Third to Eighth Weeks

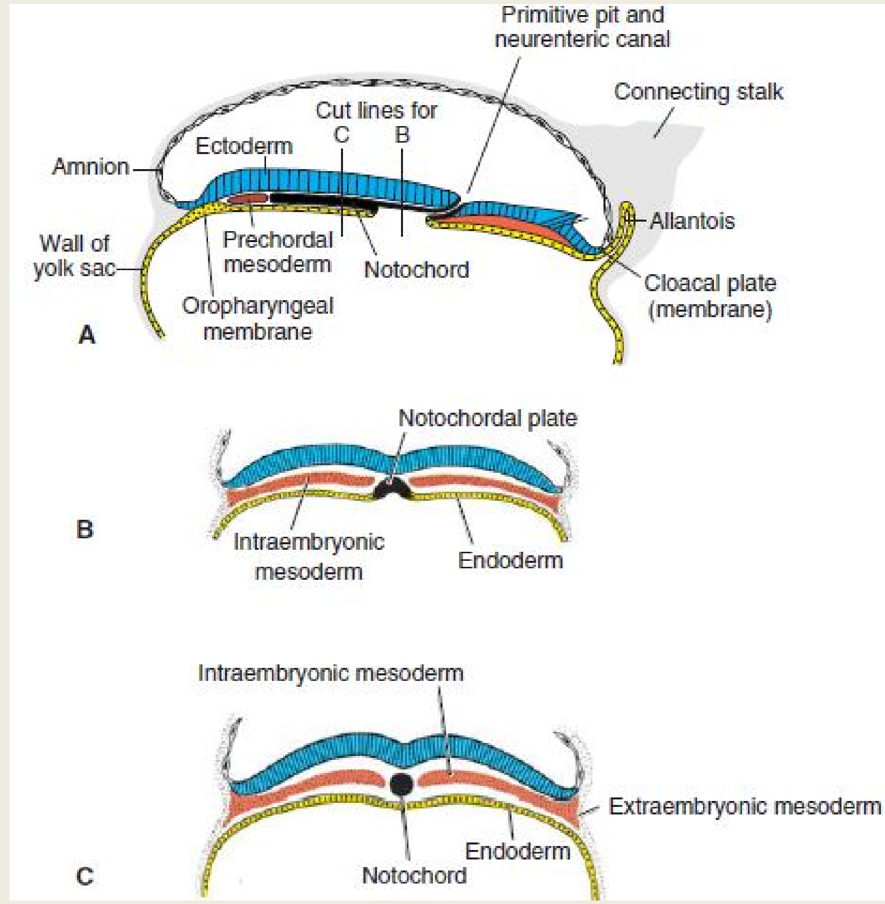
The embryonic period

Embryonic (organogenesis) period

Third to eighth weeks of development = organogenesis

- **Ectoderm**
- **Mesoderm**
- **Endoderm**

gives rise to a number of specific tissues & organs
Formation of the major features of the external



Derivatives of the ectodermal germ layer

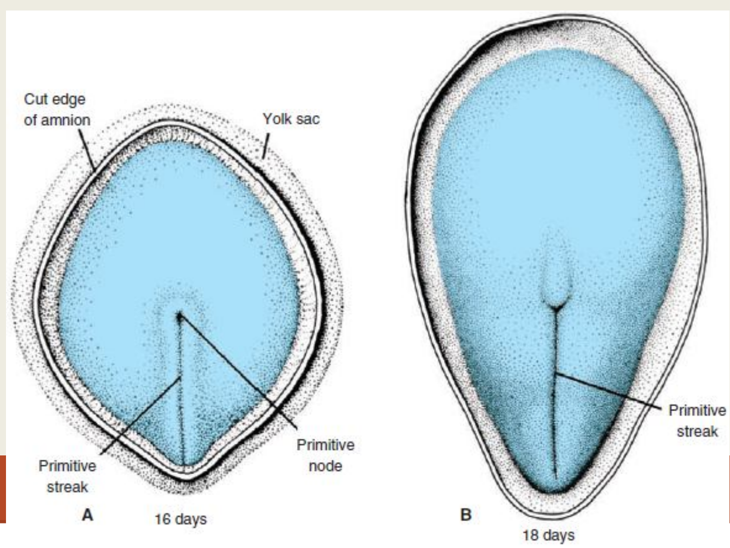
beginning of 3rd week

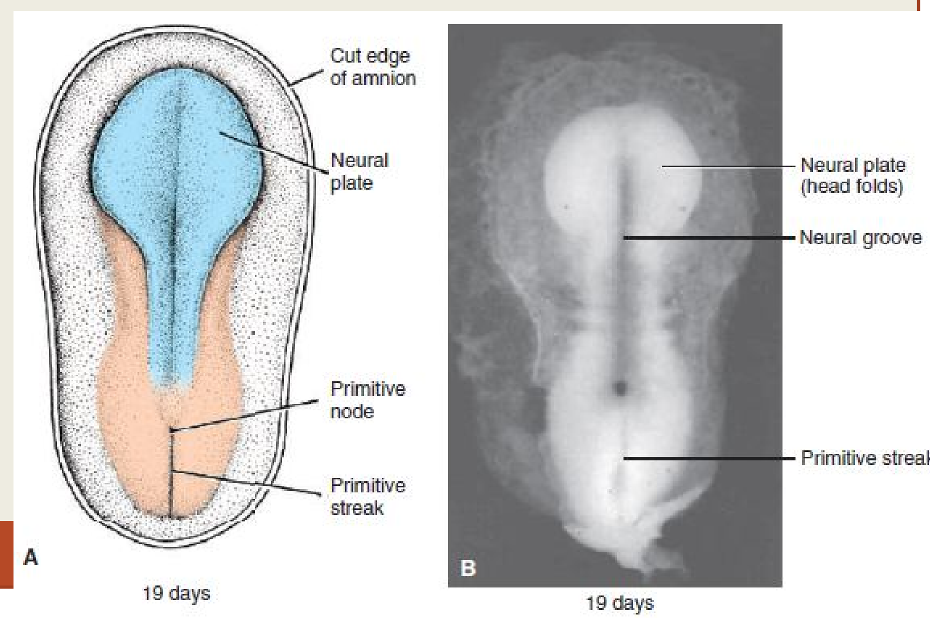
the ectodermal germ layer broader in the cephalic than in caudal region

notochord and prechordal mesoderm induces ectoderm overlying to thicken & form the **neural plate**

neuroectoderm (the cells in neural plate)

neurulation





Molecular Regulation of Neural Induction

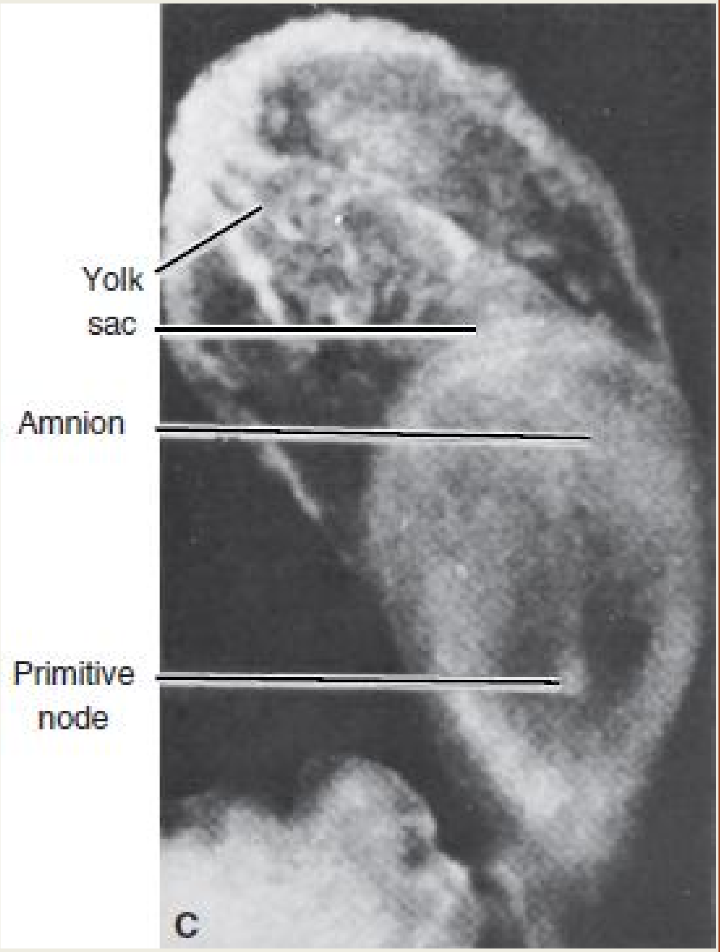
In cranial neural plate (forebrain and midbrain types of tissues) :

- **In the presence of BMP4 =**

  ectoderm is induced to form epidermis, and mesoderm forms intermediate and lateral plate mesoderm.

- **If the absence of BMPs =**

  Ectoderm become neural tissue and mesoderm forms para axial mesoderm



Molecular Regulation of Neural Induction

Secretion of three other molecules, **noggin, chordin, and follistatin, inactivates BMP4**

These three proteins are present in the **organizer (primitive node), notochord, and prechordal mesoderm**

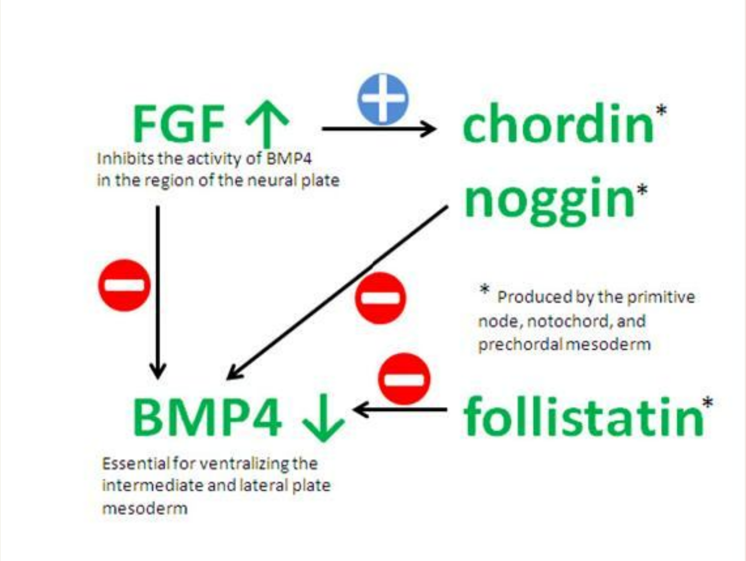
They neuralize ectoderm by inhibiting BMP and cause **mesoderm to become notochord and paraxial mesoderm** (dorsalizes mesoderm)

Induction of caudal neural plate structures (hindbrain and spinal cord) :

depends on two secreted proteins, **WNT3a** and **FGF**

- **Retinoic acid (RA)**

cranial-to-caudal axis organizer

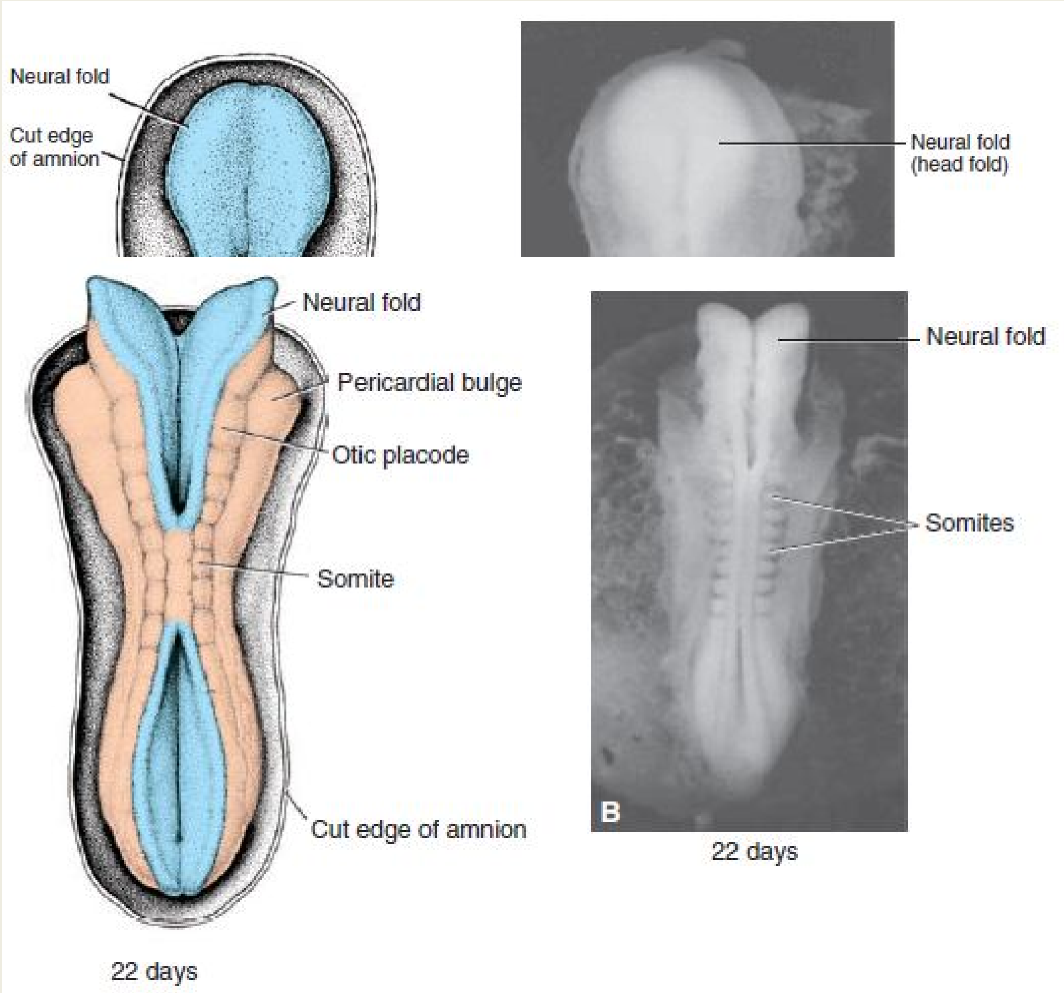


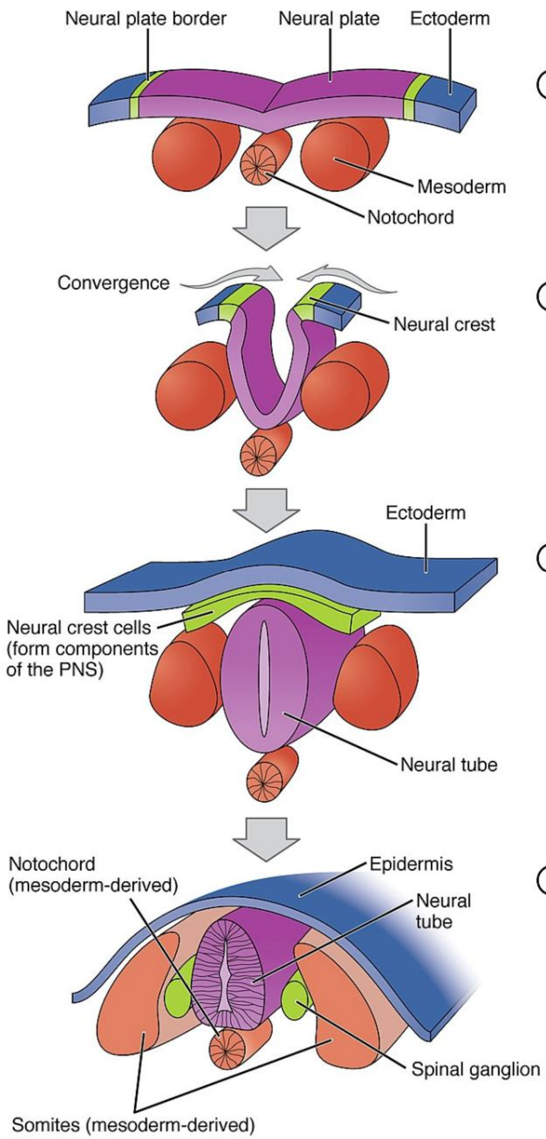
Neurulation

- Neural plate at the End of 3th week
- **Neural folds formation**
- **Neural groove**
- *Fusion of neural fold begins in the cervical* region

(5th somite)

- ***Neural*** **tube formation** (fusion in caudal & cranial direction)



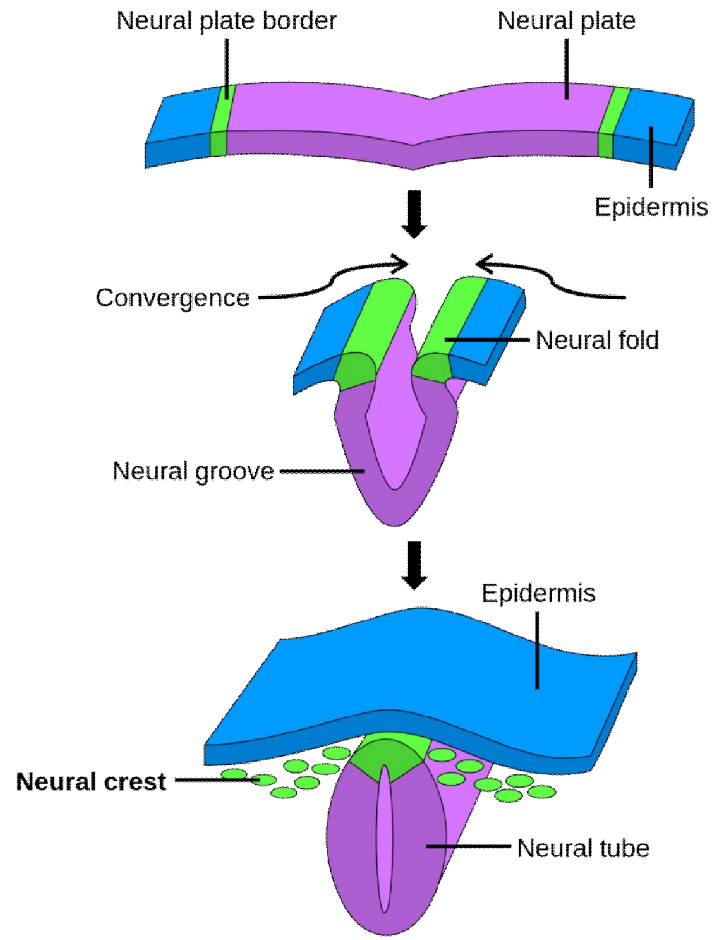


1. Neuroectodermal tissues differentiate from the ectoderm and thicken into the neural plate. The neural plate border separates the ectoderm from the neural plate.

2. The neural plate bends dorsally, with the two ends eventually joining at the neural plate borders, which are now referred to as the neural crest.

3. The closure of the neural tube disconnects the neural crest from the epidermis. Neural crest cells differentiate to form most of the peripheral nervous system.

4. The notochord degenerates and only persists as the nucleus pulposus of the intervertebral discs. Other mesoderm cells differentiate into the somites, the precursors of the axial skeleton and skeletal muscle.



Neurulation

Neural tube correlated to amniotic cavity by =

- **anterior (cranial) neuropores**
- **posterior (caudal)neuropores**

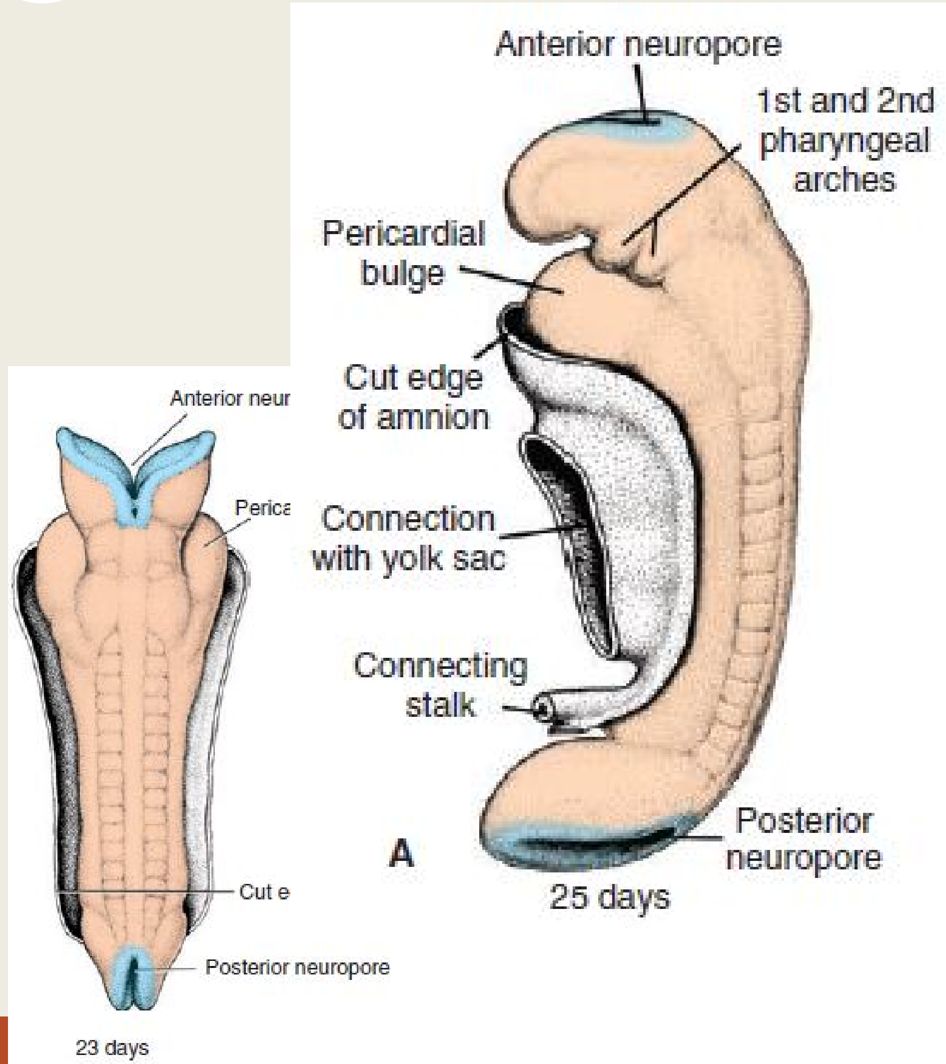
cranial neuropore closes day 25 (18- to 20-somite stage)

posterior neuropore closes at day 28 (25-somite stage)

Neurulation completed

Neural tube consist of :

1. a narrow caudal portion form the **spinal cord**
2. **A** broader cephalic portion form the **brain vesicles**



Neural Crest Cells

Neural Crest Cells =

- cells at the lateral border or crest of the neuroectoderm

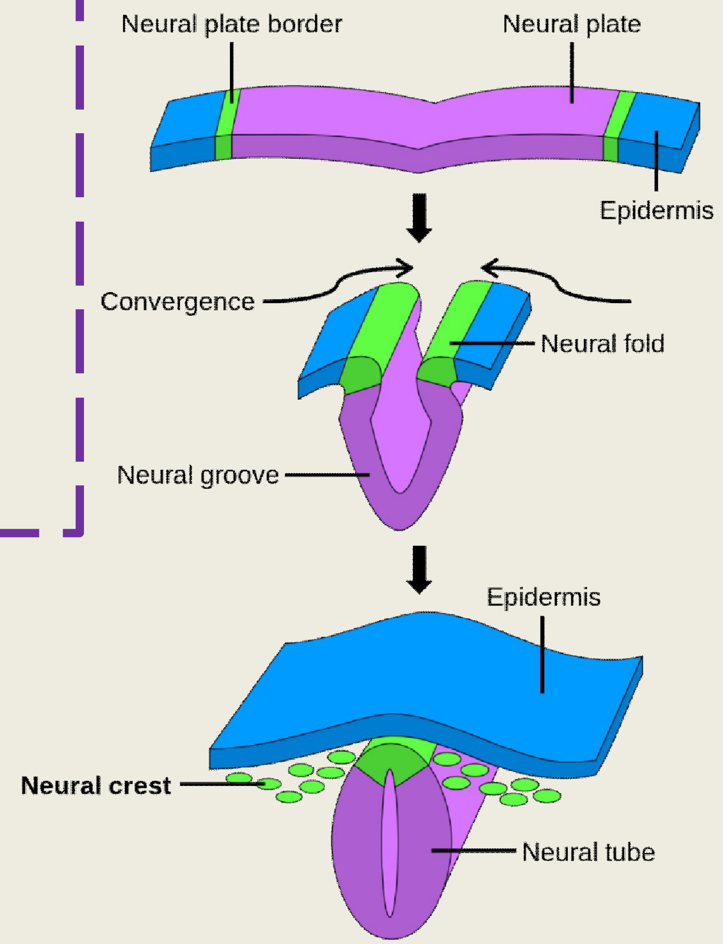
migration and displacement to enter the underlying mesoderm

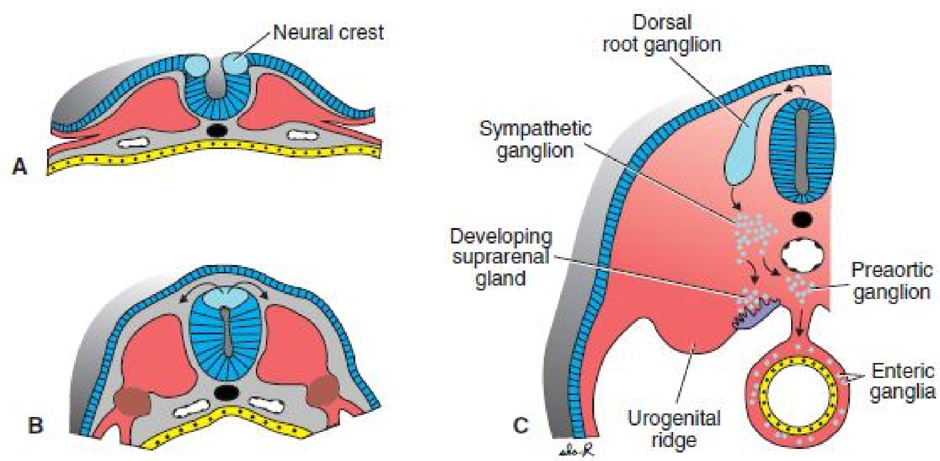
Convert from epithelial-to-mesenchymal transition

- **Migration in 2 pathways:**

(1) a dorsal pathway through the dermis (**melanocytes & hair follicles)**

(2) a ventral pathway through the anterior half of each somite to become **sensory ganglia, sympathetic & enteric neurons, Schwann's cells, and cells of the adrenal**



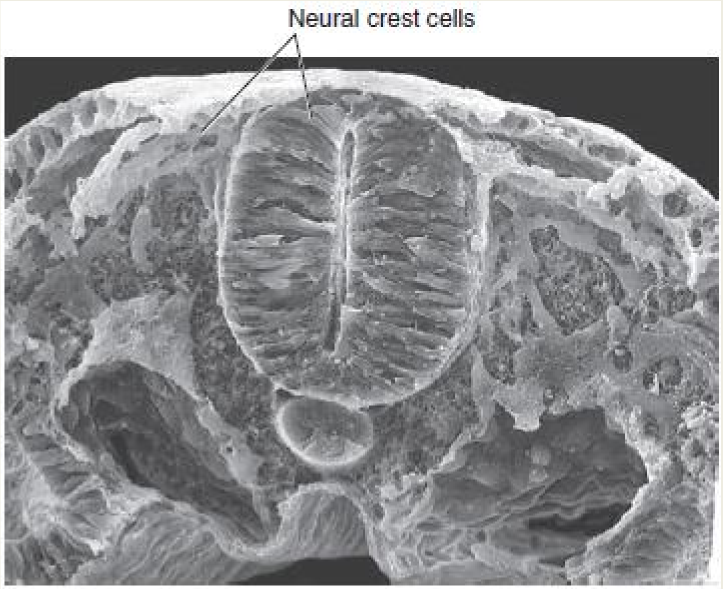


Neural Crest Cells

Neural crest from cranial neural

Formation **craniofacial skeleton, cranial ganglia, glial cells, melanocytes**

Neural crest cells are so fundamentally important and contribute to so many organs and tissues that they are sometimes referred to as the **fourth germ layer**



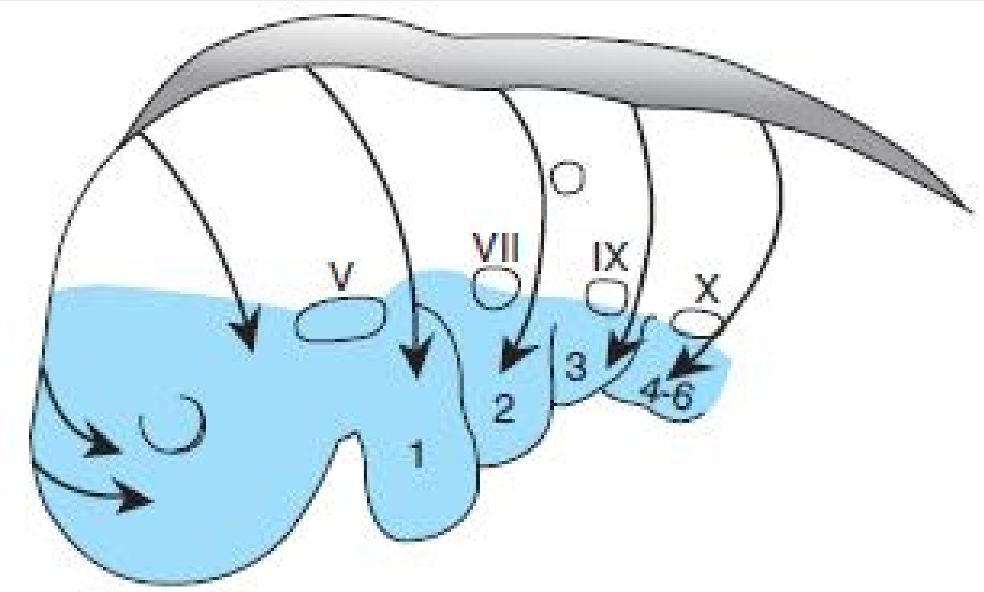


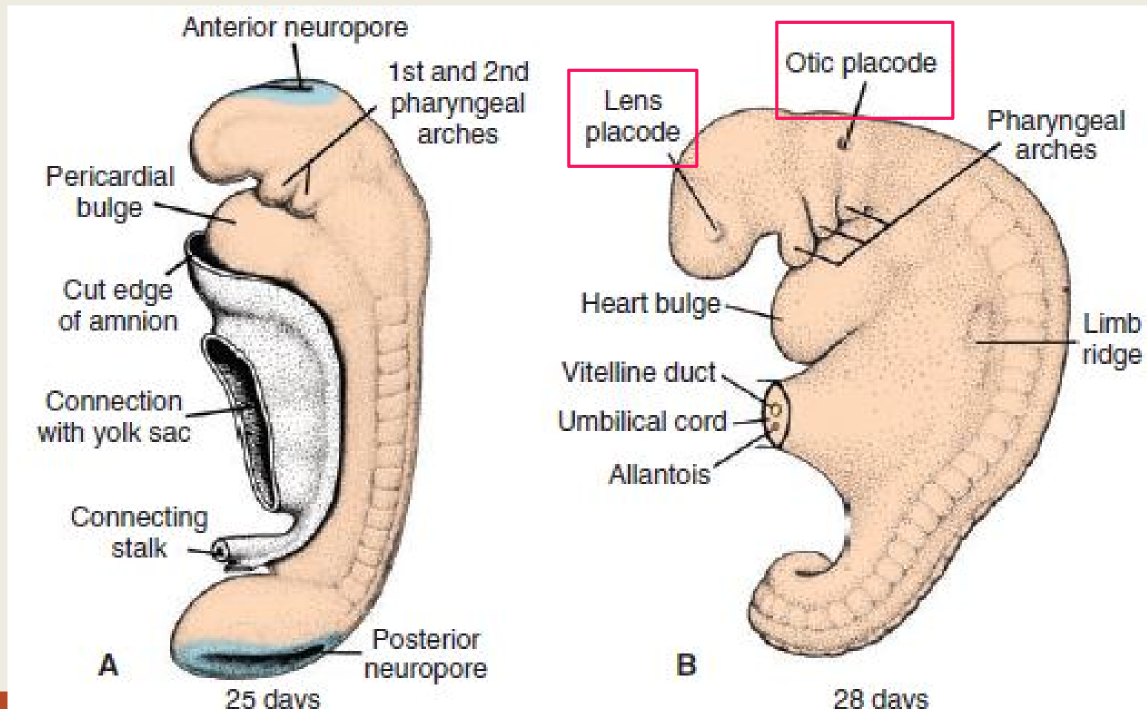
TABLE 6.1 *Neural Crest Derivatives*

Connective tissue and bones of the face and skull
Cranial nerve ganglia (see Table 17.2)
C cells of the thyroid gland
Conotruncal septum in the heart
Odontoblasts
Dermis in face and neck
Spinal (dorsal root) ganglia
Sympathetic chain and preaortic ganglia
Parasympathetic ganglia of the gastrointestinal tract
Adrenal medulla
Schwann cells
Glial cells
Meninges (forebrain)
Melanocytes
Smooth muscle cells to blood vessels of the face and forebrain

Ectodermal dervatives

By the time the neural tube is closed
bilateral **ectodermal thickenings**

1. **the otic placodes (otic vesicles)**
2. **the lens placodes (5th week,** the **lenses of the eyes)**



Ectodermal derivatives

- organs and structures that maintain contact with the outside world:
- The central nervous system;
- The peripheral nervous system;
- The sensory epithelium of the ear, nose, eye, epidermis (hair and nails)

In addition:

- Subcutaneous glands
- The mammary glands
- The pituitary gland
- enamel of the teeth

Clinical Correlates

Neural Tube Defects

Neural tube defects (NTDs) result when neural tube closure fails to occur. If the neural tube fails to close in the cranial region, then most of the brain fails to form, and the defect is called **anencephaly** (Fig. 6.7*A*). If closure fails anywhere from the cervical region caudally, then the defect is called **spina bifida** (Fig. 6.7*B*,*C*). The most common site for spina bifida to occur is in the lumbosacral region (Fig. 6.7*C*), suggesting that the closure process in this area may be more susceptible to genetic and/or environmental factors. Anencephaly is a lethal defect, and most of these cases are diagnosed prenatally and the pregnancies terminated. Children with spina bifida lose a degree of neurological function based on the spinal cord level of the lesion and its severity.

Occurrence of these types of defects is common and varies by different regions. For example, prior to fortification of enriched flour with folic acid in the United States, the overall rate was 1 in 1,000 births, but in North and South Carolina, the rate was 1 in 500 births. In parts of China, rates were as high as 1 in 200 births. Various genetic and environmental factors account for the variability, but regardless of the region rates have been reduced significantly following folic acid administration. For example, rates throughout the United States are now approximately 1 in 1,500 births. It is estimated that 50% to 70% of NTDs can be prevented if women take **400** μg of folic acid daily (the dose present in most multivitamins) beginning 3 months prior to conception and continuing throughout pregnancy. Because 50% of pregnancies are unplanned, it is

Figure 6.7 Examples of NTDs, which occur when closure of the neural tube fails. **A.** Anencephaly.

(continued on following page)

(continued from previous page)

recommended that all women of childbearing age take a multivitamin containing 400 μg of folic acid daily. If a woman has had a child with an NTD or if there is a history of such defects in her family, it is recommended that she take 400 μg of folic acid daily and then **4,000 μg** per day starting 1 month before she tries to become pregnant and continuing through the first 3 months of pregnancy.

Figure 6.7 *(Continued)* **B,C.** Infants with spina bifida. Most cases occur in the lumbosacral region. Fifty to seventy percent of all NTDs can be prevented by the vitamin folic acid.

Derivatives of mesoderm germ layer

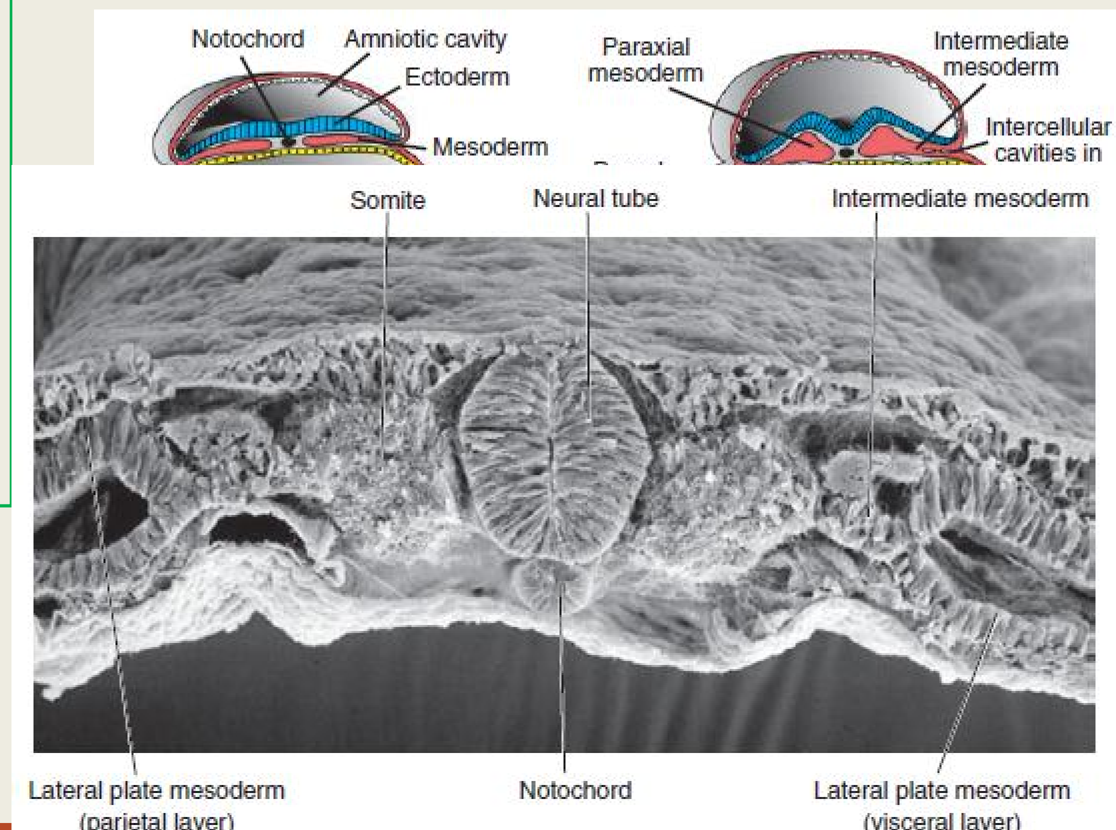
- 17th day

Paraxial mesoderm

Lateral plate mesoderm

1. Parietal or somatic mesoderm layer
2. Splanchnic or visceral mesoderm layer

Intermediate mesoderm



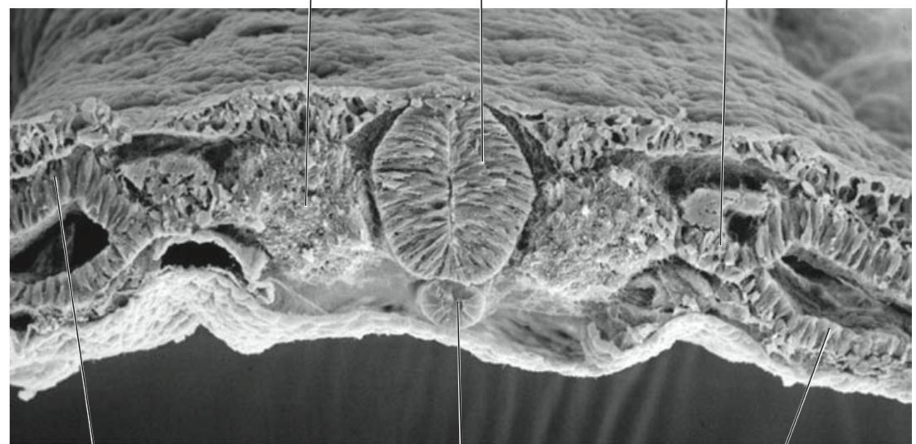
Paraxial mesoderm

At the Beginning of 3rd week

- Somitomeres (Segmentation) form

(Concentric whorls around the unit center)

- **Neuromeres = in cephalic part (head mesenchyme)**
- The first pair of somites in occipital region
- 20th day
- craniocaudal sequence
- 3 pairs per day



end of 5th week, 42 to 44 pairs

- *4 occipital*
- *8* cervical
- 12 thoracic
- 5 lumbar
- 5 sacral
- 8 to 10 coccygeal

Somite is landmark for the age of an embryo

TABLE 6.2 *Number of Somites Correlated to Approximate Age in Days*

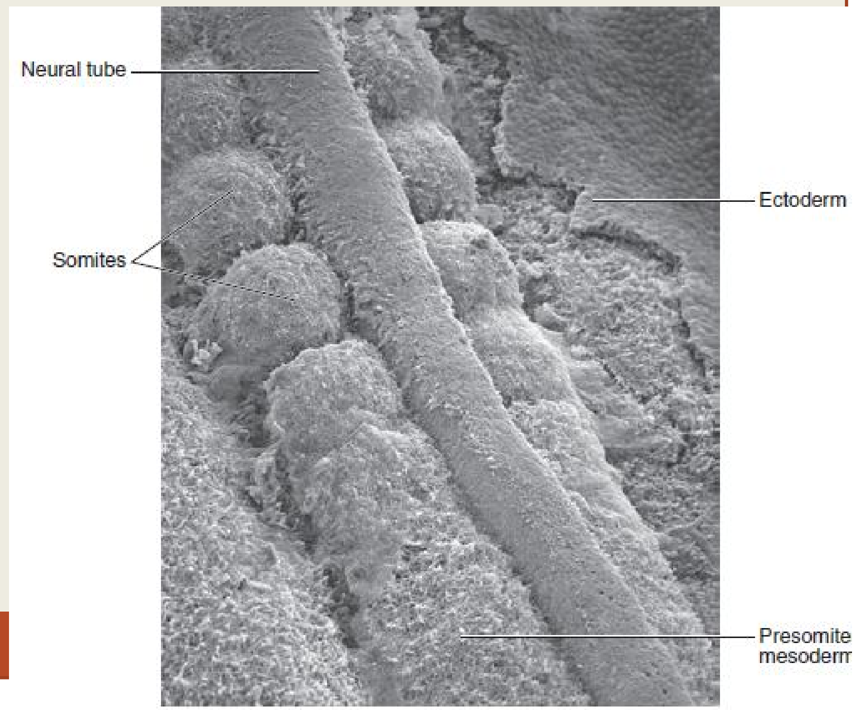
Approximate Age (Days)	Number of Somites
20	1–4
21	4–7
22	7–10
23	10–13
24	13–17
25	17–20
26	20–23
27	23–26
28	26–29
30	34–35

Molecular Regulation of Somite Formation

- Formation of segmented somites from paraxial mesoderm is dependent upon a **segmentation clock** established by cyclic expression of a number of genes

- The cyclic genes include members of the ***Notch*** and ***WNT*** signaling pathways that are expressed in an oscillating pattern in presomitic mesoderm

- **Notch protein** increased in presomitic mesoderm to form the next somite
- **Notch protein** decreases as that somite is established



Boundaries for each somite by:

- **retinoic acid (RA) (**high concentrations cranially)
- **FGF8 (**higher concentrations caudally)
- **WNT3a** (higher concentrations caudally)

Somite Differentiation

When the first somites form from presomitic mesoderm

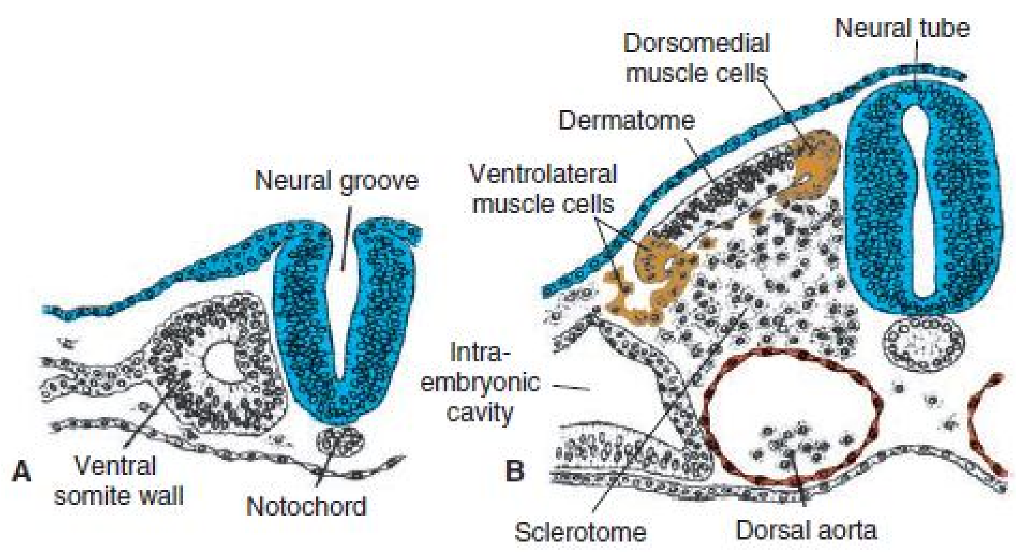
- they exist as a ball of mesoderm (fibro- blast-like) cells
- These cells then undergo a process of **epithelization** and arrange them- selves in a donut shape around a small lumen

At the beginning of the 4th week

- **cells in the ventral & medial walls of the somite**
- become mesenchymal (fibroblast-like) again
- surround the neural tube & notochord
- **Formation sclerotome**

Differentiated to =

- vertebrae
- Ribs



Somite Differentiation

precursors for muscle cells

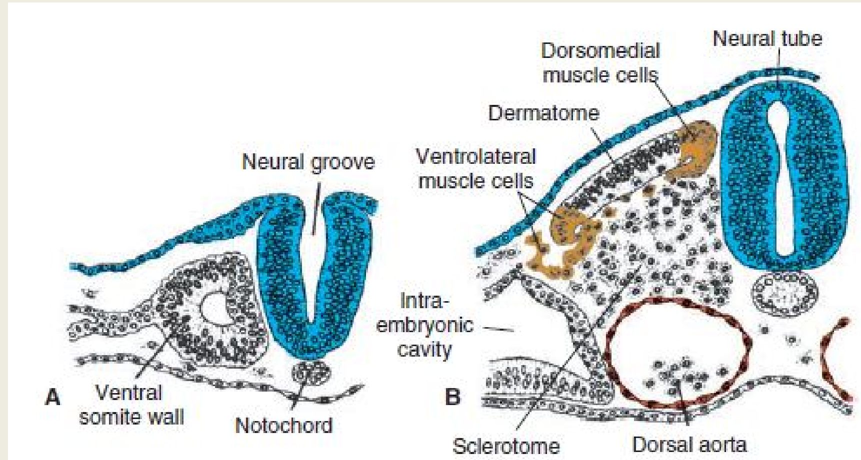
- Cells at the dorsomedial region of the somite
- Cells at the ventrolateral region of the somite

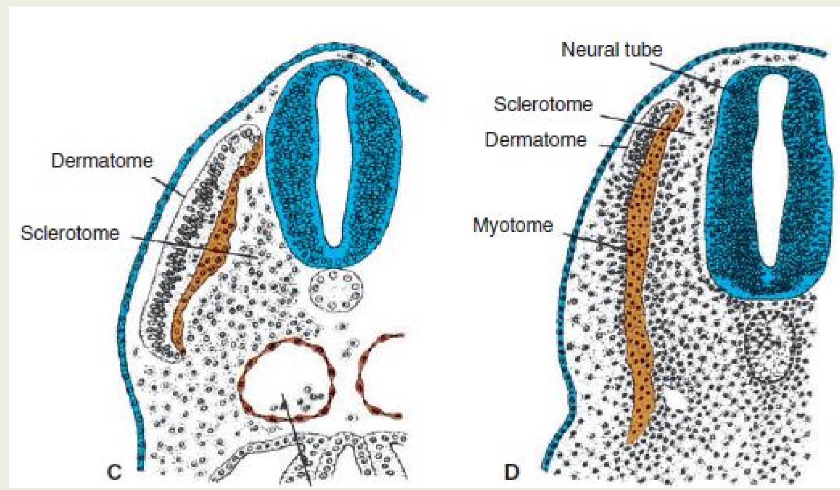
dermatome

- cells between these groups

Dermomyotome

- Cells from both muscle precursor groups become mesenchymal again and migrate beneath the dermatome





Somite Differentiation

Also :

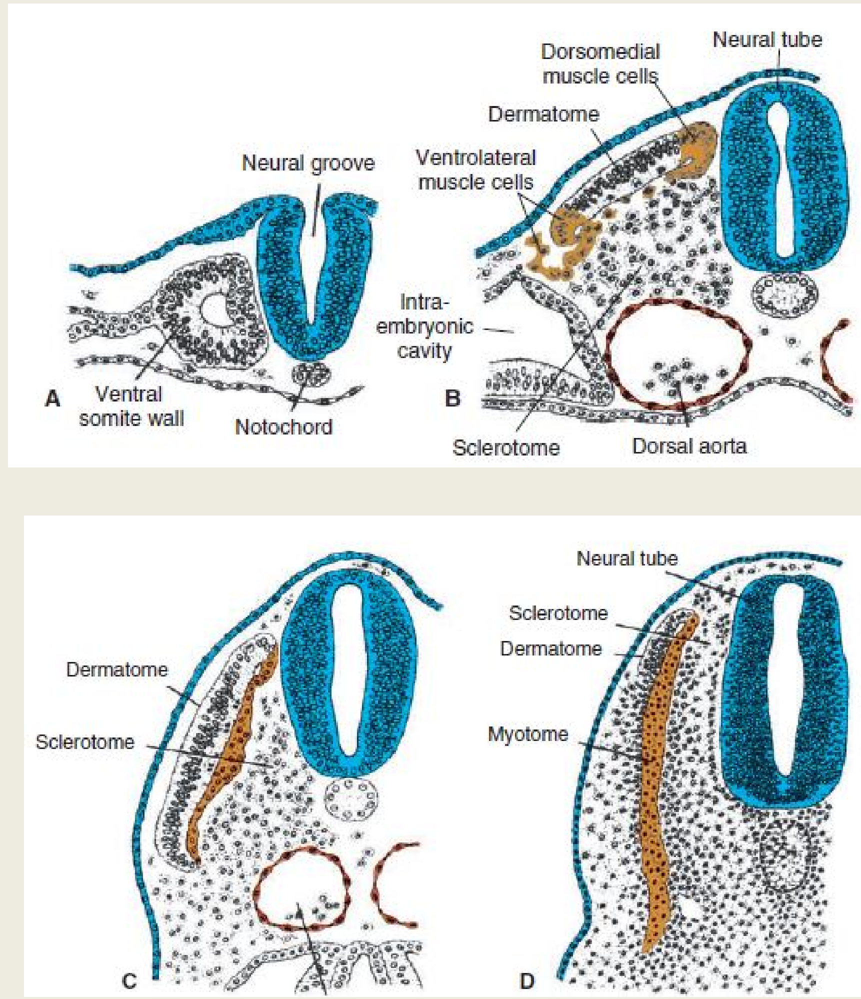
ventrolateral edge cells

<u>migrate</u> to parietal layer of lateral plate mesoderm (body wall) and **<u>form</u> =**

- ✓ external and internal oblique muscles
- ✓ transversus abdominis muscles
- ✓ Some limb muscles

Cells in dermomyotome form =

- ✓ dermis for the skin of the back
- ✓ muscles for the back
- ✓ body wall (intercostal muscles)
- ✓ some limb muscles



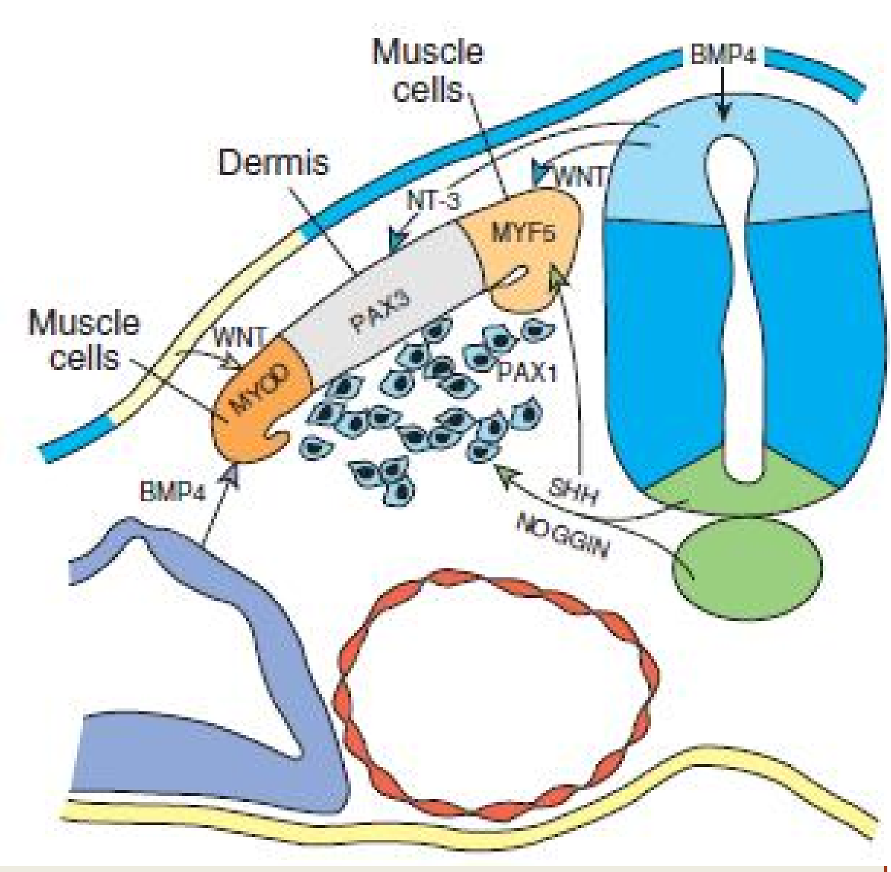
Molecular Regulation of Somite Differentiation

Signals for somite differentiation arise from =

- the notochord, neural tube, epidermis, and lateral plate mesoderm

noggin genes + sonic hedgehog (SHH) from :

- notochord and floor plate of the neural tube
- induced **ventromedial** (ventromedian) portion of the somite
- **form Sclerotome (*PAX1 secretion*)**
- Cartilage & bone genes for vertebral formation



Molecular Regulation of Somite Differentiation

- **WNT proteins from** the dorsal neural tube :

On the dorsomedial portion of the somite

MYF5 *(prim axial* muscle precursors)

- inhibiting protein **BMP4 + FGFs (**lateral plate mesoderm) + **WNT** (epidermis) :

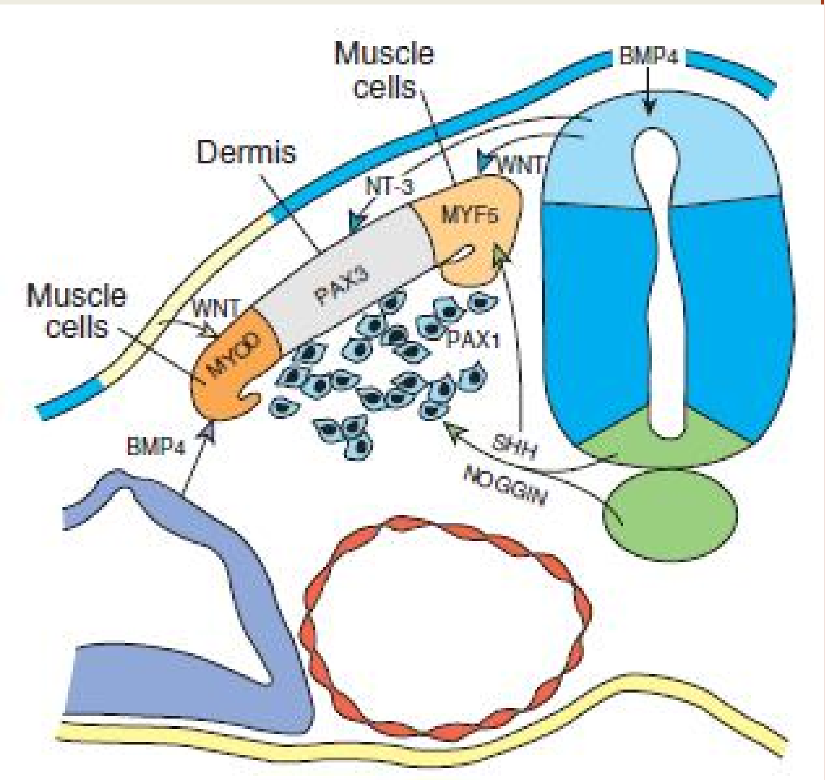
On the dorsolateral portion of the somite

MYOD ***(***prim axial and abaxial muscle precursors)

- **neurotrophin 3 (NT-3)** by the dorsal region of the neural tube :

On the The mid portion of the somite

Dermis formation by ***Expretion PAX3***



Intermediate Mesoderm

- ***connects paraxial mesoderm with the lateral plate mesoderm***

differentiates into:

***urogenital* structures**

- **In cervical and upper thoracic regions**

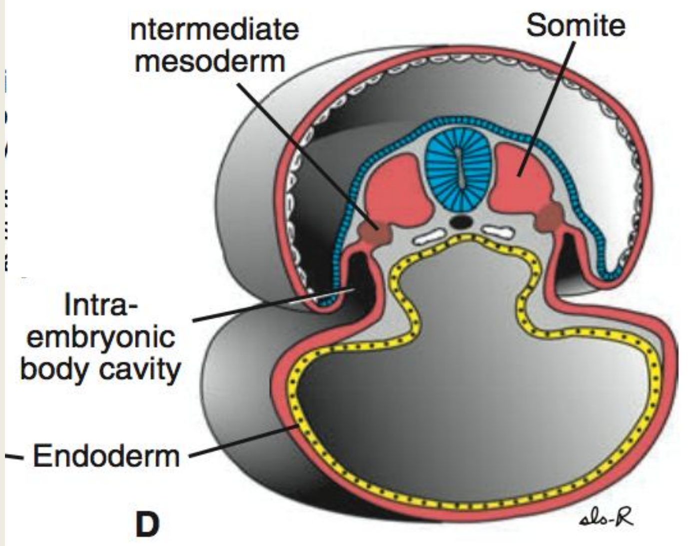
segmental cell clusters **(future nephrotomes)**

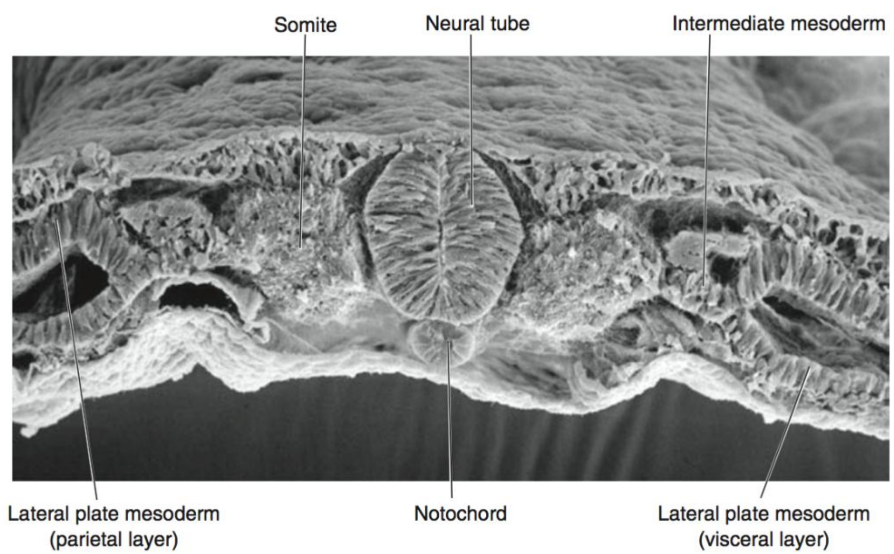
- **In caudally part**

unsegmented mass of tissue (**nephrogenic cord)**

Formation of:

- **urinary system**
- **the gonads**





Lateral Plate Mesoderm

- Lateral plate mesoderm splits into :

1. **Parietal (somatic) layer**
2. **visceral (splanchnic) layer**

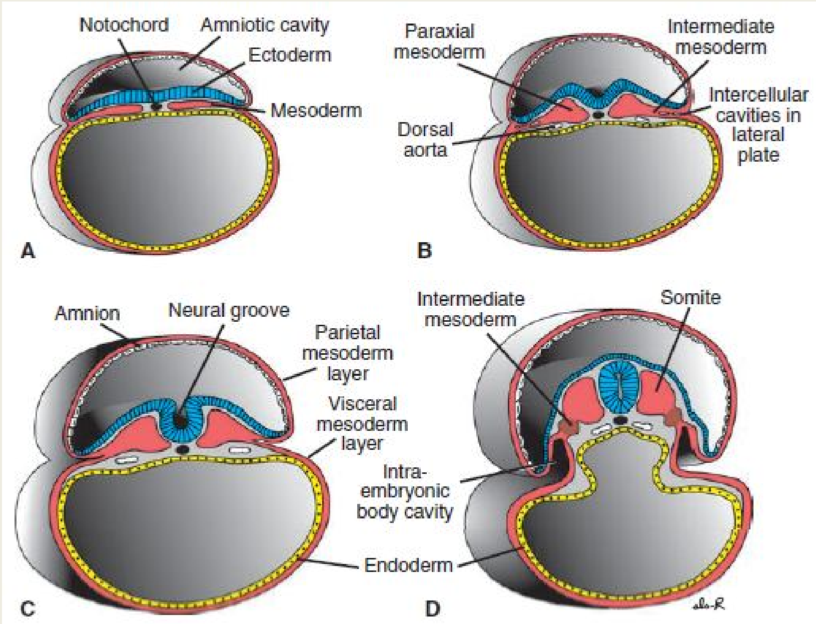
Which line the intraembryonic cavity and surround the organs

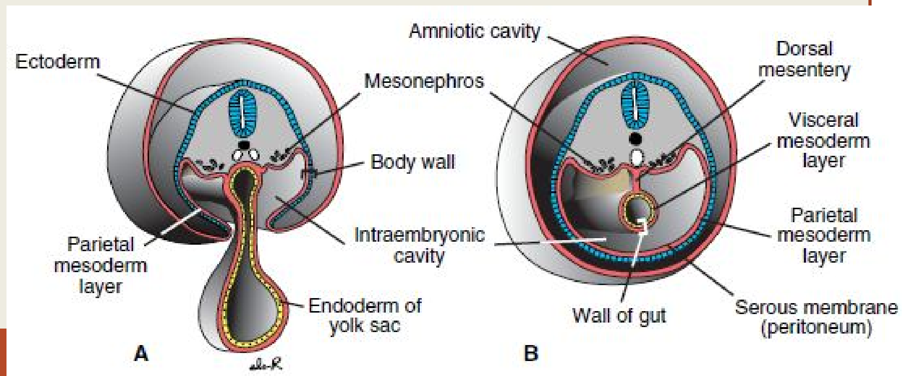
- ***parietal layer Mesoderm & overlying ectoderm form :***

lateral body wall folds + (cephalic & caudal folds) = close the ventral body wall)

- **The parietal layer mesoderm forms:**

1. the dermis of the skin in the body wall & limbs
2. the bones and connective tissue of the limbs,
3. and the sternum
4. costal cartilages
5. limb muscles
6. most of the body wall muscles





Lateral Plate Mesoderm

- The visceral layer mesoderm & endoderm form :

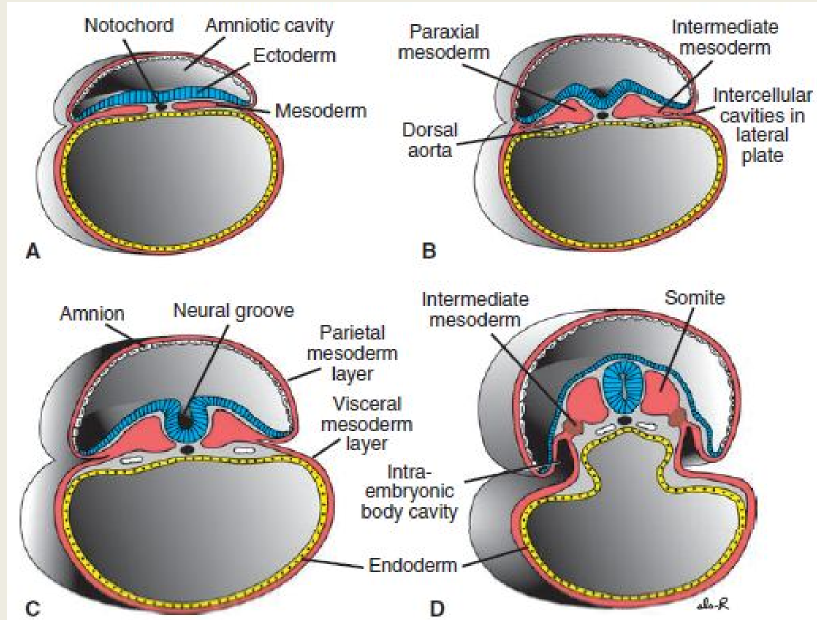
wall of the gut tube

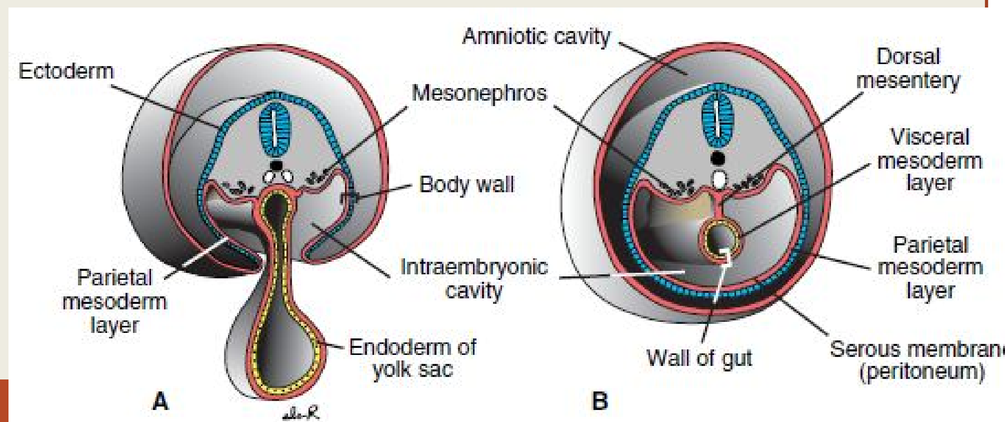
Mesoderm cells of the parietal layer surrounding the intraembryonic cavity form :

the mesothelial (serous) membranes
- peritoneal,
- Pleural
- Pericardial

- ***Mesoderm cells of the visceral layer :***

thin serous membrane around each organ





Blood and Blood Vessels

- ## *Mesoderm origin*

Blood vessels formation in two ways:

1. **Vasculogenesis** (vessels arise from blood islands)
2. **Angiogenesis** (entails sprouting from existing vessels)

In Third week :

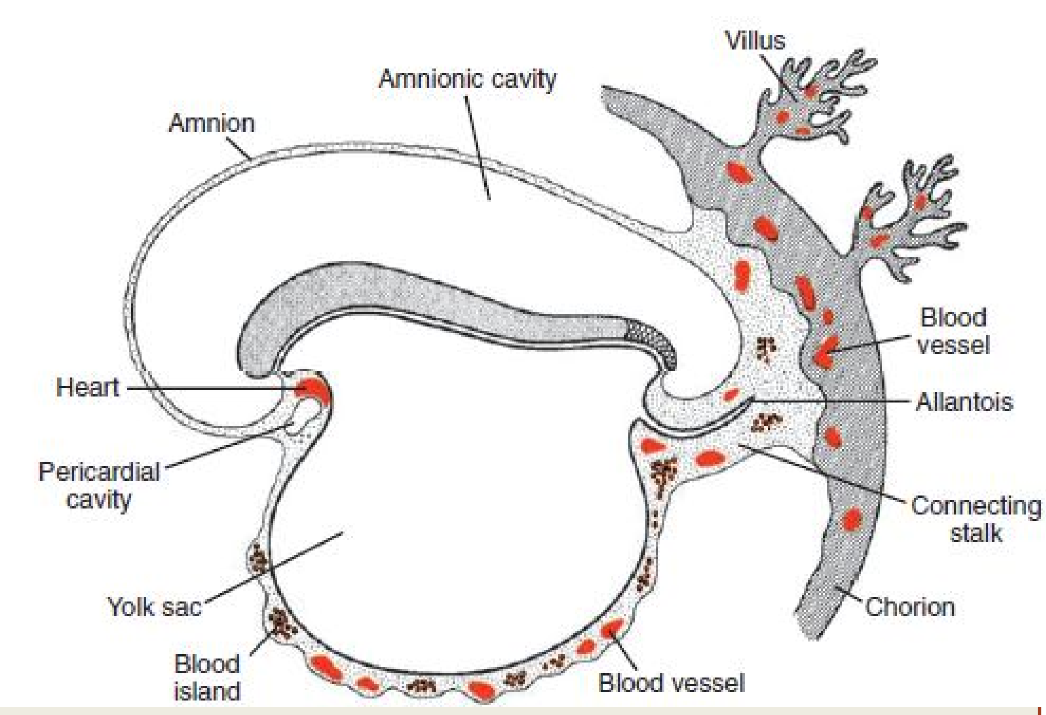
- **first blood islands** appears in mesodermic wall of the yolk sac

- Then appears in :

  lateral plate mesoderm

  &

  other regions



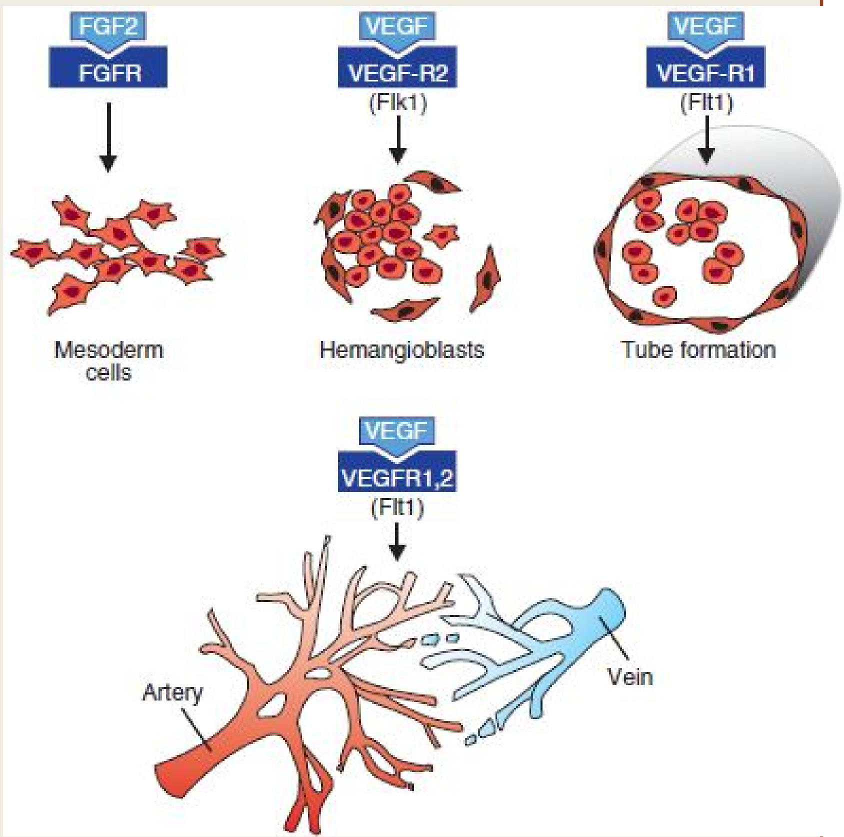
Blood and Blood Vessels

- ***These islands arise from :***

mesoderm cells that are induced to form **hemangioblasts**

(a common precursor for vessel and blood cell formation & this population is transitory)

Because of the blood islands is temporary



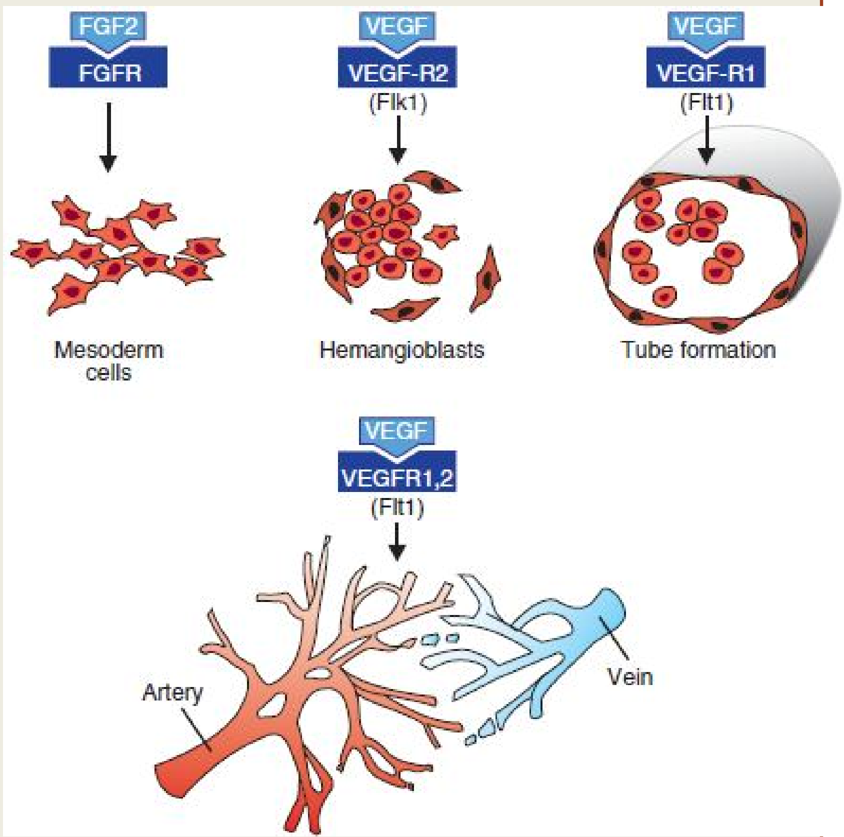
Blood and Blood Vessels

Because of the blood islands is temporary

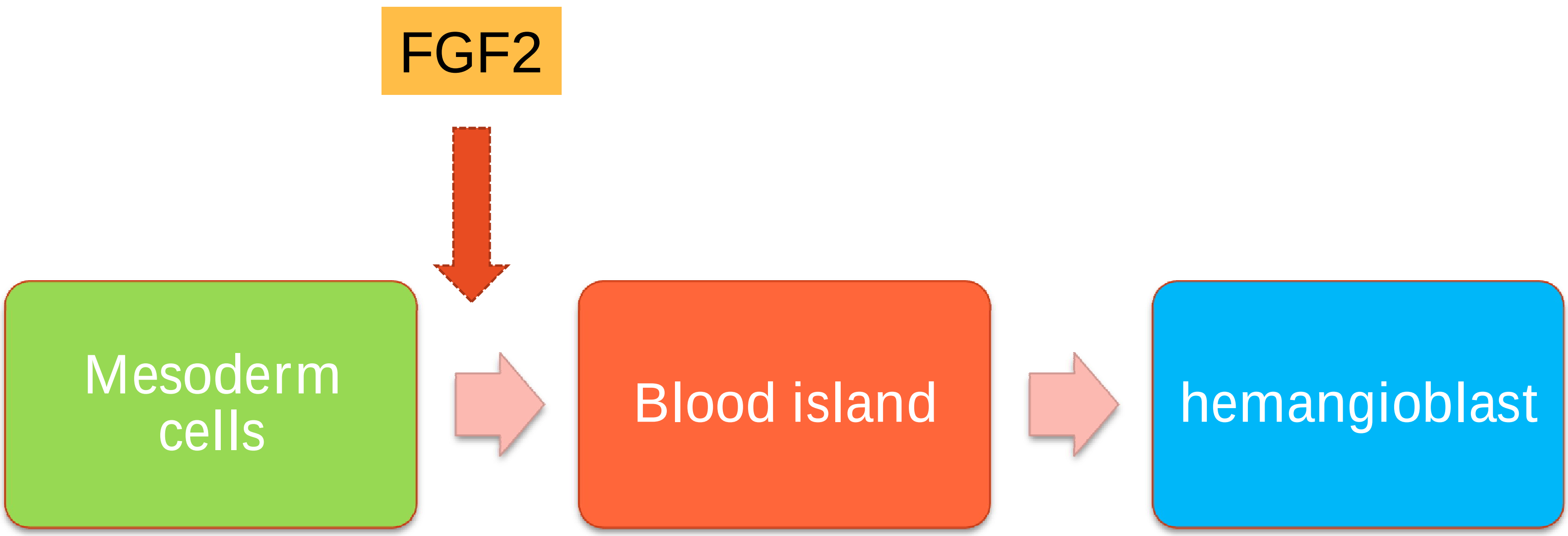
- Hence The definitive **hematopoietic stem cells** are derived from :

mesoderm surrounding the aorta in a site near the developing mesonephric kidney called the ***aorta- gonad- mesonephros region (AGM)***

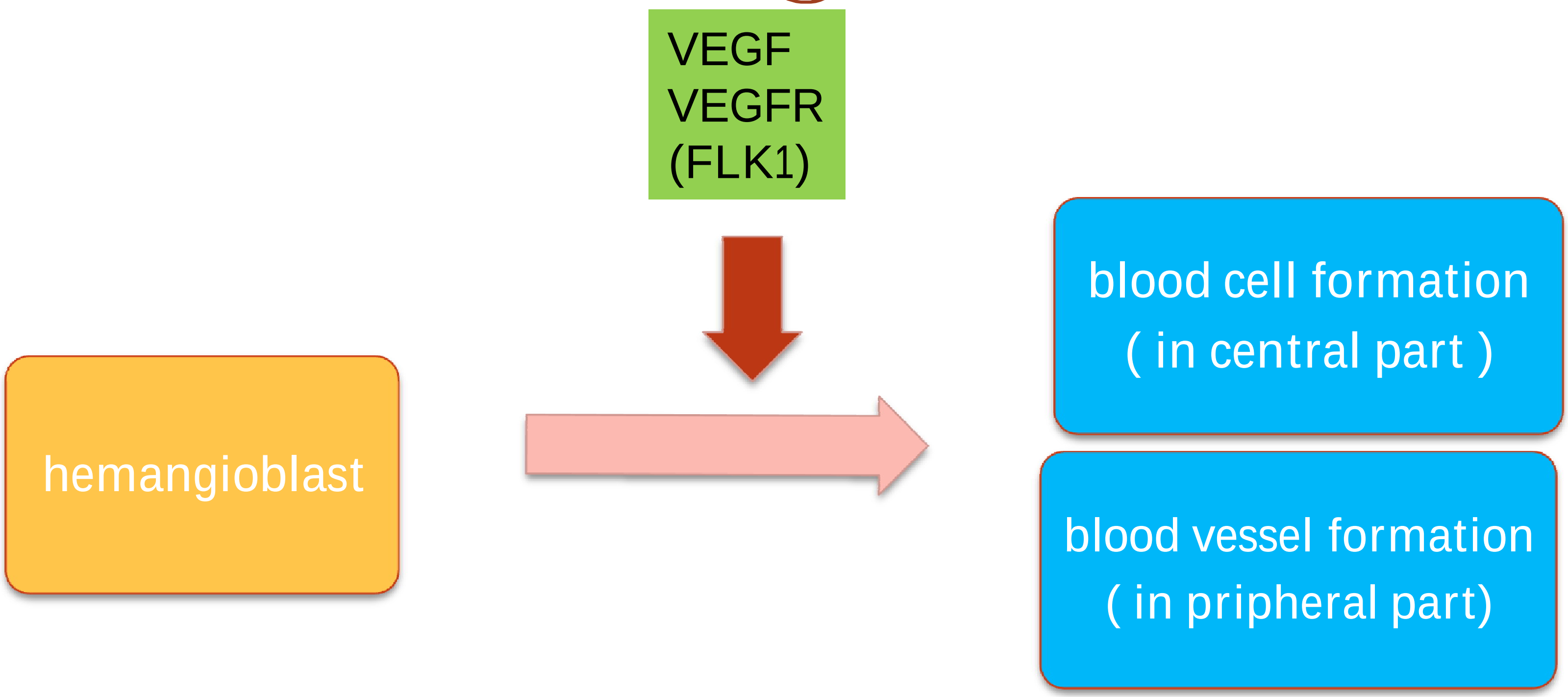
- These cells colonize in the liver (2-7th monthes)
- Then stem cells colonized in the Bone marrow (7th month)



Molecular regulation of blood vessel formation



Molecular regulation of blood vessel formation



Molecular regulation of blood vessel formation

maturation & regulation of vasculature

control by

PDGF

TGF-B

Molecular regulation of blood vessel formation

mesenchyme — SHH — VEGF production — NOTCH pathway induction — arterial development

Molecular regulation of blood vessel formation

- epherin B2
  - suppress venous formation
- notch pathway
  - EPHB4
  - venous formation

Molecular regulation of blood vessel formation

PROX1

lymphatic vessel formation

Clinical Correlates

Capillary Hemangiomas

Capillary hemangiomas are abnormally dense collections of capillary blood vessels that form the most common tumors of infancy, occurring in approximately 10% of all births. They may occur anywhere but are often associated with craniofacial structures (Fig. 6.16*A*). Facial lesions may be focal or diffuse, with diffuse lesions causing more secondary complications, including ulcerations, scarring, and airway obstruction (mandibular hemangiomas; Fig. 6.16*B*). Insulin-like growth factor 2 is highly expressed in the lesions and may be one factor promoting abnormal vessel growth. Whether or not VEGF plays a role has not been determined

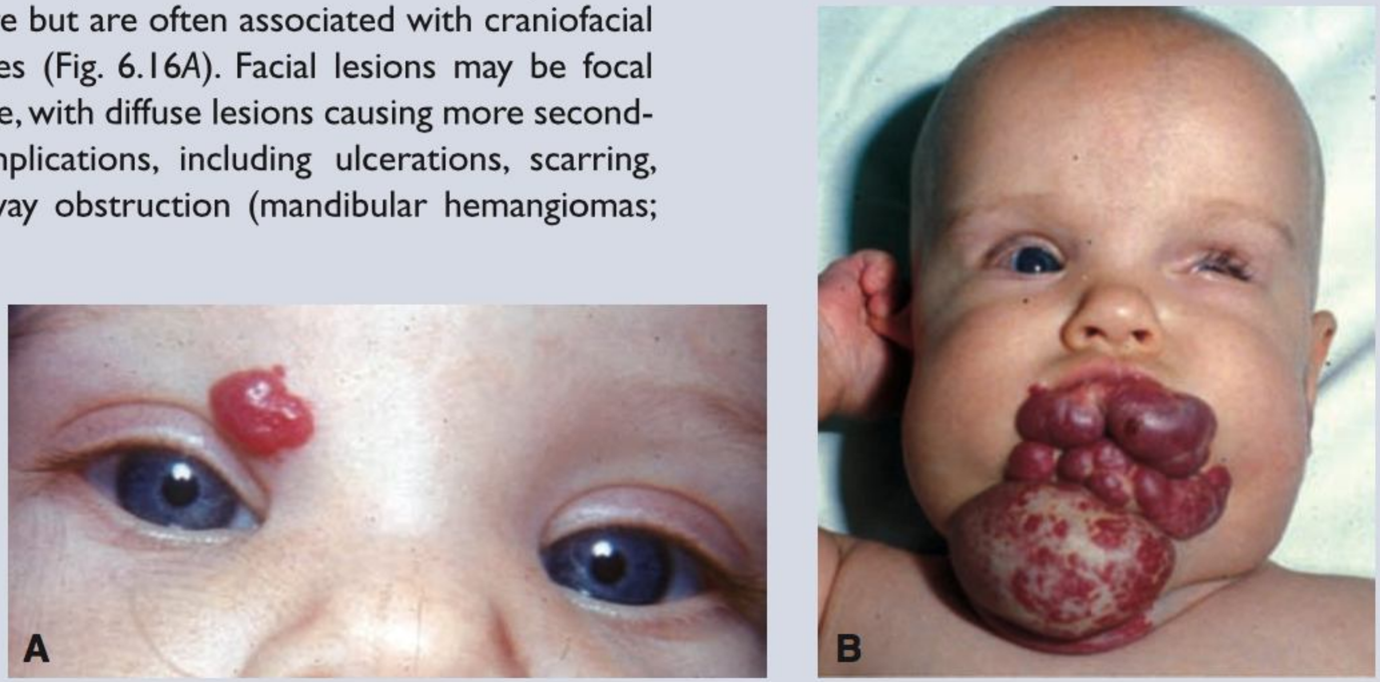


Figure 6.16 **A**. Focal capillary hemangioma. **B.** Diffuse capillary hemangioma involving the oral cavity.

Derivatives of the endodermal germ layer

- **The gastrointestinal tract**

With the brain vesicles growth & development

The embryonic disc bulge into the amniotic cavity

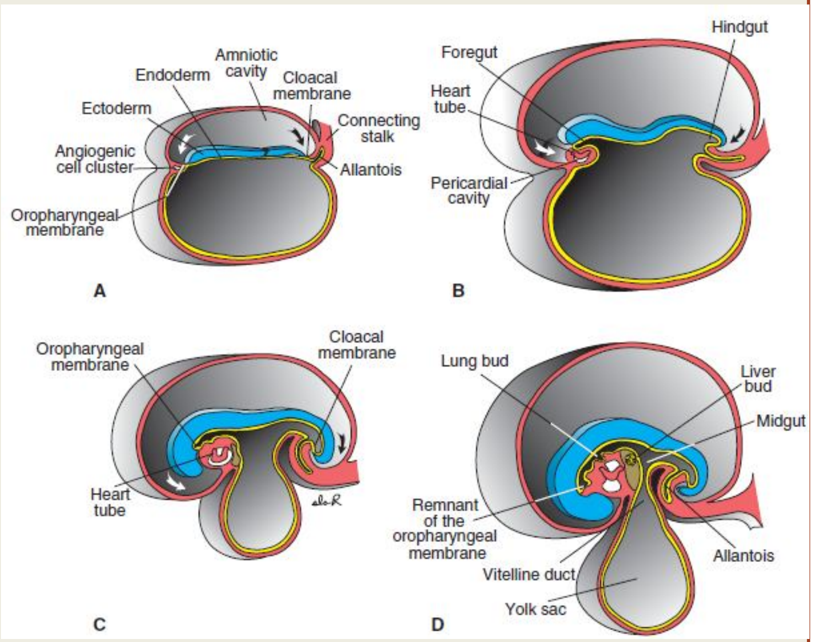
- **the neural tube Lengthening**

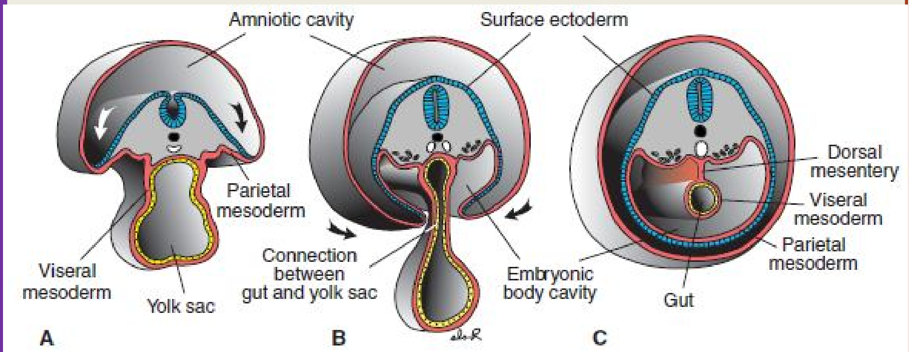
causes the embryo to curve

- Head & tail folds & two lateral folds move ventrally

The ventral body wall closes = primitive gut formation

1. Foregut
2. Midgut
3. Hindgut





Derivatives of the endodermal germ layer

In the cephalic end

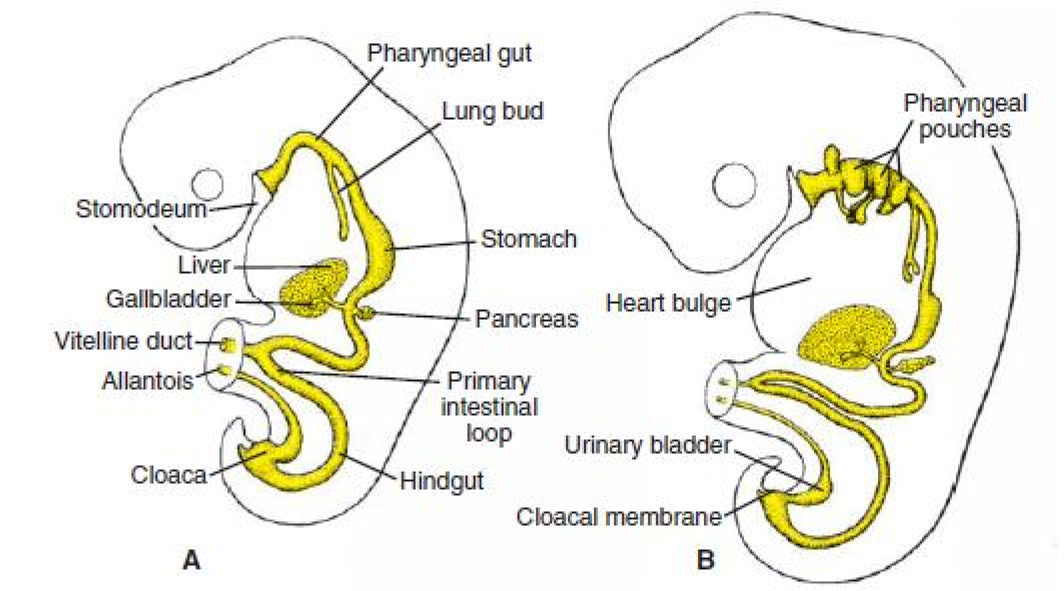
- **oropharyngeal membrane** (ctodermal–endodermal membrane)

Separate Stomadeum from the pharynx (perforated in the 4th week)

In the Caudal end

- **the cloacal membrane** (ectodermal– endodermal membrane)

separates the upper part & lower part(proctodeum) of the anal canal (perforated in the 7th week)



Derivatives of the endodermal germ layer

- ***Another important result of cephalocaudal growth and lateral folding :***

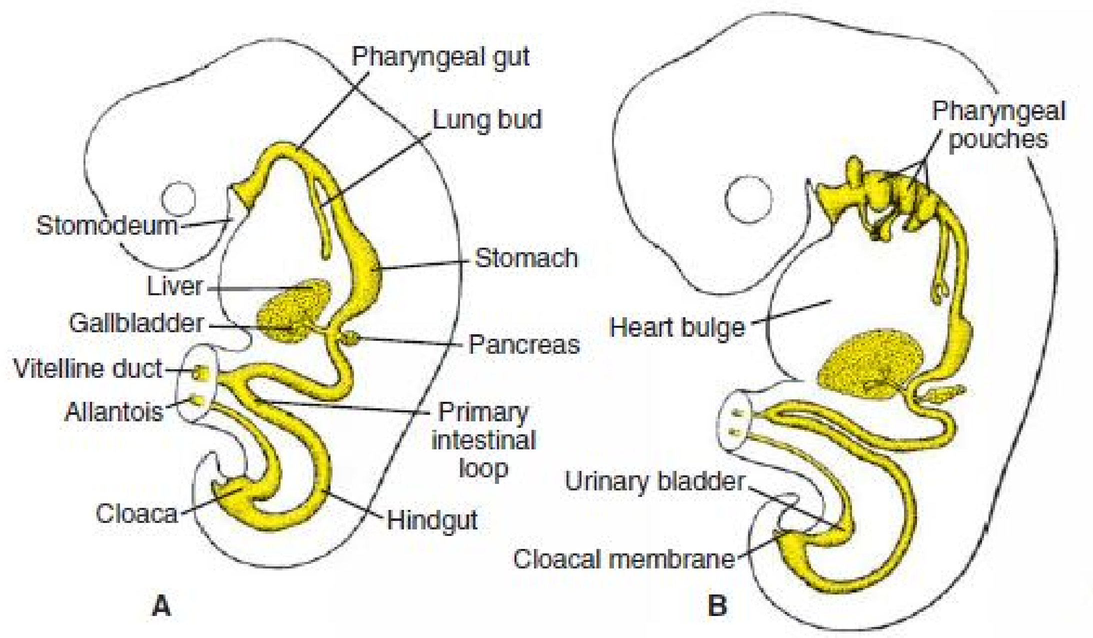
partial incorporation of the allantois into the body of the embryo, where it forms the **cloaca**

- ***5th week :***

umbilical region (yolk sac duct, allantois & umbilical vessels)

The yolk sac role:

- nutritive organ
- first blood cells formation site
- PGCs origin



Derivatives of the endodermal germ layer

- epithelial lining of the primitive gut
- intraembryonic portions of the allantois & vitelline duct

- The epithelial lining of the respiratory tract
- The parenchyma of :

thyroid

Parathyroids

Liver

Pancreas

- The reticular stroma of the tonsils & thymus
- The epithelial lining of the urinary bladder & urethra
- The epithelial lining of the tympanic cavity & auditory tube

External appearance during the second month

end of 4th week (28 somites) the main external features :

- somites
- pharyngeal arches

Age in the second month describe with:

- crown rump length (CRL)

(vertex to the midpoint between the buttocks)

During the second month:

- increase in head size
- formation of the limbs, face, ears, nose & eyes

TABLE 6.3 CRL Correlated to Approximate Age in Weeks

CRL (mm)	Approximate Age (wk)
5–8	5
10–14	6
17–22	7
28–30	8

Limb formation

beginning of 5th week

- forelimbs and hindlimbs (paddle-shaped buds)

forelimbs

dorsal to the pericardial swelling

(4th cervical to the 1st thoracic somites)

- brachial plexus

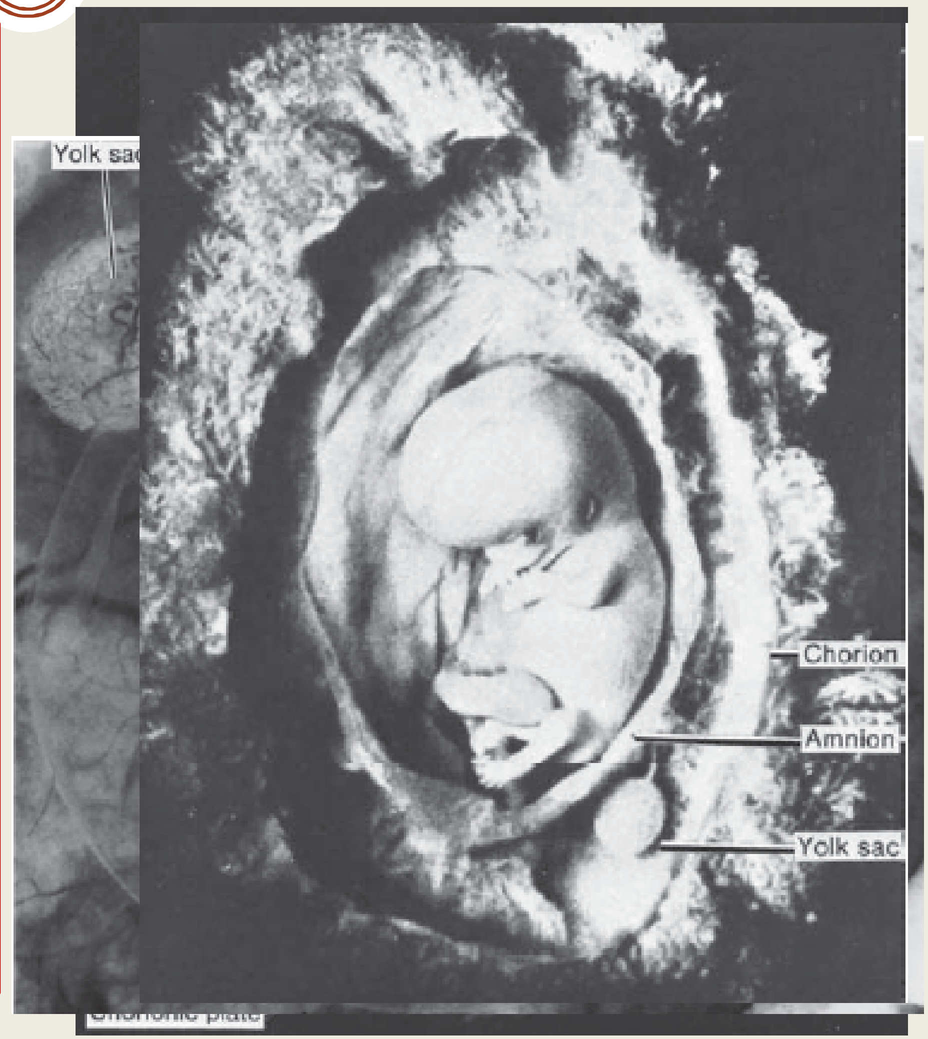
Hind limb

caudal to attachment of the umbilical stalk

(lumbar and upper sacral somites)

With further growth:

- terminal portions of the buds flatten
- a circular constriction
- 4 radial grooves (digits formation)
- Second constriction



Clinical Correlates

Birth Defects

Most major organs and organ systems are formed during the **third to eighth weeks**. This period, which is critical for normal development, is therefore called the period of **organogenesis** or **embryogenesis**. Stem cell populations are establishing each of the organ primordia, and these interactions are sensitive to insult from genetic and environmental influences. Thus, **from the third to eighth weeks is the time when most gross structural birth defects are induced**. Unfortunately, the mother may not realize she is pregnant during this critical time, especially during the third and fourth weeks, which are particularly vulnerable. Consequently, she may not avoid harmful influences, such as cigarette smoking and alcohol. Understanding the main events of organogenesis is important for identifying the time that a particular defect was induced and, in turn, determining possible causes for the malformation (see Chapter 9).

TABLE 6.4 *Summary of Key Events During the Embryonic Period*

Days	Somites	Length (mm)	Figure	Characteristic Features
14–15	0	0.2	6.1*A*	Appearance of primitive streak
16–18	0	0.4	6.1*B*	Notochordal process appears; hemopoietic cells in yolk sac
19–20	0	1.0–2.0	6.2*A*	Intraembryonic mesoderm spread under cranial ectoderm; primitive streak continues; umbilical vessels and cranial neural folds beginning to form
20–21	1–4	2.0–3.0	6.2*B,C*	Cranial neural folds elevated and deep neural groove established; embryo beginning to bend
22–23	5–12	3.0–3.5	6.5*A,B*	Fusion of neural folds begins in cervical region; cranial and caudal neuropores open widely; visceral arches 1 and 2 present; heart tube beginning to fold
24–25	13–20	3.0–4.5	6.6*A*	Cephalocaudal folding under way; cranial neuropore closing or closed; optic vesicles formed; otic placodes appear
26–27	21–29	3.5–5.0	6.8*B* 6.21*A,B*	Caudal neuropore closing or closed; upper limb buds appear; three pairs of visceral arches
28–30	30–35	4.0–6.0	6.8*B*	Fourth visceral arch formed; hindlimb buds appear; otic vesicle and lens placode
31–35		7.0–10.0	6.22	Forelimbs paddle-shaped; nasal pits formed; embryo tightly C-shaped
36–42		9.0–14.0	6.23	Digital rays in hand and foot plates; brain vesicles prominent; external auricle forming from auricular hillocks; umbilical herniation initiated
43–49		13.0–22.0	6.24	Pigmentation of retina visible; digital rays separating; nipples and eyelids formed; maxillary swellings fuse with medial nasal swellings as upper lip forms; prominent umbilical herniation
50–56		21.0–31.0	6.25	Limbs long, bent at elbows, knees; fingers, toes free; face more human-like; tail disappears; umbilical herniation persists to end of third month