | Site of proliferation                | Adult derivative                                                                                                                                                                                                                                                                                 |
|---------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Third               | Dorsal wing + ventral wing           | Dorsal wing → <b>inferior parathyroid gland (parathyroid III)</b> ; ventral wing (bilateral) → <b>thymus</b> , which fuses in the midline anterior to the great vessels                                                                                                                          |
| Fourth              | Dorsal wing + ventral wing           | Dorsal wing → <b>superior parathyroid gland (parathyroid IV)</b> ; ventral wing, together with the rudimentary fifth pouch, forms the <b>ultimobranchial (ultimopharyngeal) body</b> , which fuses into the thyroid and gives rise to the <b>parafollicular (C) cells</b> (calcitonin-secreting) |
| Fifth (rudimentary) | Fuses with ventral part of 4th pouch | Contributes to the ultimobranchial body (caudal pharyngeal complex); no independent adult structure in humans                                                                                                                                                                                    |

### Thymus and inferior parathyroid (third pouch)

- By the 6th week the ventral (thymic) and dorsal (parathyroid) primordia of each side lose their connection with the pharyngeal wall.
- The **thymus migrates caudally and medially**, fusing in the midline in the anterior mediastinum; it **pulls the inferior parathyroid with it** for part of the descent before the parathyroid separates and settles on the dorsal surface of the thyroid — hence the **inferior parathyroid's final position is more variable/inferior** than that of the superior gland, even though both eventually lie on the thyroid.
- Thymic histogenesis: epithelial cords from pouch endoderm proliferate; some cells arrange into **Hassall's (thymic) corpuscles**; bone-marrow-derived lymphocytes (thymocytes) then colonise the epithelial reticulum; neural-crest mesenchyme contributes the capsule/septa.
- The thymus is proportionately large at birth, continues growing till puberty, and then undergoes progressive **fatty involution**.

### Superior parathyroid and ultimobranchial body (fourth pouch)

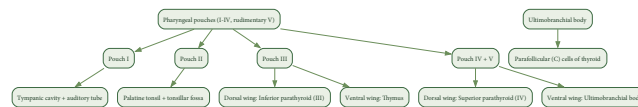
- The dorsal wing differentiates (6th week) into the **superior parathyroid gland**, which attaches to the caudally-descending thyroid and therefore occupies a **more constant position** than the inferior gland.
- Chief (principal) cells become functionally active in fetal calcium regulation; oxyphil cells appear only 5–7 years after birth.
- The ventral wing + vestigial 5th pouch form the ultimobranchial body, which is incorporated into the postero-lateral thyroid; its cells disseminate as **parafollicular/C cells**, largely of neural-crest lineage, secreting **calcitonin**.

## DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 17.31 — Development of the Pharyngeal Pouch Derivatives (Larsen — Human Embryology — 6e, p.1100)

Reproduce a sagittal schematic of the pharynx showing, craniocaudally:

- ▶ Pouches I–IV numbered along the lateral pharyngeal wall (rudimentary V fused to IV)
- ▶ I → tubotympanic recess → middle-ear cavity + auditory tube
- ▶ II → palatine tonsil primordium (crypts) + tonsillar fossa (remnant)
- ▶ III → dorsal wing = **inferior parathyroid**; ventral wing = **thymus** (bilateral, fusing in midline)
- ▶ IV → dorsal wing = **superior parathyroid**; ventral wing (+ vestigial V) = **ultimobranchial body** → C cells of thyroid
- ▶ Arrows showing caudal migration: thymus + inferior parathyroid descending into the neck/superior mediastinum; superior parathyroid settling on the posterior thyroid capsule
- ▶ Thyroid gland in the midline (from the foramen caecum/thyroglossal duct) shown for orientation



Describe the development, fate and anomalies of endodermal pouches of pharyngeal arches

## Anomalies of the pharyngeal pouches

| Anomaly                                                                    | Basis                                                                                                                                                        | Features                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DiGeorge syndrome (22q11.2 deletion; velocardiofacial/Shprintzen syndrome) | Failure of the 3rd and 4th pouches to differentiate into thymus/parathyroids, due to disrupted endoderm–neural-crest signalling; <b>TBX1</b> gene implicated | Thymic aplasia/hypoplasia → T-cell immunodeficiency and recurrent infection; parathyroid aplasia/hypoplasia → hypocalcaemia/tetany; conotruncal cardiac and aortic-arch defects; facial dysmorphism (short philtrum/"fish-mouth", micrognathia, low-set notched ears, nasal clefts); incidence ≈ 1 in 4000 births |
| Ectopic/accessory thymic tissue                                            | Isolated nests of thymic tissue break off during caudal descent                                                                                              | Persistent cord or nodule of thymic tissue in the neck, often close to an inferior parathyroid gland                                                                                                                                                                                                              |

| Anomaly                                   | Basis                                                                                                        | Features                                                                                                                                                                                                                                          |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ectopic parathyroid glands                | Variable descent, especially of the 3rd-pouch (inferior) primordium                                          | Inferior parathyroid may be found anywhere from the carotid bifurcation to the mediastinum/pericardium, or embedded in thymus/thyroid; superior gland is more constant in position — important in failed neck exploration for hyperparathyroidism |
| Supernumerary / absent parathyroid glands | Division of a primordium (supernumerary) or failure of a primordium to differentiate/early atrophy (aplasia) | More or fewer than the usual four glands                                                                                                                                                                                                          |
| Piriform sinus fistula (4th-pouch sinus)  | Persistence of remnants of the ultimopharyngeal (ultimobranial) tract along its course to the thyroid        | Congenital tract opening into the apex of the piriform fossa; classically presents as recurrent (usually left-sided) suppurative thyroiditis/neck abscess in children                                                                             |
| Internal cervical (branchial) sinus       | Persistence of the proximal part of the 2nd pharyngeal pouch                                                 | Opens into the tonsillar sinus; normal remnant of this pouch is the tonsillar fossa                                                                                                                                                               |
| Cervical (branchial) fistula/cyst         | Persistence of parts of the 2nd pharyngeal groove <b>together with</b> the 2nd pouch                         | Complete tract runs from the neck (anterior border of sternocleidomastoid) through the carotid bifurcation to open into the tonsillar sinus; isolated remnants form a cervical cyst                                                               |
| Cervical thymic cyst                      | Persistence of part of the thymopharyngeal duct along the line of thymic descent                             | Cystic swelling anywhere from the angle of the mandible to the superior mediastinum                                                                                                                                                               |

## Applied / Clinical anatomy

- **DiGeorge syndrome** is confirmed by FISH/microarray for the 22q11.2 microdeletion, echocardiography for conotruncal defects, serum calcium, and lymphocyte subset analysis; management includes thymic transplantation, calcium/vitamin D replacement and cardiac surgery.
- Knowledge of the **variable descent of the inferior parathyroid** (3rd pouch, travels with thymus) versus the **constant position of the superior parathyroid** (4th pouch) guides the surgeon during **neck exploration for primary hyperparathyroidism** and thyroidectomy — a "missing" gland is usually an ectopic inferior parathyroid, searched along the thymic tract into the mediastinum.
- **Piriform sinus fistula** (4th-pouch derivative) is a key differential for recurrent childhood neck abscess/suppurative thyroiditis; treated by barium-swallow/endoscopic identification and tract excision or endoscopic cauterisation.
- **Persistent thymic tissue** along the line of descent explains ectopic cervical thymus and is relevant in thymectomy for myasthenia gravis, where ectopic tissue must also be sought.

- ▶ The **tonsillar fossa** (2nd-pouch remnant) is the surgical bed exposed in tonsillectomy; its close relation to the internal carotid artery (via the residual 2nd-pouch/cleft tract) is clinically important in cervical sinus/fistula surgery.
- ▶ Calcitonin from **C cells** (4th pouch/ultimobranchial body) is a tumour marker for medullary carcinoma of thyroid, which arises from these neural-crest-derived cells.

### High-yield exam pointers

- ▶ Four pairs of pouches + a rudimentary fifth; each (except 5th) has a dorsal and ventral proliferative wing.
- ▶ I → tympanic cavity + auditory tube; II → palatine tonsil + tonsillar fossa; III → inferior parathyroid + thymus; IV (+V) → superior parathyroid + ultimobranchial body (C cells).
- ▶ Third-pouch derivatives (thymus, inferior parathyroid) migrate furthest caudally — mnemonic reason the "inferior" parathyroid ends up variable in position.
- ▶ Differentiation of pouch endoderm needs neural-crest mesenchyme — failure of this interaction is the basis of DiGeorge syndrome.
- ▶ DiGeorge = 22q11.2 deletion, TBX1 gene; thymic + parathyroid aplasia, conotruncal cardiac defect, characteristic facies.
- ▶ Piriform sinus fistula = 4th-pouch (ultimopharyngeal tract) anomaly → recurrent childhood neck abscess/suppurative thyroiditis.
- ▶ Internal cervical sinus = 2nd-pouch remnant; complete cervical fistula needs both 2nd-pouch and 2nd-cleft persistence.
- ▶ Ectopic/supernumerary/absent parathyroid glands are surgically important causes of failed parathyroid exploration.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Sontakke's Textbook of Human Embryology; Gray's Anatomy (Standring) 41e.



## Describe the ectodermal derivatives of the branchial arches

Asked in: Paper II May 2019 — RGUHS MD/MS Anatomy

**Definition / Introduction** The branchial (pharyngeal) arches are paired mesenchymal bars that appear in the future head and neck of the 4th–5th week embryo, numbered craniocaudally I–VI (arch V is rudimentary and contributes no permanent structure in humans). Each arch has three tissue components: an outer covering of **surface ectoderm**, an inner lining of **endoderm** forming the pharyngeal pouch, and a mesenchymal core built of paraxial-mesoderm-derived myoblasts together with neural-crest-derived skeletal/connective tissue (ectomesenchyme). Ectoderm dips inward between two adjoining arches as a **pharyngeal (branchial) cleft**; of the four such clefts, only the first contributes a permanent adult structure. This answer traces every derivative of the surface ectoderm and the ectodermal clefts — the skin/mucosal coverings of the arches, the external acoustic meatus, the auricle, and the ectodermal (epibranchial) placodes.

### 1. Ectoderm in the Arch Complex — Where It Sits

| Component           | Location                                                                | General fate                                                                            |
|---------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Surface ectoderm    | Covers each arch externally; dips in as clefts between adjoining arches | Skin/mucosa of face and neck, external acoustic meatus, auricle, sensory placodes       |
| Pharyngeal endoderm | Lines each arch internally as pharyngeal pouches                        | Middle-ear cavity/tube, tonsil, parathyroids, thymus (outside the scope of this answer) |
| Mesenchymal core    | Paraxial mesoderm (myoblasts) + neural crest (ectomesenchyme)           | Arch muscles; arch skeleton (Meckel's and Reichert's cartilages, ossicles)              |

- ▶ Neural crest cells arise from **neuroectoderm** at the neural fold, so although the arch skeleton and much connective tissue are "mesenchymal," they are ultimately of ectodermal lineage — this is why auricular and craniofacial skeletal anomalies cluster together clinically (neurocristopathies).
- ▶ Endodermal segmentation of the pharynx into pouches is now understood to be the primary event that induces the arches; the overlying ectoderm subsequently invaginates to meet each pouch, defining the rostral and caudal margins of every arch.

### 2. Fate of the Pharyngeal (Ectodermal) Clefts

There are four ectodermal clefts, in the intervals between arches 1–2, 2–3, 3–4 and 4–6.

| Cleft             | Fate                                                                                                                                                                                             |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st, dorsal part  | Persists; contributes to the <b>external acoustic meatus</b> and the outer epithelial stratum of the <b>tympenic membrane</b>                                                                    |
| 1st, ventral part | Obliterated                                                                                                                                                                                      |
| 2nd, 3rd, 4th     | Overgrown and buried by caudal expansion of the 2nd arch; transiently enclosed within the <b>cervical sinus of His</b> ; normally obliterated completely, restoring a smooth outline to the neck |

- **Cervical sinus of His:** an ectoderm-lined cavity created when the rapidly proliferating 2nd-arch mesenchyme overhangs and then fuses with tissue caudal to the arches (the epicardial ridge), thereby burying clefts 2, 3 and 4.
- Persistence of any part of this sinus, or of the first cleft in an aberrant form, is the embryological basis of **branchial cysts, sinuses and fistulae** — the second most common congenital head-and-neck lesion in children (see Applied anatomy).

□ Fig 17.3 — Development of the pharyngeal arches. A. (Langman's Medical Embryology — Sadler — 14e, p.304)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Coronal/oblique section through the head and neck of a 5-week embryo showing arches I–IV and VI with the surface ectoderm labelled outside each arch, the four ectodermal clefts labelled 1–4 in the intervals, the endodermal pouches labelled inside, and the 2nd-arch mesenchyme drawn overgrowing clefts 2–4 to enclose the **cervical sinus of His**.

### 3. Ectodermal (Surface) Derivatives, Arch by Arch

| Arch             | Surface-ectoderm derivatives                                                                                                                                                                                                                                          |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st (mandibular) | Skin over the upper and lower jaws, lips, and alveolobial sulci; the <b>dental lamina</b> (gives rise to ameloblasts that form enamel); the <b>tragus</b> of the auricle; epithelium of the external acoustic meatus; outer epithelial layer of the tympanic membrane |
| 2nd (hyoid)      | Skin covering nearly the whole remaining auricle (helix, antihelix, antitragus, lobule)                                                                                                                                                                               |
| 3rd, 4th, 6th    | No distinct named derivative — their ectoderm is carried into the transient cervical sinus and is normally lost as the sinus is obliterated; the overlying skin of the lower neck becomes smooth and continuous                                                       |

- The dental lamina, tragus and remaining-auricle derivatives above are the specific, examiner-favoured points that distinguish this question from a generic "pharyngeal apparatus" essay.
- Sensory ganglia of the cranial nerves supplying each arch (trigeminal for arch 1, facial for arch 2, glossopharyngeal for arch 3, vagus for arches 4/6) receive a contribution from ectodermal placodes as well as neural crest (Section 5).

### 4. Development of the External Ear (Auricle)

- Six mesenchymal (neural-crest-derived) swellings — the **hillocks of His** — appear around the dorsal end of the first ectodermal cleft, three on the mandibular (1st) arch and three on the hyoid (2nd) arch; they enlarge and fuse to sculpt the definitive auricle, the whole structure remaining covered by ectodermal skin throughout.

| Hillock | Classical arch of origin | Adult part formed |
|---------|--------------------------|-------------------|
| 1       | 1st arch                 | Tragus            |
| 2       | 1st arch                 | Crus of the helix |

| Hillock | Classical arch of origin | Adult part formed |
|---------|--------------------------|-------------------|
| 3       | 1st arch                 | Helix             |
| 4       | 2nd arch                 | Antihelix         |
| 5       | 2nd arch                 | Antitragus        |
| 6       | 2nd arch                 | Lobule            |

- **Current understanding** (Sadler 14e; IB Singh CBME 2021): fate-mapping shows the 1st (mandibular) arch actually contributes only the **tragus** and the meatal invagination; almost the entire remainder of the auricle — including the helix — is formed by proliferating **2nd-arch (hyoid)** neural-crest tissue. First-arch tissue is HOXA2-negative and second-arch tissue HOXA2-positive; this molecular boundary patterns the auricle, and disruption of the pathway underlies duplications, tags and pits of the external ear.
- The external acoustic meatus develops as an **invagination of first-arch ectoderm** at the site of the dorsal first cleft; a solid epithelial **meatal plug** forms by the 3rd month and canalises by the 7th month.
- The tympanic membrane has three layers, only the outer of which is ectodermal: (i) outer **ectodermal** epithelium (1st cleft/1st-arch invagination), (ii) intermediate mesenchymal fibrous stratum, (iii) inner **endodermal** epithelium (1st pouch/tubotympanic recess).
- The auricle first develops in the ventral neck and is carried to the side of the head by growth of the mandible and face.

□ Fig 24.6 — Development of external ear (Sontakke — Textbook of Human Embryology, p.279)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Lateral view of a 6-week embryo head/neck with the six hillocks of His numbered 1–6 arranged around the first ectodermal cleft; shade hillocks 1–3 over the mandibular (1st) arch and 4–6 over the hyoid (2nd) arch; alongside, draw the mature auricle with tragus, crus of helix, helix, antihelix, antitragus and lobule labelled.

### 5. Epibranchial Placodes — Ectodermal Contribution to Cranial Nerve Ganglia

- Four **epibranchial placodes** are thickened regions of surface ectoderm lying dorsal to the pharyngeal pouches/arches.
- Their cells invaginate and contribute sensory neurones to the distal (epibranchial) ganglia of cranial nerves V (**trigeminal**), VII (**geniculate ganglion**), IX (**petrosal/inferior ganglion**) and X (**nodose/inferior ganglion**) in relation with the 1st arch and the 1st, 2nd and 4th clefts — complementing the proximal ganglion cells, which are neural-crest-derived.

#### Applied / Clinical anatomy

- **Branchial cyst**: persistence of the cervical sinus of His as a cyst along the anterior border of sternocleidomastoid, most often just below the angle of the mandible; rupture/discharge produces a branchial sinus.



- ▶ **First-cleft cyst/sinus:** type I opens above the mandible (near a duplicated membranous EAM), type II opens below the angle of the mandible; both relate to an aberrant persistence of the first cleft.
- ▶ **Branchial fistula:** a complete tract connecting the pharynx (often near the palatine tonsil) to the skin of the neck, from incomplete obliteration of a cleft–pouch pair.
- ▶ **Preauricular sinus/pit and preauricular skin tag (appendage):** from faulty fusion of the hillocks of His, or incomplete first-arch meatal invagination, near the tragus.
- ▶ **Microtia and anotia:** hypoplastic or absent auricle from deficient hillock proliferation; frequently syndromic because the same neural crest also patterns the face, skull and cardiac outflow tract.
- ▶ **Congenital aural atresia / persistent meatal plug:** failure of the solid ectodermal meatal plug to canalise by the 7th month → congenital conductive deafness.
- ▶ **HOXA2-pathway disruption:** underlies duplication/tag/pit anomalies of the external ear; such external-ear defects are often associated with anomalies of the face, skull and heart, and are grouped in some syndromes with renal anomalies (branchio-oto-renal spectrum).

### High-yield exam pointers

- ▶ Ectoderm covers each arch externally and dips in as **four ectodermal clefts**; only cleft 1 (dorsal part) persists → external acoustic meatus + outer layer of the tympanic membrane.
- ▶ Clefts 2, 3 and 4 are buried within the **cervical sinus of His** (formed by 2nd-arch overgrowth) and are normally obliterated completely — persistence → branchial cyst/sinus/fistula.
- ▶ 1st-arch ectoderm → skin of jaws/lips, dental lamina (enamel), tragus, EAM epithelium; 2nd-arch ectoderm → the rest of the auricle.
- ▶ Auricle develops from **six hillocks of His** (1–3 mandibular, 4–6 hyoid); current teaching: the 1st arch actually contributes only the tragus, the 2nd (HOXA2+) arch forming nearly the whole auricle.
- ▶ Tympanic membrane = three layers — outer ectoderm, middle mesenchyme, inner endoderm.
- ▶ **Epibranchial placodes** are ectodermal thickenings contributing sensory neurones to the ganglia of CN V, VII, IX and X.
- ▶ Neural crest is neuroectoderm-derived, explaining the clustering of auricular with craniofacial skeletal anomalies.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Larsen Human Embryology 6e; Sontakke Textbook of Human Embryology.



## Describe the formation and fate of the pharyngeal arches

Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy

**Definition / Introduction** Pharyngeal (branchial) arches are a series of mesenchymal bars that appear in the lateral wall and floor of the primitive pharynx during the 4th–5th week, corresponding to the gill arches of lower vertebrates (true gills never form in humans). Six arches are described on comparative-anatomy grounds, numbered 1, 2, 3, 4 and 6 (the true 5th arch is rudimentary/transitory and leaves no recognisable derivative, so only five arches are consistently identifiable in the human embryo). Each arch is separated externally by a **pharyngeal cleft (groove)** and internally by a **pharyngeal pouch**, and each contains its own artery, cartilage, muscle mass and nerve. The arches build almost the entire skeleton, musculature, vasculature and innervation of the face and neck; disruption of neural-crest contribution to the arches underlies most craniofacial and branchial anomalies.

### Formation of the pharyngeal arches

- ▶ **Origin of the pharynx:** the embryonic pharynx is the most cranial part of the foregut; it widens where it joins the stomodeum (primitive mouth) and narrows towards the oesophagus.
- ▶ **Timing:** the first and second arches appear by day 22 (4th week); by day 28–29 (end of 4th week) four arches (1–4) are visible externally; formation of all arches is complete by Carnegie stage 14–15 (~5 weeks). The 5th/6th arches never form an external surface elevation.
- ▶ **Cellular origin of the arch core (mesenchyme):** each arch has a core of mesenchyme covered externally by **ectoderm** and internally by **endoderm**.
  - Neural crest cells migrating from the hindbrain (rhombomeres) form the skeletal element, associated connective tissue, and the outer wall of the arch (aortic) artery.
  - Paraxial (unsegmented cranial) mesoderm supplies the myogenic (muscle) and angiogenic (endothelial) components.
  - Trigeminal crest populates arch 1; hyoid crest populates arch 2; vagal crest populates arches 3, 4 and 6.
- ▶ **Signalling:** Sonic hedgehog signalling is important for first-arch patterning; a Hox-gene code (absent in arch 1, expressed from arch 2 caudally) specifies arch identity.
- ▶ **A typical pharyngeal arch contains** an artery (arising from the aortic sac/truncus arteriosus and running to the dorsal aorta), a cartilaginous rod, a muscular component, and a mixed motor–sensory nerve.
- ▶ **First arch:** unique in having dorsal and ventral processes — the **maxillary** and **mandibular prominences** — giving it a C-shape; the maxillary prominence forms the maxilla, zygomatic bone and part of the vomer, while the mandibular prominence forms the mandible.
- ▶ **Second (hyoid) arch:** by the 5th week it enlarges and grows caudally over the 3rd and 4th arches, burying them (and the intervening clefts) in an ectodermal depression, the **cervical sinus**; this normally obliterates by the 7th week, giving the neck a smooth contour.

□ Fig 17.3 — Development of the pharyngeal arches. A. (Langman's Medical Embryology — Sadler — 14e, p.304)

| Component         | Germ-layer / tissue origin                   | Fate                                                                          |
|-------------------|----------------------------------------------|-------------------------------------------------------------------------------|
| External covering | Surface ectoderm                             | Epidermis, skin appendages (arch 1); lines pharyngeal grooves elsewhere       |
| Internal lining   | Endoderm                                     | Mucosa of pharynx; lines pharyngeal pouches                                   |
| Mesenchymal core  | Neural crest (mainly) + paraxial mesoderm    | Skeletal element + connective tissue (crest); muscle + endothelium (mesoderm) |
| Arch artery       | Angiogenic mesoderm (wall from neural crest) | An aortic arch artery (fate below)                                            |
| Cartilage bar     | Neural crest                                 | Bone/cartilage/ligament (fate below)                                          |
| Muscle mass       | Paraxial mesoderm                            | Named muscle group (fate below)                                               |
| Nerve             | Neuroectoderm of hindbrain                   | Arch-specific cranial nerve                                                   |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Horizontal (transverse) section through the cranial pharynx of a 4-week embryo, labelling: **ectoderm** (outer covering) · **endoderm** (inner lining) · **mesenchyme** (**neural crest** + **paraxial mesoderm**) core · **pharyngeal arches 1, 2, 3, 4, 6** · **pharyngeal pouch** (between each pair of arches) · **pharyngeal groove/cleft** (external, opposite each pouch) · **pharyngeal membrane** (where groove ectoderm meets pouch endoderm) · **aortic (arch) artery** within each arch · **cartilage bar** (name per arch) · **cranial nerve** (name per arch) · **muscle mass** · **primordial pharynx** (lumen) · **dorsal aorta** · **stomodeum** and **oropharyngeal membrane** rostrally.

### Fate of the pharyngeal arch cartilages

| Arch             | Cartilage            | Skeletal derivatives                                                                                            | Ligament derivative                                     |
|------------------|----------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| 1st (mandibular) | Meckel's cartilage   | Malleus, incus (dorsal end); mandible ossifies membranously <i>around</i> the cartilage (not derived from it)   | Anterior ligament of malleus; sphenomandibular ligament |
| 2nd (hyoid)      | Reichert's cartilage | Stapes, styloid process of temporal bone (dorsal end); lesser cornu + upper part of body of hyoid (ventral end) | Stylohyoid ligament                                     |
| 3rd              | Third arch cartilage | Greater cornu + lower part of body of hyoid                                                                     | —                                                       |

| Arch      | Cartilage                           | Skeletal derivatives                                                                                                                                                                                               | Ligament derivative |
|-----------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| 4th & 6th | Fourth/sixth arch cartilages (fuse) | Laryngeal cartilages — thyroid, cricoid, arytenoid, corniculate, cuneiform — <b>except the epiglottis</b> , which develops from mesenchyme of the hypobranchial (hypopharyngeal) eminence, not from arch cartilage | —                   |
| 5th       | Rudimentary/absent                  | No derivative                                                                                                                                                                                                      | —                   |

### Fate of the pharyngeal arch muscles and nerves

| Arch | Nerve                                                                                 | Muscles                                                                                                                                                   |
|------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st  | Trigeminal (CN V), mandibular division; pretrematic branch = chorda tympani of CN VII | Muscles of mastication (temporalis, masseter, medial and lateral pterygoid), mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini |
| 2nd  | Facial (CN VII)                                                                       | Muscles of facial expression (buccinator, auricular muscles, occipitofrontalis, platysma), stapedius, stylohyoid, posterior belly of digastric            |
| 3rd  | Glossopharyngeal (CN IX)                                                              | Stylopharyngeus                                                                                                                                           |
| 4th  | Superior laryngeal branch of vagus (CN X)                                             | Cricothyroid, levator veli palatini, constrictors of the pharynx                                                                                          |
| 6th  | Recurrent laryngeal branch of vagus (CN X)                                            | Intrinsic muscles of the larynx, except cricothyroid                                                                                                      |

- Each arch nerve is **mixed**; a purely sensory **pretrematic branch** supplies the arch rostral to its own cleft (best developed as the chorda tympani of the first arch), while the **post-trematic** branch supplies its own arch.
- Tongue musculature (occipital myotomes, CN XII) and palatoglossus (vagus, via pharyngeal plexus) are not arch derivatives in the strict sense but are conventionally described alongside this scheme.

### Fate of the pharyngeal arch arteries (aortic arches)

| Arch artery | Fate                                                                         |
|-------------|------------------------------------------------------------------------------|
| 1st         | Largely disappears; contributes to part of the maxillary artery (transitory) |

| Arch artery | Fate                                                                                                                                                                                                                                        |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2nd         | Largely disappears; remains transiently as the stapedial and hyoid arteries                                                                                                                                                                 |
| 3rd         | Common carotid artery + proximal (first) part of the internal carotid artery                                                                                                                                                                |
| 4th         | Right: proximal part of the right subclavian artery.<br>Left: arch of the aorta, between the origins of the left common carotid and left subclavian arteries                                                                                |
| 5th         | Disappears completely; never fully forms                                                                                                                                                                                                    |
| 6th         | Right: proximal right pulmonary artery (distal connection to dorsal aorta lost). Left: left pulmonary artery + the part between pulmonary trunk and dorsal aorta becomes the <b>ductus arteriosus</b> (→ ligamentum arteriosum after birth) |

- The carotid body develops from third-arch mesenchyme; the aortic body from fourth-arch mesenchyme.
- The right recurrent laryngeal nerve hooks under the right 4th-arch-derived subclavian artery, while the left hooks under the ligamentum arteriosum (remnant of the 6th arch artery) — explaining the differing paths of the two nerves.

### Fate of pharyngeal pouches, clefts and membranes

| Pouch                               | Derivative                                                                                                                                                                                   |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st                                 | Tubotympanic recess → tympanic cavity, mastoid antrum; the elongating connection with the pharynx becomes the pharyngotympanic (auditory/Eustachian) tube                                    |
| 2nd                                 | Palatine tonsil (surface epithelium and crypt lining); residual cavity persists as the tonsillar sinus/fossa                                                                                 |
| 3rd                                 | Dorsal part → inferior parathyroid gland; ventral part → thymus (bilateral primordia fuse in the midline and descend into the thorax, carrying the inferior parathyroids caudally with them) |
| 4th                                 | Dorsal part → superior parathyroid gland                                                                                                                                                     |
| 4th/5th (caudal pharyngeal complex) | Ultimopharyngeal (ultimobranchial) body, which fuses with the thyroid; its neural-crest-derived cells disseminate as the <b>parafollicular (C) cells</b> secreting calcitonin                |

- **Clefts:** of the four pharyngeal clefts, only the **first** persists — as the epithelial lining of the **external acoustic meatus**; the 2nd–4th clefts are buried within, and obliterated along with, the cervical sinus.
- **Membranes:** only the **first pharyngeal membrane** contributes to an adult structure — the **tympanic membrane** (all three germ layers: ectoderm of the 1st cleft, endoderm of the 1st pouch, intervening mesenchyme); the remaining membranes disappear with the cervical sinus.

## Applied / Clinical anatomy

- ▶ **Branchial (cervical) cyst, sinus, fistula:** result from incomplete obliteration of the 2nd pharyngeal cleft/cervical sinus (external) and/or 2nd pouch (internal); classically found along the anterior border of sternocleidomastoid, near the angle of the mandible; a complete fistula tracks between the internal and external carotid arteries to open into the tonsillar sinus.
- ▶ **Preauricular sinus:** anomaly related to the 1st pharyngeal cleft/auricular hillocks.
- ▶ **Piriform sinus fistula:** attributed to persistence of ultimopharyngeal body remnants along its path to the thyroid; a recognised cause of recurrent neck abscess/acute suppurative thyroiditis in children.
- ▶ **DiGeorge syndrome (22q11.2 deletion, TBX1 gene):** failure of normal 3rd/4th pouch and neural-crest-derived development — thymic aplasia/hypoplasia (T-cell immunodeficiency), parathyroid aplasia (hypocalcaemic tetany), conotruncal cardiac and aortic-arch defects, and mild facial dysmorphism (short philtrum, low-set ears, micrognathia).
- ▶ **Treacher Collins syndrome (mandibulofacial dysostosis, TCOF1 gene):** 1st-arch neural crest apoptosis — hypoplastic mandible, maxilla and zygoma, down-slanting palpebral fissures, external ear/middle-ear ossicle defects with conductive deafness.
- ▶ **Pierre Robin sequence:** 1st-arch disorder — micrognathia, glossoptosis and cleft palate.
- ▶ **Hemifacial microsomia (Goldenhar/oculo-auriculo-vertebral syndrome):** asymmetric 1st- and 2nd-arch (maxillary, temporal, zygomatic, ear) hypoplasia, often with ocular and vertebral anomalies.
- ▶ Knowledge of arch-artery fate explains congenital aortic arch anomalies (e.g. right-sided aortic arch, aberrant subclavian) and guides safe identification of the recurrent laryngeal nerve in thyroid/neck surgery.

## High-yield exam pointers

- ▶ Only five arches are functionally significant (1, 2, 3, 4, 6); the true 5th arch is rudimentary/transitory and has no derivative.
- ▶ Formation: neural-crest migration (weeks 4–5) into a mesenchymal core covered by ectoderm/endoderm; each arch = artery + cartilage + muscle + nerve.
- ▶ **1st arch** = Meckel's cartilage → malleus, incus; mandible ossifies around it; nerve V3; muscles of mastication.
- ▶ **2nd arch** = Reichert's cartilage → stapes, styloid process, lesser cornu + upper hyoid body; nerve VII; facial muscles.
- ▶ **3rd arch** → greater cornu + lower hyoid body; nerve IX; stylopharyngeus.
- ▶ **4th & 6th arches** → laryngeal cartilages except epiglottis; nerve X (superior/recurrent laryngeal); pharyngeal/laryngeal muscles.
- ▶ **Arteries:** 3rd → internal carotid; 4th → aortic arch (L)/subclavian (R); 6th → pulmonary arteries + ductus arteriosus.
- ▶ **Pouches:** 1st → auditory tube/middle ear; 2nd → palatine tonsil; 3rd → inferior parathyroid + thymus; 4th → superior parathyroid + C cells (ultimopharyngeal body).

- **Clefts/membranes:** only the 1st of each persists (external acoustic meatus; tympanic membrane) — the rest are buried in, and vanish with, the cervical sinus.
- Clinical linkage: 2nd cleft/pouch → branchial cyst/fistula; 3rd/4th pouch + neural crest → DiGeorge syndrome; 1st arch → Treacher Collins/Pierre Robin.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Moore's The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Sontakke's Textbook of Human Embryology.



## Describe the formation of face and palate. What are the results of improper union of the various processes?

Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy

**Definition / Introduction** The face and palate are sculpted between the 4th and 12th weeks of intra-uterine life by the growth, apposition and fusion of five **facial prominences** — the unpaired **frontonasal prominence** and the paired **maxillary** and **mandibular prominences** of the first pharyngeal arch — which surround the primitive mouth (**stomodeum**). Localised proliferation of the frontonasal prominence around the nasal placodes further generates paired **medial** and **lateral nasal prominences**. The upper lip, nose and both parts of the palate are all formed by merging and fusion of these prominences/processes; failure of any one fusion line produces a predictable, site-specific facial or palatal cleft — the basis of the second half of this question.

### 1. Facial prominences — origin and timeline

By the **4th week**, neural-crest mesenchyme has raised the unpaired **frontonasal prominence** and paired **maxillary/mandibular prominences** around the stomodeum, and paired ectodermal **nasal (olfactory) placodes** appear on the frontonasal prominence (induced by the ventral forebrain). In the **5th week** the placodes invaginate into **nasal pits**, and the surrounding ridge splits into an outer **lateral nasal process** and an inner **medial nasal process**. Through the **5th–7th week** the enlarging maxillary prominences grow medially, compressing the medial nasal prominences to the midline and fusing with them (and, across the nasolacrimal groove, with the lateral nasal prominences — this canalises to form the nasolacrimal duct). By **stage 20 (~7–8 weeks)** the face is recognisably human.

**Table 1 — structures formed by each prominence** (after Sadler, *Langman's Medical Embryology*)

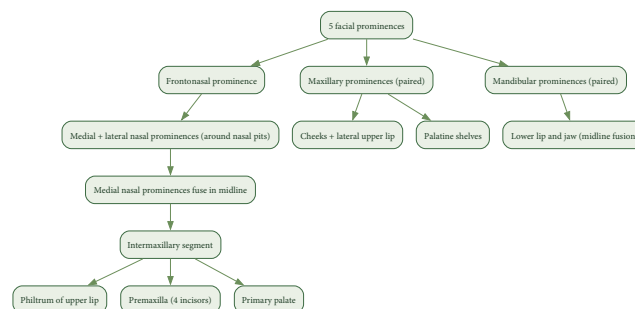
| Prominence                   | Structure(s) formed                                                            |
|------------------------------|--------------------------------------------------------------------------------|
| Frontonasal (unpaired)       | Forehead, bridge of nose                                                       |
| Medial nasal (paired, fused) | Crest/tip of nose; <b>philtrum</b> ; part of the <b>intermaxillary segment</b> |
| Lateral nasal (paired)       | Alae of nose only ( <b>no</b> contribution to the lip)                         |
| Maxillary (paired)           | Cheeks; lateral part of upper lip; upper jaw except premaxilla                 |



| Prominence          | Structure(s) formed                                             |
|---------------------|-----------------------------------------------------------------|
| Mandibular (paired) | Lower lip and jaw (fuses in the midline first, by the 4th week) |

## 2. Development of the upper lip, nose and jaw

- ▶ The **upper lip** = two fused **medial nasal prominences** (midline philtrum) + two **maxillary prominences** (lateral parts); fusion also closes the future nostril at the lower margin of the nasal pit.
- ▶ The two medial nasal prominences merge at depth too, forming the **intermaxillary segment**, with three components: (1) **labial** — philtrum; (2) **upper-jaw** — bears the four incisor teeth; (3) **palatal** — the wedge-shaped **primary palate** (ossifies as the **premaxilla**).
- ▶ The nasal pits deepen into the nasal cavities, separated from the oral cavity by the **oronasal membrane** until this ruptures to form the primitive **choanae**.
- ▶ The **lower lip and jaw** form purely from the two mandibular prominences merging across the midline.



Describe the formation of face and palate. What are the results of improper union of the various processes?

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences around the stomodeum, and their fusion to form the upper lip, nose and eyelids (Sontakke — Textbook of Human Embryology, p.118)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal/frontal series of the developing face (4th–7th week), labelled: frontonasal process, lens placode, stomodeum, mandibular process (1st arch), perforated oropharyngeal membrane; olfactory (nasal) placode, maxillary process; medial nasal process, nasal pit, lateral nasal process; naso-optic (nasolacrimal) furrow; developing eyelids, anterior nares, upper lip, philtrum of lip, lower lip.

## 3. Development of the palate

Palate development spans the **6th to 12th week** and occurs in **two stages**:

- Primary palate** (6th week) — formed by fusion, at a deeper level, of the two medial nasal processes; this wedge of mesenchyme (the palatal component of the intermaxillary segment) becomes the small, **triangular primary palate**, which ossifies to form the **premaxilla** carrying the four incisor teeth.
- Secondary palate** (6th–12th week) — forms the main part of the definitive palate:

- ▶ Two shelf-like outgrowths, the **palatine shelves (palatal processes)**, project from the inner aspect of each maxillary prominence (from ~6th week), initially growing **vertically downward** on either side of the still-domed tongue.
- ▶ During the **7th–8th week**, as Meckel's cartilage elongates and the head grows in **height but not width**, the tongue withdraws from between the shelves; the shelves rapidly **rotate to horizontal** above the tongue — aided by hyaluronan-mediated swelling of the shelf mesenchyme and fetal mouth-opening/tongue-protrusion movements.
- ▶ The shelves then **fuse with each other in the midline**, with the primary palate anteriorly, and with the **nasal septum** (a frontonasal downgrowth) superiorly — beginning anteriorly around the 9th week and complete posteriorly by the **12th week**.
- ▶ The junction of primary and secondary palate is marked, in the adult, by the **incisive fossa/foramen**; shelf elevation occurs slightly **later in females than in males**.

**Table 2 — source of the components of the adult palate** (after Vishram Singh, *Textbook of Clinical Embryology*)

| Component                                                               | Develops from                                                                                                                               |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Hard palate — anterior to incisive fossa (premaxilla, bears 4 incisors) | Fused <b>medial nasal processes</b> of the frontonasal process                                                                              |
| Hard palate — posterior to incisive fossa                               | Fusion of the <b>palatine shelves</b> of the two maxillary processes (ossification extends into the shelves from maxilla and palatine bone) |
| Soft palate, including the uvula                                        | Unossified posterior part of the fused palatine shelves that extends beyond the nasal septum                                                |

#### 4. Results of improper union — clefts of the face and lip

Failure of fusion between adjacent facial prominences produces predictable clefts along the lines of merging:

| Cleft                                     | Failed fusion                                                         | Feature                                                                        |
|-------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------|
| <b>Unilateral cleft lip</b> (commonest)   | Maxillary–medial nasal prominence, <b>same side</b>                   | Septum deviates to the <b>non-cleft</b> side (unopposed orbicularis oris pull) |
| <b>Bilateral cleft lip</b>                | Maxillary–medial nasal prominence, <b>both sides</b>                  | Premaxilla/philtrum stands free between two clefts                             |
| <b>Median cleft lip</b> ("true hare-lip") | Two medial nasal prominences fail to merge in midline                 | Very rare; may accompany <b>holoprosencephaly</b> (SHH mutation)               |
| <b>Oblique facial cleft</b>               | Maxillary– <b>lateral</b> nasal prominence, along nasolacrimal groove | Rare, usually bilateral; nasolacrimal duct exposed                             |
| <b>Cleft lower lip</b>                    | Two mandibular prominences, midline                                   | Extremely rare                                                                 |

| Cleft                     | Failed fusion                                               | Feature                     |
|---------------------------|-------------------------------------------------------------|-----------------------------|
| Macrostomia / microstomia | Arrest/excess of maxillary–mandibular fusion at mouth angle | Abnormal oral-fissure width |

Incidence: cleft lip with/without cleft palate  $\approx$  1 in 700–1000 live births (Gray's Anatomy: 0.5–3.6/1000), with a male preponderance ( $\approx$ 2:1).

## 5. Results of improper union — cleft palate

- ▶ The **incisive foramen** is the landmark dividing anterior from posterior cleft deformities.
  - **Anterior to it** (failure of the maxillary prominence to fuse with the medial nasal prominence): lateral cleft lip, cleft of the upper jaw (maxilla split between lateral incisor and canine), cleft between primary and secondary palate.
  - **Posterior to it** (failure of the two **palatine shelves** to fuse): cleft of the secondary (soft/hard) palate and cleft uvula.
- ▶ Causes of shelf non-fusion: shelves too small; failure of shelves to **elevate**; inhibition of the midline **fusion process** itself (failure of epithelial adhesion/apoptotic breakdown); or failure of the **tongue to descend** from between the shelves (e.g. in micrognathia, as in Pierre Robin sequence).

Table 3 — classification of cleft palate (after Vishram Singh)

| Type                           | Description                                                                                               |
|--------------------------------|-----------------------------------------------------------------------------------------------------------|
| Complete, unilateral           | Maxillary process on one side fails to fuse with premaxilla; always with ipsilateral cleft lip            |
| Complete, bilateral            | Both maxillary processes fail to fuse with premaxilla; premaxilla separated by an anterior V-shaped cleft |
| Incomplete — bifid uvula       | Cleft confined to the uvula; no clinical significance                                                     |
| Incomplete — soft-palate cleft | Uvula + adjoining soft palate, sometimes extending into the hard palate                                   |
| Submucous cleft                | Median V-notch of soft palate under intact mucosa; speech defect via musculus-uvulae hypoplasia           |

Isolated cleft palate is genetically distinct from cleft lip  $\pm$  cleft palate; it is **less common** ( $\approx$ 1/1500 births; Gray's: 0.4/1000) and occurs **more often in females** — because palatal-shelf fusion normally occurs about a week later in females, leaving a longer window for interference.

□ Fig 12.5 — Cleft lip and cleft palate: non-fusion of the median and lateral palatine processes resulting in unilateral/bilateral complete cleft palate, incomplete cleft palate (bifid uvula) and cleft lip (Sontakke — Textbook of Human Embryology, p.123)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Coronal palate views labelled: **nostril, upper lip, gum, premaxilla, palate, bifid uvula** — for each of: **unilateral complete cleft palate; bilateral complete cleft palate; incomplete cleft palate (bifid uvula); cleft lip only.**

**Applied / Clinical anatomy**

- ▶ **Feeding and speech:** oronasal communication impairs suckling (loss of negative intra-oral pressure) and distorts plosive consonants (D, T, G) due to nasal air escape.
- ▶ **Genetics:** most CL/P is multifactorial. **Van der Woude syndrome** (autosomal dominant, *IRF6* gene, 1p32–41, expressed in the fusing medial edge of the palatal shelves) is the commonest syndromic association — 88% of affected infants have lower-lip pits. *MSX1* mutations are also implicated.
- ▶ **Teratogens:** anticonvulsants (particularly valproic acid) and maternal smoking increase risk of orofacial clefts.
- ▶ **Dental:** cleft of the upper jaw classically splits the maxilla between the lateral incisor and canine, along the primary/secondary palate suture line.
- ▶ **Facial clefts proper** (rare, 1/50,000–1/175,000) are attributed mainly to amniotic-band pressure rather than failure of embryonic fusion.

**High-yield exam pointers**

- ▶ Face develops from **5 prominences**: 1 frontonasal + 2 maxillary + 2 mandibular, around the stomodeum; nasal placodes on the frontonasal prominence invaginate to give medial and lateral nasal processes.
- ▶ **Upper lip = 2 medial nasal + 2 maxillary prominences**; lateral nasal prominences form only the **alae of the nose**, never the lip.
- ▶ **Intermaxillary segment** = philtrum + premaxilla (4 incisors) + primary palate — all from **fused medial nasal processes**.
- ▶ **Primary palate** (6th week, from intermaxillary segment) vs **secondary palate** (from palatine shelves of maxillary prominences, fuse 7th–12th week) — **incisive foramen** is the boundary landmark.
- ▶ Palatine shelves are initially **vertical** beside the tongue and must **rotate to horizontal** after the tongue descends (~7th week) — delay here is the commonest mechanism of cleft palate.
- ▶ **Unilateral cleft lip** (maxillary–medial nasal non-fusion, commonest) deviates the septum to the non-cleft side; **oblique facial cleft** (maxillary–lateral nasal non-fusion) exposes the nasolacrimal duct; **median cleft lip** (medial nasal processes fail to merge) is linked to holoprosencephaly.
- ▶ Cleft lip ± palate ≈ 1/700–1000 births, M > F (2:1); isolated cleft palate ≈ 1/1500 births, F > M; *IRF6*/Van der Woude is the top syndromic association.

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology (figures).



## Development and Anomalies of Face

*Asked in: Paper II 14-Nov-2019 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The face develops between the **4th and 10th weeks** of intrauterine life by proliferation, growth and progressive **fusion of five neural-crest-derived mesenchymal facial prominences** (one unpaired **frontonasal** + paired **maxillary** + paired **mandibular**) that surround the primitive mouth, the **stomodeum**. Subsequent invagination of paired **nasal (olfactory) placodes** on the frontonasal prominence adds paired **medial** and **lateral nasal prominences**, whose merging shapes the nose, lips, cheeks and palate. Because the definitive face is built almost entirely by the coming-together of separate mesenchymal masses, **failure, delay, or excess of fusion** at any of these lines produces the characteristic spectrum of facial clefts and dysmorphisms — from a trivial lip notch to complete facio-palatal clefts, oblique clefts and rare midline/holoprosencephalic anomalies.

### 1. Facial prominences — origin, timeline and fusion sequence

- ▶ **End of 4th week:** five neural-crest-derived prominences appear around the stomodeum — unpaired **frontonasal** (upper border, from mesenchyme ventral to the forebrain), paired **maxillary** (lateral to the stomodeum) and paired **mandibular** (caudal to it), the latter two from the 1st pharyngeal arch.
- ▶ **5th week:** paired ectodermal **nasal (olfactory) placodes** appear on the frontonasal prominence under inductive influence of the forebrain, then **invaginate to form nasal pits**, raising a horseshoe ridge around each — outer ridge = **lateral nasal prominence**, inner ridge = **medial nasal prominence**.
- ▶ **5th–7th week:** the **maxillary prominences enlarge and grow medially**, first fusing with the **lateral nasal process** (obliterating the naso-optic/nasolacrimal furrow) and then with the **medial nasal process**, cutting the nasal pit (now the external naris) off from the stomodeum; the **mandibular prominences merge in the midline** to form the lower lip and jaw; the maxillary and mandibular prominences fuse along their line of contact to form the **cheeks**.
- ▶ **Eyes:** the lens placode (lateral and cranial to the nasal placode) sinks in to form the eyeball, initially directed laterally, coming to face forward as the frontonasal prominence narrows.
- ▶ **Nasolacrimal duct:** the ectodermal groove between the fusing maxillary and lateral nasal prominences buries as a solid cord that later canalises into the duct, its upper end widening into the lacrimal sac.
- ▶ By **stage 20 (7–8 weeks)** the face is recognisably human; thereafter only differential growth alters proportions.

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences around the stomodeum, and their fusion to form the nose, eyelids, lips and cheeks (Sontakke — Textbook of Human Embryology, p.118)

| Prominence             | Structure(s) formed                                                              |
|------------------------|----------------------------------------------------------------------------------|
| Frontonasal (unpaired) | Forehead, bridge of nose; gives rise to the medial and lateral nasal prominences |
| Maxillary (paired)     | Cheeks, lateral part of upper lip                                                |
| Medial nasal (paired)  | Philtrum of upper lip, crest and tip of nose                                     |
| Lateral nasal (paired) | Alae of the nose (takes <b>no</b> part in the upper lip)                         |
| Mandibular (paired)    | Lower lip and jaw                                                                |

- ▶ **Upper lip** = medial nasal + maxillary prominences; **lower lip** = mandibular prominences; **external nose** = frontonasal (bridge) + fused medial nasal (crest/tip) + lateral nasal (alae) — the classic "five processes" of the nose.

## 2. Intermaxillary segment and primary palate

- ▶ Deep to the surface, the two **medial nasal prominences** also merge to form the **intermaxillary segment**, composed of three parts:
- ▶ A **labial component** → philtrum of the upper lip.
- ▶ An **upper-jaw component** → carries the **4 incisor teeth**.
- ▶ A **palatal component** → the small **triangular primary palate**.
- ▶ The intermaxillary segment is continuous with the rostral part of the **nasal septum** (formed by the frontonasal/frontal prominence).

## 3. Development of the secondary palate

- ▶ **6th week**: shelf-like outgrowths from the **maxillary prominences** — the **palatine shelves** — appear, directed obliquely downward along each side of the tongue (vertical position).
- ▶ **7th–8th week** (~stage 23, day 56–57): the tongue, propelled forward and downward by growth of Meckel's cartilage and the mandible, withdraws from between the shelves; the palatine shelves rapidly **rotate to a horizontal position** above the tongue (aided by hyaluronan-driven mesenchymal swelling) and **fuse in the midline**, forming the **secondary palate**.
- ▶ The shelves also **fuse anteriorly with the triangular primary palate**; the **incisive foramen** is the midline landmark marking the junction between the primary and secondary palate.
- ▶ Simultaneously, the **nasal septum grows down** and joins the newly formed palate from above.
- ▶ Fusion occurs by adherence and **apoptotic breakdown** of the apposed epithelial seam.
- ▶ Palatal shelf elevation occurs **~1 week later in female embryos than in males** — a key reason isolated cleft palate is commoner in females.

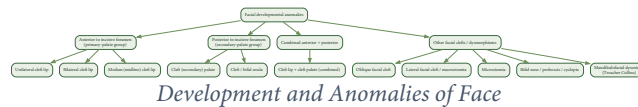
## 4. Development of the nasal cavities

- ▶ During the 6th week, the nasal pits **deepen** by growth of surrounding prominences and penetration into mesenchyme.

- ▶ Each pit is initially separated from the primitive oral cavity by an **oronasal (choanal) membrane**; its breakdown creates the **primitive choanae**, which lie on each side of the midline immediately behind the primary palate.
- ▶ With formation of the secondary palate, the **definitive choanae** come to lie at the junction of the nasal cavity and pharynx.
- ▶ **Paranasal air sinuses** develop as diverticula of the lateral nasal wall, extending into the maxilla, ethmoid, frontal and sphenoid bones; they reach maximum size at **puberty** and contribute to the definitive shape of the face.

## 5. Classification of facial anomalies

□ Fig 12.5 — Cleft lip and cleft palate: unilateral complete cleft palate, bilateral complete cleft palate (bifid uvula), and cleft lip (Sontakke — Textbook of Human Embryology, p.123)



| Anomaly                                          | Embryological basis                                                                                                                                                                                   |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unilateral cleft lip                             | Failure of fusion of the maxillary process with the medial nasal process on one side                                                                                                                  |
| Bilateral cleft lip                              | Failure of fusion of both maxillary processes with the medial nasal prominences                                                                                                                       |
| Median (midline) cleft lip (true hare-lip, rare) | Incomplete merging of the two medial nasal prominences in the midline; not a true line of fusion, so very rare                                                                                        |
| Cleft of lower lip (rare)                        | Failure of the two mandibular prominences to fuse in the midline; usually extends into the jaw                                                                                                        |
| Cleft (secondary) palate / bifid uvula           | Failure of the palatine shelves to fuse — due to shelf smallness, failure of elevation, failure of the fusion process itself, or failure of the tongue to descend (micrognathia)                      |
| Oblique facial cleft                             | Failure of the maxillary process to merge with the lateral nasal process along the line of the naso-lacrimal groove; the nasolacrimal duct is exposed on the surface                                  |
| Macrostomia (abnormally wide mouth)              | Inadequate fusion of the maxillary and mandibular processes; if unilateral, produces a <b>lateral facial cleft</b>                                                                                    |
| Microstomia (abnormally small mouth)             | Excessive fusion of the maxillary and mandibular processes                                                                                                                                            |
| Bifid nose / one-sided nasal aplasia / proboscis | Bifurcation, unilateral absence, or gross deficiency of the frontonasal process; a cylindrical <b>proboscis</b> below the forehead is a rare extreme form, often with <b>cyclopia (synophthalmia)</b> |



| Anomaly                                                                            | Embryological basis                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Holoprosencephaly spectrum</b> (cyclopia, proboscis, midline cleft lip)         | Extensive midline deficiency causing fusion of the eyes and lateral ventricles; linked to <b>SHH gene</b> mutations, disturbed cholesterol biosynthesis, or maternal teratogen exposure (e.g. alcohol) in the <b>3rd week</b> , at the start of neurulation (days 19–21) |
| <b>Mandibulofacial dysostosis</b> (Treacher Collins syndrome, first-arch syndrome) | Under-development of the entire first pharyngeal arch, uni- or bilateral — coloboma of the lower eyelid, hypoplastic maxilla/mandible, flattened cheek, low-set/malformed ear, cleft palate and faulty dentition; <b>autosomal-dominant</b> inheritance                  |
| <b>Retrognathia / agnathia</b>                                                     | Mandibular hypoplasia (receding chin) or, in extreme cases, failure of mandibular development                                                                                                                                                                            |
| <b>Hemifacial micro-/macrosomia</b>                                                | One half of the face under- or over-developed                                                                                                                                                                                                                            |
| <b>Hypertelorism</b>                                                               | Widely separated eyes and a broad nasal bridge from excess tissue in the frontonasal process                                                                                                                                                                             |
| <b>Congenital lip pits / fistulae / double lip</b>                                 | Minor defects of lip fusion                                                                                                                                                                                                                                              |
| <b>Van der Woude syndrome</b>                                                      | Commonest syndrome associated with cleft lip ± cleft palate; autosomal dominant, due to <b>IRF6</b> mutation (1p32–41); ~88% have lower-lip pits                                                                                                                         |

## 6. Genetic and environmental factors

- ▶ Common (non-syndromic) **cleft lip ± cleft palate** is **multifactorial/polygenic**, with combined genetic and environmental causation; it is **genetically distinct** from isolated cleft palate (different pathogenesis, sex ratio, recurrence risk).
- ▶ Recognised environmental contributors: maternal anti-epileptic drugs (notably **valproic acid**), poor peri-conceptional nutrition, viral infection and other teratogens; prenatal vitamins reduce incidence.
- ▶ Facial clefts can occur as part of chromosomal/genetic syndromes — **Pierre Robin sequence**, **DiGeorge syndrome** (22q11 deletion), **Edwards syndrome** (trisomy 18), **Patau syndrome** (trisomy 13) — in addition to Van der Woude and Treacher Collins syndromes (above).

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

- ▶ **Frontal view series (4 panels, progressing 4½ → 10 weeks)** — label: frontonasal prominence, maxillary prominence, mandibular prominence, stomodeum, nasal (olfactory) placode → nasal pit, medial nasal prominence, lateral nasal prominence, naso-optic (nasolacrimal) furrow, philtrum, eye, external ear.
- ▶ **Coronal/frontal section through developing palate (3 panels)** — label: primary palate, palatine shelves (vertical → horizontal), tongue, nasal septum, nasal chamber, oral cavity, fused palatal shelves, incisive foramen, uvula.
- ▶ **Anomaly panel (4 sketches)** — unilateral cleft lip, bilateral cleft lip, oblique facial cleft (line from medial canthus of eye to mouth), and cleft (secondary) palate with bifid uvula — label the line of failed fusion in each.

**Applied / Clinical anatomy**

- ▶ **Unilateral cleft lip:** the nasal septum deviates towards the **non-cleft side**, since the nasolabial, bilabial (orbicularis oris) and labiomental muscle groups on the cleft side fail to insert into the septal tissue/opposite muscles and are displaced inferiorly; the incisor-bearing maxilla is also underdeveloped. The **skin of the entire upper lip is supplied by the maxillary nerve** (the ectoderm of the maxillary process overgrows the frontonasal-derived philtrum mesoderm in the midline).
- ▶ **Cleft (secondary) palate** classically presents in the neonate as **nasal regurgitation of milk** during feeding, with feeding difficulty, failure to thrive, speech defects and recurrent otitis media; prenatal ultrasound at 16–20 weeks can detect the defect.
- ▶ **Submucous cleft palate:** an occult form seen as a median V-shaped notch of the soft palate, causing speech difficulty despite an intact mucosa.
- ▶ **Incisive foramen** is the key surgical/diagnostic landmark separating anterior (primary-palate) from posterior (secondary-palate) cleft groups; **oblique facial cleft** exposes the nasolacrimal duct on the surface.
- ▶ **Surgical correction:** cleft lip is generally repaired in early infancy and cleft palate within the first year of life to minimise speech and hearing sequelae.
- ▶ **Epidemiology** (Gray's Anatomy 41e): cleft lip ± palate **0.5–3.6/1000** live births, **M:F ≈ 2:1**; isolated cleft palate **0.4/1000**, commoner in **females**; true facial clefts are rare (**1/50,000–1/175,000**), often from amniotic-band pressure rather than a primary fusion defect.
- ▶ **Van der Woude syndrome** — the commonest identifiable syndromic cause of cleft lip/palate — should be screened for (lower-lip pits) in any child presenting with a cleft.

**High-yield exam pointers**

- ▶ **Five prominences at 4 weeks** around the stomodeum: 1 unpaired **frontonasal** + paired **maxillary** + paired **mandibular** — all neural-crest-derived.
- ▶ Nasal placodes appear in **week 5**, invaginate → nasal pits → medial + lateral nasal prominences.

- ▶ **Upper lip** = medial nasal + maxillary prominences (lateral nasal prominences do NOT contribute); **lower lip** = mandibular prominences; **nose** = frontonasal + medial nasal + lateral nasal (five processes).
- ▶ **Intermaxillary segment** (fused medial nasal prominences) → philtrum + 4 incisors + primary palate.
- ▶ **Secondary palate** (palatine shelves of maxillary prominences) elevates and fuses by the **7th–8th week**; **incisive foramen** = landmark between primary and secondary palate.
- ▶ **Cleft lip** = maxillary–medial nasal fusion failure; **cleft palate** = palatine shelf fusion/elevation failure; **oblique facial cleft** = maxillary–lateral nasal fusion failure.
- ▶ **Median cleft lip, bifid nose, proboscis, cyclopia** = midline (holoprosencephaly-spectrum) defects linked to **SHH** mutations.
- ▶ **Treacher Collins** = first-arch syndrome, autosomal dominant; **Van der Woude** = commonest CL/P syndrome (IRF6, lower-lip pits).
- ▶ Cleft lip ± palate **0.5–3.6/1000** (M>F); isolated cleft palate **0.4/1000** (F>M).

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; IB Singh Human Embryology (CBME 2021); Larsen Human Embryology 6e; Vishram Singh Textbook of Clinical Embryology — for the embedded plates, Sontakke Textbook of Human Embryology, Fig 12.1 and Fig 12.5.



## Development and Anomalies of Thyroid

*Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The thyroid is the first endocrine gland to appear in the embryo, arising in the third–fourth week as a median endodermal outgrowth from the floor of the primitive pharynx, at the site later marked by the foramen caecum of the tongue. Its two functional cell populations have entirely different embryonic sources — endoderm-derived **follicular cells** that synthesise thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>), and neural-crest-derived **parafollicular (C) cells**, carried in via the ultimobranchial body, that secrete calcitonin. Because the gland originates at the tongue base and must migrate a long distance to its definitive pretracheal position, the great majority of its congenital anomalies are disorders of this descent — of incomplete descent, excessive descent, or persistence of the connecting thyroglossal duct — making the developmental pathway the key to understanding every clinically important anomaly of the gland.

### 1. Site and time of origin

- ▶ The thyroid primordium appears as a **median endodermal thickening** in the floor of the primitive pharynx, immediately caudal to the **tuberculum impar** and between the first and second pharyngeal pouches, dorsal to the aortic sac.

- ▶ It is first identifiable at approximately the **20-somite stage** (Gray's Anatomy), about **24 days post-fertilisation** under FGF signalling (Moore); a distinct diverticulum then appears in the midline furrow **early in the fifth week** (Gray's; Langman), termed the **thyroglossal duct**.
- ▶ Its site is permanently marked in postnatal life by the **foramen caecum**, a pit at the junction of the anterior two-thirds and posterior one-third of the tongue, at the apex of the sulcus terminalis. The thyroid is the **earliest endocrine gland to develop**.

## 2. Descent — the thyroglossal duct pathway

□ Fig 11.13 — ■ *Development of the thyroid gland: ( A ) different stages in the deve (Vishram Singh — Textbook of Anatomy Vol 3 — 4e, p.505)*

- ▶ The thyroid primordium, at first hollow and then a solid cellular mass, elongates caudally as the **thyroglossal duct**, descending in the neck **ventral to the developing hyoid bone** and the pharyngeal/laryngeal cartilages, while the thyroid stays connected to the tongue by this narrow duct.
- ▶ The duct passes **in front of the hyoid bone**, then winds around its **lower border to become briefly retrohyoid**, before continuing caudally with a slight inclination to the left, to reach its definitive **pretracheal position by the end of the seventh week**.
- ▶ At its distal end the duct's tip **bifurcates**, and the resulting bilateral terminal swellings proliferate and expand to form the **two lateral lobes**, joined in the midline by an **isthmus** that comes to lie anterior to the developing second and third tracheal rings.
- ▶ The duct itself normally disintegrates during the fifth–seventh week; the now-isolated gland continues its final descent independently. A portion of duct near its lower end frequently persists as the **pyramidal lobe**, projecting upward from the isthmus (usually to the left) in roughly half of individuals, occasionally tethered to the hyoid by a fibromuscular band, the **levator glandulae thyroideae**.
- ▶ The endoderm-derived epithelium is invested throughout by **vagal neural crest mesenchyme**, forming the capsule, interlobular septa, and perifollicular stroma carrying the neurovascular/lymphatic supply. The gland begins concentrating iodine and secreting hormone by the **end of the third month**.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Reproduce a mid-sagittal schematic of the head and neck showing the pathway of descent, with these labels:

- ▶ Tongue, with foramen caecum at apex of sulcus terminalis (site of origin)
- ▶ Tuberculum impar (adjacent floor-of-pharynx landmark)
- ▶ Body of hyoid bone, with the duct passing ventral to it and winding around its lower border
- ▶ Thyroglossal duct — broken/dotted line tracing the full descent (lingual, suprahyoid, infrahyoid segments)
- ▶ Larynx (thyroid and cricoid cartilages) and upper tracheal rings
- ▶ Definitive thyroid gland — two lateral lobes + isthmus anterior to the 2nd–3rd tracheal rings
- ▶ Pyramidal lobe ascending from the isthmus, with the levator glandulae thyroideae to the hyoid
- ▶ Arrow indicating direction of migration (cranial to caudal)

**3. Dual embryonic origin of thyroid cell types**

| Cell type                             | Embryonic source                                                                                      | Secretion                                                       | Route of incorporation                                                                                              |
|---------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Follicular cells                      | Endoderm of the median thyroid diverticulum (thyroglossal duct)                                       | Thyroxine (T <sub>4</sub> ), triiodothyronine (T <sub>3</sub> ) | Floor of pharynx → foramen caecum → thyroglossal duct → bifurcated distal tip → follicular epithelium of both lobes |
| Parafollicular (C) cells              | Neural crest, via the ultimobranchial body (diverticulum of the caudal pharyngeal complex, 4th pouch) | Calcitonin                                                      | Neural crest cells migrate into the ultimobranchial body, incorporated into the lateral lobes as they form          |
| Capsule, septa, perifollicular stroma | Vagal neural crest mesenchyme                                                                         | —                                                               | Invests the endodermal epithelial primordium throughout its descent                                                 |

- ▶ This dual origin explains the two clinico-pathological tumour families: follicular-cell tumours (papillary/follicular carcinoma) versus **medullary carcinoma**, arising from neural-crest-derived C cells and marked by serum calcitonin.

**4. Histogenesis and onset of function**

- ▶ The primordium, initially a **solid mass of endodermal cells**, breaks up into a network of epithelial cords as it is invaded by surrounding vascular mesenchyme; by the **10th week** the cords

divide into small clusters, each developing a lumen with cells arranged around it as a **thyroid follicle**.

- ▶ During the **11th–12th week**, **colloid** appears within the follicles and iodine-concentrating, hormone-synthesising activity is first demonstrable — the classical "functional by the end of the third month." Fetal **TSH** and **thyroxine** rise from ~20 weeks, reaching adult levels by ~35 weeks.
- ▶ Gray's Anatomy adds three fetal/perinatal maturation stages: **Stage 1** (10–18 wk) — active folliculogenesis, colloid accumulates; **Stage 2** (19–29 wk) — relatively quiescent; **Stage 3** (after 29 wk) — epithelium/colloid ratio rises as follicular size falls, reflecting functional maturation.
- ▶ The neonatal gland is relatively large, with a long narrow isthmus not yet reaching the trachea, attaining about half the adult size by 2 years.

## 5. Molecular and genetic basis

- ▶ Thyroid bud formation and later differentiation depend on a set of transcription factors — **NKX2-1** (also called **TTF-1**), **FOXE1** (also called **TTF-2**) and **PAX8** — together with the **TSH-receptor** (**TSHR**) gene required for later functional maturation.
- ▶ Mutations in these genes are implicated in **thyroid dysgenesis** (agenesis, ectopia, or hypoplasia) and in **dyshormonogenesis**, which together constitute the commonest cause of **congenital hypothyroidism**, affecting approximately **1 in 3500 live births** — the most common congenital endocrine disorder.
- ▶ The caudal pharyngeal complex (4th pouch + ultimobranchial body) is neural-crest-dependent; its disturbance in **22q11.2 deletion (DiGeorge) syndrome** can also affect thyroid development, alongside the syndrome's better-known thymic/parathyroid defects.

## 6. Classification of congenital anomalies of the thyroid

□ Fig 11.11 — Anomalies of the position of the thyroid gland and locations of the th (Sontakke — Textbook of Human Embryology, p.115)

| Category           | Anomaly                              | Description                                                                                                                                                                                                                                                       |
|--------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Incomplete descent | Lingual thyroid                      | Base of tongue, under the mucosa or within the muscles, just deep to the foramen caecum; <b>commonest</b> site of ectopic thyroid tissue (up to ~10% of autopsies); may cause infantile dysphagia and may be the patient's <b>only</b> functioning thyroid tissue |
|                    | Suprahyoid / infrahyoid thyroid      | Midline neck tissue at, above, or just below the hyoid but superior to the normal pretracheal site                                                                                                                                                                |
| Excessive descent  | Retrosternal / intrathoracic thyroid | Whole gland, or part of it, descends beyond its usual site into the superior mediastinum                                                                                                                                                                          |

| Category                             | Anomaly                            | Description                                                                                                                                                                                                                                      |
|--------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Persistence of the thyroglossal duct | Thyroglossal cyst ( $\pm$ fistula) | Duct remnant persists anywhere along its course, always close to/in the midline; usually noticed by ~5 years; a painless, enlarging, mobile swelling; infection/rupture produces a fistula onto the neck skin; rarely undergoes malignant change |
| Ectopic/aberrant thyroid tissue      | Ectopic thyroid                    | Nodules away from the normal duct course — described in the larynx, trachea, oesophagus, pericardium, even the ovary                                                                                                                             |
|                                      | "Lateral aberrant thyroid"         | Now recognised <b>not</b> to be a true developmental rest — cervical lymph-node thyroid tissue of this kind is metastasis from an occult (usually <1.5 cm) papillary carcinoma                                                                   |
| Anomalies of lobation/number         | Thyroid hemiagenesis               | One lateral lobe (commonly the left) fails to develop; the isthmus may also be absent                                                                                                                                                            |
|                                      | Pyramidal lobe variants            | Persistent distal duct remnant, unusually long/short/detached (present in ~50% normally)                                                                                                                                                         |
|                                      | Accessory thyroid nodules          | Small extra nodules near the main gland, usually insufficient alone to maintain euthyroidism if it is removed                                                                                                                                    |
| Agensis / functional                 | Athyreosis (thyroid agenesis)      | Complete absence of thyroid tissue — an important cause of congenital hypothyroidism/cretinism, alongside dysgenesis and dyshormonogenesis                                                                                                       |

## Applied / Clinical anatomy

- **Thyroglossal cyst vs other neck swellings:** because the duct remnant remains attached, via the foramen caecum region, to the body of the hyoid, a thyroglossal cyst characteristically moves upward on protrusion of the tongue and on swallowing — the classical distinguishing sign from other midline/lateral neck swellings.
- **Surgical excision (Sistrunk's operation):** since the duct is intimately related to the hyoid, safe excision of a thyroglossal cyst/fistula requires removal of the **central part of the hyoid bone** with the tract; leaving any remnant is the chief cause of recurrence.
- **Lingual/ectopic thyroid before excision:** because it may be the patient's **only** functioning thyroid tissue, radionuclide scanning ( $^{99m}\text{Tc}$ -pertechnetate/ $^{123}\text{I}$ ) is mandatory before excision — otherwise the patient is left permanently hypothyroid.



- ▶ **Lateral aberrant thyroid rule:** apparent ectopic thyroid tissue in a lateral cervical lymph node is treated as **metastatic papillary carcinoma** from an occult primary, not as a developmental rest — a distinction with direct surgical/oncological consequences.
- ▶ **Retrosternal goitre:** excessive descent along the same pathway can carry an enlarging gland into the superior mediastinum, compressing the trachea or great veins.
- ▶ **Congenital hypothyroidism screening:** since thyroid dysgenesis (NKX2-1/PAX8/FOXE1/TSHR defects) is the leading cause, neonatal TSH/T4 screening targets exactly the defects above, preventing the neurodevelopmental damage of untreated cretinism.

### High-yield exam pointers

- ▶ Thyroid = first endocrine gland to appear (median endodermal thickening, floor of pharynx, 3rd–4th week) and first to become functional (by the 3rd month).
- ▶ Foramen caecum = permanent adult marker of the site of origin, at the apex of the sulcus terminalis.
- ▶ Descends as the thyroglossal duct, ventral to the hyoid, briefly retrohyoid, reaching the definitive pretracheal position (anterior to the 2nd–3rd tracheal rings) by the end of the 7th week.
- ▶ Dual origin: **follicular cells** from endoderm (make T3/T4); **parafollicular/C cells** from neural crest via the ultimobranchial body (make calcitonin).
- ▶ Pyramidal lobe = persistent distal duct remnant, present in ~50% of people.
- ▶ Thyroglossal cyst/fistula = commonest anomaly of duct persistence; always near/in the midline; moves with tongue protrusion and swallowing; treated by Sistrunk's operation (excise with central hyoid).
- ▶ Lingual thyroid = commonest site of ectopic thyroid tissue; may be the only functioning thyroid tissue present — confirm with a radionuclide scan before removal.
- ▶ "Lateral aberrant thyroid" is a misnomer — it is occult papillary carcinoma metastasis, not a developmental rest.
- ▶ Genes NKX2-1 (TTF-1), FOXE1 (TTF-2), PAX8 and TSHR underlie thyroid dysgenesis, the commonest cause of congenital hypothyroidism (~1 in 3500 births).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Moore's The Developing Human 9e; Vishram Singh's Textbook of Clinical Embryology; Vishram Singh's Textbook of Anatomy Vol 3 (4e); Sontakke's Textbook of Human Embryology; BD Chaurasia's Human Anatomy Vol 3–4 (8e).



## Development of tongue with its Nerve supply

*Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy*

**Definition/Introduction** — The tongue develops in the floor of the primitive pharynx from **five mesenchymal swellings** related to the first four pharyngeal arches (mucosa) and the **occipital myotomes** (musculature). Because different parts of the tongue are contributed by different arches, and the muscle mass migrates in from the occipital somites, the mature nerve supply of the tongue is a direct read-out of its embryology — a single structure ends up innervated by four cranial nerves (V, VII, IX, X) for sensation/taste and a fifth (XII) for motor function. This embryological correlation is the crux of the question and is best answered together, as done below.

### 1. Primordia in the floor of the pharynx (end of 4th week)

- ▶ A small median triangular swelling, the **tuberculum impar**, appears in the floor of the primitive pharynx just rostral to the **foramen cecum** (a landmark that later marks the site of origin of the thyroid diverticulum).
- ▶ Two oval **lateral lingual swellings** (distal tongue buds) appear one on each side of the tuberculum impar, arising from proliferating **neural-crest-derived mesenchyme** of the 1st (mandibular) pharyngeal arch.
- ▶ Caudal to the tuberculum impar, a second median swelling — the **hypobranchial eminence (copula of His)** — develops in relation to the **2nd, 3rd and 4th arches**, and soon subdivides into a larger **cranial part** (2nd/3rd arch) and a smaller **caudal part** (4th arch).
- ▶ **Five sources** in total contribute to the definitive tongue: the two lateral lingual swellings, the tuberculum impar, and the cranial and caudal parts of the hypobranchial eminence — plus myoblasts from the occipital myotomes for muscle.

### 2. Formation of the anterior two-thirds (oral part/body)

- ▶ The two **lateral lingual swellings** rapidly enlarge, overgrow the tuberculum impar, and **fuse with each other in the midline** to form the **anterior two-thirds (body)** of the tongue.
- ▶ The line of fusion is marked on the surface by the **median sulcus** and, internally, by the fibrous **lingual septum**.
- ▶ The **tuberculum impar does not form any recognisable part** of the adult tongue — it is simply overgrown.
- ▶ The mucosa covering the body of the tongue is derived from the endoderm lining the floor of the pharynx in relation to the **1st pharyngeal arch**.

### 3. Formation of the posterior one-third (pharyngeal part/root) and epiglottis

- ▶ The **copula** (2nd-arch component of the hypobranchial eminence) is progressively **overgrown and buried** by the rapidly expanding 3rd-arch mesenchyme, which fuses with the 1st-arch mesenchyme anteriorly — the 2nd arch is thereby **excluded from the tongue surface**.
- ▶ The **cranial part of the hypobranchial eminence** (3rd arch) forms the **posterior one-third of the tongue, including the circumvallate papillae**.

- ▶ The caudal part of the hypobranchial eminence (4th arch) forms the extreme posterior-most part of the tongue and the epiglottis.
- ▶ The junction between the anterior two-thirds and posterior one-third is marked by a V-shaped groove, the sulcus (terminal sulcus), whose apex points to the foramen cecum.

#### 4. Development of the tongue musculature

- ▶ Almost all tongue muscles (extrinsic and intrinsic) are formed by myoblasts that migrate from the occipital myotomes into the developing tongue.
- ▶ The hypoglossal nerve (XII), the nerve supplying the occipital myotomes, accompanies these myoblasts during their migration — this explains both the motor nerve supply of the tongue and the curved, looping course of the hypoglossal nerve in the neck.
- ▶ Exception — palatoglossus: this muscle arises from unsegmented mesenchyme of the pharyngeal (branchial) arches, not from occipital somites, and is accordingly supplied by the vagus nerve via the pharyngeal plexus, not by the hypoglossal nerve.
- ▶ The fibroareolar connective-tissue septa binding the tongue muscles together develop from the mesenchyme of the pharyngeal arches.

#### 5. Nerve supply of the tongue correlated with development

| Part of tongue                                | Embryonic source (arch)                           | General sensation                                                      | Taste (special sensation)              |
|-----------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------|----------------------------------------|
| Anterior 2/3 (body)                           | 1st arch — lingual swellings                      | Lingual nerve (mandibular div. of trigeminal, V)                       | Chorda tympani (branch of facial, VII) |
| Posterior 1/3, incl. circumvallate papillae   | 3rd arch — cranial part of hypobranchial eminence | Glossopharyngeal nerve (IX)                                            | Glossopharyngeal nerve (IX)            |
| Extreme posterior part + epiglottis/vallecula | 4th arch — caudal part of hypobranchial eminence  | Internal laryngeal nerve (branch of superior laryngeal, from vagus, X) | Internal laryngeal nerve (X)           |

| Muscles of tongue                | Embryonic source                       | Motor nerve                           |
|----------------------------------|----------------------------------------|---------------------------------------|
| All muscles except palatoglossus | Occipital myotomes                     | Hypoglossal nerve (XII)               |
| Palatoglossus                    | Unsegmented pharyngeal-arch mesenchyme | Vagus nerve via pharyngeal plexus (X) |

- ▶ Although the facial nerve is the nerve of the 2nd arch, it does not supply general sensation anywhere in the tongue — because the 2nd-arch component (copula) is buried and excluded from the surface. Its chorda tympani branch alone reaches the tongue, carrying only taste fibres to the anterior two-thirds, since taste buds are induced wherever gustatory nerve fibres invade the epithelium, independent of which arch contributed that mucosa.

- ▶ The **circumvallate papillae**, though lying along the terminal sulcus (i.e., close to the anterior part), are innervated by the **glossopharyngeal nerve** because the mucosa there is 3rd-arch (posterior-third) in origin — it is pulled slightly forward as the tongue enlarges.
- ▶ Mnemonic correlation: **arch 1→V**, **arch 2→VII (taste only)**, **arch 3→IX**, **arch 4→X**, and **occipital myotomes→XII** (except palatoglossus→X).

□ Fig 17.11 — Development of tongue (BD Chaurasia — Human Anatomy Vol 3-4 — 8e, p.324)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the floor of the primitive pharynx (dorsal/ventral view) at the 5th week and label:

- ▶ **Tuberculum impar**, two lateral lingual swellings (1st arch) → anterior 2/3
- ▶ **Copula** (2nd arch, buried) with an arrow showing 3rd arch overgrowing it
- ▶ **Hypobranchial eminence** — cranial part (3rd arch) → posterior 1/3 + circumvallate papillae; caudal part (4th arch) → extreme posterior part + epiglottis
- ▶ **Foramen cecum** and the **terminal (sulcus terminalis)** groove between the two parts
- ▶ Occipital myotomes with the **hypoglossal nerve** looping into the tongue (motor)



## 6. Lingual papillae and taste buds

- ▶ Four types of papillae differentiate over the dorsum: **filiform** (general sensation only, no taste buds), **fungiform**, **circumvallate**, and **foliate**.
- ▶ **Taste buds** differentiate around the **11th–13th week** of intrauterine life by **inductive interaction** between the tongue epithelium and invading **gustatory nerve fibres** carried by the chorda tympani, glossopharyngeal, and (superior) laryngeal nerves.
- ▶ **Reflex pathways** linking taste buds to the muscles of facial expression are established by about the **26th–28th week**, evidenced by fetal facial grimacing responses to bitter-tasting substances introduced into amniotic fluid.

## 7. Positional changes and relation to the floor of the mouth

- ▶ The ventral surface of the developing tongue is initially attached to the floor of the mouth; this attachment **regresses anteriorly**, freeing the tip and body, but **persists posteriorly** as the **frenulum linguae**. Failure of this regression produces **ankyloglossia (tongue-tie)**.
- ▶ On either side, a **linguogingival sulcus** develops, separating the tongue from the lower jaw/cheek region derived from the same mandibular-process mesenchyme.
- ▶ At birth, both anterior and posterior parts of the tongue lie within the **oral cavity**; the posterior third **descends into the oropharynx by about 4 years of age**, becoming the anterior wall of the oropharynx — so in the adult the oral part lies in the mouth and the pharyngeal part in the oropharynx.

## Applied / Clinical anatomy

- ▶ **Ankyloglossia (tongue-tie)**: frenulum extends onto the tip of the tongue, restricting protrusion and impairing articulation; an **ankyloglossia superior** variant leaves the tongue adherent to the palate.
- ▶ **Bifid tongue**: failure of fusion of the two lateral lingual swellings, splitting the anterior tongue.
- ▶ **Aglossia** (complete absence, from failure of primordia to develop), **hemiglossia** (failure of one lingual swelling), **microglossia**, and **macroglossia** are the spectrum of size/number anomalies.
- ▶ **Lingual thyroid**: ectopic thyroid tissue retained in the tongue (under the mucosa or within the muscles) near the foramen cecum, due to failure of the thyroid primordium to descend fully — may be the patient's *only* functioning thyroid tissue.
- ▶ **Thyroglossal duct cyst**: a remnant of the thyroglossal duct (which connects the descending thyroid to its origin at the foramen cecum) persisting anywhere along the duct's path in the midline of the neck; characteristically moves upward on tongue protrusion.
- ▶ **Pierre Robin sequence**: primary mandibular hypoplasia (micrognathia) causes **glossoptosis** (a posteriorly placed tongue) that mechanically obstructs elevation/fusion of the palatal shelves, producing a **secondary (U-shaped) cleft palate** — the classic triad is micrognathia, glossoptosis, and cleft palate.
- ▶ **Down syndrome**: fissuring of the tongue with hypertrophy of the lingual papillae is a recognised feature.
- ▶ **"Beer drinker's nerve"**: the **internal laryngeal nerve** carries taste from the extreme posterior tongue/vallecula — the site where bitter beer is best appreciated, a favourite viva pearl linking development to clinical taste testing.
- ▶ **Lingual nerve block / anaesthesia**: knowledge of the developmental split (V3 for the body, IX for the root) explains why anaesthetising the lingual nerve alone abolishes sensation only over the anterior two-thirds, and why gag reflex testing (afferent limb glossopharyngeal) probes the posterior tongue/pharynx.

## High-yield exam pointers

- ▶ Tongue develops from **5 sources**: tuberculum impar + 2 lingual swellings (1st arch) → anterior 2/3; hypobranchial eminence cranial part (3rd arch) → posterior 1/3; caudal part (4th arch) → posterior-most part + epiglottis; occipital myotomes → muscles.
- ▶ **2nd arch (copula) is buried** by the overgrowing 3rd arch — hence facial nerve gives **no general sensation** to the tongue, only taste (via chorda tympani) to the anterior two-thirds.
- ▶ **Nerve of each part = nerve of the arch it comes from**: 1st→lingual n.(V3)/chorda tympani(VII), 3rd→glossopharyngeal(IX), 4th→internal laryngeal(X, "beer drinker's nerve").
- ▶ **Motor supply = hypoglossal (XII)** for all muscles except **palatoglossus (vagus, pharyngeal plexus)**, because palatoglossus alone is not derived from occipital myotomes.
- ▶ **Circumvallate papillae**, despite sitting near the terminal sulcus, are supplied by **glossopharyngeal (IX)** — 3rd-arch/posterior-third territory.
- ▶ Taste buds appear at **11–13 weeks**; reflex taste–facial pathways functional by **26–28 weeks**.

- Foramen cecum = site of thyroid origin; terminal sulcus = surface line between anterior 2/3 and posterior 1/3.
- Key anomalies: ankyloglossia, bifid tongue, aglossia/hemiglossia, lingual thyroid, thyroglossal cyst, Pierre Robin sequence (micrognathia → glossoptosis → cleft palate).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Larsen Human Embryology 6e; Vishram Singh Textbook of Clinical Embryology; BD Chaurasia Human Anatomy Vol 3-4 8e.



## Development of Upper Lip

Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy

**Definition / Introduction** The upper lip forms around the **stomodeum** (primitive mouth) between the 4th and 7th weeks of intra-uterine life, by progressive medial growth and fusion of the **frontonasal process** with the two **maxillary processes** of the first pharyngeal arch. Classically it is built from the two **medial nasal processes** (median part, the philtrum) and the two **maxillary processes** (lateral parts); more recent evidence indicates the entire lip surface, including the philtrum, is ectoderally maxillary-derived, overgrowing the deeper frontonasal contribution. This dual description — and its consequence for sensory nerve supply — is the classic "**developmental enigma of the upper lip**", and explains the embryological basis of cleft lip, the commonest craniofacial congenital anomaly.

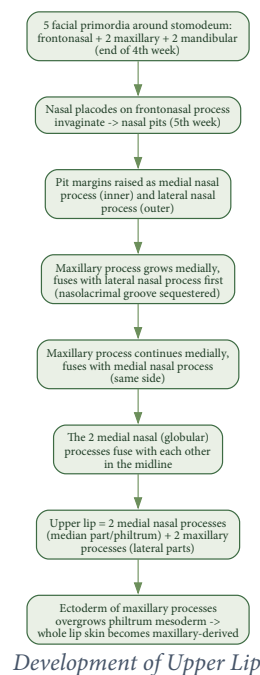
### 1. Facial primordia and the nasal processes

| Week (IUL)                           | Event                                                                                                                                                                                                                                                               |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End of 4th week                      | Five facial primordia appear around the stomodeum: unpaired <b>frontonasal process</b> (mesenchyme ventral to the forebrain) and paired <b>maxillary</b> and <b>mandibular processes</b> of the first pharyngeal arch                                               |
| 4th–5th week                         | Bilateral ectodermal thickenings, the <b>nasal (olfactory) placodes</b> , appear on the frontonasal process under inductive influence of the ventral forebrain                                                                                                      |
| 5th week                             | Placodes invaginate to form <b>nasal pits</b> ; the raised margin of each pit differentiates into an inner <b>medial nasal process</b> and an outer <b>lateral nasal process</b>                                                                                    |
| 6th–7th week (Carnegie stages 16–17) | Maxillary processes enlarge and grow medially below the developing eye, making contact with, and progressively fusing with, the lateral and then the medial nasal process of the same side; the two medial nasal processes also fuse with each other in the midline |

| Week (IUL)                     | Event                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| By ~7th–8th week (stage 20–23) | Fusion complete; upper lip, nostrils and philtrum acquire adult configuration — the face becomes "recognisably human" |

## 2. Sequence forming the upper lip

- ▶ Each **maxillary process** grows medially beneath the developing eye. It is initially separated from the **lateral nasal process** by a deep furrow, the **naso-optic (nasolacrimal) groove**; ectoderm in the floor of this groove forms a solid epithelial thickening (the lacrimal lamina) that sinks in and later canalises to form the **nasolacrimal duct and sac** (patent by about the 10th week).
- ▶ Once this epithelial cord has separated, the maxillary process fuses with the **lateral nasal process** — a comparatively simple fusion that "rarely gives rise to abnormality" — completing the ala of the nose and the upper part of the cheek. **The lateral nasal process takes no part in forming the upper lip.**
- ▶ The maxillary process then continues growing medially and fuses with the **medial nasal process** of the same side, uniting the premaxillary and maxillary parts of the upper jaw and lip. Failure of this fusion, on one or both sides, is the embryological basis of **cleft lip**.
- ▶ Meanwhile, each medial nasal process extends toward the stomodeum as a **globular process**; the two globular processes, initially separated by a small triangular notch, fuse with each other in the midline.
- ▶ **Net (classical) result: the upper lip = the two medial nasal processes (median part / philtrum) + the two maxillary processes (lateral parts).** The lower lip and jaw form separately, by fusion of the two mandibular processes in the midline, and take no part in this scheme.



□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences (Sontakke — Textbook of Human Embryology, p.118)



### 3. The intermaxillary segment — deep continuation of the median part

- ▶ As the two medial nasal processes merge, they do so not only at the surface but also at a deeper level, forming the **intermaxillary segment**, which has three components:

| Component            | Structure formed                           |
|----------------------|--------------------------------------------|
| Labial               | Philtrum of the upper lip                  |
| Upper-jaw (alveolar) | Premaxilla, bearing the four incisor teeth |
| Palatal              | Small, triangular <b>primary palate</b>    |

- ▶ The intermaxillary segment is continuous above with the rostral part of the **nasal septum** (also frontonasal-derived), and below, at the **incisive foramen**, with the **secondary palate** formed from the palatine shelves of the maxillary processes — the subsequent fusion of the secondary palate is a separate developmental event (see Development/Cleft of the Palate).

### 4. The "developmental enigma": classical vs current concept, and nerve supply

| Aspect                              | Classical description                                                                                                                                                                                                     | Current / recent concept (Frazer)                                                                                                                                                                                                                                                                               |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Median part (philtrum)              | Formed by the fused globular processes of the two medial nasal processes — frontonasal in origin                                                                                                                          | Frontonasal (globular) processes grow <b>deeply</b> to form only the premaxilla/primary palate; the visible philtrum surface is provided by <b>medial extensions of the maxillary processes</b>                                                                                                                 |
| Mechanism explaining nerve mismatch | Ectoderm overlying the maxillary processes <b>overgrows</b> the mesoderm of the philtrum, so the skin of the whole lip becomes maxillary-derived even though frontonasal mesenchyme persists deep to it as the premaxilla | Upper lip regarded as <b>entirely maxillary</b> in origin; Gray's Anatomy instead describes the frontonasal process contributing the surface epithelium of the philtrum, with the <b>maxillary nerve later invading</b> this territory, so trigeminal distribution does not coincide exactly with tissue origin |
| Shared conclusion                   | <b>The whole upper lip, including the philtrum, is supplied by the maxillary division of the trigeminal nerve (V2)</b>                                                                                                    | Same                                                                                                                                                                                                                                                                                                            |

- ▶ Corollary — nerve territories of the face follow the developmental primordia: **forehead and external nose** — ophthalmic nerve (V1); **upper part of cheek and entire upper lip** — maxillary nerve (V2); **lower lip, chin and lower part of cheek** — mandibular nerve (V3).

### 5. Muscle and vestibule of the lip

- ▶ The musculature of the lip (**orbicularis oris** and other muscles of facial expression) is derived from mesenchyme of the **second pharyngeal (hyoid) arch**, and is therefore supplied by the **facial nerve (VII)** — the trigeminal nerve here is purely sensory.

- ▶ A linear ectodermal thickening, the **labiokingival lamina**, grows into the mesenchyme of the primordial jaw to demarcate the lip/cheek from the gum. Most of the lamina degenerates to form the **labiokingival groove** (the future oral **vestibule**); a small area persists in the midline to form the **frenulum of the upper lip**.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the classical composite scheme of face development (as in the embedded plate), with these exact labels at each stage:

- ▶ **Early stage (4th–5th week):** stomodeum, frontonasal process, nasal (olfactory) placode → nasal pit, medial nasal process, lateral nasal process, maxillary process, mandibular process.
- ▶ **Fusion stage (6th–7th week):** naso-optic (nasolacrimal) groove, line of fusion of maxillary process with lateral nasal process, line of fusion of maxillary process with medial nasal process, globular process of medial nasal process, triangular notch between globular processes, fusion of mandibular processes.
- ▶ **Final labelled face:** frontonasal-process territory (forehead, external nose), philtrum, lateral part of upper lip, upper lip, lower lip, angle of mouth (junction of maxillary and mandibular processes), anterior nares.

### Applied / Clinical anatomy

- ▶ **Cleft lip** is the commonest craniofacial congenital anomaly; incidence  $\approx$  **1 in 1000** live births, with **60–80% of affected infants male**.
- ▶ **Unilateral cleft lip** (commonest type) — failure of fusion of the maxillary process with the medial nasal process of the same side; the gap lies between the philtrum and the lateral part of the lip. In an incomplete cleft, a residual bridge of tissue may persist across the defect (**Simonart's band**).
- ▶ **Bilateral cleft lip** — failure of fusion of both maxillary processes with the frontonasal (medial nasal) processes; in complete bilateral clefts with alveolar involvement, the median palatal process (premaxilla) may hang free and project anteriorly.
- ▶ **Median (mid-line) cleft lip / "hare lip"** — rare; results from a mesenchymal deficiency causing partial or complete failure of the two medial nasal (globular) processes to merge in the midline; it is a feature of the autosomal-recessive **Mohr syndrome**.
- ▶ **Oblique facial (naso-ocular) cleft** — rare, usually bilateral; due to failure of the maxillary process to fuse with the lateral nasal process; the fissure runs from the medial angle of the eye to the upper lip and exposes the nasolacrimal duct.
- ▶ Because the upper lip and the premaxilla/primary palate share the same fusion event (maxillary process with medial nasal process), cleft lip is frequently accompanied by clefting of the alveolus and primary palate — always **anterior to the incisive foramen** (as opposed to posterior/secondary-palate clefts, which arise from a separate, later fusion event).
- ▶ **Microstomia and macrostomia** — the angle of the mouth is established at the line of fusion between the maxillary and mandibular processes; excessive fusion narrows the mouth (microstomia) and arrested/failed fusion widens it (macrostomia, e.g., lateral facial cleft).

- ▶ Functional consequences of unrepaired cleft lip: cosmetic disfigurement, discontinuity of the orbicularis oris (impairing pursing/sucking of the lips), difficulty in suckling, and interference with speech, particularly formation of consonants such as D, T and G; associated dental malalignment when the alveolus is involved.
- ▶ Aetiology is predominantly **multifactorial inheritance** (combined genetic and environmental factors); teratogenic risk is well documented with maternal anticonvulsant use, especially **phenytoin**, which raises the incidence two- to three-fold.
- ▶ Antenatal diagnosis by **ultrasonography** is possible once fetal facial features are established, from the early second trimester onward.

### High-yield exam pointers

- ▶ Five facial primordia (4th week): frontonasal + 2 maxillary + 2 mandibular, around the stomodeum.
- ▶ Classical rule: **upper lip = 2 medial nasal processes (philtrum) + 2 maxillary processes (lateral parts)**; lateral nasal process forms only the ala of the nose/cheek, never the lip.
- ▶ Recent/Frazer concept: upper lip skin is **entirely maxillary-derived** by overgrowth; medial nasal (frontonasal) contribution is limited to deep premaxilla/primary palate.
- ▶ Either way — **whole upper lip (median + lateral) is supplied by the maxillary nerve (V2)**; muscles of the lip are supplied by the **facial nerve (VII)**, being 2nd-arch derivatives.
- ▶ Intermaxillary segment = philtrum + premaxilla (4 incisors) + primary palate; continuous with the nasal septum above and the secondary palate below at the incisive foramen.
- ▶ Fusion of maxillary with lateral nasal process is simple and rarely fails; fusion of maxillary with medial nasal process is the fusion whose failure causes cleft lip.
- ▶ Cleft lip: commonest craniofacial anomaly, 1:1000, 60–80% male; unilateral commonest, bilateral and median (Mohr syndrome) types also occur.
- ▶ Labiogingival lamina → labiogingival groove (vestibule) + frenulum of upper lip.
- ▶ Fusion of the upper lip is essentially complete by about the 7th week (Carnegie stage 20–23).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Development of Upper lip and its Anomalies

Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** The upper lip is a composite structure formed between the 4th and 7th weeks of intrauterine life by fusion of the paired **maxillary prominences** (of the first pharyngeal arch) with the paired **medial nasal prominences** derived from the **frontonasal process**, around the margins of the primitive mouth (stomodeum). The lateral nasal prominences take no part in lip formation. Because this fusion involves several separate mesenchymal masses meeting in the midline and bilaterally, it is the commonest site of failure in craniofacial development — **cleft lip**, with or without cleft palate, is the most common congenital facial anomaly in humans.

### 1. Facial primordia around the stomodeum (end of 4th week)

| Facial process                             | Origin                                                                    | Forms                                                                                      |
|--------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Frontonasal process                        | Mesenchyme ventral to the forebrain vesicle                               | Forehead; external nose; nasal septum; (with medial nasal processes) philtrum of upper lip |
| Maxillary process (paired, from 1st arch)  | Neural-crest mesenchyme of the maxillary extension of the mandibular arch | Lateral part of upper lip; upper cheek; maxilla; zygomatic bone; part of temporal bone     |
| Mandibular process (paired, from 1st arch) | Neural-crest mesenchyme, ventral part of 1st arch                         | Lower lip; chin; lower cheek; mandible (via Meckel's cartilage)                            |

- By stage 12 (~4 weeks) neural crest migration into the mandibular and maxillary components is complete; the three trigeminal divisions begin to grow into the frontonasal, maxillary and mandibular territories they will later innervate.
- Mandibular prominences fuse across the midline first, forming the lower lip, chin and lower cheek — well before the upper lip is completed.

### 2. Formation of nasal placodes, pits and nasal prominences (5th–6th week)

- Paired thickenings of surface ectoderm — the **nasal (olfactory) placodes** — appear on the ventrolateral frontonasal process under inductive influence of the forebrain.
- During the 5th week each placode **invaginates** to form a **nasal pit**, throwing up a horseshoe-shaped ridge of mesenchyme around it.
- The **medial limb** of this ridge is the **medial nasal process**; the **lateral limb** is the **lateral nasal process**.
- The maxillary prominences enlarge and grow medially below the developing eyes during the 6th–7th weeks, progressively narrowing the gap between the nasal pits and compressing the medial nasal processes toward the midline.

### 3. Formation of the upper lip (6th–7th week)

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences (Sontakke — Textbook of Human Embryology, p.118)

- ▶ As the maxillary processes grow medially, the shallow groove separating each of them from the corresponding medial nasal process is obliterated and the two **fuse**, on each side.
- ▶ The **upper lip is therefore formed from four elements**: the two medial nasal processes (contributing the median part/philtrum) and the two maxillary processes (contributing the lateral parts).
- ▶ The **lateral nasal processes take no part in forming the lip** — they go on to form the **alae of the nose**; the space between the maxillary and lateral nasal processes (the nasolacrimal groove) instead gives rise to the nasolacrimal duct.
- ▶ By stage 20 (7–8 weeks) the face is recognisably human, though proportions continue to change with subsequent growth.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce the four-panel sequence (stomodeum stage → nasal placode/pit stage → medial/lateral nasal process stage → completed face), labelling: **Frontonasal process**, **Lens placode**, **Olfactory (nasal) placode**, **Stomodeum**, **Mandibular process (1st arch)**, **Perforated oropharyngeal membrane**, **Maxillary process**, **Medial nasal process**, **Lateral nasal process**, **Nasal pit**, **Naso-optic furrow**, **Developing eyelids**, **Anterior nares**, **Philtrum of lip**, **Upper lip**, **Lower lip**.

### 4. The intermaxillary segment

Deeper (not merely surface) fusion of the two medial nasal processes produces a single midline block of tissue, the **intermaxillary segment**, continuous above with the rostral nasal septum (frontonasal-derived).

| Component of intermaxillary segment | Derivative                                       |
|-------------------------------------|--------------------------------------------------|
| Labial component                    | <b>Philtrum</b> of the upper lip                 |
| Upper jaw component                 | Premaxilla bearing the <b>four incisor teeth</b> |
| Palatal component                   | Triangular <b>primary palate</b>                 |

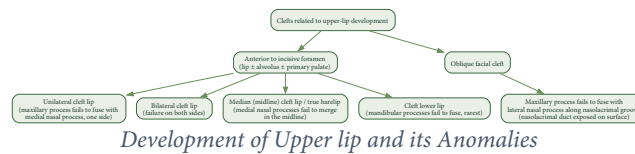
### 5. The "developmental enigma" of the upper lip

- ▶ Mesodermally, the **median part (philtrum)** is derived from the frontonasal/medial-nasal mesenchyme, while the **lateral parts** are derived from maxillary-process mesenchyme.
- ▶ However, the ectoderm covering the maxillary processes **overgrows** the mesenchymal mass of the philtrum, so that the **skin over the entire upper lip — including the philtrum — is maxillary-process ectoderm**.
- ▶ This explains why the **sensory nerve supply of the whole upper lip is from the maxillary nerve (CN V2)** alone, even though part of its mesenchymal core is frontonasal in origin — an apparent paradox resolved only by this overgrowth of maxillary skin.
- ▶ **Frazer's view**: the entire visible upper lip develops from the maxillary processes; the frontonasal (globular) contribution grows deep to form the premaxilla/primary palate — a view supported by the uniform maxillary-nerve innervation.

## 6. Related fusions sharing the same mechanism

- ▶ **Nasolacrimal duct:** the ectodermal cord in the floor of the nasolacrimal groove (between maxillary and lateral nasal processes) canalises to form the duct; only after this does the maxillary process fuse with the lateral nasal process (failure here causes oblique facial cleft).
- ▶ **Secondary palate:** paired **palatine shelves** grow from the maxillary processes from the 6th week, rotate to a horizontal position above the tongue by about the 8th week (Carnegie stage 23), and fuse with each other and with the primary palate/nasal septum in the midline.
- ▶ **Critical period of palate development:** end of the 6th week to the beginning of the 9th week — the window during which disturbance produces cleft palate.

## 7. Classification of anomalies (cleft lip and related clefts)



| Anomaly                                   | Embryological basis                                                                                                                        | Notes                                                                                                                                                                            |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unilateral cleft lip                      | Failure of fusion of maxillary process with medial nasal process on one side                                                               | <b>Commonest</b> type; often extends through the alveolus (between lateral incisor and canine) to the incisive foramen and into the primary palate                               |
| Bilateral cleft lip                       | Failure of fusion of both maxillary processes with the medial nasal processes                                                              | Often combined with a protruding premaxilla                                                                                                                                      |
| Median (midline) cleft lip / true harelip | Incomplete merging of the two medial nasal processes in the midline, or defective development of the philtrum from the frontonasal process | <b>Rare</b> ; not a normal line of fusion — associated with holoprosencephaly and SHH-gene mutations; may show a single central maxillary incisor, microcephaly and hypotelorism |
| Cleft lower lip                           | Mandibular processes fail to fuse in the midline                                                                                           | <b>Rarest</b> variety of lip cleft                                                                                                                                               |
| Oblique facial cleft                      | Maxillary process fails to fuse with the lateral nasal process along the nasolacrimal groove                                               | Nasolacrimal duct left exposed on the surface; uncommon                                                                                                                          |

## Applied / Clinical anatomy

□ Fig 12.15 — Congenital anomalies of cleft lip and cleft palate. A. Infant with uni (Vishram Singh — Textbook of Clinical Embryology, p.150)

- ▶ **Incidence:** cleft lip with or without cleft palate occurs in roughly 1 in 700–1000 live births overall (population range about 0.5–3.6/1000), with a **male preponderance (approximately 2:1; 60–80% male in Indian series)**. Incidence is highest in Asian and Native American populations (~3.5/1000) and lowest in African-Americans (~1/1000).

- ▶ **Isolated cleft palate** is genetically and pathogenetically **distinct** from cleft lip/palate, is less common (~1/1500 births), and shows a **female preponderance** (~55%), attributed to palatal-shelf fusion occurring about a week later in females, coinciding with the period of tongue withdrawal.
- ▶ **Association with cleft palate**: because the lip, alveolus and primary palate share the same developmental sources and timing, severe cleft lip commonly extends into cleft of the primary and/or secondary palate.
- ▶ **Muscular consequences (unilateral cleft lip)**: the nasolabial, bilabial (orbicularis oris) and labiomental muscle groups on the cleft side fail to insert into the muscles of the sound side or the nasal septal tissues; this deviates the nasal septum toward the **non-cleft side**, displaces the muscle groups inferiorly, and is accompanied by underdevelopment of the incisor-bearing maxilla.
- ▶ **Genetic associations**: most cases of cleft lip ± cleft palate are **multifactorial** (the commonest cause — combined genetic and environmental factors). Recognised single-gene associations include:
  - **Van der Woude syndrome** — the commonest syndrome associated with cleft lip ± cleft palate; autosomal dominant, due to mutation of **IRF6** (interferon regulatory factor 6, 1p32–p41); 88% of affected infants have **lower-lip pits**, which are the sole abnormality in 64%.
  - **MSX1** mutations — associated with nonsyndromic and syndromic clefting.
  - **SHH** (Sonic Hedgehog) mutations — cause holoprosencephaly with bilateral cleft lip/palate, microcephaly, hypotelorism, flat nasal bridge and a single central maxillary incisor.
- ▶ **Teratogens**: anticonvulsants (phenytoin, valproic acid), maternal cigarette smoking, and alcohol (fetal alcohol syndrome — thin upper lip with an indistinct/smooth philtrum) all increase the risk of orofacial clefting.
- ▶ **Surgical correction**: cleft lip is repaired (cheiloplasty) in early infancy; associated cleft palate is repaired somewhat later, restoring feeding, speech and facial appearance.

### High-yield exam pointers

- ▶ Upper lip = 2 medial nasal prominences (median part/philtrum) + 2 maxillary prominences (lateral parts), fused during the 6th–7th week.
- ▶ Lateral nasal prominences take **no part** in the upper lip — they form the **alae of the nose**.
- ▶ Intermaxillary segment = labial component (philtrum) + upper jaw component (4 incisors) + palatal component (triangular primary palate); continuous with the nasal septum.
- ▶ Skin (and hence sensory nerve supply — **maxillary nerve, V2**) of the **entire** upper lip is maxillary-process derived, because maxillary ectoderm overgrows the frontonasal-derived philtrum mesenchyme (Frazer's concept).
- ▶ **Commonest congenital anomaly of the face** = **unilateral cleft lip**; **rarest** = **median cleft of the lower lip**.
- ▶ **Multifactorial inheritance** is the commonest cause of cleft lip with or without cleft palate; **Van der Woude syndrome (IRF6)** is the commonest single-gene syndromic association.
- ▶ **Critical period of palate development**: end of 6th week to beginning of 9th week.



- Oblique facial cleft = failure of maxillary–lateral nasal fusion along the nasolacrimal groove (nasolacrimal duct exposed).
- Isolated cleft palate is a genetically distinct entity from cleft lip/palate, is less common, and shows a female preponderance.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology (figure).



## Discuss the development of face with different congenital anomalies

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The face develops between the **4th and 8th week** of intrauterine life (7th–8th week being the final period of facial morphogenesis) from **five mesenchymal facial processes/prominences** — one unpaired **frontonasal** process and paired **maxillary** and **mandibular** processes — that arise around the **stomodeum** (primitive mouth) and are populated by cranial **neural crest** mesenchyme. The frontonasal process further differentiates into **medial and lateral nasal processes** flanking the nasal placodes. Orderly proliferation, growth and fusion of these processes builds the forehead, nose, lips, cheeks and palate; failure of fusion (or excessive fusion) at any of these lines produces the entire spectrum of congenital facial clefts and dysmorphisms, of which cleft lip/palate is by far the commonest.

### 1. The five facial processes and the stomodeum

- At the end of the **4th week**, the stomodeum is bounded cranially by the bulging forebrain vesicle and caudally by the **first (mandibular) pharyngeal arch**; the buccopharyngeal membrane lies in its floor. Mesoderm proliferating around it raises five prominences:

| Process                                            | Origin                                | Chief derivatives                                                                                      | Sensory nerve   |
|----------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------|
| <b>Frontonasal</b> (unpaired)                      | Mesenchyme over the forebrain vesicle | Forehead, bridge of nose; gives rise to medial and lateral nasal processes                             | Ophthalmic (V1) |
| <b>Medial nasal</b> (paired, part of frontonasal)  | Medial margin of the nasal pit        | Nasal septum, dorsum/tip of nose, <b>intermaxillary segment</b> (philtrum, premaxilla, primary palate) | Ophthalmic (V1) |
| <b>Lateral nasal</b> (paired, part of frontonasal) | Lateral margin of the nasal pit       | Alae of the nose, lateral wall of nasal cavity                                                         | Ophthalmic (V1) |

| Process             | Origin                              | Chief derivatives                                        | Sensory nerve   |
|---------------------|-------------------------------------|----------------------------------------------------------|-----------------|
| Maxillary (paired)  | Dorsal part of 1st pharyngeal arch  | Upper cheek, lateral part of upper lip, secondary palate | Maxillary (V2)  |
| Mandibular (paired) | Ventral part of 1st pharyngeal arch | Chin, lower lip, lower cheek                             | Mandibular (V3) |

- ▶ On the frontonasal process, bilateral **nasal placodes** appear about day 28–30; each sinks in as a **nasal pit**, whose margins raise the medial and lateral nasal processes.
- ▶ Facial mesenchyme is **neural-crest derived**: frontonasal crest arises from **midbrain/forebrain** level; maxillary and mandibular crest from **both midbrain and hindbrain**.
- ▶ Facial-expression muscles are 2nd-arch derivatives supplied by the **facial nerve (VII)**, unlike the skin/skeleton of the face (trigeminal territory) — a frequently tested distinction.

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences around the stomodeum: single frontonasal process, paired maxillary and mandibular processes. (Sontakke — Textbook of Human Embryology, p.118)

## 2. Fusion sequence — nose, lip and cheek

- ▶ Between the **7th and 10th weeks**, the maxillary process fuses first with the lateral nasal process (simple, rarely disturbed) and then with the medial nasal process; this separates the nasal pit from the stomodeum into the **primitive anterior nares**.
- ▶ **External nose**: bridge from the frontonasal process; dorsum/tip from fused **medial nasal processes**; alae from **lateral nasal processes**; anterior nares from the nasal pit; posterior nares (choanae) from rupture of the **bucconasal membrane**.
- ▶ **Upper lip**: philtrum from the medial nasal process (intermaxillary segment); lateral parts from **maxillary processes**, whose ectoderm overgrows the philtrum — hence skin of the whole upper lip is supplied by the **maxillary nerve**.
- ▶ **Lower lip/chin**: bilateral mandibular processes fuse in the midline. **Cheeks**: progressive lateral fusion of maxillary and mandibular processes narrows the wide primitive oral fissure.
- ▶ **Nasolacrimal duct**: an ectodermal cord buried along the naso-optic furrow (maxillary–lateral-nasal fusion line) canalises by the 10th week; its upper end dilates into the lacrimal sac — failure causes duct atresia.
- ▶ **Paranasal sinuses** are ectodermal diverticula invading the frontal, ethmoid, sphenoid and maxillary bones; the **maxillary sinus develops first (3rd month IU)**; all sinuses begin before birth except the **frontal sinus**, which appears only postnatally (5th–6th year).

## 3. Development of the palate

- ▶ Palatogenesis spans the **5th to 12th week**. Two components form the definitive palate:

| Component      | Origin                                                                  | Timing                             | Fate                                                       |
|----------------|-------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------|
| Primary palate | Intermaxillary segment (medial nasal process) — median palatine process | Shelf forms in the <b>6th week</b> | Premaxillary part of maxilla, bearing the 4 upper incisors |

| Component        | Origin                                                       | Timing                                                                                         | Fate                             |
|------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------|
| Secondary palate | Paired lateral palatine processes of the maxillary processes | Extend medially in the 6th week; elongate and rotate to horizontal, fusing in the 7th–8th week | Rest of the hard and soft palate |

- ▶ The lateral palatine processes fuse with each other in the midline, with the **nasal septum**, and with the posterior border of the primary palate; a small **nasopalatine (incisive) canal** persists at the junction, marking the future **incisive foramen**, which demarcates primary from secondary palate.
- ▶ Timely **shelf elevation** (vertical → horizontal above the tongue) depends on hyaluronan-driven mesenchymal swelling and on growth changes withdrawing the tongue from between the shelves (weeks 9–10); delay coinciding with facial-width growth prevents midline contact and causes **cleft palate**.
- ▶ The **anterior three-fourths** ossifies to form the **hard palate**; the **posterior one-fourth** stays unossified as the **soft palate and uvula**.

#### 4. Molecular and neural-crest regulation

- ▶ Facial outgrowth is directed by **epithelial–mesenchymal signalling** (Shh, Bmp and Fgf family growth factors patterning crest-derived mesenchyme); removing the epithelium truncates the prominences.
- ▶ A rostrocaudal **HOX code** sets arch identity: the **1st arch** is **HOX-negative**, expressing **OTX2** instead; the **2nd arch** expresses **HOX-A2**; **3rd–6th arches** express **HOX-A3/B3/D3**. Named signalling molecules include **BMP7, FGF8 and SHH**.
- ▶ Loss of function of **Bmp4** (or Fgf/Wnt/Shh) causes cleft lip in animal models — showing that the same fusion defect seen clinically has a defined molecular basis, not just a mechanical one.
- ▶ Single-gene neural-crest disorders map onto this pathway: **TCOF1** haploinsufficiency (Treacher Collins) and **EFNB1** deletion, an **X-linked** gene (craniofrontonasal syndrome), each disrupt crest patterning at a different point.

#### 5. Congenital anomalies of the face

Nearly all facial anomalies reflect **non-fusion, delayed fusion or excessive fusion** of the five processes described above.

| Anomaly                   | Embryological basis                                       | Key features                                                                         |
|---------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------|
| Cleft lip — uni/bilateral | Maxillary process fails to fuse with medial nasal process | Commonest facial anomaly; 1:1000, 80% males; recurrence 4% after 1 child, 9% after 2 |
| Midline cleft lip         | Non-fusion of the two medial nasal processes              | Rare (not a normal fusion line); may coexist with <b>bifid nose</b>                  |

| Anomaly                   | Embryological basis                                               | Key features                                                                                                                                                |
|---------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cleft palate              | Non-fusion of primary + lateral (secondary) palatine processes    | 1:2500, 67% females; multifactorial; recurrence 2%; complete (uni/bilateral) or incomplete; unilateral complete cleft palate always has ipsilateral harelip |
| Oblique facial cleft      | Non-fusion of maxillary + lateral nasal process                   | Cleft from medial canthus to mouth; nasolacrimal duct absent                                                                                                |
| Macrostomia / microstomia | Inadequate / excessive fusion of mandibular + maxillary processes | Abnormally wide mouth (unilateral → lateral facial cleft) / abnormally small mouth                                                                          |
| Proboscis ± cyclopia      | Severe frontonasal dysmorphogenesis                               | Cylindrical projecting nose ± fused eyes                                                                                                                    |
| Hypertelorism             | Excess/broadening of frontonasal process                          | Widely spaced eyes, broad nasal bridge                                                                                                                      |
| Agnathia / retrognathia   | Failure/deficiency of mandibular process (Meckel's cartilage)     | Absent jaw / small receding chin                                                                                                                            |
| Lip pits, fistulae        | Minor lip developmental defects                                   | Congenital pits on vermillion border                                                                                                                        |

#### First-arch (neural-crest) syndromes

| Syndrome                                      | Gene / basis                              | Inheritance                                   | Key features                                                                                       |
|-----------------------------------------------|-------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------|
| Treacher Collins (mandibulofacial dysostosis) | TCOF1 haploinsufficiency                  | Autosomal dominant; ≈1/85,000                 | Malar + mandibular hypoplasia, down-slanting palpebral fissures, deformed ears                     |
| Pierre Robin sequence                         | Primary micrognathia → tongue obstruction | Autosomal recessive (per textbook); ≈1/85,000 | Triad: micrognathia + <b>U-shaped cleft palate</b> + glossoptosis; ~25% conotruncal cardiac defect |
| DiGeorge syndrome                             | 22q11 microdeletion                       | Sporadic                                      | Absent thymus/parathyroids, cardiac outflow defects, fish-mouth philtrum, low-set notched ears     |

□ Fig 12.5 — Cleft lip and cleft palate. Non-fusion of the maxillary process with medial nasal process results in cleft lip; non-fusion of the median and lateral palatine processes results in cleft palate. (Sontakke — Textbook of Human Embryology, p.123)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

- ▶ **Development of the face (5-process schema)** — draw the stomodeum surrounded by the five prominences and label: **Frontonasal process** (top, unpaired) → subdividing around the **nasal placode/pit** into **medial nasal process** (medial, forms septum + philtrum) and **lateral nasal process** (lateral, forms alae); paired **maxillary processes** (upper lateral, forms cheek + lateral upper lip); paired **mandibular processes** (lower, forms chin + lower lip). Mark the **naso-optic (nasolacrimal) furrow** between maxillary and lateral nasal process, and the line of fusion between maxillary and medial nasal process (site of cleft lip).
- ▶ **Cleft lip / cleft palate diagram** — draw the upper lip and hard palate from below; label the **premaxilla (primary palate)** anteriorly, the **incisive foramen**, and the two **lateral palatine processes**; shade in unilateral cleft lip (gap between maxillary and medial nasal process on one side), bilateral cleft lip, and a midline gap in the palatine processes to depict cleft palate.

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- ▶ **Unilateral cleft lip/palate is the commonest congenital facial anomaly**; a complete unilateral cleft palate is always accompanied by harelip on the same side.
- ▶ Both cleft lip and cleft palate are largely **multifactorial**, so genetic counselling uses empirical recurrence risk (4%/9% for cleft lip after 1/2 affected sibs; 2% for cleft palate), not Mendelian ratios.
- ▶ A **submucous cleft palate** (V-shaped notch of soft palate under intact mucosa) is an easily missed cause of hypernasal speech in children with feeding/speech difficulty.
- ▶ In **unilateral cleft lip**, the nasal septum deviates to the non-cleft side because the medial nasolabial/orbicularis-oris muscle slips fail to insert across the midline — the anatomical basis of rotation-advancement lip repair.
- ▶ First-arch syndromes need prompt recognition for associated **airway obstruction** (glossoptosis, Pierre Robin), **conductive deafness** (Treacher Collins), and **cardiac/immune defects** (DiGeorge).
- ▶ The "**dangerous area of the face**" drains via the facial vein into the cavernous sinus, so infection near a cleft-repair scar can cause cavernous sinus thrombosis.
- ▶ All these anomalies are surgically correctable; repair strategy follows directly from which embryonic fusion line failed.

**High-yield exam pointers**

- ▶ Face develops from **five processes** — 1 frontonasal + 2 maxillary + 2 mandibular — around the stomodeum, between the **4th and 8th week**.
- ▶ Frontonasal → ophthalmic (V1); maxillary → maxillary (V2); mandibular → mandibular (V3) nerve territories.
- ▶ Philtrum + primary palate = **medial nasal process (intermaxillary segment)**; lateral upper lip + secondary palate = **maxillary process**.
- ▶ Palatogenesis: **5th–12th week**; primary + secondary palate fuse; **incisive foramen** marks the junction; anterior 3/4 ossifies (hard palate), posterior 1/4 stays membranous (soft palate/uvula).

- ▶ **Cleft lip** = maxillary process fails to fuse with medial nasal process (1:1000, M > F). **Cleft palate** = lateral palatine processes fail to fuse (1:2500, F > M).
- ▶ **Oblique facial cleft** (maxillary–lateral nasal non-fusion) vs **macrostomia/microstomia** (mandibular–maxillary fusion defect) — do not confuse the fusion lines.
- ▶ **First-arch syndromes**: Treacher Collins (TCOF1, AD), Pierre Robin (micrognathia → glossoptosis → U-shaped cleft palate), DiGeorge (22q11 deletion) — classic PG viva triad.
- ▶ Molecular players: **SHH**, **FGF8**, **BMP** (esp. **Bmp4**), **Wnt**; HOX-negative 1st arch (OTX2) vs HOX-A2 2nd arch vs HOX-A3/B3/D3 caudal arches.
- ▶ Nasolacrimal duct forms from a buried ectodermal cord at the maxillary–lateral-nasal fusion line; its failure causes duct atresia.

### SOURCE & COVERAGE

Textbook of Human Embryology (Sontakke); Human Embryology — CBME 2021 (IB Singh); Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Textbook of Clinical Embryology (Vishram Singh); BD Chaurasia's Human Anatomy Vol 3–4 8e; Gray's Anatomy (Standring) 41e.



## Endodermal derivatives of pharyngeal pouches

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Pharyngeal pouches are paired endodermal outpocketings of the primitive pharynx (the cranial-most part of the foregut) that bulge laterally into the mesenchyme between successive pharyngeal arches, opposite the ectodermal pharyngeal clefts. There are four well-developed pairs (1st–4th) and a rudimentary 5th pouch, numbered craniocaudally. Although pouch, cleft and arch development recapitulates the branchial (gill) apparatus of lower vertebrates, no true gill slits form in the human embryo — the epithelial lining of each pouch differentiates into a distinct endocrine or lymphoepithelial organ of the head and neck. (The thyroid gland itself is **not** a pouch derivative — it arises from a median endodermal diverticulum of the pharyngeal floor at the site of the future foramen caecum; pouch-derived tissue merely migrates to fuse onto it.)

### General features of pharyngeal pouches

- ▶ Lined by **endoderm** internally; each pouch initially contacts the corresponding ectodermal cleft, the two layers forming a **pharyngeal membrane** — true perforation (a gill slit) never occurs in humans.
- ▶ Development of pouch derivatives is genetically patterned: **FGF8** is expressed in the anterior endoderm and **BMP7** in the posterior endoderm of each pouch; **SHH** is expressed in the posterior endoderm of the 2nd and 3rd pouches; **PAX1** marks the dorsalmost endoderm of every pouch. This endodermal code instructs the neural-crest-derived mesenchyme of the arches to form arch-specific skeletal elements.
- ▶ Ventrally, the pouches fuse across the midline to form the floor of the primitive pharynx, from which the tongue develops.

- The 5th pouch is rudimentary and fuses with the ventral part of the 4th pouch to form the caudal pharyngeal complex, the precursor of the ultimobranchial body.

### Summary — derivatives of the four pharyngeal pouches

| Pouch | Region                                                             | Endodermal derivative                                                                                               | Adult structure                                                                                                                                               |
|-------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st   | Entire pouch (tubotympanic recess)                                 | Stalk-like diverticulum contacting the 1st cleft                                                                    | Pharyngotympanic (auditory/eustachian) tube, tympanic (middle-ear) cavity and mastoid antrum; contributes the inner (mucosal) lining of the tympanic membrane |
| 2nd   | Ventral part                                                       | Proliferates into surrounding mesoderm as solid epithelial buds, later canalised and infiltrated by lymphoid tissue | Epithelium and crypts of the palatine tonsil; unobliterated part persists as the intratonsillar cleft (crypta magna)/tonsillar fossa                          |
| 3rd   | Dorsal wing                                                        | Differentiates in situ                                                                                              | Inferior parathyroid gland (parathyroid III)                                                                                                                  |
|       | Ventral wing                                                       | Proliferates and is invaded by mesenchyme                                                                           | Thymus — epithelial (cytoreticular) framework and Hassall's corpuscles                                                                                        |
| 4th   | Dorsal wing                                                        | Differentiates in situ                                                                                              | Superior parathyroid gland (parathyroid IV)                                                                                                                   |
|       | Ventral wing (+ rudimentary 5th pouch = caudal pharyngeal complex) | Forms the ultimobranchial body, later incorporated into the thyroid                                                 | Parafollicular (C) cells of the thyroid gland (secrete calcitonin)                                                                                            |

### First and second pharyngeal pouches

- **First pouch:** forms a stalk-like diverticulum, the **tubotympanic recess**, which grows laterally to meet the epithelial floor of the first pharyngeal cleft. Its proximal narrow part becomes the **auditory tube**; its distal, expanded part becomes the **tympanic cavity**, whose endodermal epithelium lines the medial (inner) surface of the tympanic membrane — the only structure in the body formed from all three germ layers (ectoderm of the 1st cleft, mesoderm of the arches, and endoderm of the 1st pouch).
- **Second pouch:** its ventral epithelium proliferates into the surrounding mesenchyme as solid cords that canalise; from the third to the fifth month this developing tissue is infiltrated by lymphoid tissue (of mesodermal origin) to form the **palatine tonsil**. Part of the pouch cavity persists in the adult as the **intratonsillar cleft**. The dorsal part of the 1st and 2nd pouches together contribute to the tubotympanic recess.



## Third and fourth pharyngeal pouches — thymus and parathyroid glands

- ▶ Both the 3rd and 4th pouches are characterised distally by a **dorsal wing** and a **ventral wing**.
- ▶ **Third pouch:** the **dorsal wing** forms the **inferior parathyroid gland**; the **ventral wing** forms the **thymus**. Both primordia lose their connection with the pharyngeal wall in the 5th–6th week.
- ▶ **Fourth pouch:** the **dorsal wing** forms the **superior parathyroid gland**; the ventral part (with the rudimentary 5th pouch) forms the **ultimobranchial body**, which fuses with the thyroid gland. Cells of the ultimobranchial body give rise to the **parafollicular (C) cells**, which secrete calcitonin. (Some texts hold that the C cells are themselves neural-crest derivatives that colonise the endodermal ultimobranchial body rather than differentiating from its endoderm — an accepted point of variation, but the ultimobranchial body's origin from 4th-pouch endoderm is constant.)

## Migration and the "crossed" final position — a key exam point

- ▶ After losing contact with the pharyngeal wall, the **thymus migrates caudally and medially**, dragging its attached **inferior parathyroid (from the 3rd pouch)** with it.
- ▶ The main mass of thymic tissue descends into the anterior mediastinum and fuses with its contralateral partner; a tail portion may persist as ectopic cervical thymic nests.
- ▶ The inferior parathyroid finally comes to rest on the **lower (inferior) part of the dorsal surface of the thyroid gland**.
- ▶ The superior parathyroid (from the 4th pouch) travels only a short distance and settles on the **upper (superior) part of the dorsal surface of the thyroid**.
- ▶ **Net result:** although the 3rd pouch lies cranial to the 4th pouch in the embryo, its parathyroid derivative (inferior parathyroid) ends up **caudal/inferior** to the 4th-pouch-derived (superior) parathyroid in the adult — the classic "crossed migration" fact examiners test.

□ Fig 17.31 — *Development of the Pharyngeal Pouch Derivatives* All of the pharyngeal pouches give rise (Larsen — *Human Embryology* — 6e, p.1100)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

A coronal/ventral schematic of the 5-week pharynx floor opened to show the four pouches, followed by an arrow diagram of caudal migration. Label exactly:

- ▶ Meckel's cartilage, external auditory meatus, Reichert's cartilage (landmarks only)
- ▶ **1st pouch** → tubotympanic recess → auditory tube + tympanic cavity
- ▶ **2nd pouch** → palatine tonsil (with intratonsillar cleft)
- ▶ **3rd pouch**: dorsal wing → inferior parathyroid (red); ventral wing → thymus (orange)
- ▶ **4th pouch**: dorsal wing → superior parathyroid (blue); ventral wing → ultimobranchial body
- ▶ Downward curved arrows from the 3rd-pouch inferior parathyroid and thymus, crossing past the 4th-pouch superior parathyroid, terminating on the thyroid gland (inferior parathyroid ends up below superior parathyroid) and in the superior mediastinum (thymus)

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- ▶ **DiGeorge anomaly (22q11.2 deletion / CATCH-22 spectrum)**: faulty development of the 3rd and 4th pouch derivatives (and adjoining neural-crest mesenchyme) → thymic aplasia/hypoplasia (T-cell immunodeficiency, recurrent infections) with parathyroid aplasia (neonatal hypocalcaemic tetany) plus craniofacial and conotruncal cardiac defects.
- ▶ **Ectopic thymic/parathyroid tissue**: because these glands migrate a long distance, accessory nests may persist anywhere along the path — cervical ectopic thymus, or an ectopic/undescended inferior parathyroid found as low as the carotid bifurcation or within the thymus/mediastinum; explains why a "missing" parathyroid at surgery must be sought along this migratory tract (including the mediastinum).
- ▶ **Median ectopic thymic tissue / persistent thymopharyngeal duct** can give a cervical thymic cyst.
- ▶ **Congenital deafness / middle-ear anomalies**: malformation of the tubotympanic recess (1st pouch) can produce abnormalities of the tympanic cavity, auditory tube patency (recurrent otitis media in children relates to the short, more horizontal tube) or tympanic membrane.
- ▶ **Tonsillar pathology**: the persistent intratonsillar cleft is the site where a **peritonsillar abscess** (quinsy) classically begins; recurrent tonsillitis and tonsillectomy relate directly to this 2nd-pouch derivative.
- ▶ **Thyroid C-cell (medullary) carcinoma** arises from the parafollicular cells derived from the ultimobranchial body (4th pouch) and can co-secrete calcitonin — used as a tumour marker; part of MEN 2A/2B syndromes.
- ▶ **Thymoma/thymic cysts** in the neck or mediastinum reflect the course of thymic descent.

**High-yield exam pointers**

- ▶ Four definitive pharyngeal pouches (endodermal) + a rudimentary 5th; pouches never truly perforate to form gill slits in humans.

- ▶ 1st pouch → auditory tube + tympanic cavity (+ inner lining of tympanic membrane); 2nd pouch → palatine tonsil epithelium/crypts + intratonsillar cleft.
- ▶ 3rd pouch: **dorsal** = inferior parathyroid (parathyroid III); **ventral** = thymus.
- ▶ 4th pouch: **dorsal** = superior parathyroid (parathyroid IV); **ventral** (+ rudimentary 5th) = ultimobranchial body → parafollicular C cells (calcitonin).
- ▶ Remember the mnemonic pairing: "3rd pouch gives what is inferior in position but comes from the higher (3rd) pouch" — because the thymus drags the inferior parathyroid caudally past the 4th-pouch-derived superior parathyroid.
- ▶ Thyroid gland is NOT a pouch derivative — it develops from the median thyroid diverticulum of the pharyngeal floor; only the parathyroids and ultimobranchial body/C cells attach to it secondarily.
- ▶ Lymphoid tissue within the tonsil and thymocytes within the thymus are of **mesodermal** origin, not endodermal — only the epithelial framework (crypts/Hassall's corpuscles) is endodermal.
- ▶ Clinical linkage: DiGeorge anomaly = combined 3rd/4th pouch failure (absent thymus + parathyroids); ectopic parathyroid/thymus tissue follows the migratory path.

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore, The Developing Human 9e; Larsen's Human Embryology 6e; Sontakke, Textbook of Human Embryology; BD Chaurasia, Human Anatomy Vol 3-4 8e; Gray's Anatomy (Standring) 41e.



## First Branchial Arch and its Derivatives

*Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **first pharyngeal (branchial) arch**, also called the **mandibular arch**, is the most rostral of the pharyngeal arch series that appears around the fourth week of intrauterine life. Like every arch it is a bar of mesenchyme — mainly **neural crest** in origin, with a paraxial-mesoderm contribution — covered externally by ectoderm and internally by endoderm, and it contains one cartilage, one aortic arch artery, a mass of striated muscle and its own cranial nerve. Uniquely among the arches it possesses both a dorsal and a ventral process, appearing C-shaped: a smaller cranial **maxillary process** and a larger caudal **mandibular process**. Because neural crest cells populating this arch also form much of the facial skeleton and middle ear, the first arch is of great applied importance in craniofacial and hearing disorders.

### 1. Composition and subdivision of the arch

| Component                    | Tissue origin                             | Fate                                        |
|------------------------------|-------------------------------------------|---------------------------------------------|
| Skeletal element (cartilage) | Neural crest-derived mesenchyme           | Meckel's cartilage                          |
| Muscle mass                  | Paraxial (unsegmented cranial) mesenchyme | Muscles of mastication + associated muscles |

| Component                            | Tissue origin                          | Fate                                                     |
|--------------------------------------|----------------------------------------|----------------------------------------------------------|
| Arch artery                          | Angiogenic mesoderm (endothelium)      | First aortic arch artery (mostly transitory)             |
| Nerve                                | —                                      | Trigeminal nerve (CN V)                                  |
| Maxillary process (dorsal, smaller)  | Neural crest                           | Upper jaw/face skeleton (no cartilage — intramembranous) |
| Mandibular process (ventral, larger) | Neural crest around Meckel's cartilage | Mandible (intramembranous), lower lip, chin              |

The mandibular processes grow ventromedially in the floor of the primitive pharynx and meet in the midline above the pericardial bulge; the maxillary processes become distinct slightly later and enlarge alongside the nasal (frontonasal) swellings.

## 2. Skeletal and ligamentous derivatives

The cartilage of the first arch is **Meckel's cartilage**. It extends from the developing otic capsule to the midline and acts purely as a scaffold for the mandibular process — the mandible itself ossifies **intramembranously** in the mesenchyme investing the cartilage, not from the cartilage.

| Part of Meckel's cartilage                        | Derivative                                                                                         |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Dorsal (proximal) end — endochondral ossification | Malleus and incus (ear ossicles)                                                                   |
| Perichondrium of the persisting proximal stalk    | Anterior ligament of malleus; sphenomandibular ligament (malleus to spine of sphenoid)             |
| Ventral part, near the future symphysis menti     | Small segment ossifies and is incorporated into the mandible; remainder degenerates and disappears |
| Surrounding mandibular-process mesenchyme         | Body and ramus of mandible (membranous bone; cartilage is not its precursor)                       |

The **maxillary process**, which never chondrifies, ossifies directly in membrane to give the **pre-maxilla**, **maxilla**, **zygomatic bone**, and the **squamous part of the temporal bone**.

## 3. Muscular derivatives

All striated muscle of the first arch differentiates from its paraxial mesenchyme and is supplied by the **mandibular division of the trigeminal nerve**, regardless of the final position each muscle migrates to.

| Muscle group             | Muscles                                                                      |
|--------------------------|------------------------------------------------------------------------------|
| Muscles of mastication   | Temporalis, masseter, medial pterygoid, lateral pterygoid                    |
| Other first-arch muscles | Mylohyoid, anterior belly of digastric, tensor veli palatini, tensor tympani |

Tensor tympani retains its skeletal link to the arch via its attachment to the malleus, and tensor veli palatini remains attached near the base of the medial pterygoid plate — both anatomical fossils of their arch origin.

#### 4. Nerve of the arch

The **trigeminal nerve (CN V)** is the nerve of the first arch — the only arch nerve that is predominantly sensory as well as motor, reflecting the arch's dual maxillary/mandibular subdivision:

- **Maxillary division (V2)** — purely sensory; supplies the maxillary-process derivatives (mid-face skin, upper lip, upper jaw, palate). No muscle arises from maxillary mesenchyme, consistent with V2 having no motor root.
- **Mandibular division (V3)** — both motor (to every first-arch muscle listed above) and sensory (to the mandibular-process derivatives — chin, lower lip, lower jaw, anterior two-thirds of tongue mucosa via the lingual nerve, and the tympanic membrane/external meatus region via the auriculotemporal nerve).

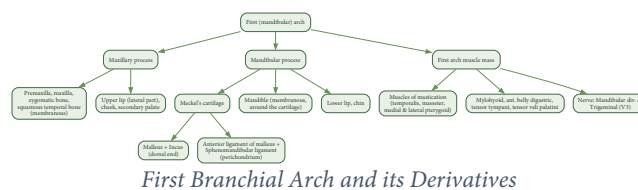
#### 5. Arterial derivative

The **first aortic arch artery** is largely **transitory** and regresses early; only a small remnant persists to form **part of the maxillary artery**. Unlike arches 3, 4 and 6, the first (and second) arch arteries make no lasting contribution to the definitive great vessels.

#### 6. Contribution to the face, external and middle ear

embed: ![Fig 11.4 — Structures derived from cartilages of the pharyngeal arches. The first arch cartilage is (Sontakke — Textbook of Human Embryology, p.107)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/b0f29ae0a72a6f56.jpg)

- **Face:** maxillary process forms the lateral part of the upper lip, the cheek, and contributes (with the palatine processes) to the **secondary palate**; mandibular process forms the lower lip and chin.
- **External ear:** of the six mesenchymal **auricular hillocks** that encircle the first pharyngeal cleft, the three on the mandibular (first) arch side form the **tragus, crus of helix and helix**; the three on the hyoid (second) arch side form the antihelix, antitragus and lobule.
- **External acoustic meatus:** the only pharyngeal cleft to persist as a definitive adult structure is the **first pharyngeal cleft**, which canalises to form the external auditory meatus.
- **Tympanic membrane:** formed at the first pharyngeal membrane — outer cuticular (ectodermal) layer from the first cleft, inner mucosal (endodermal) layer from the first pharyngeal pouch, and an intermediate fibrous (mesodermal) layer between them; the handle of the malleus and the chorda tympani nerve run within this intermediate layer.
- **Middle ear (tympanic cavity):** derived from the dorsal part of the first pharyngeal pouch (tubotympanic recess), housing the malleus and incus described above.



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a coronal/lateral schematic of the first pharyngeal arch (4th–5th week embryo) showing:

- ▶ Stomodeum, maxillary process (dorsal) and mandibular process (ventral) meeting in the midline
- ▶ **Meckel's cartilage** running through the mandibular process, with its dorsal end near the otic capsule
- ▶ The developing **malleus and incus** at the dorsal end of the cartilage; anterior ligament of malleus and sphenomandibular ligament as perichondrial remnants
- ▶ **Trigeminal ganglion** with maxillary (V2) and mandibular (V3) divisions labelled to their respective processes
- ▶ First aortic arch artery, first pharyngeal cleft (→ external acoustic meatus) and first pharyngeal pouch (→ tubotympanic recess) flanking the arch
- ▶ Auricular hillocks 1–3 (tragus, crus of helix, helix) on the mandibular-arch side of the first cleft

**Applied / Clinical anatomy**

- ▶ **Treacher Collins syndrome (mandibulofacial dysostosis)**: autosomal dominant disorder due to mutation of the **TCOF1** gene (5q32, encoding the nucleolar protein "treacle"), which impairs neural crest cell survival/proliferation (migration is normal). Presents with hypoplasia of the maxilla, zygomatic bone and mandible, down-slanting palpebral fissures with lower-lid colobomas, deformed/absent external ears with atresia of the auditory canal and ossicular anomalies causing **conductive hearing loss**, and often cleft palate — a direct consequence of deficient first-arch neural crest.
- ▶ **Pierre Robin sequence**: alters first-arch structures with the mandible most severely affected. Classic triad — **micrognathia (small mandible)** → **glossoptosis (posteriorly placed tongue)** → **cleft palate** (the retro-displaced tongue mechanically prevents fusion of the palatal shelves). May occur in isolation or as part of another syndrome, and can also arise as a deformation (e.g. chin compression in oligohydramnios).
- ▶ **Hemifacial microsomia (oculo-auriculo-vertebral spectrum / Goldenhar syndrome)**: asymmetric hypoplasia of the maxillary, zygomatic and temporal bones (all first-arch-process derivatives) with associated ear anomalies (microtia/anotia) — reflects patchy first-arch neural crest deficiency.
- ▶ **Ossicular chain and conductive deafness**: since the malleus and incus are both first-arch (Meckel's cartilage) derivatives sharing a common developmental origin, congenital malformation or fixation of this pair (as opposed to the second-arch stapes) is a recognised cause of isolated congenital conductive hearing loss.
- ▶ **Preauricular sinus/tags**: minor anomalies of fusion of the auricular hillocks; because three of the six hillocks belong to the first arch, such anomalies are frequently first-arch related and may coexist with branchial fistulae/cysts if cleft closure is also defective.

- ▶ **Cleft lip and cleft palate:** failure of the maxillary process to fuse with the merged medial nasal prominences produces cleft lip; failure of the palatine shelves (maxillary-process derivatives) to fuse in the midline produces cleft palate — both are common isolated first-arch/frontonasal fusion defects, distinct from the syndromic causes above.

### High-yield exam pointers

- ▶ First arch = **mandibular arch**; divides into a smaller dorsal **maxillary process** and a larger ventral **mandibular process** — unlike other arches, it has both.
- ▶ Cartilage = **Meckel's cartilage** → dorsal end gives **malleus + incus**; perichondrium gives **anterior ligament of malleus + sphenomandibular ligament**; the **mandible is NOT formed from the cartilage** — it ossifies in membrane around it.
- ▶ Muscles (all via **mandibular nerve, V3**): 4 muscles of mastication (temporalis, masseter, medial & lateral pterygoid) + mylohyoid + anterior belly of digastric + tensor veli palatini + tensor tympani.
- ▶ Nerve of the arch = **trigeminal (CN V)** — V2 sensory to maxillary process, V3 motor + sensory to mandibular process.
- ▶ Artery = **first aortic arch artery**, mostly transitory; remnant forms part of the **maxillary artery**.
- ▶ Maxillary process (no cartilage, membranous) → premaxilla, maxilla, zygomatic bone, squamous temporal bone, secondary palate, upper lip.
- ▶ External ear: **tragus, crus of helix, helix** from first-arch hillocks; first cleft → external acoustic meatus; first membrane → tympanic membrane (3 layers, 3 germ layers).
- ▶ Classic **first arch syndromes**: **Treacher Collins** (AD, TCOF1) and **Pierre Robin sequence** (micrognathia–glossoptosis–cleft palate triad).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; BD Chaurasia — Human Anatomy Vol 3-4 8e; Brijesh Kumar — Embryology Text & Atlas.





## Frontonasal process

*Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The frontonasal process (frontonasal prominence) is the single, unpaired facial primordium formed at the end of the 4th week by proliferation of neural-crest-derived mesenchyme (from the midbrain and forebrain) ventral to the brain vesicles; it constitutes the upper border of the stomodeum. Together with the paired maxillary and paired mandibular prominences (both derived from the 1st pharyngeal arch), it is one of the five facial primordia whose growth and fusion between the 4th and 10th weeks sculpts the definitive human face. The frontonasal process is the source of the forehead, the bridge, crest, tip and alae of the nose, the philtrum and premaxilla of the upper lip, and the triangular primary palate — making it central to understanding facial clefting.

### Origin and time course

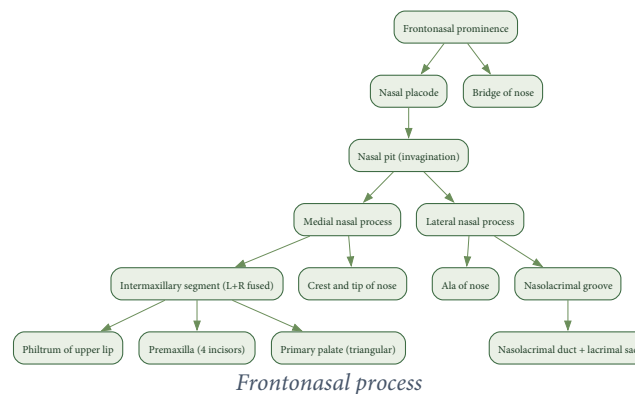
- ▶ End of 4th week: mesenchymal proliferation ventral to the forebrain forms the frontonasal prominence, forming the roof of the stomodeum (primitive mouth), which is closed by the oropharyngeal membrane.
- ▶ Its mesenchyme is neural-crest in origin, migrating from the midbrain and forebrain (unlike the maxillary/mandibular prominences, which receive crest from both midbrain and hindbrain).
- ▶ 5th week: a pair of ectodermal thickenings — the nasal (olfactory) placodes — appear symmetrically on the frontonasal prominence, induced by the ventral forebrain.
- ▶ 6th week: the central ectoderm of each placode invaginates to form an oval nasal pit. This invagination divides the frontonasal prominence, on each side, into a medial nasal process (inner ridge) and a lateral nasal process (outer ridge).
- ▶ 6th–7th week: the two medial nasal processes approach and merge in the midline (compressed medially by the enlarging maxillary prominences), forming the intermaxillary segment by the end of the 7th week.
- ▶ Because the dermis of this region is neural-crest derived, its sensory innervation is by the ophthalmic (V1) division of the trigeminal nerve — in contrast to the maxillary (V2) and mandibular (V3) skin derived from the first arch.

### Nasal placode → nasal pit → medial/lateral nasal processes

- ▶ Nasal placode: paired, disc-like ectodermal thickening on the frontonasal prominence; induction depends on signals from the ventral forebrain.
- ▶ Nasal pit: formed when the placode's central ectoderm invaginates; it later becomes continuous with the roof of the stomodeum and deepens to form the nasal cavity proper.
- ▶ The ridge surrounding each pit forms the **nasal prominences** — the outer-edge ridge is the lateral nasal process, the inner-edge ridge (nearer the midline) is the medial nasal process.
- ▶ **Nasolacrimal groove**: a deep furrow that initially separates the lateral nasal process from the adjacent maxillary prominence. Its floor ectoderm forms a solid epithelial cord that detaches and canalises (6th–7th week) into the **nasolacrimal duct**, whose upper end widens into the **lacrimal sac**. Once the cord detaches, the maxillary and lateral nasal prominences merge with each other, and the maxillary prominence enlarges to form the cheek and maxilla.

## Derivatives of the frontonasal process

| Component                                                                    | Derivative                                                                                                                                           |
|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Frontonasal prominence (as a whole)                                          | Forehead; bridge (dorsum) of the nose                                                                                                                |
| Medial nasal processes (paired, fuse in midline)                             | Crest and tip of nose; via the intermaxillary segment — philtrum of upper lip, premaxilla (4 incisor teeth), triangular primary palate; nasal septum |
| Lateral nasal processes (paired)                                             | Alae (sides) of the nose; do <b>not</b> contribute to the upper lip                                                                                  |
| Nasolacrimal groove (between lateral nasal process and maxillary prominence) | Nasolacrimal duct and lacrimal sac                                                                                                                   |
| Nasal placode / nasal pit                                                    | Olfactory epithelium of the roof of the nasal cavity; nasal pit deepens into the nasal cavity                                                        |



## Intermaxillary segment and the primary palate

- ▶ Formed by merging of the two medial nasal processes, both at the surface and at a deeper mesenchymal level, complete by the end of the 7th week.
- ▶ Three components:
  - ▶ **Labial component** — forms the philtrum of the upper lip.
  - ▶ **Upper-jaw (premaxillary) component** — carries the four incisor teeth.
  - ▶ **Palatal component** — forms the triangular **primary palate**.
- ▶ The tips of the maxillary prominences grow medially and fuse with the intermaxillary segment, completing the upper lip (maxillary prominence + two medial nasal processes); the lateral nasal processes take no part in lip formation.
- ▶ The **incisive foramen** marks, in the adult, the junction between the primary palate (frontonasal-derived) and the secondary palate (formed later from the paired palatine shelves of the maxillary prominences) — the key radiological/anatomical landmark separating anterior from posterior cleft deformities.

## Molecular control of frontonasal outgrowth

- ▶ The **frontonasal ectodermal zone (FEZ)** is a signalling centre within the frontonasal prominence defined by juxtaposed Sonic hedgehog (Shh) and Fgf8 expression domains; it drives facial outgrowth via epithelial–mesenchymal signalling (Shh, Fgf, Wnt, Bmp family members).
- ▶ Bmp and retinoic-acid (RA) signalling specify frontonasal versus maxillary prominence identity.
- ▶ Loss of Shh signalling causes collapse of the midline with loss of the medial nasal processes — the molecular basis of the holoprosencephaly/median-cleft spectrum described below.
- ▶ EFNB1 (ephrin-B1) mutation causes craniofrontonasal dysplasia, with hypertelorism from disturbed patterning at the fronto-maxillary boundary.

## Applied / Clinical anatomy

- ▶ **Cleft lip** (unilateral commoner than bilateral, left side more often, male preponderance) results from failure of fusion between the maxillary prominence and the medial nasal process; severity ranges from a notch in the vermillion border to a complete cleft reaching the nasal floor, ± cleft of the premaxilla/primary palate when the underlying bone is also split.
- ▶ **Median (midline) cleft lip** — rare; caused by incomplete merging of the two medial nasal processes in the midline; often associated with cognitive impairment and midline brain anomalies.
- ▶ **Oblique facial cleft** — failure of the maxillary prominence to merge with the lateral nasal process along the line of the nasolacrimal groove, exposing the nasolacrimal duct on the face.
- ▶ **Holoprosencephaly spectrum** — extreme deficiency of midline tissue (SHH-pathway mutation, disturbed cholesterol biosynthesis, or teratogen exposure such as alcohol in the 3rd week) causes fusion of the lateral ventricles, synophthalmia, and a single-nostril proboscis formed by fusion of the lateral nasal processes — illustrating the frontonasal prominence's role as the midline facial field.
- ▶ **Anterior vs posterior clefts** — the incisive foramen is the dividing landmark: clefts anterior to it (lip, premaxilla, primary palate) are frontonasal/medial-nasal-process defects; those posterior (secondary palate, uvula) are maxillary-prominence (palatal-shelf) defects.
- ▶ **Craniofrontonasal dysplasia** (EFNB1 mutation, X-linked) — hypertelorism and frontonasal skeletal dysmorphism, a clinical correlate of disturbed fronto-maxillary boundary signalling.
- ▶ Because frontonasal-derived skin is supplied by the ophthalmic (V1) nerve, lesions/anaesthesia in this distribution localise clinically to frontonasal derivatives (forehead, nasal dorsum) as distinct from maxillary/mandibular (V2/V3) territory.

□ Fig 12.1 — Development of the face. Five facial primordia that appear as prominences (Sontakke — Textbook of Human Embryology, p.118)

□ Fig 17.18 — Development of the Face (A, B) In the sixth week, the nasal placodes (Larsen — Human Embryology — 6e, p.1073)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a ventral-view schematic of the developing face (5th–7th week) with:

- ▶ Stomodeum (primitive mouth) and oropharyngeal membrane
- ▶ Frontonasal prominence (upper border of stomodeum)
- ▶ Nasal placode → nasal pit
- ▶ Medial nasal process (inner ridge) and Lateral nasal process (outer ridge)
- ▶ Maxillary prominence (paired) and Mandibular prominence (paired)
- ▶ Nasolacrimal groove (between lateral nasal process and maxillary prominence)
- ▶ Intermaxillary segment (fused medial nasal processes) with its three parts: philtrum, premaxilla (4 incisors), primary palate
- ▶ Incisive foramen (junction of primary and secondary palate, adult landmark)

**High-yield exam pointers**

- ▶ Frontonasal prominence = single, unpaired; the maxillary and mandibular prominences are paired — remember this asymmetry for MCQs.
- ▶ Mesenchyme of the frontonasal prominence is neural-crest derived from midbrain + forebrain; sensory supply of its skin derivatives is by the ophthalmic (V1) nerve.
- ▶ Sequence: frontonasal prominence → nasal placode (5th week) → nasal pit (6th week) → medial + lateral nasal processes.
- ▶ Medial nasal processes fuse → intermaxillary segment → philtrum + premaxilla (4 incisors) + primary (triangular) palate; lateral nasal processes → alae nasi only (no lip contribution).
- ▶ Nasolacrimal duct develops from the ectodermal cord in the floor of the nasolacrimal groove (lateral nasal process/maxillary prominence junction).
- ▶ Incisive foramen = landmark separating primary palate (frontonasal) from secondary palate (maxillary-prominence palatine shelves) — key for classifying cleft deformities as anterior or posterior.
- ▶ Cleft lip = maxillary prominence + medial nasal process fusion failure; median cleft lip = medial nasal processes fail to fuse with each other (rare, associated with holoprosencephaly); oblique cleft = maxillary prominence + lateral nasal process fusion failure along the nasolacrimal groove.
- ▶ Holoprosencephaly/SHH-pathway defects give the most severe frontonasal midline deficiency phenotype (synophthalmia, proboscis).

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Sontakke — Textbook of Human Embryology; IB Singh Human Embryology (CBME 2021); Gray's Anatomy (Standring) 41e.



## Give a detailed account of the endodermal derivatives of pharyngeal arches

Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy

**Definition / Introduction** The pharyngeal (branchial) apparatus consists of five pairs of mesenchymal arches separated externally by ectoderm-lined **pharyngeal clefts** and internally by four **pharyngeal pouches** — paired, endoderm-lined outpocketings of the cranial foregut that appear craniocaudally during the fourth week (Carnegie stages 10–13). While arch mesenchyme (neural crest + mesoderm) forms the skeletal, muscular, vascular and nerve elements of each arch, the **endoderm** lining the pouches — together with the endoderm of the median pharyngeal floor — gives rise to almost all the endocrine and lymphoid organs of the neck: the tympanic cavity and tube, the palatine tonsil, the thymus, both pairs of parathyroid glands, the thyroid gland (including its parafollicular cells), and the mucosa of the tongue. This account describes each derivative pouch by pouch, then the unpaired median floor derivatives.

□ Fig 17.31 — Development of the Pharyngeal Pouch Derivatives: all four pouches give rise to their adult structures, which migrate from the pharyngeal floor (late 5th week) to their definitive neck/thoracic positions (7th week) (Larsen — Human Embryology — 6e, p.1100)

### General plan of the pharyngeal endoderm

- ▶ The endodermal lining of the primitive pharynx bulges laterally at four levels to form the **first, second, third and fourth pharyngeal pouches**, each related to the arch immediately rostral to it.
- ▶ The **third and fourth pouches** each develop a **dorsal wing** and a **ventral wing** that differentiate into separate organs — the key to remembering their derivatives.
- ▶ A rudimentary **fifth pouch** does not persist independently; it fuses with the fourth pouch as the **ultimobranchial body**. Together, the fourth pouch and ultimobranchial body form the **caudal pharyngeal complex**.
- ▶ The oropharyngeal membrane breaks down in the fifth week, uniting the ectoderm-lined stomodeum with the endoderm-lined pharynx into one cranial foregut cavity — so the floor of the mouth/tongue is also endoderm-lined.

### First pharyngeal pouch — tubotympanic recess

- ▶ Dorsal expansion of the first pouch (with a possible contribution from the second pouch) forms the **tubotympanic recess**, which differentiates into the **tympanic (middle ear) cavity** and the **pharyngotympanic (auditory/Eustachian) tube**.
- ▶ The endoderm of the first pouch, approximating the ectoderm of the first pharyngeal cleft, contributes the **inner (mucosal) layer of the tympanic membrane** (outer layer ectodermal, core mesodermal — a trilaminar membrane).
- ▶ Lymphoid tissue accumulates at the pharyngeal opening of the tube to form the **tubal tonsil**.
- ▶ The ventral part of the first pouch is obliterated; only the dorsal part persists, expanding as the head enlarges.

### Second pharyngeal pouch — palatine tonsil

- ▶ The endodermal epithelium lining the second pouch proliferates into the underlying mesenchyme as solid buds.

- ▶ These buds are excavated by degeneration of their central cells, forming the **tonsillar fossae and crypts** of the **palatine tonsil**.
- ▶ Lymphoid cells (of mesenchymal/mesodermal origin) aggregate around the crypts from about the fifth month, forming lymphoid follicles with distinct T- and B-cell regions; mesenchyme condenses to form the tonsillar **capsule**.
- ▶ The residual lumen of the second pouch persists as the **intratonsillar cleft**.
- ▶ Similar endodermal proliferations elsewhere give lymphoid tissue similar to the palatine tonsil: the **lingual tonsil** (posterior third of tongue) and the **pharyngeal/adenoid tonsil** (nasopharyngeal roof) — together with the tubal tonsils (first pouch), these four form Waldeyer's ring.

### Third pharyngeal pouch — thymus and inferior parathyroid

- ▶ The third pouch has a **ventral (bulbar) wing** and a **dorsal wing**, which separate to form two different organs.
- ▶ **Ventral wing → thymus**. Bilateral elongated diverticula become solid cellular cords that proliferate and migrate caudally and medially through the vagal neural-crest mesenchyme; the two primordia meet ventral to the aortic sac but do not fuse — they remain united only by connective tissue — and descend into the anterior mediastinum as the neck elongates and the heart descends. The connection with the pouch is lost, though the stalk may persist transiently as a solid cord.
- ▶ Thymic histogenesis follows a defined timeline: by 10 weeks, over 95% of the gland's cells already belong to the **T-cell lineage** (with a few erythroblasts/B cells); **Hassall's corpuscles** appear early; by 12 weeks mesenchymal septa, vessels and nerves reach the newly forming medulla; macrophage-lineage cells and interdigitating cells appear by 14 weeks; the thymus is **fully differentiated by 17 weeks**, after which it produces the mature (TdT<sup>+</sup>) thymocyte that persists throughout life.
- ▶ **Dorsal wing → inferior parathyroid gland (parathyroid III)**. This differentiates from the epithelium at the dorsal aspect of the pouch, near its duct-like connection with the pharynx.
- ▶ Because parathyroid III migrates caudally together with the descending thymus, it travels further than parathyroid IV and — despite arising from the more cranial (third) pouch — ends up **inferior** to the fourth-pouch parathyroid in the adult neck, a classic examination point.
- ▶ The thymus cannot be recognised as a distinct structure until after the inferior parathyroid primordium has differentiated (around Carnegie stage 16).

### Fourth pharyngeal pouch and the caudal pharyngeal complex

- ▶ The fourth pouch, together with the vestigial fifth pouch (the **ultimobranchial body**), constitutes the **caudal pharyngeal complex**, connected to the pharynx by the pharyngobranchial duct and surrounded by vagal neural crest and developing thyroid tissue.
- ▶ **Dorsal wing/recess → superior parathyroid gland (parathyroid IV)**. It develops connective tissue elements from vagal neural-crest mesenchyme and fenestrated capillaries/lymphatics from invading angiogenic mesenchyme; it comes to lie anchored to the lateral thyroid lobe, remaining **cranial** to the descended parathyroid III.

- **Ultimobranchial body (ventral component)** → **parafollicular ("C") cells of the thyroid**. Its endodermal cells become secondarily incorporated into the lateral lobes of the thyroid gland and, together with an important neural-crest contribution, differentiate into the **calcitonin-secreting C cells**.

## Median endodermal derivatives of the pharyngeal floor — tongue and thyroid

- **Tongue mucosa**. In the fifth week (stage 14), the floor of the pharynx shows a small median **tuberculum impar** (median tongue bud) and paired **lateral lingual swellings**, all from first-arch floor endoderm; their fusion forms the endodermal covering of the **anterior two-thirds of the tongue**. Caudal to these, the **copula** (second-arch floor) and the **hypobranchial (hypopharyngeal) eminence** (third-arch floor, overgrowing the second arch, which itself contributes nothing to the tongue) fuse along the V-shaped **sulcus terminalis** at stage 17 (sixth week) to form the mucosa of the **posterior one-third of the tongue**; a further transverse groove separates the tongue rudiment from the fourth-arch swelling that forms the **epiglottis**.
- **Thyroid gland**. The thyroid is first identifiable, in embryos of about 20 somites, as a median endodermal thickening in the pharyngeal floor between the first and second pharyngeal pouches, immediately dorsal to the aortic sac. Early in the fifth week a median diverticulum — the **thyroid diverticulum** — appears at the **foramen caecum**, immediately caudal to the tuberculum impar. This extends caudally, ventral to the developing hyoid bone, as the **thyroglossal duct**; its tip bifurcates, and the resulting bilobed tissue mass descends to its definitive pretracheal position, where the two **lateral lobes** are joined by an **isthmus**. The thyroglossal duct itself normally degenerates. Follicular epithelial cells pass through three histological stages — active folliculogenesis (10–18 weeks), a quiescent phase (19–29 weeks), and a phase of rising epithelium/colloid ratio with shrinking follicles (after 29 weeks) — while the parafollicular (C) cells, described above, are incorporated secondarily from the ultimobranchial body/neural crest.

## Summary table — pharyngeal pouch derivatives

| Pouch  | Ventral part                               | Dorsal part         | Adult endodermal derivative                                                                        |
|--------|--------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------|
| First  | —                                          | Tubotympanic recess | Tympanic cavity, pharyngotympanic (auditory) tube, inner lining of tympanic membrane, tubal tonsil |
| Second | Endodermal buds invaded by lymphoid tissue | —                   | Palatine tonsil; intratonsillar cleft (remnant lumen)                                              |
| Third  | Ventral (bulbar) wing                      | Dorsal wing         | <b>Thymus</b> (ventral); <b>inferior parathyroid</b> , <b>parathyroid III</b> (dorsal)             |



| Pouch                             | Ventral part         | Dorsal part        | Adult endodermal derivative                                                                                                   |
|-----------------------------------|----------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Fourth + rudimentary fifth        | Ultimobranchial body | Dorsal wing/recess | Parafollicular (C) cells of thyroid via ultimobranchial body (ventral); superior parathyroid, parathyroid IV (dorsal)         |
| Median floor (not a paired pouch) | —                    | —                  | Tongue mucosa (ant. 2/3 from 1st arch; post. 1/3 from 2nd–3rd arch floor); thyroid gland via foramen caecum/thyroglossal duct |



Give a detailed account of the endodermal derivatives of pharyngeal arches

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce a coronal/floor-of-pharynx schematic (late 5th week, migrating to 7th week — as in the plate above) and label:

- ▶ Tubotympanic recess / external auditory meatus
- ▶ Meckel's cartilage, Reichert's cartilage (landmarks only)
- ▶ Palatine tonsil (2nd pouch)
- ▶ Inferior parathyroid + Thymus (3rd pouch, ventral and dorsal wings)
- ▶ Superior parathyroid + Ultimobranchial body (4th pouch)
- ▶ Arrows showing descent to definitive 7th-week positions: superior parathyroid and thyroid remaining in the neck; thymus migrating into the anterior mediastinum; inferior parathyroid ending up caudal to the superior parathyroid.
- ▶ On a second sketch of the tongue floor: tuberculum impar, lateral lingual swellings, foramen caecum, copula, hypobranchial eminence, sulcus terminalis, epiglottal swelling.

### Applied / Clinical anatomy

- ▶ **DiGeorge syndrome** — faulty development of the third/fourth pouches and their neural-crest mesenchyme causes thymic aplasia/hypoplasia (T-cell deficiency) and parathyroid aplasia (hypoparathyroidism/tetany), with cardiac outflow-tract anomalies and characteristic facies — a classic viva extension.
- ▶ **Ectopic/supernumerary parathyroid glands** — parathyroid III descends variably with the thymus and may be found from the angle of the mandible to the pericardium; important during parathyroidectomy/thymectomy.

- ▶ **Thyroglossal cyst/fistula** — a persistent segment of the thyroglossal duct forms a midline swelling (lingual to infrahyoid) that moves up on tongue protrusion, since it is tethered to the foramen caecum/hyoid.
- ▶ **Lingual thyroid** — failure of thyroid descent leaves ectopic tissue at the tongue base between the foramen caecum and epiglottis; may be the patient's only functioning thyroid tissue.
- ▶ **Pyramidal lobe** — persistence of the lower thyroglossal duct as ascending thyroid tissue from the isthmus, seen in about half the population.
- ▶ **Second-pouch/tonsillar anomalies** — a persistent deep intratonsillar cleft can mimic infection clinically; ectopic tonsillar tissue may occur elsewhere in Waldeyer's ring.

### High-yield exam pointers

- ▶ Four pouches, endoderm-lined; third and fourth pouches each have a ventral and a dorsal wing — this pairing is the key mnemonic.
- ▶ 1st pouch → tubotympanic recess → middle ear cavity + auditory tube + tubal tonsil.
- ▶ 2nd pouch → palatine tonsil; intratonsillar cleft = residual pouch lumen.
- ▶ 3rd pouch: ventral wing → thymus; dorsal wing → inferior parathyroid (parathyroid III) — ends up inferior in the adult despite the more cranial pouch of origin.
- ▶ 4th pouch + vestigial 5th (ultimobranchial body): dorsal wing → superior parathyroid (parathyroid IV); ultimobranchial body → parafollicular/C cells of thyroid.
- ▶ Tongue mucosa is endoderm: anterior 2/3 from tuberculum impar + lateral lingual swellings (1st arch); posterior 1/3 from copula (2nd arch, mostly overgrown) + hypobranchial eminence (3rd arch); junction = sulcus terminalis.
- ▶ Thyroid gland arises as a median endodermal diverticulum at the foramen caecum, descends via the thyroglossal duct, and secondarily incorporates neural-crest-derived C cells from the ultimobranchial body.
- ▶ DiGeorge syndrome links 3rd/4th pouch failure to absent thymus + parathyroids — a favourite applied-anatomy add-on.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Moore The Developing Human 9e; Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; IB Singh Human Embryology (CBME 2021).



## Mesodermal derivatives of the branchial arches

*Asked in: Paper II 16-Jul-2020 — RGUHS MD/MS Anatomy*

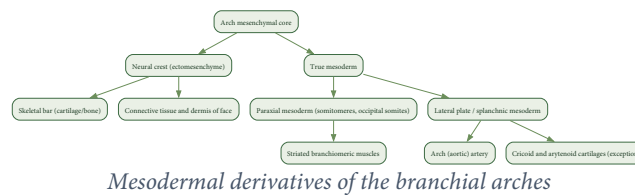
### Definition / Introduction

Each pharyngeal (branchial) arch is a bar of mesenchyme covered externally by ectoderm and internally by endoderm. Its mesenchymal core is a composite of **two embryologically distinct populations** —

neural-crest-derived ectomesenchyme, which builds almost the entire skeletal and connective-tissue framework of the arch and the dermis of the face, and **true mesoderm** (paraxial plus lateral-plate/splanchnic), which is the source of everything this question asks for: the **striated musculature**, the **arch (aortic) artery**, and, exceptionally, **two cartilages of the larynx**. This answer is restricted to the mesodermal component and its derivatives, taken arch by arch.

## 1. Origin and general plan of the arch-mesodermal component

- ▶ Each arch, in cross-section, contains: a **skeletal bar** (neural-crest ectomesenchyme — the "odd one out" is discussed below), a **muscular mass** (true mesoderm), an **arch artery** (true mesoderm), and a **cranial nerve** supplying that muscle mass.
- ▶ The **muscular mass** is populated by **myoblasts of paraxial-mesoderm origin** — from **somitomeres 4–7** and the first two **occipital somites** — which migrate into the arch core; it differentiates into striated, voluntary ("branchiomic") muscle.
- ▶ The **arch artery** differentiates within **splanchnic (lateral-plate) mesoderm** surrounding the primitive pharynx, forming the endothelium and wall of the corresponding aortic-arch vessel.
- ▶ **Rule of thumb (high-yield)**: wherever an arch-derived muscle migrates to during development, it always carries its arch nerve with it — this is how the embryonic arch of origin of any head/neck muscle is traced.



## 2. Muscular (myoblastic) derivatives — arch by arch

| Arch           | Nerve of the arch                                   | Muscles derived from arch mesoderm                                                                                                                                                                                                                                                                                                |
|----------------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I — Mandibular | Mandibular division of trigeminal (V <sub>3</sub> ) | Muscles of <b>mastication</b> (temporalis, masseter, medial and lateral pterygoids), <b>mylohyoid</b> , <b>anterior belly of digastric</b> , <b>tensor tympani</b> , <b>tensor veli palatini</b>                                                                                                                                  |
| II — Hyoid     | Facial (VII)                                        | Muscles of <b>facial expression</b> (buccinator, platysma, orbicularis oris, orbicularis oculi, zygomaticus, levator labii superioris, levator labii inferioris, levator anguli oris, nasal muscles, auricular muscles, occipitofrontalis/epicranium), <b>stapedius</b> , <b>stylohyoid</b> , <b>posterior belly of digastric</b> |
| III            | Glossopharyngeal (IX)                               | <b>Stylopharyngeus</b> — the only muscle of this arch                                                                                                                                                                                                                                                                             |

| Arch | Nerve of the arch                       | Muscles derived from arch mesoderm                           |
|------|-----------------------------------------|--------------------------------------------------------------|
| IV   | Superior laryngeal branch of vagus (X)  | Cricothyroid, levator veli palatini, constrictors of pharynx |
| V    | —                                       | Rudimentary arch; no muscle forms                            |
| VI   | Recurrent laryngeal branch of vagus (X) | All intrinsic muscles of the larynx except cricothyroid      |

- ▶ All muscles of a given arch are, without exception, supplied by that arch's own nerve — the single most examinable fact in this topic.
- ▶ The 1st arch alone has a double (pretrematic + posttrematic) nerve relationship reflected in the mixed chorda-tympani/mandibular innervation pattern of structures at the tongue-mandible junction, though this is a nerve-supply nuance rather than a muscle derivative.

embed: ![Fig 17.12 — Fate of the Pharyngeal Arch Musculature (1-5) The pharyngeal arch (Larsen — Human Embryology — 6e, p.1060)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/5f9c9c3cff5b9445.jpg)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Two-panel schematic (label exactly as follows):

- ▶ **Panel A (5-week embryo, lateral view of head/neck):** five colour-coded arch muscle anlagen labelled 1–5 (arch 5 rudimentary/not muscularised).
- ▶ **Panel B (20-week fetus, face and neck):** trace each anlage to its adult muscle, labelling — Frontalis, Temporalis, Auricularis, Buccinator, Masseter, Orbicularis oculi, Orbicularis oris, Stylohyoid, Posterior belly of digastric, Stylopharyngeus, Anterior belly of digastric, Mylohyoid, Cricothyroid, Middle constrictor of pharynx, Inferior constrictor of pharynx, Platysma.
- ▶ Colour-code each labelled muscle to its arch of origin (arch 1 vs arch 2 vs arch 3 vs arch 4) so the examiner can see the arch–muscle correspondence at a glance.

### 3. Embryonic source of the arch myoblasts — somitomeres and occipital somites

- ▶ Head musculature (including arch muscles) is **not** derived from typical somites but from **somitomeres** — partially segmented masses of paraxial mesoderm cranial to the occipital somites — together with the first few **occipital somites** proper.
- ▶ Only the somitomeres/somites relevant to the branchial arches are tabulated here:

| Paraxial-mesoderm source | Muscle group formed                  | Nerve                        |
|--------------------------|--------------------------------------|------------------------------|
| Somitomere 4             | Muscles of the 1st (mandibular) arch | Mandibular (V <sub>3</sub> ) |

| Paraxial-mesoderm source  | Muscle group formed              | Nerve                 |
|---------------------------|----------------------------------|-----------------------|
| Somitomere 6              | Muscles of the 2nd (hyoid) arch  | Facial (VII)          |
| Somitomere 7              | Stylopharyngeus (3rd arch)       | Glossopharyngeal (IX) |
| Occipital somites 1 and 2 | Laryngeal muscles (4th–6th arch) | Vagus (X)             |

- (Somitomeres 1, 2, 3 and 5 form the extra-ocular muscles, which are *not* arch derivatives and lie outside the scope of this question.)

#### 4. Arterial derivatives of arch mesoderm — fate of the aortic-arch arteries

| Aortic (arch) artery | Definitive derivative                                                                                                                                                                                                               |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st                  | Largely disappears; a small remnant contributes to the maxillary artery                                                                                                                                                             |
| 2nd                  | Largely disappears; remnants form the hyoid and stapedial arteries                                                                                                                                                                  |
| 3rd                  | Common carotid artery and the proximal (1st) part of the internal carotid artery; the external carotid artery buds off as a new sprout from this region                                                                             |
| 4th                  | Left → part of the arch of the aorta, between the left common carotid and left subclavian arteries. Right → proximal part of the right subclavian artery                                                                            |
| 5th                  | Never forms completely, or forms and regresses — no adult derivative                                                                                                                                                                |
| 6th (pulmonary arch) | Right → proximal part of the right pulmonary artery (distal part disappears). Left → proximal part of the left pulmonary artery; its distal part persists prenatally as the ductus arteriosus (→ ligamentum arteriosum postnatally) |

- Mnemonic for recall: 1-Maxillary, 2-Stapedial/Hyoid, 3-Carotid, 4-Aortic arch(L)/Subclavian(R), 5-none, 6-Pulmonary artery/Ductus arteriosus.

#### 5. The mesodermal exception in the laryngeal skeleton

- Almost every cartilage/bone attributed to an arch (Meckel's cartilage, malleus, incus, Reichert's cartilage, styloid process, hyoid bone, thyroid/corniculate/cuneiform cartilages) is a **neural-crest**, not mesodermal, derivative.
- The **cricoid** and **arytenoid cartilages** of the larynx are the recognised exception — they arise from **lateral-plate mesoderm**, making them the only skeletal elements that are genuinely mesodermal derivatives of the branchial-arch region.
- This distinction is a favourite short-answer/viva discriminator between "skeletal derivatives" (mostly neural crest) and "mesodermal derivatives" (muscle + artery + cricoid/arytenoid) questions.

## Applied / Clinical anatomy

- ▶ **Bell's palsy** — a lower motor neurone facial (VII) nerve palsy paralyses all 2nd-arch mesoderm-derived muscles of facial expression on the affected side (sagging face, loss of nasolabial fold, inability to close the eye or purse the lips), because the nerve of an arch remains fixed to its muscle wherever the muscle migrates.
- ▶ **Trigeminal motor (V<sub>3</sub>) lesion** — weakness of the 1st-arch muscles of mastication, with deviation of the open jaw towards the paralysed side (unopposed pull of the intact contralateral pterygoids).
- ▶ **Gag reflex** — tests the sensory glossopharyngeal (3rd arch) and the motor vagal supply to the pharyngeal constrictors (4th-arch muscle); its loss localises a IX–X lesion.
- ▶ **Recurrent laryngeal nerve palsy** (thyroid/parathyroid surgery, mediastinal masses, aortic aneurysm) — paralyses the 6th-arch-derived intrinsic laryngeal muscles, producing hoarseness or aphonia; the nerve's fixed embryological hook around the 6th-arch arterial derivative (ductus arteriosus on the left, subclavian remnant on the right) explains its differing course on the two sides.
- ▶ **Persistent stapedia artery** — rare failure of regression of the 2nd aortic arch remnant; presents as a middle-ear vascular mass with pulsatile tinnitus/conductive deafness.
- ▶ **Aberrant (non-recurrent) right subclavian artery / dysphagia lusoria** — abnormal regression of the right 4th aortic arch with persistence of the distal right dorsal aorta produces a retro-oesophageal right subclavian artery compressing the oesophagus; the right recurrent laryngeal nerve fails to loop and takes a direct ("non-recurrent") course, an important pitfall in neck/thyroid surgery.
- ▶ **Double aortic arch / vascular ring** — persistence of both the right and left 4th arch–dorsal aorta systems encircles the trachea and oesophagus, causing infantile stridor and dysphagia.
- ▶ **Right aortic arch** — mirror-image regression of the left (rather than right) 4th arch; frequently associated with tetralogy of Fallot.
- ▶ **Coarctation of the aorta / interrupted aortic arch** — abnormal regression at the site of the 4th-arch-derived aortic isthmus.
- ▶ **Patent ductus arteriosus (PDA)** — failure of postnatal closure of the distal left 6th-arch derivative; a classic continuous "machinery" murmur.

## High-yield exam pointers

- ▶ Arch mesenchyme = **neural crest** (skeleton + connective tissue/dermis — except cricoid & arytenoid) **plus mesoderm** (muscle + arch artery).
- ▶ Golden rule: the **nerve of an arch always follows its muscle**, however far the muscle migrates — the basis for tracing arch of origin and for the clinical correlations above.
- ▶ Muscle groups by arch: **I** – mastication (V<sub>3</sub>); **II** – facial expression (VII); **III** – stylopharyngeus only (IX); **IV** – cricothyroid + pharyngeal constrictors + levator veli palatini (superior laryngeal/vagus); **V** – none (rudimentary); **VI** – all intrinsic laryngeal muscles except cricothyroid (recurrent laryngeal/vagus).
- ▶ Myogenic precursors: **somitomere 4** (arch 1), **somitomere 6** (arch 2), **somitomere 7** (arch 3, stylopharyngeus), **occipital somites 1–2** (arches 4–6, laryngeal muscles).

- ▶ Aortic-arch-artery fates mnemonic: **1-Maxillary, 2-Stapedial/Hyoid, 3-Carotid, 4-Aorta(L)/Subclavian(R), 5-none, 6-Pulmonary/Ductus arteriosus.**
- ▶ **Cricoid and arytenoid cartilages** are the sole skeletal (mesodermal, lateral-plate) exception in an otherwise neural-crest-derived laryngeal/facial skeleton.
- ▶ Clinically, arch-mesoderm derivatives explain Bell's palsy, trigeminal motor palsy, gag reflex testing, recurrent laryngeal nerve palsy, and the entire family of aortic-arch vascular anomalies (double/right aortic arch, aberrant subclavian, coarctation, PDA).

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Sontakke Textbook of Human Embryology; Larsen Human Embryology 6e; Vishram Singh Textbook of Clinical Embryology; Gray's Anatomy (Standring) 41e.



## Neural crest derived mesenchyme

*Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — Neural crest cells arising in the **head region** are unique among neural-crest populations because, in addition to a neuronal/glial lineage, they undergo a second epithelial-to-mesenchymal transformation to produce an extensive **non-neuronal mesenchymal population** — traditionally termed **ectomesenchyme** — that behaves, in terms of patterning, like the somatopleuric mesenchyme of the trunk. This head neural-crest mesenchyme is the principal building material of the craniofacial skeleton, cranial connective tissues, forebrain meninges, ocular stroma, dental papilla and the tunica media of the great-vessel roots. Trunk neural crest, by contrast, does **not** form a comparable mesenchymal population.

### 1. Origin, induction and epithelial-mesenchymal transformation

- ▶ Neural crest arises at the tips of the neural folds, at the border between neuroectoderm (neural plate) and surface ectoderm, and is committed to a crest lineage before the neural plate folds.
- ▶ **Molecular induction:** intermediate levels of **BMP** (regulated by the BMP-antagonists **noggin and chordin**), together with **FGF and WNT** signalling, induce **PAX3** and related transcription factors that specify the neural-plate border; these in turn induce **SNAIL and FOXD3**, which commit cells to a neural-crest fate, and **SLUG**, which drives the epithelial-to-mesenchymal transition and onset of migration. High BMP → epidermis; very low BMP → neural ectoderm; intermediate BMP at the border → neural crest.
- ▶ **Head (cranial) neural crest migrates before neural tube closure** — unlike trunk crest, which detaches only after the tube has closed. The crest-cell population arising from the head is larger than at any trunk level, and each brain region contributes its own crest population that migrates dorsolaterally around the neural tube to reach the ventral head and surround the pharyngeal arches.



- Once in the head, this migratory population loses its epithelial junctions and disperses as a loose primitive connective tissue — **mesenchyme** — which, because it is derived from ectoderm via the neural crest (rather than from mesoderm), is specifically called **ectomesenchyme**.

## 2. Head versus trunk neural crest — divergent mesenchymal potential

| Feature                                 | Head (cranial) neural crest                                                                                                                                                            | Trunk neural crest                                                                   |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Timing of emigration                    | Before neural tube closure                                                                                                                                                             | After neural tube closure                                                            |
| Mesenchymal (ectomesenchyme) derivative | <b>Present</b> — extensive craniofacial mesenchyme                                                                                                                                     | <b>Absent</b>                                                                        |
| Neuronal/glia derivatives               | Sensory & parasympathetic ganglia of head and neck                                                                                                                                     | Dorsal root/sympathetic/enteric ganglia, Schwann cells                               |
| Migration constraint                    | Surrounds prosencephalic/optic vesicles, occupies each pharyngeal arch                                                                                                                 | Channelled through the rostral (permissive) half of each sclerotome                  |
| Fate map plasticity                     | Ectomesenchyme precursors are restricted to the sites they occupy in normal development (unlike neuronal crest derivatives, which are broadly interchangeable on heterotopic grafting) | Broadly plastic — grafted crest from any level can form most PNS ganglion cell types |

## 3. Cranial crest populations: rhombomeric origin and pharyngeal-arch destination

Three principal streams of head neural crest, each keyed to a hindbrain segment (rhombomere), migrate into a specific pharyngeal arch and lay down that arch's mesenchyme:

| Crest population                              | Level of origin                                                                                                                     | Arch destination                                                     | Principal mesenchymal fate                                                                                             |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| <b>Trigeminal</b>                             | Diencephalon, midbrain and rhombomeres 1–2 (prorhombomere A)                                                                        | Frontonasal process + Arch 1 (maxillary & mandibular processes)      | Frontonasal and first-arch mesenchyme → facial skeleton                                                                |
| <b>Hyoid</b>                                  | Rhombomere 4 (prorhombomere B; rhombomeres 3 & 5 contribute only sparse crest that disperses to adjacent even-numbered rhombomeres) | Arch 2                                                               | Second-arch (Reichert's) skeletal and connective tissue                                                                |
| <b>Vagal</b> (including cardiac neural crest) | Rhombomeres 6–8 (prorhombomere C, caudal to the otocyst)                                                                            | Arches 3, 4 and 6; a subset continues into the cardiac outflow tract | Third/fourth/sixth-arch skeleton and pharyngeal connective tissue; <b>conotruncal</b> (aorticopulmonary) <b>septum</b> |

| Crest population | Level of origin                                  | Arch destination                                               | Principal mesenchymal fate                |
|------------------|--------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|
| Occipital        | Rhombomere 8 region (prorhombomere D), post-otic | Migrates with occipital myoblasts to form the hypoglossal cord | Connective-tissue framework of the tongue |

□ Fig 6.6 — Drawing shows the migratory paths of neural crest cells in the head region (Langman's Medical Embryology — Sadler — 14e, p.96)

### Diagram to draw

A lateral view of a stage-12/13 embryo head: draw the closing/closed neural tube with the telencephalon, diencephalon, mesencephalon and rhombencephalon labelled; from the neural-fold tips, draw arrows sweeping ventrolaterally into (i) the **frontonasal process**, (ii) **arch 1** split into maxillary and mandibular processes, (iii) **arch 2** (hyoid), (iv) **arch 3**, (v) **arches 4 and 6**. Label the epipharyngeal (cranial sensory) placodes V, VII, IX, X at the dorsal margin of each arch, and mark the optic vesicle and otic vesicle for orientation.



## 4. Derivatives of neural-crest-derived mesenchyme (ectomesenchyme)

| Category                                                     | Structures                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Membranous (dermal) bones of face, viscerocranium & calvaria | Face/viscerocranium: frontal, nasal, lacrimal and zygomatic bones, vomer, maxilla (with premaxilla) and mandible, palatine and tympanic bones, medial pterygoid plate of the sphenoid. Calvaria: the <b>frontal and squamous temporal bones</b> only. (The <b>parietal bone</b> , by contrast, is of mesodermal origin — see below.) |
| Arch-cartilage derivatives                                   | <b>Meckel's cartilage</b> (1st arch) → malleus, incus, anterior malleolar ligament, sphenomandibular ligament, spine of sphenoid, genial tubercle region of the mandible. <b>Reichert's cartilage</b> (2nd arch) → stapes, styloid process, stylohyoid ligament, lesser horn and upper body of hyoid                                 |
| Ocular connective tissue                                     | Corneal stroma and endothelium, sclera, choroid, stroma of the ciliary body and iris, trabecular meshwork at the iridocorneal angle                                                                                                                                                                                                  |
| Dental mesenchyme                                            | Dentine, odontoblasts, dental papilla/pulp, cementum and periodontal ligament                                                                                                                                                                                                                                                        |
| Glandular stroma                                             | Connective-tissue framework of the lacrimal, nasal, labial, palatine, oral and salivary glands; connective tissue of the thyroid gland and of pharyngeal-pouch derivatives (parathyroids, thymus)                                                                                                                                    |
| Meninges                                                     | Pia-arachnoid and dura at the <b>forebrain</b> level only — the more caudal (midbrain, hindbrain, spinal) meninges are mesodermal (paraxial mesenchyme)                                                                                                                                                                              |

| Category                  | Structures                                                                                                                                                     |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dermis                    | Dermis and subcutaneous connective tissue of the face and neck                                                                                                 |
| Cardiovascular            | Tunica media of the aortic-arch-derived great vessels; <b>conotruncal (aorticopulmonary) septum</b> ; smooth muscle of blood vessels of the face and forebrain |
| General connective tissue | Cartilage, ligaments and tendons of the head not itemised above                                                                                                |

## 5. The neural crest–mesoderm boundary in the skull vault

- ▶ Lineage-tracing shows the **frontal and squamous temporal bones are neural-crest derived**, whereas the **parietal bones are mesodermal**; the **interparietal bone is a mixed crest/mesoderm population**.
- ▶ The **coronal suture** therefore forms exactly at this neural crest–mesoderm interface (as does part of the sagittal suture, owing to a tongue of crest tissue between the two parietal primordia); this tissue interface is the site of the molecular signalling (transcription factor **TWIST**, fibroblast growth factors and their receptors, **FGF/FGFR**) that regulates the balance of proliferation and osteogenic differentiation controlling suture patency.

## Applied / Clinical anatomy

- ▶ **Treacher Collins syndrome** (mandibulofacial dysostosis) — autosomal dominant, ~1/50,000 births, due to mutation of **TCOF1** (encoding the nucleolar protein *treacle*), which is needed to prevent apoptosis of first-arch neural crest mesenchyme; presents with hypoplastic/absent maxilla, mandible and zygomatic arches, cleft palate, external-ear defects with conductive deafness, and down-slanting palpebral fissures with lower-lid colobomas.
- ▶ **Robin sequence** — micrognathia, cleft palate and glossoptosis from disordered first-arch mandibular mesenchyme; may occur independently or with Treacher Collins.
- ▶ **22q11.2 deletion syndrome** (DiGeorge/velocardiofacial syndrome; **TBX1** gene) — abnormal vagal/cardiac neural crest mesenchyme causes conotruncal cardiac defects (persistent truncus arteriosus, tetralogy of Fallot) with thymic and parathyroid hypoplasia from arch 3/4 pouch-associated mesenchyme, together with craniofacial dysmorphism.
- ▶ **Cleft lip and palate** — failure of fusion/mesenchymal confluence of the frontonasal, maxillary and mandibular processes (or of the palatal shelves), all built of neural-crest mesenchyme.
- ▶ **Craniosynostosis** — premature fusion of a calvarial suture; because the coronal suture lies at the crest–mesoderm signalling boundary, mutations in **FGFR** genes (and **TWIST**) that disturb this interface produce coronal (and other) synostoses, with resultant skull-shape deformity (brachycephaly, plagiocephaly).
- ▶ **Teratogen vulnerability** — retinoic acid and alcohol are particularly toxic to migrating crest mesenchyme, explaining why craniofacial and cardiac (conotruncal) malformations cluster together in the same affected infant.

- Persistence of the Meckel's-cartilage sheath as the anterior malleolar and sphenomandibular ligaments, and of Reichert's cartilage as the stylohyoid ligament, are classic gross-anatomy correlates of arch-mesenchyme chondrification.

### High-yield exam pointers

- Only **head/cranial** neural crest forms mesenchyme (ectomesenchyme); trunk crest never does.
- Molecular induction: intermediate BMP (antagonised by noggin/chordin) + FGF/WNT → PAX3 → SNAIL/FOXD3 → SLUG.
- Three head-crest streams: **trigeminal** (r1–2 → arch 1), **hyoid** (r4 → arch 2), **vagal** (r6–8 → arches 3, 4, 6, continuing to the heart as cardiac neural crest).
- Meckel's cartilage (arch 1) → malleus, incus; Reichert's cartilage (arch 2) → stapes, styloid process, stylohyoid ligament, lesser horn/upper body of hyoid.
- Frontal and squamous temporal bones = neural-crest derived; **parietal bone = mesodermal**; coronal suture sits at this crest–mesoderm interface.
- Ectomesenchyme derivatives to reel off: facial skeleton, arch cartilages, corneal/scleral/ciliary stroma, dentine/odontoblasts, glandular connective-tissue stroma, forebrain meninges, dermis of face/neck, tunica media of great vessels, conotruncal septum.
- Clinical link: Treacher Collins (TCOF1/treacle), Robin sequence, 22q11.2 deletion/DiGeorge (TBX1, cardiac neural crest), craniosynostosis (FGFR/TWIST at the crest–mesoderm suture boundary).

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Ross Histology — A Text and Atlas 7e (ectomesenchyme terminology).



## Occipital somites

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Occipital somites are the **four most-cranial pairs of "true" (epithelial) somites**, formed in the post-otic paraxial mesoderm immediately caudal to the seven head somitomeres and cranial to the first cervical somite. Somite 1 (the first occipital somite) arises from the eighth somitomere, just caudal to the midpoint of the notochordal plate. Although transient as discrete segments, they are of high embryological importance: their **sclerotomes contribute to the base of the occipital bone (basiocciput/exoccipital, foramen magnum rim)**, and their **myotomes migrate out to form virtually the entire musculature of the tongue**, carrying with them the segmental nerve rootlets that fuse into the **hypoglossal (XII) nerve**.

### Formation and number

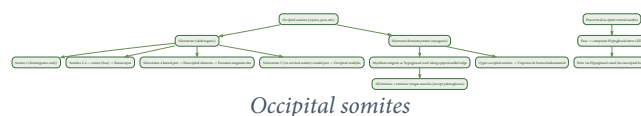
- Somites form in cranio-caudal sequence at ~3 pairs/day; ultimately **≈42–44 pairs** form, of which the terminal several regress, leaving the definitive adult count.

- Composition: **4 occipital + 8 cervical + 12 thoracic + 5 lumbar + 5 sacral + 8-10 coccygeal** somites (most coccygeal somites disappear).
- Occipital somites are **post-otic** — they appear only after the otic vesicle has formed, distinguishing them from the unsegmented **preoccipital/preotic somitomeres** (3 pairs) that lie rostral to them and form the extraocular muscles.
- The **first occipital myotome disintegrates soon after it forms**; correspondingly, the first occipital sclerotome also disintegrates early.
- Some descriptions extend the group to "4-5" because the **occipitocervical (craniovertebral) boundary** is defined embryologically at the junction between the 4th and 5th somites, making the transitional 5th somite relevant to occipital-region development even though it is the first cervical somite proper.

| Somite group               | Number                 | Innervation                                                               | Chief derivative                                    |
|----------------------------|------------------------|---------------------------------------------------------------------------|-----------------------------------------------------|
| Preoccipital (somitomeres) | 3 pairs                | Cranial nerves III, IV, VI                                                | Extraocular muscles                                 |
| Occipital somites          | 4 pairs                | Fused precervical (occipital) ventral rootlets → <b>hypoglossal (XII)</b> | Tongue musculature; part of basiocciput/exoccipital |
| Cervical–coccygeal somites | remaining ~38-40 pairs | Segmental spinal nerves                                                   | Vertebral column, trunk/limb muscle, dermis         |

### Fate of the sclerotomal (skeletogenic) component

- Occipital sclerotomes 2, 3 and 4 form mesenchymal condensations equivalent to vertebral centra; sclerotome 1 disintegrates early.
- By stage 14, sclerotomes 1-3 have fused; **sclerotome 4 remains the most distinct** and forms an **incomplete centrum axially** and **exoccipital elements laterally** — the latter correspond to neural arches and form the **rim of the foramen magnum**.
- **Hypoglossal nerve rootlets** (with the hypoglossal artery) pass through the **less-dense cranial part of occipital sclerotome 4** to reach the developing tongue — this is why the adult hypoglossal nerve exits the skull through the **hypoglossal canal in the exoccipital part of the occipital bone**, a bone derived from the very somites whose myotomes the nerve supplies.
- The **occipital condyles** develop from the **cranial part of sclerotome 5**, which is actually the **first cervical somite** — placing the occipitocervical (craniovertebral) junction precisely at the **boundary between somites 4 and 5**.
- Together, occipital somites 1-4 (with contributions from the parachordal/basal plate cartilage) form the **basiocciput** and contribute to the cartilaginous base of the skull around the cranial notochord.



## Fate of the myotomal (myogenic) component — tongue musculature

- ▶ Myogenic cells arise from the **ventrolateral edge of the epithelial plate/dermomyotome** of the occipital somites.
- ▶ These myoblasts **coalesce beside the fourth occipital somite** and extend ventrally as an elongated cellular column — the "**hypoglossal cord**" (Larsen) — migrating anteroinferiorly along the **epipericardial ridge** (Vishram Singh), around the pharynx, to invade the developing tongue primordium in the floor of the pharynx.
- ▶ These myoblasts form **all the intrinsic muscles and three of the four extrinsic muscles of the tongue** (genioglossus, hyoglossus, styloglossus) — **every tongue muscle except palatoglossus**.
- ▶ **Palatoglossus** is the exception: it develops from the **unsegmented mesenchyme of the fourth pharyngeal (branchial) arch**, not from occipital somites, and is therefore innervated by the **pharyngeal plexus of the vagus (X)**, not the hypoglossal nerve — hence the teaching that palatoglossus is embryologically "a muscle of the palate, not truly of the tongue."
- ▶ Occipital-somite myoblasts also contribute (per Larsen) to the **superior, middle and inferior constrictors of the pharynx**, whereas the cricothyroid, levator veli palatini and intrinsic laryngeal muscles arise from unsegmented cranial mesoderm of the 4th/6th arches (nerve X).
- ▶ Per current descriptions in Gray's Anatomy (41e), the **upper occipital somites** also give rise to **trapezius and sternocleidomastoid** (both innervated by the accessory nerve, XI); the myoblasts migrate into surrounding neural-crest-derived mesenchyme, which forms their connective tissue, while their bony attachments (nuchal line, spine of scapula) are derived from post-otic neural crest.

## Innervation — genesis of the hypoglossal nerve

- ▶ Each occipital myotome is innervated by its own segmental **ventral (motor) rootlet**, analogous to the ventral roots of spinal nerves — these are collectively termed the **precervical/occipital nerves**.
- ▶ As the myoblasts migrate to the tongue, these segmental rootlets migrate with them and **fuse into a single composite nerve — the hypoglossal nerve (XII)**.
- ▶ Because the hypoglossal nerve is purely a fused **motor (ventral root) nerve**, it has **no dorsal (sensory) root or ganglion** — explaining why cranial nerve XII is a pure motor nerve, unlike a typical spinal nerve.
- ▶ The nerve emerges from the medulla between the pyramid and olive (post-olivary/pre-olivary sulcus region) and leaves the skull through the **hypoglossal canal**, itself carved through the exoccipital part of occipital sclerotome 4 — the same somite that gave origin to the myotome the nerve supplies.

## Applied / Clinical anatomy

- ▶ **Basilar (craniovertebral junction) anomalies**: failure of the normal segmentation/fusion pattern of occipital sclerotomes 1-4 and cervical sclerotome 5 underlies anomalies such as **occipitalization of the atlas** (fusion of atlas to the occipital bone) — a well-recognised craniovertebral anomaly that can compress the upper cervical cord/medulla and may need surgical decompression.

- ▶ **Klippel-Feil syndrome** (congenital fusion of cervical vertebrae) and **os odontoideum/ossiculum terminale** (failure of fusion of the atlanto-axial centra) are further disorders of segmentation in this same occipitocervical developmental field.
- ▶ **Hypoglossal nerve palsy**: because the tongue musculature and its nerve share a single embryological (occipital-somite) origin, a lower motor neurone XII lesion causes **ipsilateral tongue deviation on protrusion** (due to unopposed action of the healthy genioglossus) with ipsilateral wasting/fasciculation — a direct clinical readout of occipital-somite developmental biology.
- ▶ **Palatoglossus sparing** in hypoglossal palsy (it remains active, supplied by vagus) is a useful bedside/exam discriminator confirming the different embryological source of this one tongue muscle.
- ▶ Anomalies of the **foramen magnum rim/exoccipital bone** (e.g. condylar hypoplasia, basilar invagination) reflect maldevelopment of occipital sclerotome 4.
- ▶ Recognising that **trapezius/SCM arise from occipital-somite myotomes** (not branchial arch mesoderm) explains their shared accessory-nerve (XI) innervation and the surgical plane in which they are mobilised (neural-crest-derived fascial envelope).

### High-yield exam pointers

- ▶ Occipital somites = **4 pairs**, post-otic, most-cranial "true" somites; somite 1 (and its sclerotome) **disintegrates early**.
- ▶ Total somite count  $\approx$  4 occipital + 8 cervical + 12 thoracic + 5 lumbar + 5 sacral + 8-10 coccygeal.
- ▶ Sclerotomes 2-4  $\rightarrow$  **basiocciput**; sclerotome 4 lateral part  $\rightarrow$  **exoccipital/foramen magnum rim**; sclerotome 5 (1st cervical somite) cranial part  $\rightarrow$  **occipital condyles**. Occipitocervical junction = boundary of somites 4/5.
- ▶ Myotomes migrate as the "**hypoglossal cord**" along the **epipericardial ridge** into the tongue primordium.
- ▶ Form **all intrinsic + extrinsic tongue muscles except palatoglossus** (which is a 4th-arch/vagus derivative).
- ▶ Segmental "precervical/occipital" ventral rootlets **fuse to form the hypoglossal (XII) nerve** — a purely motor nerve with no dorsal root.
- ▶ Hypoglossal nerve exits through the **hypoglossal canal**, carved in the same (exoccipital) sclerotome that its supplied muscles arise from.
- ▶ Recent Gray's-level detail: **trapezius and sternocleidomastoid** also derive from upper occipital-somite myotomes (accessory nerve, XI).
- ▶ Applied correlate: **occipitalization of atlas / Klippel-Feil** = craniovertebral segmentation anomalies of this same region; XII palsy  $\rightarrow$  ipsilateral tongue deviation with palatoglossus spared.



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Sagittal/lateral schematic of a 5-week embryo head-neck region showing occipital somites 1-4 and the migrating tongue myoblasts, labelled:

- ▶ Otic vesicle (landmark for post-otic position)
- ▶ Occipital somites 1, 2, 3, 4 (arranged in a craniocaudal row caudal to the otic vesicle)
- ▶ First cervical somite (sclerotome 5) — labelled separately, with an arrow marking the **occipitocervical junction** at the 4/5 boundary
- ▶ Basiocciput (from fused centra of somites 1-4) and exoccipital element (from sclerotome 4, lateral part) forming the **foramen magnum rim**
- ▶ Occipital condyle — arrow from cranial part of sclerotome 5
- ▶ Migrating myoblast column ("hypoglossal cord") curving anteroinferiorly around the pharynx toward the tongue swelling in the floor of the pharynx, with the fusing precervical nerve rootlets running alongside it, labelled **hypoglossal nerve**
- ▶ Tongue primordium — label the muscles formed (genioglossus, hyoglossus, styloglossus, intrinsic muscles) versus the **palatoglossus**, shown arising separately from 4th-arch mesenchyme and innervated by the vagus/pharyngeal plexus

□ Fig 17.12 — Fate of the Pharyngeal Arch Musculature (Larsen — Human Embryology — 6e, p.1060)

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Larsen's Human Embryology 6e; Moore's The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; BD Chaurasia Human Anatomy Vol 3-4 8e; AK Datta Human Anatomy Vol 2 (Head & Neck).

♦ ♦ ♦

**Pharyngeal pouch**

*Asked in: Paper II 10-Jul-2023 — RGUHS MD/MS Anatomy*

**Definition / Introduction**

Pharyngeal (pharyngobranchial) pouches are paired, endoderm-lined outpocketings of the primitive pharynx — the cranial-most part of the foregut — that bulge laterally into the mesenchyme between successive pharyngeal arches during the 4th–5th weeks of development. Each pouch abuts an externally-placed, ectoderm-lined pharyngeal cleft (groove) of the corresponding number, the two being separated by a bilaminar pharyngeal membrane; unlike gill slits in fish, this membrane never perforates in the human embryo. There are four well-defined pairs of pouches; a fifth pair is rudimentary or absent. The endodermal epithelium lining the pouches is the primordium of several major endocrine and lymphoid organs of the head, neck and thorax — the middle ear/auditory tube, palatine tonsil, thymus, and parathyroid glands — making the pouches embryologically far more important than the transient clefts.

## 1. Formation and patterning of the pharyngeal pouches

- Pouches form in **craniocaudal sequence**: the two most anterior pouches (1st and 2nd) appear together, while the more posterior pouches (3rd and 4th) form sequentially and later.
- Formation of the **posterior pouches** additionally requires **retinoid and Wnt signalling**, and the T-box gene **Tbx1**; loss of Tbx1 function causes failure of posterior pouch formation and failure of neural-crest segregation — this is the molecular basis of DiGeorge syndrome (see Applied anatomy).
- Pouch endoderm, not neural crest, patterns the pharyngeal-arch skeleton: **FGF8** is expressed in the anterior endoderm of each pouch, **BMP7** in the posterior endoderm, **PAX1** in the dorsalmost endoderm of every pouch, and **SHH** additionally in the posterior endoderm of the 2nd and 3rd pouches; these gene-expression domains instruct the neural-crest mesenchyme of the adjoining arches to form arch-specific skeletal elements.
- Pouch formation precedes neural-crest migration into the arches and occurs even in its absence, confirming the endoderm's primary patterning role.

## 2. Derivatives of the individual pouches

| Pouch               | Adult derivative(s)                                                                                                                                                                                                                                                                                                                       |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First               | Tubotympanic recess → <b>tympanic (middle ear) cavity and pharyngotympanic (auditory/Eustachian) tube</b> ; distal expanded part abuts the 1st pharyngeal membrane, contributing the mucosal (inner) lining of the <b>tympanic membrane</b> ; a minor contribution from the second pouch has also been described                          |
| Second              | Endodermal buds proliferate into the mesenchyme to form the <b>stroma and crypt epithelium of the palatine tonsil</b> ; the pouch cavity is largely obliterated but a remnant persists as the <b>tonsillar sinus (fossa) / intratonsillar cleft</b> ; lymphoid infiltration of the mesenchyme begins around the 20th week (3rd–5th month) |
| Third               | Dorsal (bulbar) wing → <b>inferior parathyroid gland</b> ; elongated ventral wing → paired primordia that meet in the midline to form the bilobed <b>thymus</b>                                                                                                                                                                           |
| Fourth              | Dorsal wing → <b>superior parathyroid gland</b> ; ventral part → <b>ultimobranchial (ultimopharyngeal) body</b> , which fuses with the thyroid and disperses to give the calcitonin-secreting <b>parafollicular (C) cells</b>                                                                                                             |
| Fifth (rudimentary) | Regarded by some authors as a separate caudal invagination that directly forms the ultimobranchial body; by others simply as the ventral part of the fourth pouch — humans have no independent fifth pouch derivative beyond this                                                                                                         |

Small amounts of lymphoid tissue resembling the palatine tonsil also develop in the first pouch (**tubal tonsil**) and on the posterior tongue (lingual tonsil), though the latter is not pouch-derived.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 17.31 — Development of the Pharyngeal Pouch Derivatives (Larsen — Human Embryology — 6e, p.1100)

Reproduce a coronal/horizontal schematic at the late-5th-week stage, then a sagittal neck schematic at the 7th week, labelling: **Meckel's cartilage**, **external auditory meatus**, **tubotympanic recess**, **Reichert's cartilage**, **palatine tonsil**, **inferior parathyroid**, **superior parathyroid**, **thymus**, **ultimobranchial body** (5th-week stage); and **superior parathyroid**, **inferior parathyroid**, **thyroid**, **thymus** in their final descended positions (7th-week stage), with arrows showing the caudal migration of the thymus and both parathyroid pairs.

### 3. Migration of derivatives and the parathyroid "positional cross-over"

- ▶ The rudiments of the **inferior parathyroid (parathyroid III)** and **superior parathyroid (parathyroid IV)** detach from the pharyngeal wall early in the 5th week and migrate inferomedially, coming to rest by the 7th week.
- ▶ Because the inferior parathyroid arises from the **more cranial** third pouch but travels the **longer distance**, descending together with the thymus, it ends up lying **below** the superior parathyroid, which arises from the more caudal fourth pouch but migrates only a short distance.
- ▶ The two glands therefore **switch position during their descent**; their adult names ("superior"/"inferior") reflect only their **final relative position**, not their pouch of origin.
- ▶ The bilateral thymic primordia (ventral third-pouch buds) similarly migrate caudally and medially, fuse in the midline in the superior mediastinum, and lose their connection with the pharynx (the proximal stalk normally degenerates, occasionally leaving fibrofatty vestiges).
- ▶ Because of this long migratory path, **ectopic (aberrant) thymic or parathyroid tissue** may persist anywhere along the route — the inferior parathyroid is particularly variable in position and is occasionally found at the **bifurcation of the common carotid artery**.

### 4. Caudal pharyngeal complex and relation to the thyroid

- ▶ The fourth pouch and its ultimobranchial body together constitute the **caudal pharyngeal complex**, connected to the pharynx by the pharyngobranchial duct and surrounded by vagal neural-crest mesenchyme and the developing thyroid.
- ▶ The **thyroid gland** itself is *not* a pouch derivative — it arises as a median endodermal diverticulum from the floor of the pharynx (at the future **foramen caecum**, between the first and second pouches) and descends via the thyroglossal duct. The lateral thyroid lobes only acquire their calcitonin-secreting C cells when the **ultimobranchial bodies of the fourth pouches** fuse with them and disperse their neural-crest-derived cells within the gland.

### Applied / Clinical anatomy

- ▶ **DiGeorge syndrome (22q11.2 deletion syndrome)**: the most severe end of a spectrum that also includes velocardiofacial and conotruncal-anomaly-face syndromes; caused by microdeletion of chromosome 22q11.2, with mutation of the **TBX1** gene reproducing the phenotype even without a deletion; occurs in roughly **1 in 4,000 births**. Embryological basis is **failure of the posterior (3rd and 4th) pharyngeal pouches to form/differentiate**, giving: (a) **thymic hypoplasia/aplasia**

→ defective T-cell-mediated immunity and recurrent infections; (b) **parathyroid hypoplasia/aplasia** → hypocalcaemia, tetany and neonatal seizures; and (c) **conotruncal cardiac defects** (the outflow-tract neural crest that patterns the posterior pouches also septates the cardiac outflow tract), together with mild facial dysmorphism.

- ▶ **Ectopic thymic/parathyroid tissue:** residual glandular tissue along the descent pathway may cause a mediastinal or cervical thymic remnant, or a "missing" parathyroid at operation (found instead near the carotid bifurcation or within the thyroid/thymic capsule) — of direct relevance during neck exploration and thyroid/parathyroid surgery.
- ▶ **Branchial (lateral cervical) cyst and fistula:** failure of obliteration of the cervical sinus (the space in which the second arch overgrows the third and fourth clefts) leaves a **lateral cervical cyst**, typically just below the angle of the mandible along the anterior border of sternocleidomastoid; if it drains to the surface it forms an **external branchial fistula/sinus**. A separate, rarer **internal branchial fistula** results from rupture of the membrane between the **second pharyngeal cleft and second pouch**, and opens into the pharynx in the region of the **palatine tonsil** — directly implicating the pouch (not just the cleft) in fistula formation.
- ▶ **Otological correlate:** because the middle-ear cavity and auditory tube are first-pouch derivatives continuous with the nasopharynx, this pathway explains the spread of nasopharyngeal infection to the middle ear (otitis media) in children.
- ▶ **Oncological correlate:** the calcitonin-secreting parafollicular (C) cells derived from the ultimobranchial body of the fourth pouch are the cell of origin of **medullary carcinoma of the thyroid**, and serum calcitonin is used as its tumour marker.

### High-yield exam pointers

- ▶ Four pairs of pharyngeal pouches (endoderm-lined); a fifth pair is rudimentary/absent — contrast with ectoderm-lined pharyngeal clefts.
- ▶ Derivatives in order: **1st** — tympanic cavity + auditory tube; **2nd** — palatine tonsil; **3rd** — inferior parathyroid + thymus; **4th** — superior parathyroid + ultimobranchial body (→ thyroid C cells).
- ▶ Only the first pharyngeal membrane persists (as the tympanic membrane); the first pouch's tubotympanic recess forms the middle ear cleft.
- ▶ **Superior parathyroid (from 4th pouch) ends up inferior in pouch-number but superior in final position** relative to the inferior parathyroid (from 3rd pouch) — the classic "positional cross-over" during descent.
- ▶ Thymus and both parathyroid pairs are the only pouch derivatives that must detach and migrate; the thyroid itself is a separate median endodermal diverticulum, not a pouch derivative.
- ▶ **DiGeorge syndrome** = failure of 3rd + 4th (posterior) pouches; gene **TBX1**, chromosome **22q11.2**; triad of thymic aplasia, parathyroid aplasia, and conotruncal cardiac defect.
- ▶ Internal branchial fistula opens at the tonsillar fossa because it follows the ruptured second pouch/cleft membrane; external branchial fistula/cyst lies along sternocleidomastoid's anterior border.
- ▶ Ultimobranchial body cells are neural-crest derived and become the calcitonin-secreting C cells — clinically the origin of medullary thyroid carcinoma.

**SOURCE & COVERAGE**

Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; Gray's Anatomy (Standring) 41e.



## Pharyngeal pouch and its derivative

*Asked in: Paper II Nov 2017 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The pharyngeal (branchial) apparatus consists of pharyngeal arches, pharyngeal pouches, pharyngeal clefts (grooves) and pharyngeal membranes, which together fashion the face, neck and viscera of the neck during the 4th-5th weeks of development. Pharyngeal pouches are paired **endodermal outpocketings** of the primitive pharynx (foregut) that bulge laterally into the mesenchyme between two successive pharyngeal arches, opposite the ectodermal pharyngeal clefts. There are **four well-formed pairs of pouches**, numbered craniocaudally (1st pouch lies between arches 1 and 2, and so on); a **rudimentary fifth pouch** fuses with the fourth. Unlike the clefts (which mostly disappear), the pouches give rise to several important endocrine and lymphoid organs of the head and neck.

### General features

- ▶ Pouches are lined by **endoderm**; the surrounding mesenchyme (largely neural-crest derived) condenses around the endodermal buds to form the connective-tissue/capsular component of each derivative.
- ▶ The **third and fourth pouches** are each differentiated distally into a **dorsal (bulbar) wing** and a **ventral (tubular) wing** — this dorsal/ventral division underlies the double derivative of each pouch.
- ▶ Except the first pouch, each pouch **loses its connection with the pharyngeal wall** and migrates into the neck/thorax as an isolated glandular primordium.
- ▶ The **first pouch alone retains an open lumen** communicating with the pharynx in adult life (as the auditory tube opening into the nasopharynx); all others become solid, detached organs.
- ▶ Corresponding pharyngeal membrane closes each pouch from the outside; only the **first membrane** persists (as the tympanic membrane).

### First pharyngeal pouch

- ▶ Elongates into a stalk-like diverticulum, the **tubotympanic recess**.
- ▶ **Proximal (tubular) part** → narrows to form the **pharyngotympanic (auditory/eustachian) tube**, maintaining communication between the nasopharynx and the middle-ear cavity.
- ▶ **Distal (expanded) part** → widens to form the **tympanic (middle-ear) cavity and mastoid antrum**; its endodermal lining contributes the inner epithelial layer of the **tympanic membrane** (the outer layer being ectodermal, from the first pharyngeal cleft).

## Second pharyngeal pouch

- ▶ Endoderm proliferates into solid epithelial buds that penetrate the surrounding mesenchyme; the central cells of these buds break down to form **tonsillar crypts**.
- ▶ Surrounding mesenchyme provides the **lymphoid tissue, fibrous capsule and connective-tissue septa** of the tonsil; lymphocytic infiltration of the crypt epithelium occurs mainly in the **3rd-5th months**.
- ▶ Together these form the **palatine tonsil**.
- ▶ The unobliterated remnant of the pouch persists in the adult as the **tonsillar fossa / intratonsillar cleft (crypta magna)**.

## Third pharyngeal pouch

- ▶ **Dorsal wing** → proliferates into the **inferior parathyroid gland (parathyroid III)**.
- ▶ **Ventral wing** → proliferates into the **thymus** (bilateral primordia that meet and fuse in the midline in the superior mediastinum).
- ▶ Both primordia lose their connection with the pharyngeal wall and migrate **caudally and medially**; the thymus migrates further and faster, **dragging the inferior parathyroid gland caudally with it** before finally separating from it.
- ▶ End result: the parathyroid derived from the (cranially placed) third pouch ends up **lower** than the parathyroid derived from the (caudally placed) fourth pouch — the classic "cross-over" of the parathyroids.
- ▶ The thymic epithelial reticulum (cytoreticulum) and **Hassall's corpuscles** are of third-pouch endodermal origin; the lymphocytes (thymocytes) that populate the gland are of separate, bone-marrow (mesenchymal/haemopoietic) origin.
- ▶ The definitive thymus lies in the **superior and anterior mediastinum**, behind the sternum and in front of the pericardium and great vessels; it grows until puberty and then undergoes fatty involution.

## Fourth pharyngeal pouch (and rudimentary fifth pouch)

- ▶ **Dorsal wing** → **superior parathyroid gland (parathyroid IV)**, which attaches to the postero-superior surface of the thyroid lobe.
- ▶ **Ventral wing fuses with the rudimentary fifth pouch** to form the **ultimobranchial body (caudal pharyngeal complex)**, which is incorporated into the developing thyroid gland.
- ▶ Cells of the ultimobranchial body are **neural-crest derived**; within the thyroid they give rise to the **parafollicular (C) cells**, which secrete **calcitonin**.
- ▶ Because the superior parathyroid migrates only a short distance, its adult position is far more constant than that of the inferior parathyroid.

| Pouch | Wing/part                         | Derivative                                                                          | Adult location                                     |
|-------|-----------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------|
| First | Whole pouch (tubotympanic recess) | Middle-ear cavity, mastoid antrum, inner lining of tympanic membrane; auditory tube | Tympanic cavity / nasopharynx-to-ear communication |



| Pouch                      | Wing/part | Derivative                                           | Adult location                                          |
|----------------------------|-----------|------------------------------------------------------|---------------------------------------------------------|
| Second                     | Ventral   | Palatine tonsil (crypt epithelium + lymphoid stroma) | Tonsillar fossa (residual pouch = intratonsillar cleft) |
| Third                      | Dorsal    | Inferior parathyroid (parathyroid III)               | Postero-inferior surface of thyroid lobe                |
| Third                      | Ventral   | Thymus                                               | Superior/anterior mediastinum                           |
| Fourth                     | Dorsal    | Superior parathyroid (parathyroid IV)                | Postero-superior surface of thyroid lobe                |
| Fourth + rudimentary fifth | Ventral   | Ultimobranchial body → parafollicular (C) cells      | Incorporated within thyroid parenchyma                  |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Fig 17.31 — Development of the Pharyngeal Pouch Derivatives (Larsen — Human Embryology — 6e, p.1100)
- Fig 17.32 — Migration of Pharyngeal Pouch Derivatives — the parathyroid glands and thymus (Larsen — Human Embryology — 6e, p.1102)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal/coronal schema of the pharynx at the late 5th week, showing the four pharyngeal arches with the pouches opening between them, labelled:

- ▶ Arches 1-4 and pouches 1-4 (with rudimentary pouch 5 fused to pouch 4)
- ▶ Pouch 1 → tubotympanic recess → **auditory tube** + **tympanic cavity**
- ▶ Pouch 2 → **palatine tonsil** primordium (tonsillar bud/crypt) → **tonsillar fossa**
- ▶ Pouch 3 dorsal wing → **inferior parathyroid**; ventral wing → **thymus** primordium
- ▶ Pouch 4 dorsal wing → **superior parathyroid**; ventral wing (+ rudimentary pouch 5) → **ultimobranchial body**
- ▶ Curved arrows showing caudal migration of the thymus (dragging the inferior parathyroid) and of the superior parathyroid, converging on the **thyroid gland** in the neck
- ▶ A second inset of the definitive neck showing thyroid gland with superior and inferior parathyroids on its posterior surface and the thymus in the superior mediastinum

### Applied / Clinical anatomy

- ▶ **DiGeorge syndrome / 22q11.2 deletion syndrome**: results from failure of the third and fourth pouches to differentiate into the thymus and parathyroid glands, due to a **microdeletion of chromosome 22q11.2** (involving the **TBX1** gene) disrupting neural-crest/endodermal signalling; it is the commonest human deletion syndrome (~1 in 4,000 births). Features: **absent/hypoplastic thymus** → defective T-cell mediated immunity and recurrent infections; **absent/hypoplastic parathyroids** → hypocalcaemia and seizures; conotruncal cardiac and aortic-arch defects; and



facial dysmorphism (short philtrum/"fish-mouth" deformity, low-set notched ears) from associated first-arch neural-crest disruption.

- ▶ **Ectopic/accessory thymic and parathyroid tissue:** because of their long migratory course, isolated nests of thymic tissue may persist anywhere along the thymopharyngeal tract (often close to an inferior parathyroid), and parathyroid glands — especially the inferior gland — show markedly variable adult position (near the carotid bifurcation, within the thyroid capsule, within the thymus, or ectopically in the mediastinum/retrosternal thymus). This variability is of direct surgical importance during thyroidectomy and parathyroid exploration. Supernumerary or absent parathyroid glands may result from division or failure of a primordium.
- ▶ **Piriform sinus fistula:** a persistent tract along the course of the fourth-pouch/ultimobranchial-body remnant to the thyroid gland; presents clinically as recurrent neck abscess or suppurative thyroiditis, typically on the left side, usually in children.
- ▶ **Internal branchial fistula/sinus:** rarely, the membrane between the second pharyngeal cleft and second pharyngeal pouch ruptures, producing a fistula that runs between the internal and external carotid arteries and opens internally into the **tonsillar sinus** (the residual second-pouch remnant) — a reminder that the tonsillar fossa is the pouch-derived opening exploited by such tracts.
- ▶ **Calcitonin-secreting C cells:** because they are neural-crest derived (via the ultimobranchial body/fourth-fifth pouch complex) rather than endodermal follicular cells, C-cell (medullary) thyroid carcinoma behaves as a distinct, often familial (MEN 2/RET-associated), neuroendocrine tumour.

### High-yield exam pointers

- ▶ 4 pairs of pharyngeal pouches (endodermal) + 1 rudimentary 5th pouch, numbered craniocaudally; contrast with pharyngeal clefts (ectodermal, mostly obliterate except the 1st).
- ▶ Quick recall table: **1st** → **ear** (auditory tube + tympanic cavity); **2nd** → **tonsil**; **3rd** → **thymus + inferior parathyroid**; **4th** → **superior parathyroid + ultimobranchial body (C cells)**.
- ▶ Only the first pouch keeps an **open communication** with the pharynx in the adult (auditory tube); 2nd-4th pouches lose pharyngeal connection and migrate as solid organ primordia.
- ▶ 3rd and 4th pouches each have a **dorsal wing** (→ parathyroid) and a **ventral wing** (→ thymus / ultimobranchial body).
- ▶ "Cross-over" mnemonic: parathyroid III (from the higher, 3rd pouch) migrates further with the thymus and ends up **inferior**; parathyroid IV (from the lower, 4th pouch) migrates less and ends up **superior**.
- ▶ Thymic Hassall's corpuscles/reticulum = **endoderm** (3rd pouch); thymocytes = **mesoderm/bone marrow** derived — a dual-origin organ.
- ▶ C cells of the thyroid are **neural-crest-derived** (via ultimobranchial body), secrete **calcitonin**, and are NOT derived from thyroglossal-duct endoderm like the follicular cells.
- ▶ **DiGeorge syndrome** = failure of 3rd + 4th pouch derivatives (thymus + parathyroids), 22q11.2/TBX1 — remember the triad of immunodeficiency + hypocalcaemia + cardiac outflow defect.

- Applied tracts to remember: **internal branchial fistula** (2nd pouch/cleft, opens into tonsillar sinus) and **piriform sinus fistula** (4th pouch/ultimobranchial remnant, opens near thyroid).

#### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Moore's The Developing Human 9e; Vishram Singh's Textbook of Clinical Embryology; Sontakke's Textbook of Human Embryology; Larsen's Human Embryology 6e (figure); Gray's Anatomy (Standing) 41e.



## Pharyngeal pouches

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Pharyngeal (branchial) pouches are paired **endodermal evaginations** of the lateral wall of the cranial foregut (primitive pharynx), lying in the interval between two successive pharyngeal arches. There are **four well-formed pairs** (numbered craniocaudally 1–4) and a rudimentary **fifth pouch** that fuses with the fourth. Each pouch meets the corresponding **ectodermal pharyngeal cleft** externally across a thin trilaminar **pharyngeal membrane** (ectoderm–mesoderm–endoderm). Because the endodermal epithelium of the pouches proliferates and differentiates into several endocrine and lymphoid organs of the head, neck and superior mediastinum, the pouches are of major surgical–endocrine importance and a recurrent PG exam topic.

### 1. General plan of development

- Pouches appear in sequence craniocaudally during the **4th–5th week** (Carnegie stages 10–13), as the pharyngeal arches form on either side of the primitive pharynx.
- Each pouch has, distally, a **dorsal wing** and a **ventral wing** (well seen in the 3rd and 4th pouches) — this dorsoventral split is the key to remembering which organ each part forms.
- The **2nd pharyngeal arch overgrows** the 2nd, 3rd and 4th clefts caudally, burying them in a temporary ectodermal-lined space, the **cervical sinus**, which normally obliterates completely.
- The 5th pouch is rudimentary in humans; it fuses with the ventral part of the 4th pouch to constitute, together with the ultimobranchial body, the **caudal pharyngeal complex**.
- Unlike the clefts (which are ectodermal and mostly disappear), **every pharyngeal pouch contributes a permanent adult structure** — this asymmetry is a favourite viva point.

## 2. Derivatives of the pharyngeal pouches (summary table)

| Pouch                                                  | Dorsal part                                                                                  | Ventral part                                                              | Final adult derivative(s)                                                                                                                                                                                                           |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First                                                  | Tubotympanic recess (dorsal part, with a contribution from the dorsal part of the 2nd pouch) | Obliterated by the developing tongue                                      | Pharyngotympanic (Eustachian) tube (proximal, narrow part) + middle-ear (tympanic) cavity, mastoid antrum and inner epithelial lining of the tympanic membrane (distal, expanded part); lymphoid tissue here forms the tubal tonsil |
| Second                                                 | Fuses with dorsal part of 1st pouch to help form tubotympanic recess                         | Endoderm proliferates into solid buds that canalise into tonsillar crypts | Epithelial lining and crypts of the palatine tonsil (mesoderm forms the lymphoid follicles/capsule); residual pouch lumen persists as the tonsillar fossa / intratonsillar cleft (crypta magna)                                     |
| Third                                                  | Proliferates → inferior parathyroid gland (parathyroid III)                                  | Proliferates → thymus                                                     | Both primordia lose their pharyngeal connection and migrate caudally together; thymus continues into the anterior mediastinum, dragging the parathyroid III with it part of the way                                                 |
| Fourth (+ rudimentary 5th = caudal pharyngeal complex) | Proliferates → superior parathyroid gland (parathyroid IV)                                   | Ultimobranchial body                                                      | Parathyroid IV attaches to the posterior surface of the thyroid lobe; ultimobranchial body is incorporated into the lateral thyroid lobes and gives rise to the parafollicular (C) cells of the thyroid, which secrete calcitonin   |

## 3. First and second pouches in detail

- **First pouch:** forms a stalk-like diverticulum, the **tubotympanic recess** — its narrow proximal part becomes the auditory tube (communicating nasopharynx with the middle ear); its expanded distal part becomes the tympanic cavity and mastoid antrum, and its epithelium lines the inner surface of the tympanic membrane.

- ▶ **Second pouch:** endodermal buds invaginate the surrounding mesenchyme and canalise to form tonsillar crypts; the pouch is almost entirely obliterated by the growing palatine tonsil, leaving only the **intratonsillar cleft** as a remnant. (Some authors describe the dorsal part of the 2nd pouch, along with the dorsal part of the 1st, contributing to the tubotympanic recess, while its ventral part alone forms the tonsil.)

#### 4. Third and fourth pouches — the parathyroid–thymus axis

- ▶ Both the 3rd and 4th pouches develop a **dorsal (parathyroid-forming) wing** and a **ventral wing**; in the 3rd pouch the ventral wing forms the **thymus** rather than the ultimobranchial body seen in the 4th.
- ▶ Both pairs of primordia lose their duct-like connection with the pharyngeal wall and migrate caudally through the neural-crest-derived mesenchyme of the neck.
- ▶ The **thymus (ventral, 3rd pouch)** continues its caudal migration into the **anterior mediastinum**, where the right and left rudiments meet (but do not fuse) ventral to the great vessels/aortic sac.
- ▶ **Parathyroid III (dorsal, 3rd pouch)** is pulled caudally along with the thymus before finally losing this connection and settling on the dorsal surface of the thyroid gland.
- ▶ **Parathyroid IV (dorsal, 4th pouch)** migrates only a short distance and anchors to the posterolateral surface of the thyroid lobe.
- ▶ **Classic "positional paradox":** although pouch 3 lies cranial to pouch 4, *\*parathyroid III (from the cranially placed 3rd pouch) ends up as the inferior parathyroid, because it is dragged further caudally by the thymus, while parathyroid IV (from the caudally placed 4th pouch) ends up superior\*\*\** because its migration is short. This inversion is a favourite MD viva/MCQ trap and also explains the wide anatomical variability (and occasional ectopic/mediastinal location) of the inferior parathyroid.

#### 5. Fifth pouch and the caudal pharyngeal complex

- ▶ The fifth pouch is only transiently present in the human embryo and fuses with the ventral part of the 4th pouch to form the **caudal pharyngeal complex**, connected to the pharynx via the pharyngobranchial duct.
- ▶ This complex contributes the **ultimobranchial body**, which becomes incorporated into the lateral lobes of the developing thyroid gland.
- ▶ **Vagal neural-crest cells** migrating into the ultimobranchial body differentiate into the **parafollicular (C) cells**, the source of **calcitonin** in the adult thyroid — the only endocrine cell line in the thyroid that is *not* endodermal/follicular in origin.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

□ Fig 17.31 — Development of the pharyngeal pouch derivatives, late 5th week and 7th week (Larsen — Human Embryology, 6e, p.1100)

For the exam, reproduce a simple coronal/ventral schematic of the pharyngeal floor at the late-5th-week stage, then a second small panel showing the 7th-week migrated positions. Label:

- ▶ Meckel's cartilage, Reichert's cartilage (landmarks of arches 1 and 2)
- ▶ External auditory meatus and **tubotympanic recess** (1st pouch)
- ▶ **Palatine tonsil** primordium (2nd pouch)
- ▶ **Inferior parathyroid** (dorsal wing, 3rd pouch) and **thymus** (ventral wing, 3rd pouch)
- ▶ **Superior parathyroid** (dorsal wing, 4th pouch) and **ultimobranchial body** (4th pouch/caudal pharyngeal complex)
- ▶ In the 7th-week panel: **thyroid gland** in the midline with **superior and inferior parathyroids** applied to its posterior surface, and the **thymus** continuing caudally into the mediastinum.

**Applied / Clinical anatomy**

- ▶ **DiGeorge syndrome (22q11.2 deletion syndrome)**: failure of the 3rd and 4th pharyngeal pouches to differentiate normally into the thymus and parathyroid glands. Caused by microdeletion of the long arm of chromosome 22 (with haploinsufficiency of the **TBX1** gene implicated); reported incidence is roughly **1 in 2,000–4,000 live births**. Presents with **thymic aplasia/hypoplasia** (defective T-cell-mediated immunity → recurrent infections), **parathyroid agenesis** (hypocalcaemia/neonatal tetany/seizures), conotruncal cardiac and aortic arch anomalies, and mild facial dysmorphism (short philtrum/"fish mouth," micrognathia, low-set/malformed ears) — also called velocardiofacial or Shprintzen syndrome. Pathogenesis is linked to a defect of the neural-crest mesenchyme into which the pouch endoderm migrates, so the epithelial–mesenchymal interaction needed for gland differentiation fails.
- ▶ **Persistent 2nd cleft–pouch membrane** → a lateral cervical (branchial) fistula/sinus that opens internally into the pharynx at the level of the **palatine tonsil (tonsillar fossa)** — the "internal branchial fistula." If the cervical sinus fails to obliterate and ruptures onto the skin, an external branchial fistula/cyst results, classically found anterior to sternocleidomastoid.
- ▶ **Aberrant migration of 3rd/4th-pouch derivatives** produces ectopic or supernumerary parathyroid tissue (e.g. an undescended/mediastinal parathyroid embedded within thymic tissue) — clinically important when localising a missing gland at parathyroidectomy for hyperparathyroidism.
- ▶ **Ultimobranchial-derived C cells** are the cell of origin of **medullary carcinoma of the thyroid**, which secretes calcitonin — a direct clinical correlate of pouch-4/caudal-pharyngeal-complex development.
- ▶ A patent, wide or dysfunctional **auditory tube** (1st-pouch derivative) predisposes to recurrent otitis media/serous effusion, especially in infants in whom the tube is short and horizontal.

## High-yield exam pointers

- ▶ **4 pairs** of true pharyngeal pouches (endodermal) + a **rudimentary 5th** that fuses with the 4th; numbered craniocaudally.
- ▶ Quick recall: **1 → ear** (tubotympanic recess/Eustachian tube/middle ear); **2 → tonsil**; **3 → inferior parathyroid + thymus**; **4 → superior parathyroid + ultimobranchial body (C cells)**.
- ▶ Every pouch is **endoderm-lined**, unlike the ectoderm-lined clefts — contrast this when the examiner asks to differentiate pouches from clefts.
- ▶ **Positional paradox**: parathyroid III (from pouch 3, cranial) migrates further and ends up **inferior**; parathyroid IV (from pouch 4, caudal) migrates less and ends up **superior**.
- ▶ **DiGeorge syndrome** = failure of 3rd + 4th pouch differentiation; 22q11.2 deletion, TBX1 gene; triad of thymic aplasia (T-cell defect), parathyroid agenesis (hypocalcaemia), and cardiac/facial anomalies.
- ▶ Ultimobranchial body is the **only non-endodermal-follicular** contributor to the thyroid — gives parafollicular C cells (calcitonin).
- ▶ Persistent 2nd pouch–cleft membrane explains internal branchial fistula opening at the **tonsillar fossa**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e (figure); Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology.



## Rathke's pouch

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Rathke's pouch (hypophyseal diverticulum) is the ectodermal evagination that arises from the roof of the stomodeum (primitive oral cavity) in the third week of intrauterine life (IUL) and is the sole embryological source of the adenohypophysis (anterior pituitary). It grows dorsally to meet a reciprocal downgrowth from the floor of the diencephalon — the neurohypophysial (infundibular) diverticulum — and the two primordia fuse to form the definitive hypophysis cerebri (pituitary gland), a classic example of a compound organ with dual germ-layer origin. The structure is named after the German anatomist and embryologist Martin Heinrich Rathke, who first described it. It is a recurring embryology and applied-anatomy topic because its mode of origin (oral ectoderm, not neuroectoderm), its fate (the entire adenohypophysis), its transient lumen (hypophyseal cleft) and its abnormal persistence (craniopharyngeal canal, pharyngeal hypophysis, Rathke's cleft cyst) each carry direct clinical correlates that are favourite viva and theory points.

### 1. Site and mode of origin

- ▶ **Germ layer**: surface ectoderm — specifically the ectodermal lining of the roof of the stomodeum. It is **not** neural crest and **not** neuroectoderm (that is the source of the neurohypophysis).

- **Site:** an ectodermal placode appears in the roof of the stomodeum immediately **rostral (in front of)** the buccopharyngeal (oropharyngeal) membrane.
- **Timing of appearance:** at approximately the **3rd week of IUL** (day 21–24), this placode invaginates to form a dorsally-directed diverticulum — Rathke's pouch — which grows toward the floor of the diencephalon.
- **Reciprocal primordium:** during the **6th week of IUL**, a neuroectodermal downgrowth — the **infundibular/neurohypophysial process** — arises from the floor of the diencephalon (future 3rd ventricle floor/hypothalamus) and grows ventrally to meet the advancing Rathke's pouch. The two diverticula come into apposition and fuse.
- **Separation from the stomodeum:** by the **end of the 2nd month (~8 weeks)** of IUL, the stalk connecting Rathke's pouch to the stomodeum degenerates, so the pouch becomes a discrete ectodermal sac applied to the cranial (dorsal) surface of the infundibulum, with no further continuity with the oral cavity.
- **Histogenesis:** differentiation of the glandular cells begins in the **4th month of IUL**; **acidophils appear first**, followed by **basophils**, and then **chromophobes**. In the neurohypophysis, neuroglial cells (future pituicytes) appear around the same time, followed by axonal colonisation from the supraoptic and paraventricular nuclei of the hypothalamus.

## 2. Sequence of development

□ Fig 25.1 — Development of pituitary gland (Sontakke — *Textbook of Human Embryology*, p.282)

| Stage (IUL)                 | Event                                                                                                                                                                                 |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ~3rd week (day 21–24)       | Ectoderm of stomodeal roof thickens and invaginates dorsally as <b>Rathke's pouch</b> , growing toward the diencephalon                                                               |
| 6th week                    | <b>Infundibular (neurohypophysial) process</b> grows from the diencephalic floor to meet Rathke's pouch; the two diverticula fuse                                                     |
| End of 2nd month (~8 weeks) | Rathke's pouch <b>loses its connection with the stomodeum</b> ; becomes a closed sac apposed to the infundibulum                                                                      |
| 4th month                   | <b>Histogenesis</b> begins — acidophils, then basophils, then chromophobes differentiate in the adenohypophysis; neuroglial cells and hypothalamic axons populate the neurohypophysis |



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A mid-sagittal schematic of the developing forebrain/stomodeum showing (label each): stomodeum (primitive oral cavity); buccopharyngeal (oropharyngeal) membrane; **Rathke's pouch** as a dorsal evagination of stomodeal ectoderm; floor of the diencephalon/3rd ventricle; the **infundibular (neurohypophysial) process** growing down to meet it; the point of attachment/stalk of Rathke's pouch to the stomodeum (later obliterated); notochord tip lying just deep to the pouch. A second panel of the definitive gland should label: **pars distalis (anterior lobe)**, **pars intermedia**, **pars tuberalis** (collectively = adenohypophysis, derived from Rathke's pouch), the **hypophyseal (intraglandular) cleft** (remnant of the pouch lumen), and **pars nervosa + infundibulum/median eminence** (collectively = neurohypophysis, derived from the infundibular process) — all seated within the hypophyseal (pituitary) fossa of the sella turcica.

### 3. Fate of Rathke's pouch — structures derived

| Part of Rathke's pouch                                        | Structure formed                                                                                                                                                                              |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anterior (thick) wall                                         | Proliferates extensively → <b>pars distalis</b> (pars anterior/glandularis) — the bulk of the adenohypophysis                                                                                 |
| A small upward extension of the anterior-wall tissue          | Grows along the infundibular stalk and encircles it → <b>pars tuberalis</b>                                                                                                                   |
| Posterior (thin) wall                                         | Remains thin, does not proliferate → <b>pars intermedia</b>                                                                                                                                   |
| Lumen/cavity of the pouch                                     | Persists as the <b>hypophyseal (intraglandular) cleft</b> , separating pars distalis from pars intermedia in fetal and early postnatal life; largely obliterated/vestigial in the adult gland |
| Stalk of attachment to the stomodeum (as the pouch separates) | Transiently patent tract running from the stomodeal roof (later the nasopharyngeal roof) to the floor of the hypophyseal fossa — the <b>craniopharyngeal canal</b> ; normally obliterated     |

### 4. Relationship to the definitive pituitary gland

The adult hypophysis cerebri is thus a **compound gland of dual origin**:

- **Adenohypophysis** (from Rathke's pouch/oral ectoderm) = pars distalis + pars intermedia + pars tuberalis.
- **Neurohypophysis** (from the infundibular/neuroectodermal diverticulum) = pars nervosa (posterior lobe) + infundibular stem + median eminence.

The two components fuse but remain histologically distinct — the hypophyseal cleft, a direct vestige of the Rathke's-pouch lumen, is the internal boundary marker between them.

### Applied / Clinical anatomy

- **Craniopharyngioma**: arises from epithelial remnants of Rathke's pouch persisting anywhere along the obliterated craniopharyngeal canal — most often in the suprasellar/sellar region related

to the sphenoid bone (roof of nasopharynx to floor of the hypophyseal fossa). It shows a **bimodal age distribution** — childhood onset (5–14 years) and adult onset (50–70 years). Growth may compress the optic chiasm (bitemporal hemianopia), obstruct CSF pathways (hydrocephalus), or produce pituitary dysfunction (growth failure, diabetes insipidus, hypopituitarism).

- ▶ **Pharyngeal hypophysis:** a small nest of Rathke's-pouch-derived (adenohypophysis-like) tissue that persists in the roof/posterior wall of the nasopharynx when the pouch fails to fully separate/ascend; usually an incidental finding, but can rarely undergo adenomatous change or act as compensatory ectopic tissue if the orthotopic pituitary is hypoplastic/absent.
- ▶ **Rathke's cleft cyst:** cystic dilation/persistence of the hypophyseal cleft (the vestigial lumen of Rathke's pouch) between pars distalis and pars intermedia; usually a small incidental finding on imaging, but a large cyst can cause headache, visual disturbance, or hypopituitarism from mass effect.
- ▶ **Pituitary agenesis/hypoplasia:** failure of Rathke's pouch to form or to differentiate normally results in congenital absence/hypoplasia of the adenohypophysis and hypopituitarism.
- ▶ **Adenohypophyseal tumours by cell type** (since all arise from the Rathke's-pouch-derived adenohypophysis): chromophobe adenoma (commonly women 20–50 years; headache, bitemporal hemianopia from suprasellar extension), acidophil adenoma (gigantism in children, acromegaly in adults), basophil adenoma (Cushing's syndrome).
- ▶ **Course of the craniopharyngeal canal:** it runs from the roof of the nasopharynx to the floor of the hypophyseal (pituitary) fossa, i.e. through the body of the sphenoid bone — which is why craniopharyngiomas and accessory pituitary remnants along this tract are described "in relation to the sphenoid bone." In the rare event of agenesis of the orthotopic pituitary, accessory hypophyseal tissue may develop in the posterior pharyngeal wall along this same tract.
- ▶ **Surgical/radiological correlate:** the transsphenoidal approach to the pituitary fossa follows the same nasopharynx-to-sella trajectory once occupied by the craniopharyngeal canal/Rathke's pouch stalk.

### High-yield exam pointers

- ▶ Rathke's pouch = ectodermal (oral ectoderm) evagination from the roof of the stomodeum, rostral to the buccopharyngeal membrane; appears in the **3rd week** of IUL.
- ▶ It gives rise to the **entire adenohypophysis** — pars distalis, pars intermedia, and pars tuberalis — **never** the posterior pituitary.
- ▶ It fuses with the **infundibular (neurohypophysial) process** of the diencephalon (arising 6th week) to build the compound pituitary gland.
- ▶ Loses its connection with the stomodeum by the **end of the 2nd month** of IUL.
- ▶ Its lumen persists as the **hypophyseal (intraglandular) cleft**, the histological boundary between pars distalis and pars intermedia.
- ▶ Histogenesis starts in the **4th month**: acidophils appear before basophils and chromophobes.
- ▶ **Craniopharyngioma** — the single most important applied fact — arises from remnants of Rathke's pouch along the craniopharyngeal canal; bimodal age peaks at 5–14 and 50–70 years.
- ▶ Persistent ectopic remnant in the nasopharyngeal roof = **pharyngeal hypophysis**; cystic persistence of the pouch lumen = **Rathke's cleft cyst**.

**SOURCE & COVERAGE**

Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Gray's Anatomy (Standing) 41e.



## Ultimobranchial body

*Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The ultimobranchial body (also called the **ultimopharyngeal body**) is a paired, transient diverticulum of the caudal-most primitive pharynx that, together with the fourth pharyngeal pouch, constitutes the **caudal pharyngeal complex**. Classically attributed to a rudimentary, short-lived **fifth pharyngeal pouch**, it detaches from the pharyngeal wall, becomes populated by vagal neural crest cells, migrates medially and caudally, and fuses with the developing thyroid gland. There it disperses to give rise to the calcitonin-secreting **parafollicular (C) cells** of the thyroid — making the ultimobranchial body the sole named derivative of the fifth pouch and the embryological key to an important group of thyroid clinical entities (C-cell hyperplasia, medullary carcinoma, solid cell nests).

### 1. Site of origin and embryological identity

- ▶ Arises as the **caudal-most endodermal evagination** of the primitive pharynx, appearing during the fourth–fifth week of intrauterine life, along with the other pharyngeal pouches.
- ▶ Described classically as forming from a **fifth pharyngeal pouch** — a very brief, rudimentary outgrowth caudal to the fourth pouch (Larsen; Sontakke; Hamilton, Boyd & Mossman); it disappears almost as soon as it forms.
- ▶ This fifth-pouch rudiment **fuses with (is incorporated into) the fourth pharyngeal pouch**; Gray's Anatomy (41e) terms the resulting combined structure — the fourth pouch plus the small medial diverticulum — the **caudal pharyngeal complex**, connected to the pharyngeal lumen via the **pharyngobranchial duct**.
- ▶ Moore (*The Developing Human*) and Sadler (*Langman's*) describe the same structure as developing from the **elongated ventral part of the fourth pouch itself**, calling it the **ultimopharyngeal body** — the differing descriptions (independent 5th pouch vs. ventral outgrowth of the 4th pouch) reflect genuine nomenclatural variation across texts, but all converge on the same fate.
- ▶ The complex is surrounded by **vagal (rhombomere-derived) neural crest mesenchyme**.

### 2. Migration and incorporation into the thyroid gland

- ▶ The ultimobranchial body **detaches from the pharyngeal wall** and migrates **medially and caudally**.

- ▶ It implants into the **dorsal/posterior wall of the developing thyroid gland** (lateral lobes), at a stage when the thyroid — having descended from the foramen caecum along the thyroglossal duct — is reaching its definitive pretracheal position.
- ▶ On fusion, the ultimobranchial body's cells **disperse and become dispersed among the thyroid follicles**, rather than persisting as a discrete mass.
- ▶ **Neural crest cells** that had colonised the ultimobranchial body/caudal pharyngeal complex migrate along with it and differentiate into the parafollicular cells; the transcription factor **Mash1 (Ascl1)** has been shown to regulate this C-cell differentiation programme.

### 3. Fate: the parafollicular (C) cells

- ▶ The dispersed ultimobranchial-body-derived cells become the **parafollicular or "C" cells** (clear cells) of the adult thyroid.
- ▶ C cells are members of the **APUD (amine precursor uptake and decarboxylation)** system of dispersed neuroendocrine cells.
- ▶ They secrete the peptide hormone **calcitonin (thyrocalcitonin)**, which **lowers blood calcium** by inhibiting osteoclastic bone resorption and reducing renal tubular calcium reabsorption — functionally the physiological antagonist of parathormone.
- ▶ Location within the gland: C cells characteristically **populate the middle third of each lateral lobe** of the thyroid, lying within the basal lamina of the follicles (not reaching the lumen); occasionally they form small interfollicular clusters.
- ▶ On routine H&E staining they appear as poorly staining ("clear") cells and are not always readily identifiable; special stains/immunohistochemistry (e.g., anti-calcitonin) are needed for confident identification.

### 4. Derivatives of the pharyngeal pouches — comparative table

| Pouch                         | Principal derivative(s)                                                                                                                                                       |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First                         | Tubotympanic recess → <b>pharyngotympanic (Eustachian) tube</b> and <b>tympanic (middle-ear) cavity</b>                                                                       |
| Second                        | Epithelial lining of the <b>palatine tonsil</b> and the <b>intratonsillar cleft</b>                                                                                           |
| Third                         | Dorsal wing → <b>inferior parathyroid</b> (parathyroid III, which migrates caudally with the thymus and so ends up <i>below</i> parathyroid IV); ventral wing → <b>thymus</b> |
| Fourth                        | Dorsal bulbar part → <b>superior parathyroid</b> (parathyroid IV); ventral part fuses with the fifth-pouch rudiment to form the <b>caudal pharyngeal complex</b>              |
| Fifth (rudimentary/transient) | <b>Ultimobranchial body</b> → incorporated into the caudal pharyngeal complex → disperses in the thyroid as <b>parafollicular (C) cells</b>                                   |

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

□ Fig 17.32 — Migration of Pharyngeal Pouch Derivatives The parathyroid glands and (Larsen — Human Embryology — 6e, p.1102)

Reproduce a sagittal/schematic view of the developing pharynx and neck (5th–7th week) showing the descent of glandular derivatives, labelling:

- ▶ **Foramen caecum** (site of origin of the thyroid diverticulum) and the **thyroglossal duct** tract
- ▶ **Thyroid gland** (bilobed, descended to its pretracheal position, isthmus anterior to 2nd–3rd tracheal rings)
- ▶ **Thymus** (from ventral third pouch), migrating into the superior mediastinum
- ▶ **Parathyroid III** (inferior parathyroid — dragged caudally with the thymus)
- ▶ **Parathyroid IV** (superior parathyroid — from the fourth pouch, remains higher)
- ▶ **Ultimobranchial body / caudal pharyngeal complex**, shown fusing into the **posterior aspect of each thyroid lateral lobe**
- ▶ Arrows indicating the direction of migration/descent of each derivative
- ▶ Hyoid bone and laryngeal cartilages as positional landmarks

**Applied / Clinical anatomy**

- ▶ **Piriform sinus fistula/sinus**: thought to result from **persistence of remnants of the ultimopharyngeal body** along its migratory path from the piriform fossa of the pharynx down to the thyroid; classically presents as a recurrent, usually **left-sided**, suppurating neck swelling/abscess or acute suppurative thyroiditis in children; treatment requires **complete excision of the fistulous tract**, often with ipsilateral hemithyroidectomy, to prevent recurrence.
- ▶ **Solid cell nests**: microscopic nests of epithelial cells found in the substance of the normal adult thyroid (usually mid/upper poles of the lateral lobes) are regarded as **embryonic remnants of the ultimobranchial body**; they are a recognised, distinct histological entity in the thyroid and are of interest as a possible source of C-cell/mixed follicular-C-cell lesions.
- ▶ **C-cell hyperplasia and Medullary thyroid carcinoma (MTC)**: MTC is the malignant tumour of the ultimobranchial-body-derived C cells; because C cells are normally confined to the **middle third of the lateral lobes**, sporadic MTC is typically found there, while hereditary MTC is characteristically **bilateral and multicentric** — an embryological fact that mandates **total (not partial) thyroidectomy** in RET-mutation carriers, even prophylactically.
- ▶ **Calcitonin as a tumour marker**: because calcitonin is secreted almost exclusively by C cells, an elevated serum calcitonin is used to **diagnose and monitor MTC** and to screen relatives in familial disease.
- ▶ **MEN2 (Multiple Endocrine Neoplasia type 2)**: an autosomal dominant disorder caused by **gain-of-function (activating) mutations in the RET proto-oncogene** (a receptor tyrosine kinase), producing constitutive kinase activation.
  - **MEN2A** — MTC (near-universal) with pheochromocytoma and/or parathyroid adenomas.

- **MEN2B** — the tumours of MEN2A plus thickening of nerves and benign **mucosal neuromas** on the lips/mouth and along the gastrointestinal tract.
- (The same *RET* gene, when carrying loss-of-function mutations, underlies **Hirschsprung disease** — a classic "same-gene, opposite-mutation, different-phenotype" teaching point.)
- ▶ **Amyloid deposition:** the stroma of medullary carcinoma characteristically contains **calcitonin-derived (A<sub>Ca</sub>-type) amyloid**, a histological hallmark linking the tumour back to its C-cell/calcitonin lineage.
- ▶ **Congenital thyroid anomalies** sharing the same developmental field include thyroglossal cyst/fistula, ectopic (lingual) thyroid, and absent isthmus/lobe — though these relate chiefly to the median thyroglossal-duct component rather than the ultimobranchial body itself.

### High-yield exam pointers

- ▶ Ultimobranchial body = derivative of the (rudimentary, transient) **fifth pharyngeal pouch**; fuses with the fourth pouch to form the **caudal pharyngeal complex** (Gray's Anatomy terminology); also called the **ultimopharyngeal body** (Moore/Sadler).
- ▶ Connected to the pharynx via the **pharyngobranchial duct**; surrounded by **vagal neural crest** mesenchyme.
- ▶ Detaches, migrates **medially and caudally**, fuses with the **dorsal/posterior aspect** of the thyroid lateral lobes, and disperses within it.
- ▶ Gives rise to the **parafollicular (C) cells** — via colonisation by neural crest cells, under regulation of the transcription factor **Mash1/Ascl1**.
- ▶ C cells secrete **calcitonin** — lowers blood  $\text{Ca}^{2+}$  ( $\downarrow$  osteoclastic bone resorption,  $\downarrow$  renal tubular  $\text{Ca}^{2+}$  reabsorption); physiological antagonist of PTH; part of the **APUD system**.
- ▶ C cells are anatomically confined to the **middle third of each lateral lobe** — surgically important.
- ▶ **Sole named derivative** of the fifth pharyngeal pouch — a favourite short-note/MCQ trigger.
- ▶ Clinical relevance: **piriform sinus fistula**, **solid cell nests**, **C-cell hyperplasia/medullary thyroid carcinoma**, **MEN2A/2B (RET proto-oncogene)**, **calcitonin as a tumour marker**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Textbook of Anatomy Vol 3 4e; Sontakke — Textbook of Human Embryology; Ross Histology — A Text and Atlas 7e; Thompson & Thompson — Genetics in Medicine 8e.





## What is branchial apparatus? Discuss the derivatives of the branchial apparatus

Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** The branchial (pharyngeal) apparatus is the collective term for four sets of paired structures — pharyngeal arches, pharyngeal pouches, pharyngeal clefts (grooves) and pharyngeal membranes — that appear in the lateral and ventral walls of the primitive pharynx during the 4th and 5th weeks of intrauterine life. "Branchial" is the older term (*branchia* = gill), reflecting the phylogenetic resemblance of these arches to the gill arches of fishes. The apparatus largely builds the face, neck, definitive mouth, pharynx and larynx, and its faulty development underlies a large group of clinically important craniofacial and neck anomalies.

### Components of the branchial apparatus and the generalised arch plan

- **Pharyngeal arches** — five horseshoe-shaped mesenchymal bars (numbered 1, 2, 3, 4, 6 craniocaudally; the 5th arch is rudimentary and disappears) that support the primitive pharynx laterally and ventrally.
- **Pharyngeal pouches** — four paired evaginations of **endoderm** on the inner (pharyngeal) aspect between successive arches.
- **Pharyngeal clefts (grooves)** — four paired invaginations of **surface ectoderm** on the outer aspect between successive arches.
- **Pharyngeal membranes** — four sites where the endoderm of a pouch and the ectoderm of a cleft appose, separated later by a thin mesodermal layer (giving an ecto-meso-endodermal trilaminar arrangement, comparable to the embryonic disc).

Each pharyngeal arch has an identical generalised plan of four components:

| Component         | Origin                                 | Fate                                                                      |
|-------------------|----------------------------------------|---------------------------------------------------------------------------|
| Mesenchymal core  | Paraxial mesoderm (+ neural crest)     | Muscles of the arch                                                       |
| Cartilaginous bar | Neural crest mesenchyme                | Skeletal elements/ligaments of the arch                                   |
| An artery         | Aortic sac (ventrally) to dorsal aorta | Great vessels near the heart                                              |
| A nerve           | Hindbrain (rhombomeres)                | Motor supply to arch muscles + sensory supply to arch-derived skin/mucosa |

Each arch is covered externally by ectoderm and internally by endoderm. Morphologically, each arch carries a **post-trematic nerve** (runs along its caudal border) and a **pre-trematic nerve** (cranial border); in humans the pre-trematic nerves disappear from every arch except the first, where it persists as the **chorda tympani**. Neural crest cells entering the arches carry a positional code from their rhombomere of origin: the **first arch is HOX-negative but expresses OTX2** (midbrain-derived crest), the **second arch expresses HOXA2**, and **arches 3–6 express HOXA3/HOXB3/HOXD3** — this code, together with FGF8/BMP7/SHH/PAX1 signals from the pouch endoderm, patterns the arch-specific skeleton.



## Derivatives of the pharyngeal arches — nerve, muscle, skeleton, ligament

| Arch                                               | Nerve                                                             | Muscles                                                                                                                                                            | Skeleton                                                                                                         | Ligament                                                |
|----------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| 1st (mandibular; maxillary + mandibular processes) | Trigeminal (V) — maxillary & mandibular divisions; chorda tympani | Muscles of mastication (temporalis, masseter, medial & lateral pterygoids), mylohyoid, anterior belly of digastric, tensor veli palatini, tensor tympani           | Premaxilla, maxilla, zygomatic bone, part of temporal bone, <b>Meckel's cartilage</b> , mandible, malleus, incus | Anterior ligament of malleus, sphenomandibular ligament |
| 2nd (hyoid)                                        | Facial (VII)                                                      | Muscles of facial expression (buccinator, auricularis, occipitofrontalis, platysma, orbicularis oris & oculi), posterior belly of digastric, stylohyoid, stapedius | <b>Reichert's cartilage</b> → stapes, styloid process, lesser cornu + upper part of body of hyoid                | Stylohyoid ligament                                     |
| 3rd                                                | Glossopharyngeal (IX)                                             | Stylopharyngeus                                                                                                                                                    | Greater cornu + lower part of body of hyoid                                                                      | —                                                       |
| 4th                                                | Superior laryngeal branch of vagus (X)                            | Cricothyroid, levator veli palatini, constrictors of pharynx                                                                                                       | Laryngeal cartilages — thyroid, cricoid, arytenoid, corniculate, cuneiform (fused 4th + 6th arch cartilage)      | —                                                       |
| 6th                                                | Recurrent laryngeal branch of vagus (X)                           | Intrinsic muscles of larynx (except cricothyroid)                                                                                                                  | (shares laryngeal cartilages with 4th arch)                                                                      | —                                                       |

Meckel's cartilage is not itself ossified into the mandible; the mandible forms by **membranous ossification** of mesenchyme around it, and the cartilage later degenerates, its perichondrium persisting as the anterior malleolar and sphenomandibular ligaments. The epiglottis is the one laryngeal cartilage that is **not** an arch derivative — it develops from the caudal hypobranchial eminence.

## Derivatives of the pharyngeal arch arteries

Each arch artery runs from the aortic sac to the dorsal aorta and later remodels into a definitive great vessel:

| Arch artery | Adult derivative                                                         |
|-------------|--------------------------------------------------------------------------|
| 1st         | Part of the maxillary artery                                             |
| 2nd         | Hyoid and stapedial arteries                                             |
| 3rd         | Common carotid artery; proximal part of internal carotid artery          |
| 4th         | Arch of aorta (left side); proximal right subclavian artery (right side) |
| 6th         | Ductus arteriosus (left side); proximal pulmonary artery (right side)    |

□ Fig 19.4 — Derivatives of pharyngeal arch arteries. First and second arch arteries mostly disappear (Sontakke — Textbook of Human Embryology, p.194)

### Derivatives of the pharyngeal pouches

| Pouch | Derivatives                                                                                                                                                                                                                                                                                         |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st   | Tubotympanic recess → <b>middle ear (tympanic) cavity, mastoid antrum</b> ; proximal part → <b>pharyngotympanic (auditory/eustachian) tube</b>                                                                                                                                                      |
| 2nd   | <b>Palatine tonsil</b> ; residual pouch persists as the <b>intratonsillar cleft (crypta magna)</b>                                                                                                                                                                                                  |
| 3rd   | Dorsal part → <b>inferior parathyroid gland</b> ; ventral part → <b>thymus</b> (migrates caudo-medially, dragging the inferior parathyroid with it — hence its lower final position)                                                                                                                |
| 4th   | Dorsal part → <b>superior parathyroid gland</b> ; the transient rudimentary <b>5th (ultimobranchial) pouch</b> fuses with the 4th to form the <b>caudal pharyngeal (ultimobranchial) complex</b> , whose neural-crest-derived cells become the <b>parafollicular (C) cells</b> of the thyroid gland |

### Derivatives of the pharyngeal clefts and membranes

| Cleft/Membrane          | Adult derivative                                                                                                                            |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 1st cleft               | <b>External auditory meatus</b>                                                                                                             |
| 2nd, 3rd, 4th clefts    | Obliterated — buried by caudal overgrowth of the 2nd arch operculum to form the transient <b>cervical sinus</b> , which normally disappears |
| 1st membrane            | <b>Tympanic membrane</b> (outer ectodermal layer)                                                                                           |
| 2nd, 3rd, 4th membranes | Obliterate/disappear                                                                                                                        |

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Reproduce the aortic (pharyngeal) arch artery derivative scheme by hand with these exact labels:

- ▶ Dorsal aorta; right dorsal aorta
- ▶ Aortic arches numbered 1–6, with disappearing parts of arches 1, 2 and 5 shown dotted
- ▶ **Internal carotid artery** and **external carotid artery** arising cranially
- ▶ **Left common carotid artery**; **right/left subclavian artery**
- ▶ **Arch of aorta** (from left 4th arch); **right recurrent laryngeal nerve** (hooks under right subclavian); **left recurrent laryngeal nerve** and **left vagus nerve** (hook under the aortic arch)
- ▶ **Ductus arteriosus / ligamentum arteriosus** and **pulmonary artery** (from the left/right 6th arch)
- ▶ **7th intersegmental artery**

Also sketch the **skeletal derivative chain**: Meckel's cartilage (1st arch) → malleus + incus (+ ant. malleolar & sphenomandibular ligaments); Reichert's cartilage (2nd arch) → stapes + styloid process + stylohyoid ligament + lesser cornu/upper body of hyoid; 3rd arch cartilage → greater cornu/lower body of hyoid; fused 4th–6th arch cartilage → thyroid, cricoid, arytenoid, corniculate, cuneiform cartilages.

**Applied / Clinical anatomy**

- ▶ **Branchial (cervical) cyst, sinus and fistula**: failure of obliteration of the cervical sinus (formed when the 2nd arch operculum overgrows and buries the 2nd–4th clefts) leaves a cyst/sinus along the **anterior border of sternocleidomastoid**, classically at the junction of its upper one-third and lower two-thirds, just below the angle of the mandible; an **external branchial fistula** opens on the skin of the neck, while a rare **internal branchial fistula** opens into the tonsillar sinus (rupture of the membrane between the 2nd cleft and 2nd pouch) and may pass between the internal and external carotid arteries (the "carotid fork").
- ▶ **First arch syndromes** — due to defective migration/survival of neural crest cells into the 1st arch:
  - **Treacher Collins syndrome (mandibulofacial dysostosis)** — autosomal dominant, *TCOF1* gene mutation; malar and mandibular hypoplasia, down-slanting palpebral fissures with lower-lid colobomas, deformed/atretic external ears with conductive deafness.
  - **Pierre Robin sequence** — micrognathia, cleft palate and glossoptosis (posteriorly placed tongue obstructing palatal shelf fusion); may be an isolated deformation (e.g., mandibular compression in oligohydramnios) or part of a syndrome.
- ▶ **22q11.2 deletion syndrome (DiGeorge anomaly / velocardiofacial syndrome)** — failure of 3rd and 4th pouch differentiation → **thymic and parathyroid hypoplasia/aplasia** (T-cell immunodeficiency with recurrent infections; hypocalcaemic seizures) combined with conotruncal cardiac and aortic arch anomalies (neural-crest-dependent outflow-tract septation) and mild facial dysmorphism; caused by deletion on chromosome 22q11.2, with *TBX1* implicated as the key dosage-sensitive gene.

- ▶ **Ectopic thymic/parathyroid tissue** may be left behind anywhere along the migratory descent path of the 3rd-pouch derivatives, including embedded within the thyroid gland.
- ▶ Persistence of the buccopharyngeal (oropharyngeal) membrane, or of the pharyngeal membranes generally, and errors of pouch/cleft closure form the embryological basis for most congenital lateral neck sinuses and cysts encountered clinically.

### High-yield exam pointers

- ▶ Branchial apparatus = arches + pouches + clefts + membranes, all in weeks 4–5; 5 definitive arches (1,2,3,4,6), 4 pouches, 4 clefts, 4 membranes.
- ▶ Every arch has 4 components — mesoderm/cartilage/artery/nerve — remember with the mnemonic "each arch: a Nerve, a Muscle, a bone (Skeleton), an Artery."
- ▶ Only the **1st cleft** and **1st membrane** persist as definitive adult structures (external auditory meatus; tympanic membrane) — all others are obliterated.
- ▶ Meckel's cartilage = 1st arch; Reichert's cartilage = 2nd arch — classic "must-name" eponyms.
- ▶ Nerve supply of a muscle reveals its arch of origin (V=1st, VII=2nd, IX=3rd, X=4th/6th).
- ▶ All laryngeal cartilages come from the fused 4th/6th arch cartilage **except the epiglottis** (hypobranchial eminence).
- ▶ 3rd pouch gives thymus + inferior parathyroid (crosses over during descent, ending up caudal to the 4th-pouch-derived superior parathyroid).
- ▶ Branchial cyst/fistula = anterior border of sternocleidomastoid, below angle of mandible — classic short-note/OSCE image.
- ▶ 22q11.2 deletion (DiGeorge) links 3rd/4th pouch failure to thymic aplasia, hypoparathyroidism and conotruncal heart defects — a favourite integrative viva question.

#### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology.



## Systemic embryology - nervous system & special senses



## Development of pituitary gland

Asked in: Paper II 10-Jul-2023 · Paper II 31-Jul-2021 · Paper II Nov 2018 (3×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — The pituitary gland (hypophysis cerebri) is unique among endocrine organs in having a **dual embryological origin**: an ectodermal (epithelial) component from the roof of the stomodeum and a neuroectodermal (neural) component from the floor of the diencephalon. These two primordia — **Rathke's pouch** and the **infundibular/neurohypophyseal process** — appear independently in the 3rd week of intrauterine life (IUL), grow towards each other, come into contact by the 5th–6th week, and together differentiate into the **adenohypophysis** and **neurohypophysis** of the definitive gland lodged in the hypophyseal fossa (sella turcica) of the sphenoid.

### 1. Dual origin — the two primordia

- ▶ **Adenohypophysis (anterior/glandular pituitary)** — develops from an ectodermal diverticulum of the roof of the stomodeum (primitive oral cavity), just anterior to the buccopharyngeal membrane, called **Rathke's pouch**.
- ▶ **Neurohypophysis (posterior/nervous pituitary)** — develops from a neuroectodermal downgrowth of the floor of the diencephalon (3rd ventricle), in the region of the future infundibulum, called the **infundibular process** (neurohypophyseal diverticulum).
- ▶ The **adenohypophyseal placode** itself is one of the cranial ectodermal placodes (with the otic, epibranchial, trigeminal, olfactory and lens placodes) arising from the horseshoe-shaped **preplacodal region**; its induction specifically requires **Sonic hedgehog (Shh)** signalling from the underlying prechordal mesoderm — in the absence of Shh the adenohypophyseal placode fails to form and the adjoining lens placode expands instead.
- ▶ This double origin explains why the mature gland is composed of two histologically and functionally distinct tissues fused into one organ.

### 2. Development of the adenohypophysis (Rathke's pouch)

| Age (IUL)                       | Event                                                                                                                                        |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 3rd week (~day 19–21)           | Oral ectoderm in the roof of the stomodeum thickens and invaginates dorsally towards the diencephalic floor — <b>Rathke's pouch</b> appears. |
| 4th week                        | Rathke's pouch elongates and projects further dorsally, closely approaching the infundibular process.                                        |
| 5th–6th week                    | The pouch becomes constricted ("nipple-like") at its stomodeal attachment and comes into close contact with the infundibulum.                |
| 6th–8th week (end of 2nd month) | The stalk of Rathke's pouch degenerates and the pouch is <b>cut off (detached) from the stomodeum</b> .                                      |
| 3rd–4th month                   | <b>Histogenesis</b> of the pars anterior begins — acidophils differentiate first, followed by basophils, then chromophobes.                  |

- ▶ **Anterior (thick) wall** of Rathke's pouch proliferates extensively → **pars anterior / pars distalis** (anterior lobe).
- ▶ **Posterior (thin) wall** of the pouch remains poorly proliferated → **pars intermedia** (rudimentary in humans).
- ▶ A small tongue of the anterior wall grows upward, wrapping around the infundibular stalk → **pars tuberalis**.
- ▶ The original **cavity/cleft of Rathke's pouch** persists as the narrow **hypophyseal (intraglandular) cleft** separating pars distalis from pars intermedia.
- ▶ With formation of the definitive oral cavity and pharynx, the original stomodeal attachment site of the pouch comes to lie in the **roof of the nasopharynx**; the track it traversed is the **craniopharyngeal canal**.

### 3. Development of the neurohypophysis (infundibular process)

- ▶ The **infundibular process** is a solid downgrowth of neuroectoderm from the floor of the diencephalon, arising during the 3rd–6th week and growing towards the stomodeum to meet the posterior aspect of Rathke's pouch.
- ▶ Its neuroepithelial cells proliferate and differentiate into **pituicytes** — modified neuroglial cells that form the bulk of the posterior lobe; the neurohypophysis is neuroectodermal but contains **no neuronal cell bodies** of its own.
- ▶ Axons of magnocellular neurones (supraoptic and paraventricular nuclei of the hypothalamus) grow down into the developing posterior lobe as the **hypothalamo-hypophyseal tract**.
- ▶ The infundibular process differentiates into three continuous parts: the **median eminence** (proximal, continuous with the tuber cinereum), the **infundibular stem** (connecting stalk), and the **pars nervosa / pars posterior** (distal, solid bulbous part).
- ▶ The cavity of the infundibulum, continuous early on with the 3rd ventricle, persists postnatally as the **infundibular recess**.

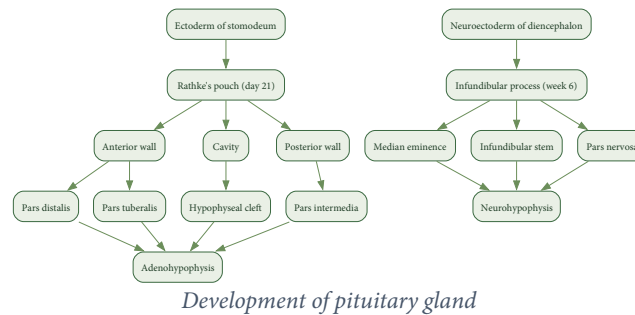
### 4. Molecular regulation of pituitary organogenesis

- ▶ Induction of the adenohypophyseal placode requires **Shh** from the prechordal mesoderm (see above).
- ▶ Reciprocal inductive signalling between the two primordia is essential — secreted molecules from the diencephalon, including **FGF8, BMP4 and Wnt5A**, pattern and drive proliferation of the anterior and intermediate lobes of the developing adenohypophysis.
- ▶ The LIM-homeobox gene **Lhx2** governs development of the posterior lobe (neurohypophysis).
- ▶ A defect of the **Wnt/ $\beta$ -catenin (CTNNB1) signalling pathway** in residual Rathke's pouch epithelium is implicated in the genesis of adamantinomatous craniopharyngioma (see Applied anatomy).

### 5. Fusion and definitive subdivisions of the pituitary

The neuroectodermal infundibular process and the ectodermal Rathke's pouch fuse to form the single, composite hypophysis cerebri, whose named subdivisions are:

| Component       | Embryonic source                    | Definitive part                                                                   |
|-----------------|-------------------------------------|-----------------------------------------------------------------------------------|
| Adenohypophysis | Ectoderm of Rathke's pouch          | Pars distalis (anterior lobe), pars intermedia, pars tuberalis, hypophyseal cleft |
| Neurohypophysis | Neuroectoderm of diencephalic floor | Median eminence, infundibular stem, pars nervosa (posterior lobe)                 |



□ Fig 25.1 — Development of pituitary gland (Sontakke — Textbook of Human Embryology, p.282)

□ Fig 25.2 — Development of pituitary gland (Sontakke — Textbook of Human Embryology, p.283)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A three-panel sagittal-section sequence through the developing hypophysis (day 24 → day 40 → day 45), labelled:

- ▶ Stomodeum (primitive oral cavity) and buccopharyngeal membrane
- ▶ Ectodermal thickening → **Rathke's pouch** (with arrow showing dorsal growth direction)
- ▶ Diencephalon (floor of 3rd ventricle) → **infundibular process**
- ▶ Notochord (for orientation)
- ▶ Point of constriction/detachment of Rathke's pouch from the stomodeum

Followed by a labelled definitive-gland panel: **pars tuberalis**, **pars distalis**, **pars intermedia**, **hypophyseal (intraglandular) cleft** (adenohypophysis) and **infundibular stem**, **median eminence**, **pars nervosa** (neurohypophysis), with the optic chiasma and sella turcica of the sphenoid shown for orientation.

### Applied / Clinical anatomy

- ▶ **Craniopharyngioma** — a benign-but-locally-aggressive tumour arising from epithelial remnants of Rathke's pouch along the craniopharyngeal canal; accounts for ~2.5–4% of intracranial tumours; shows a **bimodal age distribution** — childhood (5–14 years) and adult onset (50–70 years); implicated in **Wnt/ $\beta$ -catenin (CTNNB1)** signalling defects; may form within the sella, along the pituitary stalk, or (rarely) in the pharynx/basisphenoid; presents with raised intracranial pressure, hydrocephalus, **bitemporal hemianopia** (chiasmal compression) and pituitary dysfunction (growth failure, diabetes insipidus).



- ▶ **Pharyngeal hypophysis** — a normal accessory remnant of adenohypophyseal tissue left behind at the original stomodeal attachment site of Rathke's pouch, found in the roof/posterior wall of the nasopharynx; rarely the site of ectopic hormone-secreting tissue.
- ▶ **Basipharyngeal canal / persistent craniopharyngeal canal** — a bony remnant of the track of Rathke's pouch, occasionally seen on neonatal skull radiographs.
- ▶ **Pituitary agenesis or hypoplasia** — rare failure of Rathke's pouch development or of fusion with the infundibular process, producing combined pituitary hormone deficiency.
- ▶ **Rathke's cleft cyst** — cystic dilatation of the persistent hypophyseal cleft.
- ▶ **Pituitary adenomas**, classified by the cell of origin of the adult pars distalis (chromophobes, acidophils, basophils): **chromophobe adenoma** (commonest; headache, bitemporal hemianopia, hypopituitarism), **acidophil adenoma** (excess GH → gigantism in children, acromegaly in adults), **basophil adenoma** (excess ACTH → Cushing's syndrome).

### High-yield exam pointers

- ▶ Pituitary has **dual origin**: adenohypophysis from **oral ectoderm** (Rathke's pouch); neurohypophysis from **neuroectoderm** of the diencephalon (infundibular process).
- ▶ Rathke's pouch appears in the **3rd–4th week** IUL and is cut off from the stomodeum by the **6th–8th week** (end of 2nd month).
- ▶ Anterior (thick) wall of pouch → pars distalis; posterior (thin) wall → pars intermedia; upward extension → pars tuberalis; original cavity → hypophyseal cleft.
- ▶ Neurohypophysis differentiates into median eminence, infundibular stem and pars nervosa; its cells (pituicytes) are neuroglial — no neurones are intrinsic to it.
- ▶ **Shh** is required for adenohypophyseal placode induction; **FGF8/BMP4/Wnt5A** from the diencephalon pattern the anterior/intermediate lobes; **Lhx2** drives posterior lobe development.
- ▶ Histogenesis of adenohypophyseal cells begins in the **3rd–4th month** — acidophils first, then basophils, then chromophobes.
- ▶ **Craniopharyngioma** = tumour of Rathke's pouch remnants along the craniopharyngeal canal — classic bimodal age distribution.
- ▶ **Pharyngeal hypophysis** = normal accessory adenohypophyseal remnant in the nasopharyngeal roof.
- ▶ Original site of Rathke's pouch attachment ends up in the **roof of the nasopharynx** once the face and palate form.

### SOURCE & COVERAGE

Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Gray's Anatomy (Standring) 41e.





- ▶ Only **cranial neural crest** is skeletogenic in humans — it alone forms cartilage and bone; trunk crest, even when experimentally transplanted, does not normally do so.
- ▶ **Cardiac neural crest** is a specialised subpopulation of the vagal crest that migrates through pharyngeal arches 3, 4 and 6 to build the aorticopulmonary (conotruncal) septum and the tunica media/adventitia of the great vessels — its depletion produces persistent truncus arteriosus and related outflow-tract anomalies.
- ▶ **Vagal and lumbosacral (sacral) crest** together populate the entire enteric nervous system: vagal crest invades the gut cranial-to-caudal from oesophagus to the mid-transverse colon, while lumbosacral crest invades caudal-to-cranial into the hindgut, giving the terminal gut a dual crest origin.

#### 4. Migration routes

- ▶ **Trunk crest** leaves the neuroectoderm only after neural tube closure and migrates by two principal routes:
  - **Ventral (deep) pathway** — through the rostral (anterior) half of each somite's sclerotome — forming **dorsal root ganglia, sympathetic chain and preaortic ganglia, enteric/parasympathetic neurons, Schwann cells, and the neuroendocrine cells of the adrenal medulla.**
  - **Dorsal (superficial) pathway** — between the ectoderm and the dermomyotome, entering the epidermis through the basal lamina — forming **melanocytes** of the skin and hair follicles.
  - A further **rostrocaudal route along the dorsal aorta** produces the **pre-aortic ganglia.**
- ▶ **Head (cranial) crest** migrates dorsolaterally around the neural tube before closure, streaming from each rhombomere/brain segment into the corresponding pharyngeal arch (arches I–IV) to build the craniofacial skeleton, connective tissue, and cranial sensory/parasympathetic ganglia; some cranial crest cells also invade the surface ectoderm to form facial melanocytes.

#### 5. Derivatives of neural crest cells

□ Fig 22.3 — Derivatives of neural crest cells (Sontakke — Textbook of Human Embryology, p.245)

| System                       | Derivative                                                                                                                                                                      |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skeletal / connective tissue | Craniofacial cartilage and bones, part of the cranial vault and chondrocranium, ligaments, tendons, dermis and glandular stroma of face and neck                                |
| Odontogenic                  | Odontoblasts                                                                                                                                                                    |
| Peripheral nervous system    | Dorsal root (spinal) ganglia; cranial nerve ganglia; sympathetic chain and preaortic ganglia; parasympathetic ganglia of the gastrointestinal tract; Schwann cells; glial cells |
| Endocrine                    | Adrenal (suprarenal) medulla (chromaffin cells); C cells (parafollicular cells) of the thyroid gland                                                                            |
| Pigment                      | Melanocytes of skin and hair follicles                                                                                                                                          |

| System         | Derivative                                                                                                                             |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Cardiovascular | Conotruncal (aorticopulmonary) septum; smooth muscle of the tunica media of the aortic arch arteries and vessels of the face/forebrain |
| Meninges       | Meninges of the forebrain                                                                                                              |
| Other          | Smooth muscle to blood vessels of the face and forebrain                                                                               |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Transverse section through a trunk-level embryo (post neural-tube closure), showing the **two migration pathways of trunk neural crest**. Labels required:

- ▶ Neural tube (with central canal) and notochord
- ▶ Somite differentiated into dermomyotome (dorsal) and sclerotome (ventral), with the **rostral (anterior) half of the sclerotome** shaded to show it alone is permissive for crest migration
- ▶ Neural crest cells at the roof of the neural tube (site of origin)
- ▶ **Ventral (deep) pathway** arrow → labelled destinations: dorsal root ganglion, sympathetic ganglion (paravertebral chain), preaortic ganglion, suprarenal (adrenal) medulla
- ▶ **Dorsal (superficial) pathway** arrow, passing between ectoderm and dermomyotome → labelled destination: melanocytes in the epidermis
- ▶ Surface ectoderm and dermis

### Applied / Clinical anatomy

- ▶ **Neurocristopathies** — a unifying concept for disorders of neural crest induction, migration, proliferation or differentiation; together they account for about one-third of all human birth defects and include several neoplasms.
- ▶ **Hirschsprung disease (congenital aganglionic megacolon)** — failure of neural crest cells to migrate into (or survive within) the distal colon and rectum leaves this segment devoid of parasympathetic (myenteric and submucosal) ganglia; the aganglionic segment fails to relax, causing functional obstruction. Most familial cases result from mutations in the **RET** gene, a tyrosine-kinase receptor essential for crest cell migration/survival in the gut.
- ▶ **22q11.2 deletion syndrome** (DiGeorge syndrome/anomaly, velocardiofacial/Shprintzen syndrome, conotruncal anomaly face syndrome) — the commonest human deletion syndrome (~1 in 4000 births), due to deletion of chromosome 22q11.2 (gene **TBX1**). Neural-crest-derived mesenchyme normally supports the endodermal epithelium of the 3rd/4th pharyngeal pouches and the cardiac outflow tract; its deficiency produces **thymic and parathyroid hypoplasia/aplasia** (T-cell immunodeficiency, hypocalcaemic seizures) together with **conotruncal cardiac defects** (e.g. persistent truncus arteriosus, tetralogy-of-Fallot spectrum, interrupted aortic arch type B) from failure of the aorticopulmonary (conotruncal) septum formed by cardiac neural crest.

- ▶ **Treacher Collins syndrome (mandibulofacial dysostosis)** — autosomal dominant (1 in 50,000 births, 60% new mutations); mutation in **TCOF1** (5q32), which encodes the nucleolar protein "treacle," required for preventing apoptosis and maintaining proliferation of neural crest cells (migration itself is normal). Produces hypoplasia of the maxilla, mandible and zygomatic arches, cleft palate, down-slanting palpebral fissures with lower-lid colobomas, and external/middle-ear defects with conductive hearing loss.
- ▶ **Waardenburg syndrome and piebaldism** — defective melanocyte-lineage neural crest derivatives cause patchy depigmentation of skin and hair; Waardenburg syndrome additionally features sensorineural deafness.
- ▶ **Neoplasia of neural crest origin** — melanoma and neuroblastoma are tumours of neural-crest-derived cells; pheochromocytoma arises from crest-derived adrenal medullary (chromaffin) cells.
- ▶ **Surgical/radiological relevance** — because cardiac neural crest builds the tunica media of the great vessels and the conotruncal septum, its ablation experimentally (and its deficiency clinically) produces persistent truncus arteriosus and great-vessel anomalies relevant to the work-up of cyanotic congenital heart disease.

### High-yield exam pointers

- ▶ NCCs are a transient, multipotent, migratory population from the **neural plate border**, formed by EMT — often called the "fourth germ layer."
- ▶ Induction sequence: intermediate BMP ( $\pm$  WNT/FGF) at the neural plate border  $\rightarrow$  **PAX3** (specification)  $\rightarrow$  **SNAIL/FOXD3** (crest commitment)  $\rightarrow$  **SLUG** (EMT/migration).
- ▶ **Head crest migrates before neural tube closure; trunk crest migrates only after local tube closure.**
- ▶ Trunk crest uses two routes: **ventral** (rostral sclerotome)  $\rightarrow$  DRG/sympathetic-preaortic ganglia/adrenal medulla/Schwann cells; **dorsal** (sub-ectodermal)  $\rightarrow$  melanocytes.
- ▶ Five axial subdivisions: **cranial, cardiac, vagal, trunk, lumbosacral (sacral).**
- ▶ Only **cranial neural crest** is skeletogenic (mesectoderm) — forms craniofacial cartilage and bone; trunk crest does not.
- ▶ **Cardiac (vagal) neural crest** forms the aorticopulmonary/conotruncal septum — its loss underlies persistent truncus arteriosus and the 22q11.2/DiGeorge spectrum.
- ▶ Key neurocristopathies to name with their gene: **Hirschsprung (RET)**, **Treacher Collins (TCOF1)**, **DiGeorge/22q11.2 (TBX1)**, **Waardenburg/piebaldism** (melanocyte lineage) — plus neural-crest-derived tumours (neuroblastoma, melanoma, pheochromocytoma).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; figure from Sontakke's Textbook of Human Embryology.



## Derivatives of Neural Crest cells

Asked in: Paper II 26-Sep-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** The neural crest is a transient population of ectodermal cells that arises at the junctional border between the neural plate and the surface ectoderm during the third week. Induced by intermediate levels of BMP (regulated by the notochord-derived inhibitors noggin, chordin and follistatin, and by transcription factors PAX3, FOXD3, SNAIL and SLUG), these cells undergo an epithelial-to-mesenchymal transition, detach from the neural folds just before/after neural tube closure, and migrate extensively to give rise to an extraordinary diversity of neuronal, glial, pigmentary, endocrine and skeletal/connective-tissue structures. Because of this vast contribution the neural crest is often called the "fourth germ layer"; its maldevelopment underlies roughly a third of all congenital anomalies.

### Origin and migration pathways

- ▶ **Cranial neural crest** — leaves the neural folds of the brain *before* tube closure; uniquely forms a **non-neuronal, mesenchymal (ecto-mesenchymal) population** in addition to neurones/glia; migrates segmentally from the rhombomeres into the pharyngeal arches.
- ▶ **Trunk (spinal) neural crest** — leaves *after* tube closure; migrates along two pathways only: a **dorsolateral pathway** through the dermis (→ melanocytes) and a **ventral pathway** through the rostral half of each somitic sclerotome (→ dorsal root/sympathetic ganglia, Schwann cells, adrenal medulla). It does **not** form skeletal mesenchyme.
- ▶ **Vagal and lumbosacral (caudal) neural crest** — a special sub-population that migrates into the gut wall to form the enteric ganglia and glia of the myenteric and submucosal plexuses.
- ▶ **Cardiac neural crest** — a cranial sub-population (rhombomeres/somites at the vagal level) that migrates through pharyngeal arches 3, 4 and 6 into the cardiac outflow tract.

| Rhombomere | Pharyngeal arch invaded                                 |
|------------|---------------------------------------------------------|
| r1–r2      | 1st arch                                                |
| r4         | 2nd arch                                                |
| r6         | 3rd arch                                                |
| r7–r8      | 4th and 6th arches                                      |
| r3, r5     | small numbers disperse to adjacent even-numbered arches |

### Classification of derivatives (dorsal and ventral neural-crest masses)

On separation, neural crest cells form a **dorsal mass** (predominantly sensory/glial/pigmentary) and a **ventral mass** (predominantly autonomic/chromaffin), each further sub-classified by cell lineage.

| Mass         | Cell lineage                     | Derivatives                                                                                                                                                                                                                                                                       |
|--------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dorsal mass  | A. Neuroblasts                   | Dorsal root (spinal) ganglia; sensory ganglia of cranial nerves V, VII, IX and X; skeletal (ecto-mesenchymal) elements of the pharyngeal arches; <b>odontoblasts</b> of the teeth; <b>parafollicular (C) cells</b> of the thyroid                                                 |
|              | B. Spongioblasts                 | <b>Satellite cells</b> of peripheral ganglia; <b>Schwann cells</b> (neurilemmal sheath)                                                                                                                                                                                           |
|              | C. Pluripotent cells             | <b>Melanocytes</b> of epidermis, hair follicles and the uveal tract                                                                                                                                                                                                               |
| Ventral mass | A. Sympatho-chromaffin precursor | Common precursor giving rise to B and C below                                                                                                                                                                                                                                     |
|              | B. Sympathoblasts                | <b>Sympathetic chain and pre-vertebral (coeliac, mesenteric, aortic) ganglionic neurons</b> ; <b>parasympathetic ganglionic neurons</b> of the head (ciliary, pterygopalatine, submandibular, otic) and of the gut wall (enteric ganglia, derived from vagal + lumbosacral crest) |
|              | C. Chromaffin cells              | Chromaffin cells of the <b>adrenal medulla</b> ; <b>para-aortic bodies</b> (organ of Zuckerkandl); argentaffin cells of the respiratory tract; <b>enterochromaffin cells</b> of the gut                                                                                           |

Additional neuroglial derivatives (Gray's/Langman): all **neuroglia except microglia** (which is of mesodermal/monocyte-macrophage origin) — i.e., **astrocytes and oligodendrocytes of the CNS** derive from neural crest-related neuroepithelium/crest, while peripheral **satellite cells and Schwann cells** are unambiguously neural-crest derived. **Type I (chief) glomus cells** of the carotid and aortic bodies (chemoreceptors) are also neural-crest derivatives.

### Ecto-mesenchymal (non-neuronal) and craniofacial derivatives

Cranial neural crest alone forms mesenchyme ("ectomesenchyme"), contributing the following, organised by region:

| Region         | Structures derived from neural crest                                                                                                                                                                                                                                                                             |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skull and face | Membranous bones of the facial skeleton and vault of skull (viscerocranium and much of the desmocranium); cartilages of the pharyngeal arches, e.g., <b>Meckel's cartilage</b> (arch 1) → malleus, incus; <b>Reichert's cartilage</b> (arch 2) → stapes, styloid process, lesser cornu and part of body of hyoid |



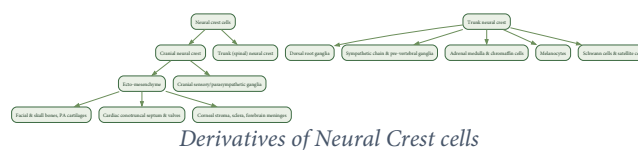
| Region                     | Structures derived from neural crest                                                                                                                                                                                                |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dermis / connective tissue | Dermis of face and neck; dental papilla/odontoblasts (dentine)                                                                                                                                                                      |
| Eye                        | Sclera and choroid of the eyeball; substantia propria and posterior (corneal endothelial) epithelium of the cornea; ciliary body muscle                                                                                             |
| Cardiovascular             | <b>Conotruncal (aorticopulmonary) septum</b> and spiral septum dividing the truncus arteriosus; <b>semilunar valves</b> ; smooth muscle of the tunica media of the great vessels arising from the pharyngeal (aortic) arch arteries |
| Meninges                   | <b>Pia-arachnoid (leptomeninges) of the forebrain</b> ; spinal and remaining cranial meninges are mesodermal                                                                                                                        |
| Vasculature of head        | Smooth muscle cells of blood vessels of the face and forebrain                                                                                                                                                                      |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

□ Fig 22.3 — Derivatives of neural crest cells (Sontakke — Textbook of Human Embryology, p.245)

Reproduce as a labelled flow diagram from a transverse section through the neural tube at the neural-crest stage, branching into:

- **Dorsal mass** → dorsal root ganglion, cranial sensory ganglia (V, VII, IX, X), satellite cells, Schwann cells, melanocytes
- **Ventral mass** → sympathetic chain ganglion, pre-vertebral/coeliac ganglion, parasympathetic (ciliary/otic) ganglia, adrenal medulla, para-aortic body
- **Cranial ecto-mesenchyme** → facial/skull bones, pharyngeal arch cartilages, cardiac conotruncal septum, meninges of forebrain, corneal/scleral mesenchyme



### Applied / Clinical anatomy

- **Neurocristopathies** — the umbrella term for diseases arising from abnormal neural-crest development, since one progenitor population affects so many organ systems.
- **Hirschsprung disease (congenital megacolon)** — failure of vagal + lumbosacral neural crest cells to colonise the terminal hindgut → an aganglionic segment with impaired peristalsis and proximal bowel dilatation.
- **DiGeorge (velocardiofacial/22q11.2 deletion) syndrome** — microdeletion on chromosome 22q11.2 disrupts cranial/cardiac neural crest migration into the 3rd–4th pharyngeal pouches and

cardiac outflow tract; presents with thymic and parathyroid aplasia (T-cell immunodeficiency, hypocalcaemia) and conotruncal cardiac defects.

- ▶ **First-arch syndromes** — Treacher Collins syndrome and Pierre Robin sequence (micrognathia, cleft palate, glossoptosis) result from disordered neural-crest-derived first arch mesenchyme.
- ▶ **Waardenburg syndrome (types I/II) and piebaldism/albinism** — pigmentary defects from abnormal melanocyte (neural crest) migration/differentiation, often with sensorineural deafness.
- ▶ **Pheochromocytoma** — tumour of neural-crest-derived chromaffin cells of the adrenal medulla; **neuroblastoma** — malignant tumour of primitive sympathoblasts; **melanoma** — of melanocytes; **neurofibromatosis (von Recklinghausen disease)** and **Charcot-Marie-Tooth disease** — Schwann cell/peripheral-nerve neural crest derivatives.
- ▶ **CHARGE syndrome** (coloboma, heart defects, choanal atresia, growth/developmental retardation, genitourinary and ear anomalies) reflects widespread cranial neural crest disruption.
- ▶ Surgical/radiological relevance: the neural-crest origin of the conotruncal septum explains why persistent truncus arteriosus, tetralogy of Fallot and transposition-spectrum lesions cluster with 22q11.2 deletion and other craniofacial anomalies.

### High-yield exam pointers

- ▶ Neural crest = "fourth germ layer"; formed by EMT at the neural plate–surface ectoderm border under an intermediate BMP gradient (noggin/chordin antagonism; PAX3, FOXD3, SNAIL/SLUG).
- ▶ Sontakke's exam-favoured classification: **Dorsal mass** (neuroblasts, spongioblasts, pluripotent melanocyte precursors) vs **Ventral mass** (sympathoblasts and chromaffin cells).
- ▶ Only **cranial** neural crest forms mesenchyme (ecto-mesenchyme — skeleton, dermis, cardiac septa); **trunk** crest never forms mesenchyme.
- ▶ **Adrenal medulla** (not cortex) and **parafollicular (C) cells of thyroid** are the two classic neural-crest components embedded within otherwise mesodermal/endodermal glands.
- ▶ **Pia-arachnoid of the forebrain** is neural-crest derived; spinal and remaining cranial meninges are mesodermal.
- ▶ All **neuroglia** are neural-crest derived except **microglia** (mesodermal, monocyte-macrophage lineage).
- ▶ **Cardiac neural crest** forms the aorticopulmonary/conotruncal septum and semilunar valves — its failure gives conotruncal cardiac anomalies, classically in 22q11.2 deletion (DiGeorge) syndrome.
- ▶ **Hirschsprung disease** = failure of caudal neural crest colonisation of the hindgut → congenital aganglionic megacolon.
- ▶ Neural-crest tumours: neuroblastoma (sympathoblasts), pheochromocytoma (chromaffin cells), melanoma (melanocytes), neurofibromatosis (Schwann cells).

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Larsen — Human Embryology 6e; Vishram Singh — Clinical Neuroanatomy 4e and Textbook of Clinical Embryology; IB Singh — Textbook of Human Neuroanatomy; Vishram Singh — General Anatomy 4e.



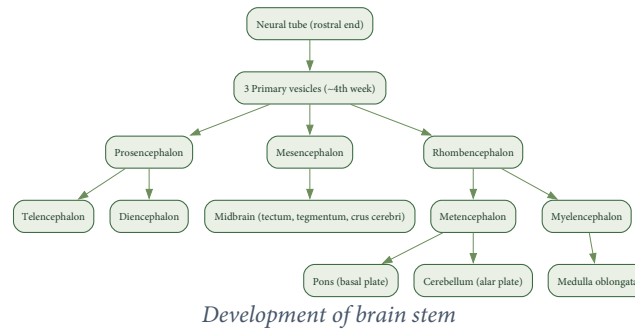
## Development of brain stem

*Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The brain stem (medulla oblongata + pons + midbrain) is the rostral continuation of the spinal cord and develops from the caudal two of the three primary brain vesicles — the **rhombencephalon** (hindbrain, minus the cerebellum) and the **mesencephalon** (midbrain) — while the cerebellum, though also a rhombencephalic derivative, is conventionally excluded from the brain stem proper. Like the spinal cord, the brain stem retains a fundamental **basal-plate (motor) / alar-plate (sensory)** organisation separated by the sulcus limitans, but the plates "evert" and expand mediolaterally around the widened fourth ventricle rather than remaining strictly dorsoventral. Development proceeds through neural tube regionalisation, flexure formation, rhombomeric segmentation, and differentiation of the three brain-stem vesicles (myelencephalon, metencephalon, mesencephalon).

### 1. Neural tube to brain vesicles — three primary → five secondary vesicles

- ▶ Even before neurulation is complete, the rostral neural plate shows three broadenings — the future **prosencephalon** (forebrain), **mesencephalon** (midbrain) and **rhombencephalon** (hindbrain) — visible as the **three primary brain vesicles** once the cranial neuropore closes (end of the 4th week).
- ▶ During the **5th week**, the prosencephalon and rhombencephalon each subdivide into two, converting the three primary vesicles into **five secondary brain vesicles**; the mesencephalon does not subdivide.
  - Prosencephalon → **telencephalon + diencephalon**
  - Rhombencephalon → **metencephalon + myelencephalon**
  - Mesencephalon → remains as the **mesencephalon**
- ▶ The **brain stem** = **myelencephalon + metencephalon (basal-plate part) + mesencephalon**; the cerebellum is the alar-plate derivative of the metencephalon.



## 2. Flexures of the neural tube

| Flexure                  | Site                                     | Concavity | Timing / significance                                                                                                               |
|--------------------------|------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------|
| Mesencephalic (cephalic) | At the midbrain                          | Ventral   | Appears earliest (stages 13–14); bends prosencephalon ventrally around the notochord/foregut                                        |
| Cervical                 | Rhombencephalon–spinal cord junction     | Ventral   | Increases 5th–7th week (hindbrain nearly right-angled to cord); diminishes and disappears after the 7th week as the head extends    |
| Pontine                  | Between metencephalon and myelencephalon | Dorsal    | Stretches and thins the thin roof plate, everting the lateral walls and flattening the cavity into the diamond-shaped 4th ventricle |

## 3. Segmental organisation — rhombomeres

- ▶ The rhombencephalon shows transient transverse segments (**neuromeres**): 4 primary rhombomeres (A–D) subdivide into 8 secondary **rhombomeres (r1–r8)** plus a rostral constriction, the **isthmus rhombencephali**, which demarcates the midbrain–hindbrain boundary.
- ▶ With the early outgrowth of the cerebellum from the isthmus/r1, the rhombencephalon is conventionally divided into the **metencephalon** (extending to about r3) and the **myelencephalon** (r4–r8, down to the spinomedullary junction).
- ▶ Rhombomeres set the segmental template for brain-stem motor nuclei: **r1** – trochlear; **r2–r3** – trigeminal; **r4–r5** – facial; **r5** – abducens; **r6–r7** – glossopharyngeal; **r7–r8** – vagal, accessory and hypoglossal nuclei. Rhombomeric boundaries fade as the medulla matures into a smooth-contoured tube.

#### 4. General plan — basal/alar plates and the seven functional cell columns

- ▶ As in the cord, the neuroepithelium differentiates into ventricular, mantle and marginal zones; the mantle layer of each lateral wall forms a ventrolateral **basal plate** (motor) and a dorsolateral **alar plate** (sensory), separated by the **sulcus limitans**.
- ▶ Because the roof plate of the hindbrain thins and spreads (pontine flexure), the alar plate comes to lie **lateral** rather than purely dorsal to the basal plate — giving the classical mediolateral arrangement of **seven discontinuous functional columns**.

| Column (motor/basal)                  | Structures innervated                                                                 | Cranial nerves    |
|---------------------------------------|---------------------------------------------------------------------------------------|-------------------|
| Somatic efferent                      | Extrinsic eye muscles, tongue                                                         | III, IV, VI, XII  |
| Branchial (special visceral) efferent | Pharyngeal-arch striated muscle (via nucleus ambiguus caudally)                       | V, VII, IX, X, XI |
| General visceral efferent             | Parasympathetic to viscera/glands (Edinger–Westphal, salivatory, dorsal vagal nuclei) | III, VII, IX, X   |

| Column (sensory/alar)       | Modality                                               | Cranial nerves |
|-----------------------------|--------------------------------------------------------|----------------|
| General visceral afferent   | Interoceptive from thoracic/abdominal/pelvic viscera   | IX, X          |
| Special (visceral) afferent | Taste — nucleus of tractus solitarius                  | VII, IX, X     |
| General somatic afferent    | Touch/pain/temperature — head, neck, oral/nasal mucosa | V, VII, IX, X  |
| Special somatic afferent    | Hearing and balance (cochlear/vestibular nuclei)       | VIII           |

□ Fig 9.5 — Organization of the Brain Stem Cranial Nerve Nuclei: the basal columns give rise to motor (efferent) nuclei and the alar columns to associational (afferent) nuclei, seven discontinuous columns in all (Larsen — Human Embryology — 6e, p.516)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Transverse (cross-sectional) scheme of the medulla/pons at the level of the 4th ventricle floor, labelled: **roof plate** (thin ependyma + pia = tela choroidea) — **floor plate** — **sulcus limitans** — medial-to-lateral basal columns (**somatic efferent** → **branchial efferent** → **general visceral efferent**) — medial-to-lateral alar columns (**general visceral afferent** → **special afferent** → **general somatic afferent** → **special somatic afferent**) — **olivary nuclear complex** (migrated alar-plate cells) — **choroid plexus** in the roof — **4th ventricle cavity**.

#### 5. Myelencephalon → medulla oblongata

- ▶ Forms a **transitional zone** between spinal cord and brain: its lateral walls **evert**, but alar and basal plates separated by the sulcus limitans remain clearly distinguishable.

- ▶ **Basal plate** — three motor groups: (i) medial **somatic efferent** (hypoglossal, XII — cephalic continuation of anterior horn cells); (ii) intermediate **special visceral efferent** (nucleus ambiguus → IX, X, XI); (iii) lateral **general visceral efferent** (dorsal nucleus of vagus, X — preganglionic parasympathetic to viscera).
- ▶ **Alar plate** — three sensory groups: lateral **general somatic (somatic) afferent** (pain/touch/temperature via IX), intermediate **special afferent** (taste and vestibulocochlear inputs, VIII), medial **general visceral afferent** (interoceptive GI/cardiac input).
- ▶ Cells of the alar plate also migrate ventrally to form the **inferior olivary nuclear complex**; some alar-plate-derived cells of the myelencephalon (and metencephalon) migrate to form the **pontine nuclei**.
- ▶ **Roof plate**: a single layer of ependyma covered by vascular pia (**tela choroidea**); proliferation produces tuft-like invaginations — the **choroid plexus** of the 4th ventricle, which secretes CSF. Perforations of the thinned roof later form the median and lateral apertures (foramina of Magendie and Luschka).

## 6. Metencephalon → pons and cerebellum

- ▶ **Basal plate → pons**: three motor groups — medial somatic efferent (abducens, VI), special visceral efferent (trigeminal V and facial VII nuclei, supplying 1st/2nd arch musculature), and general visceral efferent (fibres to submandibular/sublingual glands). The expanding marginal layer forms a transverse fibre bridge connecting cerebral and cerebellar cortices to the spinal cord — hence "pons" (bridge); it also contains the migrated **pontine nuclei**.
- ▶ **Alar plate → cerebellum**: the dorsolateral alar plate bends medially to form the **rhombic lips**; as the pontine flexure deepens, the lips are compressed cephalocaudally into the **cerebellar plate**. By 12 weeks this shows a midline **vermis** and two lateral **hemispheres**; a transverse fissure separates the (phylogenetically oldest) **flocculonodular lobe** from the rest.
- ▶ Histogenesis: neuroepithelial cells migrate to the surface to form a transient proliferative **external granular layer**; its cells later migrate inward (6th month onward) past the outward-migrating **Purkinje cells** to form the **internal granular layer**; basket and stellate cells arise from the white matter. Deep cerebellar nuclei (e.g., **dentate nucleus**) reach their final position before birth; cortical lamination completes chiefly after birth.
- ▶ The **isthmus rhombencephali** contributes the superior medullary velum and superior cerebellar peduncles.

## 7. Mesencephalon → midbrain

- ▶ **Basal plate**: (i) medial **somatic efferent** group — oculomotor (III) and trochlear (IV) nuclei, supplying extraocular muscles; (ii) small **general visceral efferent** group — the **Edinger-Westphal nucleus**, parasympathetic to sphincter pupillae/ciliaris. The enlarging marginal layer of the basal plate forms the **crus cerebri** (cerebral peduncle), carrying descending corticospinal/corticopontine/corticobulbar fibres.
- ▶ **Alar plate**: initially two longitudinal elevations flanking a shallow midline groove; a transverse groove later divides each into an **anterior (superior) colliculus** (visual reflex centre) and a **posterior (inferior) colliculus** (auditory relay), formed by neuroblasts migrating into the overlying marginal zone (**tectum**).

- ▶ Additional grey masses — the **red nucleus** and **substantia nigra** — differentiate in the tegmentum from neuroblasts migrating into the basal-plate marginal zone.
- ▶ The narrow lumen becomes the **cerebral aqueduct**, connecting the third and fourth ventricles.
- ▶ The trochlear nucleus remains near the isthmus; uniquely, its axons decussate dorsally before the nerve emerges — the only cranial nerve to exit the brain stem dorsally.

## Applied / Clinical anatomy

- ▶ **Arnold–Chiari malformation**: herniation of the medulla oblongata with the inferior cerebellar vermis/tonsils through the foramen magnum — obstructs CSF flow (hydrocephalus) and compresses IX, X, XI roots, producing dysphagia, laryngeal stridor and a diminished gag reflex; the commonest congenital anomaly involving the cerebellum.
- ▶ **Congenital aqueductal stenosis**: narrowing of the mesencephalon-derived cerebral aqueduct is the commonest cause of congenital (non-communicating) hydrocephalus.
- ▶ **Medulloblastoma**: the commonest posterior-fossa tumour of childhood, arising from residual proliferative cells of the cerebellar **external granular layer**, typically in the vermis — explains its highly cellular, small round-cell histology and midline location.
- ▶ **Choroid plexus/4th ventricle**: knowledge of the tela choroidea and its perforations (foramina of Magendie/Luschka) underlies the anatomical basis of CSF egress into the subarachnoid space and posterior-fossa hydrocephalus when obstructed.
- ▶ **Pontine flexure and cranial-nerve topography**: the dorsally-directed pontine flexure explains the everted, rhomboid floor of the 4th ventricle and the characteristic mediolateral (rather than dorsoventral) arrangement of cranial-nerve nuclear columns seen on cross-section — clinically relevant to localising brain-stem lesions by combinations of affected nuclei ("crossed" brain-stem syndromes).

## High-yield exam pointers

- ▶ Brain stem = medulla (myelencephalon) + pons (metencephalon, basal part) + midbrain (mesencephalon); cerebellum is the metencephalic alar-plate derivative, excluded from the brain stem proper.
- ▶ 3 primary vesicles (4th week) → 5 secondary vesicles (5th week): prosencephalon → telencephalon + diencephalon; rhombencephalon → metencephalon + myelencephalon; mesencephalon unchanged.
- ▶ Three flexures: mesencephalic and cervical are concave ventrally; the pontine flexure is concave dorsally and produces the diamond-shaped 4th-ventricle floor.
- ▶ Rhombomeres r1–r8 give the segmental template for brain-stem motor nuclei (r1-trochlear ... r7/8-vagal/accessory/hypoglossal); metencephalon ≈ isthmus–r3, myelencephalon ≈ r4–r8.
- ▶ Sulcus limitans persists throughout, but alar plate lies lateral (not purely dorsal) to basal plate owing to eversion at the pontine flexure — seven functional columns result (3 motor, 4 sensory).
- ▶ Cerebellum: rhombic lips → cerebellar plate → vermis + hemispheres; transient external granular layer supplies granule cells; Purkinje cells migrate outward from the mantle layer.
- ▶ Midbrain colliculi (superior-visual, inferior-auditory) form from the alar plate; crus cerebri, red nucleus and substantia nigra from/around the basal plate and tegmentum.



- Clinical correlates: Arnold–Chiari malformation, congenital aqueductal stenosis (commonest cause of congenital hydrocephalus), medulloblastoma (from residual external granular layer).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; Vishram Singh — Clinical Neuroanatomy 4e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); BD Chaurasia — Human Anatomy Vol 3-4, 8e.



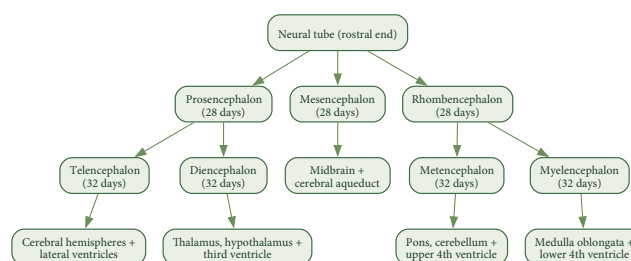
## Development of cerebrum and ventricles

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The cerebrum (cerebral hemispheres, basal ganglia and lateral ventricles) develops entirely from the **telencephalon**, the most rostral of the secondary brain vesicles derived from the prosencephalon. Beginning as paired bubble-like evaginations on day 32, the telencephalic vesicles enlarge enormously in three directions to form the frontal, temporal and occipital lobes, while their cavities become the **lateral ventricles**, which communicate with the third ventricle through the interventricular foramina of Monro. Parallel differentiation of the vesicle wall gives rise to the cerebral cortex, corpus striatum, cerebral commissures and choroid plexus.

### 1. Primary and secondary brain vesicles — origin of the telencephalon

- By day 28, the closed rostral neural tube shows **three primary cerebral vesicles**: prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain).
- By day 32, these subdivide into **five secondary vesicles**: the prosencephalon splits into **telencephalon** and **diencephalon**; the rhombencephalon splits into **metencephalon** and **myelencephalon**; the mesencephalon remains undivided.
- Each vesicle's lumen persists as part of the ventricular system: telencephalon → **lateral ventricles**; diencephalon → **third ventricle**; mesencephalon → **cerebral aqueduct (of Sylvius)**; rhombencephalon → **fourth ventricle**, continuous caudally with the central canal of the spinal cord.



Development of cerebrum and ventricles

### 2. Growth of the cerebral hemispheres

- Each cerebral hemisphere begins as a bilateral **evagination of the lateral wall of the prosencephalon** in the fifth week (day ~32).

- ▶ The basal part of the hemisphere (initially a forward extension of the thalamus) bulges into the ventricular floor and, because of its striped cut surface, is named the **corpus striatum**.
- ▶ The hemispheres enlarge in **three directions** — anteriorly (frontal lobe), dorsally/backward (occipital lobe) and inferiorly/forward (temporal lobe) — so that by 16 weeks they have expanded to completely cover the lateral aspect of the diencephalon, mesencephalon and cephalic metencephalon.
- ▶ Where the hemisphere wall meets the roof of the diencephalon it stays thin, forming a site later invaginated by vascular mesenchyme to create the **choroid plexus**.

□ Fig 9.14 — Development of the Cerebral Hemispheres and Lateral Ventricles (Larsen — Human Embryology — 6e, p.549)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal section through the telencephalon/diencephalon (10-week stage) with coronal insets, labelled:

- ▶ Telencephalic vesicle; interventricular foramen (of Monro); lamina terminalis
- ▶ Third ventricle; thalamus; internal capsule
- ▶ Corpus striatum → caudate nucleus (dorsomedial) and lentiform nucleus (ventrolateral: putamen + globus pallidus)
- ▶ Lateral ventricle — anterior (frontal) horn, body, inferior (temporal) horn, posterior (occipital) horn
- ▶ Choroid fissure with tela choroidea and choroid plexus

### 3. Corpus striatum, internal capsule and basal ganglia

- ▶ Each telencephalic vesicle wall differentiates into a **thick basal part** and a **thin superior part**. Cells of the basal mantle layer that do not migrate to the cortex form the **corpus striatum**.
- ▶ Corticofugal and corticopetal axons growing through the corpus striatum split it longitudinally into a deep and a superficial part; this fibre bundle becomes the **internal capsule**.
- ▶ The deep part of the corpus striatum becomes the **caudate nucleus**; the superficial part becomes the **lentiform nucleus**, later subdividing into **putamen** and **globus pallidus**. Together the caudate and lentiform nuclei constitute the **basal ganglia**.

### 4. Formation of the lateral ventricles, choroid fissure and choroid plexus

- ▶ Each lateral ventricle starts as a small spherical cavity within the telencephalic vesicle, then elongates antero-posteriorly with hemisphere growth.
- ▶ Backward-then-forward growth of the vesicle forms the temporal lobe, converting the ventricle into a **C-shaped** cavity with an **inferior (temporal) horn**; further backward growth of the occipital pole adds the **posterior (occipital) horn**.

| Ventricular part        | Lobe occupied         | Growth direction |
|-------------------------|-----------------------|------------------|
| Anterior (frontal) horn | Frontal lobe          | Forward          |
| Body                    | Frontal/parietal lobe | —                |

| Ventricular part           | Lobe occupied  | Growth direction      |
|----------------------------|----------------|-----------------------|
| Inferior (temporal) horn   | Temporal lobe  | Downward then forward |
| Posterior (occipital) horn | Occipital lobe | Backward              |

- ▶ Along the medial wall, where hemisphere and diencephalic walls appose, an invagination called the **choroid fissure** forms; a fold of pia mater (**tela choroidea**) with a capillary tuft protrudes through it to form the **choroid plexus**, covered by thin ependyma.
- ▶ The lateral ventricle communicates with the midline third ventricle (diencephalic cavity) through the **interventricular foramen of Monro**; the third ventricle continues caudally as the narrow **cerebral aqueduct** (mesencephalon) into the **fourth ventricle**, which drains through the foramen of Magendie (median) and paired foramina of Luschka into the subarachnoid space.

## 5. Development of the cerebral cortex: neuroblast migration, gyri and sulci

- ▶ Migrating neuroblasts reach a subpial position and differentiate; each successive wave migrates through earlier-formed layers, so the cortex is laid down **inside-out** (earliest neurons deepest, latest neurons most superficial).
- ▶ Developmentally the cortex has three components: **archicortex/hippocampal cortex** (medial wall → hippocampus, dentate gyrus, indusium griseum), **paleocortex/pyriform cortex** (marginal layer over corpus striatum → uncus, anterior parahippocampal gyrus, anterior perforated substance — olfactory), and the **neocortex** (superolateral wall), which forms ~90% of the mature cortex.
- ▶ As cortical surface area expands faster than hemisphere volume, the cortex **folds** into gyri and sulci. In the fourth month a shallow **lateral cerebral fossa** appears; the temporal lobe grows forward across it, converting the fossa into the deep **lateral (Sylvian) sulcus**, and the cortex originally floor-ing the fossa is buried as the **insula**, later overgrown by the frontal, parietal and temporal **opercula**. By the sixth month the **central sulcus** (frontal/parietal boundary) and **parieto-occipital sulcus/occipital sulcus** appear; further secondary and tertiary sulci follow through the third trimester.

## 6. Cerebral commissures and the septum pellucidum

- ▶ The median wall closing the rostral neuropore, the **lamina terminalis**, thickens into the **commissural plate**, the pathway by which fibres cross from one hemisphere to the other.
- ▶ Three commissures traverse it, in strict chronological order:
- ▶ **Anterior commissure** (7th week) — connects the olfactory bulbs and related (paleocortical) areas of the two sides.
- ▶ **Hippocampal commissure/fornix** (9th week) — connects the two hippocampi, arching outside the choroid fissure to the mamillary bodies/hypothalamus.
- ▶ **Corpus callosum** (~10th week, largest commissure) — connects the non-olfactory neocortices; its anterior part (genu/rostrum) appears first, extending backward as the **splenium** later in fetal life, arching over the thin diencephalic roof.
- ▶ The strip of lamina terminalis stretched between the corpus callosum and the fornix remains as the **septum pellucidum** (its transient split cavity being the cavum septum pellucidum).

- ▶ Outside the commissural plate, three further commissures appear: **optic chiasma**, **habenular commissure** and **posterior commissure**, related to the epithalamus/diencephalic roof.

## Applied / Clinical anatomy

- ▶ **Holoprosencephaly** — failure of midline cleavage of the prosencephalon; in the severe (alobar) form the two lateral ventricles fail to separate into a single telencephalic vesicle with fused eyes/single nasal chamber; milder forms show hypoplastic/absent olfactory bulbs and corpus callosum. Linked to *SHH* mutations and to Smith–Lemli–Opitz syndrome.
- ▶ **Agenesis of the corpus callosum** (partial or complete) — associated with low intelligence in ~70% and seizures in ~50% of cases, but some patients are asymptomatic; on imaging the lateral ventricles are moderately dilated and a high-riding, dilated third ventricle may be seen because it can extend above the (absent) corpus callosum roof. Uncrossed callosal fibres may form aberrant longitudinal bundles — **Probst bundles**.
- ▶ **Schizencephaly** — large clefts in the cerebral hemispheres due to *EMX2* mutation; **lissencephaly** — failure of neuroblast migration in the 3rd–4th month producing a smooth cortex (agyria/pachygyria) with enlarged ventricles and callosal malformation (*LIS1*, doublecortin genes).
- ▶ **Hydrocephalus** — obstruction of CSF flow (classically at the narrow cerebral aqueduct) causes progressive dilatation of the lateral and third ventricles proximal to the block, with skull enlargement if it occurs before suture fusion; **Dandy–Walker syndrome** (blocked 4th-ventricle foramina, cystic posterior fossa) and **Arnold–Chiari malformation** (cerebellar/medullary herniation through the foramen magnum, usually with meningocele) are important associated patterns.
- ▶ Radiologically, the **cavum septum pellucidum** is a normal transient fetal/neonatal ventricular-system landmark on antenatal ultrasound/MRI, present in virtually all fetuses before 36 weeks and progressively closing through infancy — its persistence beyond early childhood or absence in the second trimester is a soft marker examined on fetal neurosonography.

## High-yield exam pointers

- ▶ Telencephalon (secondary vesicle, day 32) gives cerebral hemispheres + lateral ventricles + corpus striatum; diencephalon gives thalamus/hypothalamus + third ventricle.
- ▶ Corpus striatum splits into caudate (deep) and lentiform (superficial) nuclei by fibres of the internal capsule.
- ▶ Lateral ventricle horns: anterior→frontal lobe, inferior→temporal lobe, posterior→occipital lobe; choroid fissure → tela choroidea → choroid plexus.
- ▶ Commissure sequence (mnemonic order): Anterior commissure (7 wk) → Hippocampal commissure/fornix (9 wk) → Corpus callosum (10 wk, genu first, splenium last).
- ▶ Cortical types by phylogeny: archicortex (hippocampus), paleocortex (pyriform/olfactory), neocortex (~90% of cortex, six-layered, inside-out lamination).
- ▶ Insula = area of slow growth overgrown by adjacent opercula; lateral (Sylvian) sulcus forms in the 4th month, central sulcus by the 6th month.
- ▶ Septum pellucidum = residual lamina terminalis between corpus callosum and fornix.

- Key anomalies: holoprosencephaly (SHH), agenesis of corpus callosum (Probst bundles), schizencephaly (EMX2), lissencephaly (LIS1/doublecortin), aqueductal stenosis → hydrocephalus.

### SOURCE & COVERAGE

Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Moore The Developing Human 9e; Gray's Anatomy (Standring) 41e.



## Development of Eyeball

Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy

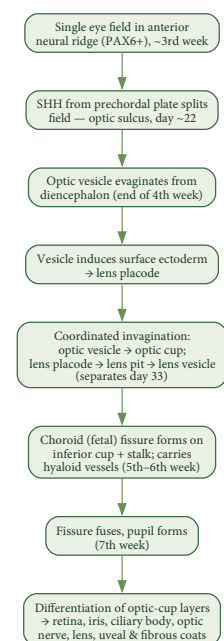
**Definition / Introduction** The eyeball develops from four embryonic sources acting through a chain of reciprocal inductions in the head region: (1) **neuroectoderm** of the diencephalon (optic vesicle → optic cup), which forms the retina, iris and ciliary epithelium and the optic nerve; (2) **surface ectoderm**, which forms the lens (via the lens placode) and the corneal epithelium, eyelids, conjunctiva and lacrimal apparatus; (3) **neural crest mesenchyme** surrounding the optic cup, which forms the corneal stroma/endothelium, sclera, choroid and the connective-tissue stroma of the iris and ciliary body; and (4) **mesoderm**, which contributes the extraocular muscles and vascular endothelium. Development begins in the fourth week (optic sulcus, ~day 22) and continues, with progressive differentiation of the retina and growth of the globe, well into postnatal life. The master regulatory gene is **PAX6**, acting with SHH, PAX2, SOX2, BMP4, CHX10 and MITF to pattern the eye field and its derivatives.

### 1. Primordia and their derivatives

| Embryonic tissue                         | Structures formed                                                                                                                                                                    |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neuroectoderm — outer layer of optic cup | Retinal pigment epithelium; pigmented epithelium of ciliary body and iris                                                                                                            |
| Neuroectoderm — inner layer of optic cup | Neural (sensory) retina; sphincter and dilator pupillae (from anterior rim of cup); ganglion-cell axons → optic nerve                                                                |
| Surface ectoderm (lens placode)          | Lens capsule, epithelium and fibres; corneal epithelium; conjunctiva; lacrimal gland, sac and nasolacrimal duct; epidermis, lashes and glands of the eyelids                         |
| Neural crest mesenchyme around optic cup | Corneal stroma (substantia propria) and endothelium; sclera; choroid; stroma and melanocytes of iris; connective tissue of ciliary body; leptomeningeal/dural sheaths of optic nerve |
| Mesoderm                                 | Extraocular muscles; vascular endothelium of the hyaloid, retinal and ciliary vessels; contribution to primary vitreous                                                              |

## 2. Formation of the optic vesicle and optic cup

- ▶ A single **eye field** is specified in the anterior neural ridge (~3rd week) by **PAX6**. **Sonic hedgehog (SHH)** from the prechordal plate splits this field in two by up-regulating **PAX2** and down-regulating **PAX6** at the midline; loss of SHH causes holoprosencephaly with cyclopia.
- ▶ A shallow **optic sulcus/groove** appears on the diencephalic wall by about **day 22**; as the neural tube closes it evaginates laterally into the **optic vesicle**, joined to the forebrain by the **optic stalk** (end of 4th week).
- ▶ The vesicle contacts the surface ectoderm and induces it to thicken into the **lens placode**.
- ▶ From about **day 33** both structures **invaginate together**: the placode forms a lens pit that pinches off as the **lens vesicle** (detaches by day 33); the optic vesicle folds into a double-walled **optic cup** — inner layer → neural retina, outer layer → retinal pigment epithelium, transiently separated by the **intraretinal space**.
- ▶ Invagination extends onto the ventral surface of vesicle and stalk as the **choroid (fetal) fissure**, through which mesenchyme and the **hyaloid artery** enter the cup (5th–6th week).
- ▶ In the **7th week** the fissure lips fuse, enclosing the hyaloid artery and forming the **pupil**. Failure of fusion here produces **coloboma**.



*Development of Eyeball*

□ Fig 23.2 — Development of eyeball on day 21 and 27 (Sontakke — Textbook of Human Embryology, p.266)

□ Fig 23.3 — Further development of eyeball (day 29 and day 33) (Sontakke — Textbook of Human Embryology, p.267)

## 3. Lens

- ▶ Lens vesicle initially a ball of cuboidal epithelium. The **posterior wall** cells elongate, lose their nuclei, and fill the cavity as **primary lens fibres** (rich in crystallins), obliterating the vesicle cavity by about the 7th week (solid lens formed).
- ▶ The **anterior wall** remains cuboidal and persists as the **lens epithelium**, whose equatorial cells continue proliferating throughout life to add **secondary lens fibres**.



- ▶ The lens is transiently vascular (posterior vascular capsule fed by the hyaloid artery, anterior pupillary membrane by anterior ciliary vessels); with hyaloid regression the lens becomes avascular, deriving nutrition thereafter from the aqueous and vitreous.
- ▶ **Molecular control:** PAX6 (via SOX2, BMP4-driven LMAF, SIX3, PROX1) drives crystallin gene expression and lens-fibre differentiation.

#### 4. Retina, ciliary body, iris and optic nerve

- ▶ The **posterior four-fifths** of the inner optic-cup layer (pars optica retinae) forms the sensory retina: proliferating progenitors give **inner and outer neuroblastic layers** (~day 37), which separate via the inner and outer plexiform layers into the **ganglion-cell**, **inner nuclear** (amacrine, horizontal, bipolar, Müller cells) and **outer nuclear** (rods, cones) layers. All named layers are present by the **8th month**; the macula matures only 15–45 months postnatally.
- ▶ The **anterior one-fifth** (pars ceca retinae) stays one cell thick and divides into the **pars iridica retinae** (posterior iris epithelium) and **pars ciliaris retinae** (ciliary body epithelium).
- ▶ **Ciliary body:** epithelium from the anterior optic-cup rim; ciliary processes (secrete aqueous humour) and ciliary muscle from adjacent neural-crest mesenchyme.
- ▶ **Iris:** both epithelial layers from the optic-cup tip; **sphincter/dilator pupillae are neuroectodermal** (unusual for muscle); stroma and melanocytes are neural-crest derived. Blue eyes have pigment only on the posterior epithelium; brown eyes also have stromal melanocytes.
- ▶ **Optic nerve:** ganglion-cell axons grow through the choroid fissure into the stalk wall, converting it into the optic nerve; the central retinal artery is the persisting proximal hyaloid artery. Myelination begins shortly before birth. The **optic chiasma** forms by partial decussation at the lamina terminalis.
- ▶ **Retinal and choroidal vasculature** develop by vasculogenesis from mesenchymal cells from week 15.

#### 5. Sclera, choroid, cornea and anterior segment

| Layer                        | Derivation                                                                                                                       |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Choroid (inner, vascular)    | Neural-crest mesenchyme around optic cup; continuous anteriorly with ciliary body, posteriorly with pia-arachnoid of optic nerve |
| Sclera (outer, fibrous)      | Same mesenchyme, continuous with dural sheath of optic nerve                                                                     |
| Corneal epithelium           | Surface ectoderm                                                                                                                 |
| Corneal stroma & endothelium | Neural-crest mesenchyme migrating between lens and surface ectoderm                                                              |

- ▶ The **anterior chamber** first appears as a cleft (vacuolisation) in this mesenchyme; tissue superficial to the cleft becomes corneal stroma/endothelium, tissue deep to it becomes the iris stroma and transient **iridopupillary membrane** (normally resorbed).
- ▶ The **iridocorneal angle** develops a **trabecular meshwork** and the **scleral venous sinus (canal of Schlemm)**, which becomes a functioning aqueous drainage channel from the 5th month; FOXC1/PITX2-expressing neural-crest cells regulate this anterior-segment differentiation.



## 6. Vitreous body

- **Primary vitreous:** gelatinous matrix secreted from about day 33 by neural-crest-derived mesenchymal cells that migrate into the space between lens vesicle and optic cup (accompanied by the hyaloid vessels entering via the choroid fissure).
- **Secondary vitreous:** forms later from the inner layer of the optic cup, surrounding and eventually replacing the primary vitreous with an avascular gel; the primary vitreous persists centrally as the **hyaloid canal**.
- Peripherally, condensation of this fibrillar network in the ciliary region forms the **suspensory ligament (zonule)** of the lens.

## 7. Accessory structures

| Structure                        | Origin / timing                                                                                                                                                                   |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eyelids                          | Cutaneous folds of surface ectoderm with a neural-crest mesenchymal core (tarsal plate, muscle); fuse in mid-3rd month, remain fused until about the 6th–7th month (~24–28 weeks) |
| Conjunctiva                      | Ectoderm lining inner lid surface; fuses with corneal epithelium when lids reopen                                                                                                 |
| Lacrimal gland                   | Ectodermal buds from the superior conjunctival fornix                                                                                                                             |
| Lacrimal sac & nasolacrimal duct | Ectoderm of the naso-optic (nasolacrimal) groove between lateral nasal and maxillary processes; canalises in the 3rd month                                                        |
| Extraocular muscles              | Prechordal/preoccipital mesenchymal condensations; supplied by cranial nerves III, IV and VI                                                                                      |
| Orbicularis oculi                | Myoblasts of the 2nd pharyngeal arch (facial nerve)                                                                                                                               |

## 8. Molecular regulation (high-yield)

| Gene / signal | Principal role                                                                                                | Anomaly if disrupted                          |
|---------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| PAX6          | Master eye-field gene; maintains lens ectoderm, drives SOX2/crystallin cascade, patterns iris/ciliary regions | Aniridia (heterozygous mutation)              |
| SHH           | From prechordal plate; splits single eye field, upregulates PAX2/downregulates PAX6 at midline                | Holoprosencephaly, cyclopia                   |
| PAX2          | Optic stalk differentiation; choroid fissure closure                                                          | Optic-nerve coloboma; renal-coloboma syndrome |
| SOX2          | Downstream of PAX6 in lens placode maintenance                                                                | Anophthalmia, microphthalmia, coloboma        |

| Gene / signal | Principal role                                   | Anomaly if disrupted               |
|---------------|--------------------------------------------------|------------------------------------|
| CHX10 (VSX2)  | Specification/proliferation of neural retina     | Microphthalmia                     |
| MITF          | Specification of pigmented epithelium            | Pigmentation/RPE defects           |
| FOXC1 / PITX2 | Neural-crest differentiation of anterior segment | Axenfeld–Rieger syndrome, glaucoma |
| MAF / PITX3   | Lens crystallin gene regulation                  | Congenital cataract                |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the schematic stage sequence (as tested in the 09-May-2022 paper), then the final composite cross-section, with these exact labels:

- ▶ **Early stages:** forebrain, optic groove/vesicle, surface ectoderm, lens placode → lens pit → lens vesicle, optic stalk, optic cup, choroid (fetal) fissure, hyaloid vessels, inner/outer layer of optic cup.
- ▶ **Final composite section:** cornea (epithelium, stroma, endothelium), anterior chamber, iris, posterior chamber, lens (epithelium, fibres, capsule), ciliary body and processes, suspensory ligament (zonule), sclera, choroid, neural and pigmented layers of retina, vitreous body, hyaloid canal, optic disc, optic nerve, central retinal artery.

### Applied / Clinical anatomy

- ▶ **Anophthalmia/microphthalmia** — absent or underdeveloped eye from failure/arrest of optic-vesicle formation; linked to SOX2, CHX10, PAX6 mutation and intrauterine rubella, CMV, toxoplasma or HSV infection.
- ▶ **Cyclopia/synophthalmos** — fusion of the two eye fields from failed SHH-mediated separation, part of the holoprosencephaly spectrum, often with a proboscis.
- ▶ **Coloboma** — persistent cleft where the choroid fissure fails to fuse (normally 7th week); may involve iris, ciliary body, choroid, retina, optic nerve or eyelid; PAX2 mutation causes optic-nerve coloboma with renal-coloboma syndrome.
- ▶ **Aniridia** — absent/hypoplastic iris from heterozygous PAX6 mutation.
- ▶ **Congenital cataract** — lens opacity at birth from maternal rubella (4th–7th week exposure), toxoplasmosis, galactosaemia, Down syndrome, or crystallin/MAF/PITX3 mutations; bilateral cases are conventionally operated before ~10 weeks to prevent amblyopia.
- ▶ **Persistent pupillary membrane** — failed resorption of the iridopupillary membrane.
- ▶ **Persistent hyperplastic primary vitreous** — failed regression of the hyaloid vasculature; causes leukocoria.
- ▶ **Axenfeld–Rieger syndrome** — anterior-segment dysgenesis from FOXC1/PITX2 mutation; predisposes to glaucoma.
- ▶ **Congenital retinal detachment** — separation along the intraretinal space, the embryonic cleavage plane between pigment epithelium and neural retina.

- ▶ **Retinopathy of prematurity** — proliferative retinopathy of preterm/low-birth-weight infants from disordered retinal vasculogenesis.
- ▶ **Eyelid anomalies** — ptosis (failed levator palpebrae superioris), coloboma of the lid, entropion/ectropion, epicanthus.

### High-yield exam pointers

- ▶ Four sources: neuroectoderm (retina, iris/ciliary epithelium, optic nerve), surface ectoderm (lens, corneal epithelium, adnexa), neural-crest mesenchyme (corneal stroma/endothelium, sclera, choroid, iris/ciliary stroma), mesoderm (extraocular muscles, vessels).
- ▶ Timeline: optic sulcus day 22 → optic vesicle end of 4th week → lens vesicle separates day 33 → choroid fissure 5th–6th week, fuses 7th week → solid lens 7th week → eyelids fuse 3rd month, reopen ~6th–7th month → retinal/choroidal vessels from week 15 → hyaloid artery occludes ~8th month → all retinal layers by 8th month.
- ▶ PAX6 = master gene; SHH splits the single eye field; PAX2 governs optic-stalk fate and choroid-fissure closure.
- ▶ Choroid fissure carries the hyaloid artery; failure to fuse = coloboma; its proximal remnant becomes the central artery of the retina.
- ▶ Retina is bilaminar in origin: outer layer → pigment epithelium; inner layer → neural retina.
- ▶ Vitreous is biphasic: primary (neural-crest, vascular) then secondary (from inner optic-cup layer, avascular); primary persists as the hyaloid canal.
- ▶ Sphincter/dilator pupillae are neuroectodermal — exception to the usual mesodermal origin of smooth muscle.
- ▶ Match each anomaly to its stage of arrest: coloboma (fissure fusion), aniridia (PAX6), cyclopia (eye-field separation), anophthalmia (optic-vesicle stage).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Development of human eye

Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy

**Definition / Introduction** The eye is a composite organ derived from **four embryonic sources** — neuroectoderm of the forebrain, surface ectoderm, mesoderm, and neural-crest mesenchyme — that undergo a tightly choreographed sequence of inductive interactions beginning in the 4th week of intra-uterine life (IUL). The neuroectoderm of the diencephalon forms the retina, optic nerve and posterior epithelial layers of the iris/ciliary body; the surface ectoderm forms the lens and corneal epithelium; and the intervening mesenchyme (largely neural-crest derived) forms the fibrous and vascular coats, cornea stroma/endothelium, and ocular muscles. **PAX6** is the master regulatory gene driving the entire process.

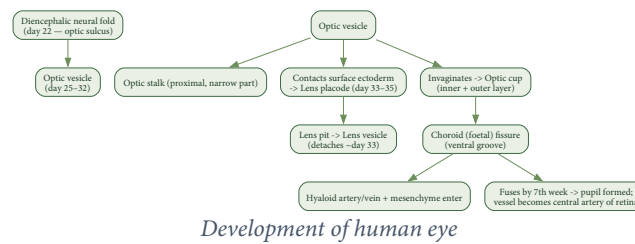
### 1. Sources and embryological derivatives of the eye

| Germ layer / source                                           | Structures formed                                                                                                                                                       |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neuroectoderm of diencephalon (optic vesicle → optic cup)     | Neural (sensory) retina, retinal pigment epithelium, epithelium of iris and ciliary body, sphincter/dilator pupillae muscles, optic nerve                               |
| Surface ectoderm (lens placode; conjunctival/eyelid ectoderm) | Lens, corneal epithelium, conjunctiva, eyelid epidermis, eyelashes, tarsal/lacrimal glands, lacrimal sac & nasolacrimal duct                                            |
| Mesoderm surrounding the optic cup                            | Extraocular muscles (from preoccipital myotomes), vascular endothelium, part of sclera/vitreous                                                                         |
| Neural crest mesenchyme                                       | Corneal stroma & endothelium, iris stroma, ciliary body connective tissue, choroid, sclera, trabecular meshwork, meningeal sheaths of the optic nerve, part of vitreous |

### 2. Optic vesicle, optic cup, lens vesicle and the choroid fissure

- ▶ **Day 22:** the diencephalic neural fold thickens and depresses into the **optic sulcus (groove)** — the first morphological sign of eye development.
- ▶ **~4th week (day 25–32):** the sulcus evaginates into the surrounding mesenchyme as a hollow **optic vesicle**, joined to the forebrain by a narrowing **optic stalk**, its lumen continuous with the diencephalon.
- ▶ The vesicle contacts the surface ectoderm and induces the **lens placode** (day 33–35), which invaginates as a **lens pit** and pinches off as the **lens vesicle** by day 33. The surface ectoderm re-forms as the future **corneal epithelium**.
- ▶ Reciprocally, the lens vesicle invaginates the distal wall of the optic vesicle, converting it into a double-walled **optic cup: inner layer** (facing lens) → neural retina; **outer layer** → retinal pigment epithelium; both are separated by a transient **intraretinal space**.
- ▶ Invagination extends along the ventral cup/stalk as the **choroid (optic/foetal) fissure**, through which mesenchyme and the **hyaloid artery/vein** enter to vascularise lens and inner retina.
- ▶ In the **7th week**, the fissure lips fuse (apoptosis at the margins), converting the cup mouth into the future **pupil** and enclosing the hyaloid vessels in the stalk. **Failure of fissure fusion** → **congenital coloboma**.

Fig 40.1 — Development and morphogenesis of the optic cup: invagination of the optic vesicle to a two-layered optic cup, formation of the lens vesicle, and closure of the choroid fissure (Gray's Anatomy — Standring — 41e, p.901)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal section through a **6th–7th week embryo eye**, labelling: surface ectoderm; lens placode → lens pit → lens vesicle; optic vesicle; optic stalk; optic cup — outer layer (future retinal pigment epithelium) and inner layer (future neural retina); intraretinal space; choroid (foetal) fissure with hyaloid artery/vein inside it; surrounding mesenchyme (neural crest + mesoderm).

## 3. Development of the retina and optic nerve

- ▶ **Outer layer** of the optic cup remains thin, acquires pigmented melanosomes (~day 36) and becomes the **retinal pigment epithelium**; firmly attached to its mesenchymal sheath, but only loosely apposed to the sensory layer — the site of pathological **retinal detachment**.
- ▶ **Inner layer** proliferates into a thick pseudostratified neuroepithelium (the future **neural retina**), forming outer (nuclear) and inner (marginal) zones that become **outer and inner neuroblastic layers** by stage 18 (44 days).
- ▶ Seven retinal cell types share a common multipotential progenitor and differentiate in a conserved order: **ganglion cells**, **amacrine cells**, **cones and horizontal cells** early; **bipolar cells**, **rods and Müller glia** late. All named layers are present by the 8th month; the macula matures only **15–45 months** postnatally.
- ▶ Only the **posterior four-fifths** (pars optica retinae) becomes photosensitive retina; the **anterior one-fifth** (pars ceca retinae) stays single-layered and forms the **pars iridica retinae** (iris epithelium) and **pars ciliaris retinae** (ciliary epithelium).
- ▶ Where the choroid fissure is deepest, the cup centre becomes the **optic disc**; ganglion-cell axons converge here and grow through the stalk, converting it into the **optic nerve** (myelination begins shortly before birth). Its core carries the hyaloid artery, later the **central artery of the retina**. The **optic chiasma** forms by partial decussation of both nerves in the floor of the third ventricle.

## 4. Development of the lens

- ▶ The lens vesicle is initially a hollow ball of cuboidal epithelium. By stage 16, its **posterior wall** cells elongate, lose their nuclei and fill the lumen as transparent **primary lens fibres** (rich in crystallin proteins), obliterating the original cavity into a slit by ~day 44; the primary fibres reach the anterior wall by the **end of the 7th week**, when the lens becomes **solid**.
- ▶ The **anterior wall** persists as a simple cuboidal **lens epithelium**, whose equatorial cells continue proliferating throughout life to add **secondary lens fibres**, allowing lifelong lens growth.
- ▶ The lens capsule is a thickened basal lamina secreted by the lens epithelium. The lens is initially vascular (via the hyaloid artery and the surrounding **vascular capsule/pupillary membrane**) but

becomes avascular once the hyaloid vasculature regresses, thereafter depending on diffusion from the aqueous and vitreous humours.

## 5. Development of the choroid, sclera and cornea

- ▶ From the **6th–7th week**, neural-crest mesenchyme surrounding the optic cup condenses into two layers: **inner vascular layer** → **choroid** (continuous with the leptomeningeal sheath of the optic nerve); **outer fibrous layer** → **sclera** (continuous with its dural sheath). Choroidal vessels appear from the 15th week.
- ▶ Anteriorly, the mesenchyme forms the **cornea**: surface ectoderm → epithelium; neural-crest mesenchyme → stroma/keratocytes (collagen lamellae, anterior acellular **Bowman's layer**) and an **endothelium** that lays down **Descemet's membrane** from the 3rd month.
- ▶ A cleft within this anterior mesenchyme forms the **anterior chamber**: tissue superficial becomes corneal stroma/endothelium, tissue deep becomes the **iris stroma/pupillary (iridopupillary) membrane**. It extends to the **iridocorneal angle**, where the **trabecular meshwork** and **canal of Schlemm** develop and drain aqueous from the 5th month.

## 6. Development of the iris, ciliary body, chambers and vitreous body

- ▶ **Iris**: develops from the extending rim/tip of the optic cup — its two epithelial layers and the **sphincter/dilator pupillae** muscles are neuroectodermal (unusual for muscle); the vascular, collagen-rich stroma is neural-crest derived. Colour depends on epithelial pigment (blue) vs added stromal melanocyte pigment (brown), fixed only after birth.
- ▶ **Ciliary body**: forms from the optic-cup region between iris and neural retina (pars ciliaris retinae) plus adjacent mesenchyme, forming vascularised folded **ciliary processes** (secrete aqueous) and an outer ciliary muscle.
- ▶ **Chambers**: anterior (cornea–iris) and posterior (iris–lens–zonule–ciliary body) communicate through the pupil once the pupillary membrane resorbs; aqueous drains via the trabecular meshwork/canal of Schlemm.
- ▶ **Vitreous body**: fills the space between lens and optic cup as a cytoplasmic network from lens/retinal cells (**primary vitreous**), vascularised via the choroid fissure; progressively replaced by avascular gelatinous **secondary (definitive) vitreous** from the inner optic-cup layer. The primary vitreous persists centrally as the **hyaloid canal** once the hyaloid vessels regress (~8th month); the proximal hyaloid artery persists as the **central artery of the retina**.
- ▶ **Accessory structures**: the 6 **extraocular muscles** (+ levator palpebrae superioris) arise from **preoccipital mesenchyme**, hence supplied by CN III, IV, VI. **Eyelids** are cutaneous folds of surface ectoderm with a neural-crest core; fuse in the 3rd month, reopen ~6th–7th month; orbicularis oculi comes from 2nd-arch myoblasts. **Lacrimal gland** buds from conjunctival-fornix ectoderm; **nasolacrimal duct/sac** canalise from an ectodermal cord in the naso-optic furrow (lateral nasal–maxillary junction).

## 7. Molecular regulation of eye development

| Gene                                   | Role                                                                                                                                         | Associated anomaly on mutation                                   |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| PAX6                                   | Master gene; establishes the eye field, maintained in optic cup and lens ectoderm; drives lens crystallin genes (via SOX2, SIX3, PROX1, MAF) | Aniridia; may contribute to anophthalmia/microphthalmia          |
| SHH (sonic hedgehog, prechordal plate) | Splits single midline eye field into bilateral primordia; upregulates PAX2 in optic stalk, downregulates PAX6 there                          | Loss of SHH → holoprosencephaly, cyclopia                        |
| PAX2                                   | Optic stalk differentiation                                                                                                                  | Optic nerve coloboma + renal aplasia (renal–coloboma syndrome)   |
| CHX10 (VSX2)                           | Neural retina specification and growth                                                                                                       | Microphthalmia                                                   |
| MITF                                   | Retinal pigment epithelium specification                                                                                                     | Pigmentation defects                                             |
| FOXC1 / PITX2                          | Neural-crest differentiation of anterior segment                                                                                             | Axenfeld–Rieger syndrome (anterior segment dysgenesis, glaucoma) |

## Applied / Clinical anatomy

| Anomaly                                                                                              | Embryological basis                                                                                                     |
|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Anophthalmia                                                                                         | Failure of optic vesicle formation/specification                                                                        |
| Microphthalmia                                                                                       | Reduced growth of optic cup (e.g. CHX10 mutation); intrauterine infection (rubella, CMV, toxoplasma)                    |
| Cyclopia / synophthalmia                                                                             | Failure of SHH-mediated separation of the single eye field; often with holoprosencephaly                                |
| Coloboma (iris/choroid/retina/optic nerve/eyelid)                                                    | Failure of fusion of the choroid (optic) fissure; PAX2 mutation for optic-nerve coloboma                                |
| Aniridia                                                                                             | Arrest of optic cup rim development; PAX6 mutation                                                                      |
| Congenital aphakia                                                                                   | Failure of lens vesicle formation                                                                                       |
| Congenital cataract                                                                                  | Rubella (4th–7th week exposure classically damages the lens), toxoplasmosis, galactosaemia, Down syndrome               |
| Persistent pupillary membrane / persistent hyperplastic primary vitreous / persistent hyaloid artery | Failure of regression of the pupillary membrane and/or primary vitreous & hyaloid vasculature (may form a cord or cyst) |



| Anomaly                                                           | Embryological basis                                                                                                                         |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Congenital glaucoma (buphthalmos); Axenfeld–Rieger/Peters anomaly | Anterior segment dysgenesis — abnormal neural-crest migration/differentiation (FOXC1/PITX2), defective trabecular meshwork/canal of Schlemm |
| Retinopathy of prematurity                                        | Aberrant retinal vasculogenesis/angiogenesis in preterm, low-birth-weight infants                                                           |
| Epicanthus; ptosis; entropion/ectropion; cryptophthalmos          | Redundant skin fold (Down syndrome feature) / failed levator development / abnormal eyelid fold formation-fusion                            |
| Congenital dacryocystocele / nasolacrimal duct obstruction        | Failure of canalisation of the naso-optic furrow cord                                                                                       |

### High-yield exam pointers

- ▶ Eye develops from 4 sources: neuroectoderm (retina, optic nerve), surface ectoderm (lens, corneal epithelium), mesoderm and neural crest (fibrous/vascular coats).
- ▶ Optic sulcus (day 22) → optic vesicle (4th week) → optic cup + lens vesicle (5th–6th week) → choroid fissure closes (7th week) → solid lens (7th week).
- ▶ Choroid fissure failure = coloboma; carries the hyaloid artery, which becomes the **central artery of the retina**.
- ▶ Sclera/choroid are outer fibrous/inner vascular condensations of neural-crest mesenchyme, continuous with the dura/pia-arachnoid of the optic nerve respectively.
- ▶ PAX6 = **master gene**; SHH separates the single eye field; PAX2→optic stalk/renal-coloboma syndrome; FOXC1/PITX2→Axenfeld–Rieger.
- ▶ Retinal cell birth order: ganglion → amacrine/cones/horizontal (early) → bipolar/rods/Müller glia (late); optic disc = site of fissure fusion, forms optic nerve.
- ▶ Extraocular muscles from preoccipital mesenchyme → supplied by CN III, IV, VI; eyelids fuse 3rd month, reopen ~6th–7th month.
- ▶ Vitreous: primary (vascular, hyaloid-vessel dependent) replaced by secondary/definitive (avascular); hyaloid canal is the vestige.
- ▶ Rubella in weeks 4–7 classically causes cataract; after week 7, cochlear (deafness) rather than lens damage.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Langman's Medical Embryology (Sadler) 14e.



## Development of lens

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The crystalline lens is the only structure of the eye derived **entirely from surface ectoderm**, with no contribution from neuroectoderm or mesenchyme except its enveloping capsule and transient vascular coat. It arises as a **lens placode**, induced by the underlying optic vesicle, which successively becomes a lens pit, a lens vesicle, and finally a solid, avascular, transparent lens made of primary and secondary lens fibres. Unlike most tissues, the lens continues to add new fibres throughout life, making it unique among ocular structures.

### 1. Inductive origin and primordia

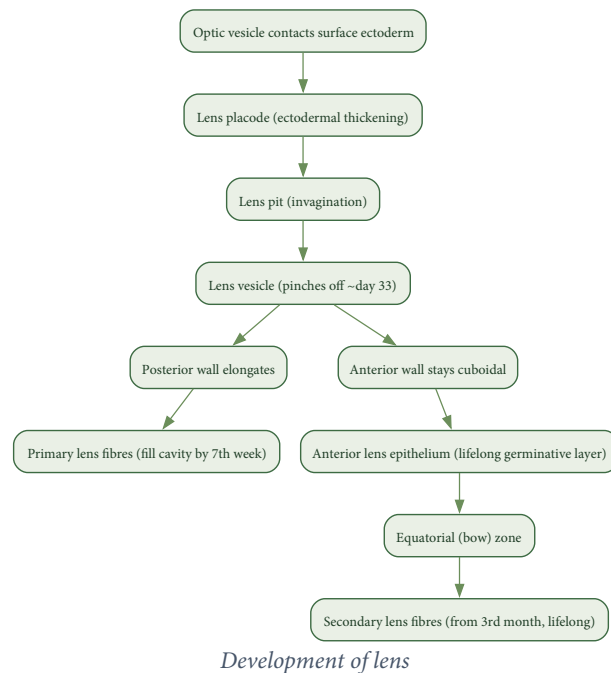
- ▶ The optic vesicle is a lateral outgrowth of the **prosencephalon** (neuroectoderm); as it grows laterally it comes into contact with the overlying **surface ectoderm**.
- ▶ This contact is a classic example of **reciprocal (embryonic) induction**: the optic vesicle induces the surface ectoderm to thicken into the lens placode, and the developing lens, in turn, is essential for normal invagination of the optic vesicle into the optic cup — without a lens placode, no cup invagination occurs.
- ▶ The lens therefore develops from a single germ layer (surface ectoderm), while the retina, iris epithelium and optic nerve develop from neuroectoderm of the optic cup, and the fibrous/vascular coats (sclera, choroid) from surrounding mesenchyme and neural crest.

### 2. Formation of the lens placode, lens pit and lens vesicle

- ▶ **Day 22** — the optic sulcus appears as a shallow groove on the neural plate (~8-somite stage).
- ▶ **Day 24** — the distal part of the optic vesicle (evagination of the diencephalic wall) contacts the surface ectoderm; the apposed ectoderm thickens to form the **lens placode**.
- ▶ **Day 28** — the distal end of the optic vesicle invaginates to form the double-layered **optic cup**; shortly thereafter the lens placode likewise invaginates to form a **lens pit**.
- ▶ **By day 33** — the lens pit pinches off completely from the surface ectoderm to form a hollow **lens vesicle**, lying free in the mouth of the optic cup and surrounded by a basal lamina that becomes the **lens capsule**. The surface ectoderm re-forms as a continuous sheet over the front of the eye, becoming the corneal epithelium.
- ▶ Initially the lens vesicle is lined by a single layer of cuboidal cells; the anterior (outward-facing) wall stays thin and cuboidal, while the posterior (deep) wall is thicker — the first sign of anteroposterior polarity in the lens.

| Age       | Developmental event                                                                     |
|-----------|-----------------------------------------------------------------------------------------|
| Day 22    | Optic sulcus appears over the neural plate                                              |
| Day 24–28 | Optic vesicle contacts surface ectoderm; lens placode forms                             |
| Day 28–30 | Lens placode invaginates → lens pit; optic vesicle invaginates → optic cup              |
| Day 33    | Lens pit separates from surface ectoderm → lens vesicle (basal lamina = future capsule) |

| Age              | Developmental event                                                                         |
|------------------|---------------------------------------------------------------------------------------------|
| 5th–7th week     | Posterior wall cells elongate → primary lens fibres; vesicle cavity obliterated by 7th week |
| 3rd month onward | Equatorial (germinative) cells → secondary lens fibres, continuing lifelong                 |



### 3. Differentiation of primary lens fibres

□ Fig 23.5 — Development of the embryonic lens (Sontakke — Textbook of Human Embryology, p.268)

- ▶ Beginning on day 33, cells of the **posterior wall** of the lens vesicle elongate anteroposteriorly, gradually filling the vesicle lumen and reducing it to a slit.
- ▶ These elongating cells lose their nuclei and other organelles and become densely packed with **crystallin proteins** ( $\alpha$ ,  $\beta$  and  $\gamma$ -crystallins), which render them transparent; they constitute the **primary lens fibres**, which reach the anterior wall of the vesicle by the end of the 7th week, obliterating the original cavity and converting the vesicle into a solid **lens body**.
- ▶ The **anterior wall** cells remain cuboidal and persist as the **anterior lens epithelium** — a single layer that remains mitotically active throughout life and is the permanent germinative zone of the lens.

### 4. Secondary lens fibres and lifelong growth

- ▶ Anterior epithelial cells migrate peripherally toward the **equatorial (germinative) zone** of the lens, where — from the **3rd month** onward — they elongate anteroposteriorly to form **secondary lens fibres** (the "lens bow").
- ▶ New secondary fibres are added concentrically to the outside of the primary fibre mass throughout fetal, childhood and adult life, so the lens keeps enlarging in diameter without ever shedding old fibres — the older primary fibres become compacted and hardened centrally as the "embryonic nucleus."

- ▶ Growth polarity depends on differentially distributed soluble factors: FGF from the vitreous humour (secreted by the retina) promotes fibre differentiation in the posterior/deep cells, while factors in the **aqueous humour** anteriorly, together with Notch signalling, sustain proliferation in the anterior epithelium rather than differentiation.

## 5. Molecular regulation of lens development

- ▶ **PAX6** is the master regulatory gene for eye and lens development; it is initially expressed broadly in the anterior neural ridge, then becomes restricted to the optic cup and the overlying surface ectoderm destined to form the lens.
- ▶ In the lens ectoderm, PAX6 upregulates **SOX2** and maintains its own expression; the optic vesicle secretes **BMP4**, which also maintains SOX2 and induces the transcription factor **MAF** (**LMAF**).
- ▶ Combined expression of PAX6, SOX2 and MAF activates **SIX3** and **PROX1**, which together drive expression of the **crystallin genes**; SIX3 also fine-tunes this process by inhibiting crystallin expression until the appropriate stage.
- ▶ **FOXE3** maintains proliferation of the anterior lens epithelium, while **PITX3** and **AP-2α** are required for normal separation of the lens vesicle from the surface ectoderm — failure here leaves a persistent lens stalk and arrests lens development.
- ▶ Loss of PAX6 in the lens ectoderm (demonstrated by conditional knockout) results in complete absence of lens structures, underscoring its non-redundant role.

## 6. Vascular relations and the lens capsule

- ▶ The developing lens is transiently vascular: a **vascular (tunica vasculosa lentis)** capsule surrounds it, its posterior part supplied by branches of the **hyaloid artery** (which reaches the eye through the choroid fissure) and its anterior part, the **pupillary membrane**, supplied by the anterior ciliary arteries.
- ▶ By the 6th month most of this vasculature has atrophied; the hyaloid artery itself occludes by the **8th month**, its proximal part persisting postnatally as the **central artery of the retina**.
- ▶ With loss of its blood supply, the mature lens becomes completely **avascular**, deriving nutrition entirely by diffusion from the aqueous and vitreous humours.
- ▶ The **lens capsule** is a thickened basement membrane secreted by the lens epithelium; it is thickest at the equator and persists as the tough acellular capsule surrounding the adult lens.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Longitudinal section through the developing eye showing lens formation — label:

- ▶ Surface ectoderm / corneal epithelium
- ▶ Optic vesicle → optic cup (outer and inner layers)
- ▶ Lens placode → lens pit → lens vesicle (with residual lens cavity)
- ▶ Anterior lens epithelium (cuboidal, germinative)
- ▶ Posterior/primary lens fibres filling the vesicle
- ▶ Equatorial (germinative) zone → secondary lens fibres
- ▶ Lens capsule (basal lamina)
- ▶ Hyaloid artery / vascular capsule (tunica vasculosa lentis)
- ▶ Choroid fissure (through which the hyaloid vessels enter)

**Applied / Clinical anatomy**

- ▶ **Congenital cataract** — opacification of the lens in utero; causes include (a) genetic mutations in crystallin genes, gap-junction proteins, or transcription factors such as **MAF** and heat-shock factor **HSF4**; (b) metabolic disease, notably **galactosemia**; and (c) intrauterine infection, classically **maternal rubella** contracted between the 4th and 7th weeks — the critical teratogenic window for the lens. Infection after the 7th week spares the lens but may still cause cochlear damage (deafness). Rubella-associated cataract has become rare since introduction of the MMR vaccine.
- ▶ **Congenital aphakia** (absent lens) and **microphakia** (abnormally small lens) result from disturbances of lens induction or of the genes governing lens placode formation/maintenance (e.g. **PAX6**).
- ▶ **Persistent lens stalk** — failure of the lens vesicle to separate completely from the surface ectoderm (implicated genes: **FOXE3**, **PITX3**, **AP-2α**), arresting further lens differentiation.
- ▶ **Persistent pupillary membrane** — failure of resorption of the anterior vascular capsule; if extensive, it can partly or completely occlude the pupil.
- ▶ **Persistence of the hyaloid artery** — failure of the normal 8th-month regression can leave a cord, cyst, or (in the eye as a whole) **persistent hyperplastic primary vitreous**, causing visual impairment.
- ▶ The whole eye, including the lens, is maximally vulnerable to teratogens between the **4th and 8th weeks**, though susceptibility continues at a lower level throughout gestation.

**High-yield exam pointers**

- ▶ Lens is derived **wholly from surface ectoderm** — the only ocular structure with no neuroectodermal or mesenchymal parenchymal contribution.
- ▶ Sequence: optic vesicle contact → **lens placode** → **lens pit** (invagination) → **lens vesicle** (separates by day 33) → primary lens fibres (fill cavity by 7th week) → secondary lens fibres (from 3rd month, lifelong).

- ▶ Posterior wall of lens vesicle → **primary lens fibres**; anterior wall persists as **lifelong germinative anterior epithelium**.
- ▶ Secondary lens fibres arise from the **equatorial (germinative) zone** and are added throughout life — the lens never stops growing.
- ▶ **PAX6** is the master gene of lens/eye development; downstream SOX2, BMP4, MAF, SIX3 and PROX1 drive crystallin gene expression.
- ▶ **Crystallins** ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) confer transparency to lens fibres.
- ▶ The lens is transiently vascular (tunica vasculosa lentis via the hyaloid artery) but becomes completely **avascular** after regression of this vasculature.
- ▶ Rubella (4th–7th week), galactosemia, and crystallin/MAF/HSF4 mutations are the classic causes of **congenital cataract**.
- ▶ Lens capsule = a **basement membrane** secreted by the lens epithelium, thickest at the equator.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology (figure).



## Development of spinal cord

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The spinal cord develops from the caudal, tubular part of the **neural tube**, which itself forms from the neural plate by neurulation during the third and fourth weeks of intrauterine life. The wall of this segment differentiates through three concentric cell layers into a grey matter core (arranged as ventral **basal** and dorsal **alar** plates) surrounded by a white matter rind, while migrated **neural crest** cells form the dorsal root ganglia and complete the spinal nerve. Because the vertebral column subsequently grows faster than the cord, the cord's caudal end appears to "ascend" relative to the vertebral canal — a phenomenon of major clinical importance for lumbar puncture and for the anomalies (neural tube defects) that follow failure of this developmental sequence.

### 1. Origin — from neural tube to spinal cord segment

- ▶ The **neural plate** (thickened dorsal midline ectoderm) appears in the third week; its lateral edges elevate as **neural folds**, which meet and fuse in the midline to form the **neural tube**.
- ▶ Fusion begins in the **cervical region** and extends bidirectionally — cranially and caudally — leaving two transient openings, the **cranial (rostral)** and **caudal neuropores**, that keep the tube lumen in communication with the amniotic cavity.
- ▶ The **cranial neuropore** closes at the 18–20 somite stage ( $\approx$ 25th day); the **caudal neuropore** closes about 3 days later ( $\approx$ 27th–28th day,  $\sim$ 25-somite stage).

- ▶ The neural tube caudal to the fourth pair of somites remains a simple, narrow tube — the **primordium of the spinal cord**; the expanded cranial part forms the brain. Its lumen persists as the **central canal**, continuous with the brain's ventricular system.
- ▶ Failure of neuropore fusion at this stage underlies the **neural tube defects** discussed under Applied anatomy.

## 2. Histogenesis — three primitive layers of the neural tube wall

The wall of the newly closed tube is a pseudostratified **neuroepithelium**; with proliferation it differentiates into three concentric layers/zones.

| Layer (older term)                | Modern term                              | Composition                                                                   | Ultimate fate                                                                                                               |
|-----------------------------------|------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Neuroepithelial / ependymal layer | Ventricular zone (germinal/matrix layer) | Pseudostratified, mitotically active neuroepithelial cells abutting the lumen | Source of all neuroblasts and glioblasts; residual cells differentiate into <b>ependymal cells</b> lining the central canal |
| Mantle layer                      | Intermediate zone                        | Neuroblasts + glioblasts that have migrated peripherally                      | Becomes the <b>grey matter</b> of the cord                                                                                  |
| Marginal layer                    | Marginal zone                            | Axonal processes of mantle-layer neuroblasts, initially free of nuclei        | Becomes the <b>white matter</b> , once myelinated                                                                           |

Cell lineages arising from the neuroepithelium:

- ▶ **Neuroblasts** — postmitotic once formed; pass through apolar → bipolar → multipolar stages to become the neurons of the grey columns.
- ▶ **Glioblasts** — differentiate into **protoplasmic and fibrillary astrocytes** (support, metabolic exchange with vessels) and **oligodendrocytes** (myelinate CNS axons in the marginal layer).
- ▶ **Microglia** — the only glial cell **not** derived from neuroepithelium; a phagocytic cell of **mesenchymal/vascular (monocyte) origin**, entering the cord with vascular ingrowth in the second half of development.
- ▶ **Ependymal cells** — terminal differentiation of neuroepithelium once neuroblast/glioblast production ceases.

## 3. Basal and alar plates — dorsoventral organisation

- ▶ Continued addition of neuroblasts makes the mantle layer thicken unevenly on each side: a **ventral (basal) plate/lamina**, containing motor neuroblasts, and a **dorsal (alar) plate/lamina**, containing sensory (association) neuroblasts.
- ▶ The **sulcus limitans**, a longitudinal groove on the internal (luminal) aspect of the lateral wall, marks the boundary between the two.
- ▶ The **roof plate** (dorsal midline) and **floor plate** (ventral midline) remain thin and free of neuroblasts; they serve as pathways for commissural (crossing) fibres.



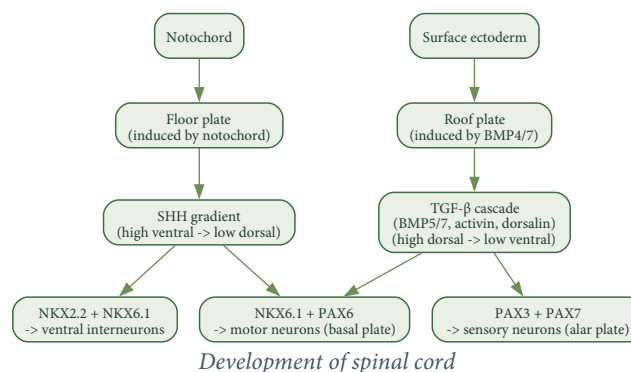
- ▶ A small group of neurons accumulating between the alar and basal plates forms the **intermediate (lateral) horn**, present only at T1–L2/3 (preganglionic sympathetic neurons).
- ▶ As the basal plate enlarges, it bulges forward on each side of the midline, leaving the **anterior (ventral) median fissure** between the two halves; as the alar plate enlarges, the dorsal part of the original lumen is obliterated, forming the **posterior median septum** — the ventral part of the lumen persists as the definitive **central canal**.

□ Fig 22.4 — Development of spinal cord (Sontakke — Textbook of Human Embryology, p.246)

#### 4. Molecular regulation of dorsoventral patterning

Differentiation of sensory (dorsal) versus motor (ventral) neuron populations is directed by two opposing morphogen gradients:

- ▶ **Sonic hedgehog (SHH)** is secreted first by the **notochord**, then by the induced **floor plate**, giving a gradient that is **highest ventrally, lowest dorsally**.
- ▶ **BMP4/BMP7**, secreted by the ectoderm overlying the tube, induce the **roof plate** to secrete a cascade of TGF- $\beta$ -family proteins (BMP5, BMP7, activin, dorsalin), giving a gradient that is **highest dorsally, lowest ventrally**.
- ▶ The overlapping gradients switch on position-specific transcription factors: high TGF- $\beta$ /low SHH activates **PAX3/PAX7** → dorsal (alar-plate) sensory neuron differentiation; high SHH/very low TGF- $\beta$  (adjoining the floor plate) activates **NKX2.2/NKX6.1** → ventral interneurons; intermediate concentrations activate **NKX6.1/PAX6** → basal-plate **motor neuron** differentiation.



#### 5. Formation of grey/white matter and the spinal nerve roots

- ▶ Neuroblasts of the **basal plate** form the **anterior (ventral) grey column**; their axons emerge at the ventrolateral angle of the cord to constitute the **ventral (motor) root**.
- ▶ Neuroblasts of the **alar plate** form the **posterior (dorsal) grey column** — second-order sensory/association neurons whose axons enter the marginal layer to ascend as **ascending tracts**, or remain as interneurons.
- ▶ The **intermediate (lateral) grey column** (T1–L2/3) supplies preganglionic sympathetic fibres via the ventral root.
- ▶ **Neural crest cells** (not derived from the neural tube proper) migrate to lie dorsolateral to the cord and aggregate as the **dorsal root ganglia** — pseudounipolar sensory neurons. Their **central process** forms the **dorsal (sensory) root**; their **peripheral process** joins the ventral root distally to complete the **spinal nerve**, which divides into **dorsal and ventral primary rami**.

- The **white matter (marginal layer)** consists of ascending axons (from the posterior grey column) and descending axons (growing down from higher centres); as the grey columns project outward, the white matter becomes subdivided into **anterior, lateral and posterior white columns (funiculi)**.

## 6. Functional (columnar) organisation of the grey matter

Unlike the seven columns of the brainstem, the spinal cord contains only **four functional columns**, since special somatic/visceral afferent and efferent columns are relevant only to the head.

| Lamina           | Column                          | Distribution                                                           | Function                                 |
|------------------|---------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Alar (afferent)  | General somatic afferent (GSA)  | Entire length of cord                                                  | Exteroceptive & proprioceptive sensation |
| Alar (afferent)  | General visceral afferent (GVA) | Thoracolumbar (T1–L2/3) + sacral (S2–S4)                               | Visceral/vascular sensation              |
| Basal (efferent) | General somatic efferent (GSE)  | Entire length of cord                                                  | Motor supply to skeletal muscle          |
| Basal (efferent) | General visceral efferent (GVE) | Thoracolumbar (T1–L2/3, sympathetic) + sacral (S2–S4, parasympathetic) | Preganglionic autonomic outflow          |

## 7. Myelination

| Site                                        | Myelinating cell | Origin                      | Ratio                                                     |
|---------------------------------------------|------------------|-----------------------------|-----------------------------------------------------------|
| CNS (marginal layer / white matter of cord) | Oligodendrocyte  | Glioblast (neuroepithelium) | One cell myelinates <b>up to 50 axons</b>                 |
| PNS (spinal nerve roots)                    | Schwann cell     | Neural crest                | <b>One cell : one axon</b> (forms the neurilemmal sheath) |

- Myelination of the cord's white matter begins at about the **4th month** of intrauterine life; some long descending motor tracts are not fully myelinated until the **first postnatal year** — tracts myelinate roughly in step with the onset of their function.

## 8. Positional changes — ascent of the spinal cord

Differential growth — the vertebral column and dura elongate faster than the neural tube/cord — produces a progressive discrepancy between cord segments and their corresponding vertebrae.

| Stage                    | Level of caudal end of cord (conus medullaris)                                                                |
|--------------------------|---------------------------------------------------------------------------------------------------------------|
| 3rd month                | Cord occupies the full length of the vertebral canal; nerve roots leave horizontally at their level of origin |
| Later fetal life         | Between L3 and S5                                                                                             |
| Neonate (premature/term) | Between L1 and L3                                                                                             |

| Stage                | Level of caudal end of cord (conus medullaris)                                     |
|----------------------|------------------------------------------------------------------------------------|
| Children (1–7 years) | Between T12 and L3                                                                 |
| Adult                | Average — middle third of L1 body ( $\approx$ transpyloric plane); range T11 to L3 |

- ▶ As the cord "ascends" relative to the canal, spinal nerve roots below the cervical region run an increasingly **oblique** course to reach their exit foramina — the obliquity is greatest for the lumbar and sacral roots, which descend as the **cauda equina** below the conus.
- ▶ The **filum terminale** (~20 cm) is the fibrous remnant marking this line of regression: its upper 15 cm (**internum**), continuous with the pia, runs within the dural sac to the **lower border of S2**; its terminal 5 cm (**externum**) fuses with the dura and descends to the first coccygeal segment.
- ▶ The **dural sac and subarachnoid space** extend to S2, well below the adult conus — the anatomical basis for **lumbar puncture** at the L3/L4 or L4/L5 interspace.

□ Fig 7.1 — Positional changes of the spinal cord at various stages of development (Vishram Singh — *Clinical Neuroanatomy* — 4e, p.180)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce as a labelled panel series:

- ▶ **Neural tube + neural crest** — surface ectoderm, neural tube, paired neural crest masses.
- ▶ **~5th-week cross-section** — central canal, ependymal/mantle/marginal layers, sulcus limitans, alar plate, basal plate, roof plate, floor plate.
- ▶ **Developed cord cross-section** — grey matter, white matter, dorsal/ventral/lateral horn, central canal, posterior median septum, anterior median fissure.
- ▶ **Sagittal ascent schematic** (3rd month / birth / adult) — conus medullaris, filum terminale, dural sac to S2, vertebral levels L1, L3, S2.

### Applied / Clinical anatomy

- ▶ **Neural tube defects (NTDs)**, from failure of neural fold fusion (3rd–4th week), form a severity spectrum: **spina bifida occulta** (skin-covered vertebral-arch defect, cord normal, often a hair tuft) → **meningocele** (meninges alone herniate) → **meningomyelocele** (sac also contains neural tissue) → **rachischisis** (tube itself unclosed, neural tissue exposed).
- ▶ **Arnold–Chiari malformation**: meningomyelocele with downward herniation of cerebellum/medulla through the foramen magnum → obstructive **hydrocephalus**.
- ▶ **Anencephaly** — the cranial counterpart (failed rostral neuropore closure); screened by raised maternal serum/amniotic **alpha-fetoprotein** and **ultrasonography**; periconceptional **folic acid** reduces NTD incidence.
- ▶ **Syringomyelia** — abnormal cavitation related to the central canal.
- ▶ **Lumbar puncture/spinal anaesthesia** at L3/L4 or L4/L5 — below the adult conus (L1) but within the dural sac (to S2); needle placed lower still in a neonate, whose conus may lie as low as L3.
- ▶ **Tethered cord syndrome**: a short/thickened filum terminale prevents normal ascent, holding the conus low and risking progressive neurological deficit with growth.

## High-yield exam pointers

- ▶ Spinal cord = caudal tubular part of the neural tube; cranial (rostral) neuropore closes day 25, caudal neuropore day 27–28.
- ▶ Three layers: **ependymal (neuroepithelial)** → **mantle (grey matter)** → **marginal (white matter)**.
- ▶ **Sulcus limitans** divides mantle layer into **basal plate (motor, ventral)** and **alar plate (sensory, dorsal)**; roof/floor plates are neuroblast-free commissural pathways.
- ▶ Molecular gradient: **SHH** (notochord/floor plate) ventral, **BMP/TGF- $\beta$**  (roof plate) dorsal → **PAX3/7** (sensory) vs **NKX2.2/6.1** and **PAX6** (motor).
- ▶ **Dorsal root ganglia are neural-crest derived**, NOT from the neural tube; ventral (motor) roots arise from the basal plate.
- ▶ Only **4 functional columns** in the cord (GSA, GVA, GSE, GVE) vs 7 in the brainstem.
- ▶ CNS myelination by **oligodendrocytes** (1:50 axons); PNS by **Schwann cells** (1:1) — begins ~4th month IUL.
- ▶ Ascent of the cord: 3rd month = full canal length; birth = L3; adult average = **L1** (range T11–L3); dural sac to S2.
- ▶ NTD spectrum: spina bifida occulta → meningocele → meningomyelocele → rachischisis; prevented by periconceptional folic acid.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Vishram Singh — Clinical Neuroanatomy 4e; Snell — Clinical Neuroanatomy 7e.



## Development of the ears

*Asked in: Paper II Nov 2018 — RGUHS MD/MS Anatomy*

**Definition/Introduction** — The ear is a composite sense organ with **three distinct embryological origins**: the internal (inner) ear arises entirely from surface ectoderm (the otic placode); the middle ear and its ossicles arise from the first and second pharyngeal arches, pouch and membrane; and the external ear arises from the first pharyngeal cleft and mesenchymal condensations of the first and second arches. Development begins in the third week and is not functionally complete until after birth, making the ear a classic site for correlated congenital anomalies of the pharyngeal apparatus.

### 1. Development of the internal (inner) ear

- ▶ Late in the **3rd week (~22nd day)**, a thickening of surface ectoderm — the **otic placode** — appears on either side of the hindbrain, adjacent to rhombomeres 5 and 6, dorsal to the second pharyngeal cleft. Induction is by **FGF signalling** from the mesoderm/hindbrain (Fgf3/Fgf10) together with **Wnt** from the hindbrain.

- ▶ The placode invaginates below the surface to form the **otic pit**, which deepens and pinches off from the surface ectoderm (day ~25–28) to form a closed, hollow **otic vesicle (otocyst)** lying free in the head mesenchyme.
- ▶ Neuroblasts delaminate from the antero-ventral wall of the otocyst to form the **vestibulocochlear (statoacoustic) ganglion** of cranial nerve VIII. These bipolar neurons are **exclusively placodal (ectodermal)** in origin — unusual, since most cranial ganglia are of mixed placodal-and-neural-crest origin. Neural crest supplies only the **Schwann cells/glia** of CN VIII and **melanocytes** of the **stria vascularis**.
- ▶ By day 28 the dorsomedial part of the vesicle elongates into an **endolymphatic appendage**, which forms the **endolymphatic duct and sac**. The remainder of the vesicle differentiates into an expanded **pars superior** (vestibular) and a tapered **pars inferior** (cochlear).

| Otic vesicle region                 | Adult derivative(s)                                                                                                    |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Endolymphatic appendage             | Endolymphatic duct + endolymphatic sac                                                                                 |
| Pars superior (dorsal)              | Utricle + 3 semicircular ducts (anterior, posterior, lateral), each with an ampulla housing a <b>crista ampullaris</b> |
| Pars inferior (ventral)             | Sacculle + cochlear duct (joined to sacculle by the <b>ductus reuniens</b> )                                           |
| Cochlear duct epithelium (7th week) | <b>Spiral organ of Corti</b> — inner and outer hair cells with stereocilia, capped by the tectorial membrane           |
| Otocyst wall (antero-ventral)       | Vestibulocochlear ganglion (bipolar neurons)                                                                           |

- ▶ The three semicircular ducts arise (from the 5th week) as flattened, bilayered evaginations from the pars superior; the epithelium at the centre of each disc regresses, leaving a tubular duct — anterior, posterior and lateral, perpendicular to one another, each with a terminal ampulla.
- ▶ The cochlear duct forms by elongation/coiling of the pars inferior's ventral tip; by the 7th week its floor differentiates into the **spiral organ of Corti**.
- ▶ Six **prosensory patches** differentiate: 3 **cristae ampullares** (semicircular ducts — angular acceleration), 2 **maculae** (utricle/sacculle — gravity, linear acceleration), and the **organ of Corti** (cochlea — hearing); all innervated by the vestibular/cochlear divisions of CN VIII.
- ▶ **Bony labyrinth**: from the 9th week, periotic mesenchyme condenses and chondrifies into the **otic capsule**; between the 3rd–5th months it vacuolises to form the **perilymphatic space** (perilymph, continuous with CSF). Around the cochlea these spaces become the **scala vestibuli** and **scala tympani** flanking the cochlear duct (**scala media**); **Reissner's membrane** separates scala vestibuli/media, the **basilar membrane** separates scala media/tympani. The capsule **ossifies** at 16–23 weeks into the **petrous temporal bone**.

## 2. Development of the middle ear

- ▶ The **first pharyngeal pouch** (endoderm) elongates as the **tubotympanic recess**, with a contribution from the second pouch; its narrow proximal part becomes the **pharyngotympanic (Eustachian) tube** and its expanded distal part becomes the mucosal lining of the **tympanic cavity**.

- ▶ The three **auditory ossicles** condense in mesenchyme adjacent to the tympanic cavity, derived from **neural crest cells** of the first and second arches: the **malleus and incus** develop from the dorsal end of **Meckel's cartilage** (1st arch), while the **stapes** develops from the dorsal end of **Reichert's cartilage** (2nd arch) — **except the footplate of the stapes**, which is of mesodermal origin (fitting into the otic capsule at the future oval window).
- ▶ The ossicles remain embedded in mesenchyme until the **8th month**, when it is resorbed; the tympanic cavity then expands (9th month) to enclose them, suspended first by transient mesenteries and later by definitive ligaments. The **ossicles are the first bones in the body to fully ossify (4th intrauterine month)**, though not free to vibrate until ~2 months postnatally.
- ▶ Two muscles develop in the 9th week: **tensor tympani** from first-arch mesoderm (innervated by CN V, its arch nerve) and **stapedius** from second-arch mesoderm (innervated by CN VII, its arch nerve).
- ▶ The **tympanic membrane** forms by apposition of the first pharyngeal cleft (ectoderm) and the tubotympanic recess (endoderm), with an intervening mesenchymal layer infiltrated by neural crest cells — giving a classic **trilaminar (tridermal) structure**: outer cuticular (ectodermal), middle fibrous (mesodermal/neural crest), inner mucous (endodermal).
- ▶ The **mastoid antrum** appears as a dorsal expansion of the tympanic cavity around the 6th–9th month; the **mastoid air cells**, however, do not form until ~2 years of age, once traction by the developing sternocleidomastoid muscle shapes the mastoid process.

### 3. Development of the external ear

- ▶ The **external acoustic meatus** develops from the dorsal end of the **first pharyngeal cleft** (ectoderm), invaginating during the 6th week as a funnel-shaped primary meatus. Its ectodermal lining proliferates into a solid **meatal plug**, which fills the deep (medial) part of the canal; this plug **canalises around the 26th week (7th month)** to form the definitive (medial two-thirds of the) meatus.
- ▶ The **auricle (pinna)** develops from **six mesenchymal (auricular) hillocks** that appear during the 5th–6th week around the dorsal part of the first pharyngeal cleft, on the apposed surfaces of the mandibular (1st) and hyoid (2nd) arches.

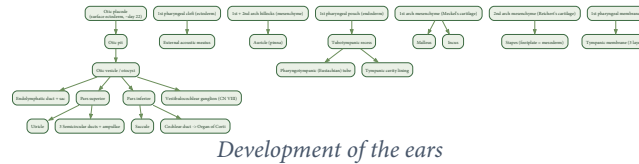
| Hillock | Pharyngeal arch  | Adult part formed |
|---------|------------------|-------------------|
| 1       | Mandibular (1st) | Tragus            |
| 2       | Mandibular (1st) | Crus of helix     |
| 3       | Mandibular (1st) | Helix             |
| 4       | Hyoid (2nd)      | Antihelix         |
| 5       | Hyoid (2nd)      | Antitragus        |
| 6       | Hyoid (2nd)      | Lobule            |

- ▶ Note that the **mandibular arch forms only the tragus and a small surrounding area**; the **bulk of the auricle is formed by the hyoid (2nd) arch** — consistent with the auricular (extrinsic/intrinsic) muscles being supplied by the **facial nerve (CN VII)**, the nerve of the second arch.



- During the 7th week the hillocks enlarge, differentiate and fuse to give the definitive auricular contours. As the face and mandible grow, the auricle **translocates** from its original low, ventro-caudal position on the side of the neck to its definitive lateral and more cranial position on the head.

#### 4. Overview: derivation flow-chart



#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Two simple hand-diagrams cover this topic in the exam:

- **Otic vesicle differentiating into the membranous labyrinth** — label: otic placode → otic pit → otic vesicle (otocyst) → endolymphatic duct and sac; pars superior giving utricle + anterior/posterior/lateral semicircular ducts (each with an ampulla); pars inferior giving saccule (via ductus reuniens) + coiled cochlear duct; vestibulocochlear ganglion (CN VIII) on the otocyst wall.
- **Cross-section through the developing ear region** — label: first cleft/meatus primordium with meatal plug; tympanic membrane (three layers); tubotympanic recess; mesenchymal condensation of ossicle chain (malleus/incus/stapes); cartilaginous otic capsule around the membranous labyrinth.

Embedded real plate for diagram (2) above — a genuine captioned schematic of the developing ear:

embed: ![Fig 25.2 — Schematic drawing showing development of the ear: external cleft/meatus (left, pink), developing ossicles (centre, red) suspended in mesenchyme, and tubotympanic recess (right, blue) approaching the otic capsule (Ross Histology — A Text and Atlas — 7e, p.955)]  
(C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/25cf4885fb4fc26c.jpg)

#### Applied / Clinical anatomy

- **Microtia/anotia**: suppressed hillock growth gives a small (microtia) or absent (anotia) auricle — up to 1 in 250 children, more common on the right and in males; isolated or syndromic (BOR, CHARGE, Treacher Collins, trisomy 21/18, oculo-auriculo-vertebral spectrum) or teratogen-related (maternal diabetes, isotretinoin, alcohol). **Macrotia** (hillock overgrowth) is seen in Fragile X syndrome.
- **Preauricular pits/tags**: accessory hillocks; a feature of BOR syndrome.
- **Atresia/stenosis of the external acoustic meatus**: failure of meatal-plug canalisation; commonly co-exists with microtia and ossicular/middle-ear anomalies.
- **Branchio-oto-renal (BOR, Melnick-Fraser) syndrome**: EYA1 mutation — cup-shaped ears, preauricular pits, branchial cysts, renal dysplasia, conductive/sensorineural hearing loss.



- ▶ **CHARGE syndrome** (CHD7 mutation): inner-ear defects range from **labyrinthine (Michel) aplasia** to **Mondini dysplasia** (cochlea <2.5 turns, normal 2.5–3, plus semicircular canal defects); external-ear anomalies are a cardinal feature.
- ▶ **Large vestibular aqueduct (LVA/EVA)**: enlarged endolymphatic-duct canal on thin-cut CT; associated with **Pendred syndrome** (gene product **pendrin**, a  $\text{Cl}^-/\text{I}^-$  transporter).
- ▶ **Connexin-26 (GJB2)** mutations (disrupting endolymph  $\text{K}^+$  recycling) are the **commonest cause of prelingual non-syndromic deafness (20–30%)**.
- ▶ **Jervell and Lange-Nielsen syndrome (KCNQ1)**: prelingual sensorineural hearing loss + long-QT cardiac arrhythmia.
- ▶ **Usher syndrome type 1**: sensorineural hearing loss + retinitis pigmentosa (stereocilia tip-link protein mutations — MYO7A, cadherin-23, harmonin, protocadherin-15).
- ▶ **Ossicular fusion/fixation/hypoplasia**: seen with achondroplasia, osteogenesis imperfecta, BOR and Treacher Collins; a persistent stapedia artery may coexist.
- ▶ **Overall congenital hearing loss**: 2–3/1000 live births (~5/1000 by 18 years); ~50% genetic, ~50% environmental (congenital CMV/rubella/Zika, neonatal aminoglycosides). Teratogen-sensitive period: **4th–9th week** (residual risk to 12th week).

### High-yield exam pointers

- ▶ Inner ear = surface ectoderm (otic placode); middle + external ear = 1st & 2nd pharyngeal arch/pouch/cleft — **three separate origins**, hence anomalies of one part need not affect the others.
- ▶ Otic placode appears **end of 3rd week**, adjacent to hindbrain rhombomeres 5–6; invaginates to otic pit, then pinches off as the otic vesicle (otocyst).
- ▶ Otic vesicle → **pars superior** (utricle + 3 semicircular ducts) and **pars inferior** (sacculle + cochlear duct), plus the endolymphatic duct/sac.
- ▶ Vestibulocochlear ganglion neurons are **purely placodal**; neural crest contributes only glia/Schwann cells and stria vascularis melanocytes.
- ▶ **Malleus and incus** = 1st arch (Meckel's cartilage); **stapes** = 2nd arch (Reichert's cartilage), **except the footplate** = mesoderm.
- ▶ Tympanic membrane is **trilaminar/tridermal**: ectoderm (outer) + neural-crest mesenchyme (middle, fibrous) + endoderm (inner).
- ▶ Auricle: 6 hillocks — **1–3 (tragus, crus of helix, helix)** from the mandibular arch, **4–6 (antihelix, antitragus, lobule)** from the hyoid arch; bulk of the auricle is a **2nd-arch** derivative (facial nerve supplies auricular muscles).
- ▶ **Ossicles are the first bones in the body to ossify** (4th intrauterine month); otic capsule ossifies at 16–23 weeks to form the petrous temporal bone; mastoid air cells appear only postnatally (~2 years).
- ▶ Key syndromes to link: BOR (EYA1), CHARGE (CHD7), Pendred (pendrin/LVA), connexin-26 (non-syndromic deafness), Treacher Collins.

**SOURCE & COVERAGE**

Larsen's Human Embryology 6e; IB Singh Human Embryology (CBME 2021); Gray's Anatomy (Standring) 41e; Ross Histology — A Text and Atlas 7e (figure).



## Differentiation of retina

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The retina is the light-sensitive neural tunic of the eyeball, developing entirely from the **neuroectoderm of the diencephalon** through the optic vesicle and optic cup — it is, embryologically, a specialised, evaginated extension of the brain rather than a peripheral sense organ derived de novo. Differentiation begins with formation of the bilaminar optic cup in the 4th–5th week and proceeds through proliferation, migration and lamination of retinal neurons until all ten definitive histological layers are identifiable by the 8th month, though photoreceptor and macular maturation continue for many months after birth. This dual origin — an outer pigmented layer and an inner neural layer, separated by the vestigial intraretinal space — explains both the definitive lamination of the adult retina and its single most important applied lesion, retinal detachment.

### 1. Formation of the optic vesicle and optic cup

- ▶ Day 22: paired **optic grooves (sulci)** appear in the neural folds of the **diencephalon** as the neural tube is closing.
- ▶ Day ~30–32: the grooves evaginate laterally to form hollow **optic vesicles**, each attached to the forebrain by a narrow **optic stalk** and invested by a mesenchymal sheath (neural crest + mesoderm).
- ▶ The optic vesicle contacts the overlying surface ectoderm and induces the **lens placode**.
- ▶ Days 33–35 (5th week): coordinated morphogenesis — the lens placode invaginates to form the lens vesicle, while the distal/lateral wall of the optic vesicle invaginates to convert it into a **double-walled (bilaminar) optic cup**.
- ▶ Invagination also involves the ventral wall and stalk, producing the **choroid (optic) fissure**, through which the **hyaloid artery** and mesenchyme enter the cup; the lips of the fissure fuse during the 7th week, converting the mouth of the cup into the future **pupil**.
- ▶ The two walls of the cup are separated by a narrow, slit-like cavity — the **intraretinal space** (the residual lumen of the optic vesicle). This space narrows progressively, but the two walls never fuse firmly — the embryological basis of retinal detachment.

### 2. Differentiation of the two walls of the optic cup

- ▶ **Outer layer (thin, single-layered)**: around day 36, cells accumulate melanosomes and differentiate into the **pigmented layer (retinal pigment epithelium, RPE)**, driven by TGF- $\beta$  signals from the surrounding peri-ocular mesenchyme and the transcription factor **MITF**. It remains a single cuboidal layer for life, firmly attached to Bruch's membrane/choroid but only loosely apposed to the neural retina.

- ▶ **Inner layer (thick):** proliferates into a **pseudostratified neuroepithelium**, the primordium of the **neural retina**, driven by FGF signals from the lens-forming ectoderm and the transcription factor **CHX10 (VSX2)**.
- ▶ The pigmented epithelium initially retains the potential to form neural retina and will do so experimentally if the young retina is wounded — demonstrating that the two fates are not irreversibly fixed at the earliest stage.

### 3. Neuroblastic layers → definitive retinal layers

- ▶ The proliferating inner-layer neuroepithelium first shows an outer, dividing **nuclear (ventricular) zone** and an inner, initially acellular **marginal zone**; around day 37 cells of the nuclear zone invade the marginal zone.
- ▶ By Carnegie stage 18 (~44 days, 6th–7th week), the nervous stratum shows two distinct strata — the **outer neuroblastic layer** and the **inner neuroblastic layer** — separated later by a transient **nerve fibre layer**; **external and internal limiting membranes** form on the outer and inner retinal surfaces respectively.
- ▶ All seven cell types of the mature retina (six neuronal types plus the Müller glial cell) arise from a **single common multipotential retinal progenitor cell**. Post-mitotic ("birth") order is conserved: **ganglion cells, amacrine cells, cone photoreceptors and horizontal cells develop early; bipolar cells, rod photoreceptors and Müller glial cells develop late**.
- ▶ Newly born neurons migrate from the apical (ventricular) surface to their definitive laminar position:
  - The **ganglion cell layer** separates first, demarcated by formation of the **inner plexiform layer**.
  - The **inner nuclear layer** (amacrine, horizontal, bipolar and Müller cells) then separates from the **outer nuclear layer** (rod and cone cell bodies) by formation of the **outer plexiform layer**.
- ▶ Differentiation proceeds centre-to-periphery — central (future macular) retina matures first. By the **8th month** all definitive layers are histologically identifiable, but photoreceptor outer segments continue to differentiate after birth, and the **macula does not reach full maturity until 15–45 months postnatally**.

□ Fig 19.5 — Differentiation of the Inner Layer of the Optic Cup to Form the (Larsen — Human Embryology — 6e, p.1173)

Ten definitive histological layers of the retina (choroidal/outer surface → vitread/inner surface):

| # | Layer                                    | Embryonic origin                                               |
|---|------------------------------------------|----------------------------------------------------------------|
| 1 | Retinal pigment epithelium               | Outer layer of optic cup                                       |
| 2 | Layer of rods and cones (photoreceptors) | Apical processes of outer neuroblastic layer                   |
| 3 | External limiting membrane               | Junctional complexes at apex of neuroepithelium                |
| 4 | Outer nuclear layer                      | Outer neuroblastic layer (photoreceptor cell bodies)           |
| 5 | Outer plexiform layer                    | Synaptic zone between outer and inner neuroblastic derivatives |

| #  | Layer                      | Embryonic origin                                                       |
|----|----------------------------|------------------------------------------------------------------------|
| 6  | Inner nuclear layer        | Inner neuroblastic layer (bipolar, horizontal, amacrine, Müller cells) |
| 7  | Inner plexiform layer      | Synaptic zone separating ganglion cells from inner nuclear layer       |
| 8  | Ganglion cell layer        | Innermost cells of inner neuroblastic layer                            |
| 9  | Nerve fibre layer          | Axons of ganglion cells                                                |
| 10 | Internal limiting membrane | Basal lamina at inner (vitread) surface, with Müller cell footplates   |

#### 4. Peripheral retina — pars ciliaris and pars iridica retinae

- ▶ Anteriorly, the inner layer remains only **one cell thick** and never becomes photosensitive — this non-visual anterior one-fifth is the **pars caeca retinae**.
- ▶ It divides into:
  - **Pars ciliaris retinae** — contributes the two-layered epithelium of the **ciliary body**; the ciliary muscle forms from adjacent mesenchyme.
  - **Pars iridica retinae** — forms the posterior pigmented and anterior unpigmented epithelial layers of the **iris**; unusually, the **sphincter pupillae** and **dilator pupillae** muscles **differentiate from this neuroectodermal epithelium itself**, not from mesenchyme.
- ▶ The true photoreceptive retina — the **pars optica retinae** — is thus restricted to the posterior four-fifths of the cup.

#### 5. Optic nerve formation

- ▶ Axons of the retinal ganglion cells converge on the inner wall of the optic stalk; as fibre numbers increase, this wall thickens and the stalk lumen (continuous with the intraretinal space) is obliterated, converting the hollow stalk into the solid **optic nerve** by the 7th–8th week.
- ▶ Neuroglial cells of the inner stalk layer form a supporting network for the nerve fibres; oligodendrocytes migrating in from the brain myelinate the nerve, beginning shortly before birth and continuing afterwards.
- ▶ The deepest part of the optic (choroid) fissure becomes the **optic disc**, where ganglion-cell axons turn to leave the eye — since no photoreceptors exist here, this corresponds to the clinical **blind spot**.
- ▶ Retinal nerve fibres remain **unmyelinated within the eyeball**; myelination begins only posterior to the lamina cribrosa.

#### 6. Vascularisation of the retina

- ▶ The **hyaloid artery**, a branch of the primitive ophthalmic artery, runs through the choroid fissure and hyaloid canal to supply the lens and the inner retinal surface during intrauterine life.

- ▶ Its distal (intravitreal) segment regresses; the proximal part persists as the **central artery of the retina**.
- ▶ Definitive retinal vasculature develops in two steps: **vasculogenesis** — aggregation of spindle-shaped angioblastic mesenchymal cells spreading from the optic disc (from about the 15th week) to form the primary (inner) vascular plexus — followed by **angiogenesis**, in which new vessels sprout and extend tangentially to reach the periphery, forming the superficial, intermediate and deep retinal capillary layers, a process not complete until near term.
- ▶ The avascular **photoreceptor layer** expresses anti-angiogenic factors and is nourished instead by diffusion from the choriocapillaris of the choroid.

## 7. Molecular regulation of retinal differentiation

| Gene / factor                                                          | Role in retinal differentiation                                                                                              |
|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| PAX6                                                                   | Master regulatory gene for the whole eye field; maintained in optic cup, ciliary/iridial epithelium and lens ectoderm        |
| SHH (sonic hedgehog)                                                   | Secreted by prechordal plate; splits the single eye field into two, upregulating PAX2 and downregulating PAX6 at the midline |
| PAX2                                                                   | Specifies the optic stalk; mutation causes optic nerve coloboma ( $\pm$ renal coloboma syndrome)                             |
| CHX10 / VSX2                                                           | Drives proliferation and fate of the inner (neural retina) layer of the optic cup; mutation causes microphthalmia            |
| MITF                                                                   | Drives fate of the outer (pigmented epithelium) layer of the optic cup                                                       |
| FGF (from lens ectoderm) vs TGF- $\beta$ (from peri-ocular mesenchyme) | Reciprocal inductive signals that regionalise the inner (neural) and outer (pigmented) walls of the optic cup respectively   |

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Reproduce Larsen's four-panel scheme of retinal differentiation (embedded plate above), labelling in each panel:

- ▶ **5 weeks** — pigmented epithelium, intraretinal space, neural retina (thick pseudostratified neuroepithelium)
- ▶ **9 weeks** — pigmented epithelium, external limiting membrane, outer neuroblastic layer, inner neuroblastic layer, nerve fibre layer, internal limiting membrane
- ▶ **Late fetal stage** — choroid, Bruch's membrane, layer of rods and cone photoreceptors, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer
- ▶ **Cellular diagram (late fetal/adult)** — pigmented epithelium, rods, cones, horizontal cell, bipolar cells, amacrine cell, Müller glia cells, ganglion cells, arrow showing direction of light and pathway "to optic nerve"

**Applied / Clinical anatomy**

- ▶ **Retinal detachment:** separation occurs along the persistent embryonic **intraretinal space**, between neurosensory retina and RPE, which never fuse firmly — so even minor trauma or vitreous traction can separate them.
- ▶ **Coloboma of retina/choroid/iris:** failure of choroid-fissure closure (normally by the 7th week); cleft may extend from iris to optic nerve; linked to **PAX2** ( $\pm$  renal coloboma syndrome) and CHX10/SOX2 mutations.
- ▶ **Microphthalmia/anophthalmia:** failure of optic vesicle induction or reduced optic-cup growth (CHX10, SOX2, PAX6 mutations). **Aniridia:** PAX6 haploinsufficiency, reflecting its role in the peripheral (iridial) rim of the cup.
- ▶ **Persistent hyaloid artery/fetal vasculature:** failed regression, seen as a retrolental cord, Mittendorf's dot, or Bergmeister's papilla.
- ▶ **Retinopathy of prematurity:** preterm retinal angiogenesis is incomplete; supplemental oxygen provokes abnormal neovascularisation, haemorrhage and detachment.
- ▶ **Retinitis pigmentosa:** hereditary photoreceptor/RPE degeneration (e.g., rhodopsin, RPE65 defects), reflecting disruption of the photoreceptor differentiation programme.
- ▶ **Retinoblastoma:** malignant tumour of retinal neuroblastic progenitor cells, associated with RB1 loss — commonest primary intraocular malignancy of childhood.
- ▶ As a direct diencephalic outgrowth, the retina is an accessible "window on the brain" on fundoscopy (e.g., papilloedema), and its blood–retina barrier (RPE tight junctions + retinal vessel endothelium) is analogous to the blood–brain barrier.

**High-yield exam pointers**

- ▶ Retina develops entirely from **neuroectoderm of the diencephalon**: optic groove  $\rightarrow$  optic vesicle  $\rightarrow$  bilaminar optic cup.

- ▶ **Outer layer of optic cup** → **pigmented epithelium** (single layer, MITF-driven); **inner layer** → **neural retina** (thick pseudostratified neuroepithelium, CHX10/FGF-driven).
- ▶ Neural retina passes through **outer + inner neuroblastic layers** (by ~44 days) before forming the **10 definitive layers**.
- ▶ Retinal cell "birth" order: **ganglion/amacrine/cone/horizontal cells early** → **bipolar/rod/Müller glia late**, all from one multipotent progenitor.
- ▶ **Intraretinal space** = residual optic-vesicle lumen; the two layers never fuse firmly → basis of **retinal detachment**.
- ▶ Anterior 1/5 (**pars caeca retinae**) → pars ciliaris + pars iridica retinae; **sphincter/dilator pupillae** are **neuroectodermal** in origin — an unusual smooth-muscle exception.
- ▶ **Optic stalk** → **optic nerve** (7th–8th week); intraocular fibres are unmyelinated — myelination begins only behind the lamina cribrosa.
- ▶ **Hyaloid artery** → **central retinal artery**; retinal vessels form by vasculogenesis then angiogenesis, completing near term (clinically relevant to ROP).
- ▶ **PAX6** = master gene; **PAX2** (stalk), **CHX10/MITF** (inner/outer cup fate) are the key downstream regulators.
- ▶ All ten layers present by the **8th month IUL**, but the **macula matures only 15–45 months after birth**.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Brijesh Kumar — Embryology Text & Atlas; IB Singh — Human Embryology (CBME 2021).



## Ecto dermal placodes

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Ectodermal placodes are focal thickenings of the cranial surface ectoderm made up of neuroepithelial cells that, unlike neural crest cells, remain within the surface ectoderm after neural tube closure. Together with the neural tube and the neural crest they constitute the **third source of cells** that build the nervous system of the head. Placodes contribute neurons to the distal (ventral) part of the cranial sensory ganglia and give rise to the lens, olfactory epithelium, adenohypophysis and membranous labyrinth. They arise from a continuous zone of epithelial thickening around the head margin called the **ectodermal ring** (O'Rahilly and Müller).

### 1. Origin — the ectodermal ring

- ▶ Three cell populations build the head nervous system: (i) **neural tube** → CNS; (ii) **neural crest cells** → almost all of the PNS (sensory, autonomic ganglia, Schwann cells, melanocytes) and craniofacial mesenchyme; (iii) **ectodermal placodes** → cranial sensory ganglia (distal part), hypophysis and inner ear.



- Prior to neural tube closure the elevating neural fold contains **two** neuronal cell populations: a larger population, the **neural crest cells**, which detach and migrate before neural tube fusion; and a smaller population, **neuroepithelial cells**, which become incorporated into the surface ectoderm after neural tube closure — these residual patches of neuroepithelium within the ectoderm are the **ectodermal placodes**.
- The ectoderm over the head and lateral borders of the embryo shows a zone of epithelial thickening, the **ectodermal ring**, discernible from **Carnegie stage 10** and complete by **stage 12**.
- Rostrally the ring contains the neurogenic placodes; more caudally (over the limb fields) it gives rise to the **mammary line**, and caudal to the lower limb field it corresponds to the ectoderm of the external genitalia/urogenital swellings.
- Placodal neuroepithelial cells are best regarded as neuroepithelium that is retained within the surface ectoderm until CNS development is advanced enough for their incorporation into sensory epithelia and cranial nerve ganglia.

## 2. Classification of ectodermal placodes

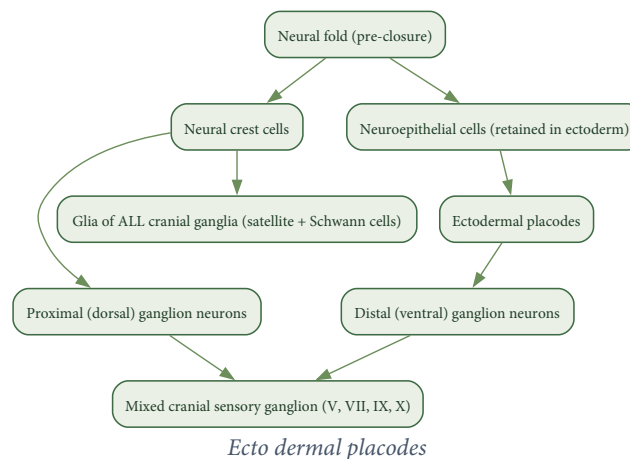
| Placode                                                                    | Position along the ectodermal ring                           | Mature derivative                                                                                                                               | Cranial nerve/ganglion |
|----------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Adenohypophysial (hypophysial)                                             | Midline, rostral to the buccopharyngeal membrane             | Invaginates as Rathke's <b>pouch</b> → adenohypophysis (anterior pituitary)                                                                     | —                      |
| Olfactory (nasal)                                                          | Paired, on the frontonasal prominence                        | Olfactory epithelium; source of GnRH-secreting neurons that migrate to the hypothalamus                                                         | CN I                   |
| Optic (lens)                                                               | Overlying the distal optic vesicle                           | Invaginates → lens vesicle → <b>lens</b> ; adjacent ectoderm reforms as corneal epithelium                                                      | — (non-neurogenic)     |
| Trigeminal (profundal + maxillomandibular; fuse in humans into one entity) | Alongside the mesencephalic–rhombencephalic junction         | Distal (peripheral) neurons of the <b>trigeminal ganglion</b>                                                                                   | CN V                   |
| Epibranchial (1st, 2nd, 3rd)                                               | Dorsal to each pharyngeal cleft, over arches 1–3             | Distal ganglia: 1st → <b>geniculate</b> ; 2nd → <b>petrosal</b> ; 3rd → <b>nodose</b>                                                           | VII, IX, X             |
| Otic                                                                       | Lateral to the hindbrain, dorsal to the 2nd pharyngeal cleft | Invaginates → otic vesicle (otocyst) → <b>membranous labyrinth</b> ; neuroblasts bud from its ventromedial wall → cochlear + vestibular ganglia | CN VIII                |

- A further, non-neurogenic specialisation of ectoderm on the frontonasal, maxillary and mandibular processes gives rise to the **tooth buds**.

### 3. Neurogenic vs non-neurogenic placodes — the developmental sequence

- ▶ After an appropriate inductive stimulus the placode thickens and then either (a) generates migratory neuroblasts that detach and migrate internally to the site of ganglion formation, or (b) invaginates in toto as a vesicle beneath the remaining surface ectoderm, or (c) undergoes both processes.
- ▶ **Neurogenic placodes** — olfactory, trigeminal, epibranchial, otic — undergo both delamination of neuroblasts and (for the otic placode) vesicle formation.
- ▶ **Non-neurogenic placodes** — the lens placode alone — only invaginate to form a vesicle (the lens vesicle), under the inductive influence of the adjacent optic vesicle; they never produce neurons.
- ▶ Sequence for a neurogenic placode: inductive signal from adjacent germ layer (e.g. pharyngeal pouch endoderm for epibranchial placodes) → focal ectodermal thickening → detachment of neuroblasts (or pit → vesicle invagination, as for the otic placode) → migration to the definitive ganglionic site → differentiation into neurons/sensory epithelium.
- ▶ Timed example (otic placode): appears lateral to the hindbrain at **stage 9** → invaginates as an **otic pit** adjacent to rhombomeres 5–6, dorsal to the 2nd pharyngeal cleft → pinched off at **stage 12** to form the **otic vesicle (otocyst)**.
- ▶ Timed example (lens placode): thickens opposite the distal optic vesicle; between **33 and 35 days**, lens placode and optic vesicle undergo coordinated invagination — the placode pinches off as the **lens vesicle**, while the optic vesicle invaginates into the optic cup (inner layer → neural retina, outer layer → retinal pigment epithelium).

### 4. Dual origin of the cranial sensory ganglia



- ▶ Sensory (root) ganglia of cranial nerves **V, VII, IX, X** have a **dual embryonic origin**: the **proximal (more dorsal)** ganglion neurons arise from **neural crest cells**; the **distal (more ventral)** ganglion neurons arise from **epibranchial/trigeminal placodes**.
- ▶ **Glial cells** (satellite cells and Schwann cells) in **both** the proximal and distal parts of these mixed ganglia are derived **exclusively from neural crest** — never from placode, even in the distal (placode-derived-neuron) segment.
- ▶ The **special sensory nerves** — olfactory (I) and vestibulocochlear (VIII) — and their end organs are derived **entirely from placodes** (olfactory and otic respectively), with no neural crest

contribution to the sensory neurons themselves; the optic "nerve" is in fact a CNS tract arising from the optic cup (diencephalic neuroectoderm), induced by the adjacent, non-neurogenic lens placode.

□ Fig 4.21 — Fate Map Showing the Contributions of Placodes (Left ; Black ) and Neu (Larsen — Human Embryology — 6e, p.269)

Fig 4.21 (Larsen): fate map of placode (black) vs neural crest (light blue) contributions to the cranial sensory ganglia — proximal ganglion neurons from neural crest, distal ganglion neurons from placodes, glia of both parts always from neural crest.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A lateral schematic of a stage-13 (4 mm) human embryo "unrolled" flat, labelling from rostral to caudal:

- ▶ Buccopharyngeal membrane
- ▶ Adenohypophysial (hypophysial) placode (midline, becoming Rathke's pouch)
- ▶ Olfactory placode (paired, frontonasal prominence)
- ▶ Optic vesicle with overlying lens placode
- ▶ Trigeminal placode (fused profundal + maxillomandibular) → trigeminal ganglion
- ▶ Otic placode/vesicle, dorsal to the 2nd pharyngeal cleft → membranous labyrinth
- ▶ Epibranchial placodes 1, 2, 3 dorsal to pharyngeal clefts 1, 2, 3 → geniculate (VII), petrosal (IX), nodose (X) ganglia
- ▶ Neural crest streams (shaded) converging on each cranial ganglion from the adjacent neural fold, shown alongside each placode to illustrate the dual (crest + placode) contribution.

### 5. Development of individual placodes

- ▶ **Adenohypophysial placode** — midline ectodermal thickening rostral to the buccopharyngeal membrane; invaginates dorsally as **Rathke's pouch**, which detaches from the stomodeal ectoderm and forms the adenohypophysis (pars distalis, tuberalis, intermedia) of the pituitary.
- ▶ **Olfactory placode** — paired thickenings on the frontonasal prominence; forms the olfactory epithelium (bipolar receptor neurons whose axons form CN I) and is also the site of origin of **GnRH-secreting neurons**, which migrate along the developing olfactory/terminal nerve tract into the hypothalamus.
- ▶ **Optic (lens) placode** — non-neurogenic; ectoderm apposed to the distal optic vesicle thickens and, in coordinated morphogenesis with the optic vesicle, invaginates and pinches off as the **lens vesicle** → lens; the surrounding surface ectoderm reforms as the corneal epithelium.
- ▶ **Trigeminal placode** — profundal and maxillomandibular components, which fuse in humans into a single placode alongside the mesencephalic–rhombencephalic junction; neuroblasts migrate from it to contribute the distal portion of the **trigeminal ganglion** (proximal portion from neural crest).
- ▶ **Epibranchial placodes** — three placodes appear in the ectoderm immediately dorsal to the forming pharyngeal clefts, after the underlying pharyngeal pouch endoderm has contacted the

overlying ectoderm (an inductive interaction); the 1st contributes to the distal **geniculate ganglion (VII)**, the 2nd to the distal **petrosal ganglion (IX)**, and the 3rd to the distal **nodose ganglion (X)**.

- ▶ **Otic placode** — appears lateral to the hindbrain at stage 9; invaginates as an otic pit adjacent to rhombomeres 5–6, pinching off at stage 12 as the **otic vesicle (otocyst)**, which differentiates into the membranous labyrinth (cochlear and vestibular parts); neuroblasts budding from its ventromedial wall form the **vestibulocochlear ganglia**.

## Applied / Clinical anatomy

- ▶ **Rathke's pouch remnants** anywhere along its migratory path from the pharyngeal roof to the sella turcica may give rise to a **pharyngeal (ectopic) pituitary**, a **Rathke's cleft cyst**, or a **craniopharyngioma**.
- ▶ **Kallmann syndrome** — failure of GnRH-neuron migration from the olfactory placode into the hypothalamus produces combined **anosmia/hyposmia and hypogonadotropic hypogonadism**; commonest cause is a *KAL1* (anosmin-1) mutation (X-linked form), with autosomal dominant/recessive and digenic forms also described.
- ▶ **CHARGE syndrome** (*CHD7* mutations) — a placode/neural-crest developmental field defect producing **coloboma, heart defects, choanal atresia, retarded growth, genital and ear anomalies**; otic placode/vesicle dysplasia manifests as inner-ear malformations ranging from complete labyrinthine (Michel) aplasia to reduced cochlear turns and semicircular canal defects (Mondini dysplasia), with sensorineural hearing loss.
- ▶ **Congenital cataract/aphakia** — failure of lens placode induction or invagination if the optic vesicle fails to make adequate contact with the surface ectoderm.
- ▶ **Anencephaly/craniorachischisis** — failure of cranial neural tube closure disrupts the adjoining ectodermal ring and the placodal field, contributing to the characteristic facial and cranial-vault anomalies.
- ▶ Deficient epibranchial/trigeminal placode contribution underlies rare congenital hypoplasia of the corresponding distal cranial sensory ganglion.

## High-yield exam pointers

- ▶ Three sources build the head PNS: **neural tube, neural crest, ectodermal placodes**.
- ▶ Placodes = **neuroepithelial cells retained in surface ectoderm** after neural tube closure (as opposed to neural crest, which delaminates and migrates).
- ▶ **Ectodermal ring** (O'Rahilly & Müller) — discernible stage 10, complete stage 12.
- ▶ Six named placodes: **adenohypophyseal, olfactory, optic (lens), trigeminal, epibranchial (×3), otic**.
- ▶ **Neurogenic** (olfactory, trigeminal, epibranchial, otic) vs **non-neurogenic** (lens) placodes.
- ▶ **Dual origin rule** for cranial sensory ganglia V/VII/IX/X: proximal neurons = neural crest; distal neurons = placode; **glia always neural crest**.
- ▶ Epibranchial correspondence: **1st → geniculate (VII), 2nd → petrosal (IX), 3rd → nodose (X)**.
- ▶ Clinical triad to recall: **Rathke's pouch → craniopharyngioma; olfactory placode → Kallmann syndrome; otic placode → CHARGE/Mondini/Michel dysplasia**.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Larsen Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh Clinical Neuroanatomy 4e.



## Neural crest

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The neural crest is a transient, migratory population of cells that arises at the junctional lateral border ("crest") of the neural plate/neural folds, undergoes an epithelial-to-mesenchymal transition, and disperses throughout the embryo to form an extraordinary diversity of neuronal, glial, endocrine, pigment, skeletal and connective-tissue derivatives. Because of this breadth of contribution — the neural crest is involved in at least one-third of all birth defects and gives rise to tumours such as neuroblastoma and melanoma — it is often termed the "**fourth germ layer**." Disorders of its development are collectively called **neurocristopathies**.

### Origin and molecular induction

- ▶ Arises from cells at the tips of the neural folds, at the boundary between neuroectoderm (neural plate) and surface ectoderm (epidermis), just before the folds fuse in the dorsal midline.
- ▶ **BMP-gradient model**: high BMP concentration → epidermis; very low BMP → neural (epithelial) ectoderm; **intermediate** BMP at the plate/epidermis border, set by the BMP-antagonists **noggin and chordin**, together with **FGF and WNT** signalling → induces the neural crest.
- ▶ Sequential transcription-factor cascade: intermediate BMP + FGF/WNT first induce **PAX3** and related factors that "specify" the neural-plate border; these in turn induce **SNAIL and FOXD3** (which commit cells to a neural-crest fate) and **SLUG** (which drives the epithelial-mesenchymal transition and onset of migration).
- ▶ Timing differs cranially vs caudally: **cranial crest migrates before neural tube closure**; **trunk crest** leaves the neuroepithelium only **after tube closure**, migrating transiently over the closed tube before dispersing laterally and ventrally; the most **caudal (sacral/coccygeal) crest** arises later, from **secondary neurulation** (from about somite 29 onward, contributed by the tail bud).
- ▶ The most rostral prosencephalic neural fold does **not** produce neural crest; instead it gives rise to the hypophyseal (Rathke's pouch) and olfactory placodes.

### Regional (craniocaudal) classification

| Region               | Level of origin                                          | Principal fate                                                                            |
|----------------------|----------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Cranial neural crest | Prosencephalon to rhombomere 8 (rostral to otic vesicle) | Craniofacial skeleton/connective tissue, cranial ganglia, cranial parasympathetic ganglia |

| Region                            | Level of origin                          | Principal fate                                                                                                                 |
|-----------------------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Cardiac neural crest              | Otic placode to caudal limit of somite 3 | Migrates through pharyngeal arches 3, 4 & 6; <b>conotruncal (aorticopulmonary) septum</b> , tunica media of great-vessel roots |
| Vagal neural crest                | Somite levels 1–7                        | Thoracic parasympathetic ganglia; enteric ganglia of foregut/midgut (with sacral crest)                                        |
| Trunk neural crest                | Caudal to somite 7                       | Dorsal root ganglia, sympathetic chain/pre-aortic ganglia, suprarenal medulla, melanocytes                                     |
| Sacral (lumbosacral) neural crest | Caudal to somite 28                      | Caudal enteric (hindgut) ganglia, caudal parasympathetic ganglia                                                               |

(For autonomic-nervous-system purposes the crest is grouped functionally into four regions — cranial, vagal, trunk and lumbosacral — the vagal and trunk components together giving the "sympathosuprarenal" lineage.)

### Migration pathways

- **Cranial crest:** migrates as a "veil-like" mass prior to tube closure, following a strict **rhombomere-to-pharyngeal-arch** correspondence — rhombomeres 1–2 → arch 1; rhombomere 4 → arch 2; rhombomere 6 → arch 3; rhombomeres 7–8 → arches 4 and 6 (rhombomeres 3 and 5 contribute only sparse crest). Crest from the mesencephalon migrates into the frontonasal process and the maxillary/mandibular processes of arch 1.
- **Trunk crest** follows two principal routes:
- **Dorsolateral (subectodermal) pathway** — through the dermis, entering the epidermis through gaps in the basal lamina → **melanocytes** of skin and hair follicles.
- **Ventral pathway** — through the **rostral (permissive) half of each sclerotome**; the caudal half is non-permissive (repulsive proteoglycans/ephrins), which is why the resulting **spinal and sympathetic ganglia are metamerically segmented** → dorsal root ganglia, sympathetic chain and pre-aortic ganglia, suprarenal medulla, enteric ganglia, and Schwann cells along the migrating axons.

### Diagram to draw

Transverse section through the trunk at the level of a somite, showing: neural tube (centre) → crest cells emerging dorsally → (a) dorsolateral pathway through dermis to epidermis, labelled "melanocytes"; (b) ventral pathway through the rostral half of the sclerotome (shade the caudal half as "non-permissive"), labelled sequentially as "dorsal root ganglion" → "sympathetic chain ganglion" → "pre-aortic ganglion" → "suprarenal medulla," with the "enteric ganglia" shown migrating into the adjacent gut tube; label the notochord, dorsal aorta and gut tube for orientation.

□ Fig 22.3 — Derivatives of neural crest cells (Sontakke — Textbook of Human Embryology, p.245)



## Derivatives of neural crest cells

| Category                     | Derivatives                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skeletal / connective tissue | Bones and connective tissue of the face and skull (craniofacial/branchial skeleton); dermis of face and neck; meninges of the forebrain                                                                                                                                                                                                                                                |
| Dental                       | Odontoblasts                                                                                                                                                                                                                                                                                                                                                                           |
| Cardiovascular               | Conotruncal (aorticopulmonary) septum of the heart; smooth muscle of blood vessels of the face and forebrain                                                                                                                                                                                                                                                                           |
| Endocrine                    | C (parafollicular) cells of the thyroid gland; chromaffin cells of the adrenal (suprarenal) medulla                                                                                                                                                                                                                                                                                    |
| Pigment                      | Melanocytes (one of three pigment-cell lineages, the others — retinal pigment epithelium and pineal pigment cells — being diencephalic in origin)                                                                                                                                                                                                                                      |
| Peripheral nervous system    | Spinal (dorsal root) ganglia; cranial sensory ganglia (proximal neurones — e.g. proximal ganglion of facial, superior ganglion of glossopharyngeal, jugular ganglion of vagus — plus all supporting cells of cranial sensory ganglia); sympathetic chain and pre-aortic ganglia; parasympathetic (including enteric) ganglia of the gastrointestinal tract; Schwann cells; glial cells |

*Distal cranial sensory ganglion neurones (geniculate, petrosal, nodose) instead arise from ectodermal placodes, not the crest — a frequently tested distinction.*

## Applied / Clinical anatomy

- ▶ **Neurocristopathies** — the umbrella term for disorders of neural-crest-derived tissue; illustrates why a single progenitor population can produce multi-system disease.
- ▶ **Neurofibromatosis type 1** (von Recklinghausen disease) — tumours (neurofibromas) of neural-crest-derived peripheral nerve sheath cells.
- ▶ **Waardenburg syndrome types I and II** — autosomal dominant, due to **PAX3** mutation; pigmentary disturbance (heterochromia iridis, white forelock) with sensorineural deafness; **dystopia canthorum** (lateral displacement of medial canthi) distinguishes type I from type II.
- ▶ **Hirschsprung disease** (congenital megacolon) — failure of craniocaudal migration of vagal (and sacral) neural-crest cells into the distal hindgut → an **aganglionic segment** (absent submucosal and myenteric ganglion cells) with loss of peristalsis and functional obstruction; major susceptibility gene is **RET**, with **EDNRB**, **EDN3**, **GDNF** and **NRTN** also implicated.
- ▶ **22q11.2 deletion syndrome** (DiGeorge / velocardiofacial syndrome) — a **cardiac neural crest** defect causing conotruncal cardiac anomalies with thymic and parathyroid hypoplasia and craniofacial dysmorphism.
- ▶ **CHARGE syndrome** — coloboma, heart defects, choanal atresia, growth/developmental retardation, genital and ear anomalies — another multisystem neurocristopathy.



- ▶ **Pheochromocytoma** — tumour of chromaffin (neural-crest-derived) cells of the adrenal medulla.
- ▶ **Charcot-Marie-Tooth disease** — chronic demyelinating peripheral neuropathy involving crest-derived Schwann cells.
- ▶ **Neural tube defects** (anencephaly, craniorachischisis, spina bifida) result from failure of neurulation and are topographically related, since crest cells emerge only at the fusing neural fold tips.
- ▶ Crest-derived malignancies: **neuroblastoma** (sympathetic neuroblasts) and **melanoma** (melanocytes).

### High-yield exam pointers

- ▶ Neural crest = migratory cells at neural fold tips undergoing epithelial-mesenchymal transition; called the "fourth germ layer."
- ▶ Molecular induction: intermediate BMP (via noggin/chordin) + FGF/WNT → PAX3 → SNAIL/FOXD3/SLUG.
- ▶ Cranial crest migrates **before** neural tube closure; trunk crest migrates **after** closure.
- ▶ Craniocaudal regions: cranial, cardiac, vagal, trunk, sacral — cardiac crest forms the conotruncal septum; vagal + sacral crest form enteric ganglia.
- ▶ Two trunk migration routes: dorsolateral → melanocytes; ventral (through rostral sclerotome only) → ganglia/adrenal medulla, explaining segmental ganglion arrangement.
- ▶ Rhombomere : pharyngeal-arch correspondence (r1–2→arch1; r4→arch2; r6→arch3; r7–8→arch4/6) is a favourite short-note/diagram.
- ▶ Distal cranial ganglion neurones (geniculate/petrosal/nodose) are placode-derived, NOT crest-derived — proximal ganglia (jugular etc.) are crest-derived.
- ▶ Key derivatives to reel off: DRG, sympathetic/enteric ganglia, Schwann & glial cells, adrenal medulla, melanocytes, thyroid C cells, craniofacial skeleton, odontoblasts, conotruncal septum, meninges (forebrain).
- ▶ Neurocristopathies to remember with gene: Waardenburg (**PAX3**), Hirschsprung (**RET**), DiGeorge/22q11.2 (cardiac crest), NF1, pheochromocytoma, CHARGE.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Thompson & Thompson Genetics in Medicine 8e; Sontakke — Textbook of Human Embryology; BD Chaurasia Human Anatomy Vol 3–4 8e (cross-reference figure).



## Systemic embryology - respiratory system & body cavities



## Septum transversum

Asked in: Paper II 10-Jul-2023 · Paper II May 2018 · Paper II Oct 2008 (3×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — The septum transversum is a thick, transverse plate of splanchnopleuric mesoderm that appears cranial to the cardiogenic area at the beginning of the fourth week of intrauterine life. After cephalocaudal folding of the embryo it comes to lie as an incomplete horizontal partition between the developing pericardial cavity (cranially) and the peritoneal cavity (caudally), separating the primitive heart from the liver. It is one of the four embryonic components that together build the definitive diaphragm, and its mesenchyme is the primordium of the central tendon of the diaphragm, the connective-tissue/haemopoietic stroma of the liver, and the ventral-mesentery-derived peritoneal ligaments of the liver.

### Origin, timing and positional change

- ▶ Arises from proliferating coelomic epithelium of the ventral body wall/caudal pericardial coelom, forming a mass of mesenchyme cranial to the cardiogenic area (Brijesh Kumar; Gray's Anatomy).
- ▶ **Before head folding** the craniocaudal order of structures is: septum transversum → pericardial cavity/heart → buccopharyngeal membrane → neural tube/notochord → primitive node/streak → connecting stalk with allantois (IB Singh, Table 7.2).
- ▶ **After head folding (~day 24)** the order reverses — the heart and pericardial cavity now lie cranial, and the septum transversum comes to lie caudal to the pericardial cavity, extending from the ventral to the dorsal body wall in the transverse plane (Moore; IB Singh).
- ▶ **Level opposite somites:** during the 4th week the septum transversum lies opposite the 3rd–5th cervical somites (C3–C5); by the 6th–8th week, due to rapid growth of the dorsal part of the embryo (brain, vertebral column) and descent of the heart, it "descends" to lie opposite the thoracic somites (T7–T12), its final thoraco-abdominal position (Vishram Singh; Moore; Langman).
- ▶ Because the myoblasts that populate the diaphragm and the phrenic nerve that supplies it are recruited at this original cervical (C3–C5) level, the **phrenic nerve (root value C3, C4, C5)** is "dragged" caudally with the descending septum transversum, explaining its unusually long (~30 cm) intrathoracic course; it reaches the diaphragm by passing through the pleuropericardial folds/membranes and ends up lying on the fibrous pericardium (Moore; Gray's Anatomy).

### Relations

| Direction             | Structure related                                                                                                                                                          |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cranial               | Primitive pericardial cavity / developing heart                                                                                                                            |
| Caudal                | Peritoneal cavity, vitelline duct                                                                                                                                          |
| Dorsal (on each side) | Pericardioperitoneal (pleuroperitoneal) canals, through which pleural and peritoneal cavities communicate; oesophagus with its dorsal mesentery lies dorsal in the midline |

| Direction          | Structure related                                                                 |
|--------------------|-----------------------------------------------------------------------------------|
| Embedded within it | The endodermal hepatic (liver) bud, which grows into its caudal part              |
| Penetrating it     | Right and left vitelline veins, which break up into the hepatic sinusoidal plexus |

- The septum transversum is **incomplete** — it never separates the thoracic and abdominal cavities completely; the pericardioperitoneal canals persist on each side of the foregut until closed later by the pleuroperitoneal membranes (Gray's Anatomy; Moore).

### Composition of the diaphragm and the septum's contribution

The diaphragm is a composite structure formed from **four embryonic components**, of which the septum transversum is the largest and most central:

| Embryonic component                                      | Adult derivative                                |
|----------------------------------------------------------|-------------------------------------------------|
| 1. Septum transversum                                    | Central tendon of the diaphragm                 |
| 2. Paired pleuroperitoneal membranes                     | Small dorsolateral peripheral part of diaphragm |
| 3. Dorsal mesentery of oesophagus                        | Crura of the diaphragm                          |
| 4. Mesoderm of the lateral body wall (muscular ingrowth) | Large peripheral (costal) part of diaphragm     |

(Table after Vishram Singh — *Clinical Embryology*, Table 17.1; confirmed in Moore and Langman.)

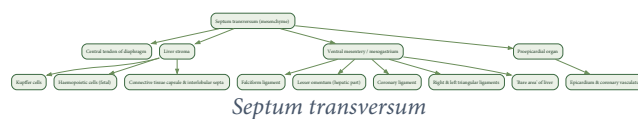
- Several candidate genes on the long arm of chromosome 15 (**15q**, candidate region **15q26**) are implicated in normal diaphragm morphogenesis; disruption here is linked to congenital diaphragmatic hernia (Moore).
- The pleuroperitoneal membranes fuse with the septum transversum and with the dorsal mesentery of the oesophagus by the end of the 6th week to complete the primordial diaphragm; muscle cells from the lateral body wall (9th–12th week) then invade the periphery, external to the pleuroperitoneal-membrane-derived part.

□ Fig 17.5 — Development of abdominothoracic diaphragm. Central tendon of diaphragm develops from septum transversum (Sontakke — *Textbook of Human Embryology*, p.171)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw four transverse/schematic panels (as in the plate above) and label:

- **Embryo, day 28** — plane of section through septum transversum, caudal to pericardial cavity
- **Week 6** — septum transversum; pleuroperitoneal fold; pleuroperitoneal canal; dorsal mesentery of oesophagus; oesophagus; aorta; inferior vena cava
- **Week 7** — muscular ingrowth from body wall; narrowing of pleuroperitoneal canal
- **Week 16** — crura of diaphragm; small peripheral part (from pleuroperitoneal membrane); large peripheral part (from body wall); central part (from septum transversum)

**Derivatives of the septum transversum**

- The **endodermal hepatic diverticulum** grows into the caudal part of the septum transversum and gives rise only to hepatocytes and the intrahepatic biliary epithelium; the **septum transversum mesenchyme itself** differentiates into the Kupffer cells, the fetal haemopoietic cells, and the liver's connective-tissue capsule and interlobular tissue (IB Singh; Gray's Anatomy).
- As the liver enlarges within it, the septum transversum's mesenchyme between the liver and the ventral body wall/foregut is drawn out to form the **ventral mesentery**, whose derivatives are the **falciform ligament** (carrying the left umbilical vein in its free edge), the hepatic part of the **lesser omentum**, the **coronary ligament**, and the **right and left triangular ligaments**; the area of liver enclosed between the two layers of the coronary ligament (devoid of peritoneum) is the "**bare area**" of the liver, where loose areolar tissue of septum-transversum origin persists (Gray's Anatomy; IB Singh).
- Vitelline and umbilical veins running longitudinally within the septum transversum are broken up by the invading hepatic cords to form the **hepatic sinusoids**; the persisting channel becomes part of the hepatocardiac (terminal/suprahepatic) segment of the inferior vena cava (Gray's Anatomy; IB Singh).
- A special group of splanchnic mesodermal cells at the septum transversum/dorsal mesocardium junction — the **proepicardial organ** (expressing Wt1 and Tbx18) — migrates over the myocardial surface to form the **epicardium and the coronary vasculature** (Larsen).

**Applied / Clinical anatomy**

- **Congenital diaphragmatic hernia (CDH)**: the commonest and most important applied correlate. Defective formation/fusion of the pleuroperitoneal membrane with the other three diaphragmatic components (including the septum transversum) leaves a **posterolateral defect (foramen of Bochdalek)**, occurring in about 1 in 2,000–2,200 live births; 85–90% are left-sided (right pleuroperitoneal canal closes earlier). Abdominal viscera (stomach, intestines, spleen, liver) herniate into the thorax, compressing the developing lung and causing **pulmonary**

**hypoplasia** — the principal cause of neonatal death in CDH. The candidate genetic region is 15q26.

- ▶ **Eventration of the diaphragm:** failure of myoblasts from the body wall to invade the pleuroperitoneal membrane on one side leaves an intact but muscle-deficient, ballooning aponeurotic sheet; not a true hernia but can mimic CDH clinically.
- ▶ **Retrosternal (parasternal) hernia / foramen of Morgagni:** a small hernia through the sternocostal hiatus (site for the superior epigastric vessels), anatomically distinct from a septum-transversum defect but classically grouped with diaphragmatic developmental hernias.
- ▶ **Congenital pericardial defect:** failure of fusion of the pleuropericardial membranes (which also fuse with the septum transversum-related mediastinum) leaves the pericardial cavity communicating with the pleural cavity, occasionally allowing herniation of the left atrium.
- ▶ **Congenital hiatal hernia:** an abnormally large oesophageal hiatus in the septum-transversum-derived crural/central region may predispose to herniation of the stomach.
- ▶ **Surgical significance of the "bare area":** because it lacks peritoneal covering, it is a site where hepatic abscess/malignancy can directly reach the retroperitoneum/right suprarenal gland, and where subphrenic collections may track; the falciform ligament (a septum-transversum/ventral-mesentery derivative) is used radiologically as a landmark for pneumoperitoneum on erect abdominal X-rays.
- ▶ **Referred pain:** since the phrenic nerve (C3, C4, C5) supplies the central tendon derived from the septum transversum, irritation of the central diaphragm (subphrenic abscess, gallbladder/liver disease near the bare area) classically refers pain to the C3/C4 dermatome — the tip of the shoulder.

## High-yield exam pointers

- ▶ Septum transversum = mesenchymal plate cranial to cardiogenic area (4th week) → becomes the **central tendon of the diaphragm**.
- ▶ Diaphragm has **4 embryonic components**: septum transversum, paired pleuroperitoneal membranes, dorsal mesentery of oesophagus, body-wall mesoderm.
- ▶ Lies opposite **C3–C5 somites** at 4 weeks; descends to T7–T12 by 6th–8th week — explains the long course and cervical (C3,4,5) root value of the phrenic nerve.
- ▶ Liver's **hepatocytes/bile duct epithelium** = endoderm (hepatic diverticulum); liver's **Kupffer cells, haemopoietic tissue, capsule** = septum transversum mesenchyme.
- ▶ Ventral mesentery from septum transversum → **falciform ligament, coronary ligament, triangular ligaments, "bare area", lesser omentum** (hepatic part).
- ▶ Candidate gene region **chromosome 15q26** linked to congenital diaphragmatic hernia (CDH).
- ▶ CDH is a **posterolateral (Bochdalek) defect**, ~1/2,000–2,200 births, **85–90% left-sided**; causes pulmonary hypoplasia.
- ▶ Proepicardial organ (septum transversum/mesocardium junction) gives rise to the **epicardium and coronary vessels**.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas.

**Coelomic cavities**

*Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **intraembryonic coelom** is a single, horseshoe-shaped cavity that appears within the lateral plate mesoderm during the third–fourth week of intrauterine life (IUL) and gives rise to all three definitive **serous body cavities** — the **pericardial, pleural, and peritoneal cavities**. It arises by splitting of the lateral plate mesoderm into an outer **somatopleuric (parietal)** layer and an inner **splanchnopleuric (visceral)** layer, which later form the parietal and visceral layers of the serous membranes. Development of the coelomic cavities is therefore a two-step process: (1) **formation** of the single intraembryonic coelom, and (2) its **partitioning** into three separate cavities by paired pleuropericardial membranes and the diaphragm. This is high-yield embryology because it directly explains the pathogenesis of congenital diaphragmatic hernia, the course of the phrenic nerve, and the relations of the mediastinal septa.

**1. Formation of the intraembryonic coelom**

- ▶ At and just before **Carnegie stage 9** (before head-fold formation), intercellular clefts/vesicles appear in the lateral plate mesenchyme cranial to the buccopharyngeal membrane; these become confluent to form a **horseshoe-shaped tube**, the intraembryonic coelom, extending caudally to the level of the first somite and laterally toward the extraembryonic mesenchyme.
- ▶ This splits the lateral plate mesoderm into: **somatopleuric (parietal) layer** — adjacent to ectoderm, continuous with extraembryonic somatic mesoderm; and **splanchnopleuric (visceral) layer** — adjacent to endoderm, continuous with extraembryonic splanchnic mesoderm covering the yolk sac.
- ▶ At this stage the intra- and extraembryonic coeloms **do not communicate**.
- ▶ With **head-fold formation**, the flat horseshoe cavity is remodelled: its midline part (originally rostral to the buccopharyngeal membrane) swings ventrally to lie **ventral to the foregut** — this becomes the **pericardial cavity**; its two caudal limbs turn 90° to lie **lateral to the foregut** and now communicate with the extraembryonic coelom **ventrally**.
- ▶ By **stage 11**, the coelom extends caudally to the level of the caudal wall of the yolk sac, and the intra- and extraembryonic coeloms **communicate widely** on each side of the midgut, from the level of the fourth somite.
- ▶ Functionally, before the vascular system takes over, the coelomic fluid (propelled from stage 10 by the first heartbeats) provides a primitive circulation carrying nutrients to the deeper mesenchyme — important up to about stage 13.

## 2. Primary compartments of the single coelom (before partitioning)

Even before any partition develops, three future compartments are already recognisable within the horseshoe-shaped coelom:

| Part of primitive coelom                                                                                                           | Position                   | Becomes                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------|
| <b>Median/central part</b> (pericardial bar), ventral to foregut, between stomodeum (cranially) and septum transversum (caudally)  | Midline, ventral           | <b>Pericardial cavity</b>                                                 |
| <b>Pericardioperitoneal canals</b> — paired canals lateral to the foregut connecting the pericardial part with the peritoneal part | Paired, lateral to foregut | <b>Pleural cavities</b> (and transiently the uppermost peritoneal cavity) |
| <b>Caudal horseshoe limbs</b> , which fuse in the ventral midline on lateral folding                                               | Caudal, paired → fused     | <b>Peritoneal cavity</b>                                                  |

- ▶ On **lateral body folding**, the two caudal limbs of the coelom are brought together ventrally and fuse in the midline to form a **single peritoneal cavity**.
- ▶ The **septum transversum** (a thick plate of mesoderm derived from splanchnic mesoderm around the developing heart) lies between the pericardial cavity cranially and the peritoneal cavity caudally, but it does **not** completely separate them — it leaves the paired pericardioperitoneal canals open on each side of the foregut.

## 3. Partitioning into the three definitive cavities

Two partitions convert the single coelom into three separate serous cavities: (a) paired **pleuropericardial membranes**, separating the pericardial from the pleural cavity; and (b) the **diaphragm** (septum transversum + pleuroperitoneal membranes + dorsal mesentery of oesophagus + body-wall mesoderm), separating the pleural from the peritoneal cavity.

### Stages in separating the pericardial and pleural cavities

- ▶ **Lung-bud invagination**: the paired lung buds (from the tracheal part of the laryngotracheal diverticulum) grow laterally into the pericardioperitoneal canals.
- ▶ **Enlargement**: as the lung buds enlarge, the canals expand to accommodate them, becoming the primitive pleural cavities.
- ▶ **Fold formation**: two ridges of somatopleuric mesoderm appear in the lateral wall of each canal — a **cranial pleuropericardial fold**, above the lung bud, and a **caudal pleuroperitoneal fold**, below it; both become continuous with the posterior border of the septum transversum.
- ▶ **Closure**: during the **sixth week**, the pleuropericardial opening closes as the pleuropericardial membrane (carrying the common cardinal vein and phrenic nerve — the "pulmonary ridge of Mall") fuses with the mesodermal tissue around the oesophagus.
- ▶ With continued expansion of the pleural cavity, the body-wall mesoderm splits into an outer layer (definitive thoracic wall) and an inner layer, the pleuropericardial membrane, which

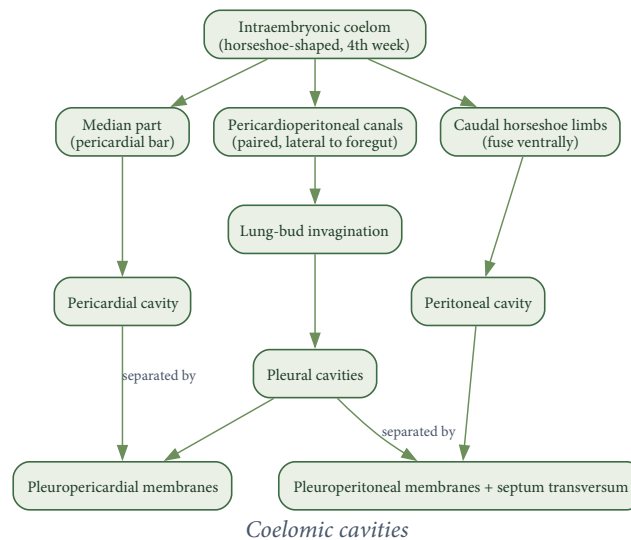


becomes the **fibrous pericardium** — hence the phrenic nerve runs over the fibrous pericardium in the adult.

#### Stages in separating the pleural and peritoneal cavities

- The **pleuroperitoneal fold/membrane** grows medially into the caudal end of the pericardioperitoneal canal; its boundaries are: ventrally, the dorsal border of the septum transversum; medially, the oesophagus with its dorsal mesentery and the dorsal aorta; dorsally, the mesonephric ridge with the gonad; laterally, the pleuroperitoneal membrane itself.
- The membrane grows ventrally to fuse with the dorsal border of the septum transversum and the dorsal mesentery of the oesophagus, closing the **pleuroperitoneal opening** — completed together with the diaphragm (below).

□ Fig 17.2 — Formation of coelomic cavities of body: cranial pleuropericardial membrane separates the pericardial cavity from the pleural cavity, and caudal pleuroperitoneal membrane separates the pleural cavity from the peritoneal cavity, both becoming continuous with the posterior border of the septum transversum (Sontakke — Textbook of Human Embryology, p.168)



#### 4. Development of the diaphragm — completing the pleural/peritoneal separation

The diaphragm is a composite musculotendinous partition derived from **four** embryonic sources:

| Part of diaphragm                   | Embryonic source                   |
|-------------------------------------|------------------------------------|
| Central tendon                      | Septum transversum                 |
| Crura (right and left)              | Dorsal mesentery of the oesophagus |
| Small dorsal peripheral part        | Pleuroperitoneal membranes         |
| Large ventrolateral peripheral part | Mesoderm of the lateral body wall  |

- The liver develops in the caudal part of the septum transversum, while its cranial part forms the central tendon.
- **Descent:** in the 4th week the septum transversum lies in the cervical region opposite somites C3–C5 (hence the **phrenic nerve**, root value C3, C4, C5, supplies the diaphragm); by the 6th week the diaphragm reaches its definitive thoraco-abdominal position opposite T7–T12 spinal segments, carrying its nerve supply caudally with it.

- ▶ Factors producing descent: elongation of the neck (pharyngeal-arch growth), enlargement of the pleural cavities, and growth/descent of the heart.

## 5. Fate and relations of the three definitive cavities

- ▶ **Pericardial cavity:** derived from the median pericardial bar; its wall (fibrous pericardium + parietal/visceral serous pericardium) forms from somatopleuric and splanchnopleuric mesoderm respectively.
- ▶ **Pleural cavities:** derived from the right and left pericardioperitoneal canals after lung-bud invagination; separated from the pericardial cavity by the pleuropericardial membrane and from the peritoneal cavity by the pleuroperitoneal membrane/diaphragm.
- ▶ **Peritoneal cavity:** the largest of the three; formed by fusion of the caudal horseshoe limbs on lateral folding. It communicates widely with the **extraembryonic coelom at the umbilicus** (site of physiological midgut herniation) until this connection is lost around the **10th week**, once the midgut loop returns to the abdomen.

## 6. Serous membranes and mesenteries

- ▶ The **somatopleuric (parietal)** layer of each cavity's wall differentiates into a mesothelial **parietal layer** of the serous membrane (parietal pericardium, parietal pleura, parietal peritoneum).
- ▶ The **splanchnopleuric (visceral)** layer differentiates into the **visceral layer** (epicardium, visceral pleura, visceral peritoneum) covering the corresponding viscus.
- ▶ The two layers remain continuous at the root of each organ; in the abdomen this line of reflection constitutes the **mesenteries** (dorsal and ventral), which convey the neurovascular supply of the gut and, through subsequent gut rotation, give rise to structures such as the greater/lesser omenta and the lesser sac (omental bursa).

## Applied / Clinical anatomy

- ▶ **Congenital diaphragmatic hernia (CDH)** — the single most important applied point: herniation of abdominal viscera into the thoracic cavity due to failure of the diaphragm to form completely.
  - **Bochdalek hernia** (posterolateral, foramen of Bochdalek — failed pleuroperitoneal membrane fusion) accounts for ~95% of CDH and is **more common on the left (85–90%)**, as the right pleuroperitoneal canal closes earlier.
  - Incidence ~1 in 2000 births; herniated bowel/stomach/spleen compress the lung causing **pulmonary hypoplasia** (commonest cause of death), with **breathlessness, cyanosis, and a flat (scaphoid) abdomen** as cardinal signs; genetic association — microdeletion of chromosome 15q26.
- ▶ **Morgagni (retrosternal) hernia:** through the foramen of Morgagni (between sternal and costal slips) — intestine may enter the pericardial sac, or the heart may prolapse caudally.
- ▶ **Congenital hiatus hernia:** fetal stomach herniates through an abnormally wide oesophageal hiatus; predisposes to acquired hiatal hernia later.
- ▶ **Eventration of the diaphragm:** a thin, non-muscularised hemidiaphragm balloons upward from failed myoblast migration into the pleuroperitoneal membrane — mimics CDH but is not a true hernia.

- ▶ **Ectopia cordis / Cantrell's pentalogy:** failure of lateral body-wall (pericardial coelom) folds to close leaves the heart outside the thorax, sometimes with an associated anterior diaphragmatic defect, pericardial and sternal defects, and omphalocele.
- ▶ The **peritoneal cavity's** transient umbilical communication with the extraembryonic coelom is the basis of **physiological umbilical herniation (6th–10th week)** and its failure of return (**omphalocele**).
- ▶ **Mesothelioma/serous effusions** arise from the mesothelial linings — direct derivatives of the somatopleuric/splanchnopleuric coelomic epithelium.

### High-yield exam pointers

- ▶ Intraembryonic coelom = single horseshoe-shaped cavity in lateral plate mesoderm (3rd–4th week) → splits mesoderm into somatopleuric and splanchnopleuric layers.
- ▶ Median part → **pericardial cavity**; paired pericardioperitoneal canals → **pleural cavities**; fused caudal limbs → **peritoneal cavity**.
- ▶ Two partitions complete the division: **pleuropericardial membranes** (pericardial/pleural) and **diaphragm** = septum transversum + pleuroperitoneal membranes + dorsal mesentery of oesophagus + body-wall mesoderm (pleural/peritoneal).
- ▶ Pleuropericardial opening closes by the **6th week**; pleuropericardial membrane later forms the **fibrous pericardium** (carries the phrenic nerve).
- ▶ Diaphragm derivation table (central tendon–septum transversum; crura–dorsal mesentery of oesophagus; small peripheral part–pleuroperitoneal membranes; large peripheral part–body-wall mesoderm) is a favourite short-note/MCQ stem.
- ▶ Phrenic nerve root value **C3, C4, C5** — because the septum transversum starts at the cervical level and is later dragged caudally to T7–T12.
- ▶ **CDH = Bochdalek hernia (95%, left side 85–90%) due to failed pleuroperitoneal membrane fusion**; three cardinal signs — breathlessness, cyanosis, flat abdomen; chromosome **15q26** deletion.
- ▶ Peritoneal cavity loses its communication with the extraembryonic coelom (umbilicus) by the **10th week**, after midgut return — basis of physiological umbilical hernia and omphalocele.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw a transverse section through a 5th-week embryo at the level of the developing lungs/foregut, with these exact labels:

- ▶ Foregut/oesophagus in the midline, flanked by the **pericardioperitoneal canal** on each side.
- ▶ Lung bud invaginating into the canal.
- ▶ Cranial pleuropericardial fold (membrane) — labelled clearly separating the **pericardial cavity** (ventral) from the developing **pleural cavity**.
- ▶ Caudal pleuroperitoneal fold (membrane) — separating the **pleural cavity** from the **peritoneal cavity** (caudal/ventral).
- ▶ Septum transversum, shown as the structure with which both membranes become continuous posteriorly.
- ▶ Outer **body wall** and the phrenic nerve running within the pleuropericardial membrane.
- ▶ Label the final three compartments distinctly: **pericardial cavity**, **right/left pleural cavity**, **peritoneal cavity**.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Langman's Medical Embryology (Sadler) 14e.



# Development of the Lungs, and the Features of Fibrocystic Lung Disease

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The lungs develop from a single midline **respiratory (laryngotracheal) diverticulum** budding from the ventral foregut endoderm in the 4th week of intrauterine life (IUL); it bifurcates into right and left lung buds and matures through a sequence of histological phases — embryonic, pseudoglandular, canalicular, saccular and alveolar — culminating in an organ capable of extra-uterine gas exchange. The epithelial lining of the respiratory tree (trachea to alveoli) is endodermal; the surrounding splanchnopleuric mesenchyme forms cartilage, smooth muscle, connective tissue, visceral pleura and pulmonary vasculature. Errors at any stage underlie most congenital and neonatal respiratory disorders. **Fibrocystic disease of the lung (cystic fibrosis, CF)** is an autosomal recessive exocrinopathy of the CFTR chloride channel; though not a disorder of morphogenesis, its lethal manifestations occur in this same endodermally-derived epithelium, and it is discussed after the developmental stages.

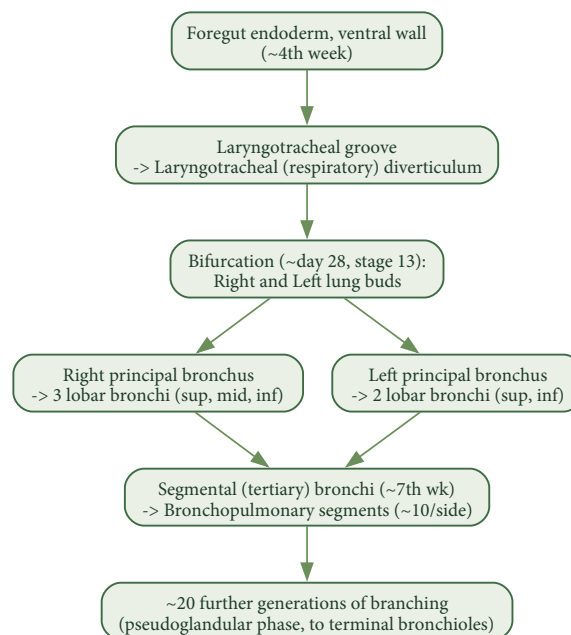
## 1. Formation of the respiratory diverticulum and lung buds

- ▶ At approximately **4 weeks (Carnegie stage 12, ~day 26)**, a sharp focus of epithelial proliferation appears in the ventral wall of the foregut endoderm — the **laryngotracheal groove**, lying just caudal to the hypobranchial eminence.
- ▶ The groove deepens into the **laryngotracheal (respiratory) diverticulum**, which grows caudally into the surrounding splanchnopleuric mesenchyme.
- ▶ Two **tracheo-oesophageal folds** arise on either side of the diverticulum and fuse craniocaudally to form the **tracheo-oesophageal septum**, partitioning the foregut into a ventral respiratory primordium and a dorsal oesophagus; incomplete fusion produces a **tracheo-oesophageal fistula (TEF)**.
- ▶ By **stage 13 (~day 28, end of 4th–early 5th week)**, the caudal end of the diverticulum divides asymmetrically into **right and left lung buds** (the right bud oriented more caudally, the left more transversely) — the primordia of the two principal bronchi.
- ▶ The lung buds grow dorsolaterally on either side of the oesophagus and bulge into the **pericardioperitoneal canals**.
- ▶ Molecular control: **TBX4** (pharyngeal mesenchyme) specifies lung-bud outgrowth; **FGF-10/FGFR2IIIb**, modulated by **Sonic hedgehog** and **TGF- $\beta$ /BMP-4**, drives and patterns dichotomous branching.

## 2. Branching morphogenesis of the bronchial tree, and the pleura

- ▶ Each lung develops by repeated **dichotomous branching**: a cleft forms in the tip of the epithelial tube, the epithelium evaginates on each side, and the process repeats — controlled by the investing splanchnopleuric mesenchyme.
- ▶ The **right principal bronchus** divides into three lobar (secondary) bronchi (superior, middle, inferior); the **left principal bronchus** divides into two (superior, inferior) — established by the 5th week.

- **Segmental (tertiary) bronchi** appear by the **7th week**, each with its own cone of splanchnopleuric mesenchyme, giving rise to the **bronchopulmonary segments** (classically ten in each lung).
- By the end of the pseudoglandular phase (~17 weeks), the airway has undergone about **20 generations** of dichotomous division and the future bronchial-tree pattern is essentially complete; a further 6–7 generations are added after birth.
- **Pleura**: as the lung buds expand into the pericardioperitoneal canals, the splanchnopleuric mesothelium investing the lung differentiates into **visceral pleura**, while the somatopleuric lining of the canal forms **parietal pleura**; pleuropericardial and pleuroperitoneal membranes separate the canal from the pericardial and peritoneal cavities to complete the definitive **pleural cavities**.



*Development of the Lungs, and the Features of Fibrocystic Lung Disease*

### 3. Histological (maturation) stages of lung development

Lung maturation is classically divided into four or five overlapping phases, defined histologically:

| Phase           | Duration  | Key events                                                                                                                                            |
|-----------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Embryonic phase | 0–7 weeks | Formation of respiratory diverticulum, lung buds, principal/lobar bronchi, and the primary pulmonary vasculature (from the 6th aortic arch arteries). |

| Phase                          | Duration                                                          | Key events                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pseudoglandular period         | 5–17 weeks (Gray's 41e); classically 5/6–16 weeks (Langman/Moore) | Airway branching virtually complete down to terminal bronchioles (~20 generations); lung resembles a branching exocrine gland histologically (hence the name); epithelium cuboidal; cartilage, smooth muscle and mucous glands differentiate; <b>fetus is NOT viable if born now</b> — no respiratory bronchioles or alveoli yet.                                                        |
| Canalicular period             | 17–27 weeks (Gray's); 16–26 weeks (Langman)                       | Terminal bronchioles divide into <b>respiratory bronchioles</b> , which give off a few <b>alveolar ducts</b> ; capillary network proliferates and comes into close apposition with the airway epithelium; cuboidal epithelium differentiates into flat <b>type I</b> and rounded <b>type II pneumocytes</b> . A fetus born late in this period may survive with intensive neonatal care. |
| Saccular (terminal sac) period | 28 weeks–term (Gray's); 24/26 weeks–birth (Langman/Moore)         | Thin-walled <b>terminal saccules</b> form at the ends of alveolar ducts; secondary crests grow into the saccules, drawing in capillary loops and subdividing them; interstitial tissue thins further; elastin is laid down beneath the epithelium; surfactant secretion by type II cells matures.                                                                                        |
| Alveolar period                | Late fetal period – ~8 years                                      | Terminal saccules mature into definitive, thin-walled <b>alveoli</b> by further secondary septation; the great majority of alveoli form <b>postnatally</b> , increasing most rapidly in the first 6 months–2 years and reaching the adult complement by about <b>8 years of age</b> .                                                                                                    |

(Ranges differ slightly between the spine text, Gray's Anatomy 41e, and the classic Langman/Moore scheme; both are acceptable in the RGUHS exam — the sequence and the histological hallmark of each phase are what is tested.)

□ Fig 11.3 — Histologic Stages of Normal Human Lung Development: (A) Canalicular stage. (B) Saccular stage. (C) Alveolar stage (Larsen — Human Embryology — 6e, p.626)



**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Draw three labelled histological panels side by side (canalicular → saccular → alveolar), each showing:

- ▶ Respiratory bronchiole / alveolar duct lumen
- ▶ Surrounding mesenchyme (progressively decreasing in amount across the three panels)
- ▶ Lining epithelium — cuboidal (canalicular) → flattening, type I and type II cells appearing (saccular) → thin squamous type I cells with interspersed type II cells (alveolar)
- ▶ Capillary network — single capillary plexus (canalicular) → double capillary layer within secondary septa/crests (saccular–alveolar)
- ▶ Secondary septa/crests subdividing the saccule into alveoli (saccular→alveolar transition)
- ▶ Label the forming **blood–air (alveolo–capillary) barrier** where capillary and thin type I epithelium are directly apposed.

**4. Surfactant system and the alveolo-capillary membrane**

- ▶ **Type II pneumocytes** differentiate from primitive cuboidal cells during the canalicular phase; they contain **lamellar bodies**, the intracellular storage form of **surfactant**, and act as the stem cell of the alveolar epithelium (capable of dividing and re-differentiating into type I cells).
- ▶ Surfactant secretion is detectable from about **20 weeks** and increases progressively towards term; it lowers alveolar surface tension and prevents alveolar collapse at end-expiration.
- ▶ **Type I pneumocytes** are thin, flat, non-dividing cells that come into direct apposition with capillary endothelium, forming the thin **blood–air (alveolo–capillary) barrier** essential for gas exchange.
- ▶ **Sexual dimorphism**: androgens delay surfactant maturation in male fetuses (type II cells mature later than in females during the canalicular phase), which is the biological basis for preterm males having a higher incidence and severity of respiratory distress than females of comparable gestation.
- ▶ Clinically, **antenatal corticosteroids** given to the mother in a threatened preterm labour accelerate fetal surfactant production and reduce the incidence of neonatal hyaline membrane disease.

**5. Fibrocystic lung disease (Cystic Fibrosis)**

- ▶ **Inheritance**: cystic fibrosis (CF) is an **autosomal recessive** disorder — disease occurs only when a defective allele is inherited from each parent; it is the prototype example of autosomal recessive inheritance in the standard genetics/embryology curriculum.
- ▶ **Gene**: the defect lies in the **CFTR (cystic fibrosis transmembrane conductance regulator)** gene, located on the **long arm of chromosome 7**; CFTR normally functions as a cAMP-regulated epithelial **chloride channel**, and its commonest mutation worldwide is the three-base-pair deletion  $\Delta F508$ .
- ▶ **Pathogenesis**: loss of CFTR chloride-channel function reduces  $\text{Cl}^-$  secretion and causes secondary  $\text{Na}^+$ /water hyperabsorption across affected epithelia, producing **abnormally thick**,

viscid mucus from exocrine and mucus-secreting cells — most prominently in the **respiratory and gastrointestinal tracts**.

- ▶ **Respiratory ("fibrocystic" lung) features:** thick airway mucus impairs mucociliary clearance → **recurrent/chronic infections** (*Staphylococcus aureus* in infancy, *Pseudomonas aeruginosa* with progression) → progressive **bronchiectasis**, chronic bronchitis and peribronchial fibrosis — the dilated, mucus-plugged, fibrotic/cystic airways that give the disease its "**fibrocystic**" name (bronchial thickening, cystic bronchiectasis, honeycombing on HRCT) → **cor pulmonale** and **respiratory failure**, the chief cause of CF mortality.
- ▶ **Extra-pulmonary features:** **meconium ileus** (thick meconium obstructing the terminal ileum) is often the **earliest clinical sign**; **exocrine pancreatic insufficiency** causes malabsorption/steatorrhoea/failure to thrive; **congenital bilateral absence of the vas deferens (CBAVD)** occurs because CFTR is required for mesonephric-duct (vas deferens) development, causing obstructive azoospermia in most affected males; and **elevated sweat chloride** underlies the diagnostic sweat test.

## Applied / Clinical anatomy

- ▶ **Pulmonary agenesis/aplasia/hypoplasia:** complete failure, or a rudimentary airway stump with no distal lung tissue, respectively, with compensatory enlargement of the contralateral lung. Bilateral **pulmonary hypoplasia** follows restricted thoracic space or fetal breathing movements — congenital diaphragmatic hernia and oligohydramnios/renal agenesis (Potter sequence).
- ▶ **Tracheo-oesophageal fistula (TEF):** failure of complete tracheo-oesophageal septation; commonest variant is proximal oesophageal atresia with a fistula from the distal segment to the trachea — polyhydramnios antenatally, choking/cyanosis with feeds postnatally.
- ▶ **Azygous lobe (lobe of Wrisberg):** accessory lobe of the right upper lobe demarcated by a vertical fissure containing the azygos vein — commonest accessory lung lobe, an incidental radiological finding.
- ▶ **Congenital cystic/sequestered lung lesions:** bronchopulmonary sequestration (embryonic tissue separated from the tracheobronchial tree, anomalous systemic arterial supply) and congenital polycystic lung (honeycomb radiographic pattern).
- ▶ **Hyaline membrane disease/IRDS:** surfactant deficiency in preterm infants causes alveolar collapse, tachypnoea and cyanosis; prevented/treated with antenatal glucocorticoids and postnatal surfactant replacement.
- ▶ **Medicolegal application:** a live-born infant's lungs float in water (air-containing); a stillbirth's do not — the hydrostatic (lung-flotation) test.

## High-yield exam pointers

- ▶ Lungs arise from a single **respiratory (laryngotracheal) diverticulum** off the ventral foregut endoderm at the **4th week**; bifurcates (~stage 13) into right and left lung buds.
- ▶ Epithelial lining of the whole respiratory tree is **endodermal**; cartilage/muscle/connective tissue/vasculature are **splanchnopleuric mesenchymal**.
- ▶ Right principal bronchus → 3 lobar bronchi; left → 2; segmental bronchi (~7th week) → **bronchopulmonary segments** (~10/lung).

- Five histological maturation phases: **Embryonic (0–7wk)** → **Pseudoglandular (5–17wk)** → **Canalicular (17–27wk)** → **Saccular/terminal sac (28wk–term)** → **Alveolar (term–8yr)**.
- **Type II pneumocytes** appear in the canalicular phase and make **surfactant**; viability threshold is around the canalicular–saccular transition (~24 weeks) when respiratory bronchioles/alveolar ducts first appear.
- Alveolar multiplication is predominantly **postnatal**, essentially complete by ~8 years.
- Failure of tracheo-oesophageal septation → **TEF**; failure of diaphragm closure/oligohydramnios → **pulmonary hypoplasia**.
- **Fibrocystic lung disease = Cystic Fibrosis**: autosomal recessive, **CFTR** gene on **chromosome 7**, defective  $\text{Cl}^-$  channel (commonly  $\Delta\text{F508}$ ) → thick mucus → **bronchiectasis + recurrent infection** (fibrocystic lung), **meconium ileus**, pancreatic insufficiency, **CBAVD**, raised **sweat chloride**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Sontakke — Textbook of Human Embryology; Brijesh Kumar — Embryology Text & Atlas; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021).

**Coverage note:** the embryology corpus confirms CF as autosomal recessive, the CFTR–chromosome 7 locus, thick mucus obstruction of respiratory/GI epithelium, meconium ileus as an early sign, and CFTR's role in vas deferens development (hence CBAVD). The  $\Delta\text{F508}$  mutation, the chloride-channel mechanism, *Pseudomonas* colonisation and the sweat-chloride test reflect standard, universally-taught genetics/clinical-medicine knowledge rather than verbatim embryology-corpus text, since fibrocystic-lung clinical detail is only thinly covered in the anatomy/embryology library itself.



## Development of respiratory system

Asked in: Paper II 08-Apr-2026 — RGUHS MD/MS Anatomy

**Definition / Introduction** The respiratory system develops from the **respiratory (laryngotracheal) diverticulum**, a midline ventral outgrowth of the **foregut endoderm** that appears at the end of the 4th week of intrauterine life, caudal to the hypobranchial eminence. The **endoderm** of this diverticulum gives rise to the entire epithelial lining and glands of the larynx, trachea, bronchi and alveoli, while the surrounding **splanchnic (visceral) mesoderm** forms the cartilages, smooth muscle, connective tissue and pleura. Development proceeds through septation of the diverticulum from the oesophagus, dichotomous branching of the bronchial tree, and four histological periods of parenchymal maturation that continue up to 8 years after birth.

### 1. Formation of the laryngotracheal groove and lung buds

- At about day 26–28 (4th week), a **laryngotracheal groove** appears in the floor of the primitive pharynx, just caudal to the hypobranchial eminence.

- ▶ The groove deepens into a **laryngotracheal tube (diverticulum)**, which grows caudally in the splanchnic mesenchyme ventral to the foregut.
- ▶ The diverticulum bifurcates into **right and left lung buds**.
- ▶ **Molecular regulation:**
  - **Retinoic acid** from adjacent mesoderm upregulates **TBX4** in the gut-tube endoderm at the site of the diverticulum — TBX4 induces bud formation and drives subsequent lung growth/differentiation.
  - **FGF10** (fibroblast growth factor) from the splanchnic mesenchyme signals outgrowth of the tracheal/lung bud; FGF-family signals from mesoderm also drive later branching.
  - **Sonic hedgehog (SHH)**–GLI signalling mediates the epithelial–mesenchymal interaction that governs branching of the tracheal bud.

## 2. Separation of the trachea from the oesophagus

- ▶ On either side of the laryngotracheal tube, two **tracheo-oesophageal ridges (folds)** appear; their fusion forms the **tracheo-oesophageal septum**, dividing the foregut into a dorsal **oesophagus** and a ventral **trachea + lung buds**.
- ▶ Cranial extension of this septum is arrested at the laryngeal inlet (**furcula of His**), so the larynx retains its communication with the pharynx through the **laryngeal orifice**.
- ▶ Failure of complete fusion of the tracheo-oesophageal septum underlies **oesophageal atresia and tracheo-oesophageal fistula** (see Applied anatomy).

□ Fig 14.2 — Successive stages in development of the respiratory diverticulum (lung bud): tracheo-oesophageal ridges fuse to form the septum, splitting the foregut into oesophagus (dorsal) and trachea with bronchial buds (ventral) (Langman's Medical Embryology — Sadler — 14e, p.243)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled sagittal/coronal schematic of the 4th–5th week foregut region, showing:

- ▶ Primitive pharynx and hypobranchial eminence
- ▶ Laryngotracheal groove (floor of pharynx)
- ▶ Laryngotracheal tube (diverticulum) growing caudally
- ▶ Paired tracheo-oesophageal ridges/folds
- ▶ Tracheo-oesophageal septum (after fusion of folds)
- ▶ Oesophagus (dorsal) versus trachea (ventral)
- ▶ Right and left lung buds at the caudal end
- ▶ Laryngeal orifice/furcula of His (site where septation is arrested)

## 3. Development of the larynx

- ▶ The **laryngeal orifice** is a sagittal slit at 4 weeks; rapid mesenchymal proliferation of the 4th and 6th arches converts it into a **T-shaped opening** by 6 weeks, acquiring the adult shape by 12 weeks as the cartilages differentiate.

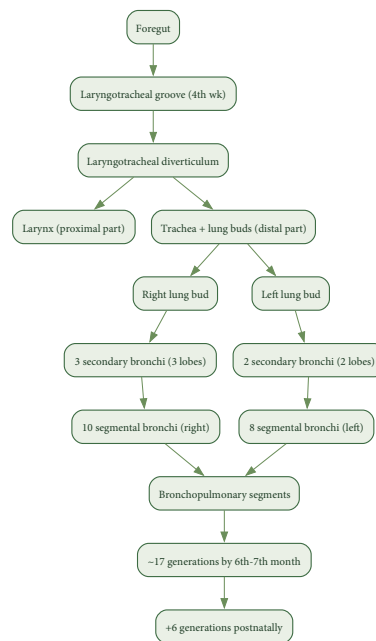
- Endodermal proliferation transiently occludes the laryngeal lumen; subsequent **vacuolisation and recanalisation** create a pair of lateral recesses (**laryngeal ventricles**) bounded by proximal (**vestibular/false vocal**) and distal (**vocal/true vocal**) folds.

| Component                                                        | Embryological source                                                                                                                          |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Mucosa (lining epithelium)                                       | Endoderm of proximal laryngotracheal tube                                                                                                     |
| Vestibular and vocal folds                                       | Endodermal folds of the laryngotracheal tube                                                                                                  |
| Cartilages (thyroid, cricoid, arytenoid, corniculate, cuneiform) | 4th and 6th pharyngeal arch mesenchyme                                                                                                        |
| Epiglottis                                                       | Hypobranchial eminence (fused ventral part of 3rd/4th arches)                                                                                 |
| Intrinsic muscles                                                | 6th arch (all) except cricothyroid — 4th arch                                                                                                 |
| Motor nerve supply                                               | Recurrent laryngeal nerve (6th arch) for all muscles except cricothyroid, by external laryngeal branch of superior laryngeal nerve (4th arch) |
| Sensory supply                                                   | Above vocal fold — internal laryngeal branch of superior laryngeal nerve; below vocal fold — recurrent laryngeal nerve                        |

#### 4. Development of the trachea, bronchi and lungs

- The **trachea** forms from the part of the laryngotracheal tube between the larynx and the point of bifurcation; its lining epithelium/glands are endodermal, its cartilage/muscle/connective tissue splanchnic-mesodermal.
- At the **beginning of the 5th week**, the bifurcation forms **right and left principal (primary) bronchi**.
- **Right principal bronchus** → 3 **secondary (lobar) bronchi** (foreshadowing 3 lobes); **left principal bronchus** → 2 **secondary (lobar) bronchi** (foreshadowing 2 lobes).
- Repeated **dichotomous branching** of secondary bronchi produces **tertiary (segmental) bronchi** — **10 on the right, 8 on the left**; each segmental bronchus with its investing splanchnopleuric mesenchyme forms one **bronchopulmonary segment**.
- Branching continues to give ~**17 orders (generations)** of subdivisions by the end of the 6th–7th month in utero, with a further ~**6 generations added after birth** before the adult bronchial tree is complete.
- Branching is regulated by reciprocal endoderm–mesenchyme signalling (FGF/SHH pathways above); the mesenchymal "template" laid down in this period determines lobar/segmental pattern and eventual alveolar number.
- **Precise Carnegie-stage correlation** (Gray's Anatomy): tracheal outgrowth begins at stage 12; lung buds bulge into the pericardioperitoneal canals by stage 13–15; lobar (secondary) bronchi appear at stage 16; bronchopulmonary segments and the start of the pseudoglandular phase appear at stage 17.

- By birth, continued caudal growth of the trachea brings the **bifurcation down to the level of the 3rd/4th thoracic vertebra**, while its cranial end remains fixed at the upper border of the 6th cervical vertebra — a relationship maintained through subsequent growth.



*Development of respiratory system*

## 5. Formation of the pleura and pleural cavity

- The lung buds grow caudally and laterally, invaginating the **pericardioperitoneal canals** (narrow spaces flanking the foregut, connecting the pericardial and peritoneal coeloms).
- As the lungs expand, **pleuropericardial folds** and **pleuroperitoneal folds** separate these canals from the pericardial and peritoneal cavities respectively, leaving the isolated **pleural cavities**.
- **Splanchnopleuric mesoderm** investing the lung buds becomes the **visceral pleura**; **somatopleuric mesoderm** lining the body wall becomes the **parietal pleura**.
- Persistence of a pleuroperitoneal canal (failure of pleuroperitoneal fold fusion) underlies **congenital diaphragmatic hernia**, commonly with ipsilateral (and sometimes contralateral) **pulmonary hypoplasia** from abnormal airway branching.

## 6. Maturation (histogenesis) of the lung parenchyma

Lung parenchymal maturation is described in four overlapping periods (cranial segments mature faster than caudal ones):

| Period          | Approximate weeks | Key events                                                                                                            | Clinical/viability correlate      |
|-----------------|-------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Pseudoglandular | 5–17 weeks        | Branching continues to terminal bronchioles; lung resembles an exocrine gland; no respiratory bronchioles/alveoli yet | Non-viable if born in this period |

| Period            | Approximate weeks           | Key events                                                                                                                                                            | Clinical/viability correlate                                                                     |
|-------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Canalicular       | 16–26 weeks                 | Each terminal bronchiole divides into respiratory bronchioles → 3–6 alveolar ducts; capillary network increases                                                       | Fetus born late in this period may survive with intensive neonatal care                          |
| Terminal saccular | 26 weeks – birth            | Terminal sacs (primitive alveoli) form; type I (lining) and type II (surfactant-secreting) pneumocytes differentiate; blood–air (endothelio-epithelial) barrier thins | Adequate gas exchange possible by end of 7th month — key viability threshold                     |
| Alveolar          | Late fetal period – 8 years | Definitive alveoli form and multiply; only ~1/6th of the adult alveolar number is present at birth                                                                    | Postnatal lung growth is by increase in alveolar/respiratory-bronchiole <b>number</b> , not size |

- **Surfactant**, a phospholipid that lowers alveolar surface tension, is secreted by **type II pneumocytes**, which differentiate progressively from around 20–24 weeks; its output rises steadily thereafter, increasing sharply in the last 2 weeks before term.
- **Sexual dimorphism**: androgens delay type II pneumocyte/surfactant maturation while promoting overall lung growth — preterm male infants therefore carry a higher risk of respiratory distress than females of comparable gestation.

### Applied / Clinical anatomy

- **Tracheo-oesophageal fistula (TEF) / oesophageal atresia** — due to deviation/incomplete fusion of the tracheo-oesophageal septum; overall incidence ≈ 1:3000–4500 births; classified into five types:

| Type | Description                                                                       | Approx. frequency   |
|------|-----------------------------------------------------------------------------------|---------------------|
| A    | Isolated oesophageal atresia — both segments blind, no communication with trachea | ~4%                 |
| B    | Proximal segment fistulates with trachea; distal segment ends blindly             | ~1% (rare)          |
| C    | Proximal segment blind (atresia); distal segment fistulates with trachea          | ~85–90% (commonest) |
| D    | Both proximal and distal segments fistulate with the trachea                      | ~1%                 |



| Type       | Description                                    | Approx. frequency |
|------------|------------------------------------------------|-------------------|
| E (H-type) | Oesophagus fistulates with trachea, no atresia | ~4%               |

- Presents with maternal **polyhydramnios** (fetus cannot swallow amniotic fluid), and postnatally with coughing, choking, cyanosis and aspiration pneumonitis on feeding.
  - Is a component of the **VACTERL association** — Vertebral, Anal atresia, Cardiac defects, Tracheo-oesophageal fistula, (o)Esophageal atresia, Renal anomalies, Limb defects; ~33% have an associated cardiac anomaly.
  - Treated by emergency surgical resection of the fistula with oesophageal end-to-end anastomosis.
- **Anomalies of the trachea:** agenesis (failure of laryngotracheal tube formation), tracheal stenosis (ventral deviation of the tracheo-oesophageal septum), tracheal bronchus (blind diverticulum from the trachea), tracheal lobe (an accessory bronchus supplying an isolated lobe).
- **Anomalies of the larynx:** laryngocele (anomalous air sac communicating with the laryngeal cavity), laryngeal atresia/stenosis (failure of recanalisation), laryngoptosis (low-lying larynx), laryngeal web (incomplete recanalisation causing partial airway obstruction).
- **Anomalies of the lung:**
- **Agenesis/hypoplasia** — unilateral or bilateral; **renal agenesis** → **oligohydramnios** → **pulmonary hypoplasia** because fetal urine maintains the amniotic fluid volume essential for normal lung growth.
  - **Abnormal lobation** — absent fissure reduces lobe number; extra fissures produce a transverse fissure in the left lung, a separate cardiac lobe (medial basal segment), or a separate apical segment of the lower lobe.
  - **Azygos lobe (lobe of Wrisberg)** — the commonest accessory lobe; part of the right upper lobe lying medial to the arch of the azygos vein, demarcated by a vertical fissure containing the vein in its floor.
  - **Pulmonary sequestration** — a segment of lung tissue separated from the tracheobronchial tree, usually with an anomalous systemic arterial supply.
  - **Ectopic lung** — an additional lung bud arising from the oesophagus, independent of the main respiratory primordium.
  - **Congenital polycystic lung (congenital cystic adenomatoid malformation)** — dilated terminal bronchioles producing multiple cysts, giving a honeycomb radiographic appearance and predisposing to chronic infection.
- **Hyaline membrane disease / infantile respiratory distress syndrome (IRDS)** — surfactant-deficiency disorder of preterm infants; affects ~1% of newborns and accounts for ~20% of neonatal deaths.
- Presents with tachypnoea, tachycardia and cyanosis; alveoli show waxy hyaline membranes on histology.

- Antenatal diagnosis: amniotic fluid **lecithin/sphingomyelin (L/S) ratio** <2:1 indicates insufficient surfactant; **surfactant/albumin (S/A) ratio** <35 = immature, 35–55 = intermediate, >55 = mature lungs.
- Prevention/treatment: antenatal maternal glucocorticoids (after 7th month) to accelerate surfactant synthesis; postnatal exogenous surfactant, oxygen therapy, CPAP.
- ▶ **Medico-legal note:** aerated (live-born) lungs float in water; unaerated (stillborn) lungs sink — used to differentiate stillbirth from live birth followed by death.

### High-yield exam pointers

- ▶ Lung bud = ventral diverticulum of foregut endoderm, appearing at the 4th week; epithelium + glands are endodermal, all cartilage/muscle/connective tissue/pleura are splanchnic-mesodermal.
- ▶ Key molecules: **TBX4** (retinoic acid-driven, initiates bud), **FGF10** (tracheal bud outgrowth), **SHH-GLI** (epithelial–mesenchymal branching signal).
- ▶ Right lung bud → 3 secondary bronchi → **10 segmental bronchi**, 3 lobes; left lung bud → 2 secondary bronchi → **8 segmental bronchi**, 2 lobes.
- ▶ Bronchopulmonary segment = segmental (tertiary) bronchus + its own splanchnopleuric mesenchyme.
- ▶ Splanchnopleure → visceral pleura; somatopleure → parietal pleura; pleural cavity is the isolated remnant of the pericardioperitoneal canal.
- ▶ Four maturation periods: **Pseudoglandular** (5–17 wk) → **Canalicular** (16–26 wk) → **Terminal saccular** (26 wk–birth) → **Alveolar** (late fetal–8 yr).
- ▶ Surfactant is produced by **type II pneumocytes**; deficiency causes hyaline membrane disease (~20% of neonatal deaths); L/S ratio <2:1 = immature lungs.
- ▶ TEF: commonest variant (~90%) is proximal oesophageal atresia with distal fistula to the trachea; TEF is part of the **VACTERL** association.
- ▶ Azygos lobe (lobe of Wrisberg) is the most common accessory lobe; renal agenesis causes pulmonary hypoplasia via oligohydramnios.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; BD Chaurasia — Human Anatomy Vol 1, 8e; IB Singh — Human Embryology (CBME 2021).



## Development of Thoraco-abdominal diaphragm

Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy

**Definition / Introduction** The diaphragm is the dome-shaped musculetendinous partition that separates the thoracic cavity (pericardial and pleural cavities) above from the abdominal (peritoneal) cavity below. Unlike most muscles it is not a single embryonic primordium but a **composite of four separate mesodermal contributions** that fuse together between the 4th and 8th weeks of intrauterine life (IUL) — the septum transversum, the paired pleuroperitoneal membranes, the dorsal mesentery of the oesophagus, and mesoderm derived from the lateral body wall. This multi-source origin is the embryological key that explains both the diaphragm's segmental (phrenic, C3–C5) nerve supply and the commonest sites of congenital diaphragmatic hernia.

### Partitioning of the intraembryonic coelom

- ▶ The single intraembryonic coelom communicates, on either side of the foregut, with the pericardial cavity above through narrow **pericardioperitoneal (pleuroperitoneal) canals**.
- ▶ As the lung buds grow dorsally into these canals, each canal is divided by a pair of crescentic membranous ridges:
  - a **cranial ridge — pleuropericardial fold** (above the lung bud) → becomes the **pleuropericardial membrane**, separating the pericardial from the pleural cavity; it carries the common cardinal vein and the phrenic nerve.
  - a **caudal ridge — pleuroperitoneal fold** (below the lung bud) → becomes the **pleuroperitoneal membrane**, separating the pleural from the peritoneal cavity.
- ▶ Thus two partitions convert the single coelom into three definitive cavities: the paired **pleuropericardial membranes** (pericardial vs pleural cavity) and the **diaphragm** (pleural/pericardial cavity vs peritoneal cavity).

### The four embryonic components of the diaphragm

The diaphragm develops from the fusion of four mesodermal components; each contributes a specific adult part.

| Embryonic component                                                                                                                                                                                                   | Adult derivative                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| <b>Septum transversum</b> — a thick plate of mesoderm occupying the space between the pericardial and peritoneal cavities; its caudal part is invaded by the hepatic bud (liver primordium)                           | <b>Central tendon</b> of the diaphragm                       |
| <b>Paired pleuroperitoneal membranes</b> — formed from the pleuroperitoneal folds; grow medially to close the pleuroperitoneal canals and fuse with the septum transversum and the dorsal mesentery of the oesophagus | Small <b>posterolateral peripheral part</b> of the diaphragm |
| <b>Dorsal mesentery of the oesophagus</b> — mesoderm between the oesophagus and the descending aorta                                                                                                                  | <b>Crura</b> of the diaphragm                                |

| Embryonic component                                                                                                                                                                               | Adult derivative                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Mesoderm of the lateral body wall — added as the expanding pleural cavities burrow/excavate into the body wall, splitting it into an outer (definitive body wall) and inner (diaphragmatic) layer | Large <b>peripheral (costal)</b> part of the diaphragm, external to the pleuroperitoneal-membrane-derived part |

## Sequence of fusion of the components

□ Fig 17.5 — Development of abdominothoracic diaphragm. Central tendon of diaphragm develops from sep (Sontakke — Textbook of Human Embryology, p.171)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Four successive transverse sections through the developing embryo (plane of section through the septum transversum, caudal to the pericardial cavity), each labelled:

- ▶ **28-day embryo** — plane of section shown on a lateral view.
- ▶ **Week 6** — Aorta; Dorsal mesentery of oesophagus; Oesophagus; Pleuroperitoneal canal (still open); Inferior vena cava; Pleuroperitoneal fold; Septum transversum.
- ▶ **Week 7** — Muscular ingrowth from body wall; Narrowing of the pleuroperitoneal canal.
- ▶ **Week 16** — Crura of diaphragm; Small peripheral part (from pleuroperitoneal membrane); Large peripheral part (from body wall); Central part (from septum transversum).
- ▶ **Weeks 4–5:** pleuroperitoneal folds appear at the caudal end of each pericardioperitoneal canal, lateral to the septum transversum and dorsal to the dorsal mesentery of the oesophagus; the pleuroperitoneal canal is still wide open, connecting the pleural and peritoneal cavities.
- ▶ **Week 6:** the folds thin out to form membranous **pleuroperitoneal membranes**; these grow medially and fuse first with the dorsal mesentery of the oesophagus (around the aorta, forming the crura) and then progressively with the septum transversum, narrowing the pleuroperitoneal canal.
- ▶ **Week 7:** the pleuroperitoneal membranes of the two sides fuse with each other and with the septum transversum in the midline, completing closure of the pleuroperitoneal canal. The **right canal closes slightly earlier than the left** — the embryological basis for the left-sided preponderance of later diaphragmatic hernias.
- ▶ **Weeks 9 onward:** as the pleural cavities continue to expand, the lungs and pleura "burrow" into the lateral body wall, splitting it into an outer layer (the definitive thoracic/abdominal body wall) and an inner layer that is added peripherally to the diaphragm — its large costal part — establishing the **costodiaphragmatic recesses** and the diaphragm's characteristic dome shape by around the 16th week.

## Positional change (descent) and nerve supply

- ▶ In the 4th week, the septum transversum lies in the cervical region (initially opposite the 2nd cervical segment, soon opposite the 3rd–5th cervical somites).

- ▶ Myoblasts, together with their nerve fibres, migrate from the **C3, C4 and C5 myotomes** into the septum transversum; the three rootlets on each side unite to form the **phrenic nerve** — the classic mnemonic being "**C3, 4, 5 keep the diaphragm alive.**"
- ▶ Mesenchyme of the septum transversum, now seeded with these cervical myoblasts, subsequently extends into the other three diaphragmatic components as they fuse, differentiating into the skeletal muscle throughout the diaphragm.
- ▶ Differential growth of the dorsal part of the embryo (brain and vertebral column growing faster than the ventral structures), elongation of the neck, descent of the heart, and expansion of the pleural cavities together produce an apparent caudal migration ("**descent**") of the diaphragm: by the 6th week it lies at the level of the thoracic somites, and by the end of the 2nd month (8th week) its dorsal attachment has reached the last thoracic/first lumbar level — though the **central derivatives remain at a relatively more cranial level** than the peripheral/crural attachments.
- ▶ Because the diaphragm is dragged caudally while its nerve supply remains fixed at its cervical origin, the **phrenic nerve is carried along with it**, acquiring its unusually long intrathoracic course (~30 cm in the adult). It enters the diaphragm by passing through the pleuropericardial membrane, which explains why the phrenic nerve subsequently lies on the fibrous pericardium (the adult derivative of this membrane).
- ▶ Because the **central part** is derived from the septum transversum (cervical/phrenic territory) while the **peripheral costal part** is derived from the invaginated lateral body wall, the phrenic nerve supplies both motor and sensory fibres to the central dome, while the peripheral rim receives its sensory supply from the **lower intercostal nerves** — direct embryological evidence of the diaphragm's dual origin.

## Applied / Clinical anatomy

□ Fig 17.6 — Congenital diaphragmatic hernia. It is herniation of abdominal content (Sontakke — Textbook of Human Embryology, p.172)

- ▶ **Congenital diaphragmatic hernia (CDH):** overall incidence ~1 in 3000–5000 live births (prenatal incidence ~1 in 2000). Its commonest form is the **posterolateral defect (foramen of Bochdalek)**, resulting from failure of closure of the pleuroperitoneal canal / failure of fusion of the pleuroperitoneal membrane with the other three diaphragmatic components — it accounts for **85–90% of CDH**, is bilateral in 5%, and among unilateral cases is **left-sided in about 80%** (because the right pleuroperitoneal canal closes earlier than the left). A thin, non-muscular membranous hernial sac (derived from the persisting canal wall) is present in 10–15% of cases, indicating an early-occurring lesion, before muscle ingrowth is complete.
- ▶ Abdominal viscera (stomach, small bowel, colon, liver and/or spleen) herniating into the thorax compress the developing lung(s), causing **pulmonary hypoplasia**; with mediastinal shift the contralateral lung may also be affected. Pulmonary hypoplasia and secondary **pulmonary hypertension** are the chief causes of neonatal death. There is increasing evidence that lung hypoplasia may actually be the primary developmental abnormality, with herniation of viscera a secondary event — an important consideration for prenatal management. Antenatal ultrasound (from ~18 weeks) shows bowel/stomach within the thorax with mediastinal shift; associated chromosomal anomalies (trisomy 13, 18) and syndromic causes are recognised.

- ▶ **Retrosternal (anterior/parasternal) or Morgagni's hernia:** occurs through the sternocostal triangle, the gap between the sternal and costal slips of origin of the diaphragm; it is uncommon (rare, ~1–2% of CDH). Intestine may herniate into the pericardial cavity, or conversely a part of the heart may herniate into the epigastric region.
- ▶ **Midline (central) defects** of the central tendon arise from primary septum-transversum defects; occasionally an entire half of the diaphragm (usually the left) may be absent.
- ▶ **Congenital hiatus hernia:** an abnormally wide oesophageal hiatus (through which the oesophagus and vagus nerves pass) permits part of the fetal stomach to herniate into the thorax; it is uncommon, but a congenitally enlarged hiatus may predispose to acquired hiatus hernia later in life.
- ▶ **Eventration of the diaphragm:** the musculature of one half (usually the left) fails to develop within an otherwise intact pleuroperitoneal membrane, so that half remains thin and membranous and balloons upward into the thorax, displacing abdominal viscera. It mimics CDH clinically and radiologically but is **not a true hernia**, since there is no actual defect/gap; management, if needed, may involve a muscular flap (e.g. latissimus dorsi) or a prosthetic patch to reinforce the diaphragm.
- ▶ **Accessory diaphragm:** a rare anomaly in which an extra fibromuscular septum partially subdivides one lung.
- ▶ **N.B.** Several genes on the long arm of chromosome 15 (15q) are known to play a critical role in diaphragm morphogenesis and are implicated in the genetics of CDH.

### High-yield exam pointers

- ▶ Four embryonic components → **septum transversum** (central tendon), **paired pleuroperitoneal membranes** (small posterolateral peripheral part), **dorsal mesentery of oesophagus** (crura), and **body-wall mesoderm** (large peripheral/costal part).
- ▶ **Phrenic nerve root value C3, C4, C5** — mnemonic "C3, 4, 5 keep the diaphragm alive"; myoblasts and nerve fibres migrate together from these cervical myotomes into the septum transversum.
- ▶ **Right pleuroperitoneal canal closes before the left** → embryological basis for the left-sided preponderance of congenital diaphragmatic hernia.
- ▶ **Foramen of Bochdalek** = posterolateral defect (pleuroperitoneal-membrane failure, commonest, ~85–90% of CDH); **foramen of Morgagni** = anterior/retrosternal defect (sternocostal triangle, rare).
- ▶ Central (dome) part → motor + sensory from **phrenic nerve**; peripheral costal rim → sensory from **lower intercostal nerves** — direct proof of the diaphragm's dual embryological origin.
- ▶ Descent of the diaphragm carries the phrenic nerve caudally with it, giving the adult nerve its unusually long (~30 cm) intrathoracic course over the fibrous pericardium.
- ▶ **Eventration of the diaphragm ≠ true hernia** — the pleuroperitoneal membrane is intact but non-muscular (thin/aponeurotic); no actual gap is present.
- ▶ Diaphragmatic development is complete (definitive dome shape) by around the 16th week; CDH is diagnosable by antenatal ultrasound from ~18 weeks onward.



**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Moore — The Developing Human, 9e; Langman's Medical Embryology (Sadler), 14e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology.



## Development of the Respiratory System and Its Congenital Anomalies

*Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy*

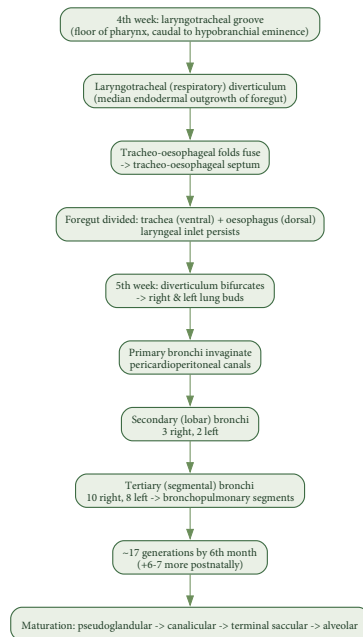
**Definition / Introduction** — The lower respiratory tract (larynx, trachea, bronchi, lungs) develops from a single median **respiratory (laryngotracheal) diverticulum**, an endodermal outgrowth from the ventral wall of the foregut appearing at the **4th week** of intrauterine life. Its epithelial lining and glands are therefore entirely **endodermal**, while the surrounding cartilage, smooth muscle, connective tissue and pleura arise from **splanchnic (splanchnopleuric) mesoderm**. Separation of this diverticulum from the oesophagus by the tracheo-oesophageal septum, its bifurcation into lung buds, and its repeated dichotomous branching together explain almost every congenital anomaly of the airway — most importantly tracheo-oesophageal fistula (TEF).

### Formation of the respiratory diverticulum and tracheo-oesophageal septation

- ▶ In the **4th week**, a midline **laryngotracheal groove** appears in the floor of the primitive pharynx, just caudal to the **hypobranchial eminence**; it is flanked by the developing 6th pharyngeal arches.
- ▶ The groove deepens into the **laryngotracheal (respiratory) diverticulum**, which grows caudally, initially in open communication with the foregut.
- ▶ Two longitudinal **tracheo-oesophageal folds/ridges** grow medially and fuse to form the **tracheo-oesophageal septum**, dividing the foregut into a **ventral trachea** and a **dorsal oesophagus**.
- ▶ Cranial extension of the septum is arrested at the **laryngeal inlet (furcula of His)**, which permanently preserves communication between the developing airway and the pharynx.
- ▶ **Molecular regulation:** retinoic acid from adjacent mesoderm upregulates **TBX4** in the foregut endoderm at the site of the diverticulum, inducing lung-bud formation and growth; **fibroblast growth factor-10 (FGF10)** from splanchnic mesenchyme drives outgrowth and branching of the tracheal/lung buds; **Sonic hedgehog (SHH-Gli)** signalling mediates the reciprocal epithelial-mesenchymal interaction that governs branching morphogenesis.

□ Fig 14.2 — Successive stages in development of the respiratory diverticulum (lung bud) showing the tracheo-oesophageal ridges and formation of the septum, splitting the foregut into oesophagus and trachea (Langman's Medical Embryology — Sadler — 14e, p.243)





*Development of the Respiratory System and Its Congenital Anomalies*

## Development of the larynx

- Larynx develops from the **cranial-most part** of the laryngotracheal diverticulum; its communication with the pharynx persists as the laryngeal inlet.
- Rapid mesenchymal proliferation (4th and 6th arches) converts the primitively **sagittal-slit** laryngeal orifice into a **T-shaped** opening over the **6th–12th week**, which then acquires its adult shape as the arch cartilages differentiate.
- The endodermal epithelium proliferates and **transiently occludes the lumen**; subsequent **vacuolization and recanalization** create two pairs of folds — an upper **vestibular fold** (→ false vocal cord) and a lower **vocal fold** (→ true vocal cord) — the intervening recess forming the **laryngeal ventricle**.

| Component                                                      | Embryological source                                                                                              |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Mucosa/lining epithelium                                       | Endoderm of laryngotracheal diverticulum                                                                          |
| Vestibular and vocal folds                                     | Endodermal folds of the diverticulum                                                                              |
| Thyroid, cricoid, arytenoid, corniculate, cuneiform cartilages | 4th and 6th arch mesenchyme (neural-crest derived)                                                                |
| Epiglottis                                                     | Hypobranchial eminence (fused 3rd/4th arch tissue)                                                                |
| Intrinsic muscles                                              | 4th arch (cricothyroid) and 6th arch (all others)                                                                 |
| Motor nerve supply                                             | External laryngeal br. of superior laryngeal n. (cricothyroid, 4th arch); recurrent laryngeal n. (rest, 6th arch) |
| Sensory nerve supply                                           | Internal laryngeal n. above vocal folds; recurrent laryngeal n. below                                             |

## Development of the trachea and bronchial tree

- ▶ The **trachea** forms from the part of the laryngotracheal tube between the larynx and the point of bifurcation; its epithelium and glands are endodermal, its cartilage/muscle/connective tissue splanchnopleuric-mesodermal.
- ▶ At the **5th week**, the caudal diverticulum bifurcates asymmetrically into **right and left primary (principal) bronchi**; the right is aligned more in line with the trachea, foreshadowing the adult tendency for inhaled foreign bodies to lodge on the right.
- ▶ Each primary bronchus invaginates its corresponding **pericardio-peritoneal canal** and divides into **secondary (lobar) bronchi** — **3 on the right, 2 on the left** — foreshadowing the three right and two left pulmonary lobes.
- ▶ Secondary bronchi divide dichotomously into **tertiary (segmental) bronchi** — **10 on the right, 8 on the left**; each, with its surrounding splanchnic mesenchyme, forms a **bronchopulmonary segment**.
- ▶ By the **end of the 6th month**, about **17 generations** of subdivisions have formed; a further **6–7 divisions** occur postnatally before the adult bronchial tree (~23 orders) is complete. Branching is driven by reciprocal endoderm–mesenchyme signalling (FGF, SHH).
- ▶ **Pleura**: lung buds expand into the pericardio-peritoneal canals; splanchnopleuric mesoderm covering the lung forms the **visceral pleura**, somatopleuric mesoderm lining the body wall forms the **parietal pleura**, and the interposed pleuro-pericardial/pleuro-peritoneal folds isolate the definitive **pleural cavities** from the pericardial and peritoneal cavities.

## Maturation of the lung (histological stages)

| Stage             | Period                                    | Key events                                                                                                                                                                                          |
|-------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pseudoglandular   | 5–16 weeks                                | Bronchial tree branches to terminal bronchioles; lung resembles an exocrine gland; no respiratory elements yet → non-viable if born now                                                             |
| Canalicular       | 16–26 weeks                               | Terminal bronchioles give respiratory bronchioles and alveolar ducts; vascularity increases; a few primitive alveoli appear → may survive with intensive care                                       |
| Terminal saccular | 26 weeks–birth                            | Numerous terminal sacs (primitive alveoli) form; capillaries bulge into them; type I (thin, gas-exchanging) and type II (surfactant-secreting from the <b>20th week</b> ) pneumocytes differentiate |
| Alveolar          | Late fetal period (~8 months) to ~8 years | Definitive alveoli multiply (only ~1/6th of the adult number present at birth); remainder formed postnatally                                                                                        |

- ▶ **Surfactant**, a phospholipid produced by **type II pneumocytes**, lowers alveolar surface tension and prevents atelectasis on expiration; its output rises sharply in the last 2 weeks before term.
- ▶ **Fetal breathing movements** begin before birth, aspirate amniotic fluid, and condition the respiratory muscles; adequate thoracic space, breathing movements and amniotic fluid volume are the three prerequisites for normal lung growth (their absence — e.g. in oligohydramnios from renal agenesis — causes pulmonary hypoplasia).

### **Congenital anomalies of the larynx and trachea**

- ▶ **Laryngeal atresia/stenosis** — failure of laryngeal recanalization; causes congenital high airway obstruction.
- ▶ **Laryngeal web** — incomplete recanalization leaves a membranous shelf, usually at the vocal folds; partial airway obstruction.
- ▶ **Laryngocele** — congenital air sac in the neck communicating with the laryngeal cavity.
- ▶ **Laryngoptosis** — abnormally low-lying larynx, sometimes with absent cartilages.
- ▶ **Tracheal agenesis** — failure of laryngotracheal tube formation.
- ▶ **Tracheal stenosis** — anomalous (usually anterior) deviation of the tracheo-oesophageal septum narrows the trachea.
- ▶ **Tracheal bronchus/tracheal lobe** — an accessory bronchus arising directly from the trachea, ending blindly or supplying an isolated **tracheal lobe**.
- ▶ **Tracheo-oesophageal fistula (TEF)**: abnormal communication resulting from failure of fusion of the tracheo-oesophageal folds/septum; incidence ~1 in 3000–4500 births.

| Type (Gross/Vogt classification) | Anatomy                                                                                 | Approx. frequency |
|----------------------------------|-----------------------------------------------------------------------------------------|-------------------|
| A — Isolated oesophageal atresia | Proximal and distal segments both blind, no fistula                                     | ~4%               |
| B                                | Proximal segment fistulates with trachea; distal segment blind                          | ~1%               |
| C (commonest)                    | Proximal oesophagus ends blindly; distal oesophagus arises from/fistulates with trachea | ~85–90%           |
| D                                | Both proximal and distal segments fistulate with the trachea                            | ~1%               |
| E (H-type)                       | Oesophagus in continuity; fistula present without atresia                               | ~4%               |

- ▶ **Clinical/embryological correlation:** in the common Type C, swallowed amniotic fluid cannot reach the stomach → **polyhydramnios**; after birth the distal fistula lets gastric contents/air reflux into the airway → choking, cyanosis and aspiration pneumonia with feeding; a nasogastric catheter cannot be passed into the stomach.

## Congenital anomalies of the lungs and pleura

- ▶ **Agenesis/aplasia of the lung** — unilateral (compatible with life) or bilateral absence; in agenesis the bronchial stump itself is absent, in aplasia a rudimentary stump remains with no distal lung tissue.
- ▶ **Pulmonary hypoplasia** — small, underdeveloped lung, classically from a **congenital diaphragmatic hernia** compressing the developing lung, or from oligohydramnios (e.g. renal agenesis).
- ▶ **Abnormal lobation** — extra or absent fissures (e.g. only two right lobes, or a supernumerary transverse fissure on the left) from variable division of the lobar bronchi.
- ▶ **Azygos lobe (lobe of Wrisberg)** — commonest accessory lobe; part of the right upper lobe displaced medial to an aberrantly placed arch of the azygos vein, separated by a vertical (meso-azygos) fissure.
- ▶ **Ectopic lung lobe** — an additional respiratory bud arising independently from the oesophagus or trachea.
- ▶ **Pulmonary sequestration** — a mass of lung tissue separated from the normal tracheobronchial tree and pulmonary circulation.
- ▶ **Congenital polycystic lung / bronchogenic cyst** — cystic dilation of terminal bronchi giving a honeycomb radiographic appearance; drains poorly → recurrent infection. On thoracic imaging such cysts are found (in descending frequency) in the **carinal** (~51%), right paratracheal (~19%), para-oesophageal (~14%), hilar (~9%) and pericardial/retrosternal/paravertebral (~7%) regions.
- ▶ **Hyaline membrane disease / infantile respiratory distress syndrome (IRDS)** — surfactant deficiency in the premature infant → alveolar collapse (atelectasis) with a proteinaceous "hyaline" membrane lining the alveoli; accounts for ~20% of neonatal deaths.

## Applied / Clinical anatomy

- ▶ TEF is frequently a component of the **VACTERL association** (Vertebral, Anal atresia, Cardiac defects, Tracheo-oesophageal fistula, Esophageal atresia, Renal anomalies, Limb defects); associated cardiovascular defects occur in ~30%, anorectal anomalies in ~15% and genitourinary anomalies in ~15% of cases.
- ▶ Antenatal ultrasound clue: absence of a fetal stomach bubble on a 20-week scan (when the oesophagus does not communicate with the stomach) should prompt evaluation for oesophageal atresia/TEF.
- ▶ Emergency **surgical repair** of TEF involves ligation of the fistula and end-to-end oesophageal anastomosis.
- ▶ Because the right main bronchus continues the line of the trachea more directly (an embryological relationship retained into adult life), inhaled **foreign bodies preferentially lodge in the right bronchial tree**.
- ▶ Amniotic-fluid indices of fetal lung maturity: **lecithin/sphingomyelin (L/S) ratio** <2:1 indicates insufficient surfactant; **surfactant/albumin ratio** <35 indicates immaturity. Antenatal glucocorticoids accelerate surfactant production and reduce RDS in threatened preterm labour.

- ▶ **Medicolegal test:** the lungs of a live-born infant contain air, float in water and crepitate; a stillborn infant's fluid-filled lungs sink and do not crepitate — used to distinguish live birth from stillbirth.
- ▶ Anomalies of bronchial branching (supernumerary lobules, tracheal bronchus) are usually functionally silent but may complicate bronchoscopy or lobar resection.

### High-yield exam pointers

- ▶ Respiratory epithelium and glands = **endoderm** of the laryngotracheal diverticulum; cartilage, muscle, connective tissue and pleura = **splanchnic mesoderm**.
- ▶ Diverticulum appears in the **4th week**; bifurcates into lung buds in the **5th week**; tracheo-oesophageal septum failure → **TEF/oesophageal atresia**.
- ▶ Right: 3 secondary bronchi/lobes, 10 tertiary (segmental) bronchi. Left: 2 secondary bronchi/lobes, 8 tertiary bronchi.
- ▶ **TBX4** (induced by retinoic acid) triggers lung-bud formation; **FGF10** and **SHH** drive branching morphogenesis.
- ▶ Four lung maturation phases in order: **pseudoglandular** → **canalicular** → **terminal saccular** → **alveolar**; surfactant from **type II pneumocytes** begins by the **20th week**.
- ▶ Commonest TEF type (~85–90%): **proximal oesophageal atresia (blind pouch) + distal oesophago-tracheal fistula**.
- ▶ TEF is a limb of the **VACTERL** association; incidence ~1 in 3000–4500 births.
- ▶ **Azygos lobe** = commonest accessory lobe; **congenital polycystic lung** = most clinically significant lung anomaly (honeycomb lung, recurrent infection).
- ▶ **Hyaline membrane disease (IRDS)** = surfactant deficiency; L/S ratio <2:1 predicts it antenatally.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; Vishram Singh — Textbook of Clinical Embryology; BD Chaurasia — Human Anatomy Vol 1 8e; IB Singh — Human Embryology (CBME 2021).



## Systemic embryology - musculoskeletal & limbs



# Somites and their derivatives

Asked in: Paper II Nov 2018 · Paper II Nov 2017 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** — Somites are paired, cuboidal blocks of segmented **paraxial mesoderm** that appear on either side of the neural tube and notochord from the end of the third week of intrauterine life. They are the primordial metameres of the body and, by regional differentiation into a **sclerotome**, a **myotome** and a **dermatome**, give rise to almost all the axial skeleton, the striated musculature of the trunk and limbs, and part of the dermis of the skin. Somite number and morphology are classical criteria used to stage a human embryo (Streeter's somite-based age tables).

## 1. Formation of somites (somitogenesis)

- ▶ Cranial to the otic vesicle, paraxial mesoderm organises into **somitomeres** (whorled, non-segmented condensations); these never form true sclerotome/dermomyotome subdivisions.
- ▶ Caudal to the otic vesicle, paraxial mesoderm undergoes a **mesenchymal-to-epithelial transition** and segments sequentially into true **somites**, in strict craniocaudal order.
- ▶ The **first pair** of somites appears on day 20 in the future occipital region; thereafter roughly 3 pairs form each day until, by the end of the fifth week, **42–44 pairs** are present (Moore, Vishram Singh).
- ▶ Regional distribution: **3 preoccipital** somitomeres, **4–5 occipital**, **8 cervical**, **12 thoracic**, **5 lumbar**, **5 sacral** and **8–10 coccygeal** somite pairs (IB Singh, Table 13.1). Most coccygeal somites and the first occipital somite subsequently degenerate or fuse into the skull base; the rest persist to build the axial skeleton.
- ▶ **Molecular segmentation clock**: cyclical, oscillating expression of **Notch**, **Delta-1**, **Mesp1/2**, **Hairy-1** and **Lunatic fringe** in the presomitic mesoderm, set against opposing caudal-to-cranial gradients of **FGF-8/Wnt** (undifferentiated, caudal) and rostral **retinoic acid** (differentiating). A somite buds off from the cranial end of the presomitic mesoderm each time the oscillator completes a cycle; **FoxC1/FoxC2** and **Hox genes** pattern craniocaudal identity.
- ▶ **Stages of somite differentiation** (Ordahl staging, used to compare somites of different maturity along the same embryo):

| Stage | Event                                                                                                                     |
|-------|---------------------------------------------------------------------------------------------------------------------------|
| 1     | Compaction of presomitic mesenchyme                                                                                       |
| 2     | <b>Epithelialization</b> — mesenchymal-to-epithelial transition forms a hollow epithelial sphere around somitocoele cells |
| 3     | <b>Sclerotome formation</b> — epithelial-to-mesenchymal transition of the ventral/ventromedial wall                       |
| 4     | <b>Sclerotome proliferation and expansion</b> around notochord and neural tube                                            |
| 5     | <b>Formation of the epaxial myotome</b> from the dorsomedial lip of the remaining epithelial plate (dermomyotome)         |

## 2. Structure and subdivision of a somite

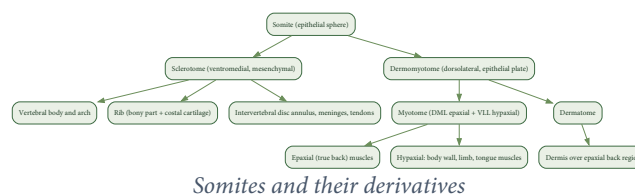
- ▶ A newly formed somite is an **epithelial sphere** enclosing loose **somitocoele** cells, applied against the neural tube medially and the surface ectoderm laterally, with the notochord medial to it and the intermediate/lateral plate mesoderm lateral to it.
- ▶ **Sonic hedgehog (SHH)** from the notochord/floor plate and **noggin** induce the ventromedial wall to undergo epithelial-to-mesenchymal transition, forming the **sclerotome**.
- ▶ The remaining dorsolateral epithelium persists as the **epithelial plate of the somite**, i.e. the **dermomyotome**, under **Wnt** signals from the overlying ectoderm and dorsal neural tube.
- ▶ The dermomyotome differentiates further: cells proliferating from its **dorsomedial lip (DML)** form the **epaxial myotome**; cells from its **ventrolateral lip (VLL)** form the **hypaxial myotome** and also migrate across the **lateral somitic frontier** into the lateral plate mesoderm to form limb and tongue musculature (the "abaxial" domain). What remains of the dermomyotome epithelium becomes the **dermatome**.
- ▶ Somitocoele cells, retained through these transitions, later contribute to the **intervertebral joints, discs and proximal rib heads**.

□ Fig 10.1 — Development of the somite. A. Paraxial mesoderm cells are arranged around a small cavity (Langman's Medical Embryology — Sadler — 14e, p.166)

Fig. 10.1 (Langman's, p.166), in full: A, paraxial mesoderm cells arranged around a small cavity. B, cells in the ventromedial wall lose their epithelial arrangement and become mesenchymal (the sclerotome); cells in the ventrolateral and dorsomedial regions form muscle cells and migrate beneath the remaining dorsal epithelium (the dermatome) to form the myotome.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A transverse section through the trunk at somite level — label: **neural tube**, **notochord**, **dorsal aorta**, **surface ectoderm**, **sclerotome** (medial, surrounding notochord/neural tube), **myotome** (middle, subdivided into dorsomedial epaxial and ventrolateral hypaxial parts), **dermatome** (lateral, deep to ectoderm), and the **spinal nerve** entering the myotome/sclerotome junction.



## 3. Derivatives of the sclerotome — axial skeleton

- ▶ **Vertebral column:** sclerotomal mesenchyme surrounds the notochord and neural tube; an intrasegmental cleft, **von Ebner's fissure**, divides each sclerotome into a loosely packed **cranial half** and a densely packed **caudal half**. **Resegmentation:** the caudal half of one sclerotome fuses with the cranial half of the sclerotome below to form a single definitive vertebral centrum/arch. Consequence — each **myotome** now bridges an intervertebral disc and spans two adjacent vertebrae, permitting the vertebral column to be moved by its muscles; **intersegmental arteries**



come to lie over the mid-body of the vertebra; **spinal nerves** emerge intersegmentally, at the level of the intervertebral disc/foramen.

- **Intervertebral disc:** the **annulus fibrosus** forms from the intersegmental (perichordal) mesenchyme between the two recombining sclerotome halves; the **nucleus pulposus** is the persisting remnant of **notochord**.
- **Ribs:** the bony rib derives from sclerotome cells remaining within the paraxial mesoderm growing out from the costal processes of thoracic vertebrae; the **costal cartilage** forms from sclerotome cells that migrate across the **lateral somitic frontier** into the adjacent (somatic) lateral plate mesoderm.
- **Sternum** is **not** a somite/sclerotome derivative — it condenses from paired **somatic (lateral plate) mesodermal sternal bars** that fuse in the midline; a common examiner pitfall.
- **Skull:** occipital sclerotomes (with occipital somites) contribute to the **chondrocranium/basiocciput** posterior to a defined limit; the rest of the neurocranium and viscerocranium form largely from **neural crest** and local head mesenchyme, not from somites.
- Sclerotomal cells also give rise to the **meninges** around the spinal cord, and — via the transcription factor **scleraxis** — to local **tendons and ligaments** of the axial skeleton.

#### 4. Derivatives of the myotome — skeletal musculature (with somitomes)

| Somite/<br>somitome group | Pairs                    | Muscle derivative                               | Nerve supply                                |
|---------------------------|--------------------------|-------------------------------------------------|---------------------------------------------|
| Preoccipital (somitomes)  | 3                        | Extraocular muscles of the eyeball              | III, IV, VI cranial nerves                  |
| Occipital                 | 4–5                      | Tongue musculature (except palatoglossus)       | XII (hypoglossal)                           |
| Cervical                  | 8                        | Neck muscles; diaphragm (via phrenic, migrated) | Cervical spinal nerves (C3–C5 to diaphragm) |
| Thoracic                  | 12                       | Intercostal, abdominal wall, back muscles       | Corresponding thoracic spinal nerves        |
| Lumbar + Sacral           | 5 + 5                    | Back muscles; lower-limb musculature            | Lumbosacral plexus                          |
| Coccygeal                 | 8–10 (mostly degenerate) | Minor perineal/coccygeal remnants               | Coccygeal nerve                             |

- **Epaxial muscles** (true back muscles — erector spinae, transversospinalis group) arise from the **dorsomedial lip (DML)** of the dermomyotome and are innervated exclusively by **dorsal (posterior) primary rami**.
- **Hypaxial muscles** (body wall — intercostals, recti/obliques/transversus abdominis; and, via long-range migration across the lateral somitic frontier, limb and tongue muscles) arise from the **ventrolateral lip (VLL)** and are innervated by **ventral (anterior) primary rami**.

- ▶ Each myotome/muscle **retains the segmental nerve supply of its somite of origin regardless of final migrated position** — this is why the phrenic nerve (C3–C5) travels a long course to the diaphragm and the hypoglossal nerve (occipital myotomes) supplies the tongue.
- ▶ Satellite cells of adult skeletal muscle are dermomyotome-derived cells that enter the myotome at a later stage.

## 5. Derivatives of the dermatome — dermis

- ▶ The dermatome is the residual dorsolateral epithelial plate after myotome cells have de-epithelialised; it classically forms the **dermis of the back skin**, overlying region.
- ▶ Modern refinement (Standring 41e): the somitic (dermomyotomal) contribution to skin is now known to be **limited to the dermis directly overlying the epaxial musculature**, not the whole trunk dermis as older texts implied — the remaining trunk/limb dermis arises from the underlying **somatic layer of lateral plate mesoderm**, and much facial dermis from **neural crest**.
- ▶ Clinically, a "**dermatome**" also denotes the cutaneous area supplied by a single spinal nerve through both its rami — used to localise spinal nerve/root/cord lesions; all spinal nerves except C1 have a cutaneous dermatome, and adjacent dermatomes overlap so a single-root lesion causes only partial sensory loss (e.g. herpes zoster distribution, sensory-level mapping in cord injury).

## Applied / Clinical anatomy

- ▶ **Hemivertebra / wedge vertebra**: asymmetric fusion of sclerotome halves, or failure of one half to form, gives a wedge or hemivertebra — a common cause of congenital **scoliosis**.
- ▶ **Klippel–Feil sequence**: failure of normal segmentation/resegmentation of cervical sclerotomes causes fusion of cervical vertebrae, producing a short, immobile neck.
- ▶ **Spina bifida** (dysraphism spectrum — occulta, meningocele, meningomyelocele, myelocele): failure of fusion of the vertebral arches (sclerotome-derived neural arch mesenchyme) in the midline, most often lumbosacral; occulta affects roughly 5% of the population and is often marked by a hairy patch, dimple or naevus overlying a bifid spinous process.
- ▶ **Cervical rib**: an extra costal process from a lower cervical sclerotome that grows out as an ectopic rib, may compress the lower brachial plexus/subclavian artery (thoracic outlet syndrome).
- ▶ **Sacral agenesis**: malformation of sacral/lumbosacral sclerotomes (associated with maternal diabetes) causes profound motor paralysis below the level with a less clear-cut sensory level.
- ▶ **Resegmentation** explains why a muscle (myotome) spans an intervertebral disc rather than a vertebral body — the basis of spinal mobility and of the intersegmental course of spinal nerves and vessels relative to the vertebral bodies.
- ▶ **Myotomal testing** in clinical neurology (e.g. biceps for C5–C6, quadriceps for L3–L4) exploits the fact that a myotome's segmental nerve supply is retained through development.
- ▶ **Dermatome mapping** is used at the bedside to localise a spinal cord/nerve root lesion and to determine the level of anaesthesia in spinal/epidural block.

## High-yield exam pointers

- ▶ Somites = segmented **paraxial mesoderm**; somitomeres (cranial to otic vesicle, non-segmented) vs true somites (occipital region caudally).

- ▶ First somite pair on day 20; **42–44 pairs** by end of 5th week (3 preoccipital, 4–5 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 8–10 coccygeal).
- ▶ Segmentation clock genes: **Notch–Delta–Mesp2–Lunatic fringe** oscillator against FGF8/Wnt (caudal) vs retinoic acid (cranial) gradients.
- ▶ Each somite → **sclerotome** (ventromedial) + **dermomyotome** (dorsolateral) → dermomyotome → **myotome** (DML epaxial, VLL hypaxial) + **dermatome**.
- ▶ **Resegmentation**: caudal half of one sclerotome + cranial half of next → definitive vertebra; explains myotomes bridging discs and intersegmental nerve/vessel position.
- ▶ Sclerotome → vertebrae, ribs (bony part + costal cartilage across lateral somitic frontier), IV disc annulus, meninges, tendons/ligaments. **Sternum is NOT somite-derived.**
- ▶ Myotome → epaxial muscles (dorsal rami) and hypaxial muscles — body wall, limb, tongue (ventral rami); segmental nerve supply is retained despite migration.
- ▶ Dermatome → dermis, classically of the back; modern view restricts this to the epaxial-overlying skin only.
- ▶ Clinical: hemivertebra/scoliosis, Klippel–Feil sequence, spina bifida, cervical rib — all trace to sclerotome segmentation/resegregation errors.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e — "Development of the back" (somitogenesis stages, segmentation clock genes, resegmentation, sclerotome/dermomyotome fate, spina bifida); Langman's Medical Embryology (Sadler) 14e — Skeletal System and Muscular System sections (sclerotome/dermomyotome differentiation, resegmentation, epaxial/hypaxial innervation, lateral somitic frontier, vertebral/rib/sternal anomalies); Moore, The Developing Human 9e (somite numbers and timing, segmentation genes); IB Singh, Human Embryology (CBME 2021) (Table 13.1 regional somite/derivative distribution); Vishram Singh, Textbook of Clinical Embryology (somite structure, somite–spinal nerve correlation, dermatome definition); Vishram Singh, General Anatomy 4e (clinical dermatome map and overlap).



## Development of Limbs and associated anomalies

*Asked in: Paper II 09-May-2022 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The limbs (including the shoulder and pelvic girdles, the appendicular skeleton) develop from **limb buds**, paired outpocketings of the ventrolateral body wall that appear at the end of the 4th week. Each bud has a **mesenchymal core** (parietal/somatic layer of lateral plate mesoderm — forms bone, cartilage, tendon, dermis) covered by an ectodermal jacket whose distal thickening, the **apical ectodermal ridge (AER)**, together with a posterior signalling centre, the **zone of polarizing activity (ZPA)**, orchestrates growth and patterning along three axes. Limb muscle is a second lineage — myogenic precursors migrating in from the somites. Disruption of any of these programmes produces the classical spectrum of limb reduction and digital anomalies.

### 1. Timeline of limb bud development

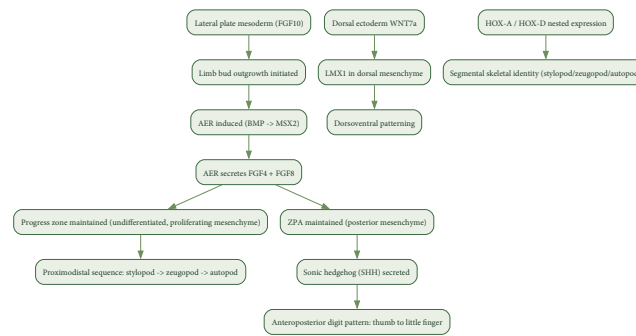
- ▶ **End of 4th week:** paired **upper limb buds** appear as ridges on the ventrolateral body wall opposite the lower cervical–upper thoracic somites (C5–T2); **lower limb buds** appear 1–2 days later opposite the lower lumbar–upper sacral somites (L2–S2). Upper limb development consistently precedes lower limb by 1–2 days throughout.
- ▶ **5th week:** the bud stage is attained; the ectoderm at the distal margin thickens into the **AER**, which keeps the underlying mesenchyme (the **progress zone/undifferentiated zone**) rapidly proliferating and undifferentiated.
- ▶ **6th week:** the terminal part of the bud flattens into a **hand-/foot-plate**, separated from the proximal segment by a circular constriction; a second constriction later demarcates arm/forearm (or thigh/leg) from the plate. Mesenchyme condenses into **digital rays**, and the first **hyaline cartilage models** of the future bones appear (proximal → distal sequence: **stylopod** – humerus/femur; **zeugopod** – radius-ulna/tibia-fibula; **autopod** – carpus-metacarpus-digits/tarsus-metatarsus-digits).
- ▶ **48–56 days (7th–8th week):** apoptosis in the AER splits it into five separate ridges over each digital ray (day 48); apoptosis in the interdigital mesenchyme then separates the digits (day 51 onward), completing digit separation by day 56 (end of embryonic period).
- ▶ **7th week:** the two limbs **rotate in opposite directions** — the upper limb rotates **90° laterally** (elbows come to point dorsally; extensors lie lateral and posterior; thumb lies laterally), the lower limb rotates **90° medially** (knees face ventrally; extensors lie anteriorly; great toe lies medially). The radius and tibia are developmentally homologous (both preaxial), as are the ulna/fibula and the thumb/great toe.
- ▶ **12th week:** **primary ossification centres** are present in all long bones (endochondral ossification proceeding from the diaphysis toward the ends). Carpal ossification begins only after birth; secondary (epiphyseal) centres appear postnatally, with an epiphyseal (growth) plate persisting until the bone attains full length.
- ▶ **Critical teratogenic window: day 24–36 post-fertilisation** (late 4th–5th week) — the period during which thalidomide produced its classical limb defects.

## 2. Molecular regulation of the three limb axes

Limb positioning along the craniocaudal body axis is set by **HOX gene** expression domains (e.g., the cranial limit of HOXB5 marks the forelimb's cranial border); forelimb identity is specified by the transcription factor **TBX5**, hindlimb identity by **TBX4** (with **PITX1**). Growth is then organised along three further axes:

| Axis                           | Signalling centre                       | Key morphogen(s)/genes                                                                                      | Effect                                                                                                                                                                |
|--------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proximodistal                  | AER (distal ectodermal ridge)           | FGF10 (initiates outgrowth from lateral plate mesoderm) → BMP induces AER via MSX2 → AER secretes FGF4/FGF8 | Maintains the progress zone; proximal cells escaping FGF influence differentiate sequentially into stylopod → zeugopod → autopod (marker genes MEIS1, HOXA11, HOXA13) |
| Anteroposterior (craniocaudal) | ZPA (posterior mesenchyme near the AER) | Sonic hedgehog (SHH), induced by retinoic acid                                                              | Digit order/identity — thumb (preaxial) to little finger (postaxial); mirror-image digit duplication if SHH is misexpressed anteriorly                                |
| Dorsoventral                   | Dorsal vs ventral ectoderm              | WNT7a (dorsal ectoderm) → LMX1 in dorsal mesenchyme; ENGRAILED-1 (ventral ectoderm) represses WNT7a         | Specifies dorsal vs ventral limb structures (e.g., nail bed dorsally)                                                                                                 |

- ▶ The three signalling centres are mutually reinforcing feedback loops: FGFs from the AER maintain SHH in the ZPA; WNT7a maintains SHH; SHH in turn helps sustain AER-FGF expression.
- ▶ **HOX-A and HOX-D clusters** are the principal determinants of segmental bone identity within the limb, expressed in three nested, overlapping phases corresponding to stylopod/zeugopod/autopod; mis-expression produces limb truncations or anteroposterior duplications.
- ▶ Two classical (competing) models explain how proximodistal position is remembered: the **progress-zone model** (a cell's fate depends on the *time* it spends proliferating under the AER before leaving) and the **early-specification model** (positional values are assigned early in the undifferentiated mesenchyme). Both are discussed in Gray's Anatomy as unresolved refinements of limb patterning.



*Development of Limbs and associated anomalies*

### 3. Skeletogenesis, joint formation, and limb rotation

- ▶ Mesenchymal condensation → **chondrification** (6th week, first hyaline cartilage models) → **endochondral ossification** beginning in the diaphysis (7th week onward) and progressing toward the cartilaginous ends.
- ▶ **Joints**: at sites of future synovial joints, condensed mesenchyme forms an **interzone**; the interzone cavitates (cell death) to create the joint cavity, while surrounding mesenchyme forms the capsule, synovium, ligaments, and menisci. **WNT14** is implicated as the inductive signal that positions joints. Fibrous joints (e.g., skull sutures) form when the interzone instead persists as dense fibrous tissue.
- ▶ **Limb rotation** (7th week) converts the primitive cranial (preaxial)/caudal (postaxial) and ventral (flexor)/dorsal (extensor) orientation into the adult pattern described above, and explains why the adult dermatomal sequence still runs obliquely down the limb.

### 4. Muscle, dermatome, and vascular development

- ▶ Limb musculature is **not** derived from local limb-bud mesenchyme; myogenic precursor cells migrate in from the **ventrolateral (hypaxial) part of the somite dermomyotome**, guided by **Pax3**-dependent expression of the c-Met receptor, and differentiate under MyoD-family regulatory factors (MyoD, Myf-5, myogenin).
- ▶ Within the bud the muscle mass splits into a **dorsal (extensor)** and a **ventral (flexor)** component; further splitting/fusion across segments obscures the original segmental pattern of the myotomes.
- ▶ **Nerve supply**: ventral primary rami of the appropriate spinal nerves enter the limb bud (5th week) with dorsal and ventral divisions that fuse into large dorsal and ventral nerves — e.g., the **radial nerve** (dorsal divisions, supplies extensors) versus the **median/ulnar nerves** (ventral divisions, supply flexors). Early nerve–muscle contact is essential for full functional differentiation.
- ▶ **Dermatomes**: sensory axons follow the motor axons into the limb; although growth and rotation distort the primordial segmental pattern, an orderly (though overlapping) dermatomal sequence persists in the adult limb.
- ▶ **Blood supply**: intersegmental arteries supply a primitive capillary plexus draining into a **marginal sinus**; a **primary axial artery** forms the template that later remodels (angiogenesis) into the definitive brachial/femoral arterial pattern.

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Real embryonic-stage plates (Sontakke, Textbook of Human Embryology) showing the external staging of upper and lower limb development:

embed: ![Fig 26.15 — Development of upper limb (Sontakke — Textbook of Human Embryology, p.298)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/0ed25dd210d51b0c.jpg)

embed: ![Fig 26.16 — Development of lower limb (Sontakke — Textbook of Human Embryology, p.298)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/9177dc22f3ce22ee.jpg)

For the exam, also be ready to reproduce the schematic cross-section of a limb bud showing its three signalling axes with these EXACT labels:

- ▶ Limb bud outline with **preaxial border** (cranial) and **postaxial border** (caudal)
- ▶ **Apical ectodermal ridge (AER)** at the distal tip
- ▶ **Zone of polarizing activity (ZPA)** in the posterior mesenchyme, adjacent to the AER
- ▶ **Progress zone / undifferentiated zone** of proliferating mesenchyme beneath the AER
- ▶ **Dorsal ectoderm vs ventral ectoderm**
- ▶ Proximodistal segments once differentiated: **stylopod – zeugopod – autopod**

**Applied / Clinical anatomy**

Limb malformations affect roughly **6 per 10,000 live births** (upper > lower limb) and are frequently associated with craniofacial, cardiac, or genitourinary defects, so any limb anomaly warrants a search for others.

| Anomaly       | Description                                                                                                | Cause / association                                                                        |
|---------------|------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Amelia        | Complete absence of a limb                                                                                 | Suppression of bud formation in early 4th week; thalidomide                                |
| Meromelia     | Partial absence of a limb (umbrella term)                                                                  | Arrest of differentiation/growth in the 5th week                                           |
| Phocomelia    | Hand/foot attached directly to the trunk by small irregular bones; long bones absent (a form of meromelia) | Classic thalidomide defect                                                                 |
| Micromelia    | All limb segments present but abnormally short                                                             | —                                                                                          |
| Brachydactyly | Short digits (short phalanges)                                                                             | Autosomal dominant                                                                         |
| Syndactyly    | Fusion of 2 or more digits (cutaneous or osseous)                                                          | Failure of interdigital apoptosis; ~1:2,000 births; commonest 3rd–4th fingers/2nd–3rd toes |
| Polydactyly   | Supernumerary digits, often poorly muscled                                                                 | Autosomal dominant; usually bilateral                                                      |



| Anomaly                            | Description                                                                                    | Cause / association                                                                              |
|------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Synpolydactyly                     | Syndactyly + polydactyly combined                                                              | HOXD13 mutation                                                                                  |
| Cleft (split) hand/foot            | Central digit(s) absent; hand/foot divides into two opposing parts                             | Failure of a digital ray; ~1:20,000; autosomal dominant, incomplete penetrance                   |
| Congenital absence of the radius   | Radial deviation of the hand, bowed ulna                                                       | Failure of the radial mesenchymal primordium (5th week); seen in Holt-Oram, TAR, Fanconi anaemia |
| Hand-foot-genital syndrome         | Carpal fusion, short digits + genital/urethral anomalies                                       | HOXA13 mutation                                                                                  |
| Holt-Oram syndrome                 | Upper-limb defects (absent digits/radius) + atrial/ventricular septal defects                  | TBX5 mutation (12q24.1)                                                                          |
| Talipes equinovarus (clubfoot)     | Foot fixed in plantarflexion (equinus) + inversion (varus); ~1:1,000 births, bilateral in ~50% | Multifactorial; linked to PITX1 microdeletions in some cases                                     |
| Developmental dysplasia of the hip | Under-development of acetabulum and femoral head with capsular laxity                          | More common in females; associated with breech delivery; multifactorial                          |
| Amniotic band syndrome             | Ring constrictions/amputations of digits or limb segments                                      | Amnion rupture/adhesion bands                                                                    |
| Osteogenesis imperfecta            | Long-bone fragility/bowing, blue sclera                                                        | Dominant COL1A1/COL1A2 mutations (type I collagen)                                               |
| Achondroplasia                     | Short, bowed limbs with normal trunk length                                                    | FGFR3 mutation; commonest cause of dwarfism                                                      |

- **Thalidomide** (a sedative/antiemetic used 1957–62) is the archetypal human limb teratogen: exposure between days 24–36 post-fertilisation produced amelia/phocomelia together with intestinal atresia and cardiac anomalies; it remains strictly contraindicated in women of child-bearing age even though it is now used for leprosy and certain malignancies.
- **Surgical relevance:** syndactyly release, polydactyly excision, radial club-hand correction, and Ponseti casting/tenotomy for talipes equinovarus are the standard corrective approaches; DDH is screened by Ortolani/Barlow manoeuvres and ultrasonography in the neonate.

### High-yield exam pointers

- Limb buds appear **end of 4th week**; upper limb precedes lower limb by 1–2 days; upper limb opposite C5–T2, lower limb opposite L2–S2.
- Three signalling centres to name together: **AER (proximodistal, FGF4/FGF8)**, **ZPA (anteroposterior, SHH)**, **dorsal ectoderm (dorsoventral, WNT7a/EN1/LMX1)**.
- Limb outgrowth is initiated by **FGF10** from lateral plate mesoderm; forelimb vs hindlimb identity by **TBX5** vs **TBX4/PITX1**.

- ▶ Digit separation is by **apoptosis**, first splitting the AER into five ridges (day 48), then clearing interdigital mesenchyme (day 51 onward) — failure gives **syndactyly**; excess AER activity/ZPA duplication gives **polydactyly**.
- ▶ Limb muscle is **somitic** in origin (migrated myoblasts), not limb-bud mesenchyme; nerve supply follows dorsal (extensor)/ventral (flexor) division of ventral primary rami.
- ▶ **Thalidomide window** = days 24–36; classical lesion = **phocomelia**.
- ▶ Know the **amelia/meromelia/phocomelia/micromelia** nomenclature cold, and be able to distinguish **syndactyly vs polydactyly vs synpolydactyly** with their genetic basis (HOXD13).
- ▶ Rotation: upper limb **90° laterally**, lower limb **90° medially** — explains adult dermatome/extensor-flexor topography.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Larsen's Human Embryology 6e; IB Singh — Human Embryology (CBME 2021); Sontakke — Textbook of Human Embryology (figures); BD Chaurasia — Human Anatomy Vol 2, 8e (molecular-regulation summary and gross/applied correlation).



## Development of muscular system

Asked in: Paper II 28-May-2025 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The entire muscular system develops from mesenchyme except the sphincter and dilator pupillae of the iris, the arrector pili of the skin, and the myoepithelial cells of sweat/mammary glands, which are of ectodermal origin. Three histological types of muscle — skeletal, smooth, and cardiac — differentiate from mesenchyme during the embryonic period, each from a different mesodermal source. Skeletal muscle arises chiefly from the paraxial mesoderm (somites and somitomeres); smooth muscle mostly from splanchnic (visceral) mesoderm; and cardiac muscle from the splanchnic mesoderm investing the primitive heart tube (myoepicardial mantle). Myogenesis is driven by a conserved family of basic helix-loop-helix (bHLH) myogenic regulatory factors (MyoD, Myf-5, myogenin, Myf-6/herculin).

### 1. Overview of origin of muscle types

| Muscle type | Principal embryonic source                                                                   | Exceptions                                                              |
|-------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Skeletal    | Paraxial mesoderm — somites (trunk/limbs) and somitomeres (head)                             | Extraocular muscles from prechordal + most rostral paraxial mesenchyme  |
| Smooth      | Splanchnic (visceral) mesoderm around gut/respiratory tube; somatic mesoderm in vessel walls | Iris muscles, arrector pili, myoepithelial cells — from <b>ectoderm</b> |

| Muscle type | Principal embryonic source                                            | Exceptions |
|-------------|-----------------------------------------------------------------------|------------|
| Cardiac     | Splanchnic mesoderm surrounding the heart tube (myoepicardial mantle) | —          |

## 2. Development of skeletal muscle — somite subdivision

- ▶ Each **somite** differentiates into a ventromedial **sclerotome** (→ vertebra/rib) and a dorsolateral **dermomyotome**.
- ▶ The dermomyotome splits into a superficial **dermatome** (→ dermis of back) and a deeper **myotome** (→ skeletal muscle).
- ▶ Each typical trunk myotome divides into:
  - **Epimere** (epaxial, dorsal part) — smaller; supplied by the **dorsal primary ramus**; forms the extensor (erector spinae/transversospinalis) muscles of the vertebral column.
  - **Hypomere** (hypaxial, ventral part) — larger; supplied by the **ventral primary ramus**; migrates ventrolaterally in the somatopleuric layer of the coelomic wall to form the muscles of the body wall.
- ▶ Head musculature is derived instead from **seven somitomeres** — partially segmented whorls of unsegmented paraxial (+ prechordal) mesoderm that never form distinct sclerotome/dermomyotome regions.
- ▶ **Modern molecular view (Sadler 14e)**: myogenic precursors are now described as **primaxial** (medial, purely somitic — deep back/intercostal muscles) and **abaxial** (cells that cross the lateral somitic frontier into lateral plate mesoderm — most limb and body-wall muscle), a scheme that supersedes but overlaps the older epimere/hypomere terminology.

□ Fig 8.14 — Fate of the Dermomyotome and Myotome (Larsen — Human Embryology — 6e, p.465)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Transverse section through the trunk of a 40–50-day embryo — label:

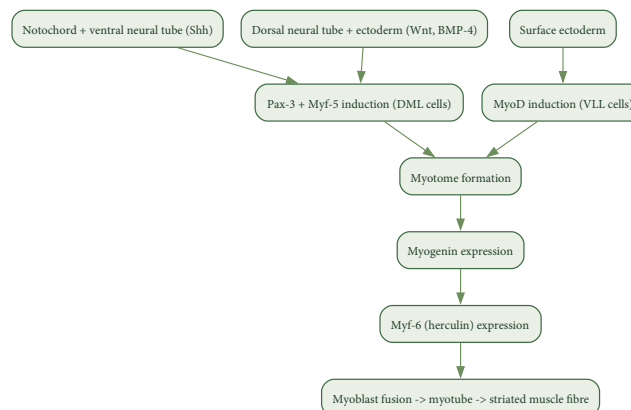
- ▶ Neural tube, notochord/dorsal aorta, somatic mesoderm layer, intraembryonic coelom
- ▶ **Somite** → **dermomyotome** (dorsolateral) + **sclerotome** (ventromedial, around neural tube/notochord)
- ▶ **Dermomyotome** → **dermatome** (superficial) + **myotome** (deep, "disintegrating dermomyotome" sending myogenic cells ventrally)
- ▶ **Myotome** → **epimere** (dorsal, small) supplied by **dorsal ramus** → erector spinae/transversospinalis
- ▶ **Myotome** → **hypomere** (ventral, large) supplied by **ventral ramus** → three concentric muscle layers of the body wall + **rectus column** (rectus abdominis/rectus sternalis/infrahyoid muscles)

## 3. Myogenesis — cellular and molecular events

Cellular sequence:

- ▶ Mesenchymal (myogenic precursor) cells elongate and differentiate into spindle-shaped **myoblasts**.
- ▶ Myoblasts fuse end-to-end into multinucleated cylindrical **primary myotubes**, nuclei initially aligned centrally.
- ▶ Further myoblasts align along and fuse with primary myotubes to form **secondary (and subsequent) generations of myotubes**.
- ▶ Contractile proteins (actin, myosin) assemble into myofilaments and myofibrils; sarcomeres form at the Z-disc; nuclei migrate to the periphery; cross-striations and primitive neuromuscular junctions appear — the structure is now a **muscle fibre**.
- ▶ Some myoblasts remain undifferentiated beneath the external lamina as **satellite cells** — the source of new nuclei for postnatal muscle growth and regeneration.
- ▶ Fibroblasts around the fibres lay down the **endomysium, perimysium, and epimysium**.
- ▶ Almost all skeletal muscles are formed by birth; mitotic activity of myoblasts ceases after birth, so postnatal growth is purely by increase in fibre diameter (more myofilaments), not new fibre number.

**Molecular regulation** — myogenic bHLH transcription factors (MyoD, Myf-5, myogenin, Myf-6) bind E-box DNA motifs to activate muscle-specific genes. Inductive signals: **Shh** (notochord/ventral neural tube) and **Wnts + BMP-4** (dorsal neural tube/overlying ectoderm) act on the dorsomedial lip (DML) of the dermomyotome to induce **Pax-3** and **Myf-5**; surface ectoderm additionally induces **MyoD** in the ventrolateral lip (VLL). Pax-3 also regulates **c-met**, required for migration of limb myogenic precursors. In the somite, expression is sequential: **Myf-5 (earliest) → myogenin → MyoD → Myf-6** (Myf-6 transient in the myotome, becoming the major transcript postnatally); knockout studies show myogenin is essential for forming functional muscle, while Myf-5/MyoD are partly redundant.



*Development of muscular system*

#### 4. Regional development of skeletal muscle

**Muscles of the body wall (trunk)** — hypomeres extend ventrolaterally to form: 3 layers in the thorax (external/internal intercostal, intercostal intimus/transversus thoracis); 3 layers in the abdomen (external oblique, internal oblique, transversus abdominis); in the neck, longus colli, longus capitis and scalenes (representing intercostal muscles). On each side, three primitive layers fuse ventrally into a **longitudinal column** represented by rectus abdominis (abdomen), rectus sternalis (thorax, inconstant),

and infrahyoid muscles (neck). The innermost thoracic layer is later split by the developing lung buds and blends with the septum transversum to help form the **diaphragm**.

#### Muscles of the head and neck

| Region                                    | Myotomic/mesodermal source                                             | Nerve                |
|-------------------------------------------|------------------------------------------------------------------------|----------------------|
| Extraocular muscles                       | 3 preotic myotomes (prechordal mesenchyme around the developing eye)   | CN III, IV, VI       |
| Tongue muscles (all except palatoglossus) | Occipital (postotic) myotomes migrating along the epipericardial ridge | CN XII (hypoglossal) |
| Palatoglossus                             | Pharyngeal arch (4th arch) mesoderm                                    | CN X (vagus)         |

Pharyngeal arch muscles derive from **unsegmented paraxial mesoderm ± prechordal plate** (not myotomes), with neural-crest mesenchyme providing the surrounding skeleton:

| Arch | Nerve                        | Musculature                                                                                     |
|------|------------------------------|-------------------------------------------------------------------------------------------------|
| 1st  | Trigeminal (mandibular div.) | Muscles of mastication, anterior belly of digastric, mylohyoid, tensor tympani, tensor palatini |
| 2nd  | Facial                       | Muscles of facial expression, stylohyoid, posterior belly of digastric, stapedius               |
| 3rd  | Glossopharyngeal             | Stylopharyngeus                                                                                 |
| 4th  | Vagus (superior laryngeal)   | Pharyngeal constrictors, cricothyroid, levator veli palatini                                    |
| 6th  | Vagus (recurrent laryngeal)  | Intrinsic muscles of larynx except cricothyroid                                                 |

**Muscles of the limbs** — myogenic precursors from the ventral (hypaxial) dermomyotome undergo epitheliomesenchymal transformation and migrate into the limb bud (guided by Pax-3/c-met), forming a dorsal and a ventral muscle mass:

- ▶ **Dorsal (extensor) condensation** → extensor/supinator muscles of the upper limb; extensor/adductor muscles of the lower limb.
- ▶ **Ventral (flexor) condensation** → flexor/pronator muscles of the upper limb; flexor/adductor muscles of the lower limb.
- ▶ Ventral primary rami entering the limb bud split into dorsal and ventral divisions that later unite: dorsal divisions → **radial nerve** (supplies extensors); ventral divisions → **ulnar and median nerves** (supply flexors).
- ▶ Upper limb bud lies opposite C4–T2 segments; lower limb bud opposite L1–S2 segments — the basis of the segmental (myotomal) innervation pattern of limb muscles.

## 5. Development of smooth muscle

- ▶ Differentiates from **splanchnic mesenchyme** surrounding the endoderm of the gut and respiratory tract; **somatic mesoderm** contributes smooth muscle to vessel and lymphatic walls.
- ▶ Muscles of the iris (sphincter/dilator pupillae), arrector pili, and myoepithelial cells of sweat/mammary glands arise from **ectoderm** (iris muscle specifically from the optic cup neuroectoderm).
- ▶ Myoblasts elongate (spindle-shaped, oval nuclei) but, unlike skeletal muscle, **do not fuse** — fibres remain mononucleated; contractile elements are non-sarcomeric.

## 6. Development of cardiac muscle

- ▶ Arises from the **myoepicardial mantle**, formed by thickened splanchnic mesoderm around the primitive heart tube; recognisable by the 4th week.
- ▶ Cardiac myoblasts grow by **differentiation of single cells** (not fusion); intervening cell membranes persist as **intercalated discs**, so true syncytium is not formed.
- ▶ Pbx proteins interacting with the transcription factor **Hand2** promote cardiac differentiation.
- ▶ Late in the embryonic period, atypical fibres with few myofibrils and large diameter form **Purkinje fibres**, the conducting system of the heart.

## Applied / Clinical anatomy

- ▶ **Duchenne muscular dystrophy (DMD)** — X-linked recessive; mutation of the *DMD* gene (Xp21) coding for **dystrophin**, which anchors the cytoskeleton (actin) to the extracellular matrix via the sarcolemma; progressive proximal weakness from early childhood, death from cardiorespiratory failure by the late teens/20s.
- ▶ **Poland syndrome** — congenital absence of pectoralis major (often sternal head) ± minor, with ipsilateral breast/nipple hypoplasia and absence of 2–4 ribs; may show syndactyly.
- ▶ **Congenital muscular torticollis** — intrapartum tearing/haematoma of the sternocleidomastoid → fibrosis and shortening → head tilt to affected side with chin turned away.
- ▶ **Arthrogryposis multiplex congenita** — multiple congenital joint contractures (incidence ≈1:3000 live births), from fetal akinesia due to neuropathic or myopathic causes restricting intrauterine movement.
- ▶ **Prune-belly (abdominal muscle deficiency) syndrome** — partial/complete absence of anterior abdominal wall muscles from intrauterine ascitic distension; associated cryptorchidism and megaureter.
- ▶ **Congenital diaphragmatic defects** — incomplete hypaxial contribution to the diaphragm → pulmonary hypoplasia/atelectasis.
- ▶ **Accessory/absent muscles** — palmaris longus, serratus anterior, quadratus femoris commonly absent; accessory soleus present in ~3% (early splitting of the soleus primordium); sternalis muscle is a normal primate remnant occasionally retained in humans.
- ▶ **Clinical correlate of segmental nerve supply** — because a muscle retains the spinal segmental innervation of the myotome from which it arose (irrespective of subsequent migration), this underlies myotomal testing in neurological examination and referred-pain patterns (e.g.,

diaphragmatic irritation referred to the C3,4,5 shoulder-tip dermatome, reflecting the diaphragm's cervical septum-transversum origin).

### High-yield exam pointers

- ▶ All muscle is mesodermal **except** iris muscles, arrector pili, myoepithelial cells (ectodermal).
- ▶ Somite → sclerotome + dermomyotome → dermatome + myotome → **epimere** (dorsal ramus) + **hypomere** (ventral ramus).
- ▶ Head muscles come from **somitomeres**, not myotomes; extraocular from 3 preotic myotomes (III, IV, VI); tongue from occipital myotomes (XII, except palatoglossus — X).
- ▶ Myogenic regulatory factor sequence: **Myf-5** → **myogenin** → **MyoD** → **Myf-6**; inducers Shh (notochord), Wnt/BMP-4 (dorsal neural tube/ectoderm), Pax-3 (regulates c-met for migration).
- ▶ Skeletal muscle forms by **fusion** of myoblasts (multinucleate); cardiac muscle grows by **division of single myoblasts** (mononucleate, intercalated discs, no true syncytium); smooth muscle myoblasts also remain **mononucleated without fusion**.
- ▶ Satellite cells (from somitic myoblasts) are the sole source of new nuclei for postnatal muscle growth/regeneration; all muscle fibres a person will ever have are present at birth.
- ▶ Limb muscle mass splits into dorsal (extensor) and ventral (flexor) condensations, innervated respectively by radial (dorsal divisions) and ulnar/median (ventral divisions) nerves.
- ▶ DMD gene — Xp21, dystrophin; Poland syndrome — pectoralis major absence with rib/breast anomalies; arthrogryposis — 1:3000.

#### SOURCE & COVERAGE

Moore & Persaud, *The Developing Human*, 9e; Vishram Singh, *Textbook of Clinical Embryology*; Langman's *Medical Embryology* (Sadler), 14e; Larsen, *Human Embryology*, 6e; Gray's Anatomy (Standring), 41e; Brijesh Kumar, *Embryology: Text & Atlas* (pharyngeal arch derivative table).

♦ ♦ ♦

### Genetics & inheritance

♦ ♦ ♦



## Craniometry

Asked in: Paper II Oct 2010 · Paper II Apr 2006 (2×) — RGUHS MD/MS Anatomy

**Definition / Introduction** Craniometry is the systematic measurement of the dry skull — its fixed bony landmarks (craniometric points), linear dimensions, and derived indices — carried out with the skull oriented in a standard reference plane. It is the classical tool of physical and forensic anthropology for comparing skulls between individuals, the two sexes, and different populations, and for studying cranial growth. Clinically and radiologically, the same fixed points serve as reproducible surface landmarks for localising intracranial structures, for neurosurgical approaches, and for medicolegal identification of skeletal remains.

### 1. Orientation for craniometry — the Frankfurt (orbitomeatal) plane

- ▶ All craniometric measurements are made with the skull held in the **anatomical position of the skull**, defined by the **Frankfurt's plane**: the lower (infraorbital) margins of both orbits and the upper margins of both external acoustic meatuses lie in one horizontal plane, with the orbits directed forwards.
- ▶ This plane fixes the skull so that measurements taken by different observers, or on serial radiographs/CT, remain comparable.

### 2. Craniometric points

The skull is conventionally described in five *normae* (views) — verticalis, frontalis, lateralis, occipitalis, basalis — and the craniometric points are named landmarks visible in one or more of these views.

#### Median (unpaired) points

| Point                   | Location                                                                                        |
|-------------------------|-------------------------------------------------------------------------------------------------|
| Glabella                | Smooth median elevation above the nasion, between the two superciliary arches (norma frontalis) |
| Nasion                  | Point where the fronto-nasal and internasal sutures meet, at the root of the nose               |
| Ophryon                 | Supranasal point in the midline of the forehead, just above the glabella                        |
| Rhinion                 | Lowest point of the internasal suture                                                           |
| Acanthion               | Tip of the anterior nasal spine                                                                 |
| Prosthion               | Most anterior point on the maxillary alveolar margin, between the central incisors              |
| Pogonion (mental point) | Most anterior midline point of the mandible (chin)                                              |
| Gnathion                | Most inferior midline point of the mandible (base of chin)                                      |
| Metopion                | Point midway between the two frontal tuberosities (norma verticalis)                            |
| Bregma                  | Junction of the coronal and sagittal sutures                                                    |

| Point                            | Location                                                                                      |
|----------------------------------|-----------------------------------------------------------------------------------------------|
| Obelion                          | Point on the sagittal suture between the two parietal foramina                                |
| Vertex                           | Highest point of the skull, a few centimetres behind the bregma                               |
| Lambda                           | Junction of the sagittal and lambdoid sutures                                                 |
| Opisthocranium (occipital point) | Most posteriorly projecting point of the occipital bone; the point farthest from the glabella |
| Inion                            | Most prominent point of the external occipital protuberance                                   |
| Opisthion                        | Mid-point of the posterior margin of the foramen magnum                                       |
| Basion                           | Mid-point of the anterior margin of the foramen magnum                                        |

#### Lateral (paired) points

| Point    | Location                                                                                               |
|----------|--------------------------------------------------------------------------------------------------------|
| Pterion  | H-shaped junction of the frontal, parietal, greater wing of sphenoid and squamous temporal bones       |
| Asterion | Junction of the lambdoid, occipitomastoid and parietomastoid sutures (parietal–occipital–temporal)     |
| Dacryon  | Junction of the fronto-maxillary and lacrimo-maxillary sutures on the medial orbital wall              |
| Jugale   | Union of the temporal and frontal processes of the zygomatic bone                                      |
| Gonion   | Most prominent point on the outer angle of the mandible                                                |
| Porion   | Point on the upper margin of the external acoustic meatus, on the posterior root of the zygomatic arch |

□ Fig 8.6 — Craniometric points. (Moore — Clinically Oriented Anatomy — 9e, p.1346)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the skull in *norma lateralis* and label: Vertex, Bregma, Lambda, Pterion, Asterion, Glabella, Nasion, Prosthion, Gnathion/Pogonion, Gonion, Porion, Inion, Opisthocranium, Basion, Opisthion, the external occipital protuberance and superior nuchal line. Mark two reference lines — glabella→opisthocranium (maximum cranial length) and basion→bregma (cranial height) — and draw the Frankfurt plane as a dashed horizontal line joining the infraorbital margin to the upper margin of the external acoustic meatus.

### 3. Principal linear measurements

| Measurement             | Landmarks used                                                                                                                | Represents                 |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Maximum cranial length  | Glabella → opisthocranium                                                                                                     | Antero-posterior diameter  |
| Maximum cranial breadth | Widest transverse diameter, taken at right angles to the median plane, usually a little below the parietal eminences (tubera) | Greatest width of calvaria |
| Cranial height          | Basion → bregma                                                                                                               | Vertical diameter          |

### 4. Craniometric indices and classifications

| Index / parameter        | Formula or basis                                                   | Classification                                                                                                                                                                         |
|--------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cephalic (cranial) index | $(\text{Maximum breadth} \div \text{maximum length}) \times 100$   | Dolichocephalic (long-headed) <75; Mesaticephalic (mid-headed) 75–80; Brachycephalic (broad/round-headed) >80                                                                          |
| Cranial capacity         | Volume of the cranial cavity                                       | Microcephalic <1350 cm <sup>3</sup> ; Mesocephalic 1350–1450 cm <sup>3</sup> ; Megacephalic >1450 cm <sup>3</sup>                                                                      |
| Facial angle             | Angle between the line nasion–basion and the line basion–prosthion | Reflects the relative development of the facial skeleton (viscerocranium) against the calvaria (neurocranium); a smaller/more acute angle indicates a more prominent, prognathous face |

### 5. Sex differences relevant to craniometry

| Feature                                                                                | Male                   | Female                 |
|----------------------------------------------------------------------------------------|------------------------|------------------------|
| Weight/bone thickness                                                                  | Heavier, thicker walls | Lighter, thinner walls |
| Cranial capacity                                                                       | Greater                | ~10% less than male    |
| Muscular ridges (glabella, superciliary arches, temporal lines, mastoid, nuchal lines) | Well-marked/prominent  | Less marked            |

| Feature               | Male                                                      | Female                                 |
|-----------------------|-----------------------------------------------------------|----------------------------------------|
| Forehead              | Sloping/receding                                          | More vertical, rounded                 |
| Supra-orbital margin  | Rounded, thicker                                          | Sharper                                |
| Mandible/gonial angle | Robust; chin squarer; gonial angle generally $<125^\circ$ | More gracile; gonial angle more obtuse |

## 6. Age-related craniometric changes

- ▶ **Neonatal skull:** facial skeleton forms only about one-seventh of the cranium (cf. much larger fraction in the adult); anterior and posterior fontanelles are present at bregma and lambda respectively.
- ▶ Fontanelles close progressively in infancy; suture fusion (coronal, sagittal, lambdoid) proceeds later and is a less reliable age marker in adults.
- ▶ **Wormian (sutural) bones** are accessory ossicles found within sutures — most common at the **lambda** and **asterion**, fairly common at the **pterion** (called an *epipteric bone*), and rare at the **bregma** (*Os Kerckring*); they are numerous in hydrocephalic skulls.
- ▶ **Abnormal crania:** **Oxycephaly/acrocephaly** ("tower/steeple skull") — an abnormally tall, antero-posteriorly short skull from premature closure of the coronal suture and the presphenoid–postsphenoid synchondrosis, with compensatory upward skull growth. **Scaphocephaly** ("boat-shaped skull") — premature synostosis of the sagittal suture producing a skull elongated antero-posteriorly but narrow from side to side.

## Applied / Clinical anatomy

- ▶ **Pterion** is the thinnest part of the lateral skull wall; it lies deep to the surface point ~4 cm above the mid-zygomatic arch and ~3.5 cm behind the fronto-zygomatic suture, and overlies the **anterior division of the middle meningeal vessels** and the **stem of the lateral (Sylvian) sulcus** — a fracture here is the classic cause of **extradural (epidural) haemorrhage**.
- ▶ **Bregma and lambda** are related to the **superior sagittal sinus**; these points are avoided/respected during burr-hole placement and ventricular shunt insertion.
- ▶ **Asterion** overlies the **sigmoid sinus** and is the key surface landmark for retrosigmoid/translabyrinthine posterior-fossa neurosurgical approaches.
- ▶ **Craniometric points as radiological landmarks:** nasion, bregma, lambda, inion and pterion are used on skull radiographs and CT to standardise cranial measurements and detect abnormal variation.
- ▶ **Forensic/medicolegal identification of skeletal remains** uses craniometry to establish **sex** (robusticity of mandible, mastoid, glabella, supraorbital ridge and gonial angle), **age** (fontanelle/suture closure sequence and, most reliably, dental maturation), and to attempt **ancestry/ethnic-group estimation** from cranial index and facial morphology; craniometric data also underpin **facial approximation (reconstruction)** and **facial superimposition** techniques used to establish personal identity of unknown skeletal remains.

- ▶ **Cephalic index and cranial-capacity classification** are used to characterise population-level variation in skull shape and size; skeletal-morphology-based ethnic classification now plays a reduced role compared with genetic (DNA) markers.

### High-yield exam pointers

- ▶ Craniometry = measurement of the dry skull's fixed points, dimensions and indices, done with the skull set in the **Frankfurt plane**.
- ▶ **Cephalic index** =  $\text{breadth/length} \times 100 \rightarrow <75$  dolichocephalic, 75–80 mesaticephalic,  $>80$  brachycephalic.
- ▶ **Cranial capacity**:  $<1350 \text{ cm}^3$  microcephalic,  $1350\text{--}1450 \text{ cm}^3$  mesocephalic,  $>1450 \text{ cm}^3$  megacephalic.
- ▶ **Facial angle** (nasion–basion–prosthion) reflects viscerocranium-to-neurocranium proportion/prognathism.
- ▶ **Pterion** is the single most clinically important craniometric point — thinnest bone, overlies anterior division of middle meningeal artery  $\rightarrow$  extradural haemorrhage on fracture.
- ▶ **Bregma/lambda**  $\rightarrow$  **superior sagittal sinus**; **asterion**  $\rightarrow$  **sigmoid sinus** — key surgical-avoidance landmarks.
- ▶ **Wormian bones**: common at lambda and asterion, epipteric bone at pterion, rare Os Kerckring at bregma; increased in hydrocephalus.
- ▶ **Oxycephaly** (premature coronal/basal synostosis, tower skull) vs **scaphocephaly** (premature sagittal synostosis, boat-shaped skull).
- ▶ Sex differences: female cranial capacity  $\sim 10\%$  less than male; male gonial angle generally  $<125^\circ$ .

### SOURCE & COVERAGE

Gray's Anatomy (Standing) 41e (forensic identification of the skull — sex, age, ethnic-origin determination, facial approximation/superimposition); BD Chaurasia Human Anatomy Vol 3–4 8e (Craniometry, Cephalic Index, Facial Angle, Abnormal Crania, sex differences of skull); AK Datta Human Anatomy Vol 2 (Head & Neck) (cephalic index, cranial capacity classification, pterion/bregma/lambda/asterion venous-sinus relations); Vishram Singh Textbook of Anatomy Vol 3 4e (Craniometry section — cranial points and measurements); IB Singh Textbook of Anatomy Vol 3 6e (comprehensive craniometric-points list); Moore's Clinically Oriented Anatomy 9e (craniometric points figure/table, clinical use in radiography).

*Coverage note:* this topic is filed under the Genetics specialty group in the RGUHS Paper II scheme, but its technical content (points, indices, sex/age changes) is standard gross-osteology material and is not covered by the assigned genetics texts (Thompson & Thompson, Gangane) — it has instead been grounded against the gross-anatomy specialty books and Gray's forensic-anatomy chapter, as noted above. Regional indices analogous to the cephalic index (e.g. nasal index, orbital index) exist in physical anthropology but their specific numeric classification cut-offs are not detailed in the texts consulted and have therefore been omitted rather than risk an unverified figure.



## Classification of race on the basis of type of hair

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Race, in classical physical anthropology, is a grouping of human populations sharing a cluster of inherited morphological characters — stature, skin colour, head form, nose form and hair character. Hair is one of the oldest anthropometric traits used for this purpose because its form (straight, wavy or woolly) is genetically determined, is stable throughout adult life, and correlates directly with the cross-sectional shape of the hair shaft and the curvature of the hair follicle. On this single character, human populations have traditionally been divided into three principal groups — straight-haired, wavy-haired and woolly-haired — a scheme later refined into composite racial types by combining hair form with skin colour, stature and cranial/facial indices. Modern population genetics, however, treats hair form as a polygenic, continuously variable trait and regards "race" itself as a social rather than a discrete biological category.

### 1. Structural (histological) basis of hair form

- ▶ A hair has three parts — **shaft** (projects above the skin), **root** (within the follicle) and **bulb** (expanded base invaginated by the vascular dermal papilla) — and, in cross-section, three concentric layers from within outward: **medulla** (loosely keratinized cells with air spaces), **cortex** (compactly keratinized cells bearing the melanin that gives hair its colour) and **cuticle** (thin, scaly, heavily keratinized surface layer).
- ▶ **The shape of the hair shaft in cross-section, and the shape/curvature of the follicle that moulds it, together determine hair texture:** a **round** cross-section produces **straight** hair; an **oval** cross-section produces **wavy** hair; a **flattened, ribbon-like (kidney-shaped)** cross-section produces **kinked/woolly** hair. A straight follicle yields a round, straight hair shaft, whereas a curved or spirally-coiled follicle twists the growing shaft into an oval or flattened profile, giving wavy or woolly hair respectively.
- ▶ Hair colour depends on the amount and type of melanin transferred from melanocytes at the follicle base into the cortex; hair form and hair colour are inherited independently of each other, which is why the same hair-form group can show a range of colour (e.g. wavy hair ranges from blond in northern Europeans to black in Mediterranean/Dravidian populations).

□ Fig 5.7 — Detailed structure of the hair follicle: (A) longitudinal section of hair in a follicle and (B) transverse section of hair in the follicle. (Vishram Singh — General Anatomy — 4e, p.192)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a longitudinal section of a hair follicle and label: epidermis, hair shaft, sebaceous gland, arrector pili muscle, external root sheath, internal root sheath, hair bulb, dermal papilla. Beside it, draw three transverse sections of the hair shaft and label each with its cross-sectional shape, resulting hair form, and representative racial group: (a) round → straight (leiotrichous) → Mongoloid; (b) oval → wavy (cymotrichous) → Caucasoid/Australoid; (c) flattened/ribbon-shaped → woolly (ulotrichous) → Negroid. Within each transverse section, label the medulla, cortex and cuticle.

## 2. Classical three-group classification of race by type of hair

Nineteenth/early-twentieth-century physical anthropologists (e.g. Haeckel, Topinard, Deniker) classified mankind primarily on hair form into three major groups, later cross-checked against skin colour and other characters:

| Group (classical term)       | Hair form                           | Shaft cross-section              | Representative racial/population groups                                                                                                                                                                                           |
|------------------------------|-------------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Leiotrichi (straight-haired) | Straight, smooth, generally coarse  | Round                            | Mongoloid races — Chinese, Japanese, Central/East Asians, Native Americans/Amerindians, circumpolar Mongoloids                                                                                                                    |
| Cymotrichi (wavy-haired)     | Wavy to loosely curled              | Oval                             | Caucasoid (Nordic, Alpine, Mediterranean, Armenoid, Dinaric — Europeans and much of the Indian Mediterranean/Dravidian population) and Australoid (Australian aborigines, Vedddoid populations of peninsular India and Sri Lanka) |
| Ulotrichi (woolly-haired)    | Tightly curled, spiralled or tufted | Flattened/ribbon (kidney-shaped) | Negroid races — African Negro populations, Oceanic Negrito/Melanesian groups, Khoisan (Bushmen/Hottentot) peoples                                                                                                                 |

This trichotomy is purely descriptive and was never meant to imply sharp genetic boundaries; considerable overlap and intermediate hair forms occur wherever populations have intermixed.



### 3. Composite racial typing built on hair form: the Indian example

In practice, hair form was combined with stature, head shape, nose form, skin and eye colour to define composite racial elements of a population — illustrated by the classical ethnographic classification of the races of India:

| Racial element                                    | Hair form                | Other features                                                                                                   |
|---------------------------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------|
| Proto-Australoid/Veddoid                          | Curly to wavy            | Short stature, long head, broad flat nose, dark skin — e.g. Chenchus, Veddahs                                    |
| Mediterranean                                     | Wavy                     | Medium/short stature, longish head, medium nose, brown skin — major element among Dravidian-speaking populations |
| Western Brachycephals (Alpinoid/Dinaric/Armenoid) | Wavy                     | Medium stature, round/broad head, convex nose                                                                    |
| Proto-Nordic (Caucasoid)                          | Straight, light-coloured | Tall stature, long head/face, narrow nose, light eyes — northern Indian populations                              |
| Mongoloid                                         | Straight, coarse, dark   | Medium stature, broad/round head, flat face, epicanthic fold                                                     |

None of these types occurs in "pure" form; hair form, like every other anthropometric character, merges gradually from one population into the next through interbreeding.

### 4. Genetic basis of hair-form variation

- ▶ **Hair texture is a classical human example of incomplete dominance:** a straight-haired parent (homozygous) crossed with a woolly/curly-haired parent (homozygous) tends to produce offspring with an intermediate, wavy texture (heterozygote), rather than one form being fully dominant over the other — the same pattern seen with nose size, skin colour and face shape.
- ▶ Hair form is, in reality, **polygenic** — governed by multiple genes acting on the follicle and shaft rather than a single Mendelian locus — which is why hair texture shows continuous (not discretely categorical) variation within and across populations.
- ▶ **Developmentally**, formation of the hair follicle itself (the hair placode) requires **ectodysplasin-A/ectodysplasin-A receptor (EDA/EDAR) and Wnt/ $\beta$ -catenin signalling** between the epidermis and dermal mesenchyme; mutations in this pathway (as in the ectodermal dysplasias) produce sparse, abnormal hair and other ectodermal defects, underscoring that the same molecular pathway that patterns follicles also underlies population-level variation in hair density and shaft form.
- ▶ Keratin genes (hard keratins of the cortex/cuticle) and the follicle inner-root-sheath keratins determine the mechanical properties (curl, coarseness) of the shaft, but no single "race gene" for hair form exists — variation results from allele-frequency differences across populations rather than qualitatively distinct genotypes.

## 5. Modern genetic perspective on race

- ▶ Population genetics documents real differences in allele frequencies (and hence in traits such as skin colour, hair form and facial structure) between geographically and historically separated populations, but it **does not provide a biological foundation for discrete "races"** — racial categories are, from a genetics standpoint, social constructs built on a few visible characters that vary continuously (clinally), not on fixed genetic boundaries.
- ▶ **Ancestry-informative markers (AIMs)** and genome-wide analyses (e.g. principal-component clustering of West African/European/Native American ancestry) now give a far more accurate estimate of an individual's biogeographic ancestry than self-declared race or visible traits such as hair form or skin colour, and are increasingly used in place of racial labels for medically relevant risk-stratification.
- ▶ This mirrors the caution attached to skull-based (craniometric) race determination — visual/morphological classification is useful for a "most likely" categorisation (e.g. in forensic settings) but shows substantial overlap between groups and a full spectrum of intermediate forms within any single population.

## Applied / Clinical anatomy

- ▶ **Forensic trichology:** at a crime scene or in disputed identity, an unknown hair is examined microscopically for shaft **cross-sectional shape** (round/oval/flattened), **curvature**, **medullary pattern** (continuous, fragmented or absent) and **pigment granule size/distribution** to give a preliminary opinion on probable ancestry/race — always confirmed, where possible, by mitochondrial or nuclear **DNA analysis**, which is the definitive method today.
- ▶ **Hair as trace evidence:** hair form and colour (root/shaft/bulb) also help estimate whether a hair was shed naturally, forcibly pulled (bulb present) or cut, and are examined alongside skin and skeletal (craniometric) features in medico-legal identification of unknown remains.
- ▶ **Clinical relevance of shaft/follicle shape:** developmental follicle/shaft anomalies unrelated to race (e.g. **pili torti** — twisted flattened shaft, **monilethrix** — beaded shaft) illustrate how structural deviation of the same medulla–cortex–cuticle architecture produces abnormal hair independent of racial hair-form variation.
- ▶ **Genetic counselling relevance:** because hair texture follows incomplete-dominance/polygenic inheritance, it is used as a simple classroom example of non-Mendelian (intermediate) inheritance when counselling about phenotype prediction in mixed-ancestry families.

## High-yield exam pointers

- ▶ Hair form depends on the **cross-sectional shape of the shaft**: round → straight, oval → wavy, flattened/ribbon → woolly; the follicle's own curvature (straight/curved/coiled) moulds this shape.
- ▶ Classical **three-group hair-based classification**: **Leiotrichi** (straight – Mongoloid), **Cymotrichi** (wavy – Caucasoid/Australoid), **Ulotrichi** (woolly – Negroid).
- ▶ Hair form is combined with stature, head shape, nose form and skin colour to define composite racial elements (e.g. Guha-type classification of Indian races: Proto-Australoid/Veddoid, Mediterranean, Western Brachycephals, Proto-Nordic, Mongoloid).

- ▶ Hair texture is a textbook human example of **incomplete dominance** (straight × woolly → wavy heterozygote) and is polygenically inherited.
- ▶ Hair follicle (placode) development requires **EDA/EDAR–Wnt/ $\beta$ -catenin signalling**; defects in this pathway cause ectodermal dysplasias with hair anomalies.
- ▶ No single racial hair-form group is "pure" — intermediate/blended forms are the rule wherever populations have intermixed.
- ▶ Modern population genetics regards race as a **social construct**, not a discrete biological/genetic category; ancestry-informative markers are more accurate than visible traits like hair form.
- ▶ **Forensic use:** hair cross-section, medullary pattern and pigment distribution give a preliminary ancestry opinion, confirmed by DNA analysis.

### SOURCE & COVERAGE

Vishram Singh — General Anatomy 4e (structure of hair, follicle, texture determined by shaft cross-section, Fig. 5.7); IB Singh — Textbook of Anatomy Vol 1 6e (hair shaft shape and straight/wavy/kinked correlation); IB Singh — Textbook of Anatomy Vol 3 6e (hair texture as an example of incomplete dominance); Larsen — Human Embryology 6e (EDA/EDAR–Wnt signalling in hair placode/follicle development); Thompson & Thompson — Genetics in Medicine 8e (population genetics and race, ancestry-informative markers, race as a social construct); Gray's Anatomy (Standring) 41e (structure of hairs; limitations of visual/morphological race classification); Handbook of Museum Technique (Govt Museum Chennai) (classical ethnographic/racial classification of Indian populations correlating hair form with composite racial type).

*Coverage note:* this topic is filed under the Genetics specialty group, but the classical hair-based racial taxonomy (Leiotrichi/Cymotrichi/Ulotrichi and their further historical subdivisions) is standard physical-anthropology/forensic-medicine teaching that is not covered in the assigned genetics texts (Thompson & Thompson, Gangane) or in Gray's Anatomy; it has therefore been grounded against the general-anatomy integument chapters and the library's ethnographic reference (Handbook of Museum Technique) for the composite Indian racial-type table, with the genetics of hair-form inheritance and the modern population-genetics view of "race" drawn from Thompson & Thompson as the specialty text. Second-order historical sub-group names and any numeric hair-curvature/hair indices are not detailed in the texts consulted and have been omitted rather than risk an unverified figure.



## Cranial index

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **cranial index** (also called the length-breadth index) is a craniometric ratio that expresses the shape of the skull, calculated as the maximum breadth of the cranium expressed as a percentage of its maximum length. It is measured directly on the dry cranium with a sliding/spreading compass — the equivalent measurement taken with calipers on the soft-tissue-covered living head is called the **cephalic index**, using the identical formula. First systematised by 19th-century physical anthropologists (Retzius) to compare skulls across human populations, the cranial index remains a classic tool of **craniometry** — the discipline of taking standardised skull measurements — and is used in physical and forensic anthropology to classify skull shape, estimate ancestry/population affinity, and, in genetics, as an example of a continuously variable, polygenically determined anthropometric (quantitative) trait.

### Craniometric points used in the measurement

Craniometry uses fixed, reproducible bony landmarks (craniometric points) to standardise measurements between observers and specimens. The points relevant to the cranial index, and other commonly tested points on the same views of the skull, are:

| Point                            | Location                                                                                      |
|----------------------------------|-----------------------------------------------------------------------------------------------|
| Glabella                         | Median elevation between the two superciliary arches, at the root of the nose                 |
| Opisthocranium (occipital point) | Most posteriorly projecting point on the occipital bone in the midline                        |
| Bregma                           | Junction of the coronal and sagittal sutures                                                  |
| Lambda                           | Junction of the sagittal and lambdoid sutures                                                 |
| Nasion                           | Junction of the nasal bones with the frontal bone                                             |
| Prosthion                        | Lowest point on the upper jaw, between the central incisors                                   |
| Gnathion                         | Midpoint of the lower border of the mandible in the midline                                   |
| Basion                           | Central point on the anterior margin of the foramen magnum                                    |
| Opisthion                        | Central point on the posterior margin of the foramen magnum                                   |
| Pterion                          | Region where the frontal, parietal, greater wing of sphenoid and squamous temporal bones meet |
| Asterion                         | Region where the occipital, parietal and temporal bones meet                                  |
| Gonion                           | Outer point of the angle of the mandible                                                      |

| Point   | Location                                                                                                                  |
|---------|---------------------------------------------------------------------------------------------------------------------------|
| Porion  | Point on the posterior root of the zygomatic arch, above the midpoint of the upper border of the external acoustic meatus |
| Dacryon | Junction of the lacrimomaxillary and frontomaxillary sutures                                                              |

## Measurement and formula

- ▶ **Maximum cranial length** is the glabello-occipital length — the straight-line distance from the centre of the **glabella** to the **opisthocranium**.
- ▶ **Maximum cranial breadth** is the greatest transverse diameter of the calvaria measured at right angles to the median sagittal plane; it is usually recorded a little below the parietal tubera/eminences, on the norma verticalis (superior) view.
- ▶ The cranial index is then:

$$\text{Cranial index} = (\text{Maximum cranial breadth} \div \text{Maximum cranial length}) \times 100$$

- ▶ Length and breadth are taken with a **spreading (or sliding) compass**; the same formula applied to soft-tissue landmarks on a living subject, measured with callipers, gives the **cephalic index** — the field-survey equivalent used in population/anthropometric studies where dry skulls are unavailable.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A norma-verticalis (superior view) outline of the skull, labelled with:

- ▶ **Glabella** — anterior end of the maximum-length line, in the midline
- ▶ **Opisthocranium** — posterior end of the maximum-length line, in the midline
- ▶ A straight line joining glabella to opisthocranium, marked "**maximum length**"
- ▶ A transverse line at the widest point of the vault (near the parietal eminences), marked "**maximum breadth**"
- ▶ **Sagittal suture** running in the midline between bregma and lambda
- ▶ The formula box:  $\text{Cranial index} = (\text{Maximum breadth} / \text{Maximum length}) \times 100$
- ▶ Three small comparison outlines beside the main diagram showing the silhouette contrast between a **narrow, elongated** (dolichocephalic), an **oval, intermediate** (mesaticephalic) and a **short, rounded** (brachycephalic) vault, so the shape-index relationship is visually obvious.

□ Fig 8.6 — Craniometric points. (Moore — Clinically Oriented Anatomy — 9e, p.1346)

## Classification of skull shape by cranial index

| Type                                         | Cranial index     | Description              |
|----------------------------------------------|-------------------|--------------------------|
| Dolichocephalic (long-headed)                | 75 or less        | Narrow, elongated skull  |
| Mesaticephalic (mesocephalic; medium-headed) | Between 75 and 80 | Intermediate, oval shape |

| Type                                       | Cranial index | Description                 |
|--------------------------------------------|---------------|-----------------------------|
| <b>Brachycephalic</b> (round/broad-headed) | Above 80      | Short, broad, rounded skull |

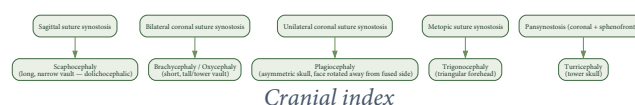
- **Dolichocephaly** is characteristic of more primitive/older human population groups, e.g. Eskimos and many African groups.
- A trend from **dolichocephaly** through **mesaticephaly** toward **brachycephaly** has been observed as a continuous change in some more recently evolved population groups, e.g. Europeans — illustrating that the index reflects population-level secular change and is not a fixed racial marker.

## Population variation and anthropological/genetic significance

- Craniometry, including the cranial index, is used by physical and forensic anthropologists in attempts to estimate **ethnic/ancestral affinity** from skeletal remains, alongside other skull features (nasal aperture shape, supraorbital ridging, prognathism, palate shape) — a core application in **personal identification** of unknown skeletal remains.
- Classical anthropological teaching recognised four broad population groupings on skull morphology — **Caucasoid, Negroid, Mongoloid and Australoid**:
  - **Caucasoid** skulls are classically described as rounded-to-long (dolichocephalic), with a narrow nasal aperture, a prominent nasal spine and a steep forehead.
  - **Negroid** skulls are also long, with a wide nasal aperture, marked alveolar prognathism and a low nasal root.
  - **Mongoloid** skulls are generally described as round, with well-developed, high cheek bones and a foreshortened, vertical-forehead profile — the group in which brachycephalic tendency is most classically emphasised.
- This classification is now understood to be an oversimplification — modern genetics recognises human variation as clinal and overlapping rather than discretely racial — but the skull (and indices such as the cranial index) remains the anatomical region most often analysed for this purpose in forensic practice.
- **Genetic basis**: like stature, the cranial index is a continuously distributed, **quantitative (polygenic/multifactorial) trait** — it is determined by the combined small effects of multiple genes plus nutritional and environmental influences during growth, rather than by a single gene, which is why it is studied statistically across populations rather than through Mendelian pedigree analysis.

## Applied / Clinical anatomy

- **Craniosynostosis and cranial shape**: premature fusion of individual cranial sutures distorts the cranial index characteristically —



- **Scaphocephaly** (sagittal synostosis) is the commonest craniosynostosis and produces an exaggeratedly dolichocephalic (long, narrow) vault.

- ▶ **Brachycephaly/oxycephaly** from bilateral coronal synostosis produces marked supraorbital recession and reduced anteroposterior growth.
- ▶ **Forensic/medicolegal use:** the cranial index contributes, together with other skull measurements, to estimation of **sex, age, stature and probable ancestry** from unidentified skeletal remains — a standard task in forensic anthropology and personal identification.
- ▶ **Wormian (sutural) bones**, additional ossicles found along the lambdoid, sagittal and other sutures, are noted incidentally during craniometric examination and are more frequent in hydrocephalic skulls.
- ▶ **Nutritional/secular trend:** because the index is a polygenic, environmentally modifiable trait, population-level shifts in cranial index over generations (the dolichocephalic-to-brachycephalic trend noted above) are attributed to changing nutrition and other environmental factors rather than to a change in gene frequency alone.

### High-yield exam pointers

- ▶ **Cranial index** =  $(\text{Maximum cranial breadth} \div \text{Maximum cranial length}) \times 100$ , measured directly on the dry skull; the same formula on the living head (calipers, soft tissue) is the **cephalic index**.
- ▶ **Length** = glabella → opisthocranium; **breadth** = greatest transverse diameter at right angles to the median plane, near the parietal tubera.
- ▶ Classification: **Dolichocephalic**  $\leq 75$ ; **Mesaticephalic** 75–80; **Brachycephalic**  $> 80$ .
- ▶ Dolichocephaly = primitive/older population groups (e.g. Eskimos, many African groups); trend toward brachycephaly through mesaticephaly seen in some recently evolved groups (e.g. Europeans).
- ▶ Four classical anthropological skull groupings: **Caucasoid, Negroid, Mongoloid, Australoid** — used (with caveats) in forensic ancestry estimation.
- ▶ Cranial index is a **polygenic/multifactorial quantitative trait**, analogous statistically to stature — continuously distributed, not single-gene.
- ▶ Applied importance: **craniosynostosis** distorts the index characteristically (sagittal → scaphocephaly/dolichocephaly; bilateral coronal → brachycephaly/oxycephaly; unilateral coronal → plagiocephaly; metopic → trigonocephaly); and it is used in **forensic personal identification** of skeletal remains.



**SOURCE & COVERAGE**

BD Chaurasia — Human Anatomy Vol 3-4, 8e; Vishram Singh — Textbook of Anatomy Vol 3, 4e; IB Singh — Textbook of Anatomy Vol 3, 6e; Moore's Clinically Oriented Anatomy, 9e; Gray's Anatomy (Standring) 41e (forensic/ethnic-origin skull morphology); Thompson & Thompson — Genetics in Medicine, 8e (quantitative/multifactorial-trait framework).

**Coverage note:** Gray's Anatomy (Standring) 41e does not define the cranial index formula or its numerical classification (confirmed by a full-text search); this content is grounded instead in the gross-anatomy/osteology texts (BD Chaurasia, Vishram Singh, IB Singh), which agree exactly on the formula and cut-offs. The genetics texts (Thompson & Thompson, Gangane) do not discuss craniometry directly — the genetics angle here is drawn from the standard quantitative/multifactorial-trait framework in Thompson & Thompson, applied to this classically anthropometric measurement.



## Describe Final Steps to Modern Man

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — Modern man (*Homo sapiens sapiens*) is the sole surviving species of family Hominidae, order Primates. Human evolution is the progressive anatomical, physiological and cultural transformation of primate ancestors into anatomically modern humans over roughly 20 million years. The "final steps" to modern man refer to the last three fossil hominid stages — *Homo erectus*, archaic *Homo sapiens* (Neanderthal man) and *Homo sapiens sapiens* (Cro-Magnon man) — that directly preceded, and gave rise to, the modern human form, together with the accompanying morphological remodelling of the head/face and the cultural transitions that made this transformation possible.

### 1. Taxonomic position of modern man (starting point of the discussion)

| Taxon     | Group      | Diagnostic feature                                           |
|-----------|------------|--------------------------------------------------------------|
| Kingdom   | Animalia   | Eukaryotic, no cell wall/photosynthetic pigment              |
| Phylum    | Chordata   | Notochord, pharyngeal pouches                                |
| Subphylum | Vertebrata | Vertebral column                                             |
| Class     | Mammalia   | Mammary glands, hair                                         |
| Order     | Primata    | Well-developed brain, prehensile hands                       |
| Family    | Hominidae  | Large cerebrum, bipedal locomotion                           |
| Genus     | Homo       | Flattened face, prominent chin, inferiorly directed nostrils |

| Taxon   | Group   | Diagnostic feature |
|---------|---------|--------------------|
| Species | sapiens | Largest cerebrum   |

Distinctive traits of modern man: erect posture, well-developed cognitive intelligence, opposable thumb, stereoscopic (binocular) vision, prominent chin, well-articulated speech, and fine coordinated skilled hand movements. Average cranial capacity of modern man is  $1200\text{--}1600\text{ cm}^3$  ( $\approx 1500\text{ cc}$ ), the two most important defining characters being the highly developed brain and the opposable thumb.

## 2. Ancestral background before the final steps (brief context)

- **Dryopithecus/Proconsul** group — Miocene ape stock (Africa), regarded in standard anatomy texts as among the earliest fossils in the human lineage; arboreal, quadrupedal, small brain.
- **Australopithecus** (e.g., *A. afarensis*, *A. africanus*) — earliest confirmed bipedal hominid, small cranial capacity ( $\approx 450\text{--}550\text{ cc}$ ), still ape-like jaws and brow ridges.
- **Homo habilis** — first habitual tool-maker (crude pebble/Oldowan tools), cranial capacity increased to  $\approx 600\text{--}750\text{ cc}$ .

These earlier stages set the stage for, but are distinct from, the "final steps" that the question specifically asks for — the transition through *Homo erectus* to modern man.

## 3. The final hominid stages leading to modern man

| Stage                                                                           | Approx. period                                                                   | Cranial capacity                                                      | Representative fossils                                                                                       | Posture / build                                                                                  | Culture                                                                          |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| <b>Homo erectus</b>                                                             | $\sim 1.8\text{ mya} - 300,000\text{ y}$                                         | $\sim 900\text{--}1100\text{ cc}$                                     | "Ape-man of Java" ( <i>Pithecanthropus erectus</i> ), "Ape-man of Peking" ( <i>Sinanthropus pekinensis</i> ) | Fully erect, robust limb bones                                                                   | First controlled use of fire, hand-axes, first hominid to migrate out of Africa  |
| <b>Archaic Homo sapiens / Homo sapiens neanderthalensis</b> ("Neanderthal man") | $\sim 400,000\text{--}40,000\text{ y}$                                           | $\sim 1200\text{--}1750\text{ cc}$ (often larger than modern average) | European and Middle-Eastern cave sites                                                                       | Short, heavily built, prominent brow ridges, receding forehead and chin                          | Mousterian flake tools, ceremonial burial of the dead, use of fire               |
| <b>Homo sapiens sapiens</b> ("Cro-Magnon man")                                  | from $\sim 300,000\text{ y}$ (Africa); reaching Europe by $\sim 45,000\text{ y}$ | $\sim 1350\text{ cc}$                                                 | Cro-Magnon (Europe)                                                                                          | Gracile skeleton, high vertical forehead, reduced brow ridges, prominent chin, fully plantigrade | Blade tools, symbolic cave art, burial ritual, language, agriculture (Neolithic) |

Anatomy texts identify **Cro-Magnon man** as the **direct ancestor of modern living man** — i.e., anatomically modern *Homo sapiens sapiens*.

#### 4. Morphological (anatomical) changes of the final steps — "evolution of the head"

The head/face changes that mark the transition to modern man result from two linked factors: **progressive reduction in jaw size** and a **concomitant increase in cranial-cavity/brain size** — the two vary inversely.

- ▶ **Posture:** change from pronograde (four-footed, e.g. dog) → orthograde (ape/monkey) → plantigrade (two-footed, modern man); this "emancipation of the forelimbs" frees the upper limb from weight-bearing.
- ▶ **Jaw and face:** a pronograde animal has large jaws/small head; an orthograde animal (ape) has smaller jaws/larger head; plantigrade man has the smallest jaws and the largest head of all. Jaw reduction follows the freed upper limbs (no longer needed for tactile feeling, holding, tearing) and the habit of eating cooked food.
- ▶ **Chin and mouth:** alveolar arches broaden and the chin is pushed forward (making the oral cavity roomier) to allow tongue mobility for articulate speech; the oral aperture is reduced, lips supported by well-developed orbicularis oris.
- ▶ **Nose:** a distinctive prominent external nose (dorsum, tip, alae) is a uniquely human feature.
- ▶ **Orbits/eyes:** eyes directed forward (not lateral, as in lower mammals) permitting stereoscopic vision; palpebral fissures larger, bony orbits smaller than in great apes; interorbital distance greater than in apes.
- ▶ **Brow ridges and forehead:** supraorbital margins are markedly reduced compared to the heavy brow ridges of *Homo erectus*/Neanderthal; a prominent vertical forehead develops (protecting the eyes from above) as the cranial cavity enlarges.
- ▶ **Special senses:** progressive reduction in importance of smell with a corresponding rise in vision, correlated with the arboreal habit of earlier primate ancestors and, later, with erect bipedal posture in man.

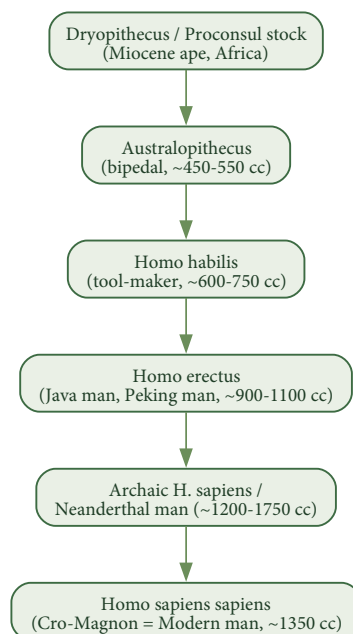
□ Fig 12.6 — Size of the jaws relative to the size of the head during evolution (BD Chaurasia — Human Anatomy Vol 3-4 — 8e, p.615)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Freehand skull-profile series (left → right) with these exact labels on each profile:

- ▶ **Pronograde stage** (dog/cow-type): large jaw, small braincase
- ▶ **Orthograde stage** (ape/monkey-type): smaller jaw, larger braincase, heavy brow ridge
- ▶ **Homo erectus**: sloping forehead, prominent brow ridge, moderate cranial capacity (~1000 cc)
- ▶ **Neanderthal** (archaic *H. sapiens*): receding forehead, heavy brow ridge, large but elongated braincase
- ▶ **Cro-Magnon / modern man (plantigrade stage)**: smallest jaw, prominent chin, vertical forehead, largest rounded braincase (~1500 cc)

Below the series, draw an arrow labelled "increasing brain size" and an inverse arrow labelled "decreasing jaw size."



*Describe Final Steps to Modern Man*

## 5. Molecular/genetic evidence for the final steps — the "Out of Africa" transition

DNA sequencing of bone samples from three Neanderthals who died approximately 38,000 years ago in Europe has directly informed the final steps to modern man:

- ▶ The most recent common ancestor of Neanderthals and *Homo sapiens* lived in Africa over **200,000 years ago**, well before Neanderthals migrated out of Africa to settle in Europe and the Middle East.
- ▶ Sequence analysis shows that **1–4% of the DNA of modern Europeans and Asians — but not of native Africans — matches Neanderthal DNA**, indicating limited interbreeding (admixture) between the two groups.

- ▶ Statistical dating places this admixture at approximately **50,000 years ago**, i.e. after modern humans had already migrated out of Africa into Europe and beyond — which explains why the Neanderthal genomic signature is absent in present-day Africans.
- ▶ Comparative analysis of Neanderthal and modern-human genomes continues to reveal characteristic differences and the relative frequency of disease-associated alleles between archaic and modern populations.

This molecular evidence supports the "**Out of Africa**" (**replacement**) **model**: anatomically modern *Homo sapiens sapiens* arose in Africa and subsequently dispersed worldwide, partially interbreeding with, and eventually replacing, archaic populations such as the Neanderthals.

## 6. Cultural evolution accompanying the final anatomical steps

Anthropological (pre-historic) staging, paralleling the biological final steps, is traditionally divided by level of culture:

- ▶ **Palaeolithic (Old Stone) Age** — man was a food-gatherer, made chipped stone/bone/antler tools for digging, hunting and fishing, knew the use of fire, and is credited with ceremonial burial of the dead (associated with Neanderthal/early *H. sapiens*).
- ▶ **Neolithic (New Stone) Age** — food-gathering gave way to **agriculture and domestication of animals**; stone tools became ground and polished; pottery-making began (associated with *Homo sapiens sapiens*).
- ▶ **Bronze and Iron Ages** — discovery of metal-working; settled river-valley urban civilisations developed.

With worldwide dispersal after the "Out of Africa" migration, geographically isolated populations of *Homo sapiens sapiens* differentiated into the major races of mankind on the basis of stature, skin/hair/eye colour and head/face/nose form — broadly grouped as **Negroid, Caucasoid, Mongoloid and Australoid**, with further subdivision of the Caucasoid group (Nordic, Alpine, Mediterranean, etc.).

## Applied / Clinical anatomy

- ▶ **Obstetric dilemma**: the combination of a narrowed, bipedal-adapted pelvis with the large cranial capacity attained in the final steps to modern man necessitates a tight fit and rotational descent of the fetal head during labour — the anatomical basis of prolonged/obstructed labour and a leading indication for instrumental delivery/caesarean section.
- ▶ **Low backache and disc disease**: erect bipedal posture, a late acquisition in the final steps, imposes axial load on the lumbosacral spine, predisposing modern man to lumbar lordosis-related backache and intervertebral disc prolapse — a "price of bipedalism."
- ▶ **Impacted third molars**: progressive jaw reduction (without matching reduction in tooth number/size) in the final steps to modern man leaves insufficient space in the modern mandible/maxilla, resulting in the very high frequency of impacted wisdom teeth.
- ▶ **Vestigial structures**: vermiform appendix, coccygeal vertebrae, and auricularis/plica semilunaris are cited as anatomical remnants of ancestral (pre-modern) organisation retained in modern man.

- ▶ **Forensic/physical anthropology:** skull morphology (brow ridge prominence, forehead slope, chin development, cranial capacity) used in the final steps described above remains the basis of skeletal age, sex and race estimation in forensic anthropology.
- ▶ **Neanderthal-derived alleles:** comparison of archaic and modern genomes (as sequenced from Neanderthal bone) is used to study frequencies of disease-predisposing alleles retained in modern non-African populations through ancient admixture.

### High-yield exam pointers

- ▶ Modern man = *Homo sapiens sapiens*; family Hominidae; order Primata; genus *Homo*.
- ▶ The "final steps" = *Homo erectus* → archaic *Homo sapiens* (Neanderthal man) → *Homo sapiens sapiens* (Cro-Magnon man).
- ▶ Anatomy texts identify Cro-Magnon man as the direct ancestor of modern living man.
- ▶ Two most important defining human characteristics: **highly developed brain** and **opposable thumb**; mode of locomotion is **bipedal**.
- ▶ Average cranial capacity of modern man: **1200–1600 cm<sup>3</sup> (≈1500 cc)**.
- ▶ Across the final steps, **jaw size is inversely proportional to cranial/brain size** (pronograde → orthograde → plantigrade).
- ▶ Molecular evidence: common ancestor of Neanderthals and *H. sapiens* lived in Africa **>200,000 years ago**; **1–4% Neanderthal DNA** persists in modern non-African genomes, absent in native Africans; admixture dated to **~50,000 years ago**, after the Out-of-Africa dispersal.
- ▶ Cultural final steps parallel the biological ones: Palaeolithic (fire, burial) → Neolithic (agriculture, pottery) → Bronze/Iron Age (urban civilisation).
- ▶ Post-dispersal geographic differentiation produced the four principal modern races: **Negroid, Caucasoid, Mongoloid, Australoid**.

### SOURCE & COVERAGE

Vishram Singh — General Anatomy 4e (taxonomic classification, characteristic features, cranial capacity, Cro-Magnon as direct ancestor of modern man); BD Chaurasia — Human Anatomy Vol 3-4 8e ("Evolution of the Head" — posture, jaw/brain-size relationship, facial/orbital changes, Fig. 12.6); Handbook of Museum Technique, Govt Museum Chennai (Physical Anthropology — Java/Peking/Neanderthal/Cro-Magnon fossil types, Palaeolithic–Neolithic–Bronze–Iron Age cultural stages, races of mankind); Thompson & Thompson — Genetics in Medicine 8e (Neanderthal genome sequencing, Out-of-Africa admixture data).

**Coverage note:** the modern specialty genetics texts in this corpus do not carry a dedicated stage-by-stage palaeoanthropology account; the specific fossil-stage sequence (Dryopithecus/Australopithecus/Homo habilis dates and cranial-capacity ranges) reflects universally accepted standard MD/MS Anatomy curriculum knowledge, layered onto the corpus-confirmed facts cited above (taxonomy, evolution-of-head morphology, and Neanderthal genomic admixture data).



## Hermaphroditism

Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** Hermaphroditism (syn. intersexuality) is the classical term for a group of congenital conditions in which the chromosomal, gonadal and phenotypic (genital) sex of an individual are discordant, so that the affected person shows genital and/or gonadal features of both sexes. Because male and female development proceeds from a common indifferent (ambisexual) precursor under the control of a small set of genes and hormones, any derangement of this cascade — chromosomal, gonadal, enzymatic or receptor-level — produces ambiguous genitalia. The 2006 Chicago consensus replaced the older, stigmatising terms "hermaphroditism"/"pseudohermaphroditism" with "Disorders of Sex Development (DSD)"; classical anatomy/embryology texts still use the old nomenclature, which is retained below alongside its modern equivalent.

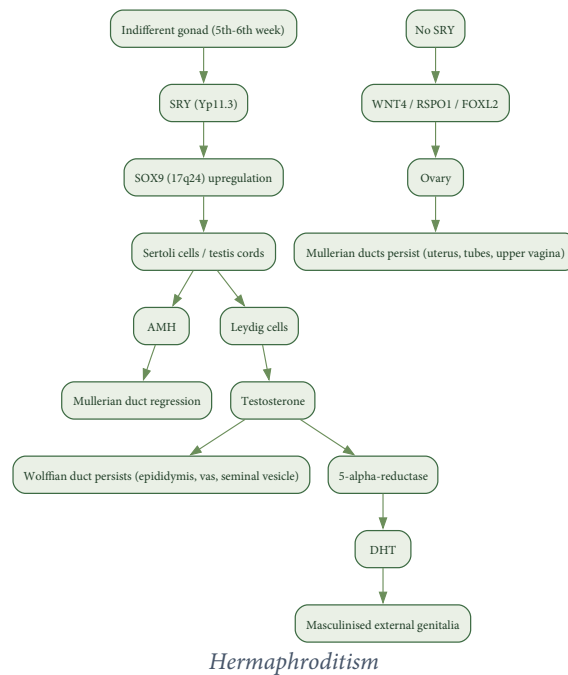
### 1. Genetic and hormonal basis of normal sex differentiation

- ▶ The bipotential (indifferent) gonad forms in the 5th–6th week from the genital ridge — mesothelium and underlying mesenchyme on the medial aspect of the mesonephros — colonised by primordial germ cells migrating from the wall of the yolk sac.
- ▶ **SRY** (Sex-determining Region of Y; locus **Yp11.3**) is the master testis-determining gene. It is expressed transiently in the pre-Sertoli cells of the indifferent gonad and up-regulates **SOX9** (locus **17q24**), committing these cells to a Sertoli rather than granulosa fate and initiating testis-cord formation.
- ▶ Sertoli cells secrete **anti-Müllerian hormone (AMH)**, causing regression of the paramesonephric (Müllerian) ducts; Leydig cells secrete **testosterone**, which stabilises the mesonephric (Wolffian) duct into epididymis, vas deferens and seminal vesicle.
- ▶ Peripheral **5 $\alpha$ -reductase** converts testosterone to **dihydrotestosterone (DHT)** in the genital tubercle, urogenital folds and labioscrotal swellings, virilising the external genitalia into glans penis, penile urethra and scrotum, and inducing prostate formation.
- ▶ In the absence of SRY, genes such as **WNT4**, **RSPO1** and **FOXL2** actively drive the ovarian pathway: Müllerian ducts persist as uterus, tubes and upper vagina, Wolffian ducts regress, and the absence of DHT keeps the external genitalia female (clitoris, labia minora/majora).
- ▶ Other genes implicated in disorders of gonadal/genital determination (Thompson & Thompson, Table 6-8):

| Gene | Locus  | Effect of mutation/duplication                                                                                     |
|------|--------|--------------------------------------------------------------------------------------------------------------------|
| SRY  | Yp11.3 | Mutation → female, 46,XY gonadal dysgenesis (Swyer syndrome); translocation to X → male, 46,XX (ovo)testicular DSD |
| SOX9 | 17q24  | Mutation → 46,XY gonadal dysgenesis + camptomelic dysplasia; duplication in 46,XX → XX testicular DSD              |



| Gene         | Locus  | Effect of mutation/duplication                                           |
|--------------|--------|--------------------------------------------------------------------------|
| NR5A1 (SF1)  | 9q33   | Mutation → ambiguous genitalia, 46,XY partial gonadal dysgenesis         |
| DAX1 (NR0B1) | Xp21.3 | Duplication antagonises SRY → female, 46,XY gonadal dysgenesis           |
| WNT4         | 1p35   | Duplication (in 46,XY) → ambiguous genitalia, cryptorchidism             |
| AR           | Xq12   | Mutation → complete/partial androgen insensitivity syndrome              |
| CYP21A2      | 6p21.3 | Mutation (21-hydroxylase deficiency) → virilisation, ambiguous genitalia |



Hermaphroditism

## 2. Classification of hermaphroditism (old term) / DSD (modern equivalent)

| Old term             | Modern DSD term   | Gonads                                      | Usual karyotype                                                      | Chief cause(s)                                                                                                |
|----------------------|-------------------|---------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| True hermaphroditism | Ovotesticular DSD | Ovary + testis, often combined as ovotestis | Majority 46,XX (~80%); also 46,XY; mosaics (45,X/46,XY; 46,XX/46,XY) | SRY translocated to X (SRY+ cases); SOX9/SOX3 up-regulation bypassing SRY requirement (SRY– cases); mosaicism |

| Old term                     | Modern DSD term | Gonads  | Usual karyotype | Chief cause(s)                                                                                                              |
|------------------------------|-----------------|---------|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| Male pseudohermaphroditism   | 46,XY DSD       | Testes  | 46,XY           | Androgen insensitivity syndrome; 5 $\alpha$ -reductase deficiency; testosterone-biosynthesis enzyme defects; Swyer syndrome |
| Female pseudohermaphroditism | 46,XX DSD       | Ovaries | 46,XX           | Congenital adrenal hyperplasia (commonest cause of ambiguous genitalia overall); maternal androgen/progestin exposure       |

Sex-chromosome DSDs — Klinefelter (47,XXY) and Turner (45,X) syndromes — are gonadal-dysgenesis disorders and are not classified as hermaphroditism; they are dealt with as separate entities.

### 3. True hermaphroditism (Ovotesticular DSD)

- ▶ Extremely rare. Gonads contain both ovarian and testicular tissue, usually combined as an ovotestis, or as a separate ovary on one side and testis on the other (about 20% of cases) — a uterine tube and single uterine horn may develop on the ovarian side.
- ▶ Karyotype: the majority (~80%) are 46,XX; the remainder are 46,XY or mosaic (45,X/46,XY; 46,XX/46,XY; 46,XX/47,XXY).
- ▶ Mechanism: in SRY-positive 46,XX cases, an SRY-bearing fragment of the Y chromosome has been translocated onto an X chromosome by aberrant paternal crossing-over; SRY-negative cases show duplication/over-expression of downstream testis genes (SOX9, SOX3) that substitutes for SRY signalling.
- ▶ External genitalia are ambiguous; internal genitalia on each side reflect the local gonad (AMH/testosterone act only locally, not systemically). Most individuals are reared as males because a phallic structure is usually present at birth; a vas deferens always accompanies a testis, and spermatogenesis is occasionally detectable, but fertility (term pregnancy or paternity) is exceptional.

### 4. Male pseudohermaphroditism (46,XY DSD)

Gonads are testes, but the duct system and/or external genitalia are incompletely masculinised or fully feminised because androgen action fails at some step.

| Cause                                                     | Defect                                                                                              | Mechanism                                                                                 | Phenotype                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Androgen insensitivity syndrome (testicular feminisation) | AR gene, Xq12 (X-linked)                                                                            | Androgen receptor absent/non-functional; testosterone and DHT cannot act on target tissue | Normal female external genitalia; blind-ending vagina; uterus/tubes absent (AMH normal → Müllerian regression); sparse axillary/pubic hair; breast development at puberty; primary amenorrhoea; testes in labia majora/inguinal canal/abdomen; complete and partial forms exist |
| 5 $\alpha$ -reductase deficiency                          | Autosomal recessive enzyme defect                                                                   | Testosterone not converted to DHT                                                         | Female-appearing or ambiguous external genitalia at birth (penoscrotal hypospadias, small phallus); normal testes and Wolffian derivatives (testosterone-dependent, so unaffected); marked virilisation at puberty when testosterone rises                                      |
| Testosterone-biosynthesis defects                         | Enzymes such as 17 $\alpha$ -hydroxylase, 17,20-desmolase, 17 $\beta$ -hydroxysteroid dehydrogenase | Deficient testosterone (and hence DHT)                                                    | Female external genitalia and gender identity; no pubertal virilisation because testosterone remains low; testes present, AMH normal so Müllerian ducts regress; Wolffian ducts poorly developed                                                                                |
| Swyer syndrome (46,XY complete gonadal dysgenesis)        | SRY mutation                                                                                        | Streak gonads; no functioning testis                                                      | Female phenotype with normal Müllerian tract; failure to enter puberty; streak gonads carry a risk of gonadoblastoma                                                                                                                                                            |

## 5. Female pseudohermaphroditism (46,XX DSD)

- Gonads are ovaries and are structurally normal — since no testis (hence no AMH) forms, Müllerian derivatives (uterus, tubes, upper vagina) develop normally; the abnormality is confined to virilisation of the external genitalia by excess androgen.
- **Congenital adrenal hyperplasia (CAH)** is the commonest cause and accounts for approximately half of all infants presenting with ambiguous genitalia. The most common enzyme defect is **21-hydroxylase deficiency** (gene CYP21A2, locus 6p21.3), with an incidence of about 1 in 12,500 births; blocked cortisol/aldosterone synthesis diverts steroid precursors into the androgen

pathway. Of classic 21-hydroxylase deficiency cases, 25% are the simple virilising type and 75% are the more severe salt-losing type (mineralocorticoid deficiency, can be fatal in the neonate if unrecognised).

- Clinical picture: clitoral hypertrophy with fusion of the labioscrotal folds producing a scrotum-like appearance; internal genitalia (ovaries, uterus, tubes) are entirely normal.
- Other cause: transplacental passage of exogenous androgens or virilising progestins administered to the mother during pregnancy (e.g. to prevent threatened abortion), or a maternal androgen-secreting tumour.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Development of the external genitalia from the indifferent stage to the male and female definitive stages — label: genital tubercle, urogenital (urethral) folds, labioscrotal swellings, urogenital membrane/sinus at the indifferent stage; then on the male side: glans penis, penile urethra (from fused urethral folds), corpus spongiosum/cavernosum, fused labioscrotal swellings forming the scrotum; on the female side: glans clitoridis, labia minora (unfused urethral folds), labia majora (unfused labioscrotal swellings), vestibule. Show DHT acting on the male side and its absence on the female side as the key branch point.

□ Fig 72.20 — The development of the external genitalia from the indifferent stage (Gray's Anatomy — Standring — 41e, p.1690)

### Applied / Clinical anatomy

- Work-up of ambiguous genitalia: karyotyping (peripheral blood lymphocytes), buccal-smear sex-chromatin (Barr body) count as a rapid screening test — the number of Barr bodies equals the number of X chromosomes minus one; serum 17-hydroxyprogesterone and electrolytes (for CAH); serum testosterone:DHT ratio (for 5 $\alpha$ -reductase deficiency); pelvic ultrasound/MRI to demonstrate or exclude Müllerian derivatives; gonadal biopsy or laparoscopy when the diagnosis remains unclear.
- Because Müllerian-duct fate (AMH-dependent) and external-genital virilisation (androgen/DHT-dependent) are governed by two separate hormonal signals acting at different sites and times, a single individual can show discordant "internal" and "external" phenotypes — this is the anatomical basis of pseudohermaphroditism.
- Any dysgenetic gonad containing Y-chromosome material (streak gonad in Swyer syndrome, mixed gonadal dysgenesis) carries a significant risk of gonadoblastoma/dysgerminoma and is an indication for prophylactic gonadectomy.
- Gender assignment and corrective genitoplasty require multidisciplinary evaluation (paediatric endocrinologist, geneticist, surgeon, psychologist); anatomical potential for adult sexual function (especially of phallus or vagina) and gonadal malignancy risk are key deciding factors.
- Descent of the gonad is itself androgen-dependent; a persistent processus vaginalis/patent canal of Nuck may coexist in these patients and predispose to inguinal hernia, since the mistaken-hernia presentation of intra-inguinal testes is a recognised finding in androgen insensitivity syndrome.

## High-yield exam pointers

- ▶ SRY (Yp11.3) → SOX9 (17q24) is the master testis-determining pathway; its absence permits the WNT4/RSPO1/FOXL2-driven ovarian default pathway.
- ▶ AMH (from Sertoli cells) causes Müllerian regression; testosterone (from Leydig cells) maintains the Wolffian duct; DHT (5 $\alpha$ -reductase product of testosterone) masculinises the external genitalia — these three separate signals explain genotype–phenotype discordance in DSD.
- ▶ True hermaphroditism = Ovotesticular DSD: both ovarian and testicular tissue present (often as an ovotestis); majority karyotype is 46,XX.
- ▶ Male pseudohermaphroditism = 46,XY DSD: testes present, feminised/ambiguous external genitalia; classic causes — androgen insensitivity syndrome (AR, Xq12), 5 $\alpha$ -reductase deficiency, testosterone-synthesis defects, Swyer syndrome.
- ▶ Female pseudohermaphroditism = 46,XX DSD: ovaries present, virilised external genitalia; commonest cause is congenital adrenal hyperplasia from 21-hydroxylase (CYP21A2) deficiency.
- ▶ Old "hermaphroditism"/"pseudohermaphroditism" terminology has been replaced by "Disorders of Sex Development (DSD)" per the 2006 Chicago consensus statement.
- ▶ Diagnosis rests on karyotype plus hormonal assay plus imaging, with gonadal biopsy reserved for unresolved cases; a Y-material-bearing dysgenetic gonad needs prophylactic gonadectomy for gonadoblastoma risk.

### SOURCE & COVERAGE

Gray's Anatomy (Standing) 41e; Thompson & Thompson Genetics in Medicine 8e; Larsen Human Embryology 6e; Moore The Developing Human 9e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Brijesh Kumar Embryology Text & Atlas.



## Comparative & applied embryology



### In vitro fertilization

*Asked in: Paper IV Nov 2017 · Paper II Oct 2009 (2×) — RGUHS MD/MS Anatomy*

#### Definition / Introduction

**In vitro fertilization (IVF)** is a process of assisted reproductive technology (ART) in which a mature oocyte is fertilised by a spermatozoon **outside the female body**, in a culture medium, and the resulting embryo is transferred back into the uterus for implantation. It is popularly called the "**test-tube baby**" technique. The first IVF baby, **Louise Brown**, was born on **25th July 1978**; the technique was developed by **Robert Edwards** (awarded the **Nobel Prize in Physiology or Medicine, 2010**) and **Patrick Steptoe**. IVF, with its variants (ICSI, GIFT, ZIFT) and adjuncts (artificial insemination, oocyte/embryo cryopreservation), is now the standard treatment for most causes of infertility, correcting for a defective step in the normal fertilisation-implantation sequence.

## Normal fertilisation vs in vitro fertilisation

| Feature                       | Normal (in vivo) fertilisation                                                         | In vitro fertilisation                                                                        |
|-------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Site                          | Ampullary region of the uterine (fallopian) tube, within ~24 hours of ovulation        | Petri dish/culture medium in the laboratory                                                   |
| Gamete transport              | Spermatozoa ascend the female tract to the ampulla; very few reach the oocyte          | Oocyte and spermatozoa are brought together directly in medium                                |
| Capacitation                  | Occurs physiologically in the uterus/uterine tube, induced by tubal/uterine secretions | Induced artificially by incubating washed sperm in a defined culture medium for several hours |
| Ovulation trigger             | Endogenous mid-cycle LH surge                                                          | Mimicked by an injectable hCG "trigger" 34–38 hours before egg retrieval                      |
| Oocyte number released        | Usually a single secondary oocyte per cycle                                            | Multiple (often 10 or more) oocytes recruited by controlled ovarian hyperstimulation          |
| Confirmation of fertilisation | Not directly observed                                                                  | Two pronuclei seen on microscopy ~12–16 hours after insemination                              |

## Indications for IVF

- ▶ **Tubal factor:** blockage/damage of the fallopian tube (the classic original indication).
- ▶ **Ovulatory disorders:** anovulation or irregular ovulation.
- ▶ **Endometriosis.**
- ▶ **Polycystic ovarian syndrome (PCOS).**
- ▶ **Cervical factor infertility** (hostile mucus, anatomical/immunological barrier to sperm ascent).
- ▶ **Severe male factor infertility** (oligo-/astheno-/teratozoospermia, obstructive/non-obstructive azoospermia) — managed by adding ICSI to the standard IVF protocol.
- ▶ **Unexplained infertility** after conventional treatment has failed.

## Stages of IVF

IVF is carried out in six sequential stages:

- ▶ **Ovarian stimulation and monitoring:** Injectable FSH (gonadotropin) drives multi-follicular development. Premature LH surge/ovulation is prevented by **pituitary down-regulation** using a **GnRH agonist** (nafarelin/leuprorelin, started early in the cycle — the "long protocol") or a **GnRH antagonist** (cetrorelix/ganirelix, added from day 5–6 of stimulation — the "antagonist protocol"). Follicle growth is monitored by serial **transvaginal ultrasound** and serum **oestradiol (E2)** levels.
- ▶ **Oocyte (egg) retrieval:** Ovulation is induced with an **injectable hCG (or LH) trigger** 34–38 hours before a pre-planned egg pickup, timed to mimic the natural LH surge. Oocytes are aspirated **transvaginally under ultrasound guidance** (mild sedation/local anaesthesia) using a

fine needle passed through the vaginal wall into the mature follicle; **laparoscopic aspiration** is used when the ovary is not accessible transvaginally (e.g. pelvic adhesions, fibroids).

- ▶ **Fertilisation:** Semen is collected and **sperm-washed** (density-gradient centrifugation or swim-up technique) to remove seminal plasma, mucus and non-motile sperm. Washed sperm and oocytes are co-incubated overnight at 37 °C (standard insemination), or, in severe male-factor cases, a single sperm is injected directly into the oocyte cytoplasm (**ICSI** — equally successful as standard IVF). Fertilisation is confirmed the next day by the presence of **two pronuclei**; roughly 80% of mature oocytes fertilise in vitro.
- ▶ **Embryo development:** The zygote undergoes **cleavage** in culture medium; embryo quality is assessed by blastomere number/symmetry/fragmentation on day 2–3, or the embryo is cultured further to the **blastocyst stage** (day 5). **Preimplantation genetic diagnosis/screening (PGD/PGS)** can be performed at this stage — one or more cells (polar body, blastomere, or trophoctoderm biopsy of the blastocyst) are removed and analysed by PCR/FISH for single-gene disorders or aneuploidy before transfer. Surplus embryos are **cryopreserved** (in glycerol, propanediol or DMSO) for future use.
- ▶ **Embryo transfer:** One or two embryos (cleavage-stage or blastocyst) are loaded into a fine catheter and transferred into the hormonally-prepared uterine cavity via the **vagina and cervical canal**, without anaesthesia.
- ▶ **Luteal phase support:** Because oocyte aspiration strips the granulosa cells that would form the corpus luteum, endogenous progesterone is deficient; **exogenous progesterone** is therefore given for at least the first two weeks after retrieval. Pregnancy is confirmed by serum **β-hCG** and later ultrasound.

□ Fig 5.1 — *In vitro* fertilisation. It involves six stages as follows: Stage 1, ovarian stimulation and monitoring; Stage 2, oocyte retrieval; Stage 3, fertilisation; Stage 4, embryo development; Stage 5, embryo transfer; Stage 6, luteal phase support (Sontakke — *Textbook of Human Embryology*, p.44)



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A simple six-box flow diagram, top to bottom, labelled exactly:

- ▶ **Ovarian stimulation & monitoring** (GnRH agonist/antagonist + FSH; USG + E2 monitoring)
- ▶ **Oocyte retrieval** (hCG trigger → transvaginal USG-guided/laparoscopic aspiration)
- ▶ **Fertilisation** (sperm washing → insemination or ICSI → pronuclei check)
- ▶ **Embryo development** (cleavage → blastocyst; ± PGD/PGS; cryopreservation of spares)
- ▶ **Embryo transfer** (catheter via vagina + cervical canal into uterus)
- ▶ **Luteal phase support** (progesterone →  $\beta$ -hCG confirmation)

### Related assisted reproductive techniques

| Technique                                | Definition                                                                                                                                           | Key indication                                                                                               | Success rate (per source)                                                           |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| ICSI (intracytoplasmic sperm injection)  | Direct microinjection of a single sperm into the oocyte cytoplasm using a glass micropipette (developed by G. Palermo)                               | Teratozoospermia, poor motility, low sperm count, obstructive azoospermia (vasectomy), anti-sperm antibodies | As successful as routine IVF                                                        |
| GIFT (gamete intrafallopian transfer)    | Collected oocytes and washed sperm are placed together directly into the uterine tube via laparoscope — fertilisation occurs in vivo, in the ampulla | Normal ovary + at least one patent tube; sperm dysfunction or unexplained infertility                        | ~25–30%                                                                             |
| ZIFT (zygote intrafallopian transfer)    | An in-vitro fertilised zygote is transferred into the uterine tube via laparoscope                                                                   | Tubal-factor cases wanting in-vivo cleavage                                                                  | ~65% (per Sontakke)                                                                 |
| Artificial insemination                  | Deliberate introduction of sperm into the cervix (intracervical, ICI) or uterus (intrauterine, IUI), other than by intercourse                       | Donor sperm, mild male infertility, unexplained infertility                                                  | ICI 10–15%/cycle; IUI 15–20%/cycle (~60–70% cumulative pregnancy over 6 IUI cycles) |
| Surgical sperm extraction                | Sperm retrieved directly from epididymis or testis (e.g. PESA/TESE)                                                                                  | Azoospermia due to ejaculatory-duct/vas obstruction or vasectomy                                             | Used to source sperm for ICSI                                                       |
| Oocyte cryopreservation ("egg freezing") | Oocytes retrieved as in IVF, vitrified and stored in liquid nitrogen (–196 °C) for later thaw/fertilisation                                          | Fertility preservation before chemotherapy/radiotherapy, or elective deferral of childbearing                | 14.8–31.5%, age-dependent                                                           |

## Recent advances in IVF

- ▶ **Artificial intelligence in embryo selection:** deep-learning models trained on time-lapse imaging and clinical metadata now grade embryo morphology, predict blastocyst formation/aneuploidy, and forecast live-birth outcome with accuracy exceeding experienced embryologists (46.1% vs 30.7% on day 3; 55.0% vs 40.7% on day 5, AUC 0.769), offering a non-invasive adjunct to conventional morphological grading (Sun et al, *Chin Med J* 2024) [DOI: 10.1097/CM9.0000000000003162]; a broader narrative review outlines AI applications across stimulation-protocol personalisation, gamete assessment and IVF-lab quality control (Olawade et al, *J Gynecol Obstet Hum Reprod* 2024) [DOI: 10.1016/j.jogoh.2024.102903], building on an earlier review of AI in the embryology laboratory (Dimitriadis et al, *Reprod Biomed Online* 2022) [DOI: 10.1016/j.rbmo.2021.11.003].
- ▶ **Refinement of PGT-A and trophectoderm biopsy:** comprehensive chromosome screening has improved detection of whole-chromosome aneuploidy, but has surfaced the unresolved problem of **embryo mosaicism** and the limits of a single trophectoderm biopsy in predicting true embryo ploidy (Morales, *Reprod Sci* 2023) [DOI: 10.1007/s43032-023-01301-0]; current biopsy technique (laser-assisted zona opening plus "pulling" or "flicking" trophectoderm excision at the expanded/hatching blastocyst stage) continues to be standardised to minimise mosaicism and safeguard neonatal outcome (De Vos & De Munck, *Genes* 2025) [DOI: 10.3390/genes16020134].
- ▶ **Fertility-preservation outcomes quantified:** a systematic review/meta-analysis of cancer survivors reports live-birth rates of **41% after embryo cryopreservation, 32% after oocyte vitrification, and 21–33% after ovarian tissue cryopreservation/transplantation**, clarifying counselling for young patients facing gonadotoxic therapy (Fraison et al, *Hum Reprod* 2023) [DOI: 10.1093/humrep/deac249].
- ▶ **In vitro gametogenesis (IVG):** an emerging, still-experimental line of research aims to reprogram somatic (e.g. dermal fibroblast) cells to induced pluripotent stem cells, then to primordial germ cell-like cells and ultimately oocytes/spermatocytes usable for embryogenesis — a potential future fertility-restoration route for oncofertility patients, though major scientific and ethical barriers remain before clinical use (Wesevich et al, *J Clin Med* 2023) [DOI: 10.3390/jcm12093305].
- ▶ **Mitochondrial replacement therapy ("three-parent IVF"):** techniques such as maternal spindle transfer, pronuclear transfer and polar-body genome transfer are being refined to prevent transmission of pathogenic mitochondrial DNA mutations to offspring conceived by IVF, alongside early exploratory work on autologous mitochondrial transplantation (AUGMENT); global ethical/legal regulation remains unsettled (Belousova et al, *Int J Mol Sci* 2025) [DOI: 10.3390/ijms26146645].

(According to PubMed.)

## Applied / Clinical anatomy

- ▶ **Ovarian hyperstimulation syndrome (OHSS):** an iatrogenic complication of the gonadotropin-stimulation step — ovaries enlarge and exude fluid into the peritoneal cavity, producing abdominal pain and bloating; antagonist protocols and careful trigger choice reduce risk.

- ▶ **Multiple pregnancy:** the principal complication of IVF/ART, arising from transfer of more than one embryo; risk is reduced by limiting the number of embryos transferred (single embryo transfer where feasible).
- ▶ **Age-dependent success:** per-cycle live-birth chance falls sharply with maternal age — approximately 30% (<35 years), 25% (35–37 years), 17% (38–40 years), and <5% (>40 years); this decline reflects age-related oocyte aneuploidy and is central to patient counselling.
- ▶ **ICSI-specific risks:** ICSI carries a slightly higher reported incidence of birth defects than standard IVF, and an increased risk of transmitting **Y-chromosome microdeletions** (and hence infertility) to male offspring, since ICSI can bypass natural sperm-selection barriers.
- ▶ **PGD/PGS in practice:** allows exclusion of embryos carrying serious single-gene disorders (e.g. haemophilia A) or aneuploidy (e.g. trisomy 21) before transfer, and can identify embryo sex to avoid transferring a male embryo at risk of a severe X-linked disorder.
- ▶ **Site relevance:** because IVF/ICSI bypasses the ampulla (the normal fertilisation site) while GIFT deliberately restores fertilisation to the ampulla in vivo, IVF is applicable even with bilateral tubal block, whereas GIFT requires at least one patent, healthy tube.

### High-yield exam pointers

- ▶ IVF = fertilisation of ovum **outside** the body, embryo transferred to uterus; "test-tube baby"; first baby **Louise Brown, 1978**; pioneers **Edwards & Steptoe** (Edwards — Nobel Prize 2010).
- ▶ Six stages: **stimulation** → **retrieval** → **fertilisation** → **embryo development** → **transfer** → **luteal support**.
- ▶ hCG trigger given **34–38 hours** before egg retrieval to mimic the LH surge; oocytes aspirated **transvaginally under USG guidance**.
- ▶ Normal fertilisation site = **ampulla of the uterine tube**; capacitation is natural in vivo, induced artificially in vitro.
- ▶ **ICSI** (Palermo) = single-sperm microinjection for severe male-factor infertility; **GIFT** = gametes placed in the tube (in-vivo fertilisation); **ZIFT** = zygote placed in the tube.
- ▶ **PGD/PGS:** biopsy of polar body/blastomere/trophoblast for single-gene disorder or aneuploidy screening before transfer.
- ▶ Complications: **OHSS**, multiple pregnancy, age-related decline in success, ICSI's Y-chromosome-deletion/birth-defect risk.
- ▶ Cryopreservation of surplus embryos/oocytes uses glycerol/propanediol/DMSO as cryoprotectant; oocytes are vitrified and stored at **–196 °C**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Langman's Medical Embryology (Sadler) 14e; Ross Histology — A Text and Atlas 7e. Recent-advances citations are from PubMed (2022–2025).



## Comparative anatomy of human respiratory system

*Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Comparative anatomy is the branch of anatomy that studies the changes in form, structure and function of a system that have occurred across the animal kingdom during evolution (phylogeny). Applied to respiration, it traces how gas-exchange organs and ventilatory mechanisms evolved from simple aquatic gills to the highly efficient bellows-and-alveolus system of terrestrial mammals, including man. Tracing this sequence — Pisces → Amphibia → Reptilia → Aves/Mammalia — explains several features of the adult and developing human respiratory tract that otherwise seem arbitrary (branchial-arch derivatives, the long course of the phrenic nerve, the design of the alveolar membrane).

### General principles of respiratory evolution

- ▶ **Aquatic → terrestrial shift:** fish exchange gases through **gills** (vascular filamentous outgrowths bathed by water); air-breathers use **lungs** (internal invaginated sacs resistant to desiccation).
- ▶ **Progressive rise in respiratory surface area:** gill filaments → saccular amphibian lung → septate reptilian lung → parabronchial avian lung → alveolar mammalian lung (300–500 million alveoli, 70–100 m<sup>2</sup> in man).
- ▶ **Progressive elaboration of the aspiration pump:** buccal (throat) pumping in fish/amphibia → costal (rib) aspiration in reptiles → the mammalian **diaphragm** added to costal aspiration.
- ▶ **Airflow pattern:** mammalian tidal (bidirectional) flow is simple but leaves dead space; the avian parabronchial lung achieves continuous **unidirectional** flow, the most efficient design among air-breathers.
- ▶ Lungs are believed to arise phylogenetically as paired ventral outpocketings of the pharyngeal gut (as in lungfish/Dipnoi, which keep both gills and a lung) — recapitulated in the human embryo, whose lung bud is a ventral diverticulum of the foregut endoderm.

### Pisces (fish) — branchial respiration

- ▶ Respiratory organ: paired **gills** — gill filaments bearing secondary lamellae, supplied by afferent/efferent branchial vessels — covered by a bony flap, the **operculum**.
- ▶ Mechanism: **buccal–opercular double pump** — buccal cavity expands to draw water in; operculum then contracts, driving water over the gills and out, giving continuous unidirectional water flow.
- ▶ Gas exchange: **countercurrent exchange** — blood flows opposite to water flow across the lamella, maintaining the diffusion gradient and permitting very high (~80%) O<sub>2</sub> extraction.
- ▶ Lungfish (Dipnoi) are the evolutionary bridge — possess both gills and a primitive lung, breathing air when water is deoxygenated.

### Amphibia — transitional (triple) respiration

- ▶ Larval stage (tadpole): external, then internal **gills**, as in fish.
- ▶ Adult stage: **three simultaneous routes** — (i) **cutaneous** (thin, moist, vascular skin; vital in hibernation/submersion), (ii) **buccopharyngeal** (vascular mouth/pharynx lining), (iii) **pulmonary** — simple, thin-walled, sac-like lungs with limited internal folding/surface area.

- ▶ Mechanism: **positive-pressure buccal pump** — mouth floor lowers to draw air in through the nares, nares close, floor raises to force air into the lungs; no true costal aspiration (ribs poorly developed/absent).

### Reptilia — first true costal (aspiration) breathing

- ▶ Respiratory organ: paired **septate/multicameral** lungs — internal septa subdivide the lung into chambers, more surface area than the amphibian saccular lung; still no true alveoli.
- ▶ Mechanism: a functional **rib cage with intercostal muscles** produces true **negative-pressure costal aspiration** — the first class whose ventilation is independent of buccal movements, freeing the mouth during breathing.
- ▶ No diaphragm; some reptiles add gular pumping, but costal aspiration is principal. Skin is dry/keratinised — no cutaneous respiration, unlike amphibians.

### Aves (birds) — the most efficient air-breathing design

- ▶ Respiratory organ: small, rigid, **non-expansile parabronchial lungs** connected to a system of **air sacs** (classically nine — interclavicular, paired cervical, anterior/posterior thoracic, abdominal) that act as bellows; the sacs themselves lack respiratory epithelium.
- ▶ Mechanism: lung volume itself does not change — sternal/costal (keel) movements drive the air sacs, which push air through the parabronchi in one direction only (**unidirectional flow**); a given air volume needs **two respiratory cycles** to traverse the system.
- ▶ Gas exchange occurs in air capillaries; blood capillaries cross them at right angles — a **cross-current exchange** more efficient than mammalian tidal exchange, permitting flight at extreme altitude. No diaphragm; the thoraco-abdominal septum is fibrous, not muscular.

### Mammalia (including man) — the alveolar lung and the diaphragm

- ▶ Respiratory organ: paired **alveolar lungs** — the human lung has 300–500 million alveoli, total surface area 70–100 m<sup>2</sup>, the highest surface-to-volume ratio among vertebrates.
- ▶ Mechanism: **tidal (bidirectional) ventilation** driven by intercostal muscles (inherited costal aspiration) plus the **diaphragm** — a dome-shaped musculotendinous partition unique to mammals, completely separating thorax from abdomen and the principal muscle of quiet respiration.
- ▶ The extensively branching bronchial tree (~23 generations) and the thin (~0.2–0.3 µm) alveolar-capillary membrane optimise diffusion despite the dead space inherent to tidal flow.
- ▶ Alveolar **surfactant** (type II pneumocytes) lowers surface tension and prevents end-expiratory collapse — required specifically by the delicate terminal-sac design, unnecessary in simpler amphibian/reptilian lungs.

### Comparative summary

| Feature           | Pisces | Amphibia                             | Reptilia                    | Aves                                | Mammalia (man) |
|-------------------|--------|--------------------------------------|-----------------------------|-------------------------------------|----------------|
| Respiratory organ | Gills  | Skin + buccal mucosa + saccular lung | Septate (multicameral) lung | Rigid parabronchial lung + air sacs | Alveolar lung  |

| Feature                | Pisces                 | Amphibia                      | Reptilia                  | Aves                                   | Mammalia (man)                                    |
|------------------------|------------------------|-------------------------------|---------------------------|----------------------------------------|---------------------------------------------------|
| Aspiration pump        | Buccal–opercular pump  | Buccal (throat) pump          | Costal (rib) pump         | Costal/sternal pump acting on air sacs | Costal pump + diaphragm                           |
| Airflow pattern        | Unidirectional (water) | Tidal                         | Tidal                     | Unidirectional (2 cycles/breath)       | Tidal (bidirectional)                             |
| Gas-exchange principle | Countercurrent         | Simple diffusion              | Simple diffusion          | Cross-current                          | Simple diffusion across alveolar membrane         |
| Respiratory surface    | Gill lamellae          | Skin/mouth lining/simple lung | Septated lung chambers    | Air capillaries                        | Alveoli (300–500 million; 70–100 m <sup>2</sup> ) |
| Cutaneous respiration  | Absent                 | Major                         | Absent (keratinised skin) | Absent                                 | Negligible                                        |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Five-panel comparative schematic (label each panel):

- **Fish gill unit** — gill arch, filaments, secondary lamellae, afferent/efferent branchial vessel, operculum, countercurrent flow arrows.
- **Amphibian** — nares, buccal floor, glottis, simple sac lung, skin labelled "cutaneous respiration", buccal-pump arrows.
- **Reptilian lung** — trachea, bronchus, internal septa/chambers, ribs + intercostal muscles.
- **Avian system** — trachea, primary/secondary bronchi, parabronchi, lung, anterior/posterior air sacs, unidirectional-flow arrows.
- **Mammalian (human) lung** — trachea, bronchial tree, alveolar duct, alveoli, diaphragm (dome, central tendon), intercostal muscles.

□ Fig 17.3 — Development of the pharyngeal arches (Langman's Medical Embryology — Sadler — 14e, p.304)

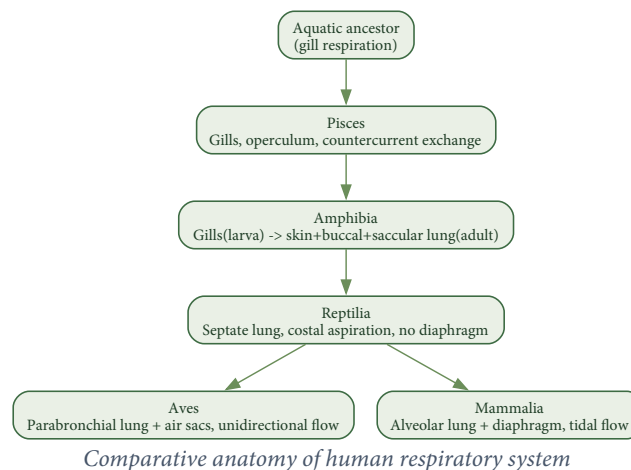
### Embryological basis — human recapitulation of phylogeny

- The human embryo transiently recapitulates chordate/fish features: a **dorsally placed neural tube**, **body segmentation**, and paired **pharyngeal (branchial) arches** separated externally by **pharyngeal clefts** and internally by **pharyngeal pouches** — homologues of the gill arches/clefts of fish.
- In fish the posterior arches are gill-bearing, covered by the **operculum**, a flap that draws water over the gills. Gray's Anatomy notes that although adult humans lack an operculum, an **operculum-homologous structure exists transiently in the human embryo**: the caudally expanding 2nd (hyoid) arch, driven by the same *Shh* signalling as the fish operculum, overgrows the more posterior (3rd/4th) arches — this is the same second-arch overgrowth that classical



embryology (Vishram Singh's Clinical Embryology) describes as burying the 2nd–4th pharyngeal clefts to form the transient **cervical sinus**.

- ▶ With the land shift to lung respiration, the gills/operculum were lost as external structures, but Gray's Anatomy records that the posterior-pouch gill-forming programme was not simply discarded — it persists as the developmental basis of the **parathyroid glands**, while the pouches also give rise to the tubotympanic recess/middle ear and palatine tonsil.
- ▶ The **lung bud** itself arises, as in the ancestral lungfish, as a ventral midline outgrowth (laryngotracheal diverticulum) of foregut endoderm — respiratory epithelium/glands are endodermal, surrounding connective tissue/cartilage/smooth muscle are splanchnic mesoderm, in both the phylogenetic and the human ontogenetic sequence.



## Applied / Clinical anatomy

- ▶ **Branchial cyst/fistula:** incomplete obliteration of the 2nd pharyngeal cleft/cervical sinus (the embryonic remnant of the fish gill-cleft/operculum region) leaves an epithelial-lined cyst or fistula along the anterior border of sternocleidomastoid.
- ▶ **Long cervical origin of the phrenic nerve (C3–C5):** the diaphragm — the mammalian innovation absent in fish, amphibians, reptiles — develops from cervical myotomes and "drags" its nerve supply down as it descends into the thorax; this gives the diaphragm's long intrathoracic nerve course and explains referred **shoulder-tip pain (C4)** in diaphragmatic irritation (subphrenic abscess, splenic/hepatic injury).
- ▶ **Bird cross-current vs mammalian tidal lung:** the unidirectional, cross-current avian system extracts  $O_2$  far more efficiently per breath, explaining why birds (e.g., bar-headed goose) sustain flight at altitudes where unacclimatised mammals develop hypoxia/acute mountain sickness.
- ▶ **Surfactant deficiency/RDS:** the delicate terminal alveolar sac is a late mammalian refinement unnecessary in simpler lower-vertebrate lungs; its patency depends on type II pneumocyte surfactant, deficient in the preterm human lung (~24–28 weeks), causing neonatal RDS.
- ▶ **Foregut septation anomalies:** laryngeal atresia, tracheo-oesophageal fistula and pulmonary agenesis reflect faulty septation of the single foregut tube giving rise to both trachea/lungs and oesophagus — the same ventral gut-outgrowth origin seen phylogenetically in Dipnoi.



## High-yield exam pointers

- ▶ Comparative anatomy = study of structural/functional change across the animal kingdom during evolution (phylogeny).
- ▶ Sequence: Pisces (gills, operculum, countercurrent) → Amphibia (skin + buccal + saccular lung, buccal pump) → Reptilia (septate lung, costal aspiration, no diaphragm) → Aves (parabronchial lung + air sacs, unidirectional cross-current flow) → Mammalia (alveolar lung + diaphragm, tidal flow).
- ▶ Diaphragm is unique to mammals — the single most important anatomical innovation in the evolution of respiration; its cervical developmental origin explains the long phrenic nerve course and referred shoulder pain.
- ▶ Countercurrent exchange (fish gills) vs cross-current exchange (bird parabronchi) vs simple diffusion across a tidal alveolar membrane (mammals) — bird lung is the most O<sub>2</sub>-efficient design.
- ▶ Human embryo recapitulates pharyngeal arches/clefts/pouches (fish gill-arch homologues); operculum has only a transient embryonic homologue (forms the cervical sinus) in humans, explaining branchial cyst/fistula.
- ▶ Lung bud = ventral outgrowth of foregut endoderm, phylogenetically prefigured by the lungfish (*Dipnoi*), which retains both gills and a lung.
- ▶ Human alveolar lung: 300–500 million alveoli, 70–100 m<sup>2</sup> surface area (Gray's Anatomy, 41e).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — General Anatomy 4e; IB Singh — Textbook of Anatomy Vol 1, 6e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Clinical Embryology.

**Coverage note:** the library corpus is a *human* anatomy/embryology collection and does not carry a dedicated cross-species comparative-anatomy chapter (as flagged in the topic spec). The vertebrate-class descriptions of gill, amphibian, reptilian and avian respiration above are standard, universally-accepted comparative-anatomy/zoology content taught in first-year general anatomy; the human-specific facts (alveolar numbers/surface area, pharyngeal-arch/operculum homology, phrenic nerve development) are grounded directly in the corpus as cited.



## Comparative anatomy of inguinal canal

Asked in: Paper II May 2011 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **inguinal canal** is an oblique intermuscular passage in the lower part of the anterior abdominal wall, lying above and parallel to the medial half of the inguinal ligament; it is, in essence, the persistent track of the **gubernaculum** through the abdominal wall, formed as the gonad migrates from the lumbar region toward the labioscrotal/scrotal swelling. This developmental plan — gubernaculum-guided gonadal descent through the ventral body wall — is shared by mammals generally, but the canal's *mechanical* behaviour differs sharply between quadrupedal mammals and erect man. The comparative significance of the canal lies precisely here: **inguinal hernia occurs only in man and in no other mammal**, a direct evolutionary price paid for adopting the erect, bipedal posture. This answer covers the human canal's gross form, its shared developmental basis, the posture-driven comparative differences, and the applied consequences.

### 1. Human inguinal canal — gross anatomy (recap)

- ▶ **Extent/direction:** from the deep (internal) inguinal ring to the superficial (external) inguinal ring; directed downward, forward and medially.
- ▶ **Length:** ~4 cm in the adult (range 3–6 cm depending on age, Gray's 41e). At birth the deep and superficial rings are nearly superimposed and the canal is extremely short (~1 cm); it lengthens progressively as the anterior abdominal wall muscles develop through childhood.
- ▶ **Deep inguinal ring:** an oval opening in the transversalis fascia, ~1.25 cm above the mid-inguinal point (midpoint between the anterior superior iliac spine and the pubic symphysis); the inferior epigastric vessels lie immediately medial to it.
- ▶ **Superficial inguinal ring:** a triangular gap in the external oblique aponeurosis just above the pubic crest/tubercle, apex directed toward the anterior superior iliac spine, bounded by medial and lateral crura reinforced by intercrural fibres.
- ▶ **Sex difference:** larger in the male than the female.

| Wall/boundary | Composition                                                                                                 |
|---------------|-------------------------------------------------------------------------------------------------------------|
| Anterior      | External oblique aponeurosis throughout; reinforced laterally by fleshy fibres of internal oblique          |
| Posterior     | Transversalis fascia throughout; reinforced medially by the conjoint tendon and reflected inguinal ligament |
| Roof          | Arched fibres of internal oblique and transversus abdominis                                                 |
| Floor         | Grooved upper surface of the inguinal ligament; lacunar ligament at the medial end                          |

| Content    | Detail                                                                                                                                                                                                                                                                           |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Male       | Spermatic cord — ductus deferens; testicular, cremasteric and deferential arteries; pampiniform plexus of veins; testicular lymphatics; genital branch of genitofemoral nerve; sympathetic/visceral afferent plexus on the artery to the vas; remnant of the processus vaginalis |
| Female     | Round ligament of the uterus                                                                                                                                                                                                                                                     |
| Both sexes | Ilioinguinal nerve — enters between external and internal oblique, traverses the canal outside the cord, and leaves through the superficial ring                                                                                                                                 |

## 2. Developmental basis shared across mammals

- ▶ The canal is, developmentally, **the passage cut by the gubernaculum** through the abdominal wall as it guides the gonad from its lumbar site of origin to the labioscrotal swelling — a plan common to mammals in general, which is why the canal (and testicular descent) is not unique to man.
- ▶ **Timeline of descent (Langman/Sadler 14e)**: testis reaches the inguinal region by ~12 weeks' gestation, migrates through the inguinal canal by ~28 weeks, and reaches the scrotum by ~33 weeks; testicular blood supply is retained from its original lumbar (aortic) origin throughout descent.
- ▶ The **processus vaginalis**, a tubular peritoneal evagination, follows the gubernaculum independently of the testis itself and accompanies the muscular/fascial layers of the body wall into the scrotal swelling; it normally obliterates around birth, leaving only the tunica vaginalis around the testis. Persistence of a patent processus vaginalis is the commonest basis of a congenital indirect inguinal hernia (and of a congenital hydrocele).
- ▶ As the testis and gubernaculum traverse the wall, they pick up coverings from each abdominal-wall layer — transversalis fascia → internal spermatic fascia; internal oblique → cremasteric fascia/muscle; external oblique aponeurosis → external spermatic fascia.

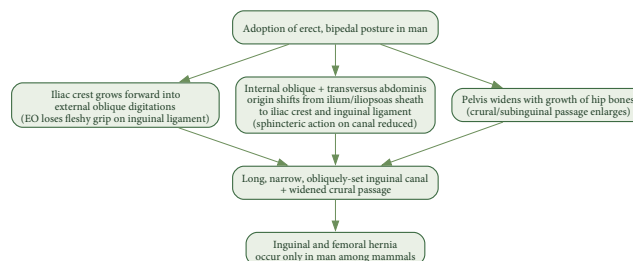
□ Fig 16.37 — Descent of the testis: second month, mid-third month, seventh month and shortly after birth, showing the gubernaculum and processus vaginalis guiding the testis through the developing inguinal canal (Langman's Medical Embryology — Sadler — 14e, p.299)

## 3. Comparative anatomy — quadrupedal mammals versus erect man

The inguinal canal is present in mammals generally, but its mechanical role is transformed by man's upright posture. The key comparative points (BD Chaurasia) are:

| Feature              | Quadrupedal (four-footed) mammals                       | Man (erect, bipedal posture)                              |
|----------------------|---------------------------------------------------------|-----------------------------------------------------------|
| Posture of the trunk | Horizontal, slung fore-and-aft between the limb girdles | Vertical, balanced directly on the pelvis and lower limbs |

| Feature                                       | Quadrupedal (four-footed) mammals                                                                                     | Man (erect, bipedal posture)                                                                                                                                                                                                      |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Direction of intra-abdominal pressure         | Borne generally along the horizontal trunk rather than concentrated at the groin                                      | Transmitted directly downward onto the pelvic floor and groin with every rise in intra-abdominal pressure (coughing, straining, lifting)                                                                                          |
| External oblique — attachment to iliac crest  | Retains a fleshy attachment to the iliac crest; can actively grip and support the inguinal ligament                   | Iliac crest has grown forward into the lower digitations of external oblique, converting this part of the muscle to aponeurosis — it can no longer be controlled by fleshy fibres, which now instead help balance the erect trunk |
| Internal oblique/transversus abdominis origin | Arise from the anterior border of the ilium and the iliopsoas sheath, acting as a powerful sphincter around the canal | Origin has shifted onto the inguinal ligament and iliac crest, which has minimised their sphincteric action on the canal                                                                                                          |
| Crural (subinguinal) passage                  | Narrower, closely applied to the hip bone                                                                             | Widened by the peculiar growth of the hip bone and pelvis — an additional predisposition to femoral hernia                                                                                                                        |
| Occurrence of groin (inguinal) hernia         | Not a naturally occurring condition                                                                                   | Peculiar to man among all mammals                                                                                                                                                                                                 |



*Comparative anatomy of inguinal canal*

#### 4. Compensatory mechanisms unique to man's obliquely-set canal

Because the erect posture makes the canal a genuine point of weakness, several compensatory mechanisms come into play whenever intra-abdominal pressure rises (coughing, sneezing, lifting, straining) — mechanisms that a short, transversely-placed quadrupedal canal does not need:

- ▶ **Obliquity of the canal ("flap-valve" mechanism)** — the two rings do not lie opposite each other; a rise in pressure approximates the anterior and posterior walls, obliterating the passage.
- ▶ **Guarding of the superficial ring** from behind by the conjoint tendon and the reflected part of the inguinal ligament.
- ▶ **Guarding of the deep ring** from in front by the fleshy fibres of internal oblique.
- ▶ **"Shutter" mechanism of internal oblique** — it forms the anterior wall, roof and posterior wall of the canal; contraction approximates roof to floor.

- ▶ **"Ball-valve" mechanism** — contraction of cremaster plugs the superficial ring with the spermatic cord.
- ▶ **"Slit-valve" mechanism** — contraction of external oblique approximates the two crura of the superficial ring, aided by the intercrural fibres.
- ▶ Hormonal tone of the inguinal musculature may also contribute.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Real plate embedded above (anterior/posterior walls, roof and floor of the human canal):

- Fig 4.5 — *Boundaries of the inguinal canal: (A) anterior and posterior walls in coronal section, (B) roof and floor in sagittal section (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.202)*

For the comparative-anatomy component (no single real captioned plate exists for this cross-species comparison), draw two simple side-by-side schematics and label:

- ▶ **Quadruped:** horizontal vertebral column and trunk; pelvis nearly vertical; short, wide inguinal canal with deep and superficial rings close together; arrow showing intra-abdominal pressure directed along the horizontal trunk (away from the groin).
- ▶ **Man:** vertical vertebral column and trunk; pelvis widened; long, narrow, obliquely-set inguinal canal with deep and superficial rings well separated; arrow showing intra-abdominal pressure directed vertically downward onto the pelvic floor/groin.
- ▶ Label on both: deep inguinal ring, superficial inguinal ring, external oblique (fleshy vs aponeurotic relation to iliac crest), internal oblique/transversus origin.

### Applied / Clinical anatomy

- ▶ **Inguinal hernia is peculiar to man** among mammals — the anatomical basis is the set of erect-posture changes above (weakened, elongated oblique canal; widened crural passage).
- ▶ **Indirect inguinal hernia:** passes through the deep inguinal ring, lateral to the inferior epigastric vessels; classically related to a persistent patent processus vaginalis (congenital) or to progressive weakening of the posterior wall near the deep ring (acquired); may reach as far as the tunica vaginalis if the processus is fully patent.
- ▶ **Direct inguinal hernia:** arises medial to the inferior epigastric vessels through an acquired weakness of the posterior wall (Hesselbach's triangle), often bulging directly through or near the superficial ring; may be difficult to distinguish clinically from an indirect hernia.
- ▶ **Femoral hernia:** exploits the widened crural (subinguinal) passage that is a further consequence of man's pelvic remodelling; never congenital, and more common in females owing to their wider pelvis and smaller femoral vessels.
- ▶ **Congenital hydrocele/encysted hydrocele of the cord:** other clinical expressions of an incompletely obliterated processus vaginalis.
- ▶ **Surface marking:** deep ring ~1.25 cm above the mid-inguinal point; superficial ring just above the pubic tubercle — used clinically to differentiate direct/indirect hernia and to mark incisions.

## High-yield exam pointers

- ▶ Inguinal canal = track of the gubernaculum through the abdominal wall; developmental basis shared by mammals in general.
- ▶ **Inguinal hernia occurs only in man, not in any other mammal** — the single most important comparative-anatomy fact for this topic.
- ▶ Three erect-posture changes underlying man's predisposition: (1) iliac crest grows into external oblique digitations, converting fleshy attachment to aponeurotic; (2) internal oblique/transversus origin shifts from ilium/iliopsoas sheath to iliac crest/inguinal ligament, reducing sphincteric action; (3) crural passage widens with pelvic growth, predisposing additionally to femoral hernia.
- ▶ Canal is oblique in man (compensatory "flap-valve") versus short/transverse orientation in quadrupeds whose intra-abdominal pressure is not directed at the groin.
- ▶ Seven protective mechanisms against herniation: obliquity, guarding of both rings, shutter mechanism (internal oblique), ball-valve (cremaster), slit-valve (external oblique), hormonal tone.
- ▶ Canal is extremely short (~1 cm) at birth, lengthening to ~4 cm (3–6 cm) in the adult as the rings separate.
- ▶ Descent-of-testis timeline: inguinal region by 12 weeks, through the canal by 28 weeks, scrotum by 33 weeks.
- ▶ Indirect hernia — lateral to inferior epigastric vessels, linked to patent processus vaginalis; direct hernia — medial to inferior epigastric vessels, acquired posterior-wall weakness.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia's Human Anatomy Vol 2 8e; Vishram Singh — Textbook of Anatomy Vol 2 4e; IB Singh — Textbook of Anatomy Vol 2 6e; Langman's Medical Embryology (Sadler) 14e.

**Coverage note:** the corpus (including the topic's assigned specialty book, Vishram Singh's *General Anatomy* 4e) does not carry a dedicated cross-species comparative-anatomy chapter for the inguinal canal; the comparative content above is grounded in BD Chaurasia's explicit "evolutionary changes of erect posture" passage (the standard source for this exact question), supplemented by Gray's/Vishram Singh/IB Singh for gross anatomy and Langman for the shared mammalian developmental basis.



## Comparative anatomy of pelvic diaphragm

Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **pelvic diaphragm** is the hammock- (gutter-) shaped musculofascial partition, formed on each side by **levator ani** and **coccygeus** together with their covering fasciae, that stretches across the lesser (true) pelvis from the pubis in front to the coccyx behind. It separates the pelvic cavity above from the perineum below and provides the principal support to the pelvic viscera. Phylogenetically the diaphragm is not a new structure created for man — it is **modified tail musculature**: in quadrupeds the same three muscle bellies (pubococcygeus, iliococcygeus, ischiococcygeus) move the tail, and with the disappearance of the tail and the adoption of the **erect posture**, they were redeployed from a locomotor/caudal role to a static, gravity-resisting, visceral-support and sphincteric role. This evolutionary re-purposing — traceable through the origin, orientation and reciprocal ligamentous change of these muscles — is the substance of the "comparative anatomy of the pelvic diaphragm."

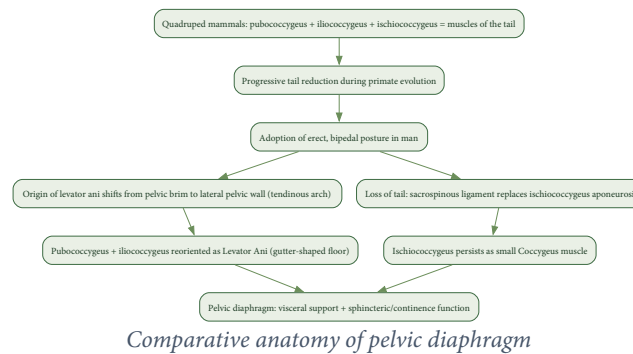
### 1. Muscular components and their homology across mammals

The levator ani and coccygeus of each side are, morphologically, **one continuous sheet**, divisible from before backwards into three named parts, with a continuous linear origin from the pubis, the obturator fascia (tendinous arch/white line) and the ischial spine:

| Part (man)                                  | Homologous component                            | Role in quadrupeds                                     | Role in man                                                                                                                                                                       |
|---------------------------------------------|-------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pubococcygeus<br>(anterior + middle fibres) | Anterior tail-muscle                            | Pulls the tail forward<br>(flexes it ventrally)        | Forms the bulk of levator ani; anterior fibres form <b>levator prostatae</b> (male)/ <b>sphincter urethrovaginalis</b> (female); middle fibres form the <b>puborectalis</b> sling |
| Iliococcygeus                               | Posterior tail-muscle<br>(with ischiococcygeus) | Moves the tail sideways, together with ischiococcygeus | Sheet-like posterior part of levator ani, inserted into the anococcygeal raphe and coccyx                                                                                         |
| Ischiococcygeus                             | Lateral tail-mover                              | Moves the tail sideways                                | Persists in man as the small <b>coccygeus</b> muscle                                                                                                                              |



## 2. The evolutionary sequence: tail-mover to visceral diaphragm



## 3. Comparative morphological changes with erect posture

| Feature                            | Lower mammals / quadrupeds                                                                                                                               | Man (erect posture)                                                                                                                                                                                                                                                                          |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary function                   | Locomotor/balance/signalling — movement of the tail                                                                                                      | Static — support of pelvic viscera against gravity + sphincteric continence                                                                                                                                                                                                                  |
| Origin of levator ani              | From the pelvic brim (higher up)                                                                                                                         | Origin has shifted down to the side wall of the pelvis (tendinous arch over obturator internus), due to the erect posture and the effect of gravity                                                                                                                                          |
| Disposition of the muscle sheet    | Runs more in line with the long axis of the trunk, consistent with viscera being slung from the dorsal body wall in the quadrupedal (horizontal) posture | Slopes steeply downward, backward and medially to the midline, forming a deep <b>gutter/funnel</b> that must resist the vertically downward pull of the viscera                                                                                                                              |
| Coccygeus vs sacrospinous ligament | Ischiococcygeus is a well-developed, functioning muscle (active tail-mover)                                                                              | Coccygeus is much reduced; the <b>sacrospinous ligament</b> — a degenerated part of its own aponeurosis — is well developed. The two are <b>inversely proportional</b> in their development: a muscular, well-developed coccygeus corresponds to a poorly developed ligament, and vice versa |
| Load-bearing demand                | Pelvic floor is not weight-bearing against gravity in the axial sense; visceral prolapse through it is not a natural hazard                              | Diaphragm now bears the full gravitational load of the abdominopelvic viscera in the erect posture — the anatomical price of bipedalism                                                                                                                                                      |

## 4. Human pelvic diaphragm — the descriptive baseline for the comparison

**Levator ani** — a wide, curved, thin sheet on each side, sloping from the lateral pelvic wall to the midline where the two sheets fuse (a "hammock"), separating the pelvis above from the ischioanal fossae below.

| Muscle part                                   | Origin                                                                 | Insertion                                                                                        |
|-----------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Pubococcygeus (anterior fibres)               | Medial part of the pelvic surface of the body of the pubis             | Perineal body — as levator prostatae (male) or sphincter urethrovaginalis (female)               |
| Puborectalis (middle fibres of pubococcygeus) | Lateral part of the pelvic surface of the body of pubis                | Forms a sling around the anorectal junction; continuous with the longitudinal rectal muscle coat |
| Pubococcygeus (posterior fibres)              | Anterior half of the white line/tendinous arch on obturator fascia     | Anococcygeal ligament and tip of coccyx                                                          |
| Iliococcygeus                                 | Posterior half of the white line + pelvic surface of the ischial spine | Anococcygeal ligament and last two pieces of coccyx                                              |
| Coccygeus (ischiococcygeus)                   | Pelvic surface of the ischial spine and the sacrospinous ligament      | Side of the coccyx and the 5th sacral vertebra                                                   |

**Nerve supply:** Levator ani — a branch from the **4th sacral nerve** (nerve to levator ani, pelvic surface) and a branch from the **inferior rectal/pudendal nerve (S2–S4)**, perineal surface. Coccygeus — ventral rami of S4 and S5.

#### Openings in the diaphragm:

- **Hiatus urogenitalis** — a triangular gap between the anterior fibres of the two levator ani, transmitting the urethra (male) or urethra + vagina (female); closed below by the urogenital diaphragm.
- **Hiatus rectalis** — a rounded opening between the perineal body and the anococcygeal raphe, transmitting the anorectal junction.

**Actions:** closes the posterior part of the pelvic outlet; fixes the perineal body and supports the pelvic viscera; resists rises in intra-abdominal pressure during coughing, straining, lifting and, most intensely, the second stage of labour, thereby maintaining continence of bladder and rectum; the puborectalis sling pulls the anorectal junction forward, maintaining the anorectal angle and preventing untimely passage of faeces; coccygeus supports and pulls forward the coccyx after it is pressed back during defaecation or parturition.

□ Fig 31.16 — Superior view of the pelvic diaphragm (the levator ani and coccygeus) (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.484)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Pelvic diaphragm viewed from below (as in the female pelvis), labelled with:

- ▶ Symphysis pubis and hiatus urogenitalis (urethra ± vagina)
- ▶ Pubococcygeus (anterior fibres — levator prostatae/sphincter urethrovaginalis)
- ▶ Puborectalis — sling around the anorectal junction
- ▶ Iliococcygeus — sheet running back to the anococcygeal raphe
- ▶ Coccygeus (ischiococcygeus) — triangular, from ischial spine + sacrospinous ligament to coccyx/S5
- ▶ Obturator internus muscle and fascia, with the tendinous arch (**white line**) giving origin to levator ani
- ▶ Ischial spine and sacrospinous ligament
- ▶ Anococcygeal raphe/ligament, perineal body, hiatus rectalis (anal canal)
- ▶ Coccyx and piriformis (posterolateral relation, through greater sciatic foramen)

**Applied / Clinical anatomy**

- ▶ **Pelvic organ prolapse** — a stretched or torn pelvic diaphragm (classically, tearing of the perineal body during difficult childbirth) can no longer support the pelvic viscera against gravity, leading to **uterine and rectal prolapse**; this vulnerability is, in comparative terms, essentially a human problem, since quadrupeds do not load their pelvic floor axially against gravity in this way.
- ▶ **Episiotomy** is performed during the second stage of labour to convert an uncontrolled perineal/pelvic-floor tear into a controlled surgical incision, protecting the diaphragm and continence mechanisms.
- ▶ **Puborectalis and faecal continence** — surgical division or neuropathic denervation (e.g., pudendal neuropathy of childbirth) of the puborectalis sling straightens the anorectal angle and causes faecal incontinence; this sling is deliberately preserved/reconstructed in anorectal malformation and incontinence surgery.
- ▶ **Pudendal nerve block**, used for perineal anaesthesia in labour and minor perineal surgery, is given at the level of the ischial spine — the same landmark that gives origin to coccygeus and the sacrospinous ligament described above.
- ▶ **Levator ani spasm/"levator ani syndrome"** presents as chronic pelvic/perineal pain, reflecting the muscle's dual (sphincteric + postural) role acquired with erect posture.
- ▶ **Stress urinary incontinence** in women is linked to weakening of the pubococcygeal part of levator ani around the urethra — the basis of pelvic-floor (Kegel) exercises.

**High-yield exam pointers**

- ▶ Pelvic diaphragm = **levator ani + coccygeus** (each side) + covering fasciae; from behind forwards — Coccygeus, Iliococcygeus, Puborectalis, Pubococcygeus (mnemonic "Could I Please Pee").
- ▶ Phylogenetically these are the **muscles of the tail** in quadrupeds — pubococcygeus pulls the tail forward; iliococcygeus + ischiococcygeus move it sideways.

- ▶ With **loss of the tail and adoption of erect posture**, the same muscles are redeployed to support the pelvic viscera against gravity.
- ▶ Origin of levator ani shifts **from the pelvic brim (lower mammals) to the lateral pelvic wall/tendinous arch (man)** because of gravity in the erect posture.
- ▶ **Coccygeus and sacrospinous ligament** are inversely related in development — the ligament is a degenerated remnant of the ischiococcygeus aponeurosis.
- ▶ Nerve supply: levator ani by S4 + pudendal (S2–S4); coccygeus by S4, S5.
- ▶ Two openings: **hiatus urogenitalis** (urethra ± vagina) and **hiatus rectalis** (anorectal junction).
- ▶ Puborectalis sling → anorectal angle → faecal continence; clinically relevant in incontinence and obstetric injury.
- ▶ Pelvic organ prolapse is, in comparative terms, a consequence unique to the human (erect) pelvic diaphragm bearing an axial gravitational load that quadrupeds never impose on theirs.

### SOURCE & COVERAGE

BD Chaurasia — Human Anatomy Vol 2, 8e (Ch 34, "Walls of Pelvis" — "Morphology of Pelvic Diaphragm"); Vishram Singh — Textbook of Anatomy Vol 2, 4e (Ch 14, "Pelvic diaphragm" — "Evolution of the pelvic diaphragm"); Gray's Anatomy (Standring) 41e — descriptive baseline of pelvic-floor/visceral relations; IB Singh — Textbook of Anatomy Vol 2, 6e.

**Coverage note:** Gray's Anatomy (41e) does not carry a dedicated comparative/evolutionary account of the pelvic diaphragm — its levator ani/pelvic-floor references are scattered, purely human-descriptive mentions across the abdomen/pelvis and urogenital chapters (confirmed by search across all its chapters). The comparative content of this answer is grounded in the "Morphology of Pelvic Diaphragm" (BD Chaurasia) and "Evolution of the pelvic diaphragm" (Vishram Singh) sections, which are the standard sources examined for this specific RGUHS ask.



## Comparative anatomy of the nose

Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy

**Definition / Introduction** The nose comprises the **external nose** (a bony-cartilaginous pyramid covered by skin) and the **nasal cavity** (lined partly by respiratory mucosa and, in its upper one-third, by olfactory mucosa), serving olfaction, respiration (warming, humidifying and filtering inspired air), and resonance for phonation. Its human form is best understood by tracing two parallel threads: its **embryological derivation** from five facial prominences around the stomodeum, and its **phylogenetic (comparative) evolution** across vertebrate classes — a classical illustration of the principle that ontogeny recapitulates phylogeny. Across Pisces, Amphibia, Reptilia, Aves and Mammalia the nasal apparatus shows a progressive trend: from a blind olfactory sac with no respiratory role, to a chamber connected to the mouth via choanae, to a fully separated respiratory-cum-olfactory passage guarded by a bony secondary palate and crowned, for the first time in mammals, by a true external nose.

### Developmental origin of the human nose

- ▶ **4th week** — the **frontonasal prominence** appears cranial to the stomodeum; paired thickenings of surface ectoderm, the **nasal (olfactory) placodes**, arise on it under inductive influence of the ventral forebrain.
- ▶ **5th week** — each placode invaginates to form a **nasal pit**, raising a horseshoe ridge of tissue around it that differentiates into the **medial and lateral nasal prominences**.
- ▶ **6th week** — the nasal pits deepen; the thin **oronasal (bucconasal) membrane** separating each pit from the primitive oral cavity ruptures, establishing the **primitive choanae** — open communication between nasal pit and mouth (complete by the **7th week**).
- ▶ The two **medial nasal prominences** fuse in the midline, both superficially and at depth, to form the **intermaxillary segment** — giving the philtrum of the upper lip, the four-incisor-bearing upper jaw segment, and the triangular **primary palate**; this segment is continuous with the rostral nasal septum (contributed by the frontonasal prominence).
- ▶ **6th–9th week** — shelf-like **palatine processes** grow medially from the paired **maxillary prominences** and fuse with each other and with the primary palate to form the **secondary palate**, definitively separating the nasal cavity from the oral cavity; the choanae are pushed posteriorly to their adult position at the nasopharynx.

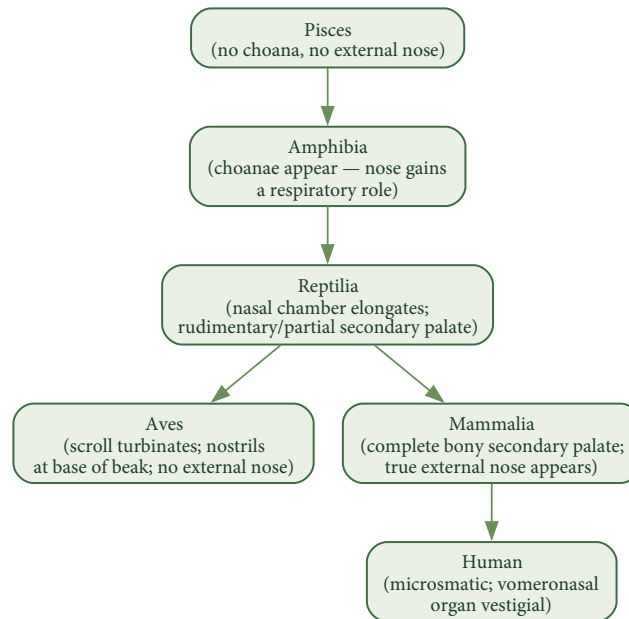
| Facial prominence                       | Adult structure derived                                                 |
|-----------------------------------------|-------------------------------------------------------------------------|
| Frontonasal prominence                  | Bridge (dorsum) of external nose; rostral nasal septum                  |
| Paired medial nasal prominences (fused) | Crest and tip of nose, columella; philtrum of upper lip; primary palate |
| Paired lateral nasal prominences        | Alae (sides/wings) of external nose                                     |
| Paired maxillary prominences            | Cheeks; secondary (definitive) palate; upper lip lateral to philtrum    |

□ Fig 12.1 — Development of the face: five facial primordia around the stomodeum (Sontakke — Textbook of Human Embryology, p.118)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal/frontal schema of a 5–6-week embryo's face, labelled: frontonasal prominence — nasal placode/pit — medial nasal prominence — lateral nasal prominence — maxillary prominence — mandibular prominence — stomodeum — nasolacrimal groove — oronasal membrane — primitive choana. A second small inset showing the 9-week stage with primary palate, secondary (palatine shelf) palate and definitive choana completes the sequence.

### Evolutionary (phylogenetic) trend across vertebrates



*Comparative anatomy of the nose*

### Comparative anatomy across vertebrate classes

| Class         | External nose | Nasal chamber / choana                                                                                                                         | Olfactory organ                                                                              | Vomeronasal (Jacobson's) organ | Distinguishing feature                            |
|---------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------------|
| Pisces (fish) | Absent        | Paired blind olfactory sacs on the snout, each with an incurrent and excurrent nostril; <b>no choana</b> — no communication with mouth/pharynx | Purely olfactory (water-borne odourants); no respiratory function — respiration is branchial | Absent                         | Nose serves smell alone; unconnected to breathing |

| Class        | External nose                                                                   | Nasal chamber / choana                                                                                                                                                                 | Olfactory organ                                                                   | Vomeronasal (Jacobson's) organ                                                                                                                                      | Distinguishing feature                                                                                         |
|--------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Amphibia     | Absent                                                                          | Choanae appear for the first time, connecting nasal chamber to the buccal cavity                                                                                                       | Simple nasal chamber, no turbinates                                               | Present — an accessory olfactory organ in the nasal floor                                                                                                           | First vertebrates in which the nose acquires a dual olfactory-cum-respiratory function as air-breathing begins |
| Reptilia     | Absent (or barely raised)                                                       | Nasal chamber elongates; a vestibule and rudimentary conchae appear; in crocodilians a bony secondary palate pushes the choana far back to the pharynx                                 | Better developed than amphibia                                                    | Well developed; often opens into the roof of the mouth — used with tongue-flicking chemoreception (snakes, lizards)                                                 | Crocodilian secondary palate lets the animal breathe while submerged or holding prey                           |
| Aves (birds) | Absent — external nostrils lie at the base of the beak (at the tip in the kiwi) | Chamber with three scroll-like conchae                                                                                                                                                 | Generally poorly developed (exceptions: kiwi, vultures, procellariiform seabirds) | Regressed/absent in most birds                                                                                                                                      | No fleshy external nose at all                                                                                 |
| Mammalia     | True fleshy external nose appears for the first time, often mobile (rhinarium)  | Complete bony (hard) + muscular (soft) secondary palate fully separates nasal from oral cavity, allowing simultaneous mastication and respiration; turbinates/conchae highly developed | Extensive olfactory epithelium in macrosmatic mammals (dog, rodent, ungulate)     | Well developed in macrosmatic mammals; a duct + vomeronasal nerve run to an accessory olfactory bulb; mediates pheromonal communication (e.g. the flehmen response) | Paranasal air sinuses well developed                                                                           |



| Class                       | External nose                                                 | Nasal chamber / choana                                                                                                                       | Olfactory organ                                    | Vomeronasal (Jacobson's) organ                                                                                                                                                                            | Distinguishing feature                                  |
|-----------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Human (microsmatic primate) | Reduced, simplified pyramid compared with macrosmatic mammals | As mammalia; upper 1/3 of cavity (roof, superior concha, adjoining septum) lined by <b>olfactory mucosa</b> , the rest by respiratory mucosa | Small dedicated area — human is <b>microsmatic</b> | <b>Vestigial</b> — a blind epithelial pit/tubule in the anteroinferior nasal septum, just dorsal to the paraseptal cartilages; no accessory olfactory bulb or vomeronasal nerve demonstrated in the adult | Functionless remnant of an ancestral chemosensory organ |

### Vomeronasal (Jacobson's) organ in the human — a worked example of comparative anatomy

- ▶ In **most amphibians, reptiles and mammals** the vomeronasal organ is the peripheral sensory organ of the **accessory olfactory system**, lying paired at the base of the nasal septum or in the roof of the mouth and mediating chemical communication, often via pheromones.
- ▶ In many **macrosmatic mammals** it consists of a vomeronasal duct with chemosensory cells and a vomeronasal nerve terminating in a dedicated **accessory olfactory bulb**.
- ▶ In the **human fetus**, paired vomeronasal organs form at Carnegie stage 18 (~6 weeks) in the developing nasal septum; between 12 and 19 weeks they show an olfactory-epithelium-like appearance with LHRH-immunoreactive cells in nerve fascicles running toward the olfactory bulb.
- ▶ This olfactory-type structure and hormone immunoreactivity are **lost later in fetal life**; although a bilateral structure presumed analogous to the vomeronasal organ persists in many adults (anteroinferior nasal septum, dorsal to the paraseptal cartilages), **no functioning vomeronasal nerve or accessory olfactory bulb has been demonstrated in the human adult**, and a pheromonal role remains unestablished (some limited evidence has been proposed for a local endocrine, rather than sensory, activity).
- ▶ This is the single best-documented example in the modern human-anatomy literature of a structure whose comparative-anatomical significance across vertebrates is retained in humans only as a vestige.

### Applied / Clinical anatomy

- ▶ **Cleft lip/palate** — failure of fusion of the medial nasal prominence with the maxillary prominence (cleft lip) or of the palatine shelves with each other/the primary palate (cleft palate); directly explained by the developmental sequence above.

- ▶ **Choanal atresia** — persistence (failure of rupture) of the oronasal membrane; since neonates are obligate nasal breathers, bilateral atresia causes life-threatening respiratory distress at birth.
- ▶ **Little's area (Kiesselbach's plexus)** — the anteroinferior nasal septum, an anastomotic capillary network of the sphenopalatine, greater palatine, superior labial and anterior ethmoidal arteries; the commonest site of epistaxis — anatomically close to the vestigial vomeronasal remnant on the septum.
- ▶ **Anosmia after head injury** — because the human olfactory epithelium is confined to a small dedicated area (unlike the extensive epithelium of macrosmatic mammals), shearing of the fine olfactory nerve filaments at the cribriform plate in even minor trauma readily causes loss of smell.
- ▶ **Rhinoplasty** — surgical remodelling exploits the embryological origin of the nasal skeleton (septal cartilage from the frontonasal prominence; alar cartilages from the lateral nasal prominences).
- ▶ **Comparative/veterinary correlate** — the well-developed mammalian vomeronasal organ underlies the **flehmen response** (lip-curl) seen in cats, horses and many ungulates, contrasting with its vestigial human counterpart.

### High-yield exam pointers

- ▶ Nose = external nose + nasal cavity; upper 1/3 olfactory mucosa, rest respiratory mucosa.
- ▶ Five facial prominences form the nose: frontonasal (bridge, septum), paired medial nasal (crest, tip, columella, philtrum, primary palate), paired lateral nasal (alae), paired maxillary (cheeks, secondary palate).
- ▶ Nasal placode → nasal pit (5th week) → oronasal membrane ruptures → primitive choana (6th–7th week) → secondary palate completes separation (9th week).
- ▶ Comparative trend: Pisces (no choana, olfaction only) → Amphibia (choanae appear, dual function) → Reptilia (elongated chamber, crocodilian secondary palate) → Aves (no external nose, scroll turbinates) → Mammalia (true external nose, complete secondary palate, macrosmatic).
- ▶ Vomeronasal (Jacobson's) organ: present and functional (accessory olfactory system) in amphibians, reptiles and macrosmatic mammals; forms in the human fetus at ~6 weeks but is **vestigial/non-functional** in the human adult.
- ▶ Human is microsmatic; most mammals other than primates are macrosmatic.
- ▶ Clinical correlates: cleft lip/palate (fusion failure), choanal atresia (persistent oronasal membrane), Little's area epistaxis, post-traumatic anosmia.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Sontakke's Textbook of Human Embryology; Hamilton, Boyd & Mossman's Human Embryology; BD Chaurasia's Human Anatomy Vol 3-4 8e; Vishram Singh's Textbook of Anatomy Vol 3 4e; Moore's Clinically Oriented Anatomy 9e.

**Coverage note:** the modern textbook corpus in this bank is human-anatomy/embryology focused (Gray's, Langman, Sontakke, etc.) and does not carry a dedicated cross-species comparative-zoology chapter for the nose. The vertebrate-class comparison above is standard, universally-accepted comparative anatomy taught alongside human embryology; the one point where the corpus directly corroborates cross-species detail — the vomeronasal (Jacobson's) organ across amphibians, reptiles and mammals, and its vestigial human status — is verbatim-grounded in Gray's Anatomy 41e.



## Describe the evolution of kidneys

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The mammalian kidney develops from intermediate mesoderm and passes, in strict cranio-caudal and temporal succession, through three organs — the **pronephros**, **mesonephros** and **metanephros** — before the last is retained as the permanent kidney. This three-stage succession in the human embryo faithfully recapitulates the evolutionary history of the vertebrate excretory organ, a classic illustration of "**ontogeny repeats phylogeny**": the pronephros is the functional kidney of primitive fish, the mesonephros of fish and amphibians, and the metanephros — found only in reptiles, birds and mammals (amniotes) — is the definitive, permanently functioning kidney of the human. Gray's Anatomy cautions, however, that reliable criteria to sharply demarcate these three stages in staged human embryos are difficult to define, since they overlap in time and space.

### 1. Common developmental origin: the nephrogenic cord

- ▶ The urinary system arises from **intermediate mesoderm**, a longitudinal strip lying between the paraxial mesoderm and the lateral plate, on either side of the notochord/dorsal aorta.
- ▶ After folding of the embryo it forms the **urogenital ridge**, which subdivides into a medial **genital ridge** (future gonad) and a lateral **nephrogenic cord** (future kidney).
- ▶ The nephrogenic cord extends from the **cervical to the sacral region** and is covered by coelomic (peritoneal) epithelium.
- ▶ It gives rise, in cranio-caudal succession, to **three overlapping kidney systems** — pronephros, mesonephros, metanephros — such that the last to appear is the one retained as the permanent kidney.

### 2. Comparative basis: how the vertebrate kidney evolved

In lower vertebrates the intermediate mesenchyme forms serial, **segmental nephrotomes**. Each nephrotome encloses a cavity, the **nephrocele**, which communicates with the coelom through a

**peritoneal funnel (nephrostome)**. The dorsal wall of the nephrotome evaginates as a nephric tubule; the tubules of successive segments fuse caudally to form a **longitudinal primary excretory (nephric) duct** that opens into the cloaca. Glomeruli develop either from the floor of the nephrocele (**internal glomeruli**) or from the coelomic roof adjacent to the nephrostome (**external/coelomic glomeruli**), or both. In amniotes (including humans) the nephrostomal/funnel communication with the coelom is transient or absent, and only internal glomeruli form.

| Feature                        | Pronephros                                                              | Mesonephros                                                                                         | Metanephros                                                                     |
|--------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Permanent/functional kidney in | Cyclostomes and some teleost fishes                                     | Fishes and amphibians (most anamniotes)                                                             | Reptiles, birds and mammals (amniotes) — definitive human kidney                |
| Segmentation                   | Segmented                                                               | Segmented                                                                                           | Non-segmented (metanephric blastema)                                            |
| Tubule number                  | Few, transient (7–10 in man)                                            | Numerous                                                                                            | ~1–3 million nephrons                                                           |
| Duct                           | <b>Pronephric (primary excretory) duct</b>                              | <b>Mesonephric (Wolffian) duct</b> — inherited from the pronephric duct                             | <b>Ureter</b> — a new outgrowth (ureteric bud) from the caudal mesonephric duct |
| Fate in the human embryo       | Regresses completely by the end of the 4th week; only its duct persists | Regresses by the end of the first trimester; caudal tubules persist in the male genital duct system | Persists permanently as the adult kidney                                        |

### 3. Recapitulation in the human embryo: the three successive kidneys

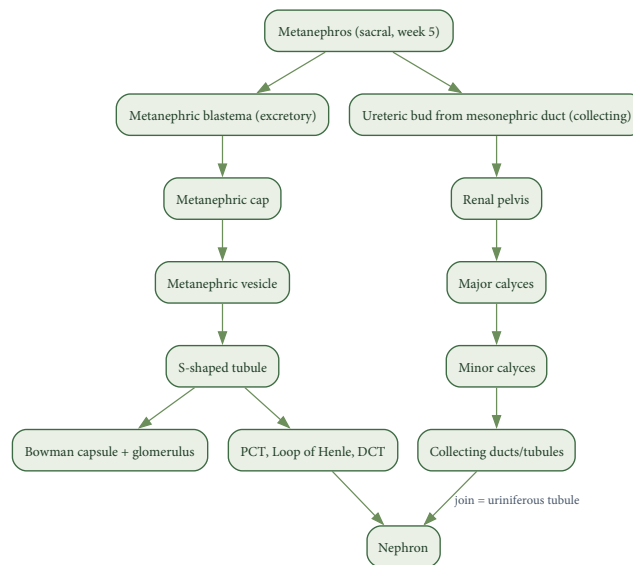
- **Pronephros** — appears at the **beginning of the 4th week** in the cervical region as 7–10 solid/vesicular cell groups (nephrotomes) derived from intermediate mesoderm. It is rudimentary, forms no glomeruli, is completely non-functional, and disappears by the end of the 4th week. Its duct — the **pronephric duct**, which has already grown caudally to reach the cloaca — persists and is annexed by the mesonephros to become the **mesonephric duct** (the pronephric duct is, in fact, an essential inductor for differentiation of the mesonephric tubules).
- **Mesonephros** — develops from intermediate mesenchyme opposite the upper thoracic to upper lumbar (L3) segments, appearing at the **end of the 4th week**. Each tubule differentiates cranio-caudally into an S-shaped tubule whose medial end is invaginated by a capillary tuft to form a glomerulus (Malpighian corpuscle), and whose lateral end joins the mesonephric duct; no loop of Henle forms. It is believed to be transiently functional in the early fetal period. Most tubules degenerate cranio-caudally by the end of the first trimester; in the male, caudal (epigenital and paragenital) tubules and the mesonephric duct persist to form the **vasa efferentia, epididymis, vas deferens and ejaculatory duct**; in the female they largely disappear.
- **Metanephros** — the **definitive, permanent kidney** — begins to develop in the sacral region early in the **5th week**, when the **ureteric bud** (an outgrowth of the caudal mesonephric duct) invades the **metanephric blastema**, the caudal-most, non-segmented condensation of the nephrogenic cord. It becomes functional (starts urine formation) about **4 weeks later, i.e., early in the third**

month, and persists permanently. It arises from two distinct sources — the metanephric blastema (excretory/secretory system) and the ureteric bud (collecting system).

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros (Sontakke — Textbook of Human Embryology, p.212)

#### 4. Development of the definitive (metanephric) kidney

- **Collecting system** (from the ureteric bud): the bud dilates to form the primitive **renal pelvis**, then divides dichotomously into cranial and caudal **major calyces**, then **minor calyces**; continued dichotomous branching through **12 or more generations** forms the **collecting ducts** and **collecting tubules**.
- **Excretory system** (from the metanephric blastema): cells condense around each collecting-tubule tip to form a **metanephric cap**, which becomes a **metanephric vesicle**, then a pear-shaped vesicle, then an S-shaped **primitive renal tubule**. Its proximal dilated end forms **Bowman's capsule**, invaginated by a capillary tuft (from angioblastic tissue of the nephrogenic cord) to form the **glomerulus**; the rest differentiates into the **proximal convoluted tubule**, **loop of Henle** and **distal convoluted tubule**. The distal convoluted tubule joins the collecting tubule to complete the **uriniferous tubule (nephron + collecting duct)**.
- Up to **1–3 million nephrons** form per kidney. New nephron formation continues into late fetal life; the fetal kidney is **lobulated**, a lobulation that normally disappears during the **first year** after birth.



*Describe the evolution of kidneys*

#### 5. Ascent, rotation and vascular change of the kidney

- The metanephros initially lies in the **sacral region**; owing to differential growth of the posterior abdominal wall and straightening of the fetal curvature, it **ascends** to its final **thoracolumbar (T12–L3)** position, opposite the second lumbar vertebra. The ureter elongates correspondingly.
- Physiological reasons for ascent: (a) space crunch in the smaller pelvic cavity, and (b) the kidney "chases" a better blood supply.
- **Vascular change during ascent**: the kidney is supplied initially by the **median sacral artery** (a pelvic continuation of the aorta); as it ascends it is supplied successively by higher **lateral**

**splanchnic branches of the aorta**, which degenerate as the kidney moves further cranially; the vessel present when it reaches its final position at L2 becomes the **definitive renal artery**.

- **Rotation:** the renal hilum, which initially faces ventrally, rotates **90° medially** during ascent so that it comes to face medially in the adult.

□ Fig 20.7 — Ascent of kidney: from its sacral position to the thoracolumbar region (Sontakke — Textbook of Human Embryology, p.216)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Panel A — the three successive kidneys in a 4th–5th week embryo (lateral view): label — *dorsal aorta; nephrogenic cord; degenerating pronephros (cervical) with pronephric duct; mesonephros (thoracolumbar) with mesonephric tubules and mesonephric duct; metanephros (sacral) with ureteric bud; cloaca; allantois*. Panel B — ascent of the kidney (coronal schematic): label — *initial sacral position; final thoracolumbar (T12–L3) position; ureter; median sacral artery; successive (transient) lateral splanchnic branches; definitive renal artery at L2; direction of 90° medial rotation of the hilum*.

### Applied / Clinical anatomy

- **Renal agenesis** — failure of ureteric bud formation/induction. *Unilateral:* relatively common, more common in males, asymptomatic (contralateral kidney hypertrophies), usually an incidental finding. *Bilateral:* rare, incompatible with life; causes **oligohydramnios**, which compresses the fetus to produce **Potter's syndrome/sequence** (deformed limbs, wrinkled skin, abnormal facial appearance) unless donor transplantation is possible.
- **Horseshoe kidney** — inferior poles of the two kidneys fuse as they are pushed together while passing through the arterial fork formed by the umbilical arteries; during ascent the fused isthmus is trapped beneath the origin of the **inferior mesenteric artery**, so the horseshoe kidney characteristically arrests at the lower lumbar level, with ureters passing anterior to the isthmus.
- **Pelvic kidney** — failure of ascent; the kidney remains in the pelvis. The commonest cause is a **sickle-shaped fold of peritoneum (containing the umbilical artery)** projecting from the lateral pelvic wall, which obstructs ascent.
- **Duplication of the kidney/ureter** — early division of the ureteric bud.
- **Congenital polycystic kidney disease** — currently attributed to abnormal dilatation of parts of the uriniferous tubule, especially the loop of Henle (an older view attributed it to failure of excretory and collecting tubules to unite). Usually bilateral and hereditary, with associated hepatic, pancreatic and pulmonary cysts; childhood-type prevalence  $\approx 1:5000$  births, adult-type  $\approx 1:600$  births.
- **Persistent lobulated kidney** — failure of the normal fetal lobulation to disappear after the first year of life.
- **Accessory/aberrant renal arteries** — persistence of one of the transient vessels that vascularised the ascending kidney; clinically relevant to hydronephrosis from a crossing lower-pole vessel at the pelvi-ureteric junction, and to renal transplant harvesting.
- Because the mesonephric duct also forms part of the male genital duct system, ipsilateral renal agenesis is frequently accompanied by absence of the vas deferens/seminal vesicle on that side

(and, via the paramesonephric duct, uterine anomalies in the female) — reflecting the shared embryological origin of the excretory and genital systems.

### High-yield exam pointers

- ▶ "Ontogeny repeats phylogeny": pronephros (fish) → mesonephros (fish/amphibia) → metanephros (reptiles, birds, mammals — definitive kidney of man).
- ▶ Only the **metanephros** persists; the pronephros and mesonephros regress, but their **ducts are never wasted** — pronephric duct → mesonephric duct → ureteric bud.
- ▶ Metanephros has **two sources**: ureteric bud (collecting system: pelvis, calyces, collecting ducts/tubules) + metanephric blastema (excretory system: the nephron).
- ▶ Kidney develops in the **sacral region**, ascends to **T12–L3**; blood supply changes serially — median sacral artery → transient lateral splanchnic branches → definitive renal artery at **L2**; hilum rotates **90° medially**.
- ▶ Fetal kidney is normally **lobulated**; lobulation disappears in the **first year**.
- ▶ Key applied anomalies: renal agenesis (→ Potter's syndrome if bilateral), horseshoe kidney (trapped beneath inferior mesenteric artery), pelvic kidney (failed ascent), polycystic kidney (loop-of-Henle dilatation), duplex ureter (early ureteric-bud division).
- ▶ **Coverage note**: Gray's Anatomy (Standring) covers only human urogenital development in detail; the comparative/phylogenetic framework (functional pronephros/mesonephros in specific vertebrate classes) is drawn from Vishram Singh, IB Singh and Hamilton, Boyd & Mossman, which is the standard depth expected at RGUHS PG level for this question.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Vishram Singh — Textbook of Clinical Embryology; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; Sontakke — Textbook of Human Embryology (figures).





## Describe the stages of evolution of heart in vertebrates

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** — The vertebrate heart has evolved from a simple single tubular pump moving blood through a single circuit in fishes to a completely septated, four-chambered double pump in birds and mammals. The principal evolutionary drivers are the replacement of gills by lungs in air-breathing, land-dwelling vertebrates (which created a second, pulmonary circuit that had to be kept separate from the systemic circuit) and, in warm-blooded (endothermic) vertebrates, the need for a higher metabolic rate that demanded fully oxygenated blood delivered without admixture with venous blood. The story unfolds in four recognisable stages — fish, amphibian, reptile, and bird/mammal — each marked by progressively greater internal septation of the primitively unpartitioned cardiac tube.

### 1. The primitive vertebrate heart — the fish stage

- ▶ In most fishes, throughout life, the heart remains a **single tubular structure** showing the primitive plan of five successive dilated chambers separated by constrictions, arranged in series from caudal (venous) to cranial (arterial) end:
- ▶ **Sinus venosus** — the receptive chamber into which systemic venous blood drains.
- ▶ **Atrium** — a single, undivided chamber.
- ▶ **Ventricle** — a single, undivided chamber; the main pumping chamber.
- ▶ **Bulbus cordis** — a muscular outflow chamber.
- ▶ **Truncus arteriosus** — the efferent vessel leaving the heart.
- ▶ Functionally this is often described as a "**two-chambered**" heart (one atrium, one ventricle), the sinus venosus and bulbus cordis being regarded as accessory chambers.
- ▶ **Circulatory pathway**: venous blood → sinus venosus → atrium → ventricle → bulbus cordis → truncus arteriosus → afferent branchial arteries → gill capillaries (oxygenation) → efferent branchial vessels → paired dorsal aortae → systemic capillary beds → back to the sinus venosus.
- ▶ This is a **single circulation**: blood passes through the heart only once per complete circuit, and only completely deoxygenated blood is ever pumped by the heart — there is no mixing problem because there is no second (pulmonary) circuit to keep separate.

### 2. The amphibian heart — the first septation (atrial division)

- ▶ In the **tadpole stage**, the heart is essentially similar to the fish heart (gill respiration, single circuit).
- ▶ After **metamorphosis**, when lungs replace gills as the organ of respiration, a **septum forms in the atrium**, dividing this single cardiac cavity into a **right and a left chamber**:
  - The **right atrium** receives systemic (deoxygenated) venous blood via the sinus venosus.
  - The **left atrium** receives oxygenated blood returning from the newly developed lungs via the pulmonary veins.
- ▶ From the two atria, blood passes into a **single, undivided ventricle** and thence into a **single truncus arteriosus**, which distributes blood both to the body generally and to the lungs.
- ▶ Because the ventricle and truncus arteriosus remain unseptated, there is **some separation but considerable mixing** of oxygenated and deoxygenated streams during passage through these

common chambers — the amphibian heart is thus often termed a "**three-chambered**" heart (two atria, one ventricle) with incomplete functional separation of the two blood streams.

### 3. The reptilian heart — septation extends to the ventricle

- ▶ In reptiles, the process of septation advances further: the **dividing septum** extends caudally into the **ventricle**, partially separating it into right and left halves.
- ▶ In **all reptiles except the Crocodilia**, this **ventricular septation** remains **incomplete**, so a degree of mixing of pulmonary-venous (oxygenated) blood with systemic-venous return still occurs within the ventricle — the reptilian heart (other than crocodilians) is commonly described as a **functionally "three-and-a-half-chambered" heart**.
- ▶ The **Crocodilia** are the **sole exception**: they possess an essentially **complete interventricular septum**, giving a truly four-chambered heart, though the two aortic trunks retain a connecting communication permitting some right-to-left shunting.
- ▶ The trend across this stage is unmistakable — with each advance from fish to amphibian to reptile, septation progresses caudally along the primitively single tube (atrium first, then ventricle), progressively reducing the admixture of oxygenated and deoxygenated blood.

### 4. The avian and mammalian heart — complete septation and true double circulation

- ▶ In the **warm-blooded vertebrates** (birds and mammals), the higher metabolic rate required by endothermy made a far more efficient circulatory arrangement necessary.
- ▶ Septation becomes **complete at every level of the primitive cardiac tube** — the atria, the ventricles, **and** the truncus arteriosus (which is septated into the aorta and the pulmonary trunk) — producing a heart of **four completely separate chambers**: a right atrium communicating only with a right ventricle, and a left atrium communicating only with a left ventricle.
- ▶ **Circulatory pathway**: systemic venous blood → sinus venosus → right atrium → right ventricle → pulmonary artery → lungs (oxygenation) → pulmonary veins → left atrium → left ventricle → aorta → systemic capillary beds.
- ▶ This yields a genuine **double circulation** — a pulmonary circuit and a systemic circuit arranged in series, with the two streams of blood never mixing — the most efficient arrangement for sustaining a high, constant metabolic rate.
- ▶ In mammals the **sinus venosus itself is not retained as a separate chamber**; instead it is progressively incorporated into the wall of the developing right atrium, its tissue giving rise to the smooth-walled part of the right atrium into which the venae cavae open, and the sino-atrial node develops within this incorporated sinus venosus tissue.

## 5. Comparative summary of the evolutionary stages

| Vertebrate class              | Functional description                                                               | Atrial septum | Ventricular septum | Truncus septum                             | Type of circulation                             |
|-------------------------------|--------------------------------------------------------------------------------------|---------------|--------------------|--------------------------------------------|-------------------------------------------------|
| Fish                          | "Two-chambered" (1 atrium, 1 ventricle) in series with sinus venosus & bulbus cordis | Absent        | Absent             | Absent                                     | Single circulation                              |
| Amphibia (post-metamorphosis) | "Three-chambered" (2 atria, 1 ventricle)                                             | Complete      | Absent             | Absent                                     | Single circuit with mixing in ventricle/truncus |
| Reptilia (non-crocodilian)    | "Three-and-a-half-chambered"                                                         | Complete      | Incomplete         | Incomplete                                 | Partial double circulation, mixing persists     |
| Crocodylia                    | Four-chambered                                                                       | Complete      | Complete           | Complete (aortic trunks still communicate) | Near-complete double circulation                |
| Aves / Mammalia               | Four-chambered                                                                       | Complete      | Complete           | Complete                                   | Complete double circulation, no mixing          |

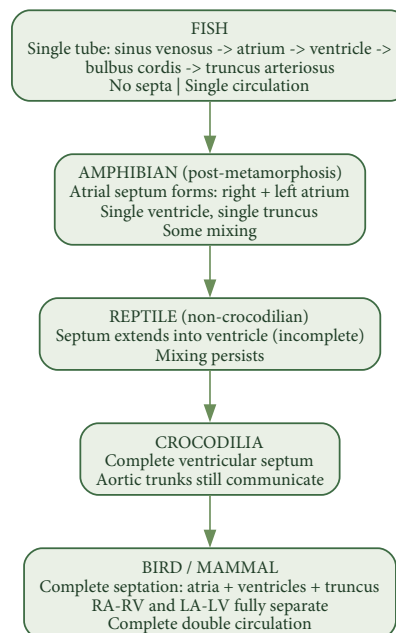
## 6. Evolutionary drivers and biological significance

- ▶ **Substitution of gills by lungs** in land-dwelling vertebrates is the primary event that created a second (pulmonary) circulatory pathway; once oxygenated pulmonary-venous blood had to return to the heart, keeping it separate from systemic-venous blood became the central evolutionary problem, solved by stepwise septation (atrium → ventricle → truncus arteriosus) across the amphibian–reptile–bird/mammal sequence.
- ▶ **Endothermy** in birds and mammals demanded a higher, sustained metabolic rate, which in turn required fully oxygenated arterial blood delivered without dilution by venous blood — driving the completion of septation at every level of the heart.
- ▶ The conducting arrangement of the heart shows deep evolutionary conservation alongside this structural change: although only mammalian hearts possess a well-defined, morphologically distinct conduction system, an essentially similar electrocardiogram can be recorded from animals as diverse as fish and humans, indicating that the electrical connections between cardiac components, and the gene-regulatory networks that pattern them, have been conserved throughout vertebrate evolution even as gross chamber anatomy diverged.
- ▶ This phylogenetic sequence is recapitulated, in compressed form, during **human cardiac embryogenesis**: the human heart begins as a single midline endocardial tube that undergoes bulbo-ventricular looping and then passes through sequential septation of the atrium, the

ventricle, and finally the truncus arteriosus (aorticopulmonary septum) — mirroring, stage for stage, the fish-to-mammal evolutionary sequence described above.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

For hand reproduction, draw four simple schematic hearts side by side (fish, amphibian, reptile, mammal) and label on each: **sinus venosus, atrium(s) — undivided/right/left, ventricle(s) — undivided/partly-divided/fully-divided, bulbus cordis, truncus arteriosus/aorta and pulmonary trunk**. Shade oxygenated blood differently from deoxygenated blood to show progressively decreasing admixture from fish to mammal.



*Describe the stages of evolution of heart in vertebrates*

### Applied / Clinical anatomy

- **Congenital heart disease can be viewed as an arrest of septation at a stage corresponding to a lower vertebrate:** a single-atrium anomaly resembles the fish/early-amphibian condition; a ventricular septal defect represents incomplete ventricular septation analogous to the non-crocodilian reptilian heart; a persistent truncus arteriosus (failure of aorticopulmonary septation) reproduces the unseptated outflow tract of fish and amphibians.
- **Sinus venosus atrial septal defect** is a direct clinical correlate of the incorporation of the sinus venosus into the right atrium during mammalian heart evolution/development — a defect at the superior or inferior margin of this incorporated region allows an interatrial shunt.
- **Patent foramen ovale / patent ductus arteriosus** in the newborn represent normal fetal shunt pathways that must close after birth to establish the complete double circulation characteristic of the adult mammalian heart; their persistence recreates a degree of the physiological right-to-left mixing seen in reptiles.

- ▶ The **crocodilian foramen connecting the two aortic trunks** (despite a complete interventricular septum) shows that a structurally complete septum need not guarantee a fully separated double circulation — relevant to shunt physiology in human congenital heart disease.
- ▶ This evolutionary ladder helps explain, and predict, the morphology of septal and outflow-tract anomalies encountered in paediatric cardiology and cardiac surgery.

### High-yield exam pointers

- ▶ Sequence to write first: **Fish** → **Amphibian** → **Reptile** → **Bird/Mammal**, with septation advancing caudo-cranially: atrium first, then ventricle, then truncus arteriosus.
- ▶ Fish heart chambers in series: **sinus venosus** → **atrium** → **ventricle** → **bulbus cordis** → **truncus arteriosus**; single circulation, "two-chambered."
- ▶ Amphibian: atrial septum only ("three-chambered"); single ventricle and truncus still allow mixing.
- ▶ Reptile: ventricular septum added but incomplete in all reptiles **except Crocodilia**, which alone achieves a complete interventricular septum.
- ▶ Bird/mammal: complete septation at atrial, ventricular, **and** truncal levels → four chambers → complete double circulation with no mixing.
- ▶ Evolutionary drivers: **gills replaced by lungs** (creates the pulmonary circuit) + **endothermy** (demands fully oxygenated, undiluted arterial blood).
- ▶ Sinus venosus is not retained as a separate adult chamber in mammals — it is incorporated into the right atrium and gives rise to the sino-atrial node region.
- ▶ Human embryonic heart development (tubular heart → bulbo-ventricular looping → atrial septation → ventricular septation → truncal septation) recapitulates this same evolutionary sequence.
- ▶ Congenital cardiac anomalies (ASD, VSD, persistent truncus arteriosus) can be conceptualised as developmental arrest at successive points along this phylogenetic ladder.

### SOURCE & COVERAGE

Hamilton, Boyd & Mossman — Human Embryology (classic "Phylogeny of the Heart" account — fish, amphibian, reptile, and bird/mammal stages, chamber nomenclature, and the sinus venosus-to-right-atrium incorporation); Gray's Anatomy (Standring) 41e (evolutionary conservation of the cardiac conduction system across vertebrates; septation of the truncus arteriosus as part of definitive heart development).

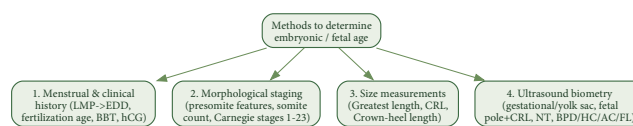
*Coverage note:* this is a comparative-vertebrate-zoology topic rather than a human-embryology topic proper. Gray's Anatomy and the modern specialty embryology texts in this bank (Langman, Moore's Developing Human, Larsen, IB Singh CBME 2021, Vishram Singh, Sontakke, Brijesh Kumar) are human-focused and describe only human cardiac embryogenesis, not inter-class phylogeny; the classic account in Hamilton, Boyd & Mossman is therefore the primary grounding source for the fish/amphibian/reptile/mammal sequence above, supplemented by standard comparative-vertebrate-zoology facts (e.g. the "two/three/three-and-a-half/four-chambered" nomenclature) taught identically across Indian MD/MS anatomy curricula.



## Describe the various methods used to determine embryonic age

*Asked in: Paper II Nov 2018 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The embryonic period extends from fertilization to the end of the 8th week (56 days) and is divided into 23 **Carnegie stages**. Because the precise moment of fertilization is almost never known clinically, the age of an embryo/early fetus is estimated **indirectly**, using several complementary methods: (i) menstrual/clinical history, (ii) morphological criteria of the embryo itself (somite counting, Carnegie staging, external landmarks), (iii) direct measurement of embryo/fetal size, and (iv) ultrasound biometry in vivo. Two time-scales run in parallel and differ by ~14 days — the **fertilization (post-ovulatory) age** used by embryologists, and the **menstrual/gestational age** used obstetrically (counted from the last menstrual period, LMP). Accurate age assignment underlies the timing of chorionic villus sampling/amniocentesis, calculation of the expected date of delivery (EDD), and detection of growth restriction.



*Describe the various methods used to determine embryonic age*

### 1. Menstrual history and other clinical criteria

- **Menstrual (gestational) age:** reckoned from the 1st day of the LMP; gestation averages 280 days/40 weeks/9 months  $\pm$  7 days. Example — LMP 10.09.2016  $\rightarrow$  EDD 17.06.2017 (subtract 3 months, add 7 days and 1 year from LMP).
- **Fertilization age** = the true developmental age of the conceptus = **menstrual age** – 14 days, since ovulation/fertilization occurs about mid-cycle, 14 days before the next expected period.

- **Coital age:** where a single act of coitus can be dated, fertilization age cannot be much less than this, limited by the short fertilizable lifespan of the oocyte and sperm.
- **Basal body temperature (BBT) charting:** temperature falls 0.3–0.5 °C just before ovulation (follicular phase) and rises thereafter due to progesterone (luteal phase) — used to time ovulation/likely conception when the menstrual history is unreliable.
- **Pregnancy (hCG) tests:** detect human chorionic gonadotropin in maternal urine/serum, confirming pregnancy but not precisely dating it.
- LMP-based dating is unreliable with irregular cycles, oligomenorrhoea, conception soon after stopping oral contraceptives, implantation "spotting" mistaken for menstruation, and IUCD use — hence the need for embryo/fetus-based methods below.

## 2. Morphological staging of the embryo (Carnegie System)

- **Presomite period (day 15–20):** embryo graded by internal landmarks — primitive streak, notochord, intraembryonic mesoderm; age reckoned in days.
- **Somite period (day 20–30):** somites appear craniocaudally at ~3–4 pairs/day (ultimately 42–44 pairs: 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 8–10 coccygeal). While somites are countable, age is read directly off the somite number:

| Age (days) | Somite pairs | Structure(s) appearing                              |
|------------|--------------|-----------------------------------------------------|
| 20         | 1–4          | Neural plate, neural folds/groove                   |
| 21         | 4–8          | Fusion of endocardial heart tubes                   |
| 22         | 8–12         | Otic placode, optic sulcus appear                   |
| 23         | 12–16        | Lens and otic placodes form                         |
| 24         | 16–20        | 1st & 2nd pharyngeal arches appear                  |
| 25         | 20–24        | Anterior neuropore closes; 3rd–5th arches appear    |
| 26         | 24–28        | Upper-limb bud appears; primitive streak disappears |
| 27         | 28–32        | Posterior neuropore closes                          |
| 28         | 32–36        | Lower-limb bud appears                              |
| 29         | 36–40        | Limb buds become paddle-shaped                      |
| 30         | 40–44        | Facial development begins                           |

- **External morphological landmarks** (once somites become too numerous to count accurately, the degree of pharyngeal-arch and limb-bud development is used): upper-limb bud clearly visible by **stage 13**; distal paddle on the upper limb by **stage 16**; lower-limb bud acquires a distal paddle while the upper-limb bud shows separating digit rays by **stage 18**; by **stage 23** the head is almost erect and rounded, eyelids are beginning to form, the limbs are in better proportion with separate fingers/toes, and external genitalia are formed (though not yet reliably sexable).



- **Carnegie Embryonic Staging System:** divides the 8-week embryonic period into **23 stages** (Streeter's study of the Carnegie collection, continued by O'Rahilly & Müller), used internationally to compare specimens (and across species — chick, mouse, rat) despite biological variability in growth rate. Crucially, stage is assigned from a **combination of external AND internal morphological criteria** — **not from length or age alone**. As a rough guide only, within the CRL range 3–30 mm, age (days) can be approximated by **adding 29 to the CRL in millimetres**.

### 3. Direct measurement of embryo/fetal size

| Measurement             | Landmarks                                                              | Period of use                                                                                                                                                  |
|-------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Greatest length (GL)    | Longest curved axis of the embryo                                      | 3rd to early 4th week, while the embryo is still straight and crown/rump are not differentiated                                                                |
| Crown–rump length (CRL) | Vertex of the skull to the midpoint between the apices of the buttocks | From ~5th week once the embryo curves; the <i>longest</i> CRL obtainable is taken as most accurate, since no fixed anatomical marker defines "crown" or "rump" |
| Crown–heel length (CHL) | Vertex of the skull to the heel (standing height)                      | Sometimes used from the 8th week onward                                                                                                                        |

CRL at approximately: 5–8 mm at 5 weeks, 10–14 mm at 6 weeks, 17–22 mm at 7 weeks, and 28–30 mm at 8 weeks.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A simple three-panel schematic comparing the three size measurements, with these exact labels:

- **Panel 1 – Greatest length (GL):** a curved, C-shaped embryo (3rd–early 4th week) with an arrow along its longest curved axis; label "no differentiated crown/rump yet."
- **Panel 2 – Crown–rump length (CRL):** a curved embryo (5th week onward) with an arrow from **Vertex of skull (crown)** to **Midpoint between apices of buttocks (rump)**.
- **Panel 3 – Crown–heel length (CHL):** an extended, upright embryo/fetus (8 weeks onward) with an arrow from **Vertex of skull** to **Heel**.

### 4. Ultrasound biometry (dating in vivo)

#### First trimester

- **Gestational sac:** the earliest ultrasonographic sign of pregnancy; visible on transvaginal scan between 3–5 weeks of gestation, and grows at ~1 mm/day.
- **Yolk sac:** visible from the 5th week of gestation, with a mean diameter of ~6 mm at 10 weeks.
- **Fetal pole / cardiac activity:** the fetal pole (curved embryo with head and tail ends) and cardiac pulsation are detectable between 5–7 weeks; cardiac activity is identifiable by the 6th menstrual week.

- **Crown–rump length:** the single most accurate predictor of menstrual age in the first trimester; transvaginal CRL measurement predicts age to within 1–4 days at 6–7 weeks.
- **Nuchal translucency:** measured at 10–14 weeks, chiefly for trisomy-21 screening rather than pure dating.

□ Fig 9.10 — *Ultrasounds showing measures used to assess embryonic and fetal growth. A. Crown–rump (Langman's Medical Embryology — Sadler — 14e, p.160)*

**Second and third trimester** — estimation is based on a combination of measurements:

| Parameter                    | Plane/technique                                                                                 | Note                                                           |
|------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Biparietal diameter (BPD)    | Through the third ventricle and thalami                                                         | Most accurate index of fetal menstrual age between 15–28 weeks |
| Head circumference (HC)      | Third ventricle/thalami plane + cavum septi pellucidi anteriorly + tentorial hiatus posteriorly | Combined with BPD                                              |
| Abdominal circumference (AC) | Plane of greatest transverse liver diameter, symmetric lower ribs, portal-vein confluence       | Reflects growth/nutrition                                      |
| Femur length (FL)            | Ossified diaphysis + metaphysis                                                                 | Also foot length, transverse cerebellar diameter used          |

□ Fig 9.10 — *Ultrasounds showing measures used to assess embryonic and fetal growth. A. Crown–rump (Langman's Medical Embryology — Sadler — 14e, p.160)*

- Multiple, serial measurements of these parameters over time improve the assessment of fetal growth rate (rather than a single reading).
- Population/ethnicity-specific ultrasound biometry charts are recommended (WHO multicentre protocol; INTERGROWTH-21st).
- Menstrual (LMP-based) age and post-ovulatory (fertilization) age differ by ~2 weeks; early routine ultrasound dating increases the reported rate of preterm delivery (<37 weeks) compared with LMP-based dating.

## Applied / Clinical anatomy

- **EDD calculation and antenatal booking:** routine LMP → EDD calculation is revised after the first ultrasound scan, which is now the preferred reference for dating.
- **Timing of invasive prenatal tests:** chorionic villus sampling and amniocentesis are scheduled against an accurately dated pregnancy; misdating risks a mistimed or non-diagnostic sample.
- **Detection of growth abnormality:** serial ultrasound biometry (BPD/HC/AC/FL) against population charts identifies small-for-dates and growth-retarded fetuses, factoring in maternal age, nutrition, height, weight, parity and smoking.
- **BBT/ovulation charting** helps establish the likely conception date in women undergoing fertility treatment or with irregular cycles.
- **Historical/medico-legal use:** age of an aborted or spontaneously miscarried embryo is estimated retrospectively from its external features, somite count or Carnegie stage — the method originally used by Streeter to build the Carnegie collection.

- ▶ **Sex determination:** external genitalia are present by Carnegie stage 23 but are not yet reliably distinguishable; definitive sonographic sex determination comes later in gestation.
- ▶ Onset of bone-marrow formation in the humerus (Streeter's historical criterion) marks the transition from the embryonic to the fetal period.

### High-yield exam pointers

- ▶ Embryonic period = fertilization to 8 weeks = **23 Carnegie stages**; fetal period = 9 weeks to term.
- ▶ **Menstrual/gestational age = Fertilization age + 14 days** — always specify which scale is used.
- ▶ Sequence of morphological dating: **presomite (day 15–20) → somite counting (day 20–30, ~3–4 pairs/day) → external features/pharyngeal arch & limb-bud stage → CRL** once somites are too numerous to count.
- ▶ **CRL** = vertex of skull to midpoint between apices of buttocks (most used measure, 5th week onward); **GL** used earlier while the embryo is straight; **CHL** (standing height) used from ~8 weeks.
- ▶ Carnegie staging is based on **external + internal morphology, not size or age alone** — a rule-of-thumb only:  $\text{age (days)} \approx \text{CRL (mm)} + 29$ , valid for CRL 3–30 mm.
- ▶ First-trimester ultrasound: **CRL is the most accurate predictor of menstrual age**; between 15–28 weeks, **BPD is the most accurate**.
- ▶ Second/third-trimester fetal ageing combines BPD, HC, AC and FL ( $\pm$  foot length, cerebellar diameter).
- ▶ LMP-based history is unreliable in irregular cycles/post-OCP conception/IUCD users — BBT charting and hCG testing supplement it, but ultrasound is now the primary clinical reference for dating.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021).



## Determination of age from humerus

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Age determination from the humerus is a practical application of the general laws of ossification: the bone develops from **one primary centre (for the shaft) and seven secondary centres (for the epiphyses)** that appear and fuse with the shaft in a strict, well-documented chronological sequence. Because this sequence is highly reproducible, the pattern of ossification centres seen on gross inspection of a dry bone or on a radiograph can be used to estimate the age of a foetus, child or young adult with reasonable accuracy up to skeletal maturity (~20 years). The method has major medicolegal value — identification of unknown skeletal remains, age verification in the living, and distinguishing a normal epiphysis from a fracture fragment on a paediatric elbow film.

### 1. General principles governing age estimation from a long bone

- ▶ **Primary centre:** single, appears in the mid-shaft before birth; forms the diaphysis.
- ▶ **Secondary centres:** appear after birth (usually birth to 5 years, with a few exceptions); each forms an epiphysis.
- ▶ **Law of ossification (law of growing end):** the epiphysis that appears **first fuses last**, and the one that appears **last fuses first**. The end at which fusion occurs latest is the **growing end** of the bone, and it lies **opposite the nutrient foramen**.
- ▶ Fusion of epiphyses starts at puberty and is normally complete by ~25 years across the skeleton as a whole; individual long bones (including the humerus) complete union earlier, by about the 20th year.
- ▶ Epiphyseal fusion occurs ~1–2 years earlier in females than in males (oestrogen accelerates epiphyseal closure).
- ▶ **Radiographic appearance:** in a newborn the ossified shaft is radiopaque (white) while the still-cartilaginous ends are radiolucent (black); as secondary centres appear, they too become radiopaque, separated from the shaft by a radiolucent epiphyseal plate — the plate disappears once fusion is complete. This appearance/disappearance sequence is the basis of radiological age estimation.
- ▶ Presence or absence of a given centre, and whether it has fused, is therefore read against known standard ages to bracket the individual's age — this is of recognised **medicolegal importance**, e.g. confirming that a dead newborn was full-term from visibility of the distal femoral epiphysis.

### 2. Ossification centres of the humerus

| Part  | Centre         | Time of appearance          | Time of fusion (with adjoining centres) | Time of fusion with shaft |
|-------|----------------|-----------------------------|-----------------------------------------|---------------------------|
| Shaft | Primary centre | 8th week, intrauterine life | —                                       | —                         |

| Part                 | Centre                               | Time of appearance | Time of fusion (with adjoining centres)                                                       | Time of fusion with shaft                                                                                 |
|----------------------|--------------------------------------|--------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Upper (proximal) end | Head                                 | 1st year           | fuses with greater & lesser tubercle centres to form one <b>compound epiphysis</b>            |                                                                                                           |
|                      | Greater tubercle                     | 2nd year           | at the <b>6th year</b>                                                                        | fuses with shaft at the <b>20th year</b> (growing end)                                                    |
|                      | Lesser tubercle                      | 5th year           |                                                                                               |                                                                                                           |
| Lower (distal) end   | Capitulum + lateral part of trochlea | 1st year           | fuses with medial-trochlea & lateral-epicondyle centres to form one <b>compound epiphysis</b> |                                                                                                           |
|                      | Medial part of trochlea              | 9th year           | at the <b>14th year</b>                                                                       | fuses with shaft at the <b>16th year</b>                                                                  |
|                      | Lateral epicondyle                   | 12th year          |                                                                                               |                                                                                                           |
| Medial epicondyle    | separate (traction) epiphysis        | 4th–6th year       | does <b>not</b> join the other distal centres                                                 | fuses <b>directly</b> with shaft at the <b>20th year</b> — the <b>last centre of the humerus to unite</b> |

(Source: *BD Chaurasia's Human Anatomy Vol 1, Table 2.1 — "Ossification of humerus, radius and ulna".*)

Key learning points from this table:

- ▶ The humerus ossifies from **1 primary + 7 secondary centres** (3 upper end, 4 lower end).
- ▶ The **upper end** is the **growing end** — its epiphysis (formed by fusion of head, greater and lesser tubercle centres at 6 years) unites with the shaft last, at ~20 years.
- ▶ The **lower end** fuses earliest of the two ends (compound epiphysis unites with shaft by 16 years) — this obeys the general law that the end appearing first (distal centres, from 1st year) fuses first.
- ▶ The **medial epicondyle** is an exception: it is a separate, extracapsular, traction epiphysis (site of attachment of the common flexor origin and ulnar collateral ligament) that never fuses with the other three distal centres; it joins the shaft directly and is the **last part of the whole bone to ossify completely**, around the 20th year.

□ Fig 20.8 — 1. Shaft of humerus. 2. Olecranon fossa. 3. Epiphyseal plate of lower (IB Singh — *Textbook of Anatomy Vol 1 — 6e, p.259*)

*Radiograph of the elbow region in a child of about 10 years: 1. Shaft of humerus. 2. Olecranon fossa. 3. Epiphyseal plate of lower end of humerus. 4. Conjoint epiphysis for capitulum and lateral epicondyle. 5. Upper epiphysis of radius. 6. Epiphysis for medial epicondyle. 7. Olecranon, medial margin. 8. Coronoid*

process. 9. Radial tuberosity. 10. Shaft of radius. 11. Shaft of ulna. The conjoined capitulo-trochlear epiphysis is seen separated from the shaft by an epiphyseal plate, and the medial epicondylar epiphysis is separate from the shaft — both still unfused at this age.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a simple line diagram of the humerus (anterior view) with the upper and lower ends expanded schematically, and label:

- ▶ Shaft — primary centre (8th week IUL)
- ▶ Head — secondary centre (1st year)
- ▶ Greater tubercle — secondary centre (2nd year)
- ▶ Lesser tubercle — secondary centre (5th year)
- ▶ Line encircling upper end at level of anatomical neck — fusion of the three proximal centres into **one compound epiphysis (6th year)** → unites with shaft (**20th year**, growing end)
- ▶ Capitulum + lateral part of trochlea — secondary centre (1st year)
- ▶ Medial part of trochlea — secondary centre (9th year)
- ▶ Lateral epicondyle — secondary centre (12th year)
- ▶ Line at lower end showing fusion of the three distal centres into **one compound epiphysis (14th year)** → unites with shaft (**16th year**)
- ▶ Medial epicondyle — separate traction epiphysis (4th–6th year) → unites directly with shaft (**20th year**, last to fuse)

Arrows/annotations: mark the "growing end" at the upper end and the direction of the nutrient foramen pointing away from it (towards the elbow).

### 3. Age-wise interpretive summary (how the humerus is "read" to bracket age)

| Approx. age | Gross/radiological finding at the humerus                                                                       |
|-------------|-----------------------------------------------------------------------------------------------------------------|
| Birth       | Only the shaft is ossified (radiopaque); both ends entirely cartilaginous (radiolucent)                         |
| 1 year      | Centres appear for the head (proximal) and for capitulum + lateral trochlea (distal)                            |
| 2 years     | Centre for greater tubercle appears                                                                             |
| 4–6 years   | Centre for medial epicondyle appears (isolated, extracapsular)                                                  |
| 5 years     | Centre for lesser tubercle appears                                                                              |
| 6 years     | Head, greater and lesser tubercle centres fuse into one proximal compound epiphysis (still separate from shaft) |

| Approx. age | Gross/radiological finding at the humerus                                                                                                                  |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9 years     | Centre for medial part of trochlea appears                                                                                                                 |
| 12 years    | Centre for lateral epicondyle appears                                                                                                                      |
| 14 years    | Capitulum, both trochlear parts and lateral epicondyle fuse into one distal compound epiphysis                                                             |
| 16 years    | Distal compound epiphysis unites with the shaft — elbow region radiologically "adult" except for the medial epicondyle                                     |
| ~20 years   | Proximal compound epiphysis unites with shaft (growing end) <b>and</b> medial epicondyle unites with shaft — humerus now a single completely ossified bone |

Beyond ~20 years the humerus gives no further chronological information by gross/plain-radiographic ossification criteria; adult skeletal age thereafter is estimated by other means (bone density, medullary widening, histomorphometry/osteon counts) that lie outside routine gross osteology.

### Applied / Clinical anatomy

- **Medicolegal age estimation:** presence, fusion status and configuration of the humeral centres are used, together with other long bones, to estimate age of unidentified skeletal remains, to verify age of the living (e.g., for determining majority, marriage-age or criminal-responsibility disputes), and in mass-disaster victim identification.
- **Distinguishing epiphysis from fracture:** on a child's elbow radiograph, an unfused epiphysis (especially the medial epicondylar or capitulo-trochlear centre) can be mistaken for an avulsed bony fragment; comparison with the contralateral, uninjured elbow and knowledge of the standard age of appearance/fusion is essential to avoid misdiagnosis.
- **Avulsion of the medial epicondyle:** because this epiphysis remains ununited with the shaft until late in the second decade, a fall producing sudden valgus stress at the elbow in a child/adolescent can avulse it, with traction injury to the adjacent ulnar nerve — a direct clinical consequence of its delayed, separate fusion.
- **Supracondylar fracture** in children characteristically occurs through the thin, weak bone of the lower end proximal to the epiphyseal plates (the plates themselves are stronger than adjacent bone), again exploiting the anatomy of the growing humerus.
- **Sex difference:** fusion is completed roughly 1–2 years earlier in females, a correction routinely applied when bracketing age from ossification status.
- **Confirming a full-term newborn:** the principle demonstrated at the distal femoral epiphysis (visible ossification centre = full-term) is analogous to using visibility/absence of the proximal humeral centre (normally appearing by the 1st year, occasionally in utero) in perinatal medicolegal assessment.



## High-yield exam pointers

- ▶ Humerus ossifies from **1 primary centre** (shaft, 8th week IUL) + **7 secondary centres** — 3 at the upper end, 4 at the lower end.
- ▶ Upper end centres: head (1y), greater tubercle (2y), lesser tubercle (5y) → fuse together at 6y → unite with shaft at **20y** (growing end).
- ▶ Lower end centres: capitulum + lateral trochlea (1y), medial trochlea (9y), lateral epicondyle (12y) → fuse together at 14y → unite with shaft at **16y**.
- ▶ **Medial epicondyle** is a separate traction epiphysis (4–6y) that fuses directly with the shaft at **20y** — the last centre of the bone to unite, and clinically important because it is prone to avulsion before fusion.
- ▶ Law of ossification: centre appearing **first fuses last**; the **growing end** is opposite the nutrient foramen.
- ▶ Fusion is ~1–2 years earlier in females than males.
- ▶ Radiograph: shaft/epiphysis = radiopaque; epiphyseal cartilage/plate = radiolucent; disappearance of the radiolucent line = fusion complete.
- ▶ Practical use: bracket age of unknown remains/the living up to ~20 years; beyond this the humerus alone cannot further refine chronological age by gross criteria.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia's Human Anatomy Vol 1 8e (Table 2.1, ossification of humerus/radius/ulna; clinical anatomy of humerus); Vishram Singh's General Anatomy 4e (laws of ossification, ossification centres, growing end, medicolegal correlation); Moore's Clinically Oriented Anatomy 9e (avulsion of medial epicondyle, bone-age assessment principle); IB Singh's Textbook of Anatomy Vol 1 6e (Fig. 20.8 — labelled elbow radiograph).

**Coverage note:** the corpus (Gray's + the listed specialty texts) is strong on the gross-osteology/ossification-timeline basis of this question, which is what the RGUHS syllabus tests. Dedicated forensic-medicine methods for adult age estimation from the humerus after epiphyseal fusion (e.g., histomorphometric/osteon-counting techniques) are outside the anatomy textbook corpus and are only briefly flagged above rather than elaborated, to avoid unsupported detail.



## Determination of sex from sacrum

Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The sacrum is a large, triangular bone formed by fusion of five sacral vertebrae; it is wedged between the two hip bones and forms the posterior wall of the pelvis. Because its shape is moulded by, and reflects, the overall shape of the bony pelvis — narrow and deep in the male, broad and shallow in the female, to accommodate parturition — the sacrum shows well-marked sexual dimorphism. In forensic osteology and physical anthropology it is examined, together with the hip bone and skull, when the sex of an isolated or skeletonised specimen has to be determined; no single criterion is used alone, and the sacrum is always assessed in conjunction with other pelvic and cranial indicators. Five morphological criteria — the sacral index, the base (body-to-ala) width relationship, the curvature, the sacro-vertebral angle, and the auricular surface — are described below.

### 1. Basis of sexual dimorphism in the sacrum

- ▶ The female pelvis is broader and shallower than the male pelvis (built for childbirth); the sacrum, forming its posterior segment, is correspondingly **shorter and wider** in the female and **longer and narrower** in the male.
- ▶ The size of the pelvic cavity is greater in the female; this is achieved partly by a more pronounced backward tilt (greater sacro-vertebral angle) of the female sacrum, which increases the anteroposterior room available in the true pelvis.
- ▶ Because these differences develop as the pelvis matures at puberty under gonadal hormonal influence, reliable sexing of the sacrum by these criteria is essentially an adult/post-pubertal phenomenon.

### 2. Morphological criteria for sexing the sacrum

| Criterion (how examined)                                                                                | Male sacrum                                                               | Female sacrum                                                                                                                |
|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| <b>Sacral index</b> = (greatest breadth across the base ÷ length from the promontory to the apex) × 100 | Average ≈ 105 — bone relatively long and narrow                           | Average ≈ 115 — bone relatively short and broad                                                                              |
| <b>Width of body of S1 vs width of ala</b> (viewed from the base) — the single most practical criterion | Width of the body is <b>distinctly greater</b> than the width of each ala | Width of the body is <b>approximately equal</b> to the width of each ala                                                     |
| <b>Curvature</b> (ventral/pelvic concavity), viewed from the side                                       | More <b>uniform</b> curve, and comparatively <b>shallower</b> overall     | Concavity is <b>more pronounced</b> and <b>irregular</b> — sharper bends are seen especially between S1–S2 and between S3–S4 |
| <b>Sacro-vertebral angle</b> (angle the base of S1 makes with the long axis of the bone below)          | Less prominent                                                            | <b>More prominent</b> ; the pelvic surface is directed more steeply downward, enlarging the pelvic cavity                    |
| <b>Auricular</b> (articular) <b>surface</b> , on the lateral aspect                                     | Relatively <b>longer</b> ; its dorsal concavity is <b>less marked</b>     | Relatively <b>shorter</b> ; its dorsal concavity is <b>more marked</b> (more curved)                                         |

| Criterion (how examined) | Male sacrum                                                                                   | Female sacrum                                                                 |
|--------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Overall build            | Bone longer, narrower, more markedly curved; base comparatively narrow relative to its length | Bone shorter, wider, flatter; base comparatively broad relative to its length |

- ▶ Of these, the **base view** (comparing the width of the body of the first sacral vertebra with the width of the ala on either side) is quoted as the quickest and most practical bedside/exam test: **body  $\geq$  ala width  $\rightarrow$  male; body  $\approx$  ala width  $\rightarrow$  female.**
- ▶ The **sacral index** gives a numerical, reproducible measure of the same basic difference (breadth relative to length) and is the criterion most used in anthropometric/forensic series.

□ Fig 2.12 — Sacrum and coccyx. A. Base and pelvic surface of sacrum and coccyx. B. (Moore — Clinically Oriented Anatomy — 9e, p.218)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the sacrum in **three views side by side** (base/superior, pelvic/anterior, and lateral), and on each mark the sexing landmarks so the male and female patterns can be compared:

- ▶ **Base view:** the **body of S1** and, lateral to it on each side, the **ala** — annotate "body clearly wider than ala (male)" vs "body  $\approx$  width of ala (female)"; mark the **sacral promontory** and the **breadth across the base** (used in the sacral index).
- ▶ **Lateral view:** mark the **length from promontory to apex** (the other arm of the sacral index); draw the **ventral (pelvic) concavity** as a smooth uniform curve (male) alongside a more angulated curve with sharper bends at S1–S2 and S3–S4 (female); label the **sacro-vertebral angle** at the base.
- ▶ **Lateral view,** also mark the **L-shaped auricular (articular) surface** spanning the upper sacral segments, noting it is comparatively longer/less concave dorsally (male) or shorter/more concave dorsally (female).
- ▶ Label **apex, ala, body of S1, promontory, auricular surface,** and the **sacral canal/hiatus** for orientation.

## 3. Why the sacrum is used for sexing — practical basis

- ▶ The sacrum is compact, dense, and survives well in skeletal/exhumed/archaeological material, making it a useful bone when the skull or complete hip bone is not available.
- ▶ It is examined as **one part of a combined skeletal assessment:** pelvis (hip bone + sacrum together) gives the most reliable single-region diagnosis of sex, the skull the second most reliable, and long bones (by size/robustness) a supportive third line of evidence.
- ▶ Sexing from an isolated sacrum alone is therefore corroborative rather than absolute — population variation and overlap of ranges mean the criteria above are used together, and ideally alongside the hip bone (subpubic angle, greater sciatic notch, pubic body shape) whenever it is present.

## Applied / Clinical anatomy

- ▶ **Forensic medicine and physical anthropology:** the criteria above are applied to isolated/skeletonised sacra recovered in medico-legal exhumations, mass-disaster victim identification, and archaeological/anthropological studies, usually alongside the hip bone and skull.
- ▶ **Obstetric correlation:** the same features that make the female sacrum "sexable" — shorter length, greater sacro-vertebral angle, more pronounced backward tilt — also enlarge the true pelvic cavity and increase the anteroposterior diameters at the inlet and outlet, which is why an unusually straight, male-type (long, narrow, less-angulated) sacrum in a woman can contribute to a **android or anthropoid pelvic contour** and predispose to obstructed labour or cephalopelvic disproportion.
- ▶ **Pelvimetry:** the sacral promontory is a key landmark for measuring the **diagonal and true (obstetric) conjugate** diameters of the pelvic inlet clinically and radiologically; a prominent, forward-projecting promontory (more a male-pattern feature) reduces the antero-posterior diameter of the inlet.
- ▶ **Sacral canal contents** (cauda equina, filum terminale, spinal meninges — ending around the middle of the sacrum) are clinically relevant to caudal epidural anaesthesia, which is sited through the sacral hiatus; sacral shape/curvature variation affects ease of catheter passage.
- ▶ **Ossification/fusion pattern of the sacral vertebrae** — 21 primary centres appear between the 2nd and 8th week of foetal life and fuse with each other between the 2nd and 8th year of life; the secondary (epiphyseal) centres appear at puberty and fuse by about 25 years — means the sexing criteria above are reliable chiefly in the **fully-formed adult sacrum**, not in juvenile or adolescent material where the five sacral vertebrae may still be incompletely united into a single bone.

## High-yield exam pointers

- ▶ **Sacral index** = (breadth across base ÷ length promontory-to-apex) × 100; **male** ≈ 105 (long, narrow); **female** ≈ 115 (short, broad).
- ▶ **Base view is the quickest test:** body of S1 clearly wider than ala → **male**; body ≈ width of ala → **female**.
- ▶ Female sacrum: **shorter, wider, more curved**, with a **more prominent sacro-vertebral angle** and a **shorter, more concave** auricular surface.
- ▶ Male sacrum: **longer, narrower, more uniformly (less) curved**, with a **less prominent sacro-vertebral angle** and a **longer, less concave** auricular surface.
- ▶ Sacral shape mirrors overall pelvic shape — female sacrum contributes to a roomier, more capacious pelvic cavity for childbirth.
- ▶ Sacrum is used **together with the hip bone and skull** in forensic sex determination; it is never conclusive in isolation.
- ▶ Sacral promontory is the landmark for the obstetric (true) conjugate diameter — clinically links sacral morphology to pelvimetry.

**SOURCE & COVERAGE**

BD Chaurasia's Human Anatomy Vol 2 8e; IB Singh — Textbook of Anatomy Vol 2 6e; Moore's Clinically Oriented Anatomy 9e; Gray's Anatomy (Standring) 41e. Coverage note: Gray's Anatomy (Standring) 41e discusses vertebral sexual dimorphism only in general terms ("received little attention"; Taylor & Twomey 1984) and gives no sacrum-specific criteria — the operative numerical/morphological criteria above are grounded in BD Chaurasia and IB Singh, which carry the dedicated "Sex Differences in the Sacrum" sections used for this answer.



## Discuss the evolution of kidney in the vertebrates

*Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The vertebrate excretory (renal) system arises from the **intermediate mesenchyme** (nephrogenic cord), which in lower vertebrates forms a longitudinal series of segmental epithelial diverticula called **nephrotomes**. Classically, the renal system is described as passing through three successive organs — the **pronephros**, **mesonephros** and **metanephros** — appearing in strict cranio-caudal sequence, each induced by and succeeding the one before it, with only the last-formed organ retained as the definitive kidney of the group concerned. Because the human embryo transiently forms and discards the two more primitive kidneys before the metanephros becomes permanent, the development of the human kidney is a classical teaching example of "**ontogeny recapitulates phylogeny**" — each embryo climbing, in miniature, the evolutionary ladder of its ancestors.

### 1. The guiding principle — ontogeny repeats phylogeny

- ▶ Each of the three kidneys corresponds to the **definitive, functional adult kidney of a different vertebrate grade**:
  - **Pronephros** — the adult/functional kidney of the most primitive vertebrates.
  - **Mesonephros** — the adult/functional kidney of most **anamniotes** (fish and amphibians, i.e. vertebrates lacking an amnion).
  - **Metanephros** — found only in **amniotes** (reptiles, birds and mammals, including Man) and is the sole permanent kidney of this group.
- ▶ In the human embryo all three appear in turn, in strict **cranio-caudal** (**cervical** → **thoracolumbar** → **sacral**) sequence, but only the metanephros persists — recapitulating, in a few weeks of intrauterine life, the succession that occurred over evolutionary time in the vertebrate line leading to Man.
- ▶ Gray's Anatomy cautions that although it is "customary" to describe three discrete organs succeeding one another, it is in practice **difficult to define precise limits** between them in the embryo — the three overlap markedly in time, space and the fate of individual nephrons.

## 2. The three excretory organs — comparative overview

| Feature                                               | Pronephros                                                               | Mesonephros                                                  | Metanephros                                                     |
|-------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------|
| Vertebrate group in which it is the definitive kidney | Cyclostomes (hagfish, lamprey) and some teleost fishes/Dipnoi (lungfish) | Most anamniotes — the majority of fishes and amphibians      | Amniotes only — reptiles, birds, mammals (incl. Man)            |
| Site in human nephrogenic cord                        | Cervical region                                                          | Thoracolumbar region                                         | Sacral region                                                   |
| Segmentation                                          | Segmented (metameric, ~1 tubule/somite)                                  | Segmented (2 or more tubules may lie opposite one somite)    | Non-segmented (an unsegmented mass — the metanephric blastema)  |
| Time of appearance (human)                            | Beginning of 4th week                                                    | End of 4th week                                              | Begins 5th week (ureteric bud invades metanephric blastema)     |
| Functional status (human)                             | Non-functional; disappears completely                                    | Functional for a short period; regresses by end of 4th month | Becomes functional (urine formation) from ~3rd month; permanent |
| Duct                                                  | Pronephric duct — persists, is annexed by the mesonephros                | Mesonephric (Wolffian) duct                                  | Ureter (from the ureteric bud)                                  |
| No. of tubules (approx.)                              | 7–8                                                                      | 70–80                                                        | Innumerable (millions of nephrons)                              |

## 3. Pronephros — the primitive (fish-grade) kidney

- Forms at the **beginning of the 4th week** as 7–8 horizontal tubules in the cervical/upper thoracic nephrogenic cord.
- Each tubule opens into the coelomic cavity by a ciliated **peritoneal funnel (nephrostome)**, and is provided with an **external glomerulus** — a tuft of capillaries bulging into the coelom adjacent to the funnel, rather than being invaginated into the tubule itself.
- The tubules unite laterally to form a single descending **pronephric duct**, which grows caudally to open into the cloaca.
- In Man the pronephros is **entirely non-functional** and its tubules disappear completely by the end of the 4th week; only its duct persists, being taken over by the mesonephros as the **mesonephric duct**.
- Comparatively, the pronephros is retained as the **functioning adult kidney only in cyclostomes and a few teleosts/Dipnoi** — in all higher vertebrates it is a strictly transient embryonic stage.

## 4. Mesonephros — the anamniote kidney

- Forms at the **end of the 4th week** in the **thoracolumbar** region (intermediate mesenchyme between somite levels 8–20, extending to about somite 24), as **70–80 excretory tubules**.
- Each tubule develops a **cup-shaped (Bowman-capsule-like) depression enclosing an internal glomerulus** — capillaries invaginated into the blind end of the tubule rather than lying free in the

coelom; nephrostomes and external glomeruli are absent or vestigial. This is a key evolutionary advance over the pronephric nephron: a **closed** system in continuity with the vascular tree rather than an open, coelom-draining one.

- ▶ The tubules drain into the now-renamed **mesonephric (Wolffian) duct** — first described by Casper Friedrich Wolff in 1759 — which opens into the cloaca.
- ▶ The mesonephros is transiently functional in the human embryo (producing dilute urine by ultrafiltration, lacking a loop of Henle) but becomes completely non-functional by the **end of the 4th month**, as the metanephros takes over.
- ▶ Comparatively, the mesonephros **persists as the permanent, functioning adult kidney in most fishes and in amphibians** — the anamniote condition.
- ▶ Most mesonephric tubules degenerate, but in the **male**, tubules adjoining the developing testis persist as the **vasa efferentia (efferent ductules)**, and the mesonephric duct itself persists as the **epididymis, vas (ductus) deferens, seminal vesicle and ejaculatory duct**. In the **female**, the mesonephros and its duct largely regress (see Applied anatomy below).

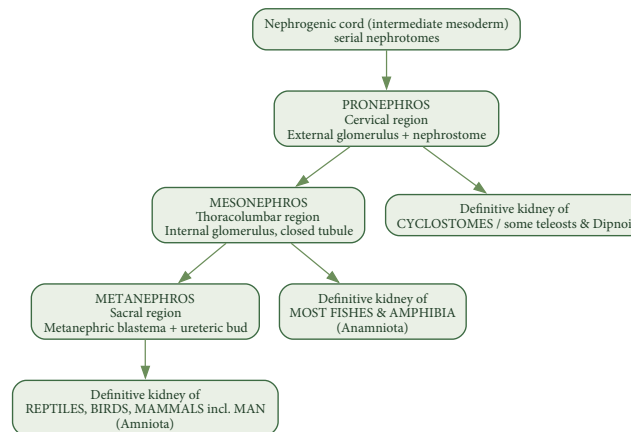
## 5. Metanephros — the amniote (definitive human) kidney

- ▶ Arises at the **beginning of the 5th week** in the **sacral** region of the nephrogenic cord, from **two distinct sources**:
- ▶ The **metanephrogenic blastema** (caudal, unsegmented nephrogenic tissue) — forms the **secretory/excretory part**: renal vesicle → nephron (Bowman's capsule, PCT, loop of Henle, DCT) up to the junction with a collecting tubule.
- ▶ The **ureteric bud** (an outgrowth of the caudal mesonephric duct) — forms the **collecting/excretory-duct system**: ureter, renal pelvis, major and minor calyces, collecting tubules and ducts of Bellini.
- ▶ Begins forming urine from about the **3rd month**, taking over as the mesonephros regresses, and remains the **permanent kidney of Man and all amniotes**.
- ▶ The metanephros ascends from its initial sacral/pelvic position to the adult lumbar level between the 5th and 9th weeks (relative growth of the caudal body wall, straightening of embryonic curvature), with a corresponding shift in blood supply from the median sacral/common iliac vessels to the definitive renal arteries from the aorta.
- ▶ Comparatively, the metanephros is found **exclusively in amniotes** (reptiles, birds, mammals) — it has no counterpart as the definitive adult kidney in fish or amphibians.

## 6. Unifying concept — the "holonephros"

- ▶ Because the three organs overlap so extensively in time, space and cell fate (individual nephrons cannot always be assigned unambiguously to one category), some comparative embryologists (Torrey) prefer to regard the entire renal excretory system as **one continuous unit, the holonephros**, parts of which mature and regress at different times and places rather than three genuinely separate organs — the traditional three-part terminology being retained chiefly for descriptive convenience.





Discuss the evolution of kidney in the vertebrates

□ Fig 20.3 — A 28 days foetus showing pronephros, mesonephros and metanephros. Pronephric tubules appear in the cervical region and soon disappear; ureteric bud arises from the mesonephric duct and grows towards the metanephros (Sontakke — Textbook of Human Embryology, p.212)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Reproduce a lateral view of a 4th–5th week human embryo showing the nephrogenic cord and the three successive kidneys, labelling:

- ▶ Nephrogenic cord (intermediate mesoderm)
- ▶ Pronephros (cervical, degenerating) and pronephric duct
- ▶ Mesonephros (thoracolumbar) with mesonephric tubules
- ▶ Mesonephric (Wolffian) duct
- ▶ Ureteric bud arising from the caudal mesonephric duct
- ▶ Metanephros / metanephric blastema (sacral) capping the ureteric bud
- ▶ Cloaca and allantois

A second small inset panel showing a single nephron in cross-section for each stage: (a) pronephric tubule with **peritoneal funnel + external glomerulus** opening to the coelom, versus (b) mesonephric/metanephric tubule with a **closed, cup-shaped capsule enclosing an internal glomerulus** — to illustrate the key structural advance from an open to a closed excretory unit.

### Applied / Clinical anatomy

- ▶ **Persistence of mesonephric derivatives in the female** — since the mesonephros and its duct normally regress in females, incomplete regression gives rise to clinically important vestiges along the broad ligament/mesovarium: **epoophoron** (from cranial mesonephric tubules), **paroophoron** (from caudal tubules), and **Gartner's duct cyst** (from a persistent segment of the mesonephric duct in the broad ligament, lateral vaginal wall or cervix) — the latter a recognised cause of a lateral vaginal wall swelling/cyst.
- ▶ **Persistence of mesonephric derivatives in the male** — most of the mesonephric duct persists physiologically as the epididymis, vas deferens and seminal vesicle; its most cranial remnant may persist as the vestigial **appendix epididymis**, and residual caudal mesonephric tubules that fail to join the rete testis form the **paradidymis**.

- ▶ **Renal agenesis / horseshoe kidney / pelvic (ectopic) kidney / malrotation** all reflect errors in metanephric induction, ascent or fusion — e.g. failure of the ureteric bud to develop causes unilateral or bilateral renal agenesis (bilateral agenesis → oligohydramnios → Potter sequence); fusion of the lower poles of the two metanephric masses during ascent gives a **horseshoe kidney**, typically arrested below the inferior mesenteric artery.
- ▶ **Congenital multicystic/polycystic kidney** results from failure of the metanephric (secretory) tubules to unite properly with the collecting (ureteric bud) tubules.
- ▶ The comparative concept of external vs internal glomerulus underlies the modern understanding that the mammalian **renal corpuscle (Bowman's capsule + glomerulus)** is a phylogenetically advanced, closed derivative of the primitive open coelom-draining pronephric nephron — relevant to understanding the filtration-barrier physiology taught alongside renal histology.
- ▶ Persisting mesonephric duct anomalies can coexist with ipsilateral **renal agenesis or ectopic ureteric insertion**, since the ureteric bud is itself a mesonephric-duct derivative — a clinically important embryological link between genital and urinary anomalies.

### High-yield exam pointers

- ▶ Three successive kidneys, strict cranio-caudal sequence: **pronephros (cervical) → mesonephros (thoracolumbar) → metanephros (sacral)** — classical example of **ontogeny recapitulating phylogeny**.
- ▶ **Pronephros** = definitive kidney of cyclostomes/some teleosts & Dipnoi; open nephrostome + **external glomerulus**; non-functional and transient in Man; only its duct persists.
- ▶ **Mesonephros** = definitive/functional kidney of **anamniotes (most fishes + amphibians)**; **internal glomerulus**, closed tubule; functional briefly in the human embryo (4th week – 4th month); duct and some tubules persist in the male genital tract (vasa efferentia, epididymis, vas deferens).
- ▶ **Metanephros** = definitive kidney of **amniotes only** (reptiles, birds, mammals, Man); dual origin — **metanephric blastema** (secretory part) + **ureteric bud** (collecting part); begins 5th week, functional from ~3rd month, ascends sacral → lumbar between 5th–9th weeks.
- ▶ **Mesonephric duct = Wolffian duct = archinephric/nephric duct**, first described by C.F. Wolff (1759).
- ▶ Unifying comparative concept: the "**holonephros**" (Torrey) — the three stages are not always sharply separable; Gray's Anatomy itself notes the difficulty of defining precise limits between them.
- ▶ Clinically relevant vestiges: **epoophoron, paroophoron, Gartner's cyst (female); appendix epididymis, paradidymis, vasa efferentia (male)** — all mesonephric remnants.
- ▶ Common metanephric anomalies for viva: **renal agenesis, horseshoe kidney, pelvic kidney, multicystic dysplastic kidney** — all traceable to errors in ureteric-bud/metanephric-blastema induction or in renal ascent.

**SOURCE & COVERAGE**

Gray's Anatomy (Standring) 41e; Hamilton, Boyd & Mossman — Human Embryology; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Langman's Medical Embryology (Sadler) 14e; AK Datta — Human Anatomy Vol 1 (Thorax & Abdomen); Larsen — Human Embryology 6e.



## Evolution of branchial apparatus

*Asked in: Paper II Oct 2009 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The branchial (pharyngeal) apparatus is the segmented series of arches, pouches, clefts and membranes that appears on the lateral wall of the developing pharynx in the 4th–5th weeks of human life. It is a **phylogenetic relic** — a mammalian embryo transiently rebuilds the gill-bearing pharynx of fish-like ancestors and then dismantles it, remodelling every component (skeleton, muscle, nerve, artery, pouch epithelium) into structures of the adult head, neck and thorax that have nothing to do with respiration. "Ontogeny repeats phylogeny" is nowhere better illustrated in human embryology than in the branchial apparatus, and understanding this evolutionary transformation explains the definitive nerve/artery/skeletal pattern of the adult head and neck as well as the common branchial anomalies seen clinically.

### 1. From gill arches to pharyngeal arches — the vertebrate ground plan

- ▶ In all **vertebrates** the pharynx develops a series of mesenchymal bars — **visceral (branchial) arches** — separated externally by ectodermal **pharyngeal clefts/grooves** and internally by endodermal **pharyngeal pouches**.
- ▶ In **fish and larval amphibians**, the arches from the 3rd pair caudally are perforated to form true **gill slits**; each such arch is a genuine **branchial arch** bearing a respiratory gill.
- ▶ In **amniotes (reptiles, birds, mammals, including humans)** the clefts and pouches approach one another but never perforate — a plate of fused ectoderm + endoderm (the **pharyngeal/closing membrane**) always intervenes, so true gill slits never form; the term "**pharyngeal arch**" is therefore more accurate for humans, "branchial arch" being retained only for historical/comparative reasons.
- ▶ Humans form **five arches**, numbered 1, 2, 3, 4 and 6 (a transient 5th arch has been postulated but has no substantiated derivative).
- ▶ In all jawed vertebrates (**Gnathostomata**) the **1st and 2nd arches** are recruited early to form the **jaw and hyoid apparatus** and never bear gills; only the **3rd arch caudally** was ever gill-bearing — so the vertebrate pharynx is fundamentally split into an **anterior feeding segment** and a **posterior respiratory segment**, a division whose molecular signature (see §6) persists even in humans.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Generalised cross-section through one branchial arch of a lower vertebrate (label all 4 constituents and their human fate):

- ▶ Outer covering: **ectoderm** (→ skin/epithelium of cleft)
- ▶ Inner lining: **endoderm** (→ epithelium of pouch)
- ▶ Central **cartilaginous/skeletal bar** (→ named cartilage, e.g. Meckel's/Reichert's)
- ▶ **Muscle mass** derived from arch mesenchyme (→ named muscle group)
- ▶ **Cranial (special visceral) nerve** supplying the muscle mass (→ same nerve in adult)
- ▶ **Aortic (arch) artery** running in the arch core (→ named great vessel)
- ▶ Show gill filaments/gill slit on the fish side of the diagram and its obliterated/internalised counterpart on the human side.

□ Fig 17.3 — Development of the pharyngeal arches. A. (Langman's Medical Embryology — Sadler — 14e, p.304)

## 2. Evolutionary fate of the arch skeleton

Each arch classically carries a cartilaginous bar that in fish supported the gill and jaw apparatus; in mammals these bars are almost wholly re-purposed into the facial skeleton, hyoid and ear ossicles.

| Arch             | Skeletal element (cartilage bar)                    | Adult human derivative                                                                                                                                                        |
|------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st (mandibular) | Meckel's cartilage (+ maxillary/quadrato component) | Malleus, incus, anterior ligament of malleus, sphenomandibular ligament; body of mandible ossifies membranously alongside Meckel's cartilage, which itself mostly degenerates |
| 2nd (hyoid)      | Reichert's cartilage                                | Stapes, styloid process, stylohyoid ligament, lesser cornu and upper body of hyoid                                                                                            |
| 3rd              | —                                                   | Greater cornu and lower body of hyoid                                                                                                                                         |
| 4th & 6th        | —                                                   | Thyroid, cricoid, arytenoid, corniculate and cuneiform cartilages of the larynx                                                                                               |

- ▶ This table is itself a fossilised record of vertebrate jaw evolution: in fish and reptiles the **quadrato** (upper-jaw element of the 1st arch) articulated with the **articular** (posterior end of Meckel's cartilage/lower jaw) to form the **primary jaw joint**. In the mammalian lineage a new **dentary-squamosal joint** took over mastication, freeing the old quadrato-articular joint to be miniaturised into the **incudomalleal joint** of the middle ear — the classic evolutionary explanation for why the mammalian ear ossicles are pharyngeal-arch derivatives.
- ▶ Reichert's cartilage is named for this same comparative correlation in the hyoid arch: its dorsal end becomes the stapes (further linking the ear to the branchial skeleton) while its ventral end becomes hyoid/styloid structures.

### 3. Evolutionary fate of the aortic (branchial) arch arteries

- ▶ In fish, each gill-bearing arch carries a **branchial artery** with an afferent limb (deoxygenated blood from the ventral aorta to the gill capillaries) and an efferent limb (oxygenated blood to the dorsal aorta) — true respiratory vessels.
- ▶ Because their sequence and remodelling are so consistent across all vertebrate classes, the aortic arches are considered one of the best textbook examples of the **recapitulation of phylogeny in ontogeny**.
- ▶ In humans the six paired aortic arches (arch 5 rudimentary/non-persistent) are progressively remodelled from purely respiratory vessels into the great vessels of the neck and thorax:

| Aortic arch          | Adult derivative                                                       |
|----------------------|------------------------------------------------------------------------|
| 1st                  | Largely disappears; contributes to maxillary artery                    |
| 2nd                  | Largely disappears; contributes to stapedial/hyoid arteries            |
| 3rd                  | Common carotid artery + proximal internal carotid artery               |
| 4th (left)           | Arch of the aorta (between left common carotid and left subclavian)    |
| 4th (right)          | Proximal right subclavian artery                                       |
| 5th                  | Never forms completely / disappears                                    |
| 6th (pulmonary arch) | Proximal pulmonary arteries; left 6th also gives the ductus arteriosus |

□ Fig 36.9 — Aortic arch arteries and their derivatives. (Gray's Anatomy — Standring — 41e, p.840)

### 4. Evolutionary fate of the arch musculature and nerves

Every branchial arch muscle mass keeps the same **special visceral (branchiomotor) nerve** it was innervated by in the fish ancestor, however far the muscle itself migrates in mammals — nerve supply is therefore the most reliable guide to an adult muscle's arch of origin.

| Arch      | Nerve                                            | Muscle groups                                                                                        |
|-----------|--------------------------------------------------|------------------------------------------------------------------------------------------------------|
| 1st       | Trigeminal (mandibular division, V3)             | Muscles of mastication, mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini |
| 2nd       | Facial (VII)                                     | Muscles of facial expression, stapedius, stylohyoid, posterior belly of digastric                    |
| 3rd       | Glossopharyngeal (IX)                            | Stylopharyngeus                                                                                      |
| 4th & 6th | Vagus (superior laryngeal / recurrent laryngeal) | Pharyngeal constrictors, cricothyroid, intrinsic laryngeal muscles                                   |

- The migration of arch-derived muscle far from its cartilage of origin (e.g. facial muscles spreading over the whole face and scalp) while retaining its original branchiomotor nerve is direct embryological proof of arch identity, and is regularly tested.

## 5. Evolutionary fate of the pharyngeal pouches, clefts and membranes

Gill slits of the fish ancestor are represented in the human embryo only transiently, by paired pharyngeal pouches (endoderm) and clefts (ectoderm) that never perforate; instead of forming respiratory gills, the pouch epithelium is redirected into endocrine and lymphoid organs.

| Pouch/cleft    | Derivative                                                                                     |
|----------------|------------------------------------------------------------------------------------------------|
| 1st pouch      | Tubotympanic recess → middle-ear cavity, tympanic antrum, pharyngotympanic (auditory) tube     |
| 1st cleft      | External acoustic meatus                                                                       |
| 2nd pouch      | Palatine tonsil epithelium/tonsillar fossa                                                     |
| 2nd–4th clefts | Normally obliterated (buried by overgrowth of the 2nd arch, forming the cervical sinus of His) |
| 3rd pouch      | Inferior parathyroid glands + thymus                                                           |
| 4th pouch      | Superior parathyroid glands + ultimobranchial body (→ parafollicular/C cells of thyroid)       |

## 6. The evolutionary logic behind pharyngeal remodelling

- Recent work (cited in Gray's Anatomy) shows the **endoderm**, not neural crest, is the primary organiser of arch formation: segmentation of the pharyngeal pouches is the first sign of arch patterning, after which neural crest and cranial paraxial mesoderm migrate into the pre-formed epithelial segments.
- **Anterior pouches (1st, 2nd)** form together and are retinoid/Wnt-independent; **posterior pouches (3rd, 4th)** form sequentially and require **retinoid and Wnt signalling**, with *Tbx1* driving endodermal proliferation — mutations in *TBX1* underlie **DiGeorge syndrome**, in which posterior pouch derivatives (thymus, parathyroids) fail to form.
- Evolutionarily, the posterior arches of fish were covered by a protective flap, the **operculum**, which drew water over the gills. In amniotes the **2nd arch expands caudally to cover the posterior arches**, closely paralleling — and driven by the same **Shh** signalling as — the fish operculum; this is why an operculum-like flap exists transiently even in the human embryo. Fusion of its caudal edge with subjacent tissue (mirroring the thyroid-hormone-dependent internalisation of gills at amphibian metamorphosis) obliterates the resulting **cervical sinus of His**, giving the neck its smooth outline.
- Far from being vestigial and discarded, the fish **gill** and the mammalian **parathyroid gland** share the same developmental programme arising from the posterior pharyngeal pouches — i.e. the gill-forming genetic programme was not lost in amniotes but **transformed into an endocrine (parathyroid) programme**.

## Applied / Clinical anatomy

- ▶ **Branchial (cervical) cyst/sinus/fistula:** incomplete obliteration of the cervical sinus of His (persistent 2nd-arch overgrowth remnant) — presents as a lateral neck swelling anterior to sternocleidomastoid; second most common congenital head-and-neck lesion in children.
- ▶ **First-arch syndromes** (Treacher Collins syndrome, Pierre Robin sequence): mandibular hypoplasia, external/middle ear defects, cleft palate — from disturbed neural-crest/1st-arch development.
- ▶ **DiGeorge syndrome:** failure of 3rd/4th pouch derivatives (thymic aplasia → T-cell immunodeficiency; parathyroid aplasia → hypocalcaemia), classically linked to *TBX1/22q11* deletion and to the same posterior-pouch signalling pathway described above.
- ▶ **Preauricular sinus/fistula:** faulty fusion of the auricular hillocks derived from 1st/2nd arch mesenchyme around the 1st pharyngeal cleft.
- ▶ **Ectopic thymus/parathyroid:** aberrant descent of 3rd-pouch derivatives along their migration path.
- ▶ **Persistent pyriform sinus fistula/thyroglossal remnants of ultimobranchial body:** linked to 4th-pouch derivative anomalies and medullary thyroid carcinoma (C-cell origin).
- ▶ **Congenital aural atresia / ossicular anomalies:** disturbed 1st/2nd arch cartilage or 1st pouch/cleft development.

## High-yield exam pointers

- ▶ Humans have **5 pharyngeal arches** (1,2,3,4,6); true gill slits never form — a fused pharyngeal membrane always intervenes, unlike fish.
- ▶ Each arch has **4 constituents:** cartilage bar, muscle mass, nerve, aortic arch artery — nerve supply is the most reliable marker of arch origin even after muscle migration.
- ▶ Meckel's cartilage (1st arch) → malleus; Reichert's cartilage (2nd arch) → stapes, styloid process — comparative anatomy explains this as the miniaturised reptilian primary jaw joint (quadrate-articular → incudomalleal joint).
- ▶ Aortic arch fate: 3rd = common/internal carotid; 4th (L) = arch of aorta, (R) = proximal subclavian; 6th = pulmonary arteries + ductus arteriosus.
- ▶ Pouch fate: 1st = tubotympanic recess; 2nd = palatine tonsil; 3rd = inferior parathyroid + thymus; 4th = superior parathyroid + ultimobranchial body (C cells).
- ▶ 2nd arch overgrowth buries arches 3,4,6 to form the **cervical sinus of His**, homologous to the fish **operculum**; incomplete obliteration → branchial cyst/fistula.
- ▶ Posterior pouch formation needs retinoid/Wnt signalling and **Tbx1**; its failure = **DiGeorge syndrome**.
- ▶ "Ontogeny repeats phylogeny" — the branchial apparatus is the classic human example of recapitulation, especially well shown by the aortic arch series.



### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen's Human Embryology 6e; Hamilton, Boyd & Mossman — Human Embryology; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Vishram Singh — Textbook of Clinical Embryology.

Coverage note: the comparative/phylogenetic ("evolution") framing of the branchial apparatus is thin in the modern spine text beyond its one dedicated commentary (Gray's 41e, Commentary 2.2); the arch-by-arch skeletal/muscular/arterial derivative tables above are cross-confirmed against the older comparative-anatomy-oriented Hamilton, Boyd & Mossman text and the standard embryology texts to keep every fact verifiable.



## Evolution of cloaca

*Asked in: Paper II May 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The **cloaca** (Latin, "sewer") is the endoderm-lined, dilated terminal chamber of the primitive **hindgut**, continuous cranially with the gut tube and ventrally with the **allantois**, and closed caudally by the **cloacal membrane** (an area of apposed endoderm and ectoderm with no intervening mesoderm). It is the single common receptacle into which the **urinary, genital and alimentary tracts** open in early development — the "evolution" (developmental unfolding) of the cloaca is the process by which this single chamber is progressively **partitioned by the urorectal septum** into a dorsal **anorectal canal** and a ventral **urogenital sinus**, each subsequently differentiating along male or female lines. This single-chamber plan is also the **ancestral vertebrate condition** (retained in fish, amphibians, reptiles, birds and monotremes), so human cloacal development recapitulates, then abandons, a phylogenetically older arrangement.

### 1. Formation of the cloaca

- ▶ The **hindgut** terminates caudally in a slightly dilated, endoderm-lined **cloaca**, which receives the **allantois** ventrally as a blind diverticulum passing into the connecting stalk.
- ▶ Caudally the cloaca is separated from a shallow ectodermal depression — the **proctodeum** (**external cloaca / anal pit**) — by the **cloacal membrane** (endoderm of cloaca + ectoderm of proctodeum, no mesoderm between them).
- ▶ The paired **mesonephric (Wolffian) ducts** open into the cloaca early in development, at approximately the junction of its cranial and middle thirds; as the mesonephric folds from each side approach the cloaca they fuse to form a transverse partition (the **genital cord**) between the developing bladder ventrally and rectum dorsally.
- ▶ Using crown–rump (CR) length as a marker of staging: the cloaca is already a distinct dilated chamber by embryos of about **5 mm CR length**, at which point the urorectal septum first appears in the angle between hindgut and allantois.

## 2. Partitioning by the urorectal septum

- ▶ A wedge of mesenchyme proliferates in the **angle of junction between the hindgut and the allantois** — the **urorectal septum**, also called the **intercloacal mesenchyme**. Molecular markers of this mesenchyme include **Six1** and **Six2**.
- ▶ Classically the septum is described as forming from two integrated folds: a cranial **Tourneux fold**, growing towards the cloacal membrane, and a pair of lateral **Rathke folds**, growing towards the midline of the cloaca and fusing with the Tourneux fold. (Newer studies in mouse, rat and human embryos suggest the septum instead forms by fusion of yolk-sac and allantoic extraembryonic mesoderm, and that the embryo may grow *around* this tissue wedge rather than the septum actively descending — the mechanism is still debated.)
- ▶ The septum grows/approaches caudally and **divides the cloaca**, incompletely at first, into:
  - a **dorsal part** — the presumptive **rectum and anorectal canal**; and
  - a **ventral part** — the presumptive **urinary bladder and urogenital sinus**.
- ▶ It does **not fuse** with the cloacal membrane but approaches it closely, thereby also dividing the cloacal membrane into a ventral **urogenital membrane** and a dorsal **anal membrane**. The point at which the septum reaches the membrane becomes the **perineal body** (site of insertion of several perineal muscles).
- ▶ **Timing**: division of the cloaca occurs through the **4th–7th week**; in classic staged embryos the septum has reached and fused toward the cloacal membrane by about **16 mm CR length**. The **urogenital membrane ruptures earlier** (~7th week), opening the urogenital sinus to the exterior; the thicker **anal membrane ruptures later, in the 8th week**, establishing continuity between the anal pit and the rectum.
- ▶ **Shh signalling** is necessary for continued proliferation of both the urorectal septum and the surrounding pericloacal mesenchyme — loss of Shh signalling in animal models causes failure of cloacal division, and mutations in hedgehog-pathway genes in humans are linked to anorectal defects.

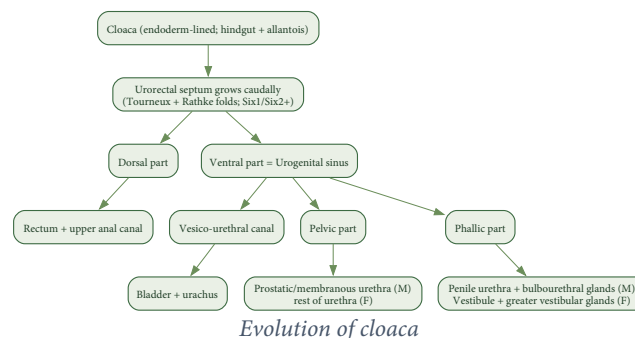
## 3. Fate of the anal membrane and formation of the anal canal

- ▶ The persisting ectodermal floor of the proctodeum, now called the **anal pit**, deepens as the anal membrane bulges into it.
- ▶ When the anal membrane ruptures (8th week), continuity is established between the anal pit (ectodermal) and the rectal (endodermal) part of the hindgut, forming the **anal canal**.
- ▶ This dual origin explains the **pectinate (dentate) line**: the **upper ~two-thirds of the anal canal is endodermal** (hindgut-derived — columnar epithelium, superior rectal vessels, inferior mesenteric lymph nodes, autonomic/visceral innervation), while the **lower one-third is ectodermal** (proctodeum-derived — stratified squamous epithelium, inferior rectal vessels, superficial inguinal lymph nodes, somatic/pudendal innervation) — a classic applied point growing directly out of cloacal partitioning.
- ▶ **Puborectalis** appears in 20–30 mm embryos, following opening of the anal membrane; striated fibres of the anal sphincter and urethral sphincter are seen by the 15th week.

#### 4. Derivatives of the cloaca

The urogenital sinus itself is conventionally divided into three parts once formed: a cranial **vesico-urethral canal** (continuous with the allantois — gives the bladder and urachus), a narrow middle **pelvic part**, and a caudal, deep **phallic part** (closed externally by the urogenital membrane, later pulled ventrally as the genital tubercle grows).

| Embryonic cloaca / urogenital sinus    | Male derivative                                               | Female derivative                    |
|----------------------------------------|---------------------------------------------------------------|--------------------------------------|
| Dorsal part of cloaca                  | Rectum + upper (proximal) anal canal                          | Rectum + upper anal canal            |
| Ventral part of cloaca                 | Most of the bladder + part of the prostatic urethra           | Most of the bladder + urethra        |
| Vesico-urethral canal + allantoic duct | Bladder body/apex; <b>urachus</b> → median umbilical ligament | Same                                 |
| Pelvic part of urogenital sinus        | Prostatic urethra (distal to utricle) + membranous urethra    | Rest of the urethra                  |
| Phallic part of urogenital sinus       | Penile urethra to the glans; bulbourethral glands             | Vestibule; greater vestibular glands |



#### 5. Comparative note

The single terminal cloacal chamber receiving alimentary, urinary and genital ducts is the **ancestral vertebrate arrangement**, still retained as a single external opening in fish, amphibians, reptiles, birds and the egg-laying monotremes. In human (and other placental-mammal) development, the cloaca is only a **transient embryonic stage**: the urorectal septum subdivides it so that separate anal and urogenital openings are established well before birth — i.e., the embryo transiently recapitulates, then departs from, the phylogenetically primitive single-outlet plan. *Coverage note: the corpus consulted here is essentially human developmental embryology; comparative cross-species detail beyond this general statement is not covered in the library texts and is not elaborated further to avoid speculation.*

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

embed: ![Fig 14.12 — Development of the anal canal. Urogenital septum divides cloaca into ventral primitive urogenital sinus and dorsal primitive rectum (Sontakke — Textbook of Human Embryology, p.144)](C:/Users/Harshad/Documents/anatomy-notes/answer-bank/rguhs-anatomy/answers/figures/plates/900e51417a72c9c6.jpg)

Reproduce three panels of the mid-sagittal section through the caudal end of the embryo, labelling in each:

- ▶ **Genital tubercle** (cranial to the membrane)
- ▶ **Allantois** (running cranially from the cloaca)
- ▶ **Urorectal (urogenital) septum** — shown descending in the angle between allantois and hindgut
- ▶ **Cloaca and cloacal membrane** (panel A — undivided)
- ▶ **Procodeum (anal pit) and anal membrane** (panel B — septum approaching membrane; perineal body forming at point of contact)
- ▶ **Anal canal after rupture of the anal membrane** (panel C) — mark the **pectinate line** with endoderm above / ectoderm below, and label **anal columns** and **anal sinuses**.

**Applied / Clinical anatomy**

- ▶ **Persistent (common) cloaca**: a female anorectal malformation in which the urorectal septum fails to complete separation, so rectum, vagina and urethra open into a single common perineal channel/outlet.
- ▶ **Anorectal malformation spectrum** (failure/incompleteness of urorectal septation or of anal-membrane rupture): **anal stenosis**, **anal atresia** (**imperforate anus** — an abnormally thick anal membrane fails to rupture), **anal agenesis** with or without a perineal fistula, **anorectal agenesis with rectovaginal fistula**, **anorectal agenesis with rectourethral fistula**, and **rectal atresia**.
- ▶ **Congenital rectovesical fistula** and **congenital vesicovaginal fistula** result from an incompletely formed urorectal septum leaving an abnormal communication between the rectum/vagina and the bladder.
- ▶ **Exstrophy of the bladder (ectopia vesicae)**: a ventral body-wall defect — infra-umbilical abdominal wall and anterior bladder wall fail to form, exposing the posterior bladder mucosa on the surface; **epispadias** is a **constant accompaniment**. Reported incidence varies between textbooks — roughly 1 in 5,000–10,000 births (Langman: 2/10,000 live births; Vishram Singh: 1:10,000).
- ▶ **Exstrophy of the cloaca / OEIS complex**: the urorectal septum fails to develop and mesenchymal migration around the ventral body wall (to support the umbilical cord) also fails, producing a large abdominal-wall defect with a central colonic segment flanked by two halves of an exposed bladder, together with imperforate anus — the **OEIS complex** (Omphalocele, Exstrophy of bladder/cloaca, Imperforate anus, Spinal defects). It is much rarer than isolated bladder exstrophy (quoted as ~1:30,000 by Langman; ~1:200,000 pregnancies by Sontakke). A

characteristic clinical sign is the "**elephant-trunk sign**" produced by an intussuscepted loop of terminal ileum protruding through the exposed bowel segment.

- ▶ **Hypospadias**: incomplete canalisation of the urethral plate/failure of genital-fold fusion causes the urethra to open on the ventral aspect of the penis — a downstream consequence of abnormal phallic-segment development after cloacal/urogenital-membrane partitioning.

### High-yield exam pointers

- ▶ Cloaca = endoderm-lined dilated terminal chamber of the hindgut, receiving the allantois ventrally; closed by the **cloacal membrane** (no mesoderm between endoderm and ectoderm).
- ▶ Divided by the **urorectal septum** (intercloacal mesenchyme; Six1/Six2<sup>+</sup>) arising in the hindgut–allantois angle, classically via **Tourneux (cranial) + Rathke (lateral) folds**.
- ▶ Division into **dorsal (rectum/anal canal)** and **ventral (urogenital sinus)** parts occurs through the **4th–7th week**; urogenital membrane ruptures ~7th week, anal membrane ~8th week.
- ▶ Point of septal contact with the membrane = **perineal body**.
- ▶ Urogenital sinus has three parts: **vesico-urethral canal** → **bladder + urachus**; **pelvic part** → **prostatic/membranous urethra (M)**; **phallic part** → **penile urethra/vestibule**.
- ▶ **Pectinate line** = boundary of endodermal (upper) vs ectodermal (lower) anal canal — directly explains the differential blood/nerve/lymphatic supply above and below it.
- ▶ Single-cloaca body plan = **ancestral vertebrate condition** (fish/amphibians/reptiles/birds/monotremes); mammals transiently recapitulate then partition it.
- ▶ Key anomalies: **persistent cloaca**, **anorectal malformations** (stenosis/atresia/fistulae), **bladder exstrophy** (with epispadias), **cloacal exstrophy/OEIS complex** (elephant-trunk sign).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; Vishram Singh — Textbook of Clinical Embryology; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology.



## Evolution of head

Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** The vertebrate head is not a simple cranial extension of the trunk — it is an evolutionarily composite structure built around a novel embryonic cell population, the **neural crest**. The "new head hypothesis" holds that the vertebrate head evolved by adding neural-crest-derived structures cranial to the notochord, superimposed on an older, mesoderm-built axial body plan; this is confirmed by cell-lineage tracing in the mouse. Human head development recapitulates this history through (i) a segmental (neuromeric) organisation of the hindbrain and occipital somites, (ii) a neural crest–mesoderm mosaic that builds the definitive skull, and (iii) a pharyngeal arch series that is a developmental echo of the ancestral gill-arch scaffold of fishes. Each of these is described below with its modern clinical correlates.

### 1. The neural crest — the key evolutionary innovation

- ▶ Evolution of the vertebrate head was made possible by the origin of the **neural crest**, a cell population with the unique potential to form connective and skeletal tissue in the head (unlike the mesoderm-only skeletogenesis of the trunk).
- ▶ In mammalian embryos, cranial neural crest cells emigrate from the edges of the *still-open* cranial neural folds (unlike trunk crest and the cranial crest of other vertebrates, which migrate only after neural tube closure).
- ▶ Three separate cranial neural crest streams arise, each with neuronal and non-neuronal progeny:
  - **Trigeminal stream** — from the diencephalon, midbrain and prorhombomere A (future rhombomeres 1–2); non-neuronal cells form the frontonasal mesenchyme and the maxillary/mandibular mesenchyme of arch 1.
  - **Hyoid stream** — from prorhombomere B (rhombomeres 3–4); gives the otic ganglion and migrates into the 2nd pharyngeal arch.
  - **Vagal stream** — from the neural folds caudal to the otocyst (prorhombomere C); contributes to glossopharyngeal and vagal ganglia and migrates into arches 3, 4 and 6, some cells continuing into the heart to septate the cardiac outflow tract.
  - **Occipital crest** (prorhombomere D / rhombomere 8) migrates with occipital myoblasts to form the hypoglossal cord — the connective tissue and (with the myoblasts) musculature of the tongue; notably, **no sensory ganglion** is formed from occipital crest.
- ▶ Ectodermal placodes cooperate with crest: three sensory placodes (olfactory, lens, otic) and epipharyngeal placodes in arches 2–4 contribute neurons to the Vth, VIIth, IXth and Xth cranial sensory ganglia (geniculate, petrosal, nodose).
- ▶ Comparative anatomy note: the membrane-bone armour that covered the skull of piscine ancestors (bony fishes) is represented in humans by the membrane bones of the skull — the flat bones of the calvaria and much of the facial skeleton — built from a mixture of neural crest and mesoderm-derived mesenchyme.

### 2. Segmental (neuromeric) organisation of the head

The head is patterned by a metameric hindbrain scheme rather than by classical somites throughout, reflecting its distinct evolutionary and developmental logic.

| Prorhombomere | Becomes                               | Neural crest stream | Ganglion formed                  | Arch(es) entered                         |
|---------------|---------------------------------------|---------------------|----------------------------------|------------------------------------------|
| A             | Rhombomeres 1–2                       | Trigeminal          | Trigeminal ganglion              | 1st arch + frontonasal region            |
| B             | Rhombomeres 3–4                       | Hyoid               | Otic ganglion                    | 2nd arch                                 |
| C             | Rhombomeres 5–7 (caudal to otocyst)   | Vagal               | Glossopharyngeal & vagal ganglia | 3rd, 4th, 6th arches (+ cardiac outflow) |
| D             | Rhombomere 8 (unsegmented, occipital) | Occipital           | None                             | Hypoglossal cord → tongue                |

- The **preotic sulcus** is the first transverse division of the embryonic brain (between prorhombomeres A and B); it is functionally decisive because it separates the crest destined for the **skull** (rostral) from crest destined for **neck skeleton** (hyoid bone, larynx — caudal).
- Caudal to the segmented rhombencephalon lie **four occipital somites** (post-otic); somite 1 is the **first occipital somite**. Paraxial mesoderm *rostral* to the otic vesicle was classically thought not to segment; the older idea of seven distinct **cranial somitomeres** is no longer generally accepted.
- Segmentation is patterned by evolutionarily conserved **Hox genes**, whose rostral expression boundaries align with specific rhombomere divisions and are mirrored in the neural crest that migrates from them: skeletal patterning of **arch 1** depends on the *absence* of Hox expression in its crest, patterning of **arch 2** depends on **Hoxa2**, while Hox expression in arches 3–6 has not shown a clear skeletal-patterning role.

### 3. Neural crest–mesoderm mosaic of the definitive skull

□ Fig 17.4 — *Developmental Origins of the Bones of the Skull* (Larsen — *Human Embryology* — 6e, p.1038)

| Skull component                                                                   | Embryonic origin       | Comparative-evolutionary note                                              |
|-----------------------------------------------------------------------------------|------------------------|----------------------------------------------------------------------------|
| Entire viscerocranium (face)                                                      | Neural crest           | Face is wholly crest-derived                                               |
| Frontal bone, part of interparietal bone                                          | Neural crest           | Rostral to notochord                                                       |
| Sphenoid, ethmoid bones                                                           | Neural crest           | Rostral to notochord                                                       |
| Parietal bones, lateral part of interparietal bone                                | Paraxial mesoderm      | Caudal/lateral territory                                                   |
| Occipital bone                                                                    | Paraxial mesoderm      | Around/caudal to cranial tip of notochord                                  |
| Hypochiasmatic cartilage (extraocular-muscle attachment, contributes to sphenoid) | Mesoderm               | <i>Exception</i> — mesoderm-derived despite lying rostral to the notochord |
| Laryngeal cartilages (arytenoid, cricoid)                                         | Lateral plate mesoderm | Only lateral-plate contribution in the head                                |



| Skull component                                                                   | Embryonic origin                        | Comparative-evolutionary note |
|-----------------------------------------------------------------------------------|-----------------------------------------|-------------------------------|
| Craniofacial voluntary muscles, cranial dermis, meninges caudal to prosencephalon | Paraxial mesoderm (somites/somitomeres) |                               |

- ▶ The **neural crest–mesoderm boundary** lies at the **spheno-occipital junction** in the cranial base and runs through the **coronal and sagittal sutures** in the vault (crest cells lie between the paired parietal bones).
- ▶ This crest–mesoderm interface is where craniofacial suture growth is regulated; its disruption underlies **craniosynostosis**.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Sagittal/lateral schematic of the fetal skull, two shading codes, labelled:

- ▶ **Neural-crest territory** (tan) — frontal bone, entire facial skeleton, sphenoid, ethmoid, part of interparietal bone.
- ▶ **Mesoderm territory** (yellow) — parietal bones, occipital bone, lateral part of interparietal bone, hypochiasmatic cartilage (exception, mark within crest territory).
- ▶ Mark the **spheno-occipital synchondrosis** and **coronal/sagittal sutures** as the crest–mesoderm boundary.

#### 4. Pharyngeal arch series — the repurposed gill-arch scaffold

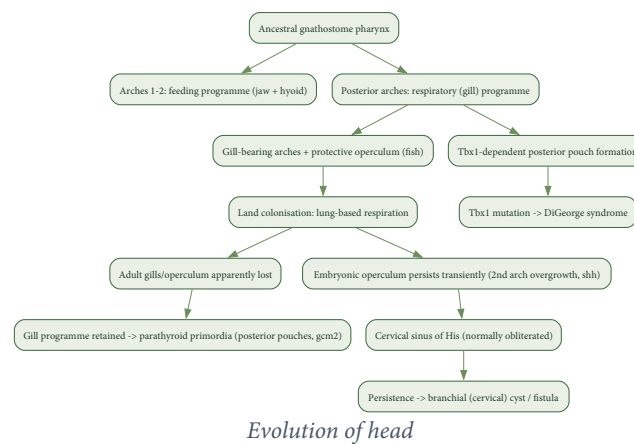
- ▶ Each pharyngeal arch is a disparate multi-tissue unit: ectoderm outside, endoderm inside, a mesenchymal core of **neural crest** surrounding a central group of **cranial paraxial mesoderm**; each therefore carries its own cartilage, muscle, nerve and artery.
- ▶ Formation is endoderm-first: outpocketing of the **pharyngeal pouches** (four in number) precedes and directs arch formation — neural crest and paraxial mesoderm migrate into pre-existing endodermal segments, and FGF signalling from the endoderm promotes chondrogenesis in the crest; the pouches also induce the epibranchial placodes.

| Arch             | Skeletal element                                                                                                | Nerve | Comparative-evolutionary note                                                   |
|------------------|-----------------------------------------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------|
| 1st (mandibular) | Meckel's cartilage → <b>malleus, incus</b> , ant. ligament of malleus, sphenomandibular ligament                | V     | Ancestral "jaw arch"; posterior remnants become the first two auditory ossicles |
| 2nd (hyoid)      | Reichert's cartilage → <b>stapes</b> , styloid process, stylohyoid ligament, lesser cornu + upper body of hyoid | VII   | Ancestral "hyoid arch"; contributes the third ossicle                           |
| 3rd              | Greater cornu + lower body of hyoid                                                                             | IX    |                                                                                 |

| Arch      | Skeletal element                                                               | Nerve | Comparative-evolutionary note                         |
|-----------|--------------------------------------------------------------------------------|-------|-------------------------------------------------------|
| 4th & 6th | Laryngeal cartilages (thyroid; cricoid/arytenoid) — exact contribution debated | X     | Gill-arch derived; posterior, "respiratory" territory |

- All three auditory ossicles thus derive from the cartilages of the first two pharyngeal ("jaw" and "hyoid") arches — a direct embryological trace of structures once part of the ancestral feeding apparatus being repurposed for hearing.

## 5. Comparative-evolutionary logic of the pharynx: feeding vs respiration



- In all gnathostomes the first two pharyngeal arches form the **jaw and hyoid** (feeding), while the more posterior arches are **gill-bearing** (respiration); in many fish the gills are covered by a protective flap, the **operculum**, which draws water over the gills.
- When vertebrates colonised land, the pharynx was substantially remodelled with the shift to lung-based respiration, and the gills and operculum were apparently lost.
- However, the gills were **not simply lost**: the same posterior pharyngeal pouches, under the same gene (**gcm2**), give rise to the **parathyroid glands** in amniotes — the early gill-forming developmental programme persists, repurposed.
- An embryonic **operculum-like structure** does transiently exist in amniotes: the posteriorly expanding 2nd pharyngeal arch that comes to cover the posterior arches is homologous to the fish operculum, driven by **shh signalling** in both. In amniotes its leading edge fuses at the level of the cardiac eminence, enclosing the posterior arches in the **cervical sinus of His**, which is then normally eliminated. This mirrors gill internalisation during amphibian metamorphosis; both processes require **thyroid hormone signalling**.
- The two anterior pharyngeal pouches form simultaneously, while posterior pouches form sequentially under **retinoid and Wnt signalling** and require **Tbx1**; Tbx1 drives endodermal proliferation, and its loss causes failure of posterior pouch formation with failure of neural-crest segregation — the basis of **DiGeorge syndrome**.

- ▶ This anterior/posterior developmental asymmetry "betrays our evolutionary history": the ancestral functional division of the pharynx into an anterior feeding region and a posterior respiratory region still exists in amniotes.

## Applied / Clinical anatomy

- ▶ **Branchial (cervical) cyst/fistula** — persistence of the cervical sinus of His (failure of 2nd-arch overgrowth to obliterate the posterior arches); the second most common congenital lesion of the head and neck in children; may have internal, external, or both openings.
- ▶ **DiGeorge syndrome** — Tbx1 mutation → failure of posterior pharyngeal pouch formation → defects of posterior pharyngeal-arch derivatives (thymic/parathyroid hypoplasia, great-vessel and cardiac outflow anomalies), reflecting the vagal crest's contribution to cardiac outflow septation.
- ▶ **Treacher Collins syndrome** (mandibulofacial dysostosis) — a neural-crest disorder of arch 1: hypoplasia/absence of maxilla, mandible and zygomatic arches, cleft palate, external-ear defects with auditory-canal atresia and middle-ear ossicle abnormalities → conductive hearing loss.
- ▶ **Craniosynostosis** — premature fusion of a cranial vault suture; because the coronal and sagittal sutures form at the neural crest–mesoderm interface, mutations disturbing this boundary (e.g. FGFR-related syndromes) cause characteristic skull deformities (dolichocephaly, brachycephaly, plagiocephaly).
- ▶ **Achondroplasia** — a defect of endochondral (cartilage) growth at the cranial base synchondroses causes midface hypoplasia, illustrating how disordered chondrocranial growth reproduces a comparative-anatomy relationship between cranial-base and long-bone growth-plate biology.

## High-yield exam pointers

- ▶ The "new head hypothesis": the vertebrate head evolved by adding neural-crest-derived structures cranial to the notochord — confirmed by mouse lineage tracing.
- ▶ Three cranial neural crest streams (trigeminal, hyoid, vagal) plus a ganglion-free occipital crest stream (→ tongue via the hypoglossal cord).
- ▶ Preotic sulcus separates skull-forming (rostral) from neck-forming (caudal) crest; 4 post-otic occipital somites; the "seven cranial somitomere" theory is no longer accepted.
- ▶ Neurocranium is a neural crest–mesoderm mosaic: face/frontal/sphenoid/ethmoid = crest; parietal/occipital = mesoderm; boundary = spheno-occipital synchondrosis + coronal/sagittal sutures (exception: mesoderm-derived hypochiasmatic cartilage).
- ▶ Pharyngeal pouches (endoderm) form first and direct arch formation via FGF signalling; crest is not obligatory for rudimentary arch formation.
- ▶ Meckel's cartilage (arch 1) → malleus, incus; Reichert's cartilage (arch 2) → stapes, styloid process, stylohyoid ligament, lesser cornu/upper body of hyoid.
- ▶ Gnathostome pharynx is split anterior (feeding: jaw/hyoid) vs posterior (respiratory: gill); land vertebrates lose the adult gills/operculum, but the developmental programme is repurposed to form the parathyroid (gcm2) — an embryonic operculum-homologue transiently persists (shh-driven 2nd-arch overgrowth → cervical sinus of His).
- ▶ Tbx1 is required only for posterior pouch formation; its loss underlies DiGeorge syndrome.

- Persistent cervical sinus of His → branchial cyst/fistula, the second commonest congenital head-and-neck lesion in children.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; IB Singh Human Embryology (CBME 2021). Coverage note: a niche, comparative/evolutionary embryology topic asked only once (Oct 2010); grounded chiefly in Gray's "Development of the head and neck" chapter (with its evolutionary commentary on pharyngeal development) and Larsen's "Origin of the Vertebrate Head" research-focus box.



## Evolution of mandible

*Asked in: Paper II Apr 2006 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The human mandible is a mammal-specific membrane (dermal) bone, and its ossification pattern, its transient cartilaginous scaffold, and its unusual jaw joint are all best understood in the light of vertebrate jaw evolution. In fish, amphibians and reptiles the lower jaw is built around Meckel's cartilage and articulates with the skull through a single, endochondral **quadrate-articular joint**; in the lineage leading to mammals a second, membrane-bone jaw joint (**squamosal-dentary**) arose and became dominant, so the old quadrate and articular bones were freed from load-bearing duty and were recruited into the middle ear as the **incus and malleus**. The 6-week human embryo briefly recapitulates this history: the mandible ossifies in membrane around a transient Meckel's cartilage whose own remnant becomes the malleus and its ligaments, while the definitive lower jaw is itself a new "dentary-like" bone, exactly as in the mammalian lineage. This comparative-embryological story explains both the dermal-bone origin of the human temporomandibular joint (TMJ) and why mammals uniquely possess three middle-ear ossicles.

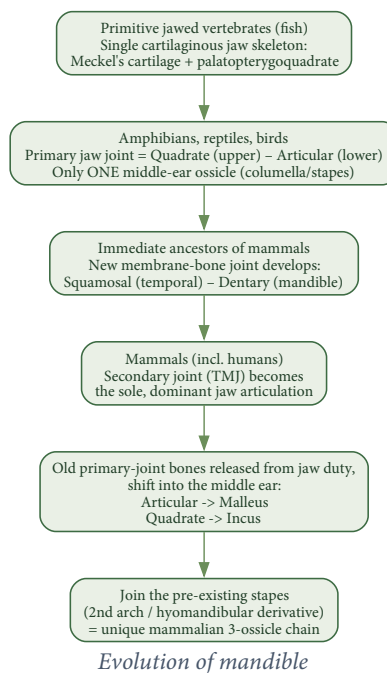
### 1. Comparative basis — Meckel's cartilage and the vertebrate jaw skeleton

- In all gnathostomes (jawed vertebrates), the first two pharyngeal arches form the jaws and hyoid apparatus, while the more posterior arches remain gill-bearing.
- The **first (mandibular) pharyngeal arch** differentiates into a smaller, cranial **maxillary process** and a larger, caudal **mandibular process**.
- The cartilaginous core of the mandibular process is **Meckel's cartilage**; the cartilaginous core of the maxillary process is the **palatopterygoquadrate ("maxillary") cartilage** — together these constitute the "first-arch cartilage."
- In lower vertebrates these cartilages ossify to form the definitive jaw skeleton, and the primitive vertebrate jaw articulates through a joint formed between the caudal ends of these two cartilage-derived bones — the **primary (craniomandibular) jaw joint**.
- The **second (hyoid) arch cartilage** — Reichert's cartilage, corresponding to the hyomandibular element of fishes — braces the jaw to the neurocranium and, in tetrapods, forms the **stapes**, styloid process, stylohyoid ligament, and the lesser cornu and part of the body of the hyoid bone.

- Molecular note: mandibular (Dlx5/6–Hand2–endothelin-1) identity of the first arch is genetically distinct from maxillary identity; experimental loss of Dlx5/6 in mice homeotically transforms the mandibular prominence (Meckel's cartilage + dentary bone) into a mirror-image maxilla — direct molecular evidence that the mandible and maxilla are serially homologous structures patterned by a shared first-arch programme.

## 2. Primary → secondary jaw joint: the reptile–mammal transition

- In all jawed vertebrates **except mammals** (fish, amphibians, reptiles, birds) the jaw joint remains the primitive **endochondral quadrate (upper jaw)–articular (lower jaw) joint**, both bones derived from the first-arch cartilages.
- Among the immediate ancestors of mammals, a **second, novel articulation** evolved between two **membrane (dermal) bones** — the **squamous temporal bone** and the **mandible** (the "dentary" in comparative terminology) — the future **temporomandibular joint (TMJ)**.
- As this dentary–squamosal joint became the dominant, load-bearing jaw articulation, the old quadrate and articular bones were released from jaw duty; they shifted into the adjacent middle ear and joined the pre-existing single ear ossicle (the hyomandibular/second-arch derivative) to form the unique **three-ossicle mammalian auditory chain**.
- Homology established in the spine text: the incus and malleus "are homologous with the quadrate and articular bones of reptiles, and the joint between them is evolutionarily derived from the reptilian jaw articulation."
- Net result: non-mammalian tetrapods (reptiles, birds, amphibians) retain only **one** middle-ear ossicle (the columella/stapes), whereas **mammals alone possess three** (malleus, incus, stapes) — a direct fossil of this jaw-joint transition preserved in every mammalian ear.



### 3. Ontogeny recapitulates phylogeny — development of the human mandible from the first arch

- ▶ The mandible is the **second bone in the body to ossify**, after the clavicle; each half ossifies from a **single centre** appearing at about the **6th week of intra-uterine life**, in the mesenchymal sheath lateral to Meckel's cartilage, near the site of the future mental foramen.
- ▶ Almost the whole bone forms by **intramembranous ossification** — i.e., the definitive mandible is itself a new dermal ("dentary-like") bone and is **not** formed from Meckel's cartilage; ossification spreads to cover the area between the mandibular and mental foramina.
- ▶ The **ramus above the mandibular foramen** — the **condylar and coronoid processes, and the angle region** — ossifies from **independent secondary cartilages** attached to (but distinct from) Meckel's cartilage, not from Meckel's cartilage itself.
- ▶ Fate of **Meckel's cartilage**: most of it degenerates and is resorbed or becomes embedded within the developing bone; its **proximal (dorsal) end** undergoes endochondral ossification to form the **malleus**; its perichondrial sheath persists as the **anterior ligament of malleus** and the **sphenomandibular ligament**; a small ventral-most portion near the future symphysis contributes transient **mental ossicles** that fuse into the mandible.
- ▶ The **maxillary (palatopterygoquadrate) cartilage** similarly ossifies at its caudal end to form the **incus**, and also contributes to part of the greater wing of the sphenoid and the roots of the pterygoid plates.
- ▶ At birth the two mandibular halves are still separate, joined only by the fibrous **symphysis menti**, which ossifies during the first to second year of life.

□ Fig 11.4 — Structures derived from cartilages of the pharyngeal arches. The first arch cartilage is Meckel's cartilage (Sontakke — Textbook of Human Embryology, p.107)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw a schematic lateral view of a reptilian skull above a mammalian (human) skull, aligned so the jaw joints line up vertically, and label:

- ▶ **Reptile:** Quadrate (part of upper jaw/squamosal complex) — Articular (posterior end of lower jaw) — arrow showing these two form the **primary jaw joint**; a single rod-like **columella (stapes homologue)** running from the oval window to the tympanic membrane.
- ▶ **Mammal:** Squamosal (temporal bone) — Dentary (mandible) — arrow showing these form the **new secondary joint (TMJ)**; below/behind it, three small bones in the middle ear labelled Malleus (= old articular), Incus (= old quadrate), Stapes (unchanged, 2nd-arch derivative).
- ▶ Dashed arrows from Articular → Malleus and Quadrate → Incus crossing between the two skulls to show the evolutionary transposition.
- ▶ A small inset of the 6-week human embryo mandibular arch showing **Meckel's cartilage** with the mandible ossifying in membrane lateral to it, and the **condylar/coronoid secondary cartilages**.

## 4. Structure-by-structure evolutionary correlation

| Ancestral / non-mammalian element                                      | Arch of origin                          | Human (mammalian) derivative                                                                            |
|------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------|
| Dentary (a membrane bone of the lower jaw)                             | 1st arch, lateral to Meckel's cartilage | Body and most of the ramus of the mandible (intramembranous ossification)                               |
| Articular (endochondral, proximal/dorsal end of Meckel's cartilage)    | 1st arch, mandibular process            | Malleus                                                                                                 |
| Quadrate (endochondral, caudal end of palatopterygoquadrate cartilage) | 1st arch, maxillary process             | Incus (+ part of greater wing of sphenoid and pterygoid plates)                                         |
| Hyomandibular element                                                  | 2nd (hyoid) arch, Reichert's cartilage  | Stapes, styloid process, stylohyoid ligament, lesser cornu + part of body of hyoid                      |
| Primary (quadrate-articular) jaw joint                                 | —                                       | Lost as a jaw joint; incorporated into the ossicular chain of the middle ear                            |
| — (newly evolved joint)                                                | —                                       | Secondary jaw joint = the human <b>temporomandibular joint</b> (squamous temporal – mandibular condyle) |
| Perichondrial sheath of Meckel's cartilage                             | 1st arch                                | Anterior ligament of malleus + sphenomandibular ligament                                                |



## Applied / Clinical anatomy

- ▶ **First-arch (branchial-arch) syndromes:** because the mandible, malleus and incus all arise from first-arch neural-crest mesenchyme, disorders of first-arch patterning classically combine micrognathia with conductive deafness from ossicular malformation — e.g. **Treacher Collins syndrome (mandibulofacial dysostosis):** autosomal dominant, hypoplastic mandible with malformed malleus/incus, ear defects, and an antimongoloid palpebral slant; **Pierre Robin sequence:** severe micrognathia → posteriorly displaced tongue (glossoptosis) → cleft palate and neonatal airway obstruction.
- ▶ **Ossicular chain anomalies:** congenital malformation/fixation of the malleus–incus complex (their shared first-arch/quadrato-articular origin) produces a distinct pattern of conductive hearing loss from stapes fixation (otosclerosis), which instead reflects a second-arch/otic-capsule problem.
- ▶ **TMJ is a genuinely "new" joint:** being evolutionarily recent and formed between two membrane bones (unlike most other body joints, which are primarily endochondral in origin), the TMJ is unusual in having a fibrocartilaginous (not hyaline) articular surface and an intra-articular disc — clinically relevant to TMJ dysfunction and internal derangement.
- ▶ **Symphyseal (bifid) mandible:** rare failure of fusion at the symphysis menti (normally ossifying by the 1st–2nd year) briefly reproduces the paired-dentary condition seen in every mammalian embryo and in non-mammalian jaws.
- ▶ **Forensic/comparative relevance:** the mandible's unique intramembranous origin (unlike much of the rest of the facial skeleton, which is part cartilaginous) and its being the only mobile bone of the skull make it a key specimen for age, sex and species identification in forensic osteology and comparative anatomy.

## High-yield exam pointers

- ▶ Meckel's cartilage = skeletal core of the **mandibular process of the 1st pharyngeal arch**; the mandible itself does **not** ossify from Meckel's cartilage — it forms by **intramembranous ossification** of mesenchyme lateral to it, from a single centre per half appearing at the **6th week IU** (mandible = **2nd bone in the body to ossify**, after the clavicle).
- ▶ Primary (non-mammalian) jaw joint = **quadrato (upper)–articular (lower)**, both first-arch endochondral bones.
- ▶ Secondary (mammalian) jaw joint = **squamosal (temporal)–dentary (mandible)**, both membrane bones = the human TMJ.
- ▶ As the secondary joint took over, the primary-joint bones were incorporated into the middle ear: **articular → malleus, quadrato → incus**, joining the pre-existing **stapes** (2nd-arch/hyomandibular derivative) — the basis of the unique mammalian 3-ossicle chain.
- ▶ Non-mammalian tetrapods retain only **one** middle-ear ossicle (columella/stapes); mammals alone have three.
- ▶ The **condylar, coronoid and angle** regions of the mandible ossify from **independent secondary cartilages**, never from Meckel's cartilage.

- ▶ Meckel's cartilage's own remnant forms the **malleus + anterior ligament of malleus + sphenomandibular ligament**; the maxillary (palatopterygoquadrate) cartilage forms the **incus** (+ part of sphenoid).
- ▶ First-arch syndromes (Treacher Collins, Pierre Robin) combine micrognathia with ossicular/ear defects precisely because mandible, malleus and incus share a common first-arch neural-crest origin.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen's Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Sontakke — Textbook of Human Embryology; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology; Brijesh Kumar — Embryology Text & Atlas; Gangane — Human Genetics 5e; AK Datta — Human Anatomy Vol 2 (Head & Neck); BD Chaurasia's Human Anatomy Vol 3–4 8e.



## Evolution of thumb

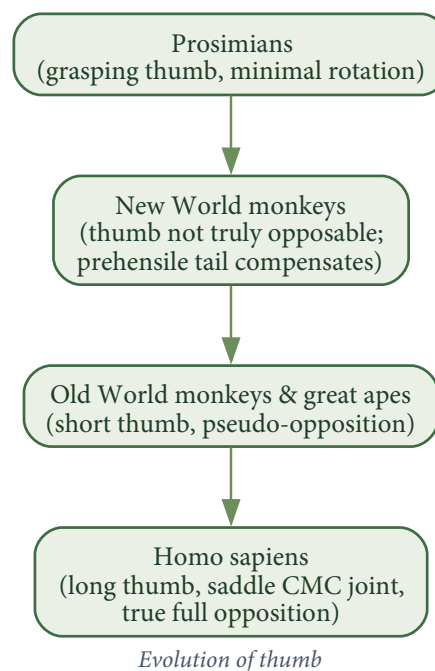
*Asked in: Paper II Sep 2007 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The thumb (**pollex**, digit 1) is the shortest, most mobile, and phylogenetically most specialised digit of the hand. Unlike the other four fingers, it possesses only two phalanges, a saddle-shaped basal joint, and an independent set of extrinsic and intrinsic muscles that together allow **true opposition** — rotation of the thumb pulp into contact with the pulp of each of the other digits. This capacity is progressively acquired across the primate order and reaches its most complete anatomical and functional expression only in *Homo sapiens*. Its evolution is therefore studied under three heads — comparative (phylogenetic) anatomy across primates, the embryological patterning that lays down digit 1 as a distinct structure, and the structural/muscular specialisations of the adult human thumb that make full opposition possible.

### Comparative (phylogenetic) anatomy of the thumb across primates

- ▶ Human taxonomic position: Kingdom Animalia → Phylum Chordata → Subphylum Vertebrata → Class Mammalia → **Order Primata** (well-developed brain, prehensile hands) → **Family Hominidae** (large cerebrum, bipedal locomotion) → **Genus Homo** → **Species sapiens**. An **opposable thumb** is listed, alongside a large cerebrum, bipedal gait, stereoscopic vision and articulate speech, as one of the defining anatomical traits that separate humans from other animals.
- ▶ **Prosimians** (lemurs, lorises): a divergent, grasping thumb adapted for gripping branches, but with little independent rotation — grasping rather than true opposition.
- ▶ **New World monkeys** (Platyrrhines): the thumb is set only slightly apart from the other digits and is not truly opposable in most genera; a prehensile tail compensates as an additional grasping organ.

- ▶ **Old World monkeys and great apes** (chimpanzee, gorilla, orangutan): a shorter, more mobile thumb with a degree of "pseudo-opposition" sufficient for grooming and holding food, but short relative to the fingers, limiting pulp-to-pulp precision contact and force.
- ▶ **\*Homo sapiens: the longest thumb relative to finger length\*** among primates, with a fully rotatory, saddle-jointed base — the only primate hand capable of complete, forceful pulp-to-pulp opposition to all four fingers.
- ▶ Evolutionary drivers classically cited: **bipedal posture** freed the forelimb from locomotor duty; parallel enlargement of the cortical hand-representation area permitted fine independent finger/thumb control — the human motor cortex devotes a disproportionately large somatotopic area to the fingers, matching the small motor units of the lumbricals and interossei that execute precision movements.
- ▶ The human hand uses three basic grips — **power, hook and precision**. Power and hook grips are phylogenetically older, "acquired by man from his arboreal ancestors," while the **precision grip** (thumb tip opposed to finger tip, for a pen, needle or fine tool) is the grip *characteristic of man* and underlies tool use, writing and skilled manipulation — the functional culmination of thumb evolution.



### Embryological development of digit 1 (the pollex)

- ▶ The upper-limb bud arises (~stage 12–13) as a mesenchymal thickening of the lateral body wall, capped by the **apical ectodermal ridge (AER)**, which drives outgrowth along the **proximodistal axis** (humerus → fingers). The distal bud flattens into a **hand plate**, within which **digital rays** appear; the intervening tissue is later removed by programmed (apoptotic) cell death to separate the five digits.
- ▶ Three developmental axes are laid down simultaneously: **proximodistal** (AER-dependent), **dorsoventral** (extensor ↔ flexor surfaces, controlled by dorsal/ventral ectodermal signals), and **craniocaudal** — the standard textbook example of the craniocaudal axis is precisely "**thumb to little finger**."

- ▶ The craniocaudal axis is controlled by the **zone of polarizing activity (ZPA)**, a group of mesenchymal cells at the **postaxial (little-finger) border** of the limb bud that secretes **Sonic hedgehog (Shh)**. Digit identity is graded by Shh concentration: the digit closest to the ZPA differentiates as the **most postaxial digit (little finger)**, while the thumb differentiates furthest from the ZPA, at the **preaxial border**, under the lowest Shh exposure. This positional-information gradient is the molecular explanation for the thumb consistently forming as **digit 1**, on the radial (preaxial) side of the hand.
- ▶ Cartilage models of the first metacarpal and phalanges chondrify from mesenchymal condensations of the hand plate (a **Sox9**-dependent step), later ossifying endochondrally. The thumb is unique among the digits in developing only **two phalanges** (proximal and distal — no middle phalanx), reflecting an early, digit-specific truncation of phalangeal segmentation.
- ▶ Thenar musculature differentiates from the **ventral (flexor) premuscle mass** of the limb bud and is therefore predominantly innervated by the **median nerve**, consistent with its ventral origin — the anatomical basis of the "ape hand" deformity seen after a proximal median-nerve lesion.
- ▶ The base of the first metacarpal and the trapezium develop reciprocally concavoconvex articular facets, producing a **saddle (sellar) joint** — a configuration unique among the carpometacarpal joints and the structural key to the additional axis of rotation that makes opposition possible.

□ Fig 20.3 — *Axes and Digits of the Developing Limb: the three axes of symmetry for limb development, showing the craniocaudal (preaxial–postaxial) axis along which the thumb and little finger are specified (Larsen — Human Embryology — 6e, p.1198)*

## Structural basis of thumb opposition — the first carpometacarpal joint

□ Fig 18.15 — *Carpometacarpal joint of the thumb: sections of the metacarpal and of the trapezium showing the reciprocal saddle (sellar) surfaces (IB Singh — Textbook of Anatomy Vol 1 — 6e, p.244)*

| Feature            | First CMC joint (thumb)                                                                                  | 2nd–5th CMC joints                           |
|--------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Joint cavity       | Separate, independent synovial cavity                                                                    | Share a common (midcarpal-continuous) cavity |
| Type               | <b>Saddle (sellar)</b> — biaxial                                                                         | Mostly <b>plane</b> joints, little movement  |
| Articular surfaces | Trapezium (concave sagittally, convex coronally) and base of 1st metacarpal (reciprocal)                 | Flat/plane facets                            |
| Movements          | Flexion–extension, abduction–adduction, plus axial rotation → combine as <b>opposition/circumduction</b> | Limited gliding only                         |

- ▶ Because the thumb does not lie in the standard anatomical position, clinical terminology substitutes **palmar, dorsal, radial and ulnar** for anterior, posterior, medial and lateral. Basic active movements are flexion–extension (parallel to the palm), **palmar abduction–adduction** (at right angles to the palm), **radial abduction/ulnar (transpalmar) adduction**, and **circumduction**.
- ▶ **Opposition** is the composite movement — flexion + abduction + medial (axial) rotation at the saddle-shaped first CMC joint — that brings the thumb pulp into contact with the pulp of each finger; it is this extra rotatory freedom, absent at the other CMC joints, that anatomically distinguishes the human thumb.

## Muscles and nerve supply that execute opposition

| Muscle                                                    | Action                                    | Nerve                                                                                                |
|-----------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------|
| Opponens pollicis                                         | Opposition                                | Median n. (recurrent branch); variable ulnar contribution                                            |
| Abductor pollicis brevis                                  | Palmar abduction                          | Median n. (recurrent branch) — the <i>only</i> thenar muscle constantly supplied by the median nerve |
| Flexor pollicis brevis                                    | Flexion (MCP joint)                       | Superficial head — median n.; deep head — ulnar n. (deep branch)                                     |
| Adductor pollicis                                         | Adduction                                 | Ulnar n. (deep branch)                                                                               |
| Flexor pollicis longus                                    | Flexion (IP joint, chief action)          | Median n. (anterior interosseous branch)                                                             |
| Extensor pollicis longus/brevis, abductor pollicis longus | Extension, radial abduction               | Radial n. (posterior interosseous branch)                                                            |
| First dorsal interosseous                                 | Stabilises index finger during pinch grip | Ulnar n. (deep branch)                                                                               |

- This dual median/ulnar supply explains the clinical "**ulnar paradox**": a proximal median-nerve lesion abolishes thenar opposition and abduction (loss of the precision grip that anatomically defines the human thumb) while power grip, driven largely by ulnar-supplied intrinsics and the long flexors, is relatively preserved.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Craniocaudal axis of the developing limb bud** — draw a hand plate with digital rays 1–5; label the **preaxial border** (thumb side), **postaxial border** (little-finger side), the **zone of polarizing activity (ZPA)** at the postaxial border, and an arrow showing the **Shh concentration gradient** (high at postaxial → low at preaxial), with a note that digit 1 (thumb) forms furthest from the ZPA.
- **Sagittal section of the first carpometacarpal joint** — label the **trapezium** (concave in sagittal plane, convex in coronal plane), the reciprocally shaped **base of the 1st metacarpal**, the **capsular ligament** (thick dorsally and laterally), the **separate joint cavity**, and the **biaxial saddle configuration** that permits opposition.

## Applied / Clinical anatomy

- **First CMC (basal thumb) osteoarthritis**: a common, painful degenerative condition of the saddle joint, reflecting the repetitive shear loading imposed by frequent opposition movements.
- **De Quervain's tenosynovitis**: stenosing tenovaginitis of the tendons of **abductor pollicis longus** and **extensor pollicis brevis** as they cross the radial styloid; movement of the thumb aggravates the pain.

- ▶ **Bennett's fracture-dislocation**: an intra-articular fracture of the base of the first metacarpal with subluxation at the CMC joint, occurring because the saddle joint's mobility makes this region biomechanically vulnerable to axial thumb trauma.
- ▶ **Gamekeeper's/skier's thumb**: rupture (acute or chronic) of the ulnar collateral ligament of the thumb's metacarpophalangeal joint, causing an unstable pinch grip.
- ▶ **Median nerve injury** (carpal tunnel syndrome, supracondylar humeral fracture): thenar wasting with loss of abduction and opposition — the classic "**ape thumb**" deformity, in which the thumb falls back into the plane of the palm alongside the other digits, losing its evolutionarily distinctive rotated posture.
- ▶ **Congenital anomalies of the thumb**: polydactyly (radial duplication), triphalangeal thumb, congenital trigger thumb, and hypoplastic/absent thumb (a radial-ray deficiency, seen in syndromes with severe limb malformation); a hypoplastic or amputated thumb may be reconstructed by **pollicization** of the index finger to restore an opposable digit.
- ▶ **Forensic/identification relevance**: the unique friction-ridge pattern of the thumb pulp (dactylography) is exploited for personal identification, an indirect consequence of the same tactile pulp specialisation that underlies precision grip.

### High-yield exam pointers

- ▶ Thumb = digit 1 = pollex; the **most preaxial digit** of the hand; unique in having only **two phalanges** (no middle phalanx).
- ▶ **True/full opposition** is unique to *Homo sapiens* among primates — power and hook grips are older, "arboreal" grips; the **precision grip** is the grip characteristic of man alone.
- ▶ Craniocaudal limb axis (classic example: "thumb to little finger") is patterned by the **ZPA/Sonic hedgehog gradient** at the postaxial border — thumb forms furthest from the ZPA.
- ▶ First CMC joint = **saddle (sellar) joint**, the only carpometacarpal joint with its own separate synovial cavity — the structural basis of opposition.
- ▶ Thenar muscles are chiefly **median-nerve**; adductor pollicis, deep head of FPB and the interossei are **ulnar-nerve** — basis of the "ulnar paradox" in median-nerve palsy.
- ▶ Human taxonomic markers of thumb evolution: **Family Hominidae** (bipedalism, large cerebrum) and **Genus Homo**, with the opposable thumb listed among defining human anatomical traits.
- ▶ Applied cluster to remember: basal-joint OA, De Quervain's tenosynovitis, Bennett's fracture, gamekeeper's thumb, congenital polydactyly/triphalangeal thumb, and the "ape thumb" of median-nerve palsy.



### SOURCE & COVERAGE

Gray's Anatomy (Standing) 41e — Development of the limbs (limb axes, ZPA/Shh) and Wrist and hand (movements of the thumb, first CMC joint, thenar/hypothenar innervation); Vishram Singh — General Anatomy 4e (taxonomic classification, human characteristic features); AK Datta — Human Anatomy Vol 3 (Upper & Lower Limb) (power/hook/precision grips, cortical hand representation); BD Chaurasia — Human Anatomy Vol 1, 8e (first CMC joint, applied anatomy); IB Singh — Textbook of Anatomy Vol 1, 6e (CMC joint figure, movements of thumb); Larsen — Human Embryology, 6e (axes and digits of the developing limb); Moore's Clinically Oriented Anatomy 9e (opposable thumb, grips).

**Coverage note:** the library carries no single dedicated "evolution of thumb/comparative primate hand" chapter; this answer synthesises confirmed comparative-anatomy statements (Vishram Singh, AK Datta), developmental-axis/ZPA-Shh grounding (Gray's Anatomy, Ch. "Development of the limbs"), and CMC-joint/muscle/clinical detail (BD Chaurasia, Gray's Anatomy "Wrist and hand", IB Singh) that are each individually verified in the source text; primate-by-primate comparative detail beyond what is stated above reflects standard, universally accepted anatomy teaching rather than a single cited passage.



## Evolution of tongue in the vertebrates

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

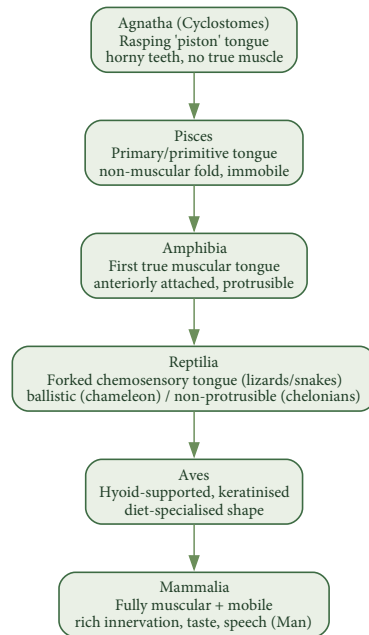
**Definition / Introduction** — The tongue is a mobile, muscular organ of the oral cavity that manipulates food, carries the special sense of taste, and — in Man alone — is refined for articulate speech. Phylogenetically it is not a single, pre-formed organ but a **composite structure assembled from several pharyngeal (branchial) arches**, arches which are themselves the vertebrate descendants of the gill-bar apparatus of the earliest aquatic chordates (Gray's Anatomy notes that pharyngeal arches are also called branchial arches "because of their evolutionary origin supporting the gills in the earliest vertebrates"). Tracing the tongue from jawless fish to mammals shows a consistent trend — from a non-muscular, immobile mucosal fold to a fully muscular, richly innervated, freely mobile organ — and the multi-arch mode in which the human tongue develops is itself a living record of this evolutionary assembly ("ontogeny recapitulates phylogeny").

### 1. Evolutionary trend across vertebrate classes

| Class                                           | Tongue in this class                                                                                                                  | Key feature                                                                                                |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Agnatha</b> (Cyclostomes — lamprey, hagfish) | No true tongue; a muscular, piston-like protrusible structure in the floor of the buccal funnel, armed with horny (keratinised) teeth | Rasping/scraping organ for a parasitic/scavenging habit; not homologous to the tongue of jawed vertebrates |



| Class                 | Tongue in this class                                                                               | Key feature                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pisces (fish)         | "Primary" or primitive tongue — a fold of mucous membrane over the basihyal/basibranchial skeleton | Non-muscular or minimally muscular, immobile; takes no active part in seizing or swallowing food (jaws, pharyngeal teeth and water currents do this); no salivary glands                                                                                                                                                                                                                    |
| Amphibia (frog, toad) | First <b>true muscular, protrusible</b> tongue                                                     | Attached <b>anteriorly</b> to the floor of the mouth (free posteriorly) — the reverse of the mammalian pattern; flipped out on a sticky secretion to capture insect prey; correlates with the shift to terrestrial, insectivorous life                                                                                                                                                      |
| Reptilia              | Highly variable                                                                                    | Lizards/snakes: long, thin, often <b>bifid (forked)</b> tip that samples chemical particles and delivers them to the vomeronasal (Jacobson's) organ — a chemosensory rather than mechanical role; <b>chameleon</b> : extraordinarily elongated, ballistic/projectile tongue for prey capture; chelonians and crocodilians: short, poorly protrusible, mainly pushes food toward the pharynx |
| Aves (birds)          | Supported internally by the bony/cartilaginous hyoid apparatus; surface often horny/keratinised    | Shape is diet-specialised — long barbed tongue (woodpecker), tubular/brush-tipped (nectar feeders), thick fleshy tongue (parrots), lamellate (ducks, for filtering); compensates for absent teeth in food handling, but intrinsic musculature and mobility remain less developed than in mammals                                                                                            |
| Mammalia (incl. Man)  | Fully muscular, richly innervated, freely mobile — the <b>definitive tongue</b>                    | Extrinsic muscles anchor it to the skeleton (mandible, hyoid, styloid, palate) while intrinsic muscles alter its shape; well-developed papillae with numerous taste buds; multiple cranial nerves supply it (reflecting its multi-arch origin); in Man it additionally subserves articulate speech — the most specialised tongue function in the animal kingdom                             |



*Evolution of tongue in the vertebrates*

## 2. The human tongue's development mirrors this evolutionary assembly

Because the definitive mammalian tongue is phylogenetically a fusion of several originally separate branchial-arch elements, its **ontogeny in the human embryo recapitulates this composite ancestry** — it is built from *four* pharyngeal arches, not one:

| Embryonic swelling                                                   | Arch of origin        | Adult contribution                                                | Nerve supply (general sensation / taste)                                         |
|----------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Two lateral lingual swellings + median tuberculum impar (disappears) | 1st (mandibular) arch | Anterior two-thirds (oral part)                                   | Lingual n. (general sensation) / chorda tympani (taste, except vallate papillae) |
| Copula                                                               | 2nd (hyoid) arch      | Overgrown and largely obliterated                                 | (2nd-arch nerve, facial, contributes taste via chorda tympani)                   |
| Hypobranchial (hypopharyngeal) eminence — large cranial part         | 3rd arch              | Posterior one-third (pharyngeal part), including vallate papillae | Glossopharyngeal n. (general sensation + taste)                                  |
| Hypobranchial eminence — small caudal part                           | 4th arch              | Posteriormost part / root, near epiglottis                        | Internal laryngeal branch of vagus                                               |

- The **terminal sulcus** marks the surface boundary between the 1st-arch and 3rd-arch contributions; the **foramen caecum**, at its apex, marks the point of origin of the thyroglossal duct (thyroid descent).

- ▶ Because the growing **third-arch endoderm overgrows the second arch's copula**, the posterior one-third is supplied by the nerve of the third arch (glossopharyngeal) rather than the second (facial) — the single most tested "why" in this topic.
- ▶ **All intrinsic and extrinsic muscles of the tongue (except palatoglossus)** develop from **occipital myotomes** (somitic mesoderm) that migrate forward into the tongue primordium, carrying with them their own nerve — the **hypoglossal (XII)**; this explains why the motor supply follows a segmental (somite-derived) pattern quite independent of the branchial-arch pattern that governs sensory supply. **Palatoglossus** alone develops from more caudal arch mesoderm and is supplied via the pharyngeal plexus of the vagus (cranial root of the accessory).
- ▶ Connective tissue of the tongue develops from local (neural-crest-derived) mesenchyme.

This layered, multi-arch, multi-nerve construction — quite unlike the single, simple mucosal fold of a fish's tongue — is the developmental fingerprint of the tongue's long evolutionary journey from an immobile pharyngeal-floor fold to the mammalian organ of mastication, taste, and speech.

□ Fig 17.11 — Development of tongue (BD Chaurasia — Human Anatomy Vol 3-4 — 8e, p.324)

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A floor-of-pharynx view (4–5 week embryo) labelled with:

- ▶ 1st (mandibular) arch → two **lateral lingual swellings** flanking the median **tuberculum impar**
- ▶ 2nd (hyoid) arch → **copula** (being overgrown)
- ▶ 3rd arch → large cranial part of **hypobranchial eminence**
- ▶ 4th arch → small caudal part of hypobranchial eminence, leading into the **epiglottis**
- ▶ Surface landmarks on the adult dorsum: **terminal sulcus**, **foramen caecum**, **median sulcus**, **sulcus terminalis** dividing oral (anterior 2/3) from pharyngeal (posterior 1/3) parts

### Applied / Clinical anatomy

- ▶ **Lingual thyroid**: failure of the thyroid primordium to descend from the foramen caecum leaves ectopic thyroid tissue at the tongue base — a direct clinical marker of the foramen caecum's developmental significance.
- ▶ **Thyroglossal cyst/fistula**: along the line of descent of the thyroglossal duct from the foramen caecum to the thyroid bed.
- ▶ **Ankyloglossia (tongue-tie)**: failure of regression of the ventral tongue-to-floor-of-mouth attachment, leaving an abnormally short/anteriorly-placed frenulum that restricts tongue mobility.
- ▶ **Carcinoma of the tongue**: anterior two-thirds lesions drain chiefly to the submandibular/submental nodes and present relatively early; posterior one-third (pharyngeal part) lesions drain to the deep cervical (jugulodigastric/retropharyngeal) nodes bilaterally and are typically diagnosed later — hence the classically poorer prognosis of posterior one-third growths.

- ▶ **Referred otalgia:** pain from posterior-tongue/tonsillar lesions is referred to the ear because the glossopharyngeal nerve (posterior 1/3) also gives the tympanic branch (Jacobson's nerve) to the middle ear.
- ▶ **Genioglossus as the "safety muscle" of the tongue:** its tonic activity keeps the tongue (and airway) forward; bilateral hypoglossal palsy or loss of tone under anaesthesia/sleep predisposes to posterior tongue-fall and airway obstruction.
- ▶ **Comparative correlation:** the reptilian/avian pattern of a chemosensory or diet-adapted, less-muscular tongue versus the mammalian pattern of a fully muscular, speech-capable tongue underlines why articulate language is uniquely human among tetrapods.

### High-yield exam pointers

- ▶ Tongue phylogeny: Agnatha (rasping piston) → Pisces (immobile mucosal fold) → Amphibia (first true muscular, anteriorly-fixed, protrusible tongue) → Reptilia (chemosensory/forked or ballistic) → Aves (hyoid-supported, keratinised, diet-specialised) → Mammalia (fully muscular, mobile, richly innervated, capable of speech in Man).
- ▶ Human tongue develops from **four** pharyngeal arches: 1st → anterior 2/3 (tuberculum impar + lateral lingual swellings); 2nd → copula (overgrown); 3rd → posterior 1/3 (large part of hypobranchial eminence); 4th → posteriormost part/root.
- ▶ Posterior 1/3 is supplied by **glossopharyngeal (IX)**, not facial (VII), because 3rd-arch tissue overgrows the 2nd-arch copula — the classic "why" question.
- ▶ All tongue muscles **except palatoglossus** are from **occipital myotomes**, supplied by **hypoglossal (XII)**; palatoglossus alone is supplied via the vagal pharyngeal plexus.
- ▶ Foramen caecum = surface marker of the thyroid diverticulum's origin; terminal sulcus = boundary of anterior 2/3 and posterior 1/3.
- ▶ Amphibian tongue is attached **anteriorly** (opposite of mammals); reptilian forked tongue serves chemoreception via Jacobson's organ; chameleon tongue is ballistic; avian tongue is hyoid-supported and keratinised.
- ▶ Clinical correlates: lingual thyroid, thyroglossal cyst, ankyloglossia, and the poorer prognosis of posterior one-third tongue carcinoma (bilateral deep cervical drainage, late presentation).

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 3-4 8e; Vishram Singh — Textbook of Anatomy Vol 3 4e; Larsen — Human Embryology 6e; Moore — The Developing Human 9e; IB Singh — Human Embryology (CBME 2021); Hamilton, Boyd & Mossman — Human Embryology.

**Coverage note:** The library's textbooks are human-embryology/anatomy texts and do not carry a dedicated comparative-vertebrate-zoology chapter on the tongue; the cross-class comparison in Section 1 (Agnatha–Pisces–Amphibia–Reptilia–Aves–Mammalia) is composed from standard, universally-taught comparative-anatomy knowledge rather than grepped from this corpus, while the human developmental section (Section 2) and all applied points are fully corpus-grounded.



## Facial angle

*Asked in: Paper II Oct 2008 — RGUHS MD/MS Anatomy*

### Definition / Introduction

The facial angle is a craniometric index that expresses the degree of forward projection (prognathism) of the facial skeleton relative to the base of the skull, and is used to compare the relative proportion between the viscerocranium (facial skeleton) and the neurocranium (calvaria, the brain-case). It is measured on the dried skull, in norma lateralis, as the angle included between a line joining the nasion to the basion and a line joining the basion to the prosthion. The concept is historically credited to the Dutch anatomist Petrus Camper (1722–1789), whose name is also attached to the reference "Camper's line/plane" (ala of the nose to the tragus), and the index remains a classical tool of physical and forensic anthropology for comparing races, sexes, and even fossil hominids.

### Craniometric landmarks required to construct the angle

| Landmark       | Location                                                                                                                                                                             |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nasion (N)     | Median point at the root of the nose, where the internasal suture meets the fronto-nasal suture.                                                                                     |
| Glabella       | Median elevation connecting the two superciliary arches, just above the nasion; used to orient the profile.                                                                          |
| Basion (Ba)    | The anterior margin of the foramen magnum (midline).                                                                                                                                 |
| Prosthion (Pr) | The central point on the alveolar margin of the maxilla, between the two upper central incisors.                                                                                     |
| Gnathion       | Median point on the lower border of the body of the mandible ("mental point") — a related landmark for the mandible/gonial region, not itself used in the facial-angle construction. |
| Gonion         | The point at the angle of the mandible.                                                                                                                                              |

For orientation of the skull before any craniometric measurement, either the **Frankfurt horizontal plane** (infra-orbital margin to the upper margin of the external acoustic meatus) or **Reid's base line** (infra-orbital margin to the centre of the external acoustic meatus, i.e. the auricular point) is conventionally used as the horizontal reference.

### Definition and construction of the facial angle

- ▶ Two lines are drawn on the skull in norma lateralis: (i) the **naso-basilar line**, from the nasion to the basion; (ii) the **basio-alveolar line**, from the basion to the prosthion.
- ▶ The **facial angle** is the angle included between these two lines at their point of intersection, the basion.
- ▶ It is, in effect, a measure of the angle between the neurocranium (represented by the nasion–basion line running along the cranial base) and the viscerocranium (represented by the basion–

prosthion line running to the upper jaw); the two components are inversely proportional to one another — the more one is developed, the less prominent the other.

- ▶ A **wider (more obtuse) angle** corresponds to a more vertical, retracted facial profile, i.e. **orthognathous**; a **narrower (more acute) angle** corresponds to greater forward projection of the jaws, i.e. **prognathous**.

## Biological and evolutionary significance

- ▶ The facial angle is used as a **rough index of the degree of development of the brain**, because it reflects the balance between growth of the facial skeleton and growth of the cranial vault that houses the brain.
- ▶ Comparative trend: the angle is **smallest in anthropoids, larger in the less-evolved ("lower") human races, and largest (most obtuse, most vertical-faced) in the most-evolved modern human races** — i.e. facial prognathism decreases, and the facial angle widens, with increasing evolutionary/cranial development.
- ▶ This mirrors the reciprocal pattern of craniofacial growth seen through hominid evolution: as relative neurocranial volume increased, the jaws and facial skeleton became comparatively smaller and less protrusive.
- ▶ The facial angle is used, together with the **cephalic index** ( $\text{breadth} \times 100 / \text{length of the skull}$  — dolichocephalic  $\leq 75$ , mesaticephalic  $75-80$ , brachycephalic  $> 80$ ), as one of the standard indices of comparative and racial craniometry, though the two measure different things (a ratio of breadth to length versus an angle of facial projection).

## Racial and comparative craniofacial variation

| Group     | Typical degree of prognathism                                          | Effect on facial profile                                |
|-----------|------------------------------------------------------------------------|---------------------------------------------------------|
| Caucasoid | Little prognathism; steep forehead, prominent chin, long narrow palate | More orthognathous — wider (more vertical) facial angle |
| Negroid   | Strong alveolar prognathism, wide nasal aperture, larger teeth         | More prognathous — narrower facial angle                |
| Mongoloid | Moderate prognathism, tented nasal root, forward-rotated mandible      | Intermediate facial angle                               |

The classification of humans into discrete "races" purely by craniofacial morphology is now recognised as an oversimplification, with considerable overlap between groups; nevertheless, the descriptive differences in the degree of prognathism above remain of practical use in forensic anthropology when attempting to assign a "most-likely" ancestral group to unidentified skeletal remains.

## Related craniometric/eponymous terms — do not confuse with facial angle

- ▶ **Camper's line**: the line running from the inferior border of the ala of the nose to the superior border of the tragus of the ear — a soft-tissue, roughly horizontal reference line.

- ▶ **Camper's plane:** the plane defined bilaterally by the alae of the nose and the superior borders of both tragi; this horizontal was the reference against which Camper's own original facial-profile angle was measured, distinct from — though sharing the same eponym and underlying concept as — the dry-skull nasion–basion–prosthion construction used in modern craniometry.
- ▶ **Cephalic index:** a ratio of skull breadth to length, not an angle.
- ▶ **Gonial (mandibular) angle:** the angle at the gonion (angle of the mandible) — a separate craniometric feature that becomes more obtuse in old age with tooth loss and alveolar resorption, altering the lower-facial contour; this is not the same measurement as the facial angle proper.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Draw the skull in **norma lateralis** (right lateral view), oriented with the Frankfurt horizontal (infra-orbital margin to upper margin of external acoustic meatus) parallel to the base line.
- ▶ Mark and label three points: **Nasion (N)** at the root of the nose; **Basion (Ba)** at the anterior margin of the foramen magnum; **Prosthion (Pr)** on the upper alveolar margin between the central incisors.
- ▶ Draw **Line 1: N → Ba** (naso-basilar line) and **Line 2: Ba → Pr** (basio-alveolar line).
- ▶ Mark the **facial angle** as the angle enclosed between these two lines at their meeting point, Basion, with a small arc and the label "Facial angle."
- ▶ Optionally add **Glabella** (above nasion) and, as a dotted reference line for orientation, **Camper's line** (ala of nose to tragus).

### Applied / Clinical anatomy

- ▶ **Forensic and anthropological identification:** skull morphology, including the degree of facial prognathism/facial angle, is used along with other craniometric parameters in the medico-legal identification of skeletal remains (assigning probable ancestry, age, and sex), and in craniofacial "superimposition" and forensic facial-reconstruction techniques that match a recovered skull to an ante-mortem photograph.
- ▶ **Comparative and evolutionary anatomy:** the facial angle is a classic teaching tool for tracing hominid evolution — the angle widens (the jaw becomes progressively less prognathous and the forehead more vertical) with increasing cranial capacity from earlier hominins to modern *Homo sapiens*.
- ▶ **Dental / orthodontic relevance:** the underlying principle of relating jaw position to the cranial base is the conceptual ancestor of modern lateral cephalometric analysis (e.g. the SNA, SNB and ANB angles measured on a lateral skull radiograph/cephalogram), which is used clinically to classify skeletal Class I/II/III jaw relationships and to plan orthodontic or orthognathic surgical treatment.
- ▶ **Age-related change:** with progressive loss of teeth and alveolar-bone resorption in old age, the mandible becomes relatively prognathic ("mandibular prognathism"/over-closure) and the **mandibular (gonial) angle becomes more obtuse**, visibly altering the facial profile even though



the skeletal facial angle measured on fixed cranial points is otherwise a stable feature of an individual skull.

- ▶ **Sex differences:** the male facial skeleton is generally more rugged, with more prominent muscular markings and a more angular mandible than the smoother, lighter female skull — a feature assessed alongside craniometric indices such as the facial angle during skeletal sexing.

### High-yield exam pointers

- ▶ Facial angle = the angle at the **basion**, between the **nasion–basion line** and the **basion–prosthion line**.
- ▶ Landmarks to know: **Nasion** (root of nose), **Basion** (anterior margin of foramen magnum), **Prosthion** (upper alveolar point between central incisors).
- ▶ It is a **rough index of brain development**, reflecting the inverse relationship between the viscerocranium and neurocranium.
- ▶ Comparative trend: smallest in **anthropoids** → larger in "lower" human races → largest (most vertical profile) in the most-evolved modern races.
- ▶ Eponym: **Petrus Camper** (Dutch anatomist, 1722–1789); **Camper's line** = ala of nose to tragus; **Camper's plane** = the bilateral version of the same line.
- ▶ Do **not** confuse with the **cephalic index** (a breadth : length ratio, not an angle) or the **gonial/mandibular angle** (the angle of the jaw, which becomes more obtuse in edentulous old age).
- ▶ **Orthognathous** = more vertical, less prognathic profile (wider facial angle); **prognathous** = more forward-projecting jaws (more acute facial angle).
- ▶ Applied uses: forensic/medico-legal skeletal identification, comparative and evolutionary anthropology, and — conceptually — the basis of modern cephalometric jaw-relation angles used in orthodontics.

### SOURCE & COVERAGE

BD Chaurasia's Human Anatomy, Vol 3–4, 8e (Introduction and Osteology chapter — definition of the facial angle, craniometric landmarks, cephalic index); Gray's Anatomy (Standring) 41e (Eponyms appendix — Camper's line/plane and Petrus Camper; Head and Neck chapter — comparative racial craniofacial variation and forensic facial-reconstruction/superimposition); IB Singh's Textbook of Anatomy Vol 3, 6e and Moore's Clinically Oriented Anatomy 9e (mandibular prognathism and alveolar resorption in edentulous ageing).

**Coverage note:** facial angle is a physical-anthropology/craniometric topic covered only briefly (a single short paragraph) in Gray's 41e; BD Chaurasia's Vol 3–4 8e osteology chapter is the primary source used here for the operational definition and landmarks. Precise degree cut-offs sometimes quoted in physical-anthropology texts for "orthognathous/mesognathous/prognathous" grades are not given in the available corpus and have therefore been omitted rather than invented.



## Fossil evidences in modern man

Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** Physical (biological) anthropology is the branch of anatomical science that studies man's evolutionary relationship to other primates through the comparative morphology of extinct and extant forms — the "content" of this science being man's descent traced through a chain of fossil hominids leading to anatomically modern *Homo sapiens*. "Fossil evidences in modern man" therefore denotes the composite skeletal, archaeological (cultural) and molecular fossil record that documents the phylogenetic pathway from Miocene ape ancestors, through the Australopithecines and archaic *Homo*, to Cro-Magnon man — the direct ancestor of living man. This evidence is built from comparative taxonomy, comparative osteology and, most recently, ancient-DNA analysis.

## Taxonomic position and defining anatomical characters of modern man

Man's place in the animal kingdom is itself the starting point of the fossil argument — each taxon reflects an anatomical character that becomes progressively more refined in the fossil sequence.

| Taxon     | Name       | Defining feature                                                       |
|-----------|------------|------------------------------------------------------------------------|
| Kingdom   | Animalia   | Eukaryotic cells, no cell wall or photosynthetic pigment               |
| Phylum    | Chordata   | Notochord and pharyngeal pouches present                               |
| Subphylum | Vertebrata | Vertebral column present                                               |
| Class     | Mammalia   | Mammary glands and hair                                                |
| Order     | Primata    | Well-developed brain, prehensile hands                                 |
| Family    | Hominidae  | Large cerebrum, bipedal locomotion                                     |
| Genus     | Homo       | Flattened face, prominent chin, nose with inferiorly-directed nostrils |
| Species   | sapiens    | Largest cerebrum of the genus                                          |

Anatomical traits unique to man, each of which is tracked backward through the fossil record as an "evolutionary marker":

- ▶ A large, well-developed brain (adult weight 1350–1400 g) — the highest brain-to-body-weight ratio among primates.
- ▶ Bipedal locomotion — standing and walking on two limbs, with reciprocal arm swing.
- ▶ An opposable thumb — a versatile, precision-grip hand adapted for tool use.
- ▶ Well-developed articulate speech.
- ▶ Stereoscopic (binocular) vision.
- ▶ Erect posture and a prominent bony chin.

## Chronological fossil hominid record

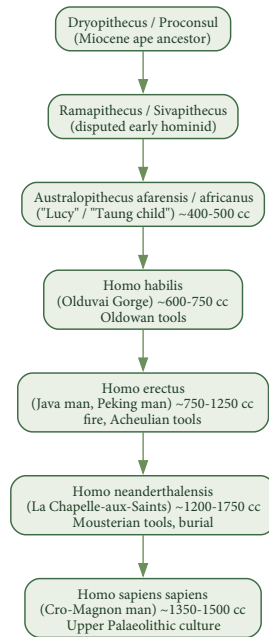
The fossil case for man's ancestry rests on a sequence of type fossils, each recovered from a named site and dated, showing progressive approach to the modern anatomical pattern.

| Fossil form                                       | Approx. antiquity  | Type fossil / site (discoverer)                | Cranial capacity | Key evidence contributed                                                                                                                                                                    |
|---------------------------------------------------|--------------------|------------------------------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dryopithecus / Proconsul                          | Miocene, ~20–9 mya | East African and European sites                | Ape-sized        | Generalised dentition; regarded as common ancestral stock of great apes and hominids (Vishram Singh's revision table names <b>Proconsul</b> as the oldest fossil credited to man's lineage) |
| Ramapithecus (Sivapithecus)                       | ~14–8 mya          | Siwalik hills (India/Pakistan)                 | Ape-sized        | Once proposed as the earliest hominid on jaw/tooth form; now reassigned to the great-ape (orangutan) lineage                                                                                |
| <i>Australopithecus afarensis</i> ("Lucy")        | ~3.9–2.9 mya       | Hadar, Ethiopia (Johanson, 1974)               | ~400–500 cc      | Pelvis, femur and the Laetoli footprints (~3.6 mya) prove obligate bipedalism despite an ape-sized brain                                                                                    |
| <i>Australopithecus africanus</i> ("Taung child") | ~3–2 mya           | Taung, South Africa (Dart, 1924)               | ~450 cc          | Anteriorly-placed foramen magnum — earliest skeletal marker of upright posture                                                                                                              |
| <i>Homo habilis</i> ("handy man")                 | ~2.5–1.5 mya       | Olduvai Gorge, Tanzania (L. & M. Leakey, 1964) | ~600–750 cc      | Associated with the earliest recognised stone (Oldowan) tools                                                                                                                               |

| Fossil form                                  | Approx. antiquity   | Type fossil / site (discoverer)                                                                                                                             | Cranial capacity                   | Key evidence contributed                                                                                                                                                                     |
|----------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Homo erectus</i>                          | ~1.8 mya–300,000 yr | Java man/ <i>Pithecanthropus erectus</i> (Dubois, 1891, Trinil); Peking man/ <i>Sinanthropus pekinensis</i> (Black, 1927, Zhoukoudian); Turkana boy (Kenya) | ~750–1250 cc                       | Controlled use of fire; Acheulian hand-axes; first hominid to migrate out of Africa                                                                                                          |
| <i>Homo neanderthalensis</i>                 | ~400,000–40,000 yr  | La Chapelle-aux-Saints, France (1908)                                                                                                                       | ~1200–1750 cc                      | Robust build, occipital "bun", Mousterian flake tools, earliest deliberate burials                                                                                                           |
| <i>Homo sapiens sapiens</i> (Cro-Magnon man) | ~40,000 yr–present  | Cro-Magnon rock-shelter, Les Eyzies, France (1868)                                                                                                          | ~1350–1500 cc (range 1200–1600 cc) | Fully modern skeleton; per Vishram Singh's General Anatomy, <b>Cro-Magnon is the direct ancestor of modern living man</b> ; Upper Palaeolithic blade tools, cave art, personal ornamentation |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A vertical lineage chart from Miocene ape to modern man; label each box with the fossil/type name + site, approximate cranial capacity, and one diagnostic feature (bipedalism / tools / fire / burial / culture) as tabulated above:



*Fossil evidences in modern man*

## Skeletal (morphological) trends across the fossil record

Comparative osteology of the type fossils above reveals a consistent direction of change, which is itself cited as anatomical evidence for the evolutionary sequence.

| Feature            | Early hominid pattern                         | Trend through the fossil record                                    | Modern Homo sapiens                                    |
|--------------------|-----------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------|
| Cranial capacity   | ~400–500 cc (Australopithecus)                | Progressive increase                                               | ~1350–1500 cc (range 1200–1600 cc)                     |
| Forehead / vault   | Low, sloping, flattened                       | Vault rounds and rises                                             | High, vertical, globular                               |
| Supraorbital ridge | Massive, continuous (H. erectus, Neanderthal) | Progressively reduced                                              | Slight, discontinuous; separate supraorbital foramina  |
| Facial profile     | Prognathic (jaws project forward)             | Orthognathism increases                                            | Orthognathic (flat) face                               |
| Mandible / chin    | Receding, no bony chin                        | Mental protuberance appears late                                   | True bony chin — a feature unique to <i>H. sapiens</i> |
| Dentition          | Larger canines, diastema present              | Canine and molar size reduces                                      | Small canines, no diastema, parabolic dental arch      |
| Foramen magnum     | Posteriorly placed (as in quadrupedal apes)   | Shifts to a central/anterior position from Australopithecus onward | Centrally placed — marker of erect bipedal posture     |
| Vertebral column   | Single (C-shaped) curve                       | Cervical and lumbar lordoses develop                               | Double S-shaped curve for erect stance                 |

| Feature                                        | Early hominid pattern                | Trend through the fossil record                 | Modern Homo sapiens                                                                                               |
|------------------------------------------------|--------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Pelvis                                         | Narrow, elongated ilium              | Ilium shortens, broadens, blade turns laterally | Short, broad, bowl-shaped — supports viscera and the gluteal abductor mechanism of single-limb stance             |
| Femur                                          | Vertical shaft, no valgus angle      | Bicondylar (valgus) angle develops              | Knees brought under the body's centre of gravity                                                                  |
| Foot                                           | Grasping, opposable hallux           | Hallux adducts; arches develop                  | In-line, non-opposable hallux; longitudinal and transverse arches (confirmed by the Laetoli footprints, ~3.6 mya) |
| Intermembral index (upper : lower limb length) | >100 (forelimb-dominant, as in apes) | Index falls through the sequence                | ~70–75 (hindlimb-dominant)                                                                                        |

### Cultural (archaeological) evidence — tool industries and behaviour

Stone-tool and behavioural evidence, recovered alongside the skeletal fossils, corroborates the same evolutionary sequence and additionally documents the growth of cognition.

| Culture / industry                            | Associated hominid                       | Approx. age         | Key feature                                                                                                   |
|-----------------------------------------------|------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------|
| Oldowan (pebble/chopper tools)                | <i>Homo habilis</i>                      | ~2.5 mya            | Earliest recognised stone tools                                                                               |
| Acheulian (bifacial hand-axes)                | <i>Homo erectus</i>                      | ~1.7 mya–300,000 yr | Symmetric bifacial tools; controlled use of fire                                                              |
| Mousterian (prepared-core flake tools)        | <i>Homo neanderthalensis</i>             | ~300,000–40,000 yr  | Levallois technique; earliest deliberate burials — first evidence of ritual/symbolic behaviour                |
| Upper Palaeolithic (blade, bone/antler tools) | <i>Homo sapiens sapiens</i> (Cro-Magnon) | ~40,000 yr onward   | Blade technology, personal ornaments, cave art (e.g. Lascaux, Altamira) — evidence of full symbolic cognition |

### Molecular / genetic fossil evidence

Ancient-DNA analysis has added a molecular layer of "fossil" evidence to the skeletal and cultural record:

- DNA sequenced directly from the bones of three Neanderthal individuals who died approximately 38,000 years ago in Europe showed that the most recent common ancestor of

Neanderthals and *Homo sapiens* lived in Africa over 200,000 years ago — well before Neanderthals migrated out of Africa into Europe and the Middle East.

- ▶ Comparison of this ancient Neanderthal genome with modern human genomes revealed that approximately **1–4% of the DNA of modern Europeans and Asians, but not of Africans**, matches Neanderthal DNA — statistically dated to an admixture event around 50,000 years ago, after modern humans had already left Africa. This absence of Neanderthal ancestry in modern Africans is itself a genetic fossil marker of the "Out of Africa" dispersal of modern man.
- ▶ Comparable ancient-genome studies have identified a second archaic population, the Denisovans, whose DNA similarly persists at low levels in some modern Asian and Oceanic populations — reinforcing that the genome of modern man is a mosaic retaining traces of extinct hominid lineages, rather than a "clean" isolated line.

### Applied / Clinical anatomy

- ▶ **Forensic/medico-legal anthropology:** the same craniometric methods used to classify fossil hominids (cranial capacity, cephalic index, supraorbital and mandibular morphology) are applied clinically to establish age, sex, stature and ancestry from unidentified skeletal remains.
- ▶ **Vestigial ("living fossil") structures:** the vermiform appendix, coccyx, plica semilunaris of the conjunctiva, palmaris longus and auricular muscles are anatomical remnants of the ancestral primate body plan and are examined clinically for absence/anomaly.
- ▶ **Third-molar impaction:** reduction of jaw length has outpaced reduction in tooth number through the fossil sequence, explaining the high prevalence of impacted third molars in modern man — a directly applied clinical consequence of hominid jaw evolution.
- ▶ **Atavistic skeletal variants:** a persistent metopic suture or a cervical rib are explained on an evolutionary/developmental basis and carry surgical relevance (e.g. thoracic outlet syndrome from a cervical rib).
- ▶ **Museum teaching collections:** plaster-cast reconstructions of the type fossils — the Ape-man of Java, the Ape-man of Peking, Neanderthal man and Cro-Magnon man — are standard "Physical Anthropology" exhibits in anatomy museums, used for undergraduate and postgraduate teaching of human evolution.

### High-yield exam pointers

- ▶ Physical anthropology is the biological study of man and his evolutionary relationship to apes and ape-men, based on comparative structural features.
- ▶ Man's taxonomic position: Kingdom Animalia → Phylum Chordata → Class Mammalia → Order Primata → Family Hominidae → Genus *Homo* → Species *sapiens*.
- ▶ Two most important defining characters of man: a highly developed brain and an opposable thumb; erect bipedal gait, articulate speech and stereoscopic vision complete the set.
- ▶ Evolutionary sequence: Dryopithecus/Proconsul → Ramapithecus → Australopithecus → *Homo habilis* → *Homo erectus* → *Homo neanderthalensis* → *Homo sapiens sapiens* (Cro-Magnon — the direct ancestor of modern man).



- ▶ Key named fossils: "Lucy" (*A. afarensis*, Ethiopia), "Taung child" (*A. africanus*, South Africa), Java man and Peking man (*H. erectus*), La Chapelle-aux-Saints skeleton (Neanderthal), Cro-Magnon man (*H. sapiens*).
- ▶ Cranial capacity rises from ~400–500 cc (Australopithecus) to ~1500 cc (modern man; accepted range 1200–1600 cc).
- ▶ Bipedalism evidence: anteriorly-placed foramen magnum, broad bowl-shaped pelvis, valgus femoral angle, and the Laetoli footprints (~3.6 mya).
- ▶ Tool-culture sequence: Oldowan → Acheulian → Mousterian → Upper Palaeolithic (blade tools and cave art).
- ▶ Molecular evidence: ancient Neanderthal DNA shows 1–4% admixture in modern non-African populations (~50,000 years ago), against a Neanderthal–sapiens common ancestor >200,000 years old in Africa.

### SOURCE & COVERAGE

Vishram Singh — General Anatomy, 4e (taxonomic classification table, defining human characters, "Golden Facts" quick-revision points on cranial capacity, Proconsul and Cro-Magnon); Thompson & Thompson — Genetics in Medicine, 8e (ancient Neanderthal-DNA sequencing and admixture data); Handbook of Museum Technique (Govt Museum, Chennai) (definition of physical anthropology, named fossil-hominid museum exhibits — Ape-man of Java, Ape-man of Peking, Neanderthal man, Cro-Magnon man).

**Coverage note:** this topic is human evolution/physical anthropology and, as flagged in the spec, is not carried as a dedicated chapter in Gray's Anatomy (Standring) 41e or in Gangane's Human Genetics 5e — both were searched but yielded no dedicated content. The named type-fossils, sites, discoverers and dates given above (Lucy, Taung child, Java man, Peking man, La Chapelle-aux-Saints, tool-culture sequence) reflect standard, universally-taught palaeoanthropology rather than a single verbatim RGUHS-library citation, and are combined here with the anatomy-specific facts actually confirmed in the corpus (taxonomy, defining human characters, cranial-capacity figures, and the Neanderthal ancient-DNA evidence).



## Gender differences in the bony pelvis

Asked in: Paper II Nov 2016 — RGUHS MD/MS Anatomy

**Definition / Introduction** — The bony pelvis is the ring formed by the two hip bones (ilium, ischium, pubis), the sacrum and the coccyx, joined at the paired sacroiliac joints and the pubic symphysis. Of every bone in the human skeleton, the pelvis shows the **most marked sexual dimorphism**, so much so that it is the single most reliable bone for medico-legal sexing of skeletal remains. The differences arise from two functional determinants: the heavier build and stronger muscles of the male, which produce thicker bone and more prominent markings, and the adaptation of the female lesser (true) pelvis to the mechanics of **parturition**, which makes the female pelvic canal comparatively wider and shallower.

### Basis and timing of the dimorphism

- ▶ Sexual differences are conventionally divided into **metrical** (measurable diameters and angles) and **non-metrical** (morphological/shape) features; the range of most features overlaps between the sexes, so no single feature is decisive — all must be assessed together.
- ▶ Distinction begins even in **fetal life**, particularly in the subpubic arch.
- ▶ In infancy, overall pelvic dimensions are already greater in males, while the size of the pelvic cavity is usually greater in females; this pattern persists through childhood, with the difference maximal at about 22 months.
- ▶ The greatest divergence develops after **puberty**, driven by the actions of sex steroids on pelvic growth, and pelvic shape continues to change gradually throughout adult life.
- ▶ In forensic practice, combining a range of metrical pelvic data gives about **95% accuracy** in sex determination; if the rest of the skeleton is also available, accuracy approaches 100%.

### General architecture of the pelvis

| Feature                    | Male                                                         | Female                                                           |
|----------------------------|--------------------------------------------------------------|------------------------------------------------------------------|
| General build              | Thick, heavy; muscle/ligament markings prominent             | Thin, light; markings smoother                                   |
| Greater (false) pelvis     | Deep                                                         | Shallow                                                          |
| Lesser (true) pelvic canal | Narrow and deep, tapering — a "long segment of a short cone" | Wide and shallow, cylindrical — a "short segment of a long cone" |
| Pelvic inlet outline       | Heart-shaped (indented by the jutting sacral promontory)     | Transversely oval / rounded                                      |
| Pelvic outlet              | Comparatively small                                          | Comparatively large                                              |

□ Fig 13.1 — ■ (A) Male and (B) female pelvis. (Vishram Singh — *Textbook of Anatomy Vol 2 — 4e*, p.595)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw paired anterior-view outlines of a male and a female bony pelvis, side by side, and label:

- ▶ Iliac crest and ala (more flared/everted in female)
- ▶ Pelvic inlet outline — heart-shaped (male) vs oval/rounded (female)
- ▶ Sacrum — long & narrow (male) vs short & wide (female)
- ▶ Acetabulum and its distance from the pubic symphysis
- ▶ Obturator foramen outline
- ▶ Subpubic angle (mark 50–60° male / 80–90° female with the two converging ischiopubic rami)
- ▶ Greater sciatic notch (mark ~50° male / ~75° female)
- ▶ Ischial tuberosities and ischial spines (closer/inturned in male)

### Regional (bone-by-bone) differences

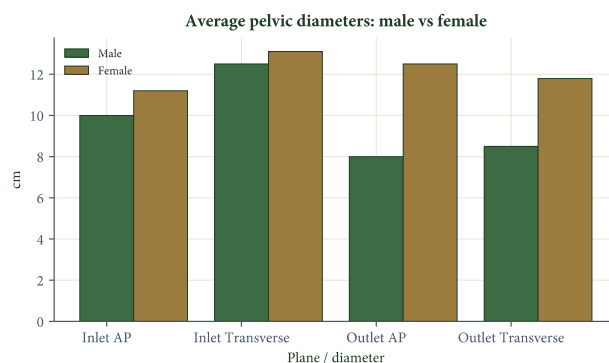
| Region                                      | Male                                                                               | Female                                                                                                              |
|---------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Iliac crest/ala                             | More rugged, curves medially anteriorly; ala ascends more → deeper iliac fossa     | Less curved; ala more vertical, ascends less → shallower iliac fossa (contributes to the prominence of female hips) |
| Sacrum                                      | Long, narrow; evenly and smoothly curved pelvic surface; often exceeds 5 segments  | Short, wide; less curved, with a flatter mid-segment; abruptly curved pelvic surface                                |
| Sacral index (breadth ÷ length × 100)       | ≈ 105%                                                                             | ≈ 115%                                                                                                              |
| Sacral base (articular facet for L5 + disc) | Occupies a larger share (approaching half) of the sacral base width                | Occupies about one-third or less of the sacral base width (sacrum relatively broader)                               |
| Sacroiliac (auricular) surface              | Larger; extends down to about the lower border of S3                               | Smaller and more oblique; extends only to about the upper border of S3                                              |
| Acetabulum                                  | Large; its diameter ≈ the distance from its anterior margin to the pubic symphysis | Smaller; that distance is distinctly greater than the acetabular diameter                                           |
| Obturator foramen                           | More ovoid                                                                         | Relatively more triangular (reduced height of pubic symphysis)                                                      |
| Ischial spines                              | Closer together, more inturned                                                     | More widely separated, less inturned                                                                                |
| Ischial tuberosities                        | Turned inward — smaller outlet                                                     | Everted outward — larger outlet                                                                                     |
| Ischiopubic rami (near symphysis)           | Rough, everted edge for attachment of the crura of the penis                       | Lightly built, narrow; crural attachment poorly marked                                                              |

| Region                                                                                  | Male                              | Female                                                       |
|-----------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|
| Pubic arch / subpubic angle                                                             | Narrow, angular — 50–60°          | Wide, rounded — 80–90° (most important single discriminator) |
| Greater sciatic notch                                                                   | Narrow — mean $\approx$ 50°       | Wide — mean $\approx$ 74–75°                                 |
| Preauricular sulcus                                                                     | Faint or absent                   | Deep and well marked                                         |
| Chilotic line (iliopubic eminence<br>→ nearest point on auricular margin → iliac crest) | Sacral (posterior) segment longer | Pelvic (anterior) segment longer                             |

## Pelvic inlet, cavity and outlet — dimensions

Average diameters (cm), sexed comparison:

| Plane      | Diameter                         | Male | Female |
|------------|----------------------------------|------|--------|
| Inlet      | Anteroposterior (true conjugate) | 10.0 | 11.2   |
| Inlet      | Transverse (maximum)             | 12.5 | 13.1   |
| Inlet      | Oblique                          | 12.0 | 12.5   |
| Mid-cavity | Anteroposterior                  | 10.5 | 13.0   |
| Mid-cavity | Transverse                       | 12.0 | 12.5   |
| Mid-cavity | Oblique                          | 11.0 | 13.1   |
| Outlet     | Anteroposterior                  | 8.0  | 12.5   |
| Outlet     | Transverse (bituberous)          | 8.5  | 11.8   |
| Outlet     | Oblique                          | 10.0 | 11.8   |



Comparative pelvic diameters (Gray's Anatomy 41e)

- All three inlet diameters, and especially both outlet diameters, are consistently larger in the female — the divergence is greatest at the outlet, least at the brim.
- The **plane of greatest pelvic dimensions** (obstetric concept) lies between the inlet and mid-cavity; the **plane of least pelvic dimensions** is at mid-cavity, its interspinous (bi-ischial-spinous)

transverse diameter being only about 9.5 cm in the female — just enough to admit the fetal biparietal diameter (~9 cm), making this the commonest site of obstructed descent.

- These measurements vary with the individual and with racial/population group.

### Morphological (Caldwell–Moloy) classification of the pelvic inlet

| Type         | Inlet shape                                                      | Approx. frequency | Remarks                                                                                                                                                  |
|--------------|------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gynaecoid    | Round/slightly oval; transverse diameter placed well forward     | ≈ 41.4%           | The "normal" female pelvis; permits normal vaginal delivery                                                                                              |
| Android      | Triangular; greatest transverse diameter close to the promontory | ≈ 32.5%           | Resembles the male pelvis; narrow subpubic angle and sciatic notch make the cavity funnel-shaped with a contracted outlet                                |
| Anthropoid   | Oval, with a long anteroposterior diameter                       | ≈ 23.5%           | Resembles the pelvis of anthropoid apes; commoner in women of African ancestry; may coexist with a "high-assimilation" pelvis (an extra lumbar vertebra) |
| Platypelloid | Flattened, wide transversely, short anteroposteriorly            | ≈ 2.6%            | Rare; historically associated with rickets                                                                                                               |

Only the gynaecoid type is fully favourable for normal labour; the android, anthropoid and platypelloid types represent varieties of contracted pelvis and predispose to prolonged or obstructed labour.

### Applied / Clinical anatomy

- **Forensic/medico-legal sexing:** the pelvis is the single most reliable bone for sex determination from skeletal remains; the subpubic angle and greater sciatic notch are the most discriminating individual features, and combining several metrical indices gives ~95% accuracy.
- **Obstetric pelvimetry:** clinical/radiographic (or CT/MRI) measurement of inlet, mid-cavity and outlet diameters helps predict cephalopelvic disproportion; the interspinous diameter (plane of least pelvic dimensions) is the critical bottleneck for descent of the fetal head.
- **Contracted pelvis:** the android, anthropoid and platypelloid variants each narrow one or more key diameters (outlet, transverse or anteroposterior respectively) and may necessitate instrumental delivery or caesarean section; the platypelloid type was classically associated with rickets.
- **Radiological correlation:** anteroposterior pelvic radiographs and CT are used to assess pelvic type and diameters when clinical pelvimetry is inconclusive, and to identify sex from an isolated pelvis in forensic/archaeological material.

- ▶ **Age-related change:** in elderly women the upper iliac fossae become thin and translucent from osteoporosis, and overall pelvic shape continues to remodel throughout life, which must be borne in mind when sexing an aged or pathological specimen.

### High-yield exam pointers

- ▶ Pelvis = most sexually dimorphic bone in the body; ~95% accuracy in sexing when metrical features are combined.
- ▶ **Subpubic angle** is the single most important discriminator: narrow/angular 50–60° (male) vs wide/rounded 80–90° (female).
- ▶ **Greater sciatic notch:** narrow, ~50° (male) vs wide, ~75° (female).
- ▶ Mnemonic for the pelvic canal: male = "long segment of a short cone" (narrow, deep); female = "short segment of a long cone" (wide, shallow).
- ▶ Pelvic inlet: heart-shaped (male) vs transversely oval/rounded (female); every inlet, mid-cavity and outlet diameter is equal to or larger in the female.
- ▶ Only the **gynaecoid** pelvis (Caldwell–Moloy, ≈41%) allows a normal vaginal delivery; android, anthropoid and platypelloid are varieties of contracted pelvis.
- ▶ Preauricular sulcus is deeper in the female; the chiotic line's pelvic segment exceeds its sacral segment in the female (reverse in the male).
- ▶ Sacrum: long, narrow, evenly curved, often >5 segments in the male vs short, wide, flat mid-segment in the female; sacral index ≈105% (male) vs ≈115% (female).
- ▶ Dimorphism starts in fetal life (subpubic arch) but is maximal only after puberty.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2 8e; Vishram Singh — Textbook of Anatomy Vol 2 4e; IB Singh — Textbook of Anatomy Vol 1 6e; Moore's Clinically Oriented Anatomy 9e.



## GIFT

*Asked in: Paper II Nov 2018 — RGUHS MD/MS Anatomy*

### Definition / Introduction

**Gamete intrafallopian transfer (GIFT)** is an assisted reproductive technology (ART) in which harvested oocytes and prepared (capacitated) spermatozoa are placed together, by laparoscope, directly into the **ampulla of the uterine (fallopian) tube** — the same site at which fertilisation occurs naturally — so that fertilisation and the earliest cleavage divisions proceed **in vivo** rather than in a culture dish. It differs fundamentally from in vitro fertilisation (IVF), in which fertilisation is achieved outside the body and only the resulting embryo is transferred to the uterus. GIFT requires a functioning, patent uterine tube and is used mainly for unexplained infertility or mild sperm dysfunction where tubal transport and the ampullary environment can still support fertilisation.

## 1. Definition and principle

- ▶ **GIFT = direct laparoscopic placement of collected oocytes and processed sperm into the ampullary part of the uterine tube**, so that gamete fusion, and all subsequent early development up to tubal transport and implantation, occurs by the **normal physiological route**.
- ▶ **Rationale:** fertilisation normally occurs in the ampullary region of the uterine tube, within about 24 hours of ovulation. Only capacitated spermatozoa can fertilise the oocyte — capacitation is a period of conditioning in the female genital tract (removal of a glycoprotein coat and seminal plasma proteins from the sperm plasma membrane) that takes approximately 7 hours and occurs mainly in the uterus and uterine tube. GIFT exploits this by introducing **precapacitated** sperm together with the oocytes straight into the ampulla, allowing the tube's own secretions/epithelium and the normal fertilisation cascade (capacitation completion, acrosome reaction, sperm–zona binding and fusion) to take over from that point.
- ▶ Because fertilisation and the first few cleavage divisions occur inside the tube exactly as in a natural conception, GIFT is sometimes termed "**assisted in vivo fertilisation**."

## 2. Indications and prerequisites

- ▶ **Essential prerequisite:** the ovary and **at least one uterine tube must be anatomically and functionally normal (patent, with intact fimbrial pick-up and ciliary/muscular transport)** — GIFT cannot be used if both tubes are blocked or absent.
- ▶ **Indications:**
  - Unexplained infertility (couple with a normal-appearing reproductive tract but failed natural conception).
  - Mild male-factor infertility — an innate deficiency of spermatozoon motility (where sperm cannot reach the ampulla in adequate numbers/time on their own), provided sperm numbers/quality are otherwise adequate for fertilisation once placed at the site.
  - Failure of simpler measures (ovulation induction, intrauterine insemination) in a couple with patent tubes.
- ▶ **Not suitable for:** bilateral tubal block/damage, severe male-factor infertility requiring ICSI, or when in vitro embryo screening (PGD/PGS) is required before transfer.

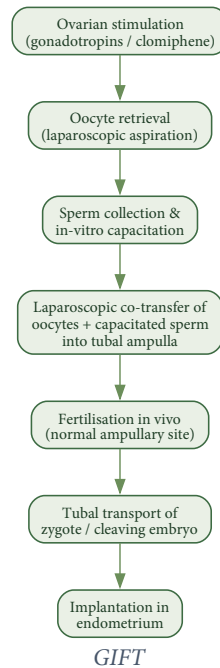
## 3. Technique

GIFT is carried out in four linked stages:

- ▶ **Ovarian stimulation and monitoring** — gonadotropins (or clomiphene citrate) are given to recruit multiple mature follicles, monitored by follicle tracking, exactly as for IVF.
- ▶ **Oocyte retrieval** — mature oocytes are aspirated from the stimulated ovarian follicles at **laparoscopy** (or occasionally by ultrasound-guided needle aspiration).
- ▶ **Sperm collection and capacitation** — semen is collected and the spermatozoa are washed/processed in vitro to induce capacitation, so they are placed in a fertilisation-ready state.
- ▶ **Laparoscopic gamete transfer** — the harvested oocytes, together with the precapacitated spermatozoa, are loaded into a laparoscopic transfer catheter and introduced together directly into the **ampulla of the uterine tube**; fertilisation then takes place in vivo at its usual location,



and the resulting zygote/early embryo undergoes normal cleavage while being transported towards the uterine cavity for implantation, exactly as in a natural pregnancy.



#### 4. Applied embryology — why the ampulla is the transfer site

□ Fig 18.9 — Parts of the uterine tube. (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.754)

- ▶ The uterine tube has four parts, lateral to medial — **infundibulum** (fimbriated, closely related to the ovary), **ampulla** (widest, thin-walled, longest part — the normal site of fertilisation), **isthmus** (narrow, muscular), and **intramural part** (traversing the uterine wall).
- ▶ GIFT deliberately targets the **ampulla**, not the uterine cavity, because that is where the oocyte is normally held by tubal peristalsis/ciliary action long enough (~24 hours) for capacitated sperm to reach and fertilise it; placing the gametes here reproduces the natural sequence rather than substituting a laboratory dish for it.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the uterine tube running from the ovary to the uterine cornu with its four parts labelled exactly, top to bottom:

- ▶ **Infundibulum** (funnel-shaped, fimbriated end, overlying the ovary)
- ▶ **Ampulla** (widest, longest segment) — mark with an arrow "GIFT: oocytes + capacitated sperm placed here by laparoscope; fertilisation occurs in vivo"
- ▶ **Isthmus** (narrow, muscular)
- ▶ **Intramural part** (within the uterine wall) leading to the **uterine cavity** — mark "IVF: cleaving embryo transferred here (bypasses the tube)"

## 5. Comparison with other assisted reproductive techniques

| Feature                    | GIFT                                                | IVF                                                       | ZIFT                                        | ICSI                                                |
|----------------------------|-----------------------------------------------------|-----------------------------------------------------------|---------------------------------------------|-----------------------------------------------------|
| Where fertilisation occurs | In vivo, in the ampulla                             | In vitro, in a Petri dish                                 | In vitro (as for IVF)                       | In vitro (micro-injection)                          |
| What is transferred        | Oocytes + precapacitated sperm together             | Cleaving embryo (4–8 cell/blastocyst)                     | Zygote (pronuclear stage)                   | Cleaving embryo (as IVF)                            |
| Route of transfer          | Laparoscopic, into the ampulla                      | Catheter via vagina/cervix, into the uterine cavity       | Laparoscopic, into the ampulla              | Catheter via vagina/cervix, into the uterine cavity |
| Tubal patency required     | Yes — at least one healthy, patent tube             | Not required (tubes may be blocked/absent)                | Yes — at least one patent tube              | Not required                                        |
| Key indication             | Unexplained infertility, mild sperm-motility defect | Tubal blockage, ovulatory/cervical factors, endometriosis | Tubal-factor cases wanting in-vivo cleavage | Severe male-factor infertility                      |
| Success rate (per source)  | ≈25–30%                                             | Variable (overall ART success ≈18% per one series)        | ≈65% (per source)                           | As successful as routine IVF                        |

## 6. Success rate and outcome

- ▶ Reported success rate for GIFT is **approximately 25–30%** per treatment cycle.
- ▶ Success depends on the same variables as other ART techniques — maternal age, tubal and endometrial health, sperm quality, and the cause of infertility.
- ▶ Because fertilisation is not directly witnessed (unlike IVF, where two pronuclei are seen under the microscope), fertilisation failure in GIFT cannot be confirmed or corrected before the gametes are transferred.

## 7. Advantages and limitations

- **Advantages:** reproduces the natural fertilisation sequence and tubal/uterine environment for the early embryo; avoids laboratory culture of gametes/embryos; historically used where religious/ethical concerns favoured in-vivo over in-vitro fertilisation.
- **Limitations:** mandatorily requires laparoscopy (and therefore general anaesthesia) for both oocyte and transfer steps; strictly requires at least one healthy, patent tube — useless in tubal-factor infertility, the single commonest indication for ART overall; fertilisation cannot be confirmed before transfer; cannot incorporate ICSI or preimplantation genetic diagnosis/screening (PGD/PGS), since no embryo is ever handled outside the body; largely superseded today by IVF/ICSI, which are less invasive (no laparoscopy needed) and allow fertilisation/embryo quality to be directly assessed.

## Applied / Clinical anatomy

- **Ectopic (tubal) pregnancy risk:** the ampulla is also the commonest site of tubal ectopic implantation; because GIFT places gametes directly in the tube, it carries the same order of risk of tubal/ectopic pregnancy as natural ampullary fertilisation, and this must be considered in follow-up (serum  $\beta$ -hCG/ultrasound).
- **Laparoscopic access:** both oocyte retrieval and gamete transfer in GIFT require transabdominal laparoscopic access to the tube and ovary, with attendant general-anaesthesia and laparoscopy-related risks (bowel/vessel injury, pneumoperitoneum complications) not shared by transvaginal IVF oocyte retrieval or catheter-based embryo transfer.
- **Site relevance versus IVF:** IVF deliberately bypasses the ampulla (the natural fertilisation site) and can therefore be used even with bilateral tubal block, whereas GIFT deliberately restores fertilisation to the ampulla and so is only usable when at least one tube is patent and functional — this contrast is a favourite viva/theory discriminator.
- **Multiple pregnancy:** as with other ART techniques, placing more than one oocyte increases the chance of multiple gestation.

## High-yield exam pointers

- GIFT = oocytes + capacitated sperm placed together by laparoscope into the ampulla of the uterine tube; fertilisation occurs **in vivo**, at the normal site.
- Contrast: IVF — fertilisation in vitro, embryo transferred to uterus; ZIFT — zygote (already fertilised in vitro) transferred to the ampulla; GIFT — unfertilised gametes transferred to the ampulla.
- **Essential prerequisite:** at least one healthy, patent uterine tube — the key discriminator from IVF, which does not need a patent tube.
- Best indications: **unexplained infertility** and **mild sperm-motility defects**.
- Success rate  $\approx 25\text{--}30\%$  (Sontakke); ZIFT  $\approx 65\%$  by comparison.
- Normal fertilisation site = **ampulla**; capacitation ( $\sim 7$  hours in vivo) must be complete before the oocyte can be fertilised — this is why GIFT uses **precapacitated** sperm.
- Requires laparoscopy (general anaesthesia) for both oocyte retrieval and transfer — a key practical disadvantage versus IVF.

- ▶ Cannot combine with ICSI or PGD/PGS, since gametes (not an assessed embryo) are transferred.

### SOURCE & COVERAGE

Gray's Anatomy (Standing) 41e; Sontakke — Textbook of Human Embryology; Moore — The Developing Human 9e; Larsen — Human Embryology 6e; Langman's Medical Embryology (Sadler) 14e; Vishram Singh — Textbook of Anatomy Vol 2 4e.



## Lateral line organs

Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy

**Definition / Introduction** Lateral line organs are cutaneous mechanoreceptor (and, in some species, electroreceptor) sense organs of fishes and aquatic-stage/permanently aquatic amphibians, arranged in a characteristic pattern of lines over the head and along the trunk. They form part of the **acoustico-lateralis system** — the ancestral vertebrate hair-cell sensory apparatus that also gives rise to the inner ear — and detect water displacement, low-frequency vibration and pressure gradients, a modality often called "distant touch." Humans and all other amniotes lack lateral line organs, having lost them with the evolution of a fully terrestrial, keratinised integument; the topic is examined in Anatomy because the lateral-line placode belongs to the same series of cranial ectodermal placodes (otic, epibranchial, trigeminal) whose human derivatives — the membranous labyrinth and cranial-nerve sensory ganglia — are core embryology. It is thus a classical comparative-embryology bridge between fish sensory biology and the development of the human ear.

### 1. Occurrence and distribution

- ▶ Present in: cyclostomes (lampreys, hagfish), elasmobranchs (sharks, rays), teleost and other bony fish, and aquatic amphibians — both larval stages (tadpoles) and permanently aquatic adults (e.g. clawed frog *Xenopus*, axolotl and other neotenic urodeles).
- ▶ Absent in: all amniotes (reptiles, birds, mammals, including humans) — loss of the lateral line coincides with the transition to a fully terrestrial existence and a cornified epidermis that would obstruct the organ's function.
- ▶ Distribution pattern:
  - **Cephalic (head) lines** — supraorbital, infraorbital, mandibular, preopercular and otic/occipital lines encircling the eye, jaw and operculum.
  - **Trunk (main) lateral line** — a single line running from just behind the head to the tail along each flank, visible externally in many fish as a row of pored scales.

### 2. The unit organ — the neuromast

| Component  | Description                                                                                                                                |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Hair cells | Mechanosensory cells, each bearing a bundle of graded <b>stereocilia</b> and a single, longest <b>kinocilium</b> at one edge of the bundle |

| Component                        | Description                                                                                                                                                |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Supporting (sustentacular) cells | Surround and nourish the hair cells; contribute to bundle renewal                                                                                          |
| Mantle cells                     | Peripheral cells that secrete/maintain the cupula                                                                                                          |
| Cupula                           | A gelatinous dome that caps the hair-cell bundles; deflected by water movement, it bends the stereocilia                                                   |
| Innervation                      | Afferent (and some efferent) fibres of the <b>lateral-line nerve component</b> , running with the facial, glossopharyngeal and vagus nerve complex in fish |

- **Transduction physiology** is identical in principle to the cochlear/vestibular hair cell: deflection of stereocilia **toward** the kinocilium depolarises the cell (opens mechanotransduction channels, increases afferent firing); deflection **away** from it hyperpolarises the cell — the same "morphological polarisation" rule used to explain directional sensitivity in the human macula and crista.

### 3. Types of lateral-line organ

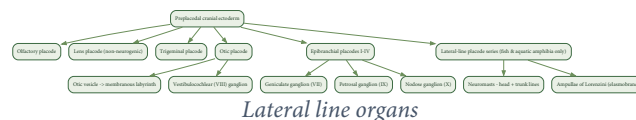
| Type                                                                     | Location                                                                                                  | Stimulus detected                                                                                                                                 |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Superficial (free) neuromasts                                            | Sit directly on the epidermis, exposed to the water                                                       | Slow water currents, near-field low-frequency disturbances                                                                                        |
| Canal neuromasts                                                         | Lie within fluid-filled sub-epidermal canals that communicate with the exterior through a series of pores | Faster, more localised water movements/pressure gradients; better signal-to-noise in turbulent water                                              |
| Ampullary electroreceptors (e.g. ampullae of Lorenzini of elasmobranchs) | Modified lateral-line derivatives opening onto the skin via jelly-filled canals                           | Weak bioelectric fields generated by prey/other organisms (electroreception) — a specialised derivative of the same octavolateral placodal system |

### 4. Function

- Detection of water displacement, hydrodynamic pressure gradients and low-frequency vibration — the sense of "distant touch"/rheoreception.
- **Schooling behaviour** — maintaining position and spacing relative to neighbouring fish without vision.
- **Prey detection and localisation**, obstacle avoidance and predator evasion in turbid or dark water.
- **Rheotaxis** — orientation of the body to the direction of water current.
- Electroreceptive derivatives (ampullae of Lorenzini) detect the weak bioelectric fields of buried or camouflaged prey.

## 5. Embryological development — the acoustico-lateralis placode field

- ▶ All lateral-line organs, like the inner ear, arise from **ectodermal placodes** — focal thickenings of head ectoderm lying alongside the neural folds, distinct from neural-crest-derived structures. In humans these placodes are classified as **neurogenic placodes** (olfactory, otic, epibranchial and trigeminal) and the **non-neurogenic lens placode**.
- ▶ The **otic placode** appears late in the third week lateral to the hindbrain, invaginates through an otic pit (by ~day 25) to form the closed **otic vesicle (otocyst)** by the end of the fourth week; its pars superior forms the semicircular canals and utricle, its pars inferior the cochlear duct and saccule (together the membranous labyrinth), and its ventral wall delaminates neurons that form the **vestibulocochlear (VIII) ganglion**.
- ▶ A row of **epibranchial placodes** (I–IV) forms in the ectoderm immediately dorsal to the pharyngeal (branchial) clefts; the first contributes to the **geniculate ganglion (VII)**, and the second/third/fourth to the **petrosal (IX)** and **nodose (X)** ganglia.
- ▶ In fishes and aquatic amphibians, this same posterior placodal territory additionally lays down a **series of lateral-line placodes** caudal (and dorsal) to the otic placode; these migrate as coherent placodal primordia along the head and flank, depositing neuromast rudiments at intervals that differentiate in situ into the lines described above. Amniotes never form this migratory lateral-line placode series — only the otic and epibranchial elements are retained.
- ▶ The shared molecular programme is conserved across the whole hair-cell family: the proneural bHLH transcription factor **Atoh1 (Math1)** drives differentiation of the sensory precursor into a hair cell, while **Hes1/Hes5** (Notch-pathway effectors) maintain the surrounding supporting-cell fate through lateral inhibition — the same logic that specifies hair versus supporting cells in the developing organ of Corti and cristae.



□ Fig 10.12 — Development of the Cranial Nerves and Their Ganglia (A, B) (Larsen — Human Embryology — 6e, p.613)

**DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**

Label a single **neuromast** in cross-section:

- ▶ Hair cell with graded stereocilia bundle
- ▶ Single kinocilium at the tall edge of the bundle
- ▶ Cupula (gelatinous dome) capping the bundle
- ▶ Supporting (sustentacular) cell
- ▶ Mantle cell at the periphery
- ▶ Afferent lateral-line nerve fibre beneath the hair cell
- ▶ For a canal neuromast — the surrounding fluid-filled canal wall and its surface pore (contrast with a superficial neuromast sitting free on the epidermis)

**6. Comparative fate — the acoustico-lateralis system in humans**

- ▶ Gray's Anatomy explicitly frames the human inner ear hair cell as evolutionarily continuous with this system: "hair cells... underlie acoustico-lateralis sensory systems in all vertebrates." In humans there are **six** such mechanosensory epithelia — the **organ of Corti** (cochlea, hearing), the **utricle and saccule** (static balance) and the **cristae ampullares** of the three semicircular canals (dynamic balance/rotation) — and no lateral-line neuromasts, since the migratory lateral-line placode series is never induced in amniote development.
- ▶ The comparison is therefore not one of homologous adult structures in humans but of a **shared developmental and physiological ancestry**: the same hair-cell/kinocilium mechanotransduction unit, the same placodal mode of origin, and (in fish) direct developmental continuity between the otic and lateral-line placode fields.

**Applied / Clinical anatomy**

- ▶ **No direct human structure**: because lateral-line organs are absent in amniotes, there is no adult human correlate to examine clinically — the relevance to Anatomy is purely developmental/comparative.
- ▶ **Zebrafish lateral-line model**: the externally visible, superficial neuromasts of the zebrafish are a widely used experimental model for studying vertebrate hair-cell development, mechanotransduction and — because these hair cells regenerate readily after damage — for screening **ototoxic drugs** (aminoglycoside antibiotics, platinum-based chemotherapy) and for hair-cell regeneration research, work that directly informs understanding of irreversible cochlear hair-cell loss in humans (sensorineural hearing loss).
- ▶ **Shared molecular vulnerability**: the conserved Atoh1-driven hair-cell differentiation programme underlying both the neuromast and the organ of Corti is the basis for cross-species extrapolation of ototoxicity and regenerative-medicine studies from fish to the clinical problem of irreversible mammalian hair-cell loss.
- ▶ **Viva relevance**: the topic is classically used to test whether the candidate understands the full spread of cranial ectodermal placode derivatives (otic, epibranchial, trigeminal) rather than the otic placode in isolation, and to test awareness of comparative embryology beyond strictly human development.



## High-yield exam pointers

- ▶ Lateral line organs = mechanoreceptor ( $\pm$  electroreceptor) sense organs of fish and aquatic amphibians; absent in all amniotes including humans.
- ▶ Unit organ = **neuromast**: hair cells (stereocilia + single kinocilium) + supporting cells + mantle cells, capped by a **cupula**; directional sensitivity follows the kinocilium-polarisation rule shared with the human macula/crista.
- ▶ Two structural types: **superficial (free) neuromasts** and **canal neuromasts** (within pored sub-epidermal canals); specialised electroreceptive derivative = **ampullae of Lorenzini** in elasmobranchs.
- ▶ Distribution: cephalic lines (supraorbital, infraorbital, mandibular, preopercular) + a single trunk lateral line.
- ▶ Function: "distant touch"/rheoreception — detects water currents, vibration, pressure gradients; used in schooling, prey/predator detection, rheotaxis.
- ▶ Embryological origin: a **series of ectodermal placodes** contiguous with the otic/epibranchial placode field — part of the acoustico-lateralis placodal system; never induced in amniotes.
- ▶ Human correlate: the **otic placode alone** persists in amniotes, forming the membranous labyrinth (organ of Corti, utricle, saccule, three cristae) and the vestibulocochlear ganglion — the six surviving acoustico-lateralis epithelia in humans.
- ▶ Shared molecular programme: **Atoh1 (Math1)** drives hair-cell fate; **Hes1/Hes5**-mediated lateral inhibition maintains supporting cells — conserved across the whole vertebrate hair-cell family.
- ▶ Translational link: zebrafish lateral-line neuromasts are a standard research model for hair-cell regeneration and ototoxic-drug screening relevant to human sensorineural hearing loss.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Larsen Human Embryology 6e.

**Coverage note:** the human-anatomy/embryology textbook corpus in this library does not carry a dedicated ichthyology/comparative-anatomy account of the lateral-line system itself (as expected, since it is not a human structure) — grepping across the full corpus returned only incidental "lateral line" hits (bibliographic references and unrelated uses of "lateral line" meaning the midclavicular line). The developmental/placodal framework above (otic, epibranchial, trigeminal placodes; Atoh1/Hes-driven hair-cell differentiation; the acoustico-lateralis concept) is grepped and confirmed verbatim from Gray's 41e and Larsen 6e. The comparative ichthyology/amphibian content — neuromast structure, canal vs superficial types, cephalic/trunk line distribution, function, and ampullae of Lorenzini — is standard, universally accepted comparative-embryology/zoology curriculum content used to complete the answer, per the spec's thin-corpus allowance; no numeric value, classification or citation has been invented.

♦ ♦ ♦

## Neanderthal man

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** Neanderthal man (*Homo neanderthalensis*, sometimes classified as the subspecies *Homo sapiens neanderthalensis*) is an extinct archaic human who lived across Europe and western Asia through the Middle and early Late Pleistocene, broadly from about 400,000 to 40,000 years ago. Named after the Neander Valley (Neandertal) in Germany where the type specimen was recovered in 1856, it is the best-studied fossil hominid because of the large number of skeletons found and, more recently, because its genome has been fully sequenced. It occupies a pivotal place in the study of human evolution — anatomically robust and cold-adapted, culturally sophisticated (Mousterian tool industry, fire, deliberate burial), and now known on genomic grounds to have interbred with the anatomically modern humans who displaced it.

### Taxonomic position & nomenclature

| Rank    | Classification                                                                                 |
|---------|------------------------------------------------------------------------------------------------|
| Kingdom | Animalia                                                                                       |
| Phylum  | Chordata                                                                                       |
| Class   | Mammalia                                                                                       |
| Order   | Primates                                                                                       |
| Family  | Hominidae                                                                                      |
| Genus   | Homo                                                                                           |
| Species | <i>Homo neanderthalensis</i> (King, 1864) — alternatively <i>Homo sapiens neanderthalensis</i> |

- ▶ The genus and family placement follow the standard primate taxonomy used for modern man (*Homo sapiens*), whose family is likewise **Hominidae** and whose scientific name was fixed by **Carolus Linnaeus**.
- ▶ The species name commemorates the **Neander Valley** (German *Tal* = valley), the 1856 discovery site near Düsseldorf.
- ▶ Whether Neanderthal is a separate species or a subspecies of *Homo sapiens* remains debated; genomic proof of fertile interbreeding with modern humans favours the subspecies view, though *Homo neanderthalensis* remains the conventional usage in most texts.

### Discovery & key fossil sites

- ▶ The type specimen — a skullcap and limb bones — was found in **1856** by quarry workmen in the **Feldhofer grotto, Neander Valley**, near Düsseldorf, Germany; it was formally described and named by the anatomist **William King in 1864**.
- ▶ Earlier, unrecognised Neanderthal remains had already been found at **Engis, Belgium (1829)** and **Forbes' Quarry, Gibraltar (1848)**, but their distinct nature was appreciated only after the 1856 find.

| Site                             | Country   | Significance                                                                                                             |
|----------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------|
| Feldhofer grotto, Neander Valley | Germany   | Type specimen (1856)                                                                                                     |
| La Chapelle-aux-Saints           | France    | "Old Man of La Chapelle" (1908)<br>— near-complete robust skeleton,<br>basis of classic (now revised)<br>reconstructions |
| Shanidar Cave                    | Iraq      | Multiple burials; flower pollen<br>around "Shanidar IV" suggested<br>ritual burial                                       |
| Krapina                          | Croatia   | Large fossil assemblage; possible<br>cannibalism/mortuary processing<br>debated                                          |
| Vindija Cave                     | Croatia   | Source of high-quality DNA for<br>the first draft Neanderthal<br>genome (Pääbo and colleagues)                           |
| Gorham's Cave, Gibraltar         | Gibraltar | One of the latest-surviving<br>Neanderthal populations                                                                   |

### Geographical & temporal distribution

- **Geographic range:** Europe (from Iberia and Britain to the Ural mountains) and the Middle East/western Asia (Levant, Iraq); Neanderthals never reached sub-Saharan Africa or East Asia.
- **Temporal range:** appeared roughly 400,000–350,000 years ago, evolving in Europe from an earlier *Homo erectus*/*Homo heidelbergensis*-like ancestor, and became extinct by about 40,000 years ago (with a few refugial populations, e.g. at Gibraltar, persisting somewhat later).
- Their range overlapped anatomically modern humans (*Homo sapiens*) migrating out of Africa into the Levant and then Europe from roughly 60,000–45,000 years ago, setting the stage for the contact/interbreeding discussed below.

### Morphological characteristics

| Feature          | Neanderthal man                                                                  | Modern man ( <i>Homo sapiens sapiens</i> )      |
|------------------|----------------------------------------------------------------------------------|-------------------------------------------------|
| Cranial capacity | ~1200–1750 mL (mean higher than modern man)                                      | ~1200–1600 mL (mean ~1500 mL)                   |
| Skull shape      | Long, low vault (platycephalic); prominent, continuous supraorbital (brow) ridge | Rounded, high vault; brow ridges reduced/absent |
| Occiput          | Prominent posterior bulge — the "occipital bun"                                  | Rounded occiput, no bun                         |
| Forehead         | Low, receding                                                                    | High, vertical                                  |
| Face             | Large, mid-facial prognathism; very large nasal aperture (cold-air conditioning) | Flatter face; smaller nasal aperture            |

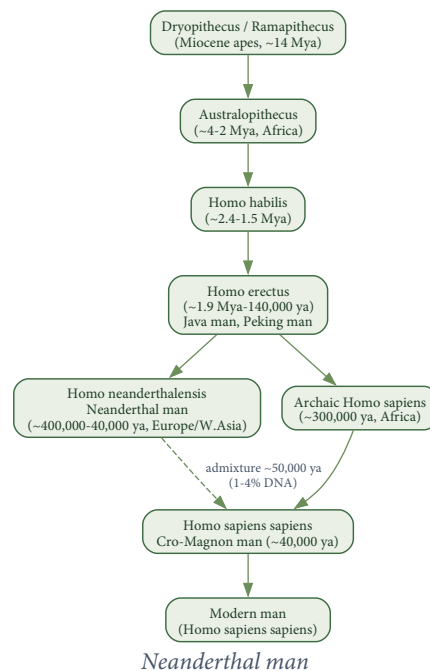
| Feature        | Neanderthal man                                                                                                        | Modern man ( <i>Homo sapiens sapiens</i> ) |
|----------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Mandible       | Robust, <b>no true chin</b> (mental eminence absent/poorly developed)                                                  | Prominent bony chin                        |
| Build          | Short, stocky, heavily muscled limbs; barrel-shaped chest — cold-adapted body proportions (short distal limb segments) | Taller, more linear limb proportions       |
| Bones          | Thick cortical bone, curved long bones, strong muscle markings                                                         | More gracile skeleton                      |
| Average height | ~155–170 cm                                                                                                            | Variable, generally taller on average      |

- ▶ The short-limbed, stocky Neanderthal body plan is the classic textbook example of **Bergmann's and Allen's rules** — a low surface-area-to-volume body build that conserves heat in a cold Ice-Age European climate.
- ▶ Despite the popular image of a "brutish ape-man," the large cranial capacity, well-developed hyoid bone (implying capacity for speech), and sophisticated tool-making show Neanderthals were cognitively advanced archaic humans, not evolutionary intermediates between apes and man.

### Culture, technology & behaviour

- ▶ **Stone-tool industry:** Mousterian industry (Middle Palaeolithic) — flake tools made by the Levallois prepared-core technique; used for hunting, hide-working and woodworking.
- ▶ **Fire:** controlled use of fire for warmth and cooking is well attested at Neanderthal sites.
- ▶ **Subsistence:** skilled big-game hunters (bison, reindeer, horse, mammoth) using close-range thrusting spears, supplemented by plant foods.
- ▶ **Burial practice:** deliberate burial of the dead is documented at several sites (e.g. La Chapelle-aux-Saints, Shanidar), the earliest clear evidence of intentional human burial — though the extent of "ritual"/symbolic behaviour (e.g. the Shanidar "flower burial") remains debated.
- ▶ **Anatomy of speech:** the Neanderthal hyoid bone and the shape of the ear ossicles/cochlea are similar to modern man, supporting the capacity for spoken language, though the extent of true language remains uncertain.

## Evolutionary lineage of man



- ▶ Neanderthal man is thus placed as a **side-branch (sister lineage)** that diverged from the line leading to modern man after *Homo erectus*, rather than as a direct ancestor — contrary to the older, purely morphological view that placed Neanderthal man as a stage directly preceding **Cro-Magnon man** (the earliest anatomically modern European, ~40,000 years ago), which then gave rise to modern man.
- ▶ **Cro-Magnon man**, found in the Cro-Magnon rock-shelter, France, is anatomically identical to living humans and is regarded as the direct ancestor of modern man.

## Relationship to modern *Homo sapiens* — genomic evidence

- ▶ The **most recent common ancestor** of Neanderthals and *Homo sapiens* lived in Africa **over 200,000 years ago**, well before Neanderthals themselves migrated out of Africa to settle in Europe and the Middle East.
- ▶ The **first draft Neanderthal genome** was sequenced from bones of three Neanderthal individuals who died approximately **38,000 years ago** in Europe (work led by Svante Pääbo, recognised with the 2022 Nobel Prize in Physiology or Medicine).
- ▶ Genomic comparison shows that **1–4% of the DNA of modern Europeans and Asians (but not modern Africans)** matches Neanderthal DNA — direct proof of interbreeding (gene flow/admixture) between the two populations.
- ▶ Statistical modelling places this **admixture event at approximately 50,000 years ago**, in the Middle East, after modern humans had already begun migrating out of Africa but before they dispersed further into Europe and Asia — which explains why the Neanderthal genomic signature is absent in present-day sub-Saharan Africans.
- ▶ Ongoing comparison of Neanderthal and modern human genomes is informative for identifying genes/alleles that differ in frequency between archaic and modern populations, including those

relevant to immune function and other disease-associated variation — an active area of population and medical genetics research.

- ▶ Neanderthal man became **extinct by roughly 40,000 years ago**; proposed explanations include competitive replacement by/assimilation into incoming modern humans, small and fragmented population size, and Ice-Age climatic stress — most likely a combination of these factors rather than a single cause.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A side-by-side lateral (norma lateralis) outline comparison of the Neanderthal skull and the modern human skull, labelling:

- ▶ Long, low cranial vault vs rounded, high vault
- ▶ Prominent continuous supraorbital (brow) ridge vs reduced brow ridge
- ▶ Occipital bun (posterior cranial bulge) vs rounded occiput
- ▶ Receding forehead vs vertical/high forehead
- ▶ Mid-facial prognathism and large nasal aperture vs flatter face, smaller nasal aperture
- ▶ Robust mandible with no mental eminence (no chin) vs mandible with a prominent bony chin
- ▶ Position of foramen magnum (relatively posterior, but still indicating habitual bipedalism in both)

### Applied / Clinical anatomy

- ▶ **Forensic and physical anthropology:** the morphological criteria used to characterise Neanderthal remains (cranial capacity, supraorbital ridge, presence/absence of mental eminence, limb bone robusticity and curvature) are the same parameters routinely applied in forensic osteology for age, sex and ancestry (race) estimation from a skeleton.
- ▶ **Museum/teaching collections:** plaster-cast reconstructions of early fossil man — the Ape-man of Java, the Ape-man of Peking, Neanderthal man and Cro-Magnon man — are traditionally displayed together under "Physical Anthropology" exhibits in anatomy/medical museums, alongside regional skeletal material, precisely to teach this comparative sequence.
- ▶ **Medical genetics:** the demonstrated 1–4% Neanderthal admixture in non-African genomes is a standard teaching example of **ancient gene flow/migration** in human population genetics, and underlies current research correlating archaic-derived alleles with variation in immune response and other traits in modern populations.
- ▶ **Comparative anatomy teaching point:** Neanderthal anatomy is used to illustrate adaptive (cold-climate) skeletal proportion (Bergmann's/Allen's rules) and the concept that a *larger* cranial capacity does not equate to greater cognitive/cultural sophistication than modern man.

### High-yield exam pointers

- ▶ Scientific name: **Homo neanderthalensis** (or *Homo sapiens neanderthalensis*); named after the Neander Valley, Germany (type fossil, 1856; named by William King, 1864).
- ▶ Lived in Europe and western Asia, roughly 400,000 to 40,000 years ago.

- ▶ Cranial capacity ~1200–1750 mL — comparable to or exceeding modern man — but skull is long/low with a prominent brow ridge, occipital bun, and **no chin**.
- ▶ Stocky, cold-adapted build (short limbs, barrel chest) — classic example of Bergmann's/Allen's rules.
- ▶ Associated with the **Mousterian** stone-tool industry; used fire; practised deliberate burial (e.g. La Chapelle-aux-Saints, Shanidar).
- ▶ **Not a direct linear ancestor** of modern man — a sister lineage that diverged after *Homo erectus*; **Cro-Magnon man** is the true direct ancestor of modern man.
- ▶ Genomic proof of **interbreeding**: 1–4% Neanderthal DNA persists in modern non-African populations; admixture dated to ~50,000 years ago; common ancestor with *Homo sapiens* lived in Africa >200,000 years ago.
- ▶ Became extinct by ~40,000 years ago, likely from a combination of replacement/assimilation by modern humans and climatic pressures.

### SOURCE & COVERAGE

Thompson & Thompson — Genetics in Medicine (8e); Vishram Singh — General Anatomy (4e); Handbook of Museum Technique (Govt Museum, Chennai); standard physical-anthropology/human-evolution content (evolutionary lineage, fossil sites, morphology, culture) drawn from established, universally-accepted paleoanthropological teaching supplementing these sources.

**Coverage note:** Neanderthal man/human evolution is classical physical-anthropology content outside the scope of Gray's Anatomy (Standring) 41e and only lightly touched in the specialty texts on disk; the genomic admixture facts are directly grounded in Thompson & Thompson (Ch 9), and the taxonomy/cranial-capacity facts in Vishram Singh's General Anatomy — the discovery history, fossil sites and morphological/cultural detail reflect standard, non-controversial paleoanthropological teaching.





## Neolithic man

Asked in: Paper II Oct 2006 — RGUHS MD/MS Anatomy

**Definition / Introduction** "Neolithic man" denotes human populations of the New Stone Age (Neolithic period), the last and most advanced stage of the Stone Age in physical and cultural anthropology, defined by the shift from a purely food-gathering economy to a settled, food-producing one. The term is a cultural/archaeological label, not a biological one — by the Neolithic period man was already anatomically modern *Homo sapiens sapiens*, essentially identical in skeleton to present-day humans. Classical Indian anatomical teaching studies Neolithic man under Anthropology, the subject that specially studies primitive and ancient man, through three interrelated aspects: the historical (prehistory/prehistoric archaeology), the biological (physical anthropology/human biology, based on the principle of evolution) and the sociological (social/cultural anthropology).

### 1. Anthropology and its three aspects

- ▶ **Prehistory / Prehistoric archaeology** (historical aspect) — study of early man and his material remains; covers the successive stone, bronze and iron age cultures.
- ▶ **Physical anthropology / Human biology** (biological aspect) — study of man's relationship to the animal world on the principle of evolution; his relationship to extinct hominin species, ape-men/man-apes and living apes, based on structural (anatomical) features.
- ▶ **Social / Cultural anthropology** (sociological aspect) — study of man as a social being: manners, customs, arts, industries, material and moral culture, tradition, social structure, language and religion.
- ▶ Neolithic man is best understood by combining all three: his tools/settlements (prehistory), his skeletal status (physical anthropology), and living tribal analogues of his economy in India (cultural anthropology).

### 2. Neolithic man's place in the Stone Age chronology

| Age                           | Approx. antiquity (South India) | Technology                                                                 | Economy & culture                                                                                                                                 |
|-------------------------------|---------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Palaeolithic (Old Stone Age)  | Mid-Pleistocene                 | Stone (quartzite), antler, bone and wood tools, roughly chipped and flaked | Food-gathering/collecting, hunting and fishing; knowledge of fire; ceremonial burial of the dead; <b>no</b> agriculture, domestication or pottery |
| Mesolithic (Middle Stone Age) | Transitional phase              | Small, flaked microlithic tools                                            | Transitional economy bridging hunting-gathering and food-production                                                                               |

| Age                       | Approx. antiquity (South India) | Technology                                                                                                                                                      | Economy & culture                                                                                                                                                                                                                                                         |
|---------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neolithic (New Stone Age) | ~10,000 years                   | Stone tools ground and <b>polished</b> ("celts" — pointed butt, oval cross-section, fine cutting edge, of trap rock) plus small flake tools of chert and jasper | Discovery of <b>agriculture and animal domestication</b> ; manufacture and use of <b>pottery</b> ; settled village life                                                                                                                                                   |
| Bronze / Chalcolithic Age | ~5,000 years                    | Copper and bronze tools/weapons; iron unknown; Neolithic stone tools persisted side by side with bronze                                                         | Settled agriculture led to river-valley urban civilisations (Nile, Euphrates, Indus, e.g. Mohenjo-daro, Harappa); also recognised in South India (Mysore and other places)                                                                                                |
| Iron Age                  | >2,000 years                    | Iron implements and pottery                                                                                                                                     | <b>Megalithic</b> burial monuments — cairns, cists, dolmens, stone circles; urn/pit-burials (Adichanallur, Tirunelveli district) and sarcophagus burials (Chingleput and South Arcot districts), with associated bronze objects, pottery, beads and chank-shell ornaments |

- ▶ South Indian Palaeolithic quartzite implements are recorded from the lateritic formations of the Chingleput, Nellore and Kurnool districts.
- ▶ The Neolithic celts (large numbers of ground and polished stone implements) are recorded from the Bellary district.

### 3. Cultural characteristics that define Neolithic man

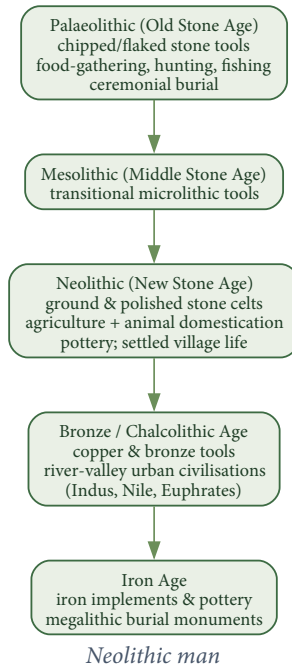
- ▶ No longer food-gathering-dependent — discovered **agriculture and animal domestication**; made and used **pottery**.
- ▶ Perfected stone-tool manufacture — tools **ground and polished** into **celts** (pointed butt, oval cross-section, fine edge, trap rock), replacing the rough chipped/flaked Palaeolithic quartzite tools; small flake tools of chert/jasper occur alongside.
- ▶ Neolithic-type shifting cultivation is comparable to that still practised by some present-day Indian aboriginal peoples.
- ▶ Settled Neolithic agriculture is regarded as the base from which river-valley urban civilisations (Nile, Euphrates, Indus) arose once copper and bronze were discovered.

#### 4. Physical (anatomical) status of Neolithic man

By the Neolithic period, man had attained the full skeletal and anatomical status of modern *Homo sapiens*:

| Taxon                    | Diagnostic feature                                                                     |
|--------------------------|----------------------------------------------------------------------------------------|
| Kingdom: Animalia        | Eukaryotic cells, no cell wall or photosynthetic pigment                               |
| Phylum: Chordata         | Notochord and pharyngeal pouches                                                       |
| Subphylum: Vertebrata    | Vertebral column                                                                       |
| Class: Mammalia          | Mammary glands and hair                                                                |
| Order: Primata           | Well-developed brain, prehensile hands                                                 |
| Family: <b>Hominidae</b> | Large cerebrum, bipedal locomotion (humans are the sole living members of this family) |
| Genus: <i>Homo</i>       | Flattened face, prominent chin and nose with inferiorly directed nostrils              |
| Species: <b>sapiens</b>  | Largest cerebrum                                                                       |

- Characteristic anatomical features of *Homo sapiens*: a large well-developed brain (average adult weight 1350–1400 g), **bipedal locomotion**, an **opposable thumb**, well-developed **articulated speech**, and **stereoscopic (binocular) vision** — together with erect posture and a prominent chin.
- Modern cranial capacity in man ranges from **1200–1600 cm<sup>3</sup>** (average ~1500 cc).
- **Cro-Magnon man** is regarded as the direct ancestor of modern living man; anatomically-modern populations of the Neolithic period represent this fully modern (Cro-Magnon-type) skeletal build, in contrast to the earlier, more archaic fossil hominins associated with the Old Stone Age — the "Ape-man of Java" and the "Ape-man of Peking" (both now classed as *Homo erectus*) and **Neanderthal man**.
- Man's nearest living relatives among the primates are the great apes; the scientific name *Homo sapiens* was assigned by Carolus Linnaeus.
- The evolutionary transition from a quadrupedal to a **bipedal** gait — already complete by Neolithic times — was a considerable biomechanical milestone, reflected in the anatomy of the human hip, knee, ankle and foot, which are markedly different from the quadrupedal limb.



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A labelled outline of the skull (lateral/frontal view) showing the craniometric landmarks used in physical/forensic anthropology to classify racial and ancestral skull types — since Neolithic-onward man is studied through exactly these criteria:

- ▶ Cephalic index landmarks — maximum head length (glabella to occiput) and maximum head breadth (biparietal), to distinguish **dolichocephalic** (long-headed) from **brachycephalic** (round-headed) skulls.
- ▶ Supraorbital ridging and glabella.
- ▶ Nasal aperture (narrow/wide), nasal root and nasal spine.
- ▶ Interorbital distance.
- ▶ Degree of prognathism (alveolar/maxillary protrusion vs mandibular retrusion).
- ▶ Palate shape (long-narrow vs short-wide) and relative tooth size.
- ▶ Forehead slope (steep vs vertical vs rounded).

## 5. Racial strata attributed to Stone-Age settlement of India

Physical anthropology classifies mankind on the basis of measurements and anatomical characters diagnostic of racial groups — stature, colour of eyes/hair/skin, and head/face/nose form — into broad groups: **Negroid**, **Caucasoid**, **Mongoloid**, **Australoid**, of which Caucasoid is further subdivided into Nordic, Alpine, Armenoid, Dinaric, Oriental and Mediterranean types. Most of these racial strata, laid down over successive prehistoric and historic migrations/settlements, are represented in the population of India:

| Racial type             | Physical characteristics                                                                                                                                    | Representative groups                                                                     |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Australoid / Veddoid    | Short stature, long (dolichocephalic) heads, prominent eyebrow ridges, broad short faces, flat broad noses, curly/wavy hair, dark brown skin, dark eyes     | Most aboriginals of peninsular India, e.g. Chenchus of the Nallamalais, Veddahs of Ceylon |
| Mediterranean           | Medium/short stature, longish heads, faintly marked eyebrow ridges, broad short faces, prominent medium noses, wavy hair, dark/light brown skin, brown eyes | Major element of India's population; most Dravidian-speaking peoples                      |
| Brachycephalic Armenoid | Medium stature, round heads with flattened occiput, long convex noses, brown skin and eyes                                                                  | Majority of the peoples of Maharashtra, Gujarat, Bengal and Canara                        |
| Proto-Nordic            | Tall stature, long heads, long faces, prominent narrow noses, light straight hair, light eyes                                                               | Populations of Northern India                                                             |
| Mongoloid               | Medium stature, often broad round heads, medium noses, flat faces, dark coarse straight hair, yellowish skin, brown eyes, epicanthic (Mongolian) fold       | Assam, the eastern border regions and the cis-Himalayan region                            |

None of these types is "pure" — all are the products of an age-old process of interbreeding, so intermediate racial types occur, one merging into another (e.g. in South India, Veddoids merge into Mediterraneans, and Mediterraneans merge into Brachycephals on one side and Mongoloids on the other).

## Applied / Clinical anatomy

- **Forensic/physical anthropological identification from the skull:** modern craniofacial forensic anatomy still classifies four traditional races by skull morphology — **Caucasoid** (dolichocephalic, narrow nasal aperture, moderate supraorbital ridging, long narrow palate); **Negroid** (long skull, wide nasal aperture, alveolar prognathism, wider palate, larger teeth); **Mongoloid** (round skull, moderate prognathism, shovel-shaped incisors, foreshortened palate); **Australoid** (broad nasal aperture, marked supraorbital ridging/ glabella, wide palate). These same criteria are applied to unidentified skeletal or archaeological (including Neolithic) remains to establish biological identity (sex, age, stature, ethnic origin) before facial approximation/superimposition for personal identification.
- **Museum/preservation relevance:** prehistoric-archaeology exhibits comprise stone/bronze/iron tools, pottery and shell/bone/horn ornaments from excavations or surface finds; physical-anthropology exhibits include skull types, race photographs and plaster-cast reconstructions of fossil hominin types (Ape-man of Java, Ape-man of Peking, Neanderthal man, Cro-Magnon man).

- ▶ **Living cultural analogues** in India show the persistence of pre-Neolithic/Neolithic-type economies: Kadars of Cochin and Chenchus of the Nallamalais are food-gatherers (digging-stick culture); Kurumbas and Todas of the Nilgiris are pastoralists; Mannans and Muthuvans of Travancore practise axe (Podu) cultivation; Savaras of the Agency districts are settled agriculturists.
- ▶ **Evolutionary/comparative-anatomy teaching value:** the bipedal-gait transition, complete by the Neolithic stage, underlies the applied biomechanics of the hip, knee, ankle and foot; the erect posture and enlarged cranial capacity underlie applied osteology of the vertebral column, pelvis and skull.

### High-yield exam pointers

- ▶ Neolithic = New Stone Age; the third and most advanced Stone Age culture after Palaeolithic (and transitional Mesolithic), preceding the Bronze/Chalcolithic and Iron Ages.
- ▶ Defining Neolithic advances: agriculture, animal domestication, pottery, and ground/polished stone tools (celts) — as opposed to the roughly chipped/flaked tools of the Palaeolithic.
- ▶ Neolithic in South India  $\approx$  10,000 years old; Bronze Age  $\approx$  5,000 years old; Iron Age  $>$  2,000 years old (per South Indian archaeological reckoning).
- ▶ Neolithic man is anatomically modern *Homo sapiens sapiens* — the label is cultural, not a distinct biological taxon; Cro-Magnon man is regarded as the direct ancestor of modern man.
- ▶ Modern human cranial capacity: 1200–1600 cm<sup>3</sup>; family Hominidae's sole living members are humans.
- ▶ Anthropology has three branches — prehistoric/historical, physical/biological, and social/cultural — all relevant to studying Neolithic man.
- ▶ India's population reflects a mosaic of prehistoric racial strata: Australoid/Veddoid, Mediterranean, Brachycephalic Armenoid, Proto-Nordic and Mongoloid, none pure, all interbred.
- ▶ Forensic anthropology still uses skull morphology (cephalic index, nasal aperture, prognathism, palate shape) — the same criteria physical anthropologists use to classify Neolithic-descended racial groups — for medico-legal identification.

### SOURCE & COVERAGE

Handbook of Museum Technique (Govt Museum Chennai) — "Man and His Cultural Beginnings" (prehistory, physical and social anthropology, Stone-Bronze-Iron age chronology, races of India); Vishram Singh — General Anatomy 4e (taxonomic classification of man, characteristics of *Homo sapiens*, cranial capacity, Cro-Magnon ancestry); Gray's Anatomy (Standring) 41e (bipedal-gait biomechanics; skull-based forensic/physical-anthropological determination of ethnic origin). Coverage note: this paleoanthropology topic lies outside the clinical scope of Gray's Anatomy and the modern genetics texts in the specialty list; core grounding is drawn from the Government Museum Chennai handbook, supplemented by universally accepted human-evolution facts (Mesolithic transition; *Homo erectus* identity of the "Java"/"Peking" ape-men) not disputed in mainstream teaching.



## Orbital index

Asked in: Paper II May 2009 — RGUHS MD/MS Anatomy

**Definition / Introduction** The **orbital index** is a craniometric ratio that expresses the shape of the bony orbit, calculated as the maximal height of the orbital margin expressed as a percentage of its maximal breadth. It is measured directly on the dry skull, in the same tradition as the cranial (cephalic), nasal and facial indices, and is used in **physical and forensic anthropology** to classify orbital shape and to assist in sex and ancestry estimation from skeletal remains. Because the orbital margin is formed by four different bones meeting at defined sutures, the index also serves as a compact, testable summary of orbital osteology.

### Boundaries forming the orbital margin (the base of measurement)

The orbital index is measured on the **orbital margin** — the quadrangular base of the four-sided bony pyramid of the orbit. Each side of the margin is formed by specific bones:

| Margin                         | Bones forming it                                                                              | Notable feature                                                                           |
|--------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Supraorbital (superior) margin | Frontal bone                                                                                  | Supraorbital notch/foramen at the junction of its lateral two-thirds and medial one-third |
| Infraorbital (inferior) margin | Zygomatic bone (laterally) + Maxilla (medially)                                               | Continuous medially with the anterior lacrimal crest                                      |
| Medial margin                  | Frontal bone (above) + lacrimal crest of the frontal process of the maxilla (below)           | Ill-defined compared to the other three margins                                           |
| Lateral margin                 | Zygomatic process of the frontal bone (above) + frontal process of the zygomatic bone (below) | Most exposed margin; weakest bony protection to the globe                                 |



- ▶ **Dacryon**, a craniometric point on the medial wall at the junction of the fronto-maxillary and lacrimo-maxillary sutures, marks the anteromedial corner of the orbital margin and is commonly tested alongside the index.
- ▶ All four margins are readily palpable in the living subject, which is why the orbital index — unlike many internal orbital measurements — can, in principle, be estimated clinically as well as on the dry skull.

## Measurement and formula

- ▶ **Maximal orbital height** — the greatest vertical distance between the supraorbital and infraorbital margins.
- ▶ **Maximal orbital breadth** — the greatest transverse distance between the medial and lateral margins.
- ▶ Both dimensions are taken with a sliding/spreading compass on the dry skull, exactly as the maximum length and breadth of the calvaria are taken for the cranial index.
- ▶ **Orbital index** = (Maximal orbital height ÷ Maximal orbital breadth) × 100
- ▶ Standard Indian textbook figures give the orbital margin as approximately **35 mm in height and 40 mm in breadth**, which computes to an index of about **87–88** — placing the average adult human orbit in the medium ("mesoseme") category described below.
- ▶ The orbital index is thus, dimensionally, the mirror-image companion of the cranial index (breadth/length of the vault): here it is height/breadth of the orbital aperture.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Anterior view of the bony orbital margin, labelled with:

- ▶ **Supraorbital margin** (frontal bone) with the **supraorbital notch/foramen**
- ▶ **Infraorbital margin** (zygomatic bone laterally, maxilla medially)
- ▶ **Medial margin** (frontal bone above, frontal process of maxilla below) with **Dacryon** marked at its upper end
- ▶ **Lateral margin** (zygomatic process of frontal bone above, frontal process of zygomatic bone below)
- ▶ A vertical line between the mid-points of the supraorbital and infraorbital margins, labelled "**maximal height (≈35 mm)**"
- ▶ A horizontal line between the medial and lateral margins, labelled "**maximal breadth (≈40 mm)**"
- ▶ A formula box: **Orbital index = (Height ÷ Breadth) × 100**

□ Fig 19.2 — Orbit. (A) Margins and walls. (B) Schematic diagram to show the bones forming the walls of the orbit. (Vishram Singh — Textbook of Anatomy Vol 3 — 4e, p.818)

## Classification of orbital shape by the index

Analogous to the cephalic index (dolichocephalic/mesaticephalic/brachycephalic), the orbital index is classically graded into three descriptive categories:

| Category  | Orbital index | Orbit shape                                |
|-----------|---------------|--------------------------------------------|
| Megaseme  | $\geq 89$     | Large, rounded orbital aperture            |
| Mesoseme  | 83–88.9       | Medium, intermediate shape                 |
| Microseme | $\leq 82.9$   | Small, more rectangular/elongated aperture |

- ▶ The average human orbit (index  $\approx 87$ –88, calculated above) falls in the **mesoseme** range.
- ▶ **Coverage note:** the AK Datta text used here for the formula and the 35 mm/40 mm dimensions does not itself state these numerical cut-offs; the megaseme/mesoseme/microseme grading is standard physical-anthropology/craniometry teaching taught alongside the cephalic-index grading, and is included here as universally accepted classical craniometry rather than as a corpus-verbatim quote.

### Sex and age-related variation

- ▶ **Sex dimorphism of the margin:** the supraorbital margin itself is a classical, corpus-confirmed sex marker — it is **more rounded in males** and **sharper (sharp-edged) in females** — used together with the orbital index in forensic sex estimation from the skull.
- ▶ Related skull sex differences (heavier, thicker-walled, more marked muscular ridges and glabella in males; lighter, thinner, smoother contours in females) support the overall pattern of a more robust, angular male orbit versus a smoother, sharper-margined female orbit.
- ▶ **Age-related change:** with advancing age the dimensions of the orbital aperture increase, chiefly through recession of the inferolateral rim (by more than 10%), which is the change that most alters overall orbital shape. This change shows sexual dimorphism — a small increase in transverse orbital width/aperture area occurs earlier in women, while superomedial recession occurs later and to a greater extent in men — so the orbital index is not fixed for life but drifts with age-related bony remodelling.

### Related craniometric indices (for context)

- ▶ The orbital index belongs to the same family of skull-shape ratios as the **cephalic (cranial) index** — breadth/length of the vault  $\times 100$ , graded dolichocephalic/mesaticephalic/brachycephalic — which is measured by the identical sliding-compass technique and is the index most commonly cross-referenced with the orbital index in exam questions on craniometry.
- ▶ Other paired indices (nasal index, facial index) are constructed on the same height/breadth logic applied to different craniofacial regions; together they form the standard toolkit of physical/forensic anthropology for describing skull morphology.

### Applied / Clinical anatomy

- ▶ **Forensic anthropology:** orbital shape (margin contour and index) is used, together with the cranial index, supraorbital ridging and other skull features, in estimating **sex and probable ancestry** from unidentified skeletal remains — a routine task in medico-legal skeletal identification.
- ▶ **Orbital (blowout) fracture:** because the medial and inferior walls of the orbit are much thinner than the stout orbital margin, a blunt blow that suddenly raises intra-orbital pressure displaces

the walls (medial wall into the ethmoidal sinuses, floor into the maxillary sinus) while the margin itself often remains intact — this is a **blowout fracture**. Restoring normal orbital height/breadth proportions (and hence orbital volume) with an implant is the surgical goal in floor reconstruction, and pre-operative CT measurement of the orbital aperture is conceptually an imaging analogue of the dry-skull orbital index.

- ▶ **Orbital trauma sequelae:** intra-orbital bleeding from margin or wall fractures raises pressure and causes **exophthalmos**; fractures may also involve the maxillary or ethmoidal sinuses, nasal bones and, rarely, the frontal lobe through the thin (but strong) roof.
- ▶ **Distinguish from interorbital measurements:** the orbital index (height/breadth of one orbital aperture) must not be confused with the **interorbital distance** used to define hypertelorism/hypotelorism in craniofacial syndromes — a separate measurement between the two orbits, not within one.
- ▶ **Craniosynostosis/craniofacial anomalies:** conditions that distort overall skull growth (e.g. bilateral coronal synostosis, or syndromic craniosynostoses such as Crouzon/Apert syndrome) commonly alter orbital shape and spacing secondarily, which is why orbital measurements are recorded alongside cranial-index-type ratios in craniofacial assessment.

### High-yield exam pointers

- ▶ **Orbital index** = (Maximal orbital height ÷ Maximal orbital breadth) × 100, measured on the dry skull with a sliding/spreading compass.
- ▶ Average orbital margin dimensions (Indian textbook figures): **height** ≈ 35 mm, **breadth** ≈ 40 mm → **index** ≈ 87–88.
- ▶ Height = supraorbital margin ↔ infraorbital margin; breadth = medial margin ↔ lateral margin.
- ▶ Classical grading: **Megaseme** ≥ 89; **Mesoseme** 83–88.9; **Microseme** ≤ 82.9 (parallel to cephalic-index grading).
- ▶ Orbital margin bones: supraorbital = frontal; infraorbital = zygomatic + maxilla; medial = frontal + frontal process of maxilla; lateral = zygomatic process of frontal + frontal process of zygomatic. **Dacryon** marks the medial wall junction point.
- ▶ **Supraorbital margin: more rounded in males, sharper in females** — a classical forensic sex marker used with the index.
- ▶ Orbital aperture widens with age (inferolateral rim recession); the change is earlier in women (transverse widening) and later/greater in men (superomedial recession).
- ▶ Companion index to the **cephalic/cranial index**; do not confuse with **interorbital distance** (hypertelorism/hypotelorism).
- ▶ Clinically relevant to **blowout fractures** of the thin medial wall/floor, where the margin (and hence the index-defining points) typically stays intact.

### SOURCE & COVERAGE

AK Datta — Human Anatomy Vol 2 (Head & Neck) — orbital margin dimensions and orbital-index formula; Vishram Singh — Textbook of Anatomy Vol 3, 4e — orbital margins, boundaries and figure; BD Chaurasia — Human Anatomy Vol 3-4, 8e — craniometry (cephalic index) and sex-differences-in-the-skull table; IB Singh — Textbook of Anatomy Vol 3, 6e — craniometric points (Dacryon); Gray's Anatomy (Standring) 41e — age-related change in orbital aperture dimensions; Moore's Clinically Oriented Anatomy, 9e — orbital wall thickness and blowout fracture.

**Coverage note:** the orbital index is a narrow, thinly covered topic across this library — only AK Datta states the formula and representative dimensions verbatim, and Gray's Anatomy (Standring) 41e does not define the index at all (confirmed by full-text search). The megaseme/mesoseme/microseme classification cut-offs are included as standard, universally taught physical-anthropology/craniometry knowledge (directly analogous to the cephalic-index cut-offs already grounded in BD Chaurasia) rather than as a verbatim quotation from any single corpus text.



## Pelvimetry

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Pelvimetry is the measurement of the diameters, planes and capacity of the bony pelvis, undertaken chiefly to judge whether the maternal pelvis is adequate for safe vaginal passage of the fetal head during labour. Since the fetal head is the largest, least compressible part of the fetus, the dimensions of the **true (lesser, obstetric) pelvis** — the bony canal traversed at childbirth — are of prime obstetric importance; the same measurements are also used forensically (skeletal sex determination) and anthropologically. Pelvimetry is performed in three ways: on the dry skeletonised pelvis, clinically on the living subject (external and internal/digital), and radiologically (X-ray, CT or MRI).

### 1. True and false pelvis

- ▶ The bony pelvis is divided by an oblique plane — the **pelvic inlet/brim** — into a greater and a lesser segment. This plane passes through the **sacral promontory** posteriorly and, on each side, the **linea terminalis** (arcuate line of ilium + pecten pubis + pubic crest).
- ▶ The **greater (false) pelvis**, bounded by the iliac fossae and the base of the sacrum, is really part of the abdominal cavity and has no obstetric significance.
- ▶ The **lesser (true, obstetric) pelvis**, bounded by the inlet above, the outlet below, the pubic bones/symphysis anteriorly, the ischia laterally and the sacrum/coccyx posteriorly, is the bony birth canal. Pelvimetry addresses its three levels — **inlet, cavity (mid-pelvis) and outlet**.
- ▶ The pelvic canal is curved (roughly J-shaped) — first directed down and back, then down and forward; the plane of the inlet makes an angle of 50–60° with the horizontal, and the plane of the outlet about 15°, when the subject stands erect.

## 2. Diameters of the true pelvis

□ Fig 13.13 — Diameters at the pelvic inlet. (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.612)

□ Fig 13.14 — Diameters at the pelvic outlet. (Vishram Singh — Textbook of Anatomy Vol 2 — 4e, p.613)

The classic teaching values (adult female, in cm) are:

| Level                                                                                           | Anteroposterior | Oblique | Transverse |
|-------------------------------------------------------------------------------------------------|-----------------|---------|------------|
| <b>Inlet</b> (promontory–symphysis / iliopubic eminence–SI joint / max width of brim)           | 11              | 12      | 13         |
| <b>Mid-cavity</b> (mid-S3–symphysis / SI joint–obturator membrane / widest side wall)           | 12              | 12      | 12         |
| <b>Outlet</b> (coccyx tip–symphysis / sacrotuberous ligament–ischiopubic junction / bituberous) | 13              | 12      | 11         |

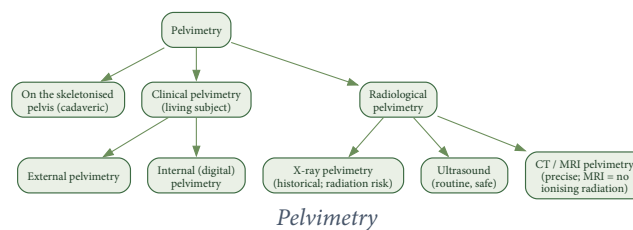
- **Mnemonic pattern:** the AP diameter *increases* from inlet (11) to outlet (13) while the transverse diameter *decreases* from inlet (13) to outlet (11); the oblique diameter stays constant (12) throughout. This reciprocal change is why the fetal head must rotate as it descends (see Applied anatomy).
- Gray's Anatomy gives more precise, sex-differentiated averages: inlet AP (true conjugate) **10 cm (male) / 11.2 cm (female)**; inlet transverse **12.5/13.1 cm**; inlet oblique **12/12.5 cm**; mid-cavity AP **10.5/13 cm**; outlet AP **8/12.5 cm**; outlet transverse (bituberous) **8.5/11.8 cm**.
- **Plane of greatest pelvic dimensions** — the roomiest level, from the mid-symphysis to the S2–S3 junction — offers least resistance to descent.
- **Plane of least pelvic dimensions** — at the level of the ischial spines, transverse (interspinous) diameter only about **9.5 cm** in the adult female — is the narrowest part of the canal and, since it barely exceeds the fetal biparietal diameter (~9 cm), is the commonest site of difficulty/arrest during labour.

## 3. Conjugate (anteroposterior) diameters — clinical shorthand

| Conjugate                        | Landmarks                                                                  | Typical value                     | How assessed                                                                     |
|----------------------------------|----------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------|
| <b>True/anatomical conjugate</b> | Midpoint of sacral promontory → upper border of pubic symphysis            | ~11 cm (avg. 11.2 cm, female)     | Not palpable directly; skeleton/imaging                                          |
| <b>Diagonal conjugate</b>        | Midpoint of sacral promontory → lower (inferior) border of pubic symphysis | At least 11.5 cm (up to ~12.5 cm) | <b>Digital vaginal examination</b> — the single most useful clinical measurement |

| Conjugate                                   | Landmarks                                                                                                      | Typical value                                                                | How assessed                                                  |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------|
| Obstetric conjugate                         | Shortest AP distance, from sacral promontory to the pelvic (posterior, bulging) surface of the pubic symphysis | The narrowest fixed AP diameter of the inlet; should not be less than ~11 cm | Estimated by subtracting 1.5–2 cm from the diagonal conjugate |
| External conjugate (Baudelocque's diameter) | Tip of the spine (spinous tubercle) of the 5th sacral segment → upper border of pubic symphysis                | Not less than 19 cm                                                          | External calipers (largely of historical value)               |

#### 4. Methods of pelvimetry



- **External pelvimetry** — measures surface bony landmarks; now "mostly given up" for limited predictive value, retained only to screen for gross pelvic contraction:
  - **Interspinous diameter** (between outer borders of the anterior superior iliac spines): 22–25 cm.
  - **Intercristal diameter** (widest distance between outer borders of the iliac crests): 25–28 cm.
  - **External conjugate/Baudelocque's diameter**: ≥19 cm (definition above).
  - **Intertuberous diameter** (between the ischial tuberosities): ~10 cm.
- **Internal (digital) pelvimetry** — per vaginal examination, ideally in later pregnancy when hormone-softened tissues permit easier assessment:
  - **Diagonal conjugate** (most useful measurement; ≥11.5 cm), from which the true/obstetric conjugate is estimated (subtract 1.5–2 cm).
  - **Interischial spinous diameter** (~9 cm) — corresponds to the plane of least pelvic dimensions but is difficult to assess digitally.
  - **Subpubic-arch assessment**: in a normal gynaecoid pelvis, the knuckles of a clenched fist should fit comfortably between the ischial tuberosities below the symphysis.
  - Palpation of **sacral curvature**, **coccygeal mobility**, **sacrospinous ligament length** (should exceed the width of two examining fingers), and the **side walls** for any tendency to funnelling.
- **Radiological pelvimetry** — historically by plain X-ray, now largely superseded by **ultrasound** for routine screening; **CT pelvimetry** gives accurate bony measurement at lower dose than plain film, and **MRI pelvimetry** avoids ionising radiation altogether, making it the imaging method of choice when precise pelvic assessment is genuinely needed (e.g., before a trial of vaginal breech delivery).

## 5. Morphological types of the female pelvis (Caldwell–Moloy classification)

| Type                                              | Inlet shape                                          | Approx. incidence | Obstetric note                                                     |
|---------------------------------------------------|------------------------------------------------------|-------------------|--------------------------------------------------------------------|
| <b>Gynaecoid</b> (mesatipellic) — the normal type | Transversely oval; transverse diameter slightly > AP | ~42%              | Roomy, well-shaped cavity; most favourable for vaginal delivery    |
| <b>Android</b> (brachypellic) — male type         | Heart-shaped/triangular; AP diameter > transverse    | ~32%              | Funnel-shaped cavity, narrowed outlet; may cause obstructed labour |
| <b>Anthropoid</b> (dolichopellic) — ape type      | AP diameter much > transverse (oval front-to-back)   | ~23.5%            | Long, narrow pelvis; usually compatible with delivery              |
| <b>Platypelloid</b> (platypellic) — flat pelvis   | Transverse diameter much > AP (flattened)            | ~2.5% (rarest)    | Inlet compressed front-to-back; poses difficulty in delivery       |

- Pure types are uncommon; most female pelvises are mixed forms. Absolute dimensions matter more for the outcome of labour than the shape category alone.

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

A median sagittal section through the female pelvis, labelling: (1) Sacral promontory; (2) Pubic symphysis (upper and lower borders marked separately); (3) Plane of the pelvic inlet (angled 50–60° to horizontal); (4) Plane of the pelvic outlet (angled ~15° to horizontal), showing its two components — anterior (from symphysis) and posterior (from coccyx tip); (5) Tip of coccyx; (6) Linea terminalis/pelvic brim (boundary between greater and lesser pelvis); (7) Curved (J-shaped) axis of the pelvic cavity; (8) True conjugate, diagonal conjugate and obstetric conjugate drawn as separate labelled lines on the same figure to show their distinct landmarks; (9) Ischial spine marking the plane of least pelvic dimensions.

## Applied / Clinical anatomy

- **Cephalopelvic disproportion (CPD)**: the fetal head is too large relative to the maternal pelvis, causing obstructed labour; suspected when the diagonal conjugate is <11.5 cm (obstetric conjugate <~11 cm), or the pelvis is contracted (small but normally shaped) or abnormally shaped (android, platypelloid, or trefoil pelvis).
- **Mechanism of engagement and rotation**: since the inlet's greatest diameter is transverse (13 cm) but the outlet's greatest diameter is AP (13 cm), the fetal head engages transversely (occiput transverse), then rotates ~90° during descent so its AP diameter comes to lie in the outlet's AP diameter at delivery.
- **The plane of least pelvic dimensions** (interspinous, ~9.5 cm), being only slightly wider than the fetal biparietal diameter (~9 cm), is the classical site of arrest of descent in a difficult labour.
- **Hormonal softening**: oestrogen, progesterone and relaxin (from ovary and placenta) soften the pelvic ligaments in late pregnancy, increasing sacroiliac and symphyseal mobility and marginally



enlarging pelvic dimensions during labour — but predisposing to postpartum sacroiliac strain or subluxation.

- ▶ **Trefoil (trifoliated) pelvis:** osteomalacic softening of the hip bones in pregnancy pushes the acetabula inward while the sacrum and symphysis are pushed forward, producing a trefoil-shaped inlet and severe cephalopelvic disproportion.
- ▶ **Pelvic fractures:** disruption of the pelvic ring at two points (e.g., both ischiopubic rami, or one ramus with sacroiliac dislocation) can injure the bladder, urethra, rectum or vagina and cause severe haemorrhage from pelvic vessels; malunion can permanently distort obstetric dimensions.
- ▶ **Forensic/anthropological use:** pelvic dimensions and the subpubic angle are the most reliable skeletal indicators of sex — sexual dimorphism is present even in fetal life and is maximal at about 22 months of age.
- ▶ **Selective use of imaging pelvimetry today:** before trial of vaginal breech delivery, or in women with prior pelvic fracture, short stature, rickets/osteomalacia, or a previous difficult delivery.

### High-yield exam pointers

- ▶ Pelvic brim (sacral promontory + linea terminalis) divides **false (greater) pelvis** — part of the abdomen — from the **true (lesser, obstetric) pelvis**, the bony birth canal, at three levels: inlet, cavity, outlet.
- ▶ Classic female diameters (cm): inlet 11-12-13, mid-cavity 12-12-12, outlet 13-12-11 (AP-oblique-transverse) — a reciprocal AP/transverse relationship that drives fetal head rotation.
- ▶ **Diagonal conjugate** ( $\geq 11.5$  cm, per vaginal exam) is the most clinically useful measurement; **true/obstetric conjugate** = diagonal conjugate – 1.5–2 cm.
- ▶ **Plane of least pelvic dimensions** = interspinous plane (~9.5 cm) — the commonest site of difficulty in labour.
- ▶ Three broad methods: pelvimetry on the **skeletonised pelvis**, **clinical** pelvimetry (external + internal/digital), and **radiological** pelvimetry (X-ray/CT/MRI) — ultrasound and MRI have largely replaced plain X-ray.
- ▶ **Caldwell–Moloy classification:** gynaecoid (~42%, normal), android (~32%), anthropoid (~23.5%), platypelloid (~2.5%, rarest).
- ▶ Clinical importance: detecting **cephalopelvic disproportion/contracted pelvis**, especially before trial of vaginal breech delivery or in short stature, previous pelvic trauma, or rickets/osteomalacia.
- ▶ Also used forensically/anthropologically for skeletal **sex determination**.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia — Human Anatomy Vol 2 8e; Vishram Singh — Textbook of Anatomy Vol 2 4e; IB Singh — Textbook of Anatomy Vol 2 6e; Moore's Clinically Oriented Anatomy 9e. Coverage note: pelvimetry is fundamentally gross/applied osteology of the bony pelvis rather than embryology — none of the assigned embryology specialty texts (Langman, Moore's The Developing Human, Larsen, IB Singh Human Embryology, Hamilton-Boyd-Mossman, Vishram Singh Clinical Embryology, Sontakke, Brijesh Kumar) mention pelvimetry, so gross-anatomy texts (BD Chaurasia, Vishram Singh, IB Singh, Moore COA) supply the clinical/measurement depth alongside the Gray's Anatomy spine chapter on the pelvic girdle (Ch. 80).



## Phylogeny of the Heart

Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy

**Definition / Introduction** — Phylogeny is the evolutionary history of a species, as distinct from ontogeny, the developmental history of an individual; Haeckel's biogenetic law (1866) states that "ontogeny recapitulates phylogeny" — the developing individual transiently passes through stages resembling its evolutionary ancestors. The vertebrate heart illustrates this well: it evolved from a single unpaired tubular pump in fishes to the fully septated, double (systemic + pulmonary) circulation of birds and mammals, driven chiefly by the replacement of gill respiration by lung respiration in land-dwelling vertebrates. The human embryonic heart briefly recapitulates this sequence, passing through an unseptated tubular stage before septation produces the definitive four-chambered heart.

### The primitive vertebrate heart plan — the fish heart

- ▶ In most fishes, throughout adult life, the heart remains a **single tubular structure** arranged as five successive dilated chambers in series, each separated from the next by a constriction.
- ▶ The five chambers, from the venous to the arterial end, are:

| Order | Chamber            | Nature                                                         |
|-------|--------------------|----------------------------------------------------------------|
| 1     | Sinus venosus      | receptive chamber — receives systemic venous return            |
| 2     | Atrium             | single chamber                                                 |
| 3     | Ventricle          | single, muscular pumping chamber                               |
| 4     | Bulbus cordis      | contractile chamber continuous with the outflow tract          |
| 5     | Truncus arteriosus | efferent vessel giving rise to the afferent branchial arteries |

- ▶ **Circulatory pathway (single circulation):** systemic venous blood → sinus venosus → atrium → ventricle → bulbus cordis → truncus arteriosus → afferent branchial arteries → capillaries of the gills (oxygenation) → efferent branchial vessels → paired dorsal aortae → distributed to the body.
- ▶ Blood therefore passes through the heart **only once** per complete circuit — a single circulation, with no admixture of oxygenated and deoxygenated blood because there is, as yet, no separate pulmonary circuit.

### The amphibian heart — onset of double circulation

- ▶ The **tadpole** (larval, gill-breathing) heart is essentially identical to the fish heart described above.
- ▶ After **metamorphosis** (onset of lung breathing), a septum develops in the atrium, dividing it into **right and left atria**:
  - the **right atrium** receives systemic (deoxygenated) venous blood via the sinus venosus;
  - the **left atrium** receives oxygenated blood via the newly established pulmonary veins.
- ▶ Both atria empty into a **single, unseptated ventricle**, from which blood is ejected through a single truncus arteriosus to be distributed both to the body and to the lungs.
- ▶ There is **some separation** of oxygenated from deoxygenated streams during passage through the ventricle and truncus (owing to streaming and to a partial spiral fold within the truncus), but separation is **incomplete** and appreciable mixing of the two streams occurs (Foxon, 1955).
- ▶ This represents the earliest appearance of a **double circulation** (systemic + pulmonary) superimposed on an as-yet incompletely partitioned heart.

### The reptilian heart — ventricular septation begins

- ▶ In reptiles, septation extends further to include the **ventricle**, which now possesses an incomplete interventricular septum.
- ▶ **With the exception of the Crocodilia**, ventricular septation in reptiles remains incomplete, so that in all other reptiles there continues to be some mixing of oxygenated pulmonary-venous blood with the systemic venous return within the heart.
- ▶ Crocodilia are unique among reptiles in achieving a **complete ventricular septum**, anticipating the fully divided heart of birds and mammals, although (as in other reptiles) the outflow arrangement still permits some communication between the two circulations outside the heart.

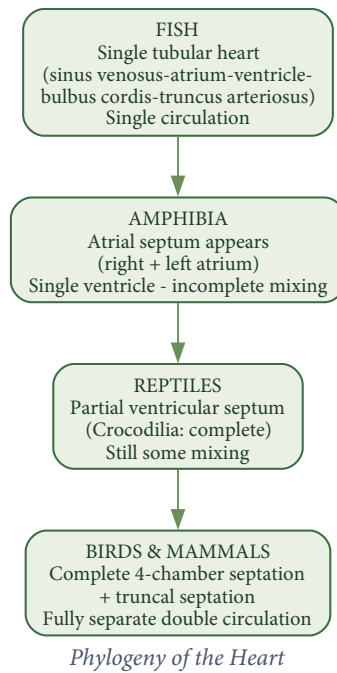
### The avian and mammalian heart — complete septation, full double circulation

- ▶ Birds and mammals are **warm-blooded (homeothermic)**; their higher metabolic rate demanded a more efficient circulatory system.
- ▶ The heart becomes **completely septated into four chambers**: a right atrium communicating only with a right ventricle, and a left atrium communicating only with a left ventricle — there is no direct communication between the two sides.
- ▶ **Circulatory pathway**:
  - Systemic venous blood from the body → **sinus venosus** (incorporated into the right atrium) → **right atrium** → **right ventricle** → **pulmonary artery** → lungs (oxygenation).

- Oxygenated blood from the lungs → **pulmonary veins** → **left atrium** → **left ventricle** → **aorta** → distributed to the body generally.
- Complete septation of the atria and ventricles necessarily requires an accompanying **septation of the truncus arteriosus/bulbus cordis complex** into a separate pulmonary trunk and aorta; without truncal septation, chamber septation alone cannot achieve two fully separate circuits.
- The outflow (bulbar) segment shows a clear phylogenetic naming continuity: the **conus arteriosus** of primitive fish and the **bulbus cordis** of amphibia are together presumed to give rise to the definitive **right ventricle (outflow tract/infundibulum)** of higher vertebrates.

### Comparative summary across vertebrate classes

| Vertebrate class              | Chambers                                                                   | Septation                                       | Circulation type                | Mixing of blood                           |
|-------------------------------|----------------------------------------------------------------------------|-------------------------------------------------|---------------------------------|-------------------------------------------|
| Fish                          | 1 atrium, 1 ventricle, bulbus cordis, truncus, sinus venosus (5 in series) | None                                            | Single                          | Not applicable (single circuit)           |
| Amphibia (post-metamorphosis) | 2 atria, 1 ventricle                                                       | Atrial septum only                              | Double (incompletely separated) | Marked, in ventricle/truncus              |
| Reptiles (non-crocodilian)    | 2 atria, 1 ventricle (incompletely septated)                               | Atrial + partial ventricular septum             | Double (incompletely separated) | Present, reduced                          |
| Crocodylia                    | 2 atria, 2 ventricles                                                      | Complete atrial + ventricular septum            | Double                          | Minimal (extracardiac communication only) |
| Birds & mammals               | 2 atria, 2 ventricles                                                      | Complete septation (atria, ventricles, truncus) | Double, fully separated         | None                                      |



### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the vertebrate heart series left to right or top to bottom, one schematic per class, each labelled:

- ▶ **Fish heart** (single tube): label, in order, *sinus venosus* → *atrium* → *ventricle* → *bulbus cordis* → *truncus arteriosus*; show afferent branchial arteries leaving the truncus and the paired dorsal aortae receiving oxygenated blood from the efferent branchial vessels.
- ▶ **Amphibian heart**: label *right atrium* and *left atrium* (with an atrial septum between them), converging on a single *ventricle*, then a single *truncus arteriosus*; show systemic veins entering the right atrium and pulmonary veins entering the left atrium.
- ▶ **Reptilian heart**: as above but add a partial (incomplete) *interventricular septum*; annotate "complete in Crocodilia only".
- ▶ **Avian/mammalian heart**: fully septated four chambers — *right atrium*, *right ventricle*, *left atrium*, *left ventricle* — with the *pulmonary artery* leaving the right ventricle and the *aorta* leaving the left ventricle; no interchamber communication.
- ▶ Use arrows to show the direction of blood flow in each schematic, and shade oxygenated blood (light) versus deoxygenated blood (dark) to visually demonstrate progressively better separation across the series.

### Applied / Clinical anatomy

- ▶ **Congenital heart disease as arrested phylogeny**: many congenital cardiac anomalies can be conceptually understood as an arrest of septation at an earlier phylogenetic stage — e.g., a **common atrium** or **single/common ventricle** resembles the amphibian/early-reptilian plan; an **atrial septal defect (ASD)** or **ventricular septal defect (VSD)** represents incomplete completion of the septation that is normally achieved in mammals.

- ▶ **Persistent truncus arteriosus** — failure of septation of the truncus/bulbus cordis into separate aorta and pulmonary trunk — mirrors the un-septated outflow tract of fish and amphibia, and is a direct illustration of why chamber septation and truncal septation must proceed together.
- ▶ **Sinus venosus fate:** in the human embryo, as in lower vertebrates, the sinus venosus is initially paired (right and left horns); the right horn enlarges and is incorporated into the right atrium (forming the smooth-walled sinus venarum) while the left horn regresses to become the coronary sinus — a phylogenetic reduction from bilateral symmetry to right-sided dominance, clinically relevant to anomalies such as persistent left superior vena cava draining into an enlarged coronary sinus.
- ▶ **Teaching value:** understanding the phylogenetic sequence gives residents a logical framework for classifying and explaining congenital cyanotic and acyanotic heart disease to undergraduates, rather than requiring rote memorisation of each anomaly in isolation.
- ▶ **Cross-sectional/imaging correlate:** echocardiographic assessment of chamber septation in the fetus/neonate is, in effect, a check that the heart has completed the phylogenetic sequence described above; failure of any step is directly visualised as the corresponding congenital defect.

### High-yield exam pointers

- ▶ Haeckel's biogenetic law (1866): "ontogeny recapitulates phylogeny."
- ▶ Fish heart = single tube, 5 chambers in series: sinus venosus → atrium → ventricle → bulbus cordis → truncus arteriosus; single circulation.
- ▶ Amphibian heart: atrial septum appears (2 atria) but ventricle remains single and unseptated — incomplete separation of oxygenated/deoxygenated blood.
- ▶ Reptiles: ventricular septation begins but is incomplete in all reptiles **except Crocodilia**, which alone achieve a complete ventricular septum.
- ▶ Birds and mammals: warm-blooded, higher metabolic demand → complete 4-chambered heart with full septation of atria, ventricles, and the truncus arteriosus (into aorta + pulmonary trunk) → fully separated double circulation.
- ▶ Outflow tract homology: conus arteriosus (fish) and bulbus cordis (amphibia) are presumed precursors of the definitive right ventricle/outflow tract in higher vertebrates.
- ▶ Septation of chambers alone is insufficient — truncal (bulbo-arterial) septation must occur in parallel for a true double circulation.
- ▶ Human embryonic heart transiently recapitulates the un-septated tubular (fish-like) stage before septation produces the definitive mammalian 4-chambered heart — the conceptual basis for interpreting many congenital cardiac anomalies.

### SOURCE & COVERAGE

Hamilton, Boyd & Mossman — Human Embryology (primary source for this classical comparative-anatomy topic — "Phylogeny of the Heart," including the fish/amphibian/reptile/bird-mammal sequence and the Foxon 1955 reference on incomplete separation); Gray's Anatomy (Standring) 41e (outflow-tract/conus arteriosus-bulbus cordis homology across vertebrate classes); Sontakke — Textbook of Human Embryology (definitions of phylogeny/ontogeny and Haeckel's biogenetic law).

**Coverage note:** This is a classical comparative-embryology topic that lies outside Gray's Anatomy's human-centred narrative; the corpus's primary and near-exclusive grounding for the vertebrate-class-by-class sequence is the dedicated "Phylogeny of the Heart" section in Hamilton, Boyd & Mossman. Widely-taught comparative-anatomy details not independently verifiable in the present corpus (e.g., the specific eponymous inter-arch communication in Crocodilia) have been deliberately omitted rather than stated as unverified fact.



## Placental barriers in mammals

*Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction.** The **placental barrier (placental membrane)** is the layer, or set of layers, of maternal and fetal tissue that intervenes between the maternal and fetal blood streams at the definitive site of exchange in a chorioallantoic placenta, so that the two circulations never mix while gases, nutrients, waste products, hormones and (selectively) antibodies and pathogens pass across it. Comparative embryologists classify the placentae of different mammalian orders according to **how many maternal tissue layers have been lost** at this interface — **Grosser's classification (1927)** — because this determines both the intimacy of maternal–fetal contact and, functionally, what the barrier will and will not let through. The human placenta is **haemochorial**, the most invasive type in this scheme, with maternal blood in direct contact with the fetal chorion.

### 1. Grosser's classification of the placental barrier in mammals

- Based on the **tissues in contact** at the zone of interchange, not the tissues present overall — as the trophoblast becomes progressively more invasive, one maternal layer after another is stripped away.
- Gray's Anatomy (41e) itself notes that "different grades of fusion exist between the maternal and fetal tissues in many other mammals (e.g. **epitheliochorial**, **syndesmochorial**, **endotheliochorial**)" as against the human **haemochorial** state.

| Type             | Maternal tissue in contact with chorion | Representative mammals                                           |
|------------------|-----------------------------------------|------------------------------------------------------------------|
| Epitheliochorial | Intact uterine epithelium               | Pig, horse, donkey, whale/cetaceans, lemurs and other prosimians |



| Type                   | Maternal tissue in contact with chorion                                                                               | Representative mammals                                                                                                                                                                                    |
|------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Syndesmochorial        | Uterine epithelium lost; endometrial connective tissue in contact                                                     | Ruminants — cow, sheep, goat, deer (classical Grosser category; the contact zone is limited and largely non-functional, so some authors merge it functionally with the epitheliochorial group)            |
| Endotheliochorial      | Uterine epithelium and connective tissue lost; endothelium of maternal vessel in contact                              | Carnivora — dog, cat, seal                                                                                                                                                                                |
| Haemochorial           | All maternal tissue lost; chorion bathed directly in maternal blood                                                   | Primates (including <b>Man</b> ), most rodents, many Insectivora                                                                                                                                          |
| Haemoendothelial       | Maternal blood in direct contact with fetal capillary endothelium (trophoblast apparently absent by light microscopy) | Historically ascribed to rabbit and certain rodents; electron microscopy (Enders, 1965) shows an extremely thin (~0.5 µm) residual trophoblast layer, so a <i>true</i> haemoendothelial state is doubtful |
| Endothelio-endothelial | Maternal vessel endothelium directly opposed to fetal capillary endothelium                                           | Some shrews (anatomically endotheliochorial, but functionally endothelio-endothelial because the intervening trophoblast is thin and perforated/spongy)                                                   |



## 2. Correlation with gross architecture and deciduate status

- The barrier type correlates loosely with the gross (macroscopic) shape of the mature placenta and with whether maternal tissue is shed at birth.

| Barrier type      | Gross shape (example)                                                                | Deciduate at parturition?                                                                                                                                                      |
|-------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epitheliochorial  | Diffuse — villi scattered over whole chorionic sac (pig)                             | Non-deciduate — separates without tearing maternal tissue                                                                                                                      |
| Syndesmochorial   | Cotyledonary — villi grouped into discrete tufts/cotyledons (cow, deer)              | Non-deciduate                                                                                                                                                                  |
| Endotheliochorial | Zonary/annular — villi confined to a girdle around the sac (dog and other Carnivora) | Deciduate, though without the specific decidual (glycogen/lipid-laden) cells typical of Man — separation instead follows tearing of the richly glandular, vascular endometrium |

| Barrier type | Gross shape (example)                                                  | Deciduate at parturition?                                                                       |
|--------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Haemochorial | Discoid/bidiscoid (Man, monkey) or diffuse-labyrinthine (many rodents) | <b>Deciduate</b> — true decidual-cell reaction, with loss of maternal tissue and blood at birth |

- ▶ **Non-deciduate placentae** (epitheliochorial, syndesmochorial) involve no true invasion of maternal tissue by trophoblast; **deciduate placentae** (endotheliochorial, haemochorial) do, with variable maternal tissue and blood loss at parturition.

### 3. The human placental barrier — a haemochorial membrane

- ▶ Maternal blood in the **intervillous space** bathes the chorionic villi directly; the human placenta is therefore **haemochorial**. From the third week of gestation, terminal villi form and branch continuously within the intervillous space throughout pregnancy.
- ▶ **Early pregnancy (up to about the 20th week / third–fourth month)** — the barrier is described as **five to six histological layers** (texts differ slightly in how the two basement membranes are enumerated), from maternal to fetal blood:
  - ▶ **Syncytiotrophoblast** — multinucleated outer covering, in direct contact with maternal blood.
  - ▶ **Cytotrophoblast (Langhans' cells)** — a discontinuous germinal layer beneath the syncytium, present up to about 20 weeks.
  - ▶ **Basement membrane of the cytotrophoblast.**
  - ▶ **Extraembryonic mesoderm/connective tissue** in the villous core.
  - ▶ **Basement membrane of the fetal capillary endothelium.**
  - ▶ **Endothelium of the fetal capillary.**
- ▶ **Late pregnancy** — cytotrophoblast progressively disappears, both basement membranes fuse, and the villous mesoderm thins, reducing the barrier to a **thin syncytiotrophoblast directly apposed to fetal capillary endothelium** (the "vasculo-syncytial membrane"), which markedly increases diffusional efficiency as fetal demand rises.
- ▶ **Thickness and area:** the membrane thins from about **0.025 mm in early pregnancy to about 0.002 mm at term**; total exchange surface area is roughly **11–14 m<sup>2</sup>**, comparable to the absorptive surface of the gut.
- ▶ Factors responsible for this progressive thinning: attenuation of the syncytiotrophoblast; disappearance of the cytotrophoblast from the villi; fusion/disappearance of the two basement membranes; and thinning of the fetal capillary endothelial cells.
- ▶ At term, **fibrinoid material** deposits on parts of the villous surface (Nitabuch's membrane at the decidual junction; Rohr's fibrinoid stria on the intervillous surface), which paradoxically reduces the efficiency of the membrane even as its cellular layers thin.
- ▶ **Note (Gray's 41e):** recent in-vivo and anatomical studies (Jauniaux et al., 2003) show that the human placenta is **not truly "open" haemochorial in early pregnancy** — extravillous trophoblast forms a continuous shell at the decidual level and plugs the tips of the spiral arteries, so that only plasma (not whole maternal blood) initially perfuses the intervillous space until about 10–12 weeks; free maternal blood flow into the space is established only thereafter.

□ Fig 9.6 — Placental barrier. In early foetal life, placental barrier consists of endothelium of foetal blood vessels, its basement membrane, mesodermal layer, cytotrophoblast and syncytiotrophoblast; from the fourth month onwards it is represented only by thin syncytiotrophoblast and foetal capillary endothelium (Sontakke — Textbook of Human Embryology, p.86)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw the placental villus in transverse section, in two panels (early vs late pregnancy), labelling from the maternal (intervillous space) to the fetal (capillary lumen) side:

- ▶ Maternal blood in intervillous space
- ▶ Syncytiotrophoblast (label as continuous in both panels, thick early/thin late)
- ▶ Cytotrophoblast (Langhans' layer) — present in the early panel; label "disappears after ~20 weeks" in the late panel
- ▶ Basement membrane of cytotrophoblast
- ▶ Villous mesoderm/connective tissue core
- ▶ Basement membrane of fetal capillary endothelium
- ▶ Endothelium of fetal capillary
- ▶ Fetal blood in capillary lumen
- ▶ Annotate the late panel as the "vasculo-syncytial membrane" (fused basement membranes + thin syncytium + thin endothelium)

## 4. Functional correlation of barrier structure with permeability

- ▶ **Barrier type dictates transplacental immunoglobulin transfer.** In haemochorial placentae (Man, most rodents) IgG is selectively, actively transported across the syncytiotrophoblast, providing passive immunity; cord IgG can exceed maternal levels at term. In mammals with syndesmochorial/epitheliochorial placentation the barrier is **essentially impermeable to maternal immunoglobulins** — in cattle, for instance, the placenta is "apparently completely impermeable to immune bodies (globulins)," so passive immunity is transferred entirely **postnatally through colostrum**, absorbed by the permeable neonatal gut in the first hours of life — the classical functional correlate of the Grosser classification.
- ▶ **Barrier thickness and diffusional efficiency** are only loosely related — thinner is not invariably more efficient, and comparative electrolyte-transfer studies show some thick placentae outperform thinner ones; no single structural parameter (layer count, thickness) fully explains inter-species differences in transfer rate.
- ▶ **Trophoblast as an immunological barrier:** the syncytiotrophoblast expresses neither class I nor class II MHC antigens, which is thought to protect the genetically "foreign" fetal tissue from maternal immune rejection despite intimate contact with maternal blood in haemochorial placentation.
- ▶ **What normally crosses:** respiratory gases ( $O_2$ ,  $CO_2$ ), glucose, amino acids, fatty acids, vitamins, electrolytes, urea/uric acid (fetal to maternal), and maternal IgG (only IgG among the immunoglobulins; IgA and IgM do not cross).
- ▶ **What is normally excluded/restricted:** maternal blood cells (largely, though a small fetomaternal leak of erythrocytes occurs physiologically), IgA and IgM, and most large protein complexes —

but the barrier is not absolute, and many pathogens, toxins and small lipophilic drugs cross readily (see Applied anatomy).

## Applied / Clinical anatomy

- ▶ **TORCH infections** — *Treponema pallidum*, *Toxoplasma gondii*, rubella, cytomegalovirus and other organisms cross the haemochorial barrier, especially when it is thin (later pregnancy) or breached by placental pathology, causing congenital infection syndromes.
- ▶ **Teratogenic drugs** — thalidomide, phenytoin, alcohol, warfarin and other small lipid-soluble drugs cross readily; classification of drug safety in pregnancy is built directly on knowledge of transplacental transfer across this barrier.
- ▶ **Rh isoimmunization** — a small volume of fetal Rh-positive erythrocytes normally leaks across the barrier into the Rh-negative maternal circulation (fetomaternal haemorrhage); this sensitizes the mother, and subsequent anti-D IgG crosses back across the barrier to cause haemolytic disease of the fetus/newborn in later pregnancies.
- ▶ **Abnormal trophoblastic invasion** — shallow trophoblastic invasion of spiral arteries (failure of the normal remodelling described above) is implicated in pre-eclampsia and intrauterine growth restriction; excessive invasion underlies placenta accreta/increta/percreta.
- ▶ **Comparative/veterinary relevance** — neonatal ungulates (calves, foals, lambs, piglets) are born **agammaglobulinaemic** for exactly this reason, making early colostrum feeding an obstetric/veterinary emergency rather than a convenience.
- ▶ **Radiological/practical correlate** — chorionic villus sampling exploits direct access to trophoblast tissue at the maternal–fetal interface for prenatal genetic diagnosis, reflecting the haemochorial anatomy of the human placenta.

## High-yield exam pointers

- ▶ **Grosser's classification (1927)** — six types by maternal tissue in contact with chorion: epitheliochorial, syndesmochorial, endotheliochorial, haemochorial, haemoendothelial, endothelio-endothelial.
- ▶ **Human placenta = haemochorial** — maternal blood directly bathes the chorionic villi in the intervillous space.
- ▶ Gross shape correlates: **diffuse** (pig), **cotyledonary** (ruminants), **zonary** (Carnivora), **discoid/bidiscoid** (primates, Man).
- ▶ **Non-deciduate**: epitheliochorial, syndesmochorial. **Deciduate**: endotheliochorial, haemochorial.
- ▶ Human barrier layers, maternal→fetal: **syncytiotrophoblast** → **cytotrophoblast** → **its basement membrane** → **villous mesoderm** → **fetal capillary basement membrane** → **fetal capillary endothelium** — reduces to a thin **vasculo-syncytial membrane** after ~20 weeks.
- ▶ Thickness falls from ~0.025 mm (early) to ~0.002 mm (term); total area ~11–14 m<sup>2</sup>.
- ▶ Only **IgG** crosses the human placenta (not IgA/IgM) — basis of neonatal passive immunity; ruminant syndesmochorial placentae are impermeable to immunoglobulins, so colostrum is the sole route of passive immunity in those species.

- Modern data show the earliest human placentation is not fully "open" haemochorial — a trophoblastic shell/plugs limit maternal blood flow into the intervillous space until ~10–12 weeks.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Hamilton, Boyd & Mossman's Human Embryology (Grosser's classification, comparative placentation, immunoglobulin transfer); Vishram Singh's Textbook of Clinical Embryology; Sontakke's Textbook of Human Embryology; Brijesh Kumar's Embryology Text & Atlas. Coverage note: the six-type Grosser scheme (especially the syndesmochorial and haemoendothelial/endothelio-endothelial categories) is documented in the classical comparative-embryology text (Hamilton, Boyd & Mossman) rather than in the human-focused Indian embryology texts, which mostly teach a five-type version omitting syndesmochorial; both are presented here for completeness, with the discrepancy noted explicitly.



## Placentation in mammals

*Asked in: Paper II May 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** Placentation is the apposition or fusion of the fetal membranes (chorion, and in eutherians usually the allantois) to the uterine mucosa so as to permit physiological exchange of gases, nutrients and waste products between mother and fetus. The definitive, permanent placenta of every eutherian ("placental") mammal is the **chorio-allantoic placenta**, although transient **chorio-vitelline** and **inverted-yolk-sac** placental mechanisms also operate earlier in gestation in several orders. Mammalian placentae show enormous comparative variation, and are classified on four independent bases — (1) the type of implantation, (2) the gross shape/distribution of villi, (3) the histological intimacy of fetomaternal contact (Grosser's classification), and (4) the presence or absence of a decidual reaction at parturition. The human placenta is one specific combination of these — discoid, villous, hemochorial and deciduate.

### 1. Types of implantation

The manner in which the blastocyst embeds itself determines the subsequent architecture of the placenta.

| Type                                     | Description                                                                               | Examples                         |
|------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------|
| Central<br>(circumferential/superficial) | Chorionic sac remains free in the uterine lumen and expands to fill it; no deep burrowing | Pig, sheep, cow, horse, dog, cat |
| Eccentric                                | Blastocyst lodges in a recess of the uterine cavity that becomes partly walled off        | Mouse, rat, hamster              |

| Type                    | Description                                                                                                                                                                       | Examples                   |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Interstitial (complete) | Blastocyst, while still <0.5 mm, penetrates the uterine epithelium and becomes wholly embedded in the endometrium, at a much earlier developmental stage than the other two types | Man, chimpanzee, some bats |

The implantation site also varies — antimesometrial in most rodents and insectivores, mesometrial in some bats and *Tarsius*, and strictly lateral (alternating) in tenrecs.

## 2. Sources of placentation in Eutheria

- **Chorio-vitelline (yolk-sac) placenta** — vascularised trilaminar omphalopleure apposed to the endometrium; transient, nutritive, seen in many carnivores, rodents and insectivores before the allantois vascularises the chorion; homologous to the definitive marsupial placenta.
- **Inverted yolk-sac placenta** — in mammals showing "inversion of the germ layers" (entopy) — rodents, rabbit (Lagomorpha), many bats and insectivores — the vascular embryonic yolk-sac endoderm inverts and lies directly against the endometrium; in the rabbit it is functionally important for passive transfer of maternal immunoglobulins to the fetus.
- **Chorio-allantoic placenta** — the definitive, persisting placenta in all Eutheria; the rest of this answer classifies this type.

## 3. Classification by gross form of the chorio-allantoic placenta

Based on the distribution of villi over the chorionic surface (Grosser/Mossman):

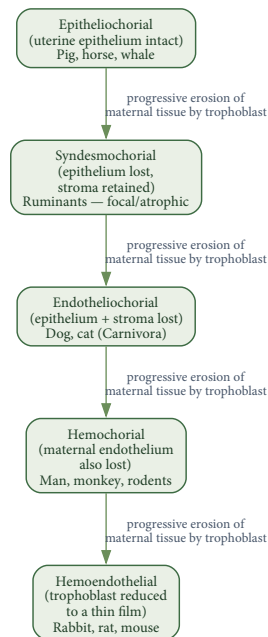
| Gross type          | Villous distribution                                                          | Examples                                                              |
|---------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Diffuse             | Villi scattered uniformly over the entire chorionic surface                   | Pig, horse                                                            |
| Cotyledonary        | Villi aggregated into discrete tufts (cotyledons) separated by smooth chorion | Cow, sheep, deer                                                      |
| Zonary (annular)    | Villi confined to a girdle/band around the equator of the chorionic sac       | Dog, cat, seal (carnivores); incomplete zonary in the raccoon         |
| Discoid / Bidiscoid | Villi restricted to one (or two) disc-shaped area(s)                          | Rodents and most primates — discoid (man); some monkeys — bidiscoidal |

## 4. Classification by intimacy of fetomaternal tissue contact — Grosser's histological classification

This is the most important scheme functionally, since it defines the **zone of interchange** (the "placental membrane") through which all materno-fetal exchange occurs. Progressive erosion of maternal tissue by invading trophoblast produces five recognised grades:

| Type              | Maternal tissue retained                                                                                                                                                           | Approx. layers | Examples                                                                                                                                                                                                                           |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epitheliochorial  | Endothelium + connective tissue + intact uterine epithelium, apposed to trophoblast                                                                                                | 6              | Pig, horse, whale, lemur (prosimian)                                                                                                                                                                                               |
| Syndesmochorial   | Endothelium + connective tissue (uterine epithelium lost); trophoblast contacts maternal connective tissue                                                                         | 5              | Classically described in ruminants (cow) — but Grosser himself noted this condition is limited to small, probably atrophic/non-functional areas, so the main ruminant placenta is better regarded as epitheliochorial-cotyledonary |
| Endotheliochorial | Only maternal endothelium retained; epithelium and stroma eroded                                                                                                                   | 4              | Dog, cat and other Carnivora (labyrinthine arrangement)                                                                                                                                                                            |
| Hemochorial       | All maternal tissue eroded; trophoblast bathed directly in maternal blood                                                                                                          | 3              | Man, higher primates, rodents                                                                                                                                                                                                      |
| Hemoendothelial   | Even the trophoblast is reduced to an extremely thin ( $\sim 0.5 \mu\text{m}$ ) discontinuous layer, so only the fetal capillary endothelium truly separates the two blood streams | 1–2            | Rabbit and certain rodents (rat, mouse, hamster, guinea pig) — demonstrable only by electron microscopy                                                                                                                            |





Placentation in mammals

Electron microscopy (Enders) further subdivides the trophoblastic layer itself into **mono-, bi- and tri-chorial** placentae according to the number of trophoblast cell layers, regardless of the Grosser grade.

## 5. Deciduate vs non-deciduate placentation

- ▶ **Non-deciduate placentae** — trophoblast merely apposes maternal tissue without true invasion, so no maternal tissue is shed and no bleeding occurs at parturition. All **epitheliochorial** placentae (diffuse and cotyledonary) are non-deciduate.
- ▶ **Deciduate placentae** — trophoblastic invasion destroys maternal tissue, which is shed with the afterbirth. Both **endotheliochorial** (labyrinthine) and **hemochorial** (labyrinthine, trabeculate or villous) placentae are deciduate.
- ▶ **Decidual cells** (large glycogen- and lipid-laden polyhedral stromal cells) are conspicuous in hemochorial deciduate placentae (primates, rodents) but are typically **absent** in the endotheliochorial deciduate placenta of carnivores, where the plane of separation at birth is instead provided by attenuated septa between dilated, torn endometrial glands.

## 6. Arrangement of the zone of interchange — labyrinthine, trabeculate and villous placentae

- ▶ **Labyrinthine** — trophoblast forms thin lamellae bridging adjacent fetal villi, creating tubules through which maternal blood circulates in intimate contact with fetal capillaries; seen as endotheliochorial-labyrinthine (most carnivores) and hemochorial-labyrinthine (rabbit, rodents, some primitive New-World monkeys).
- ▶ **Trabeculate** — the intervillous trophoblastic lamellae are incomplete/fenestrated, giving a sponge-work of maternal blood spaces; an intermediate hemochorial condition in many Old- and New-World monkeys.
- ▶ **Villous** — intervillous trabeculae have virtually disappeared, leaving free, tree-like terminal villi bathed in a continuous intervillous space; the hemochorial-villous condition of higher Old-World monkeys, great apes and Man, evolved from the hemochorial-labyrinthine pattern.

- ▶ Maternal and fetal blood streams typically flow in **opposite directions** across the zone of interchange in labyrinthine placentae — a counter-current arrangement of physiological advantage that probably also operates, in modified form, in the villous human placenta.

## 7. Human placenta — a worked example of the classification

The human placenta at term is **discoid** (single disc, 15–20 cm diameter, ~3 cm thick, ~500 g), **hemochorial-villous**, **deciduate**, and derived from the **chorio-allantoic** mechanism, developing after **complete interstitial implantation**. Maternal blood in the intervillous space bathes free-floating and anchoring chorionic villi whose core (allantoic) fetal capillaries are separated from maternal blood only by trophoblast (syncytiotrophoblast, and cytotrophoblast till mid-pregnancy), villous connective tissue and fetal capillary endothelium — the three-layered hemochorial barrier that thins further as pregnancy advances.

□ Fig 6.3 — Human Placenta (A) Fetal side of the mature placenta with attached umbilical cord (B) Maternal side showing several cotyledons (Larsen — Human Embryology — 6e, p.355)

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Two panels side by side, as in the figure above:

- ▶ **Fetal surface** — smooth, covered by amnion; branching chorionic (subchorial) vessels converging to the **umbilical cord** inserted near the centre.
- ▶ **Maternal surface** — rough, divided by placental (decidual) **septa** into 15–20 **cotyledons**; label the **basal plate/decidua basalis**.
- ▶ Alongside, a labelled cross-section box showing: chorionic plate → intervillous space (maternal blood) → anchoring villus → free villus → basal plate/decidua basalis, with the placental-barrier layers (syncytiotrophoblast, cytotrophoblast, villous mesenchyme, fetal capillary endothelium) named at a villus tip.

## Applied / Clinical anatomy

- ▶ **Interstitial implantation** in Man means the blastocyst is normally embedded well within the stroma; when the decidua basalis is deficient (e.g., a previously scarred lower uterine segment), trophoblast invades abnormally deeply — the clinical **placenta accreta spectrum** (accreta/increta/percreta).
- ▶ **Chorionic villus sampling** exploits direct access to trophoblast for first-trimester prenatal genetic diagnosis, made possible only because the human placenta is hemochorial-villous with trophoblast at the fetomaternal interface.
- ▶ **Species choice in teratology/toxicology** must respect placental type: the rodent hemo(-endothelio)chorial placenta is often used as a proxy for the human hemochorial placenta because both lack an intact maternal epithelial/endothelial barrier, whereas epitheliochorial (pig) or endotheliochorial (dog) placentae transfer maternal antibody far less efficiently in utero and are poor models for transplacental drug/antibody passage.
- ▶ **Antigenic tolerance of pregnancy** — syncytiotrophoblast expresses neither class I nor class II MHC antigens, an adaptation of particular interest across all deciduate (invasive) placental types,

where fetal (paternal-antigen-bearing) trophoblast is in direct contact with maternal tissue/blood.

- ▶ **Zonary placenta (dog, cat)** explains the characteristic band-like placental scar and the pattern of placental separation in veterinary obstetric practice.
- ▶ **Velamentous/marginal (battledore) cord insertion** and **vasa praevia**, seen in the human discoid placenta, are clinically important causes of antepartum haemorrhage and fetal compromise.

### High-yield exam pointers

- ▶ Placentation = apposition/fusion of fetal membranes to uterine mucosa for materno-fetal exchange; definitive type in all Eutheria is chorio-allantoic.
- ▶ Three implantation patterns: central/superficial, eccentric, interstitial (complete) — Man shows interstitial.
- ▶ Gross shape: diffuse (pig) → cotyledonary (cow) → zonary (dog/cat) → discoid/bidiscoid (rodents, primates, Man).
- ▶ Grosser's histological (barrier) classification, in order of increasing intimacy: epitheliochorial → syndesmochorial → endotheliochorial → hemochorial → hemoendothelial.
- ▶ Human placenta = hemochorial, villous, discoid, deciduate.
- ▶ Non-deciduate = epitheliochorial (no invasion, no bleeding at birth); deciduate = endotheliochorial and hemochorial types (invasion, decidua shed at parturition).
- ▶ Decidual cells: present in hemochorial deciduate placentae (primates, rodents); absent in endotheliochorial deciduate placentae (carnivores).
- ▶ Labyrinthine → trabeculate → villous describes increasing separation of maternal blood spaces from a tubular network to a free intervillous space.
- ▶ Enders' mono-/bi-/tri-chorial subdivision refers to the number of trophoblast layers within any Grosser grade.

### SOURCE & COVERAGE

Hamilton, Boyd & Mossman — Human Embryology (comparative chorio-allantoic placentation, Grosser's classification, implantation types, labyrinthine/trabeculate/villous zone of interchange); IB Singh — Human Embryology (CBME 2021) (phylogenetic classification table, shape classification, human placental measurements); Gray's Anatomy (Standring) 41e (human implantation and placentation, trophoblast biology); Langman's Medical Embryology (Sadler) 14e (hemochorial designation of the human placenta); Larsen — Human Embryology 6e (gross structure/figure of the mature human placenta).



## Slide calipers

*Asked in: Paper II Apr 2008 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The slide caliper (sliding caliper, sliding compass) is one of the three basic direct-measuring instruments of craniometry and physical anthropometry — the other two being the spreading caliper and the anthropometer rod. It consists essentially of a graduated straight bar carrying one fixed and one sliding arm, and is used to record precise straight-line (linear) distances between two definite, reproducible bony landmarks on the dry skull or the living body. Together, these instruments allow the anthropologist/anatomist to derive cranial, facial and other indices used to compare races, sexes and populations, to follow craniofacial growth, and to identify skeletal remains in forensic practice — a topic examined under the Genetics/Physical-anthropology component of the MD/MS Anatomy curriculum.

### 1. Craniometry, anthropometry and the place of the slide caliper

- ▶ **Anthropometry** is the science of taking standardised measurements on the living or dead human body; **craniometry** is its application specifically to the skull, using fixed bony landmarks ("craniometric points") so that measurements are reproducible between observers and across studies.
- ▶ Three classical direct instruments are described for taking such measurements:
- ▶ **Sliding caliper (slide caliper)** — a straight, graduated bar with a fixed and a sliding arm; used whenever both landmarks lie in (or close to) a single straight line of sight that a rigid rod can span directly.
- ▶ **Spreading caliper** — two curved branches hinged together like a pair of compasses/dividers; used when the two landmarks lie across a convexity, so that a straight bar cannot be laid directly between them.
- ▶ **Anthropometer (anthropometer rod)** — a tall, sectional graduated rod (commonly assembled to about 2 metres), used chiefly for standing height and long body-segment lengths; fitted with sliding cross-bars it can also serve as a large-scale sliding caliper.
- ▶ The slide caliper is thus the instrument of choice for straight, directly-accessible linear distances — classically the **maximum cranial length** (glabella to the occipital point).

### 2. Description and parts of the slide caliper

- ▶ A **graduated horizontal bar (beam)**, usually about 20–30 cm long for craniometric work, marked in **centimetres and millimetres**; finer instruments carry a **vernier scale** permitting readings to a fraction of a millimetre.
- ▶ A **fixed arm (branch)**, rigidly set at the zero end of the bar, ending in a contact tip.
- ▶ A **sliding (movable) arm**, which runs freely along the graduated bar and can be clamped at any position with a small **locking screw**; it also ends in a contact tip that faces the fixed arm.
- ▶ Both tips may be **pointed** (for precise contact with a bony landmark on a dry skull) or **rounded/blunted** (for use on the soft tissue-covered landmarks of a living subject, to avoid injury).

- ▶ The distance between the two landmarks is read directly off the graduated bar, at the point indexed by the sliding arm, once both tips are gently but firmly touching the two designated points.

### 3. Technique of use

- ▶ The skull (or head) is first oriented in the **Frankfort horizontal (orbito-meatal) plane** — the plane joining the inferior orbital margin to the superior margin of the external acoustic meatus on each side — so that every subsequent measurement is taken with the head in a standard, reproducible position.
- ▶ The fixed arm's tip is rested lightly on the first landmark; the sliding arm is then moved along the bar until its tip just touches the second landmark, without indenting soft tissue or slipping on the bone surface.
- ▶ The arm is locked and the reading taken directly from the scale, to the nearest millimetre (or 0.1 mm with a vernier).
- ▶ By convention each measurement is repeated **three times** and the mean value recorded, to reduce inter- and intra-observer error — a discipline emphasised in physical-anthropology fieldwork and in forensic skeletal examination alike.

### 4. Craniometric points commonly measured with the slide caliper

| Landmark                         | Location                                                                                 |
|----------------------------------|------------------------------------------------------------------------------------------|
| Glabella                         | Smooth median prominence above the root of the nose, between the two superciliary arches |
| Opisthocranium (occipital point) | The most posteriorly projecting point of the occipital bone                              |
| Nasion                           | Point where the internasal suture meets the frontonasal suture                           |
| Bregma                           | Junction of the coronal and sagittal sutures                                             |
| Lambda                           | Junction of the sagittal and lambdoid sutures                                            |
| Inion                            | Tip of the external occipital protuberance                                               |
| Vertex                           | Highest point of the calvaria with the head in the Frankfort plane                       |
| Basion                           | Central point on the anterior margin of the foramen magnum                               |
| Opisthion                        | Central point on the posterior margin of the foramen magnum                              |
| Prosthion                        | Lowest point on the upper jaw between the central incisors                               |
| Gnathion                         | Midpoint of the lower border of the mandible (chin point)                                |

| Landmark           | Location                                                                                                                                                          |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pterion / Asterion | Junction of frontal–parietal–squamous temporal–greater wing of sphenoid (pterion), and of parietal–occipital–temporal (asterion) — chiefly surface-marking points |

□ Fig 8.6 — Craniometric points. (Moore — Clinically Oriented Anatomy — 9e, p.1346)

## 5. Measurements and indices derived using the slide caliper

| Measurement            | Landmarks (straight line, slide caliper)       | Index / use                                 |
|------------------------|------------------------------------------------|---------------------------------------------|
| Maximum cranial length | Glabella → opisthocranium (occipital point)    | Numerator/denominator of the cephalic index |
| Cranial height         | Basion → bregma                                | Cranial vault proportion                    |
| Facial height          | Nasion → gnathion                              | Facial index                                |
| Nasal height / breadth | Nasion → acanthion; width of piriform aperture | Nasal index                                 |
| Facial angle           | Nasion–basion line vs basion–prosthion line    | Index of jaw/brain-case proportion          |

- **Cephalic index (CI)** = (Maximum cranial breadth ÷ Maximum cranial length) × 100, where the length is glabella-to-occipital point and the breadth is the greatest width measured a little below the parietal tubera.
  - **Dolichocephalic** (long-headed): CI ≤ 75 — typical of more primitive/ancestral racial groups.
  - **Mesaticephalic** (medium-headed): CI 75–80.
  - **Brachycephalic** (short/round-headed): CI > 80 — the trend in more evolved/advanced racial groups.
- The **maximum cranial breadth**, being taken across the convex parietal eminences, is in practice measured more accurately with the **spreading caliper** even though the length is taken with the slide caliper — the two instruments are therefore used together, not as substitutes for each other.
- **Facial angle** — the angle between the nasion–basion line (facial skeleton/viscerocranium) and the basion–prosthion line — is a rough index of relative brain-case development: smaller in the most evolved races of man, larger in "lower" races, and largest in anthropoid apes.

## 6. Slide caliper vs spreading caliper vs anthropometer

| Feature         | Slide (sliding) caliper                    | Spreading caliper                             | Anthropometer rod                     |
|-----------------|--------------------------------------------|-----------------------------------------------|---------------------------------------|
| Shape of arms   | Straight, graduated bar                    | Two curved, hinged branches (compass-like)    | Tall sectional straight rod (~2 m)    |
| Best suited for | Straight-line distances directly reachable | Distances across a convexity (curved surface) | Standing height, long segment lengths |

| Feature           | Slide (sliding) caliper                      | Spreading caliper                            | Anthropometer rod                            |
|-------------------|----------------------------------------------|----------------------------------------------|----------------------------------------------|
| Classic example   | Glabella–opisthocranium (cranial length)     | Maximum cranial breadth, bizygomatic breadth | Sitting/standing height, limb-segment length |
| Reading mechanism | Direct scale reading where sliding arm locks | Scale on the hinge/pivot arc                 | Sliding cross-bar on the graduated rod       |

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Since the library plates of the skull show the *landmarks* rather than the instrument, hand-draw the slide caliper itself and label:

- ▶ The **graduated horizontal bar (beam)**, marked in cm/mm.
- ▶ The **fixed arm** at the zero end, with its contact tip.
- ▶ The **sliding (movable) arm**, its contact tip, and the **locking screw**.
- ▶ Arrowed line showing the **direction of sliding** along the bar.
- ▶ A small inset skull showing the caliper's two tips placed on **glabella** and the **occipital point**, to illustrate measurement of maximum cranial length.

### Applied / Clinical anatomy

- ▶ **Forensic identification:** slide- and spreading-caliper measurements of the skull and long bones are central to medico-legal estimation of **sex, race/ethnic affinity, age, and stature** from skeletal remains.
- ▶ **Comparative racial craniology:** the cephalic index derived from slide-caliper measurements historically classified populations as dolichocephalic, mesocephalic or brachycephalic, and remains a standard teaching example of a simple, reproducible anthropometric index.
- ▶ **Craniofacial growth and pathology:** serial craniometric measurement is used to track normal calvarial growth in infancy and to detect abnormal skull shape in **craniosynostosis** (e.g., scaphocephaly from premature sagittal synostosis, oxycephaly from premature coronal/sphenobasal synostosis).
- ▶ **Orthodontics/cephalometrics:** the same craniometric landmarks (nasion, bregma, gnathion, basion) underpin cephalometric analysis, though modern cephalometry is generally performed on standardised lateral skull radiographs rather than directly with a hand caliper.
- ▶ **Genetics/physical anthropology correlation:** craniometric indices, along with dermatoglyphics and other anthropometric parameters, form part of the physical-anthropology toolkit taught alongside population and forensic genetics in the MD/MS Anatomy syllabus.

### High-yield exam pointers

- ▶ Slide caliper = **straight graduated bar + one fixed arm + one sliding arm**, for landmarks lying in a straight, directly-accessible line.
- ▶ Spreading caliper = **two curved, hinged branches**, for measurements across a **convex** surface (e.g., maximum cranial breadth).



- ▶ Anthropometer rod = tall sectional rod for **height/segment lengths**; can be adapted as a giant sliding caliper.
- ▶ Classic slide-caliper measurement: **cranial length** = glabella → **opisthocranium (occipital point)**.
- ▶ **Cephalic index** = (**breadth/length**) × 100: dolichocephalic ≤ 75, mesaticephalic 75–80, brachycephalic > 80.
- ▶ Always orient the skull in the **Frankfort (orbito-meatal) plane** before taking any craniometric reading; take each measurement **three times** and average.
- ▶ Applied uses: forensic sex/race/stature/age estimation, craniofacial growth monitoring, craniosynostosis diagnosis, cephalometrics.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia's Human Anatomy Vol 3–4 8e (Cranimetry — cephalic index, facial angle); Vishram Singh — Textbook of Anatomy Vol 3 4e (craniometric points, cephalic index); Moore's Clinically Oriented Anatomy 9e (Table 8.1, Fig 8.6 — craniometric points); IB Singh — Textbook of Anatomy Vol 3 6e (craniometric points); Gangane — Human Genetics 5e (physical anthropology/dermatoglyphics context).

**Coverage note:** the anatomy textbook corpus in this library describes the craniometric *landmarks and indices* (cephalic index, facial angle, cranial points) in detail, but none of the specialty texts on disk gives a verbatim mechanical description of the sliding-caliper apparatus itself (bar/fixed-arm/sliding-arm/vernier) — that instrument description follows universally-accepted, standard physical-anthropology/forensic-medicine teaching and is presented here as such, clearly separated from the corpus-grounded landmark and index data above.



## Types of pelvis

*Asked in: Paper II Oct 2010 — RGUHS MD/MS Anatomy*

**Definition / Introduction** The bony pelvis is formed by the two hip bones, the sacrum and the coccyx, and is divided by the pelvic inlet (terminal line) into a larger **false (greater) pelvis**, belonging to the abdominal cavity, and a smaller **true (lesser) pelvis**, of prime obstetric and forensic importance. Because the female pelvis is adapted for parturition, its shape shows continuous variation between a typical "female" and a typical "male" pattern. This variation is classified in two complementary ways: (1) the basic **sex-based (anatomical)** classification — male vs female pelvis — which supplies the two extremes; and (2) the **morphological classification of Caldwell and Moloy**, which divides the female pelvis into four types — **gynaecoid, android, anthropoid and platypelloid** — chiefly on the shape of the pelvic inlet. A parallel **anthropological (pelvic-index) classification** uses the same four shapes under different names.

### 1. True (lesser) and false (greater) pelvis

- ▶ The **false/greater pelvis** lies above the pelvic inlet; it is part of the abdominal cavity and supports the abdominal viscera — not obstetrically significant.

- The **true/lesser pelvis** lies below the inlet and has an **inlet (brim)**, a **cavity** and an **outlet**; its shape and dimensions determine which "type" a given pelvis belongs to and whether it is adequate for childbirth.
- All classifications of "types of pelvis" are described chiefly with reference to the shape of the **pelvic inlet** of the true pelvis.

## 2. Sex differences in the pelvis — the basis of the gynaecoid–android spectrum

The female pelvis is basically a modification of the male pattern for childbearing; every "type" is a point on this male–female spectrum.

| Feature               | Male pelvis                                    | Female pelvis                                     |
|-----------------------|------------------------------------------------|---------------------------------------------------|
| False pelvis          | Deep                                           | Shallow                                           |
| Pelvic inlet          | Heart-shaped (sacral promontory juts forward)  | Transversely oval                                 |
| Pelvic cavity         | Smaller, deeper — long segment of a short cone | Roomier, shallower — short segment of a long cone |
| Pelvic outlet         | Smaller; ischial tuberosities turned in        | Larger; ischial tuberosities everted              |
| Sacrum                | Long and narrow                                | Short and wide                                    |
| Subpubic angle        | Narrow, 50°–60°                                | Wide, 80°–85° (most important sex difference)     |
| Greater sciatic notch | Narrower, ~50°                                 | Wider, ~75°                                       |
| Acetabulum            | Large                                          | Smaller                                           |
| Preauricular sulcus   | Faint/absent                                   | Well marked                                       |

□ Fig 29.7 — Shape of pelvic inlet in the male and in the female (BD Chaurasia — Human Anatomy Vol 2 — 8e, p.459)

## 3. Caldwell–Moloy morphological classification of the female pelvis (the four types)

This is the classification in standard use for obstetric/anatomical description of the female pelvis, based mainly on the **shape of the pelvic inlet**.

| Type                      | Approx. incidence | Inlet shape                                                                          | Side walls / forepelvis       | Subpubic angle & outlet           | Obstetric significance                                    |
|---------------------------|-------------------|--------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|-----------------------------------------------------------|
| Gynaecoid (normal female) | ~41–42%           | Round/oval, transverse diameter slightly > AP diameter, well forward from the sacrum | Straight, vertical side walls | Wide subpubic angle, ample outlet | Roomy cavity — suitable for easy, normal vaginal delivery |

| Type                              | Approx. incidence | Inlet shape                                                                                 | Side walls / forepelvis                             | Subpubic angle & outlet                                                      | Obstetric significance                                                                                                                               |
|-----------------------------------|-------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Android</b> (male type)        | ~32–33%           | Triangular/heart-shaped; greatest transverse diameter placed close to the sacral promontory | Convergent side walls; narrow greater sciatic notch | Narrow subpubic angle; funnel-shaped cavity; outlet reduced in all diameters | May result in obstructed labour                                                                                                                      |
| <b>Anthropoid</b> (ape type)      | ~23–24%           | Oval, AP diameter much greater than transverse diameter (compressed side-to-side)           | Long, narrow cavity                                 | Subpubic angle narrow-to-normal                                              | Poses difficulty in smooth delivery; more common in women of African ancestry; may coexist with a "high-assimilation" pelvis (extra lumbar vertebra) |
| <b>Platypelloid</b> (flat pelvis) | ~2–3% (rarest)    | Flat, oval side-to-side; transverse diameter much greater than AP (inlet AP-compressed)     | Wide but shallow cavity                             | Wide subpubic angle but reduced AP room                                      | Poses difficulty at the inlet; historically associated with rickets                                                                                  |

Only the **gynaecoid** pelvis is regarded as normal and consistently permits an easy vaginal delivery; the other three are variants that predispose to a degree of **contracted pelvis** and abnormal labour if the absolute dimensions are also reduced.

#### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Superimposed outline of the pelvic inlet for the four Caldwell–Moloy types, labelled:

- ▶ **Gynaecoid** — rounded/oval inlet, transverse  $\approx$  AP, well-rounded forepelvis
- ▶ **Android** — heart-shaped/triangular inlet, narrow forepelvis, promontory encroaching
- ▶ **Anthropoid** — oval inlet elongated antero-posteriorly (AP  $\gg$  transverse)
- ▶ **Platypelloid** — flattened, transversely oval inlet (transverse  $\gg$  AP)
- ▶ Mark the **transverse diameter** and **anteroposterior (true conjugate)** diameter on each; annotate approximate incidence (%) beside each type.

## 4. Determining the type of pelvis — clinical & radiological pelvimetry

The type of pelvis and its adequacy for labour are assessed by three complementary methods:

- ▶ **External pelvimetry** (largely given up now, but useful for gross contraction): **interspinous diameter** (between the outer borders of the anterior superior iliac spines) 22–25 cm; **intercristal diameter** (widest distance between the outer borders of the iliac crests) 25–28 cm; **external (Baudelocque) conjugate**, from the tip of the S5 spine to the upper border of the pubic symphysis,  $\geq 19$  cm.
- ▶ **Clinical (internal) pelvimetry**, by digital vaginal examination: the **diagonal conjugate** (promontory to lower border of the pubic symphysis,  $\geq 11.5$  cm) — the true/obstetric conjugate is estimated by deducting 1.5–2 cm from it; the **interischial spinous diameter** ( $\sim 9$  cm, difficult to assess digitally) at the plane of least pelvic dimensions; palpation of the sacral curvature, sacrospinous ligament length and side-wall convergence (funnelling); and the **subpubic-arch knuckle test** — a clenched fist should be comfortably accommodated between the ischial tuberosities in a normal gynaecoid pelvis.
- ▶ **Radiological pelvimetry** (X-ray/CT) gives precise bony measurements but carries radiation risk; **ultrasound** and **MRI pelvimetry** are now preferred as they avoid ionising radiation while still delineating the inlet shape.

Some constant reference points aid orientation and are frequently tested:

- ▶ The **pelvic axis** is **J-shaped**, curving from the inlet down and back, then forward through the outlet.
- ▶ The **plane of greatest pelvic dimensions** passes through the middle of the pubic symphysis and the S2–S3 junction; the **plane of least dimensions** is at the level of the ischial spines (interspinous diameter  $\sim 9.5$  cm) — the site of maximum difficulty during parturition, since it barely admits the fetal biparietal diameter ( $\sim 9$  cm).
- ▶ The **inlet makes an angle of  $50^\circ$ – $60^\circ$  with the horizontal plane** in the erect posture (anatomical position: anterior superior iliac spines and pubic tubercles lie in the same coronal plane).

## 5. Anthropological (pelvic-index) classification

An older, parallel nomenclature used in physical anthropology/forensic anatomy, based on the **pelvic index** (relationship of the anteroposterior to the transverse diameter of the inlet), and corresponding closely to the four Caldwell–Moloy types:

| Anthropological term | Basis                                                       | Corresponds to |
|----------------------|-------------------------------------------------------------|----------------|
| Mesatipellic         | Transverse diameter slightly more than AP diameter (normal) | Gynaecoid      |
| Brachypellic         | AP diameter slightly more than transverse diameter          | Android        |
| Dolichopellic        | AP diameter much more than transverse diameter              | Anthropoid     |
| Platypellic          | Transverse diameter much greater than AP diameter           | Platypelloid   |

## Applied / Clinical anatomy

- ▶ Only the **gynaecoid pelvis** permits smooth, normal vaginal delivery; android, anthropoid and platypelloid pelvises are variants of **contracted pelvis** — android may cause obstructed labour, while anthropoid and platypelloid pelvises pose difficulty in smooth delivery if absolute dimensions are also reduced.
- ▶ **Clinical pelvimetry**: the **diagonal conjugate** (per-vaginal, promontory to lower border of pubic symphysis,  $\geq 11.5$  cm) is the single most important obstetric measurement; the true (obstetric) conjugate is estimated by subtracting 1.5–2 cm from it. Adequacy of the outlet is checked by the **knuckle test** for the subpubic arch and by measuring the intertuberous diameter.
- ▶ **Radiological/USG pelvimetry** has largely replaced manual/clinical pelvimetry for precise assessment; MRI pelvimetry avoids ionising radiation.
- ▶ The **anthropoid pelvis** is commoner in women of African ancestry and may be associated with a high-assimilation pelvis (an additional lumbar-type vertebra).
- ▶ The **platypelloid pelvis**, historically linked to **rickets/osteomalacia**, is rarely seen today; an extreme osteomalacic variant produces a **trefoil (trifoliated) pelvis**, with indented acetabula and a forward-pushed sacrum and pubic symphysis, causing cephalopelvic disproportion.
- ▶ Sex-typing of an isolated hip bone/pelvis (subpubic angle, greater sciatic notch, preauricular sulcus) is a key **forensic/medico-legal** application of these morphological differences.

## High-yield exam pointers

- ▶ Four Caldwell–Moloy types (mnemonic **G-A-A-P**): Gynaecoid, Android, Anthropoid, Platypelloid — classified by pelvic inlet shape.
- ▶ Approximate incidence: gynaecoid ~41%, android ~32%, anthropoid ~24%, platypelloid ~2–3% (rarest).
- ▶ Only gynaecoid = normal/roomy pelvis suitable for easy delivery; the rest are contracted-pelvis variants.
- ▶ Subpubic angle is the single most reliable sex-determining feature: 50–60° (male) vs 80–85° (female).
- ▶ Diagonal conjugate ( $\geq 11.5$  cm) is the most important clinical (obstetric) pelvic measurement.
- ▶ True pelvis vs false pelvis divided by the pelvic inlet/terminal line; true pelvis alone matters for labour.
- ▶ Anthropological synonyms: gynaecoid = mesatipellic; android = brachypellic; anthropoid = dolichopellic; platypelloid = platypellic (based on pelvic index).
- ▶ Platypelloid historically linked to rickets; trefoil pelvis is an extreme osteomalacic contracted variant.

### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; BD Chaurasia Human Anatomy Vol 2, 8e; Vishram Singh Textbook of Anatomy Vol 2, 4e; IB Singh Textbook of Anatomy Vol 2, 6e.



## Applied & clinical anatomy



### Branchial cyst

*Asked in: Paper II Nov 2017 · Paper IV Oct 2006 (2×) — RGUHS MD/MS Anatomy*

**Definition/Introduction** — A branchial cyst (lateral cervical cyst) is a congenital, epithelium-lined cystic swelling that results from failure of obliteration of the **cervical sinus of His**, the transient ectoderm-lined cavity formed when the rapidly-growing second pharyngeal arch buries the second, third and fourth pharyngeal clefts. It classically presents as a smooth, painless, slowly enlarging swelling along the anterior border of sternocleidomastoid (SCM) in a child or young adult, and forms a developmental continuum with the branchial sinus and fistula.

#### 1. Embryological basis — formation and fate of the cervical sinus of His

- ▶ The pharynx is flanked by four pairs of **pharyngeal (branchial) arches**, separated externally by ectoderm-lined **pharyngeal clefts (grooves)** and internally by endoderm-lined **pharyngeal pouches**.
- ▶ The **second pharyngeal arch** proliferates and grows caudally over the third and fourth arches (as an "operculum") and fuses with the **epicardial ridge** (cardiac eminence) inferiorly.
- ▶ This overgrowth buries/traps the second, third and fourth clefts in a slit-like, ectoderm-lined cavity — the **cervical sinus (of His)** — lying between the operculum of the second arch superficially and the third/fourth (and vestigial sixth) arches deeply.
- ▶ Normally, the walls of the cervical sinus appose and fuse, and the cavity is obliterated as the neck elongates, giving the lateral neck a smooth contour.
- ▶ Only the **dorsal part of the first pharyngeal cleft persists** as a definitive structure — the external acoustic meatus and the cuticular (epithelial) layer of the tympanic membrane; the second, third and fourth clefts are normally obliterated along with the sinus.
- ▶ **Persistence of the cervical sinus, wholly or in part, gives rise to the branchial cyst/sinus/fistula group of anomalies** — the second most common congenital lesion of the head and neck in children.

□ Fig 17.27 — *Normal and Abnormal Fates of the Pharyngeal Clefts (A–C) Three stages in normal development (Larsen — Human Embryology — 6e, p.1092)*

### DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Draw (i) a coronal/transverse schematic of the developing neck at three successive stages and (ii) a lateral neck outline, labelling:

- ▶ Pharyngeal clefts (1st–4th), 2nd pharyngeal arch expanding caudally over 3rd/4th arches
- ▶ Hypopharyngeal eminence, copula, median and lateral tongue buds, entrance to oesophagus (landmarks of the floor of the pharynx used to orient the section)
- ▶ **Lateral cervical sinus** — the trapped, ectoderm-lined cavity deep to the 2nd-arch operculum
- ▶ Four outcome panels: (a) isolated **lateral cervical cyst** (no communication), (b) cyst with **external fistula** only, (c) cyst with **internal fistula** only, (d) cyst with **both external and internal fistulae** (complete fistula)
- ▶ Lateral neck outline showing sternocleidomastoid muscle and the classic sites of aural (pre-auricular) and cervical (upper, mid third of SCM) cysts/fistulae

## 2. Pathogenesis and classification of cervical-sinus remnants

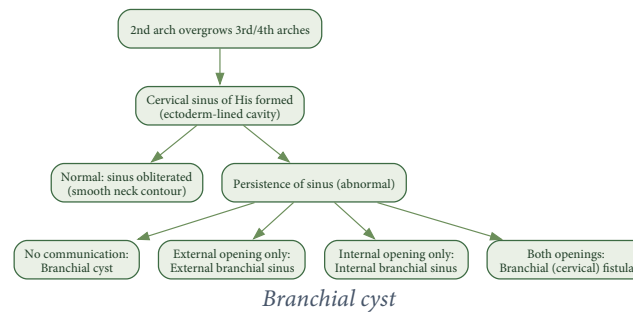
Depending on how much of the cervical sinus persists and whether it retains a communication with the skin (external, via the 2nd cleft) and/or the pharynx (internal, via rupture of the 2nd pharyngeal membrane into the tonsillar region), four clinical entities are described:

| Anomaly                           | External opening (skin of neck)       | Internal opening (pharynx/tonsillar fossa)             | Embryological basis                                                                                            |
|-----------------------------------|---------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Branchial (lateral cervical) cyst | Absent                                | Absent                                                 | Persistent, walled-off cervical sinus with no external or internal communication                               |
| External branchial sinus          | Present, along anterior border of SCM | Absent                                                 | Cervical sinus retains its connection with the overlying skin                                                  |
| Internal branchial sinus          | Absent                                | Present, in the tonsillar fossa/palatine tonsil region | Cervical sinus communicates with the pharynx after rupture of the membrane between the 2nd cleft and 2nd pouch |
| Branchial (cervical) fistula      | Present                               | Present                                                | Both external and internal communications persist, connecting the pharynx to the skin of the neck              |

- ▶ A branchial cyst that ruptures onto the surface becomes a branchial sinus; thus cyst, sinus and fistula are a developmental continuum of the same defect rather than separate anomalies.



- Most (>90%) of these lesions arise from the **second pharyngeal cleft/pouch complex**; anomalies of the first, third and fourth clefts are much rarer variants of the same principle.



### 3. Site, age of presentation and clinical features

- **Site:** along the anterior border of sternocleidomastoid, classically at the junction of its upper one-third and lower two-thirds, just below and behind the angle of the mandible (though it may occur anywhere along the anterior SCM border).
- **Age:** usually **not evident at birth**; the cyst is asymptomatic in infancy and becomes clinically apparent as a lateral neck swelling in later childhood or early adulthood as it gradually enlarges.
- **Presentation:** a smooth, soft-to-firm, non-tender, slowly enlarging lateral neck mass; it characteristically **increases in size during an upper respiratory tract infection** (due to reactive hyperplasia of lymphoid tissue in its wall).
- Complications include recurrent infection/abscess formation and, if a sinus or fistula coexists, intermittent mucoid/salivary discharge onto the neck skin.

### 4. Histopathology

- The cyst wall is lined by either **stratified squamous epithelium** or, less commonly, **simple/pseudostratified columnar (ciliated) epithelium**, reflecting its origin from the ectodermal cervical sinus (and, in variants with pouch contribution, respiratory-type endoderm).
- The wall typically contains abundant **lymphoid tissue**, and the cyst fluid is characteristically a turbid or mucoid fluid.
- Recurrence after surgery is common if excision of the tract/wall is **incomplete**.

### 5. First branchial cleft cyst — a related but distinct entity

- Occasionally cysts/sinuses arise in relation to the **first** branchial cleft rather than the second; these are anatomically and clinically distinct because the first cleft's dorsal part contributes to the external acoustic meatus.
- Two types are described based on the level of the tract relative to the angle of the mandible/jaw line — **Type I** (opening above the jaw line, close to the external auditory meatus) and **Type II** (opening below the jaw line) — and these lesions run in close relation to the parotid gland and facial nerve, unlike second-cleft lesions which relate to the carotid vessels.

### 6. Genetic and molecular correlates (recent advances)

- Formation of the pharyngeal arches and their derivatives is driven by reciprocal endoderm–ectoderm–neural crest signalling; **fibroblast growth factor (FGF) signalling** from the pharyngeal

pouch endoderm promotes chondrogenesis in the neural-crest-derived arch mesenchyme and also induces the **epibranchial placodes** (ectodermal thickenings at the dorsal ends of the 1st, 2nd and 4th clefts that later contribute neurons to the geniculate, petrosal and nodose sensory ganglia of cranial nerves VII, IX and X).

- ▶ **Branchio-oto-renal (BOR) syndrome** is the key genetic disorder linked to persistent branchial-cleft remnants: an **autosomal dominant** condition caused by mutation of **EYA1** (chromosome 8q13), a gene encoding a protein phosphatase used by conserved developmental pathways shared by the ear and kidney (the related gene **SIX1** interacts with EYA1 in the same pathway). It presents with cup-shaped/malformed external ears, pre-auricular pits/tags, mixed hearing loss, **branchial cysts and fistulae in the neck**, and renal anomalies (dysplasia, collecting-duct malformations).
- ▶ This genotype–phenotype link is why any child presenting with a branchial cystic anomaly together with ear or renal abnormalities warrants screening for BOR syndrome.

### Applied / Clinical anatomy

- ▶ **Surgical relations:** during excision the cyst/tract lies in close relation to the **hypoglossal, glossopharyngeal and spinal accessory nerves**; a fistulous tract ascends from its cervical opening along the anterior border of SCM, traverses the platysma and cervical fascia to enter the **carotid sheath**, and then passes **between the internal and external carotid arteries** (the "carotid fork") en route to its internal opening in the tonsillar sinus — these relations must be protected during dissection.
- ▶ **Investigations:** ultrasonography and FNAC to characterise the swelling and exclude a solid/lymph-nodal lesion; CT/MRI or fistulography to delineate a fistulous tract before surgery.
- ▶ **Differential diagnosis:** thyroglossal cyst (midline, moves with tongue protrusion/deglutition), cystic hygroma (multiloculated, posterior triangle, transilluminant), tuberculous cervical lymphadenitis, and — importantly in adults over 40 — a **cystic metastatic lymph node** from an occult tonsillar/base-of-tongue squamous carcinoma, which can closely mimic a branchial cyst and must be excluded before assuming a benign congenital diagnosis.
- ▶ **Treatment:** complete surgical excision of the cyst together with its sinus tract; incomplete removal is the principal cause of recurrence.

### High-yield exam pointers

- ▶ Branchial cyst = persistence of the **cervical sinus of His** (2nd, 3rd, 4th cleft remnants buried by 2nd-arch overgrowth); lined by ectoderm.
- ▶ Site: anterior border of SCM, junction of upper 1/3–lower 2/3, below/behind angle of mandible.
- ▶ Not present at birth; appears in later childhood/early adulthood; enlarges with URTI.
- ▶ Cyst (no opening) → sinus (one opening, external or internal) → fistula (both openings) is a developmental continuum, not separate lesions.
- ▶ Histology: stratified squamous or columnar epithelium with lymphoid tissue in the wall.
- ▶ Only the 1st cleft has a definitive normal derivative (external acoustic meatus/tympanic membrane); 2nd–4th clefts are normally obliterated.

- ▶ Fistulous tract passes between internal and external carotid arteries to reach the tonsillar fossa; close to hypoglossal/glossopharyngeal/accessory nerves surgically.
- ▶ BOR syndrome (EYA1, 8q13, autosomal dominant) = branchial cysts/fistulae + ear anomalies + renal dysplasia — key gene–anomaly correlation for viva.
- ▶ Incomplete excision → recurrence; must differentiate from cystic nodal metastasis in an older patient.

#### SOURCE & COVERAGE

Gray's Anatomy (Standring) 41e; Langman's Medical Embryology (Sadler) 14e; Larsen Human Embryology 6e; Moore The Developing Human 9e; Moore's Clinically Oriented Anatomy 9e; IB Singh Human Embryology (CBME 2021); Vishram Singh Textbook of Clinical Embryology; Sontakke Textbook of Human Embryology; Brijesh Kumar Embryology Text & Atlas; Thompson & Thompson Genetics in Medicine 8e.

