Chapter 5
Third Week of Development: Trilaminar Germ Disc

Gastrulation (Formation Of Embryonic Mesoderm And Endoderm)

A. Implantation site at the end of the second week.
B. Representative view of the germ disc at the end of the second week of development. The amniotic cavity has been opened to permit a view of the dorsal side of the epiblast. The hypoblast and epiblast are in contact with each other, and the primitive streak forms a shallow groove in the caudal region of the embryo.

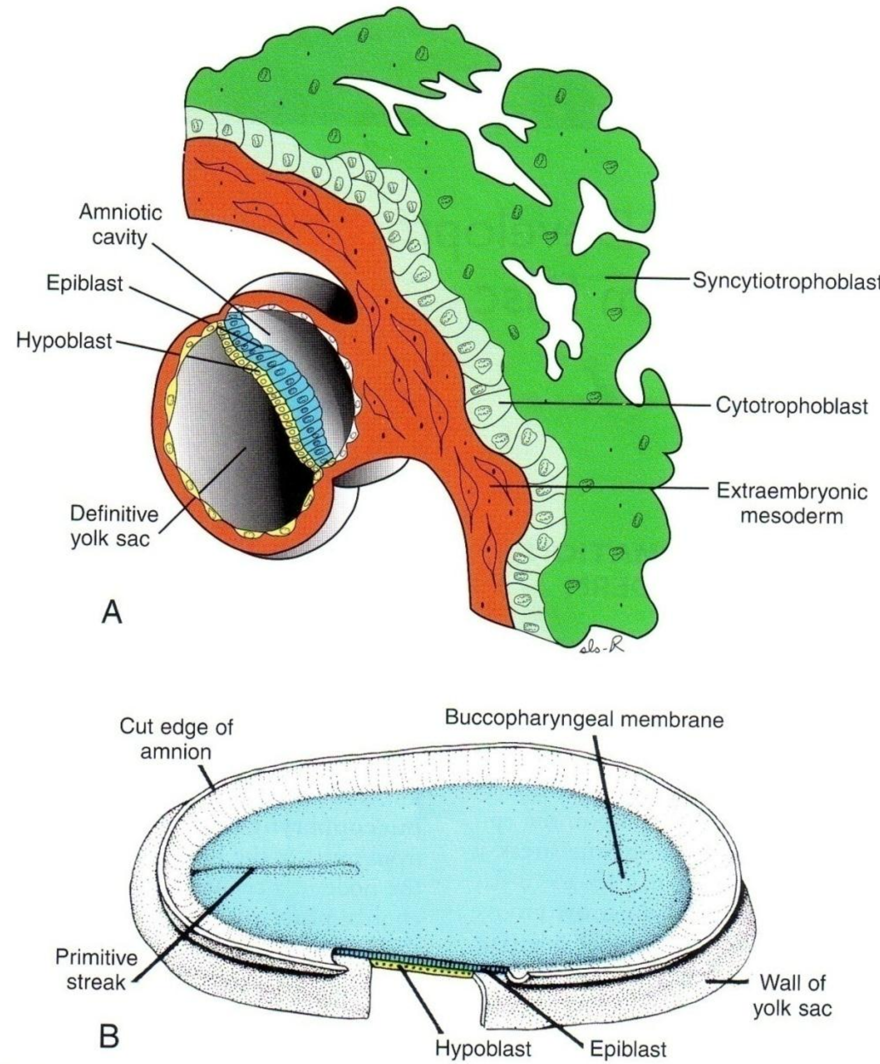


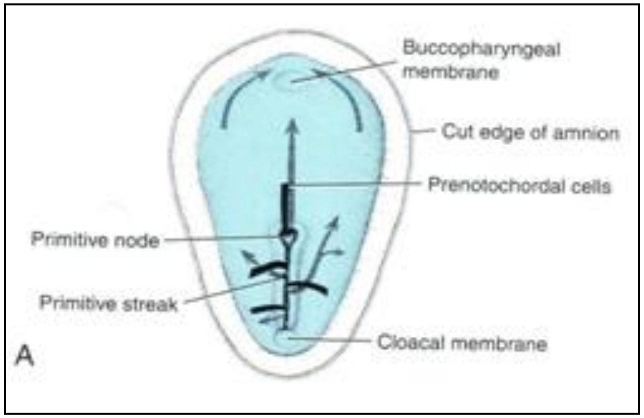
Figure 5.1 **A.** Implantation site at the end of the second week. **B.** Representative view of the germ disc at the end of the second week of development. The amniotic cavity has been opened to permit a view of the dorsal side of the epiblast. The hypoblast and epiblast are in contact with each other, and the primitive streak forms a shallow groove in the caudal region of the embryo.

Gastrulation

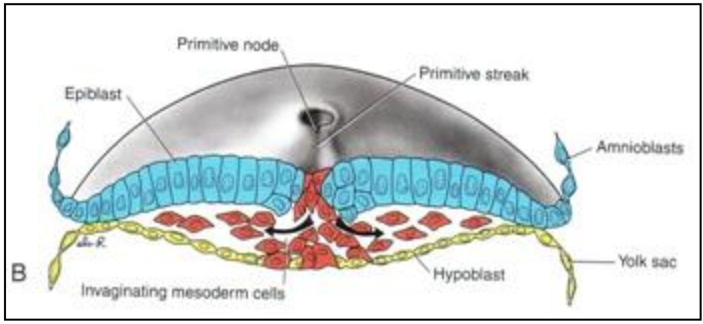
- **Gastrulation**: Third week of gestation
  - Process that establishes all three germ layers (ectoderm, mesoderm, and endoderm).
  - Begins with formation of the **primitive streak** on the surface of the epiblast.
- The primitive node surrounds the small primitive pit.
- Invagination: cells of the epiblast migrate toward the primitive streak and slip beneath it.
- Controlled by fibroblast growth factor 8 (FGF8),
- Once the cells have invaginated, some displace the hypoblast, creating the embryonic **endoderm**, and others come to lie between the epiblast and newly created endoderm to form **mesoderm**.
- Cells remaining in the epiblast then form **ectoderm**.
- Thus, the **epiblast**, through the process of gastrulation, is the **source** of **all of the germ layers.**
- cells in these layers will give rise to all of the tissues and organs in the embryo.
- They contact with the extra embryonic mesoderm covering the yolk sac and amnion.

Invagination

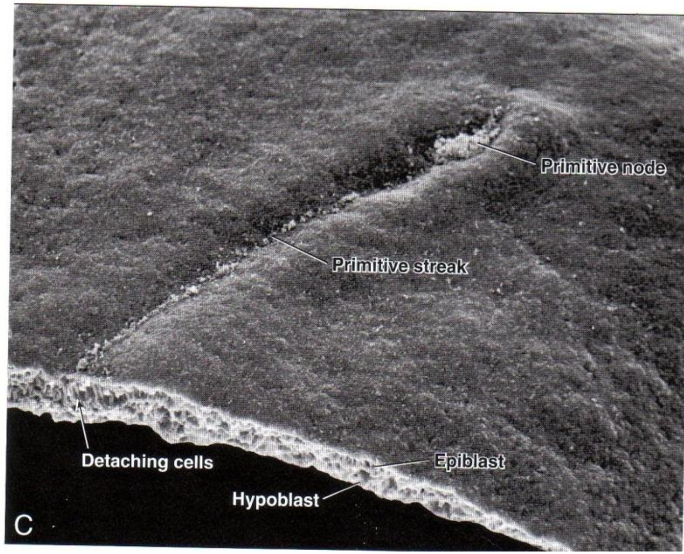
A. Dorsal side of the germ disc from a 16-day embryo indicating the movement of surface epiblast cells (solid black lines) through the primitive streak and node and the subsequent migration of cells between the hypoblast and epiblast (broken lines).



B. Cross section through the cranial region of the streak at 15 days showing invagination of epiblast cells. The first cells to move inward displace the hypoblast to create the definitive endoderm. Once definitive endoderm is established, inwardly moving epiblast forms mesoderm.

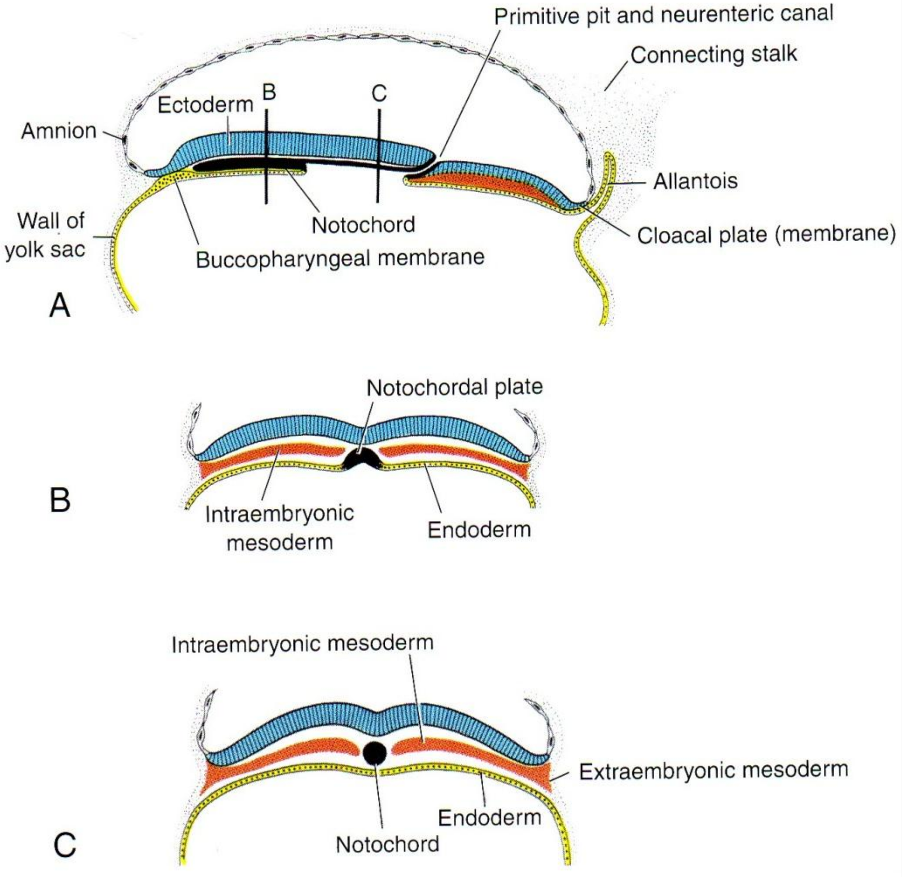


C. Dorsal view of an embryo showing the primitive node and streak and a cross section through the streak. Arrow, detaching epiblast cells in the primitive streak.



FORMATION OF THE NOTOCHORD

- **Prenotochordal cells→** invaginate in primitive node, reach **prechordal plate**
- Prenotochordal cells + hypoblast = **notochordal plate**.
- Notochordal plate then forms a solid cord of cells, the definitive **notochord**
- The **notochord** underlies the neural tube and serves as the basis for the axial skeleton.
- The notochord and prenotochordal cells extend cranially to the prechordal plate (an area just caudal to the oropharyngeal membrane) and caudally to the primitive pit.



- The **oropharyngeal** membrane at the cranial end of the disc consists of a small region of tightly adherent ectoderm and endoderm cells that represents the future opening of the oral cavity
- The **cloacal membrane** is formed at the caudal end of the embryonic disc consists of tightly adherent ectoderm and endoderm cells with no intervening mesoderm.
- The allantoenteric diverticulum, or **allantois:** from the posterior wall of the yolk sac, extends into the connecting stalk.

ESTABLISHMENT OF THE BODY AXESE

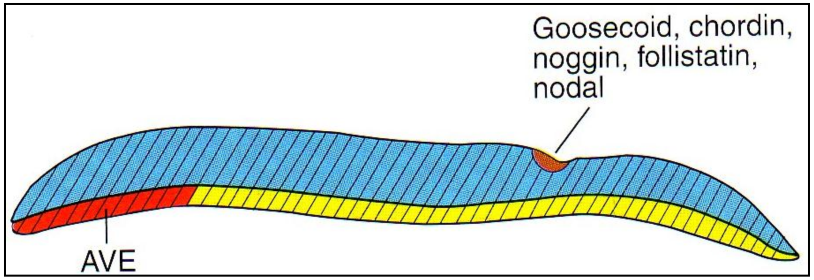
- Body axes, antero-posterior, dorso-ventral, and left–right, takes place before and during the period of **gastrulation**.
- Sagittal section through the node and primitive streak showing the expression pattern of genes regulating the cranio- caudal and dorso- ventral axes.

Antero-posterior axis

- Cells at the prospective cranial end of the embryo in the **anterior visceral endoderm (AVE)** express the transcription factors **OTX2, LIM1**,and **HESX1**and the secreted factor **cerberus** and **lefty** which inhibit nodal activity in the cranial end of the embryo. These genes establish the cranial end of the embryo **before gastrulation.**

Dorso-ventral axis

- The node is the **ORGANIZER (nodal)**.
- **Nodal** is involved in initiating and maintaining the primitive streak.
- Once the streak is formed and **gastrulation** is progressing, **bone morphogenetic protein (BMP4**; hatched areas), secreted throughout the bilaminar disc, acts with **FGF** to **ventralize mesoderm** into kidneys (**intermediate mesoderm)** and blood and body wall mesoderm (**lateral plate mesoderm)**.



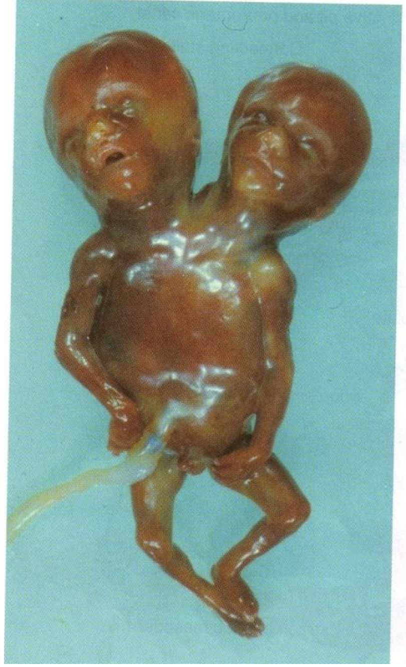
The Node Is The Organizer.

- **All mesoderm would be ventralized if the activity of BMP4 were not blocked by other genes expressed in the node. For this reason the node is the organizer.**
- **These genes are: Chordin (activated by the transcription factor Goosecoid)**, **noggin** and **follistatin** antagonizes the activity of BMP4.
- As a result, cranial mesoderm is dorsalized into **notochord** , **somites** and **somitomeres** in the head region.

Goosecoid gene

- Because **Goosecoid** activates inhibitors of BMP4 and regulates head development, over or under expression of this gene results in severe malformation in the head region: as duplications of head as in some types of **conjoined twins**.

Conjoined twins



- If the gene **Goosecoid** is overexpressed in frog embryos, the result is a two-headed tadpole. Perhaps, overexpression of this gene explains the origin of this type of conjoined twins

Brachyury (T) gene

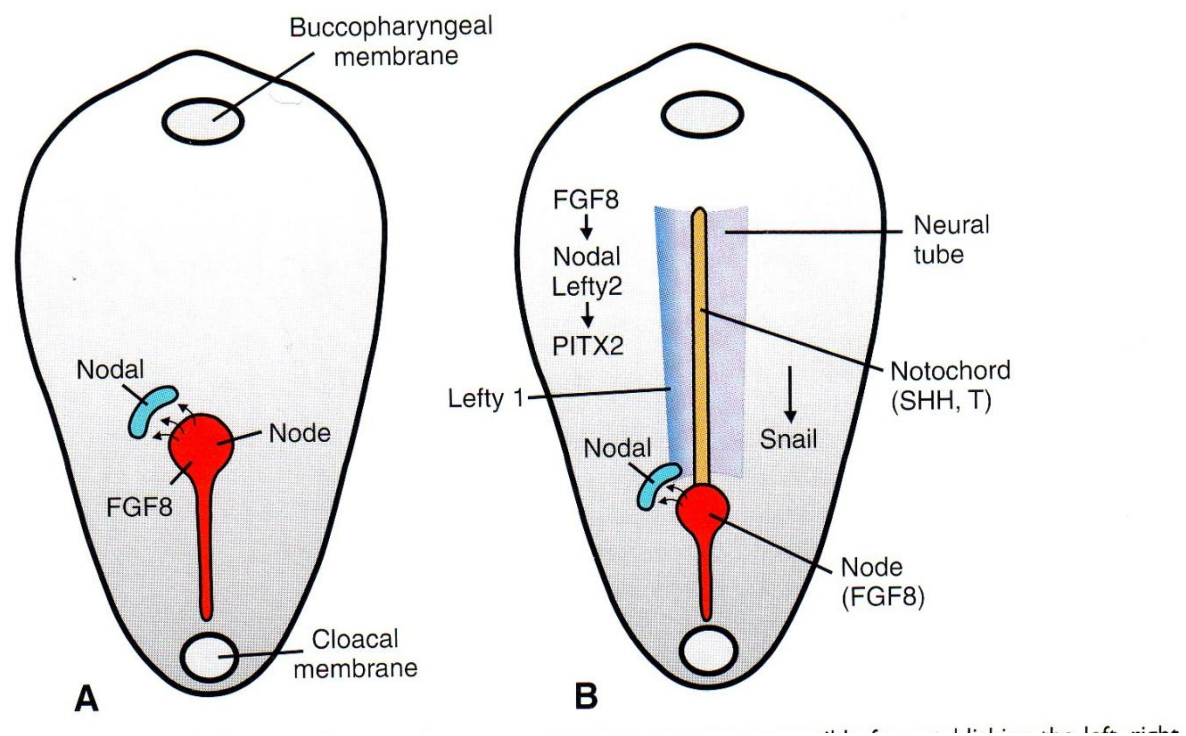
- Regulation of dorsal mesoderm formation in middle and caudal regions is controlled by the **Brachyury (T) gene** expressed in the node.
- Absence of ***Brachyury (T)*** gene results in shortening of the embryonic axis **(caudal dysgenesis).**

- **Insufficient mesoderm** is formed in the caudal most region of the embryo. Because this mesoderm contributes to formation of the lower limbs, urogenital system (intermediate mesoderm), and lumbosacral vertebrae, abnormalities in these structures ensue. Affected individuals exhibit a variable range of defects, including hypoplasia and fusion of the lower limbs, vertebral abnormalities, renal agenesis, imperforate anus, and anomalies of the genital organs.
- In humans, the condition is associated with **maternal diabetes** and other causes.
- In mice, abnormalities of **Brachyury(T)** produce a similar phenotype.

Caudal dysgenesis (sirenomelia)

A, B. Two examples of sirenomelia (caudal dysgenesis). Loss of mesoderm in the lumbosacral region has resulted in fusion of the limb buds and other defects.

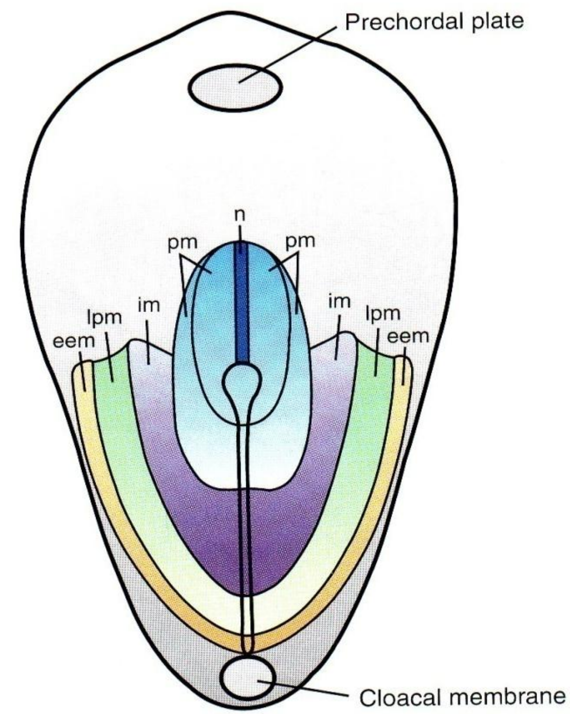
Gene expression patterns responsible for left-right body axis



- Left–right asymmetry is regulated by a cascade of genes; first, **FGF8**, secreted by cells in the node and streak, induces **Nodal** and **LEFTY-2** expression on the left side.
- These genes up-regulate **PITX2**, a transcription factor responsible for left-sidedness.
- Heart, stomach and other gut primordia.

Fate map established during gastrulation

- Epiblast cells moving through the node and streak are predetermined by their position to be-come specific types of mesoderm and endoderm. Thus, it is possible to construct a fate map of the epiblast showing this pattern .



Dorsal view of the germ disc showing the primitive streak and a fate map for epiblast cells. Specific regionsof the epiblast migrate through different parts of the node and streak to form mesoderm. Thus, cells migrating at the cranial most part of the node will form the notochord (n); those migrating more posteriorly through the node and cranial most aspect of the streak will form paraxial mesoderm (pm;somitomeres and somites); those migrating through the next por-tion of the streak will form intermediate mesoderm (im;urogenital system); those migrating through the more caudal partof the streak will form lateral plate mesoderm (lpm;body wall); and those migrating through the most caudal part will contribute to extraembryonic mesoderm (eem;chorion)

Teratogenesis associated with gastrulation

- Beginning of 3rd wk:
- Gastrulation
- Sensitive to teratogenes: fate map to organ systems: eyes & brain
- Alcohol: HOLOPROSENCEPHALY
- Genetic abnomalities:
  - caudal dysgenesis (sirenomelia):
    - maternal diabetes
    - abnormalities of Brachyury (T)

Situs inversus (complete)

- A condition in which transposition of the viscera in the thorax and abdomen occurs.
- With few other structural abnormalities
- With bronchiectasis and chronic sinusitis
  - because of abnormal cilia (Kartagener syndrome).

Laterality sequences

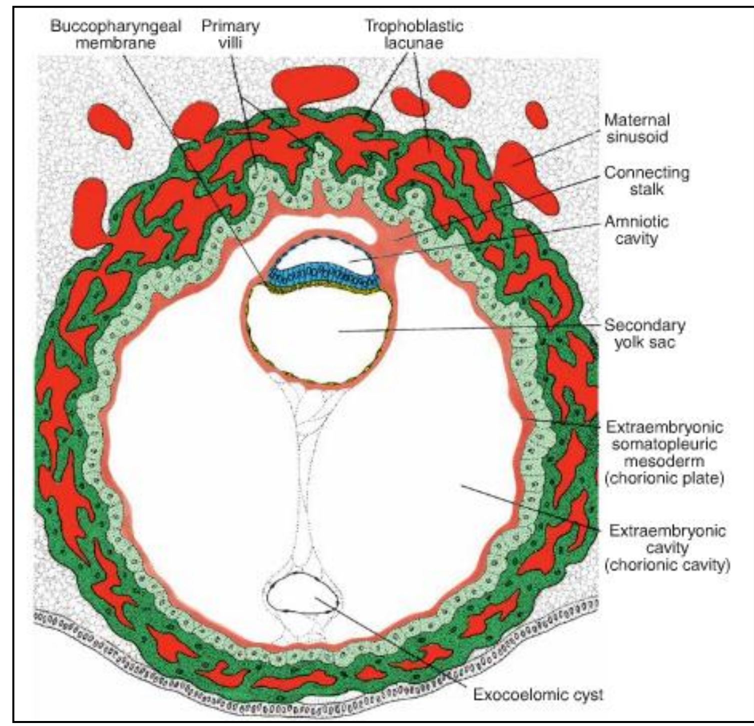
- do not have complete situs inversus
- predominantly bilaterally left-sided or right-sided
- The spleen reflects the differences
- left-sided bilaterality have polysplenia
- right-sided bilaterality have asplenia or hypoplastic spleen.
- Patients with laterality sequences are also likely to have other malformations, especially heart defects.

Sacrococcygeal teratoma

- **Tumors Associated With Gastrulation**
- remnants of the primitive streak persist in the sacrococcygeal region. These clusters of pluripotent cells proliferate and form tumors, known as sacrococcygeal teratomas, that commonly contain tissues derived from all three germ layers.
- This is the most common tumor in newborns, occurring with a frequency of one in 37,000. These tumors may also arise from primordial germ cells that fail to migrate to the gonadal ridge.

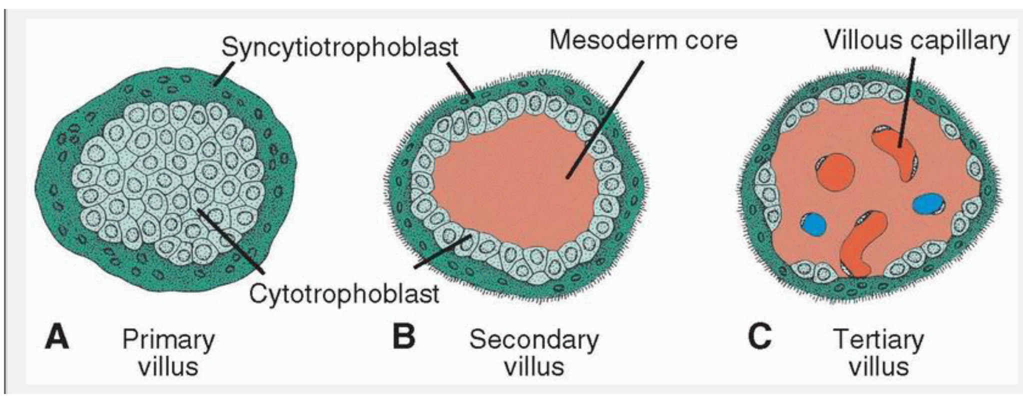
Further development of the trophoblast

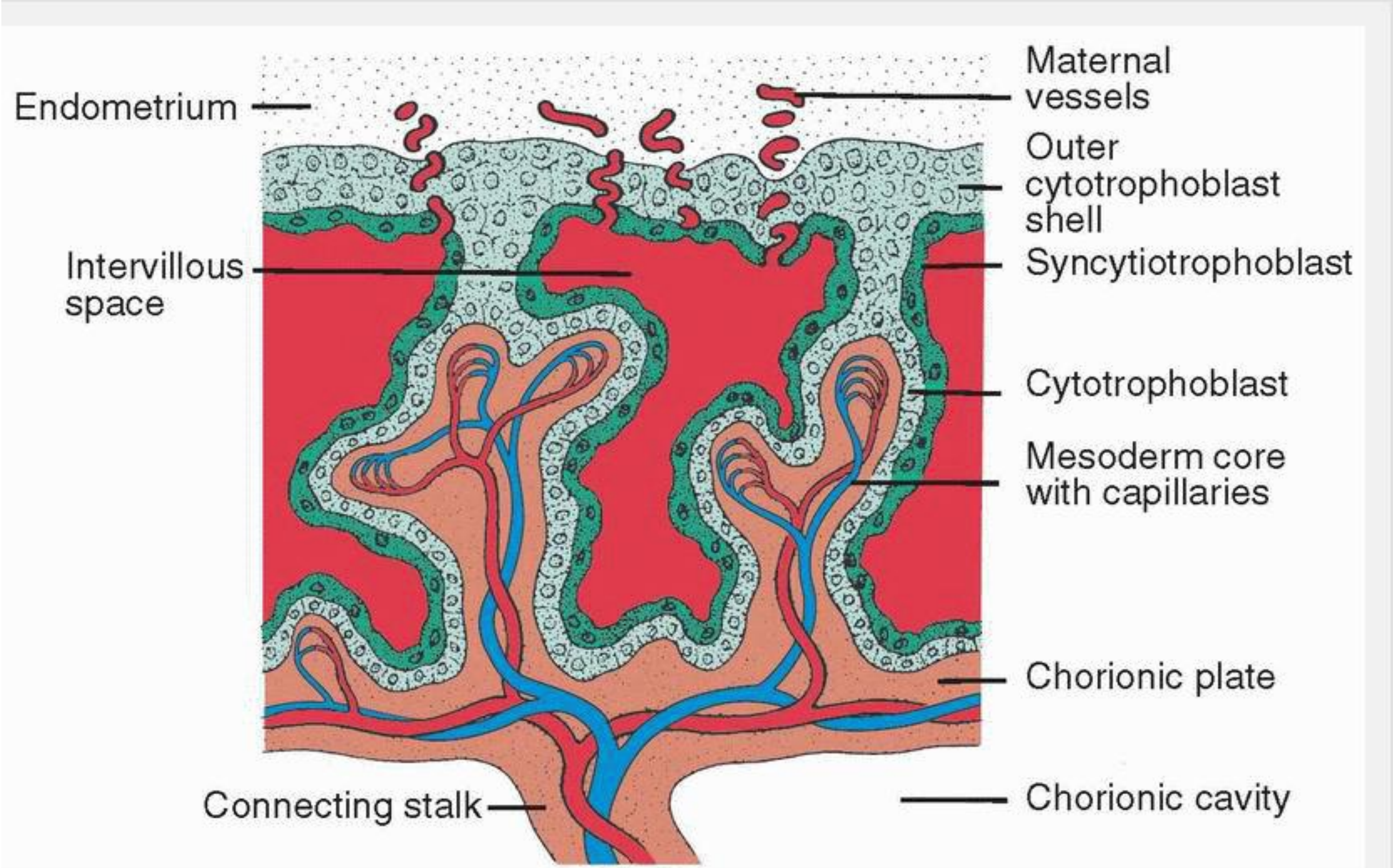
- The trophoblast progresses rapidly.
- Primary villi obtain a mesenchymal core in which small capillaries arise. When these villous capillaries make contact with capillaries in the chorionic plate and connecting stalk, the villous system is ready to supply the embryo with its nutrients and oxygen



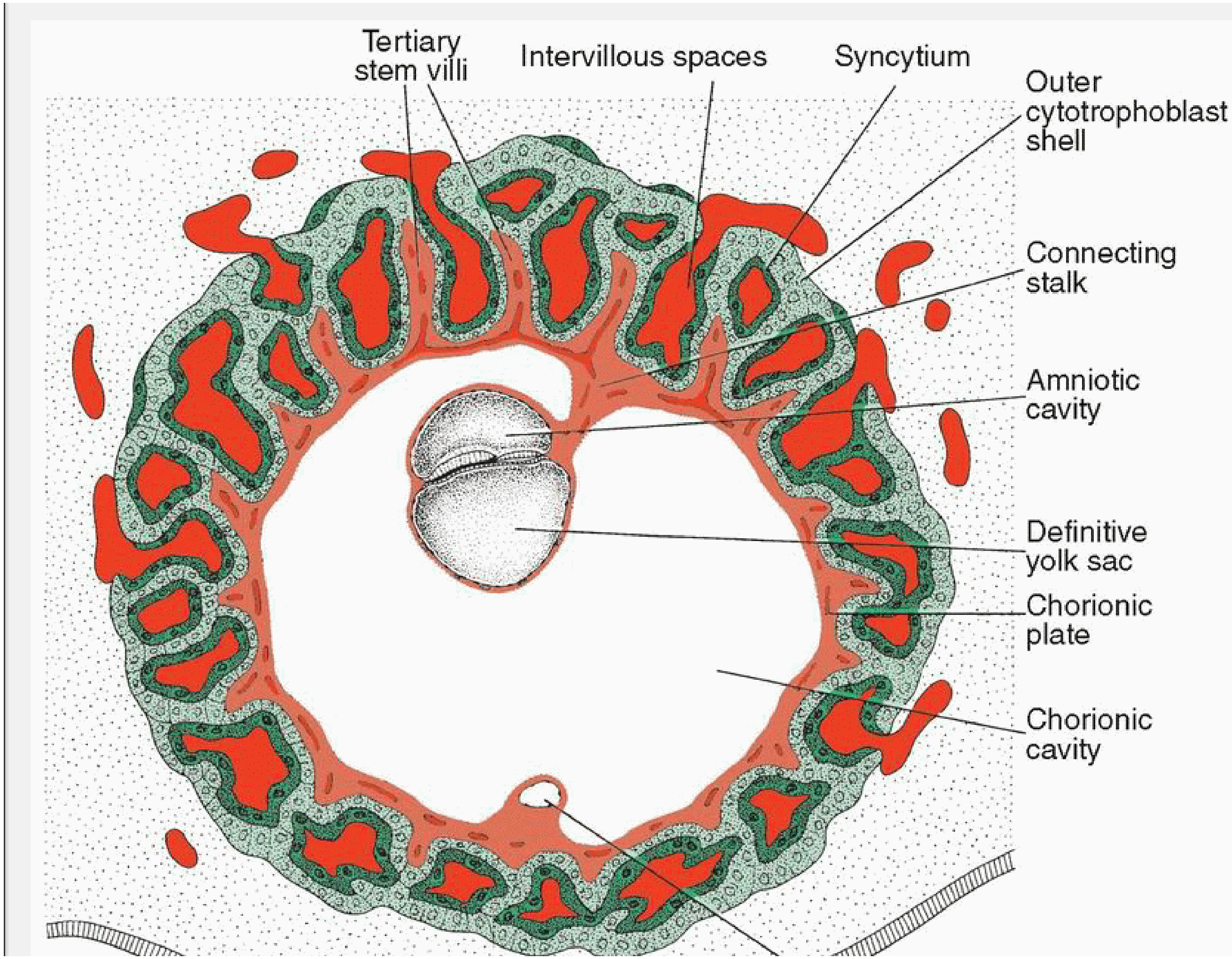
A 13-day-old implantation site showing **primary villi** of the trophoblastic shell just beginning to be invaded by mesoderm from the chorionic plate.

Development of a villus.





Longitudinal section through a villus at the end of the third week of development. Maternal vessels penetrate the cytotrophoblastic shell to enter intervillous spaces, which surround the villi. Capillaries in the villi are in contact with vessels in the chorionic plate and in the connecting stalk, which in turn are connected to intra embryonic vessels



Presomite embryo and the trophoblast at the end of the third week. Tertiary and secondary stem villi give t he trophoblast a characteristic radial appearance. Intervillous spaces, which are found throughout the trophoblast, are lined with syncytium. Cytotrophoblastic cells surround the trophoblast entirely and are in direct contact with the endometrium. The embryo is suspended in the chorionic cavity by means of the connecting stalk