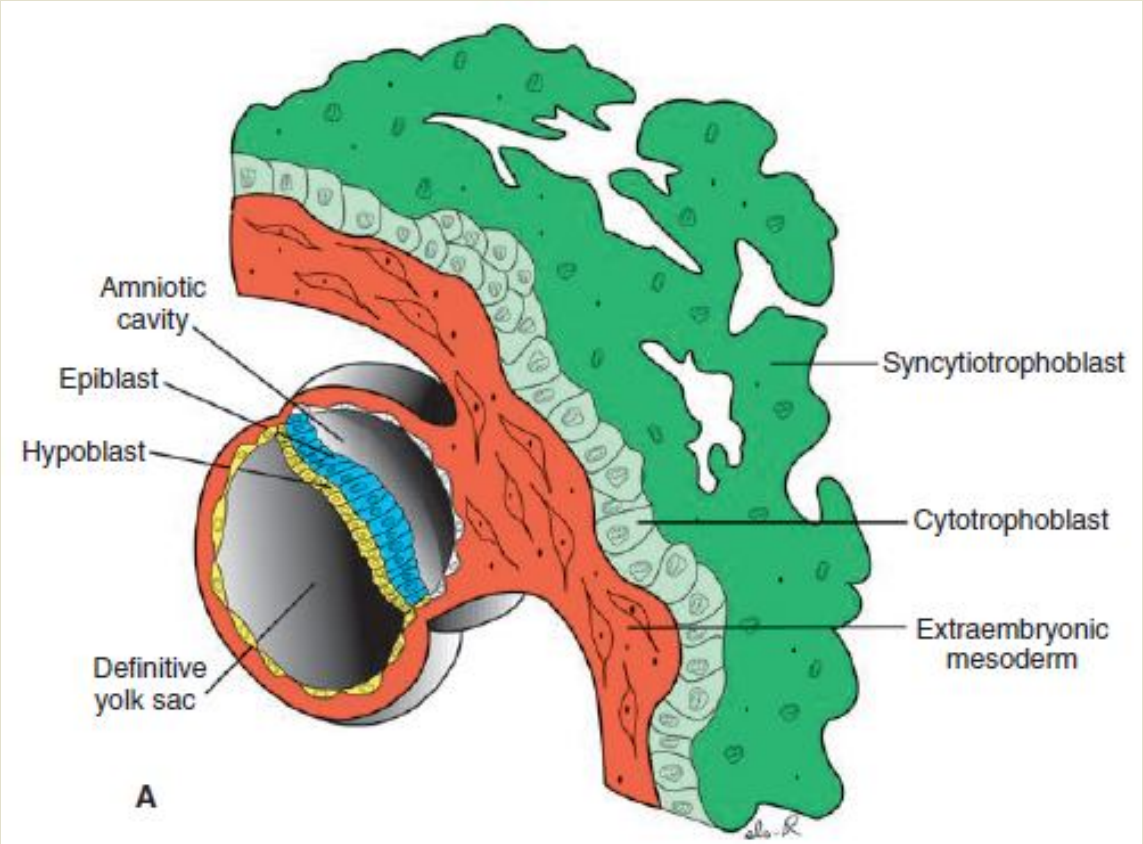
Third Week of Development

Trilaminar germ disc

GASTRULATION

Gastrulation = 3 **germ layers formation in 3th week**

- Ectoderm
- Mesoderm
- Endoderm

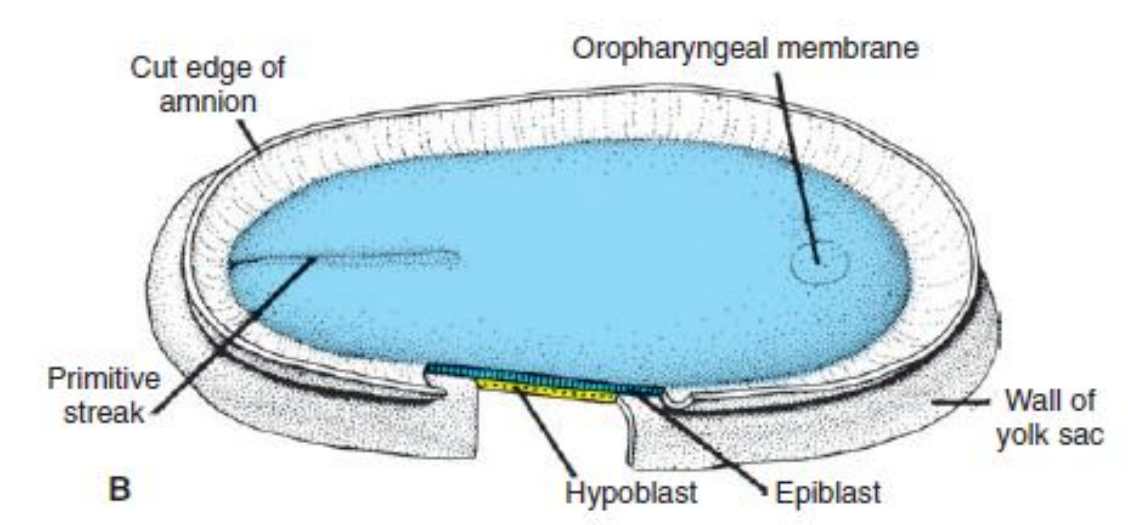


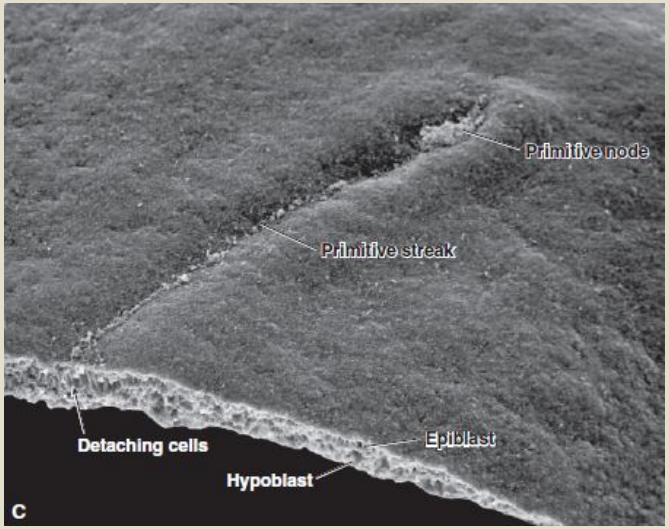
GASTRULATION

- **primitive streak** formation **(on the epiblast surface)**

in a 15- to 16-day embryo

- **primitive node = in Cranial end / that surround primitive pit**
- **Primitive pit**



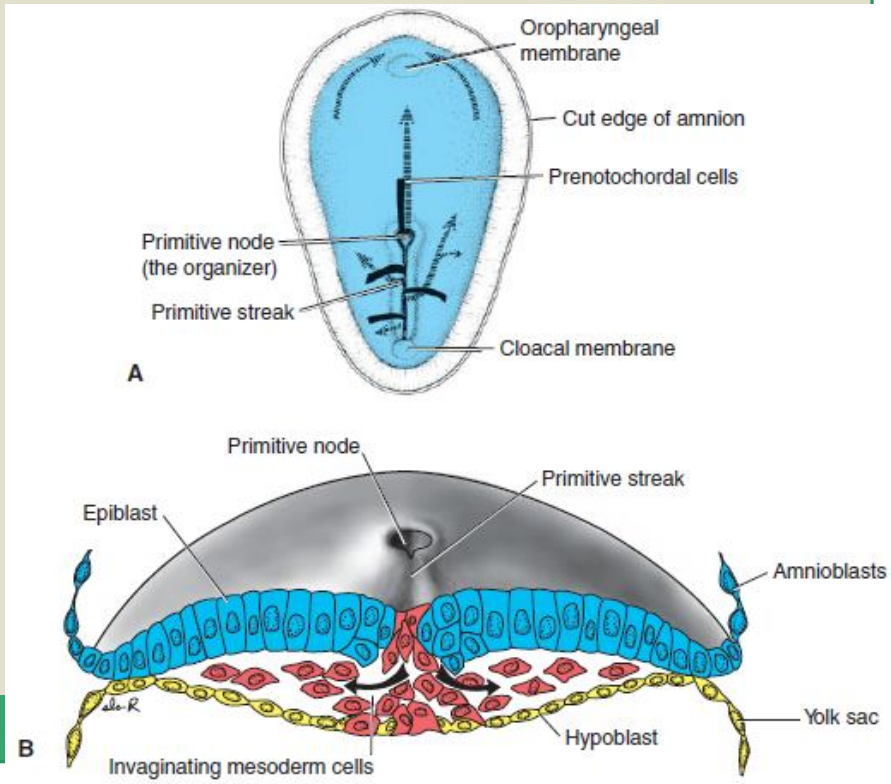


GASTRULATION

- epiblast Cells migration **(Invagination)**
- Cell migration and specification are controlled by **fibroblast growth factor 8 (FGF8)**, which is **synthesized by streak cells themselves**

fibroblast growth factor 8 (FGF8), controls cell movement by downregulating E-cadherin,a protein that normally binds epiblast cells together

FGF8 then controls cell specification into the mesoderm by **regulating *Brachyury (T)* expression**

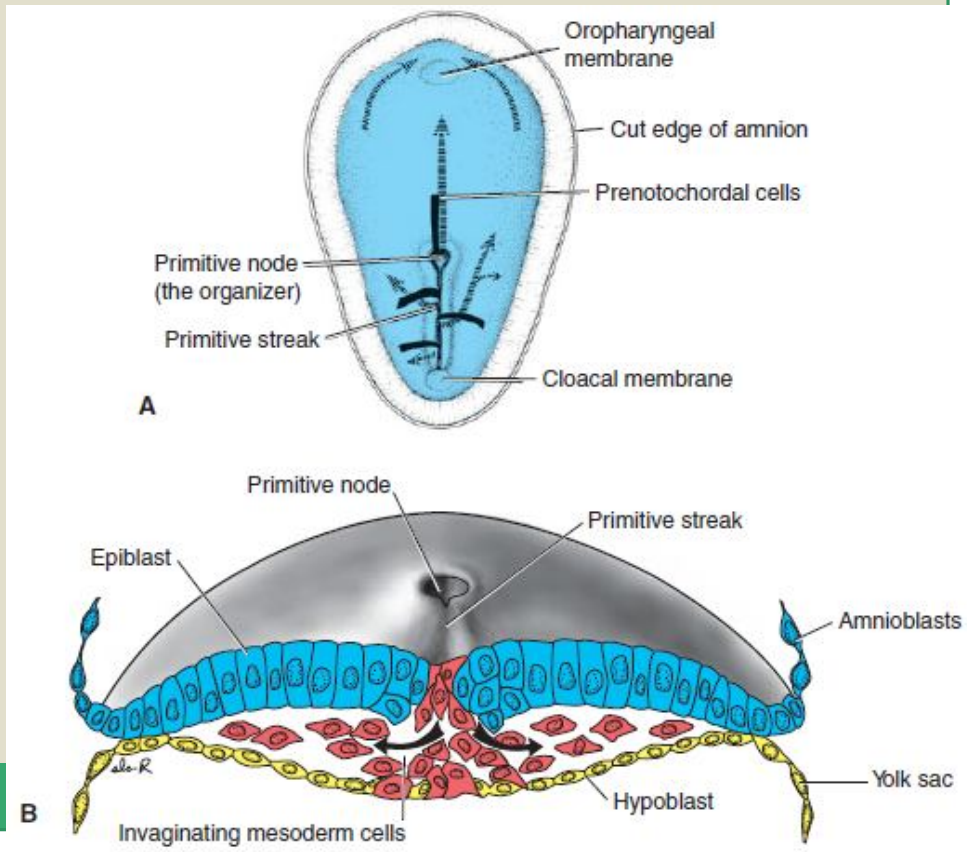


GASTRULATION

cells displace the hypoblast (**endoderm)**

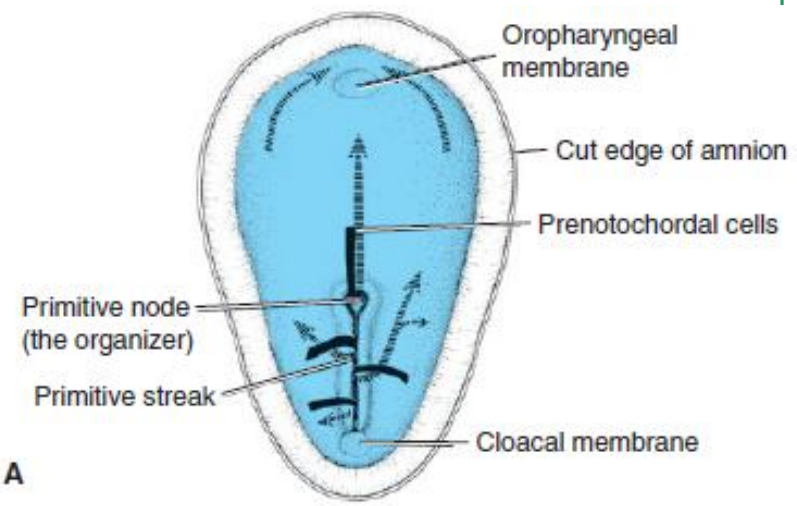
Cells lie between epiblast & endoderm (**mesoderm)**

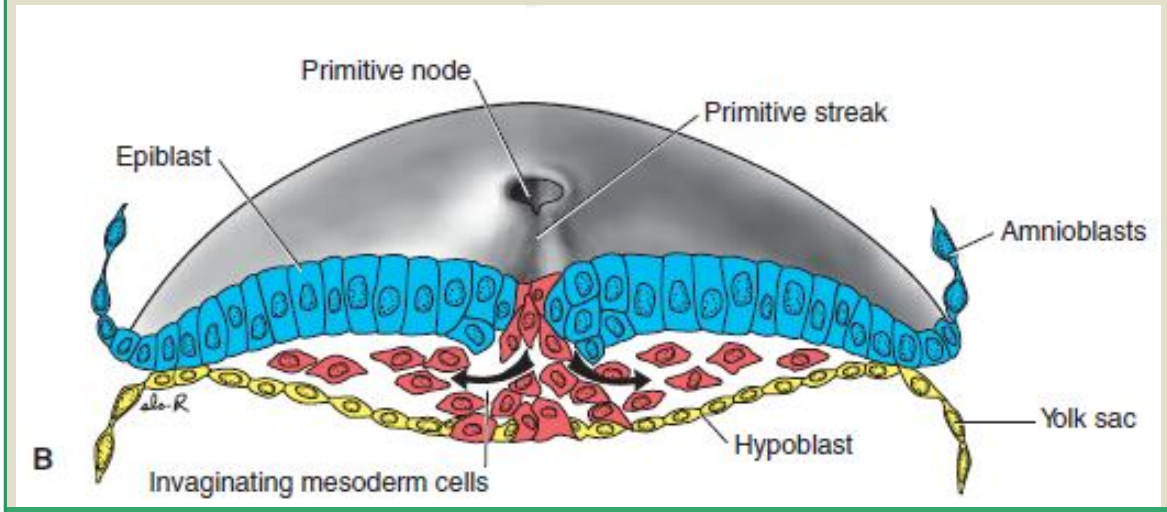
Cells remaining in the epiblast (**ectoderm)**

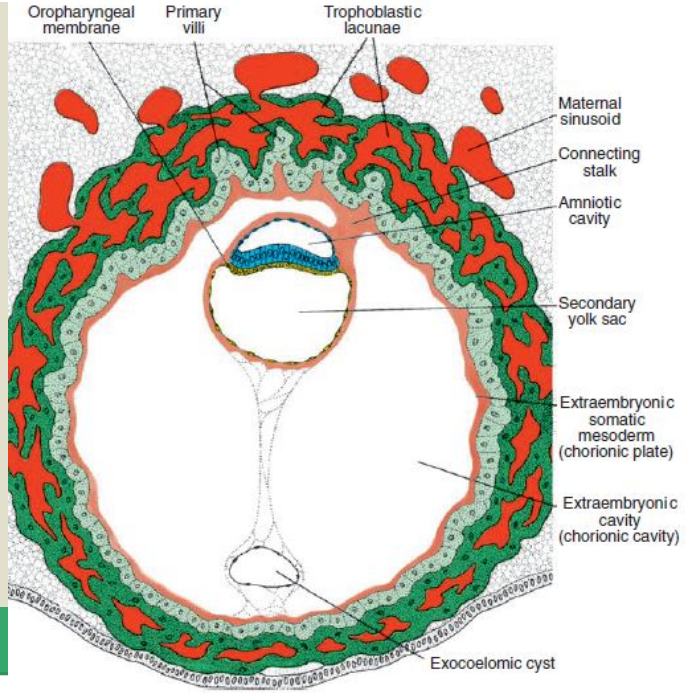


GASTRULATION

- cell movement between epiblast & hypoblast layers
- Cells spread laterally & cranially
- Cells migrate beyond the margin of the disc
- Cells contact with the **extraembryonic mesoderm covering the yolk sac and amnion**







GASTRULATION

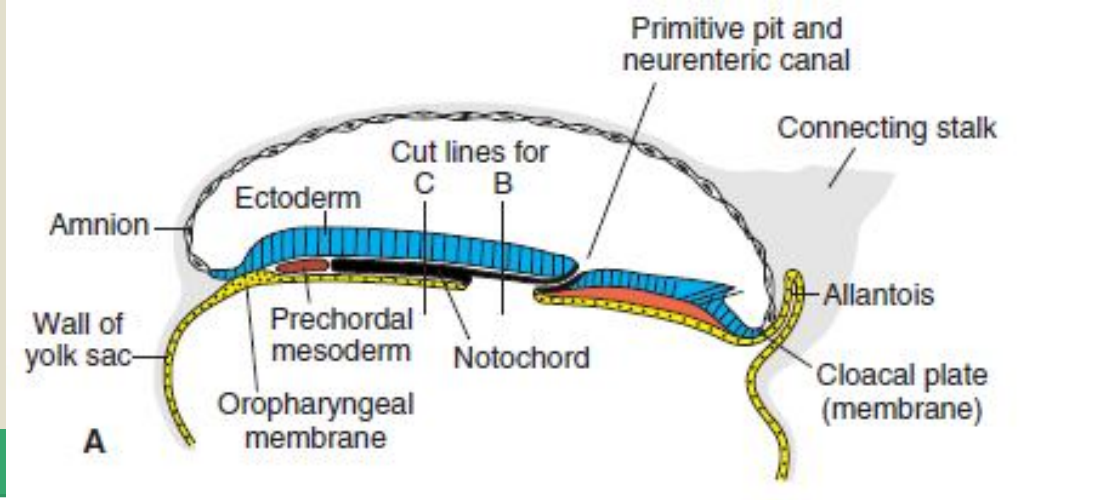
- Mesoderm Cells pass the **prechordal plate =**

Is located **between the tip of the notochord and the oropharyngeal membrane**

And

is **derived from** some of the **first cells that migrate through the node in the midline** and move in a cephalic direction

- prechordal plate (induction of the forebrain)
- The oropharyngeal membrane (ectoderm + endoderm)



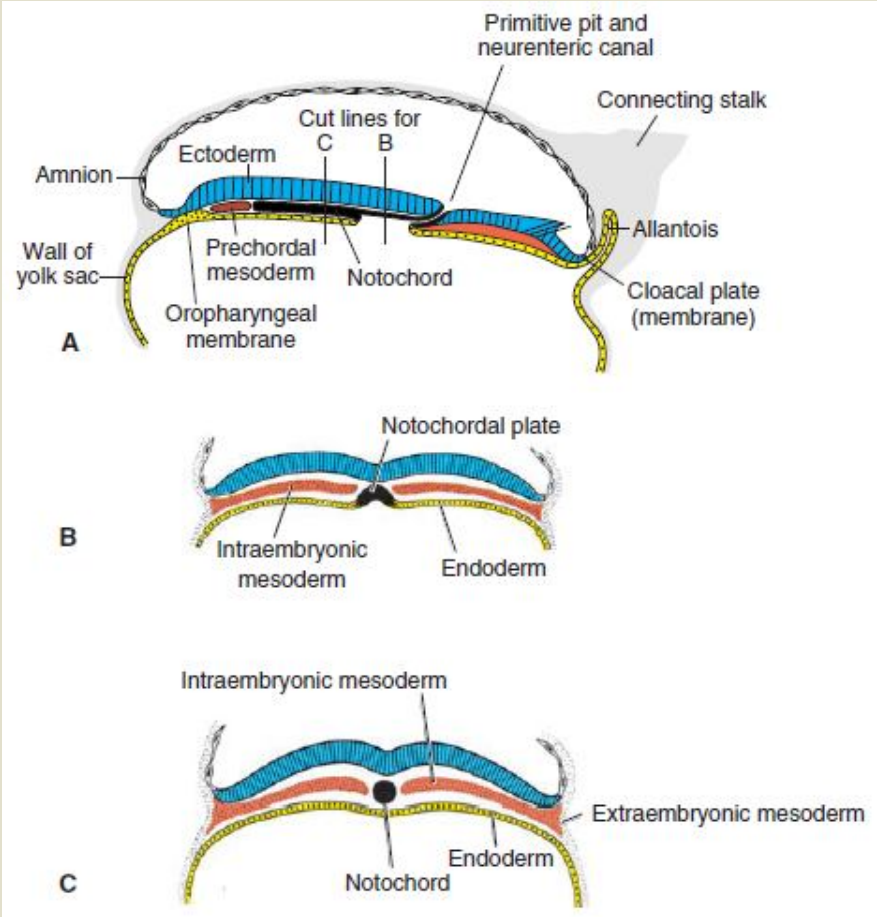
Notochord formation

Prenotochordal cells move forward cranially in the midline & reach the prechordal plate

prenotochordal cells become intercalated in the hypoblast

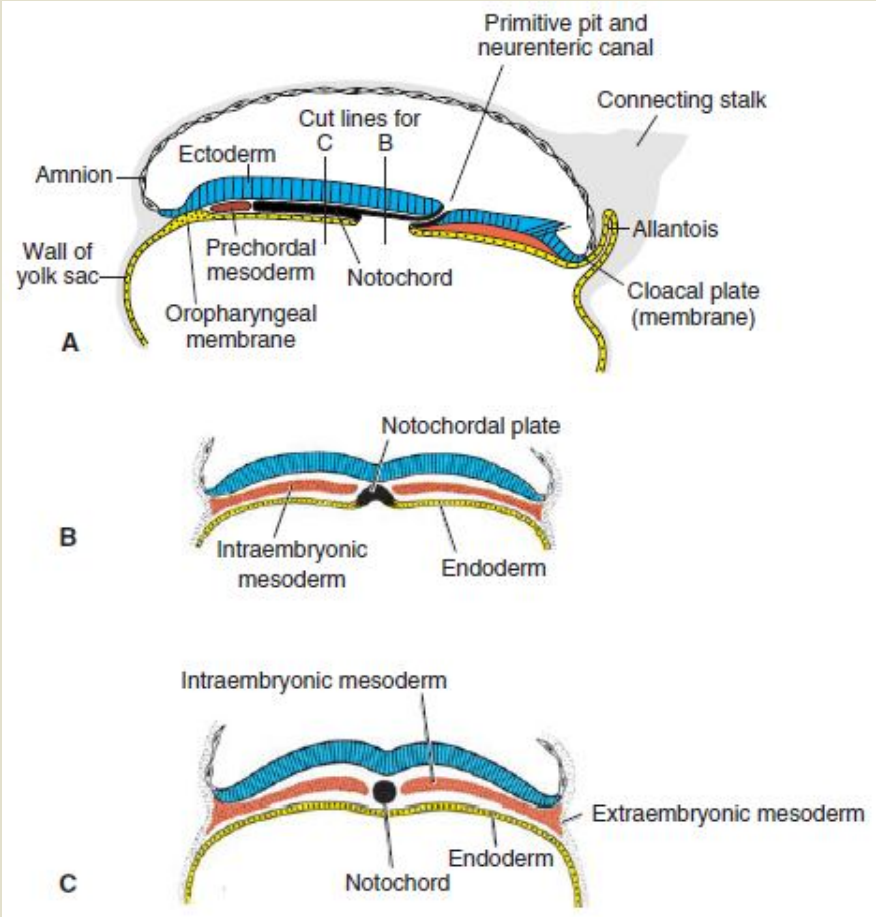
formation the **notochordal plate in midlin**

notochordal plate (prenotochordal + hypoblast)



Notochord formation

- As the hypoblast is replaced by endoderm cells moving in at the streak,
- cells of the notochordal plate proliferate and detach from the endoderm
- **definitive notochord formation**
- The notochord and prenotochordal cells extend caudally to the primitive pit



Notochord formation

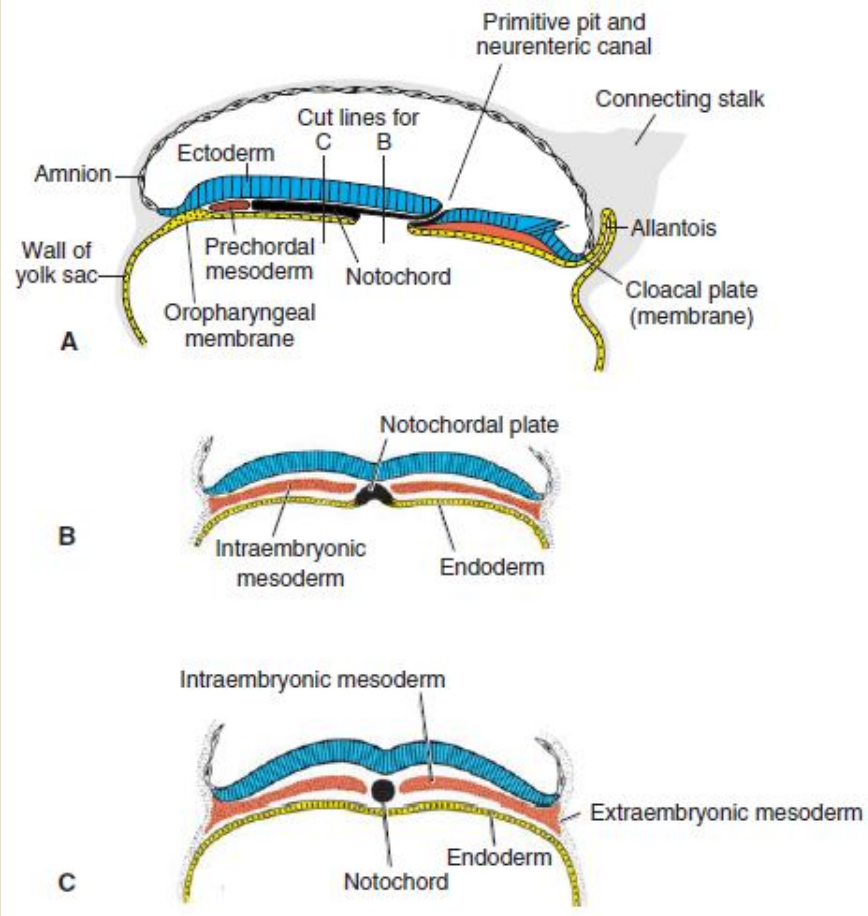
At the primitive pit :

- Forms the **neurenteric canal /** temporarily connects the amniotic and yolk sac cavities

- **cloacal membrane formation =**
- similar in structure to the oropharyngeal membrane, consists of tightly adherent ectoderm & endoderm cells with no intervening mesoderm

- **Formation allantoenteric diverticulum, or allantois =**
- the posterior wall of the yolk sac forms a small diverticulum that extends into the connecting stalk

(16th day of development)



Body axes establishment / cranial or caudal

The anteroposterior axis is signaled by cells at the anterior (cranial) margin of the embryonic disc

This area, the **anterior visceral endoderm (AVE)**, expresses genes essential for head formation

secreted factors **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

primitive streak initiated and maintained by expression of *Nodal* (TGF-b)

Once the streak is formed, *Nodal* upregulates a number of genes responsible for formation of dorsal and ventral mesoderm and head and tail structures

Body axes establishment ventral or dorsal

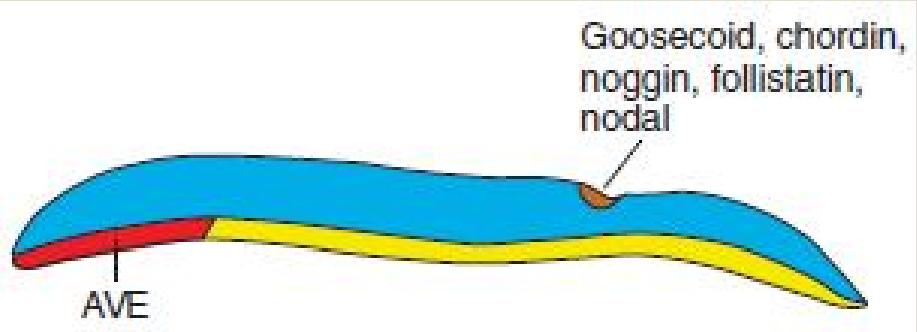
- **Another member of the TGF-b family, bone morphogenetic protein 4 (BMP4), is secreted throughout the embryonic disc**
- **By BMP4 (**TGF-b) & **FGF, mesoderm** ventralized to contribute to kidneys (intermediate mesoderm), blood, and body wall mesoderm (lateral plate mesoderm).
- all mesoderm would be ventralized if the activity of BMP4 were not blocked by other genes expressed in the node.
- the node is **organizer**
- **antagonize the activity of BMP4 :**

Chordin (***Goosecoid)***
Noggin
Follistatin
In the presence of this 3 gens :
cranial mesoderm is dorsalized into notochord, somites, and somitomeres these three genes are expressed in the notochord (neural induction in cranial region)

Body axes establishment ventral or dorsal

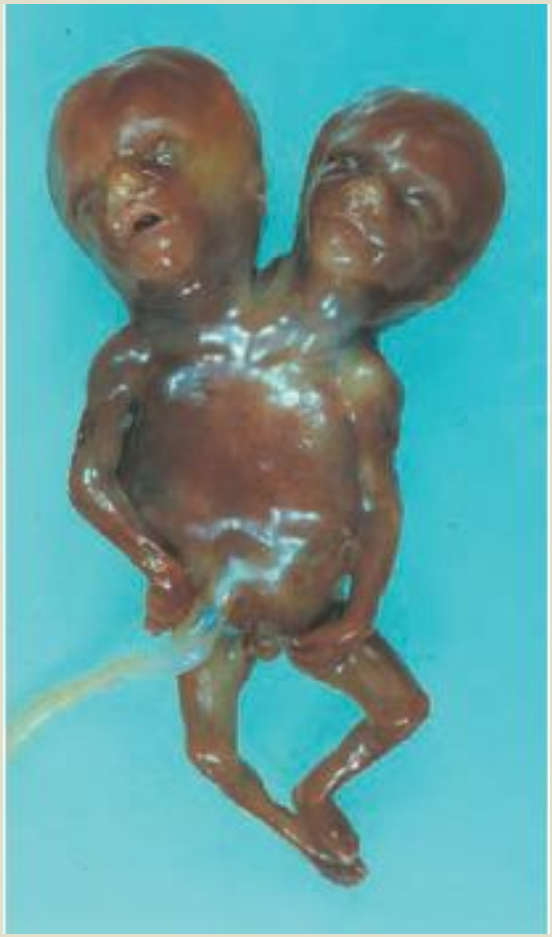
HNF-3b ***(***Hepatocyte nuclear factors***) maintains the node & induces*** forebrain and midbrain formation

Regulation of dorsal mesoderm formation in middle and caudal regions of the embryo is controlled by the ***Brachyury (T)*** **gene** expressed in the node, notochord precursor cells, and notochord



Body axes establishment ventral or dorsal

- *Goosecoid* activates inhibitors of BMP4 and contributes to regulation of head development
- Over- or underexpression of this gene in laboratory animals results in severe malformations of the head region, including duplications, similar to some types of conjoined twins



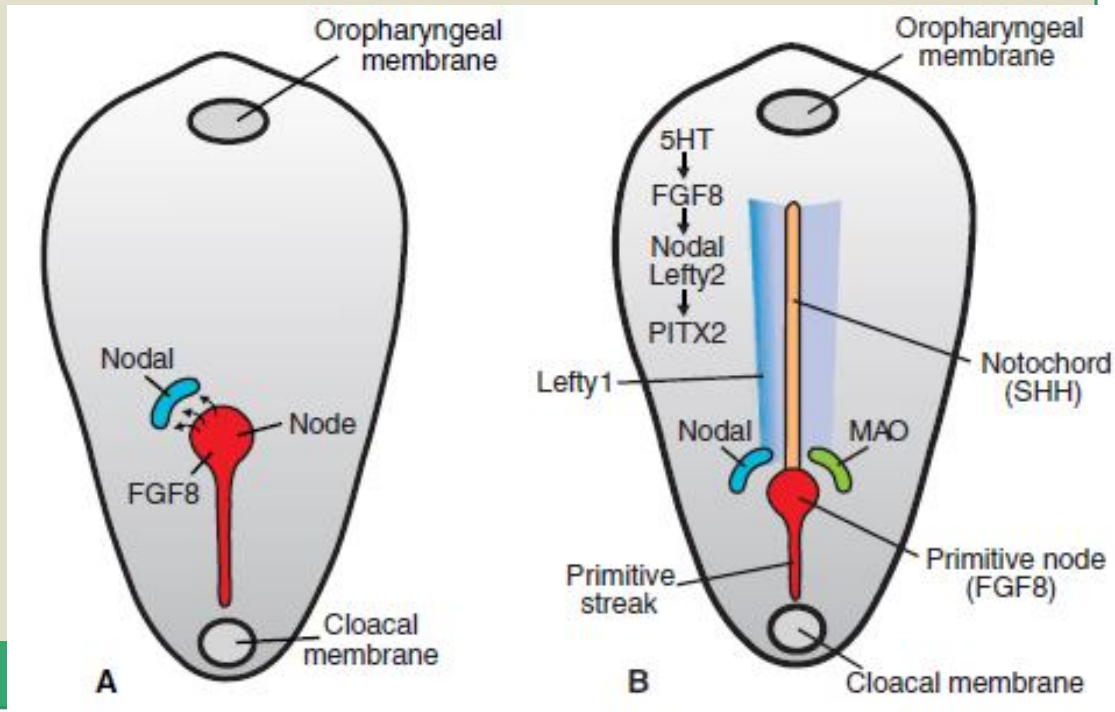
Laterality (left–right-sidedness)

- **FGF8 expression** (in node & primitive streak) = induces *Nodal* Expression in *left side*
- **FGF8** induce *Nodal* + ***LEFTY*** expression in the lateral plate mesoderm = establishing left-sidedness

(left side of the heart, stomach, and gut primordia)

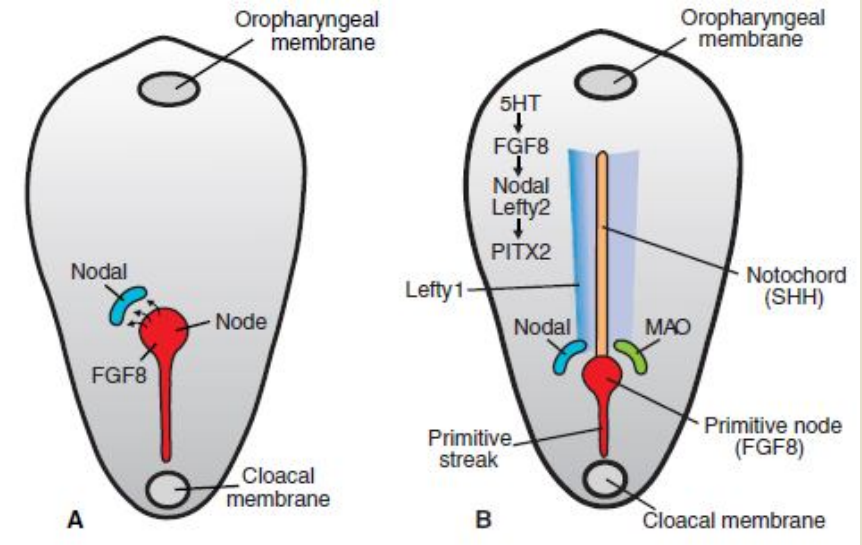
If the gene is expressed ectopically (e.g., on the right side), this abnormal expression results in laterality defects, including situs inversus and dextrocardia (placement of the heart to the right side)

- ***Sonic hedgehog (SHH)***
- ***Brachyury (T) gene***
- ***serotonin (5HT)***



Laterality (left–right-sidedness)

Expression of the transcription factor ***Snail*** may regulate downstream genes important for establishing ***right-sidedness***



Why the cascade is initiated on the left remains a mystery, but the mechanism may involve **cilia** on cells in the node that beat to create a gradient of *Nodal* toward the left or by a signaling gradient established by **gap junctions** and small ion transport.

Fate map established during gastrulation

- cranial region of the Node

Prechordal plate

Notochord

- lateral edge of the Node + cranial end of streak

Paraxial mesoderm

- Mid streak region

Intermediate mesoderm

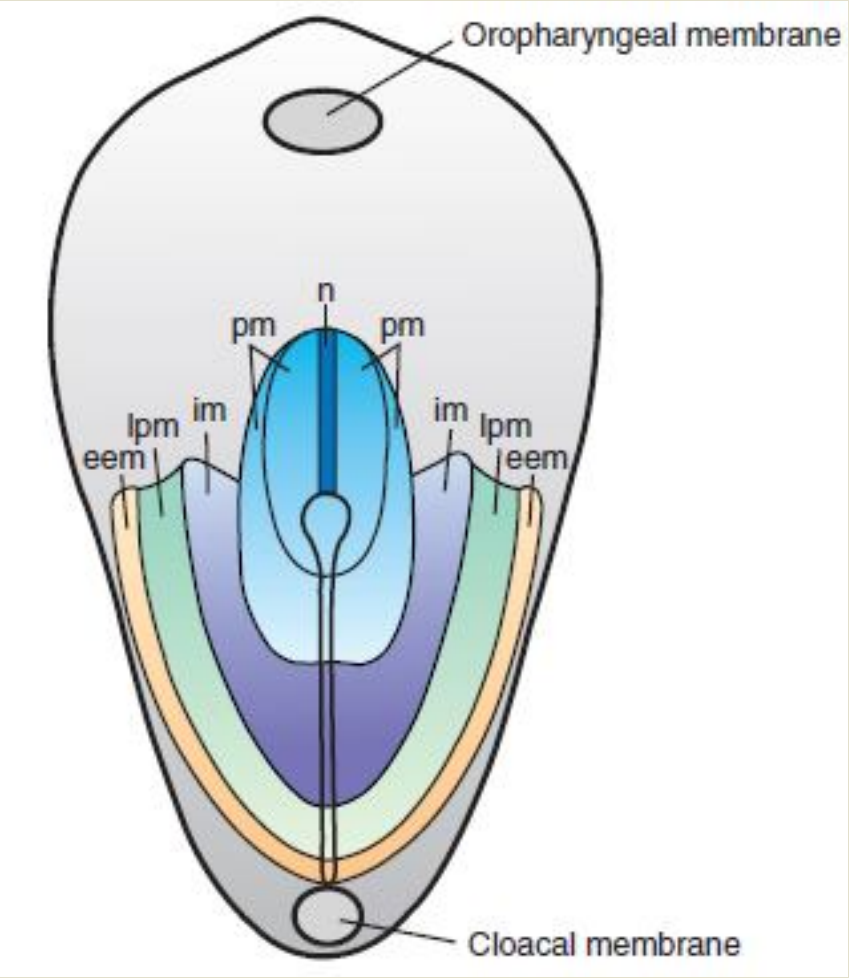
- Caudal part of streak

Lateral plate mesoderm

- The caudal most region of streak

Extraembryonic mesoderm

(primitive yolk sac, hypoblast)



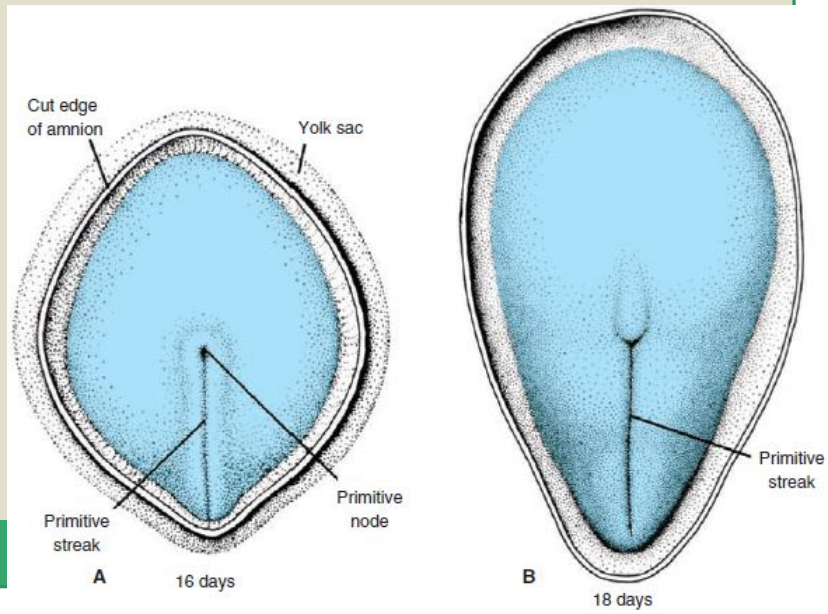
Growth of Embryonic disc

- Embryonic disc initially Flat & round disc
- Broad cephalic & narrow caudal disc

- **In caudal parts :**
- Cell migration up to end of 4th week
- Cell differentiation start at the end of 4th week

- **In cephalic parts :**
- Cell differentiation start at the middle of 3rd week
- Primitive streak disappears

- Cephalocaudal growth differentiation

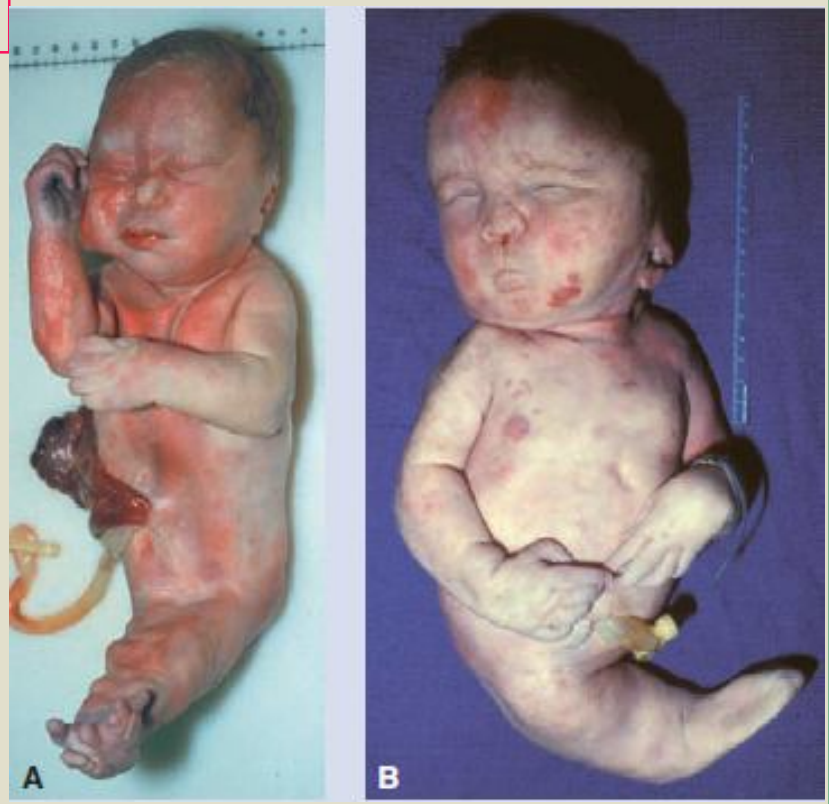


Clinical correlation

- In the beginning of 3rd weeks Teratogens like Alcohol =
  - Holoprosencephaly
  - Hypotelorism

Gastrulation itself may be disrupted by genetic abnormalities and toxic insults. In **caudal dysgenesis (sirenomelia)**, insufficient mesoderm is formed in the caudalmost 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.

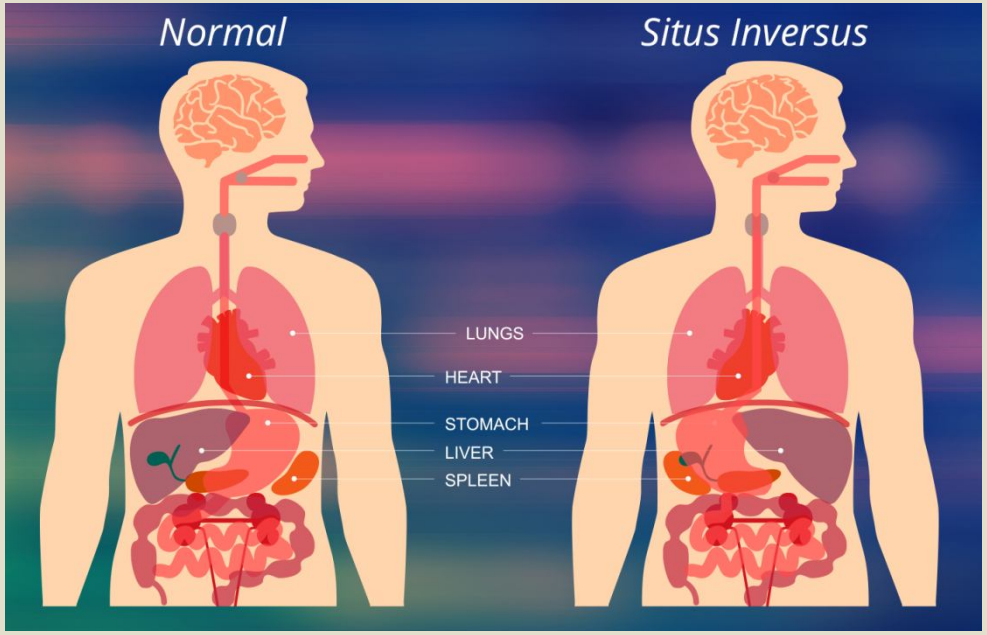
Affected individuals exhibit a variable range of defects, including hypoplasia and fusion of the lower limbs, vertebral abnormalities, renal agenesis, imperforate anus, and anomalies of the genital organs (Fig. 5.8*A*,*B*). In humans, the condition is associated with maternal diabetes and other causes. In mice, abnormalities of *Brachyury (T), WNT,* and *engrailed* genes produce a similar phenotype.



Clinical correlation

Situs inversus is a condition in which transposition of the viscera in the thorax and abdomen occurs. Despite this organ reversal, other structural abnormalities occur only slightly more frequently in these individuals. Approximately 20% of patients with complete situs inversus also differences; those with left-sided bilaterality have polysplenia, and those with right-sided bilaterality have asplenia or hypoplastic spleen. Patients with laterality sequences are also likely to have other malformations, especially heart defects.

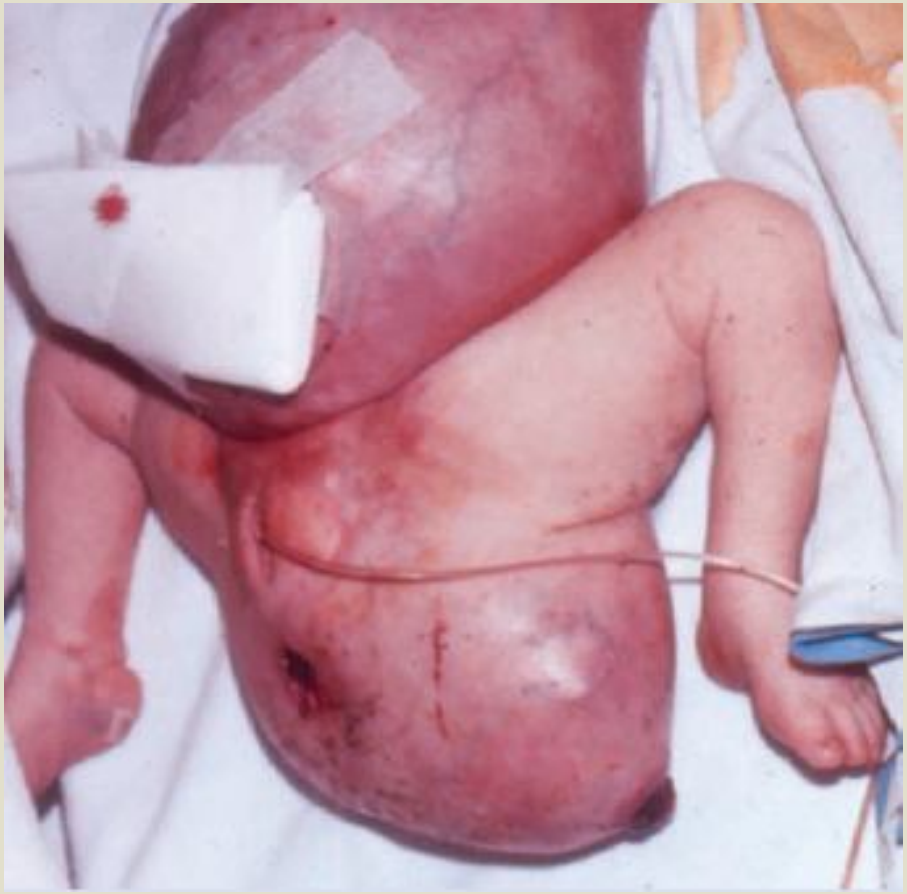
The **neurotransmitter serotonin (5HT)** is an important signal molecule for establishing laterality, and animal studies show that disrupting 5HT signaling results in cases of situs inversus, dextrocardia, and heart defects (see Chapter 13). Recent results also show that children born to mothers who take antidepressants from the class of drugs called **selective serotonin reuptake inhibitors (SSRIs)** have an increased risk of having a variety of heart malformations, thus providing additional evidence for 5HT's importance in establishing laterality.



Clinical correlation

Tumors Associated with Gastrulation

Sometimes, remnants of the primitive streak persist in the sacrococcygeal region. These clusters of pluripotent cells proliferate and form tumors, known as **sacrococcygeal teratomas**, which commonly contain tissues derived from all three germ layers (Fig. 5.9). This is the most common tumor in newborns, occurring with a frequency of one in 37,000. Teratomas may also arise from **primordial germ cells** that fail to migrate to the gonadal ridge (see p. 10).



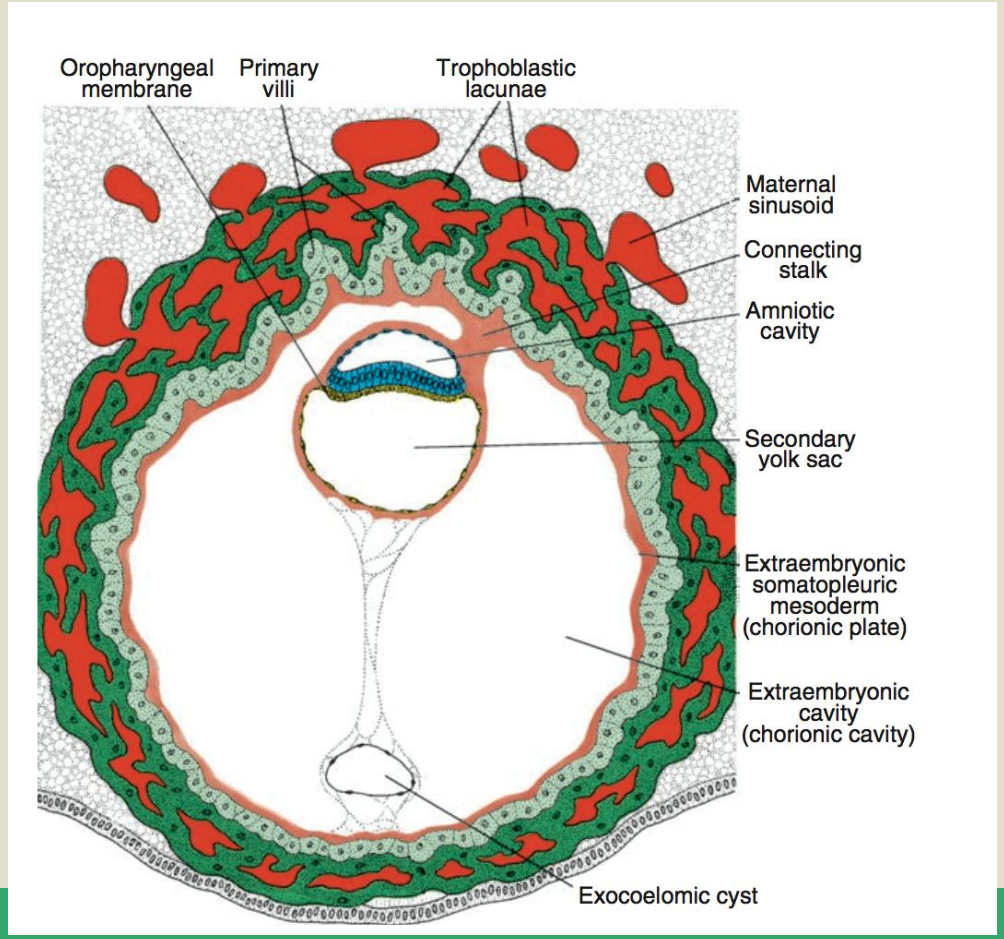
Further development of trophoblast

- At the Third week the trophoblst is caracterized by =
- **Primary villi =**

Column:

Cytotrophoblastic core

Syncytial layer



Further development of trophoblast

- **Secondary villi**

Mesodermal cells

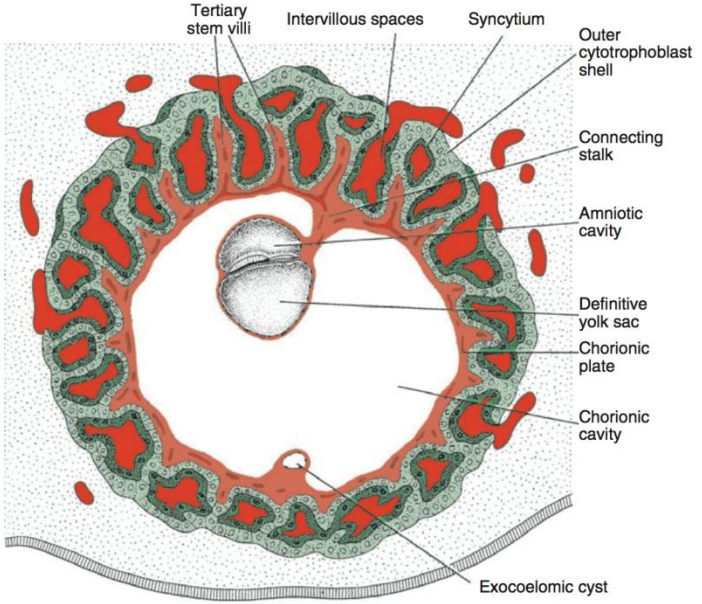
penetration to core of primary villi

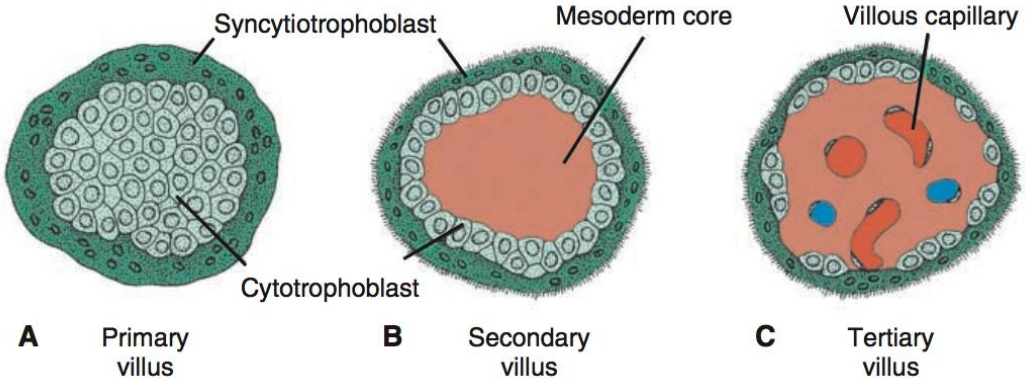
- **Tertiary villi**

Definitive villi

Mesoderm differentiated to blood cells &

small blood vessel





Further development of trophoblast

- **Tertiary villi**

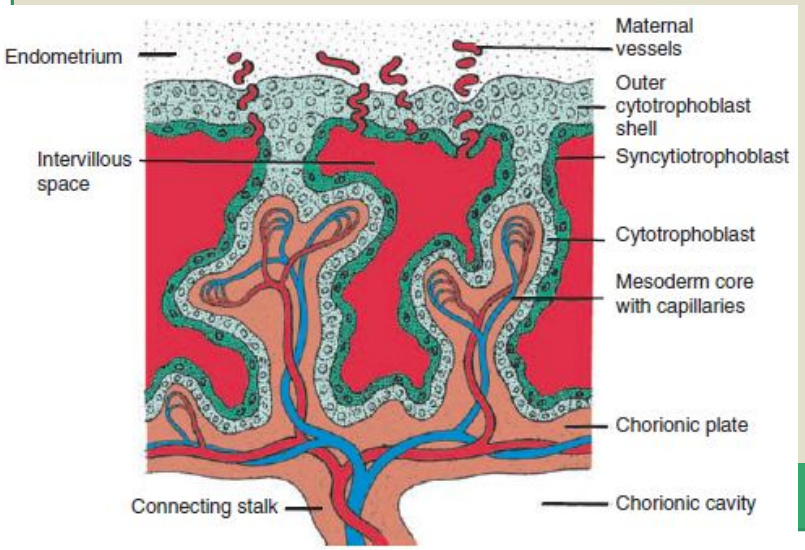
Definitive placental villus

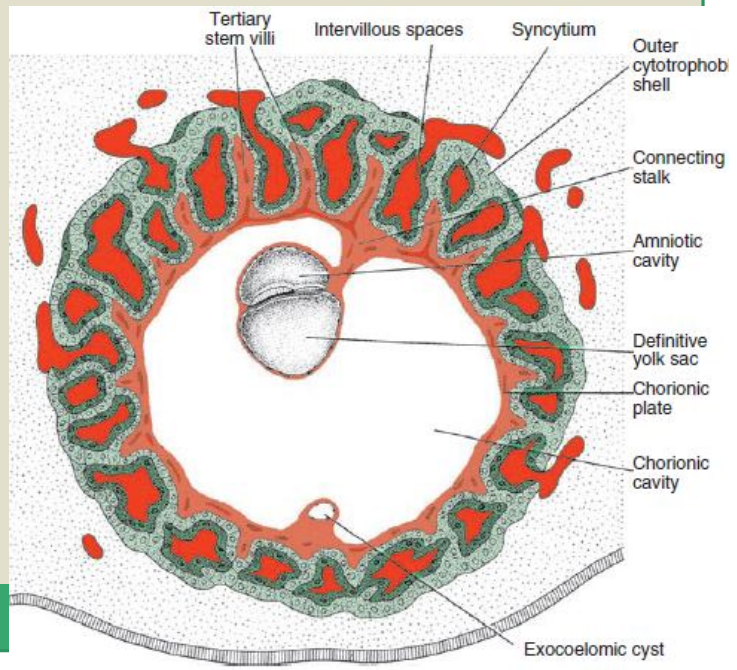
Mesoderm differentiated to blood cells & small blood vessel

cytotrophoblastic cells in the villi penetrate progressively into the overlying syncytium

Form Outer cytotrophoblastic shell

1. **Stem or anchoring villi**
2. **Free villi**





Further development of trophoblast

The chorionic cavity becomes larger, and by the 19th or the 20th day, the embryo is attached to its trophoblastic shell by a narrow **connecting stalk**

The connecting stalk later develops into the **umbilical cord**, which forms the connection between the placenta and embryo.