Third to Eighth Weeks

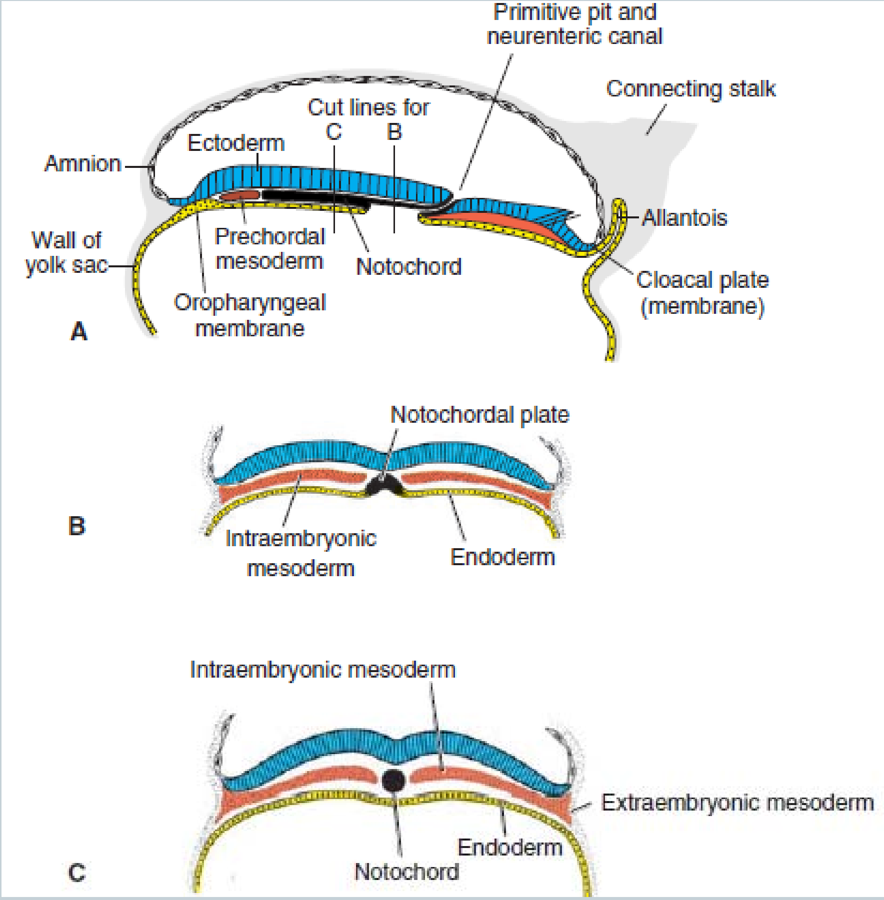
The embryonic period

Embryonic (organogenesis) period

Third to eighth weeks of development

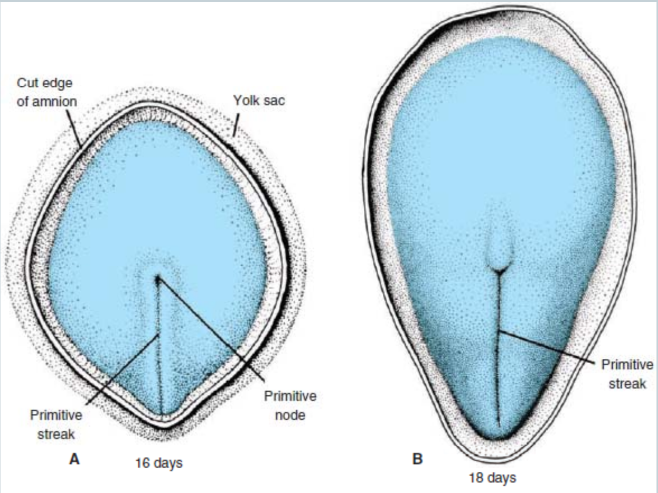
- **Ectoderm**
- **Mesoderm**
- **Endoderm**

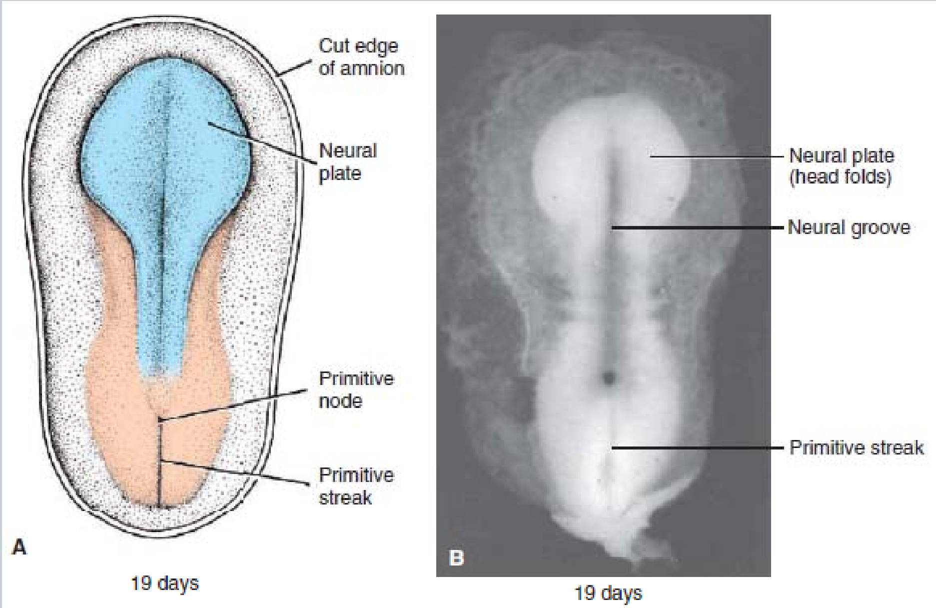
gives rise to a number of specifi c tissues & organs
Formation of the major features of the external



Derivatives of the ectodermal germ layer

- beginning of third week
- the ectodermal germ layer broader in the cephalic than in caudal region
- notochord and prechordal mesoderm induces ectoderm to thicken & form the **neural plate**
- **neuroectoderm**
- **neurulation.**



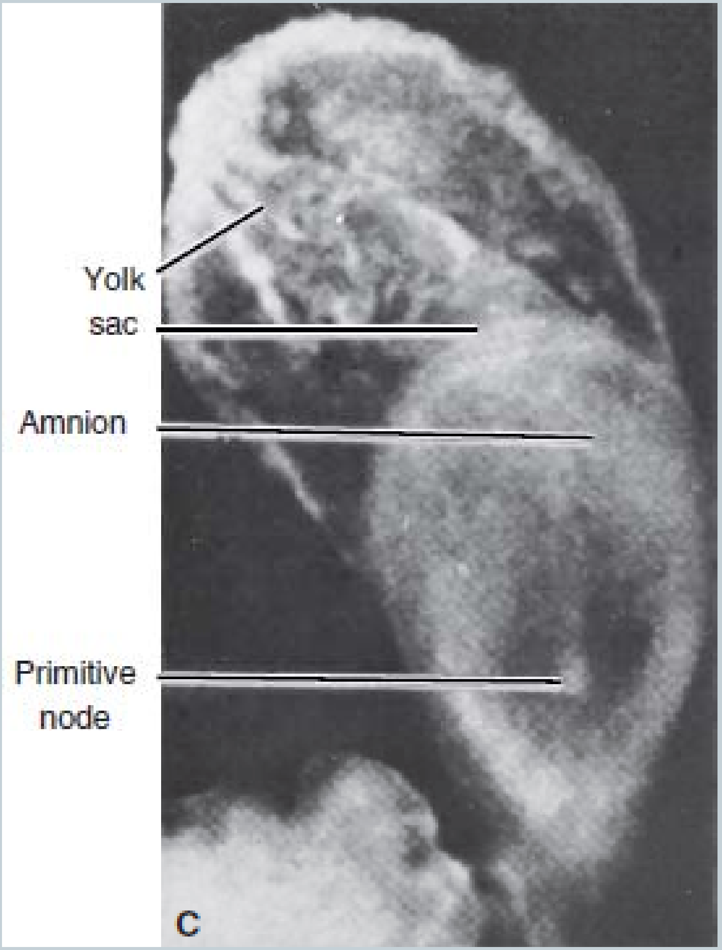


Molecular Regulation of Neural Induction

- **FGF** Upregulation
- **BMP4 inhibition**(TGF-b)
- ***chordin* & *noggin* & follistatin in:**
- primitive node, notochord & prechordal mesoderm
- forebrain & midbrain induction

- Caudal neural plate structures Induction
(hindbrain and spinal cord)
- depends on **WNT3a & FGF**

- **Retinoic acid (RA)**
cranial-to-caudal axis organizer

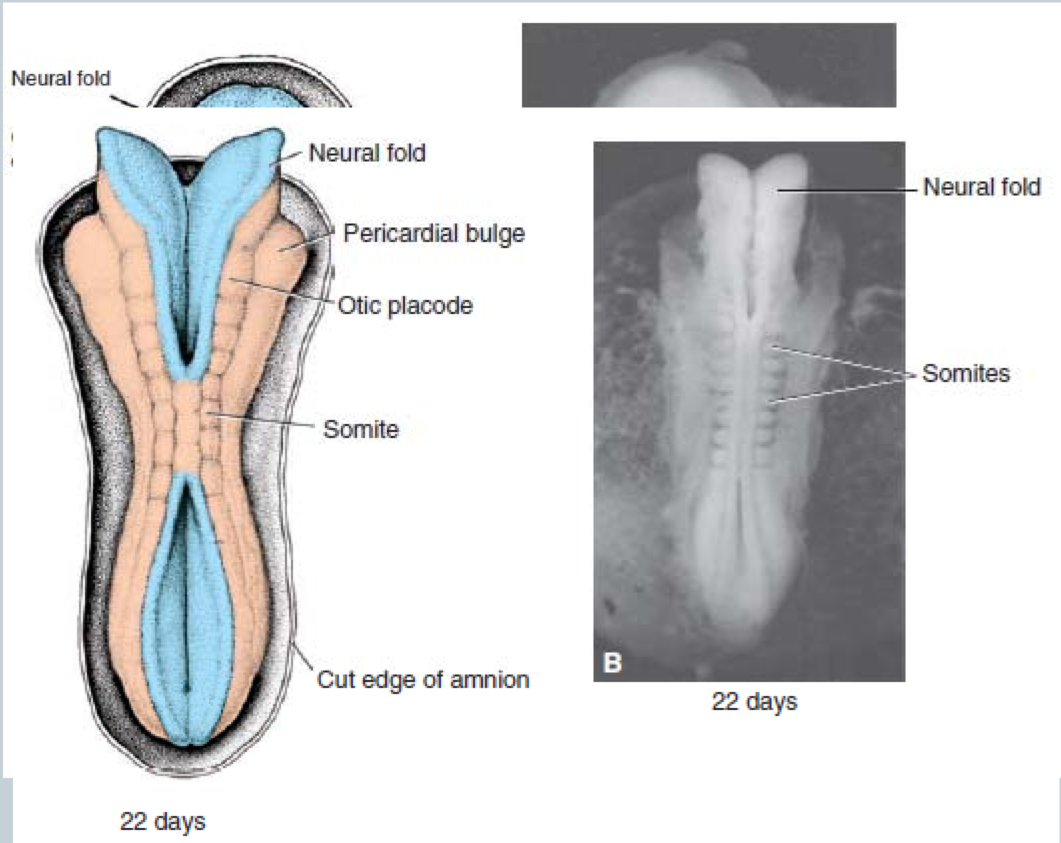


Neurulation

- Neural plate
- Neural tube

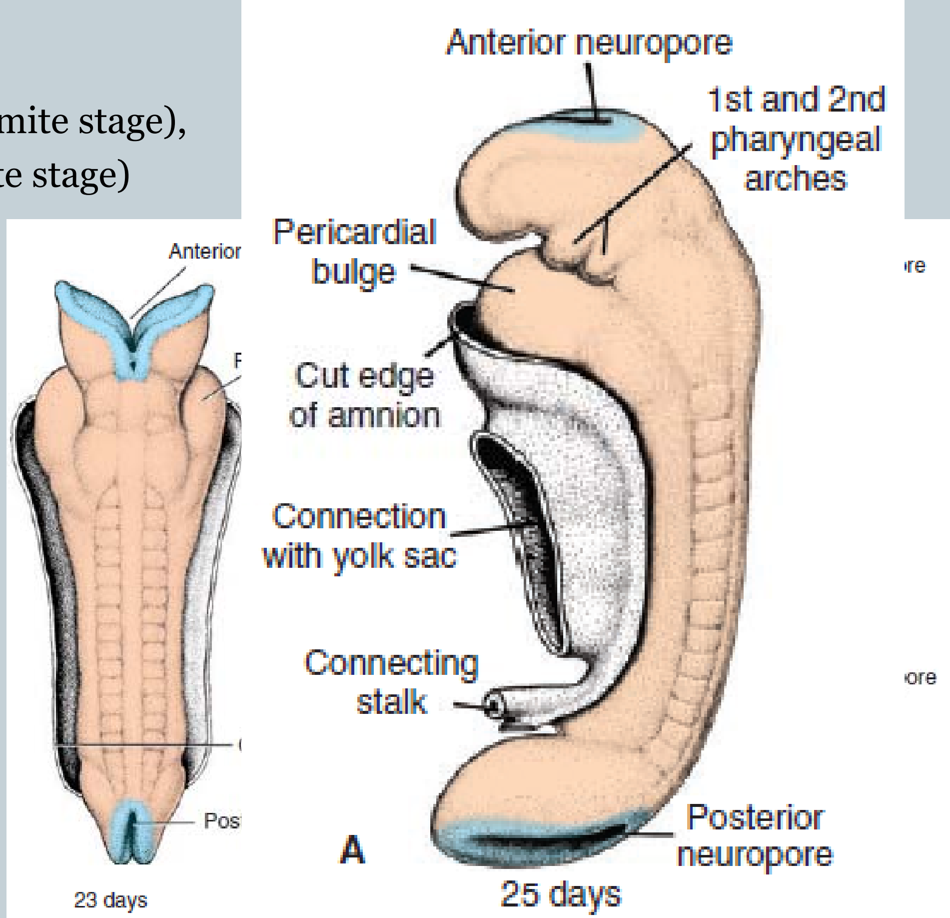
- End of third week
- **Neural folds**
- **Neural groove**
- *Fusion begins in the cervical* region

(5th somite, cervical part)
- ***Neural* tube**



Neurulation

- amniotic cavity
- **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)
- a narrow caudal portion, the **spinal cord**
- **A** broader cephalic the **brain vesicles**



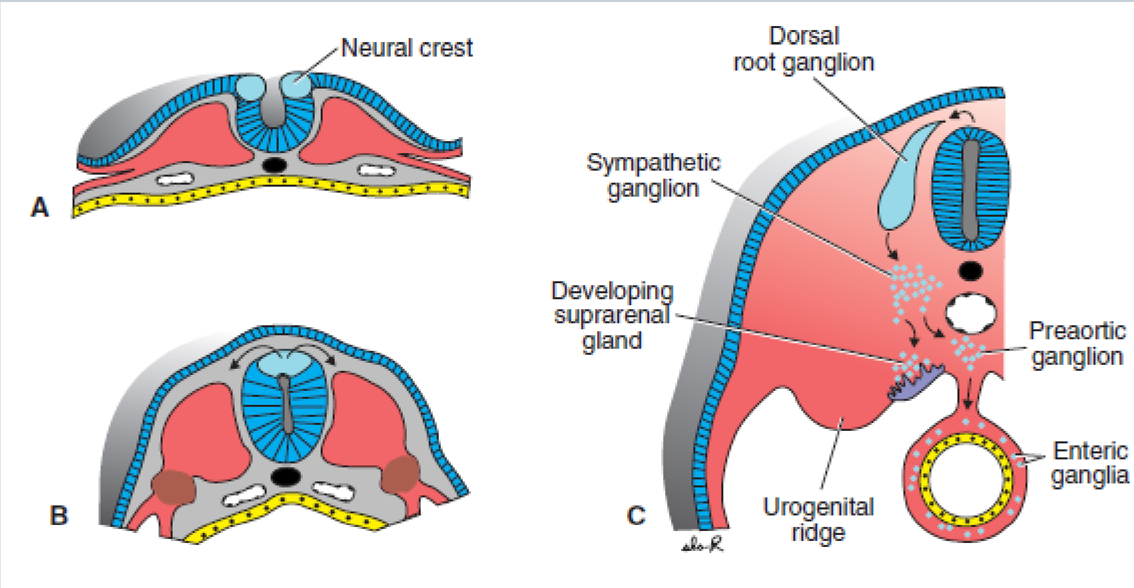
Neural Crest Cells

- cells at the lateral border or crest of the neuroectoderm
- **epithelial-to-mesenchymal transition**

- **Migration in 2 pathways:**

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

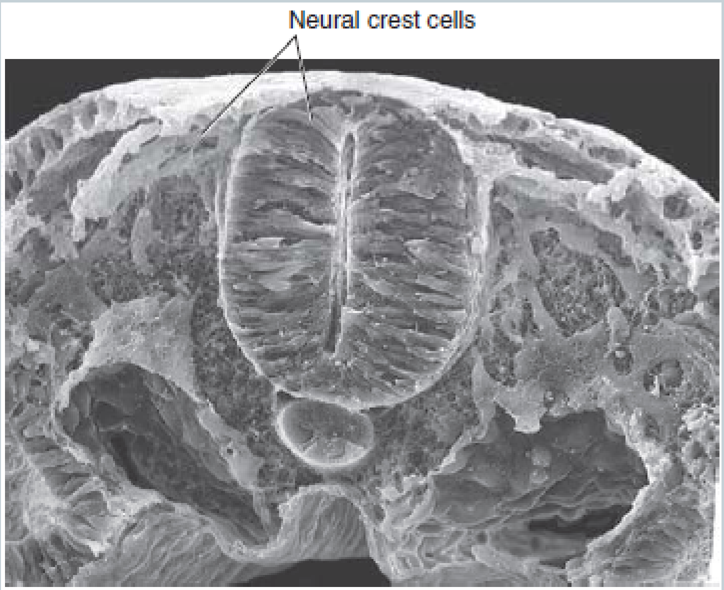
(2) a ventral pathway through the anterior half of each somite to become **sensory ganglia, sympathetic & enteric neurons, Schwann's cells, and cells of the adrenal**



Neural Crest Cells

Neural crest from cranial neural
(**craniofacial skeleton, cranial ganglia, glial cells, melanocytes**)

- **4th germ layer**



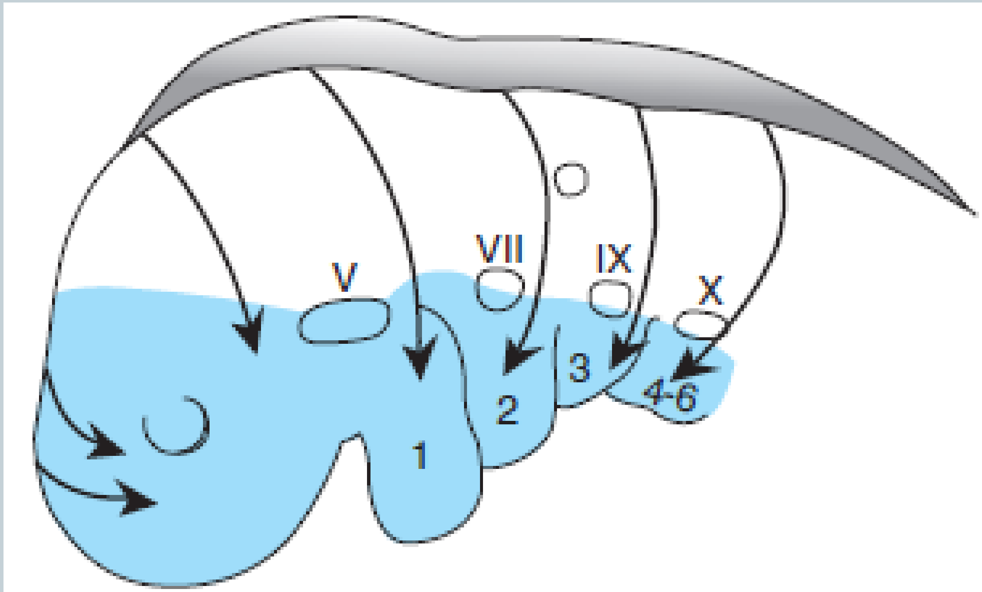
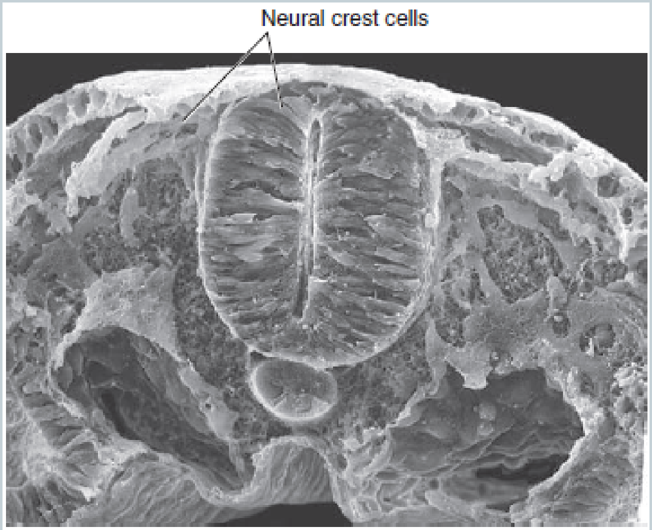


TABLE 6.1 *Neural Crest Derivatives*
Connective tissue and bones of the face and skull
Cranial nerve ganglia (see Table 17.2)
C cells of the thyroid gland
Conotruncal septum in the heart
Odontoblasts
Dermis in face and neck
Spinal (dorsal root) ganglia
Sympathetic chain and preaortic ganglia
Parasympathetic 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

Molecular process

- High BMPs concentration induce epidermis
- Moderate BMPs concentration induce neural crest
- Low BMPs concentration induce neural plate

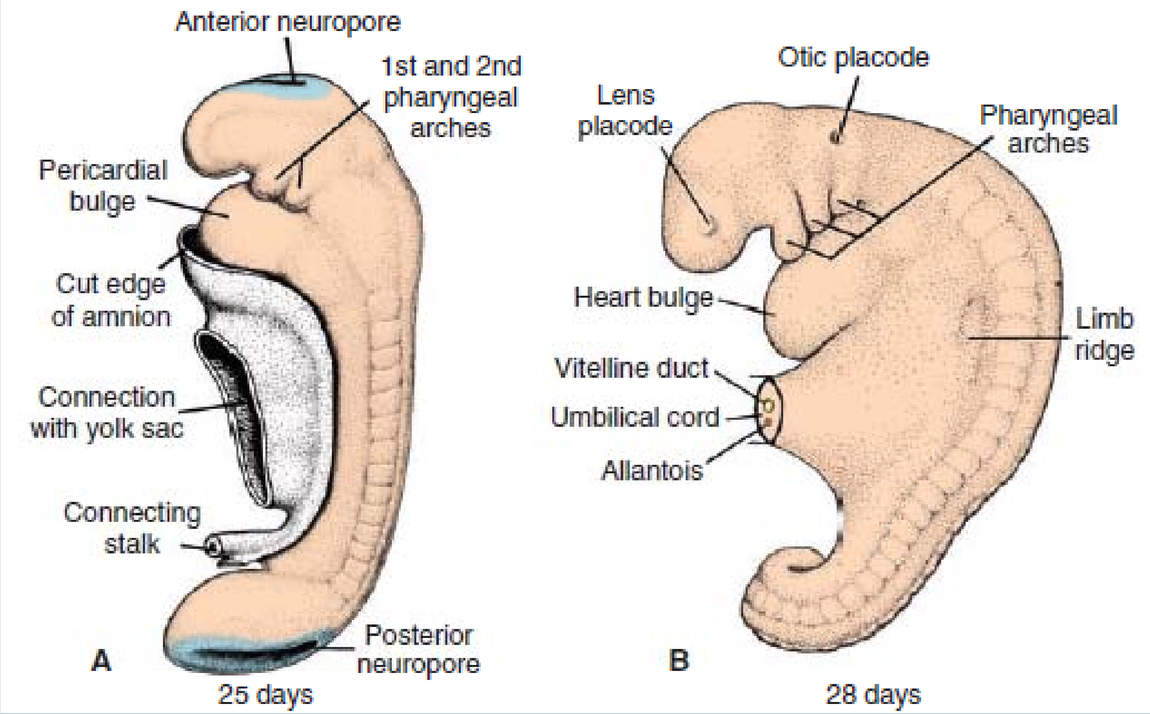


- Moderate BMPs, FGF & Wnt
- PAX3 & other transcription factors
- SNAIL & FOXD3 (Neural Crest Specification)
- SLUG (Neural Crest Migration)

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)

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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.

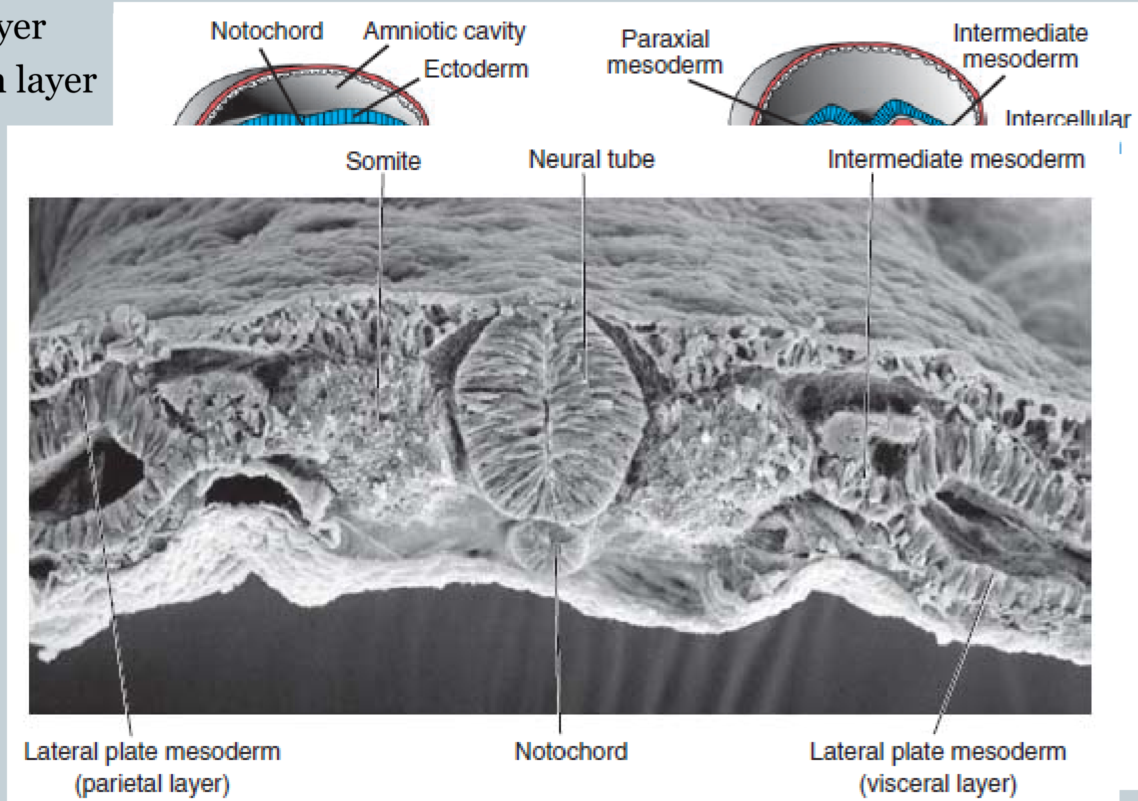
Derivatives of mesoderm germ layer

- 17^{th} day
- Paraxial mesoderm

- Lateral plate mesoderm

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

- Intermediate mesoderm

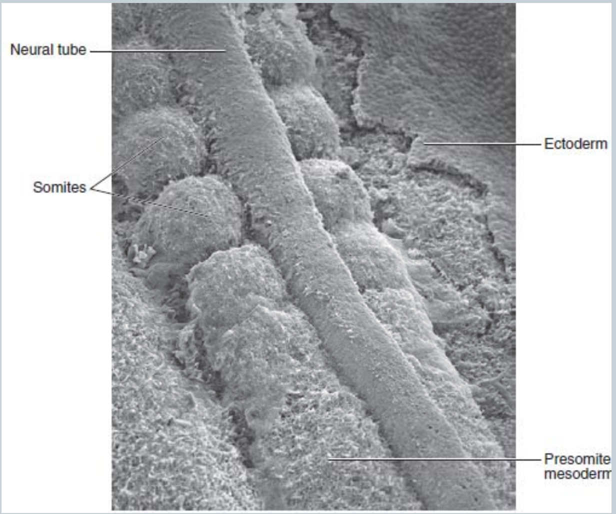


Paraxial mesoderm

Beginning of third week

- Somitomeres (Segmentation)

Concentric whorls around the unit center



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

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

end of 5th week, 42 to 44 pairs

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

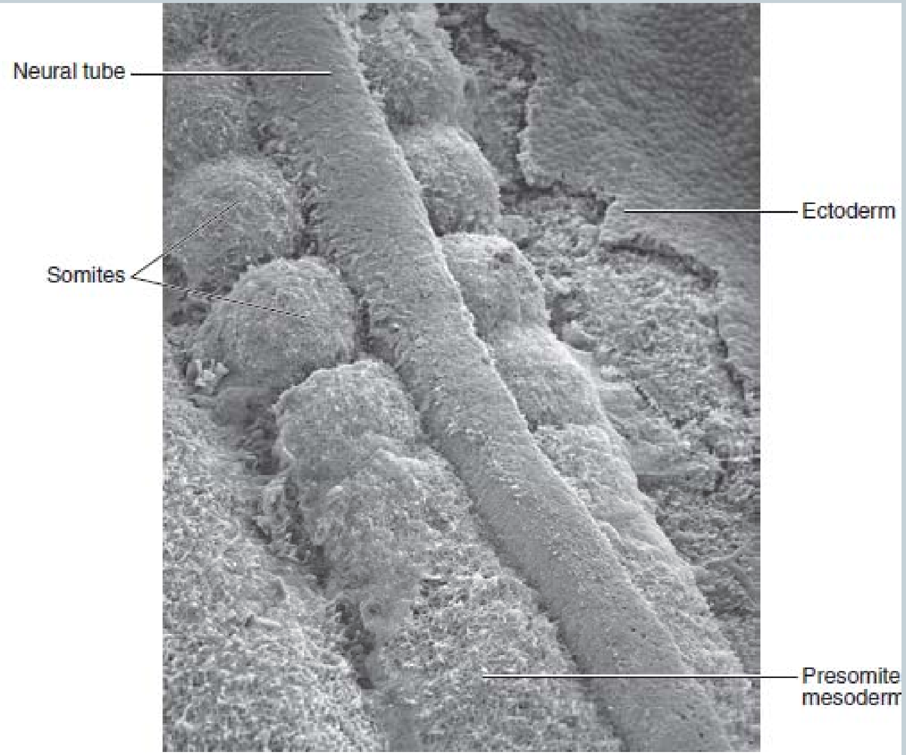
the age of an embryo

Molecular Regulation of Somite Formation

- paraxial mesoderm
- **segmentation clock**
- cyclic expression of a number of genes

- ***Notch & WNT signaling pathways***

Notch protein (in presomitic mesoderm)
next somite



Boundaries for each somite by:

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

Somite Differentiation

- presomitic mesoderm,
- fibroblast- like cells
- **Epithelization (**donut shape **arrangement** around a small lumen)

beginning of the 4th week

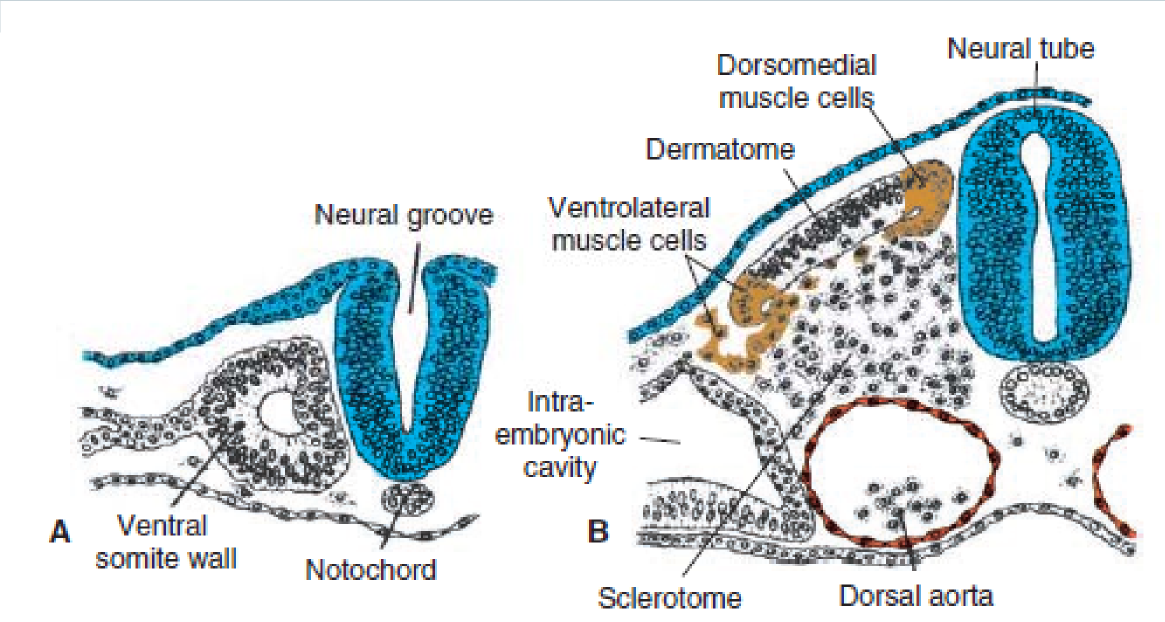
- **cells in the ventromedial walls of the somite**

become mesenchymal (fibroblast-like) again

surround the neural tube & notochord

sclerotome

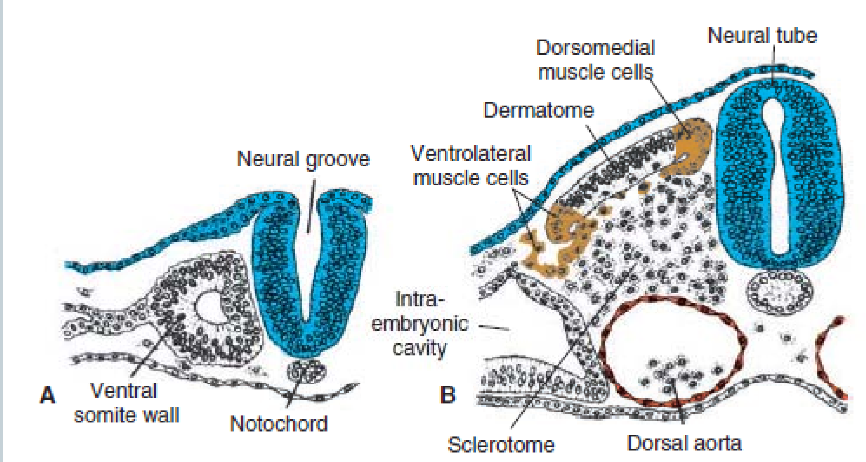
- vertebrae
- Ribs



Somite Differentiation

precursors for muscle cells

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



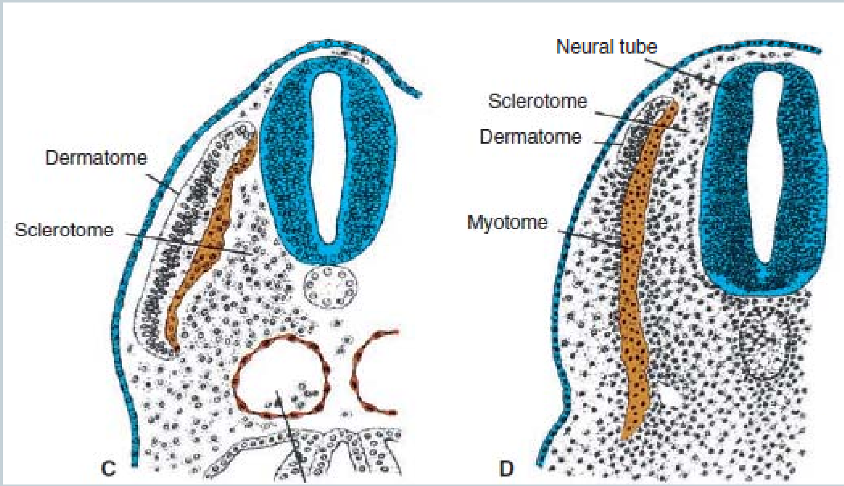
- **dermatome**

cells between these groups

- **Dermomyotome**

- **ventrolateral edge cells**

migrate to parietal layer of lateral plate mesoderm (body wall)
external and internal oblique muscles
transversus abdominis muscles
Some limb muscles



- ***Cells in dermomyotome***

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

Molecular Regulation of Somite Differentiation

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

PAX3 (dermomyotome region)

- **WNT proteins**

dorsomedial portion of the somite

MYF5 (*primaxial* muscle precursors)

- inhibiting protein **BMP4 & FGFs (**lateral plate mesoderm)

WNT (epidermis)

dorsolateral portion of the somite

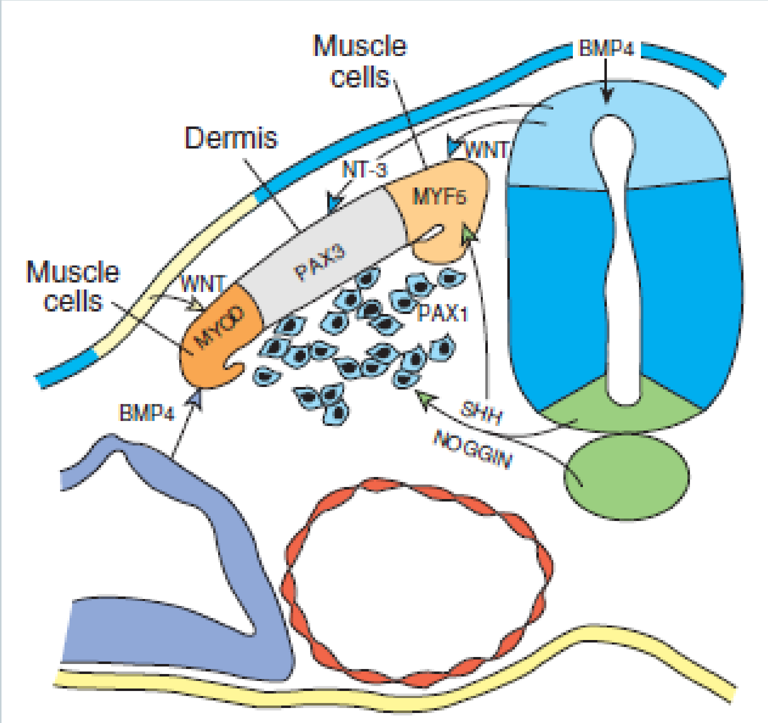
MYOD **(**primaxial and abaxial muscle precursors)

- The midportion of the somite dorsal epithelium

neurotrophin 3 (NT-3)

by the dorsal region of the neural tube

Dermis.formation



Molecular Regulation of Somite Differentiation

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

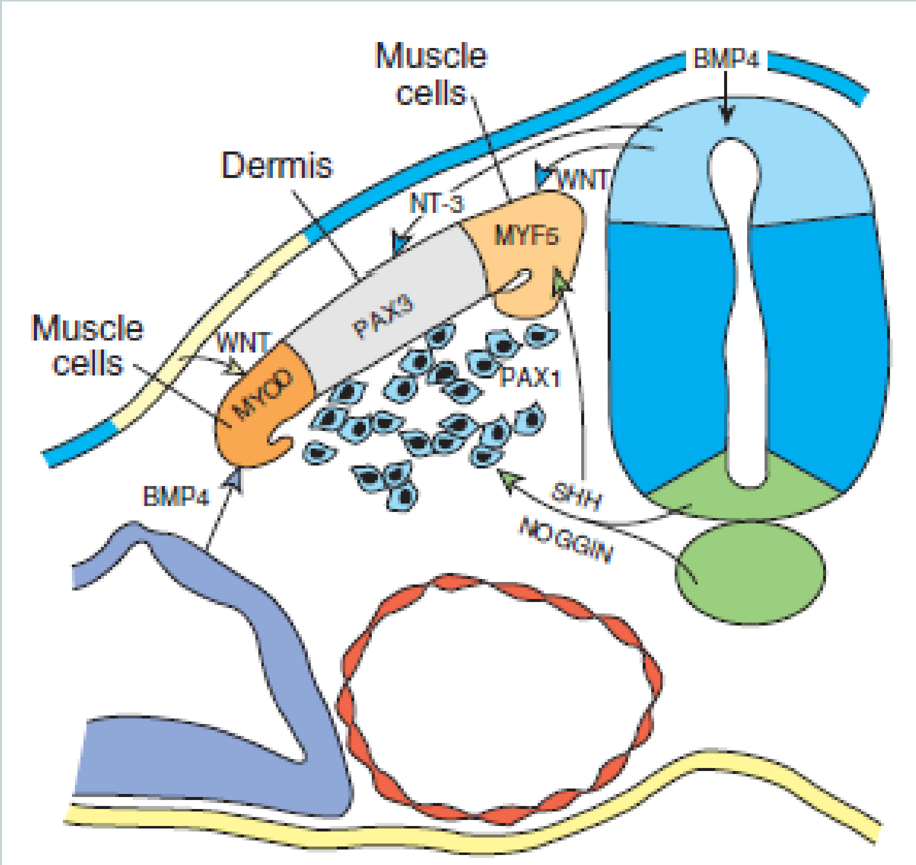
- ***noggin genes***
- ***sonic hedgehog (SHH)***

notochord and floor plate of the neural tube

ventromedial portion of the somite

Sclerotome (*PAX1*)

Cartilage & bone



Intermediate Mesoderm

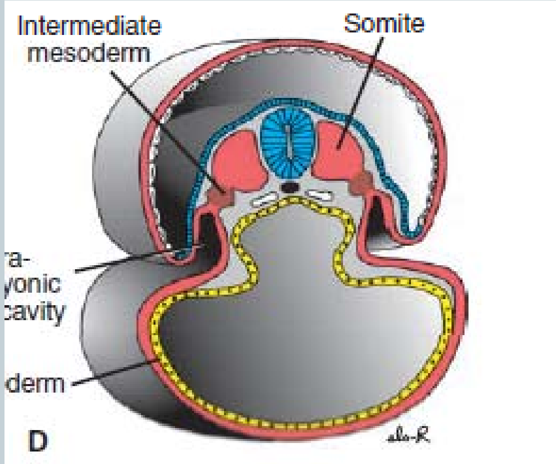
- connects paraxial mesoderm with the lateral plate

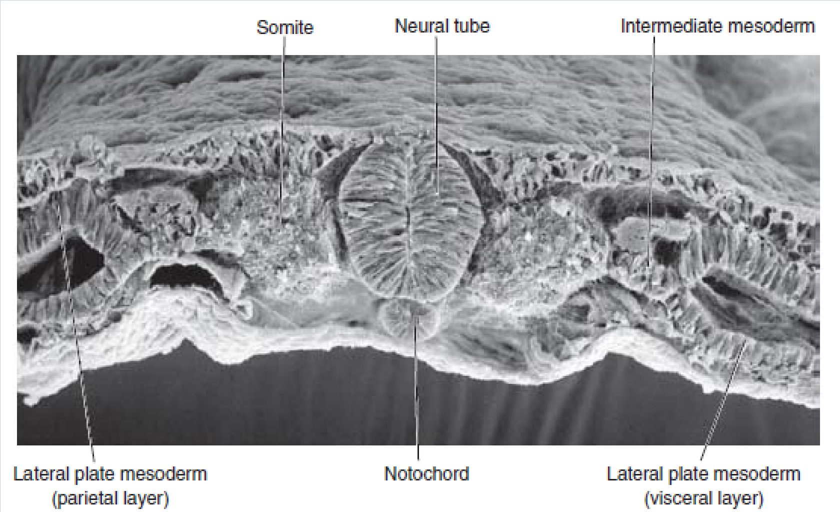
differentiates into:
***urogenital* structures**

- **In cervical and upper thoracic regions**
segmental cell clusters **(future nephrotomes)**

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

urinary system
the gonads



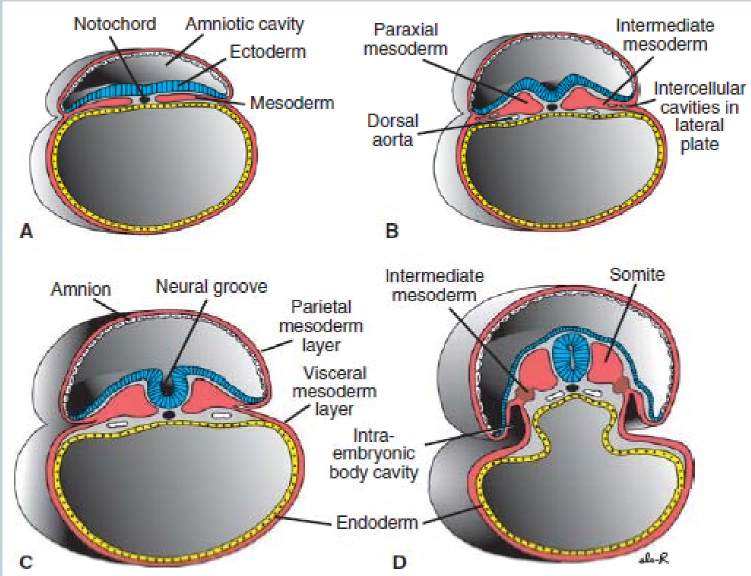


Lateral Plate Mesoderm

- **Lateral plate mesoderm**

1. **Parietal (somatic) layer**
   line the intraembryonic cavity

2. **visceral (splanchnic) layer**
Surround the organs



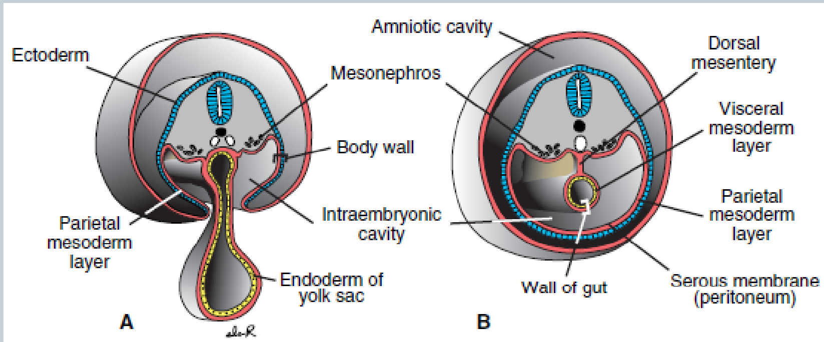
- ***parietal layerMesoderm* & overlying ectoderm**
- lateral body wall folds & cephalic & caudal folds
- close the ventral body wall

- **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

Cell migration from paraxial mes. To lateral plate mes.

1. costal cartilages
2. limb muscles
3. most of the body wall muscles



Lateral Plate Mesoderm

- **The visceral layer mesoderm & endoderm**

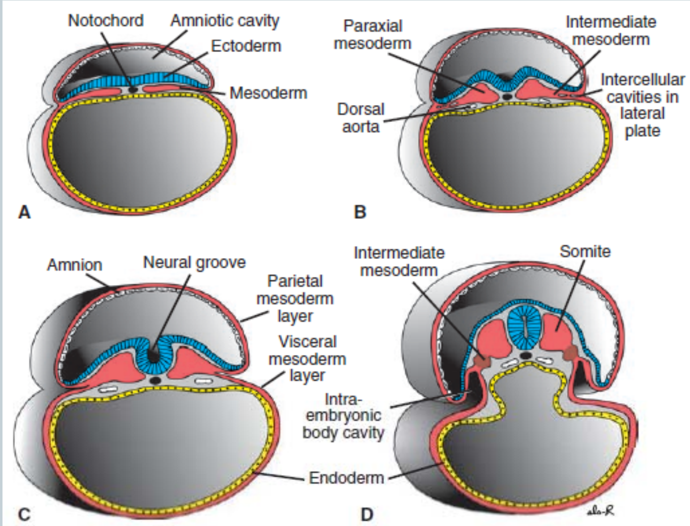
wall of the gut tube

***Mesoderm cells of the* parietal layer**

surrounding the intraembryonic cavity

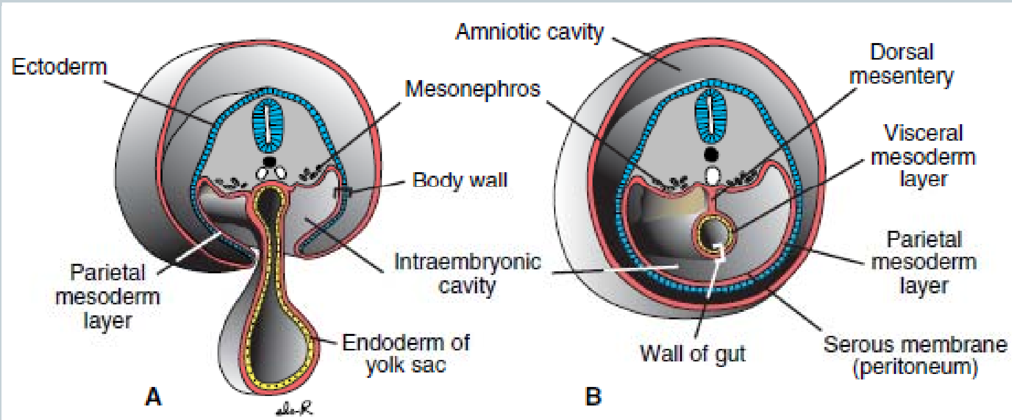
the mesothelial (serous) membranes

- peritoneal,
- Pleural
- Pericardial



- **Mesoderm cells of the visceral layer**

thin serous membrane around each organ



Blood and Blood Vessels

- **Mesoderm origine**

vessels formation:

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

Third week

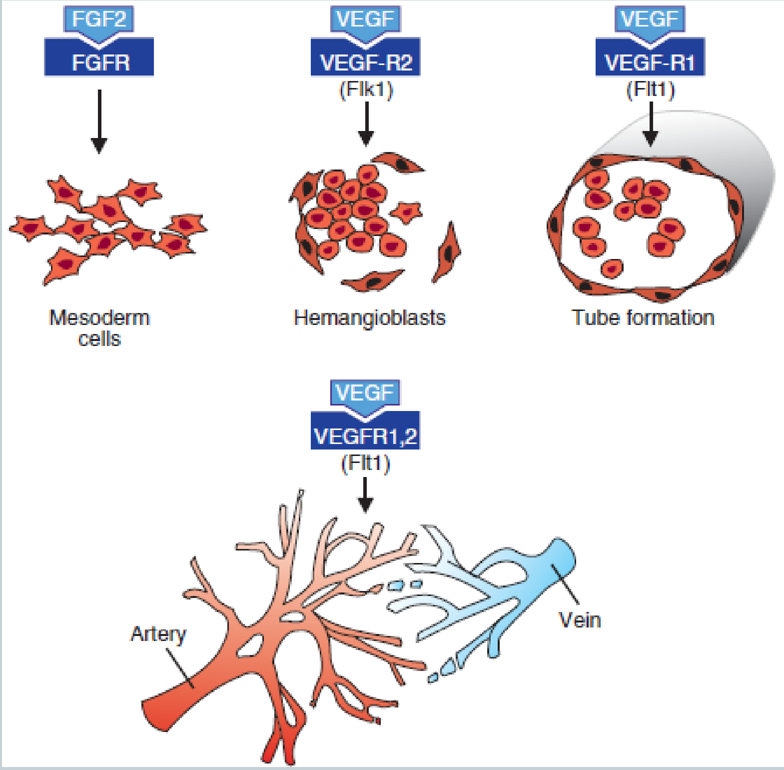
Hemangioblasts (temporary)

first blood islands (mesodermic wall of the yolk sac)

lateral plate mesoderm

other regions

- definitive **hematopoietic stem cells**
- **aortagonad- mesonephros region (AGM)**
- colonize the liver (2-7th monthes)
- Bone marrow (7th month)



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lateral plate mesoderm

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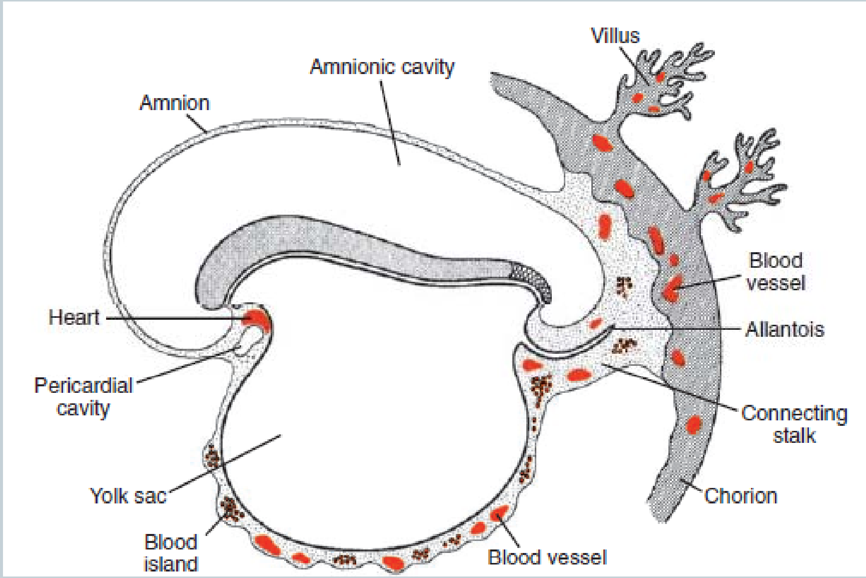


Molecular Regulation of Blood Vessel Formation

FGF2
VEGF

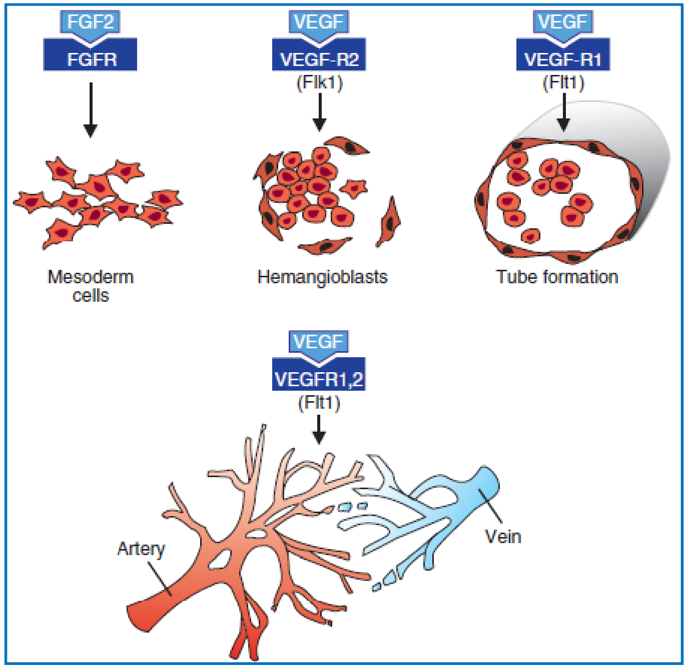
hematopoietic stem cells,

angioblasts

dorsal aorta and cardinal veins

Maturation and modeling of the vasculature
PDGF

specifies arterial development
SHH
VEGF
Notch pathway
ephrinB2



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

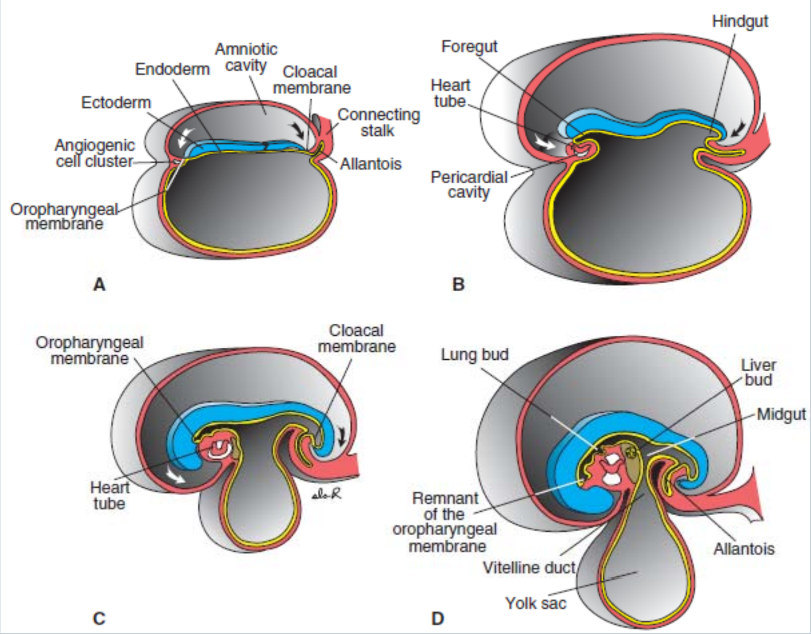
- **The gastrointestinal tract**

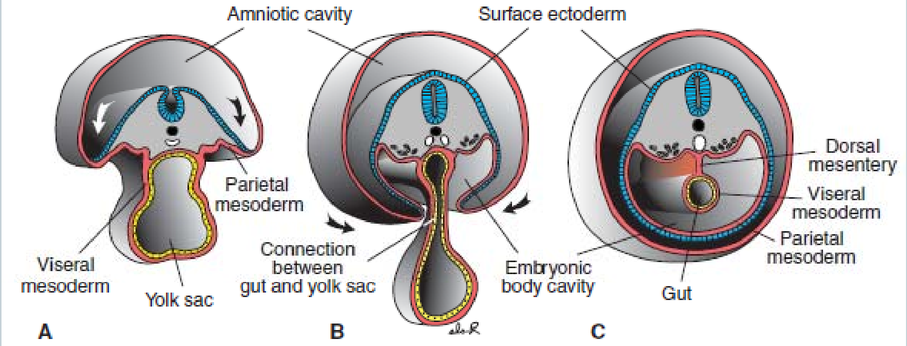
- brain vesicles growth & development
embryonic disc bulge into the amniotic cavity

- the neural tube Lengthening
embryo to curve

- Head, tail & two lateral folds move ventrally
The ventral body wall closes

1. Foregut
2. Midgut
3. Hindgut





Derivatives of the endodermal germ layer

cephalic end

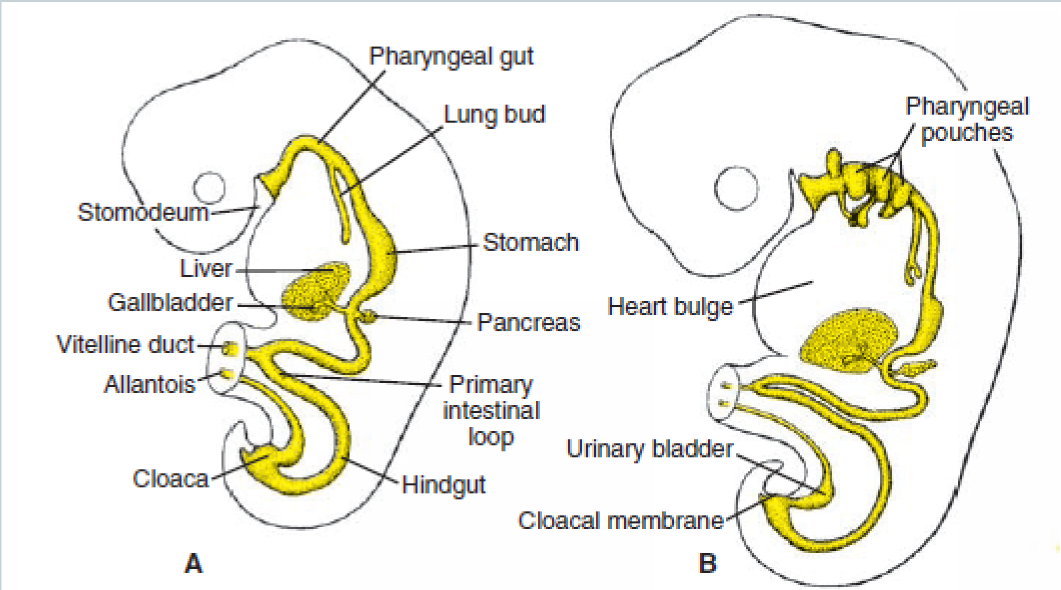
- **oropharyngeal membrane** (ctodermal–endodermal membrane)

Separate Stomadeum from the pharynx (4th week)

Caudal end

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

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



Derivatives of the endodermal germ layer

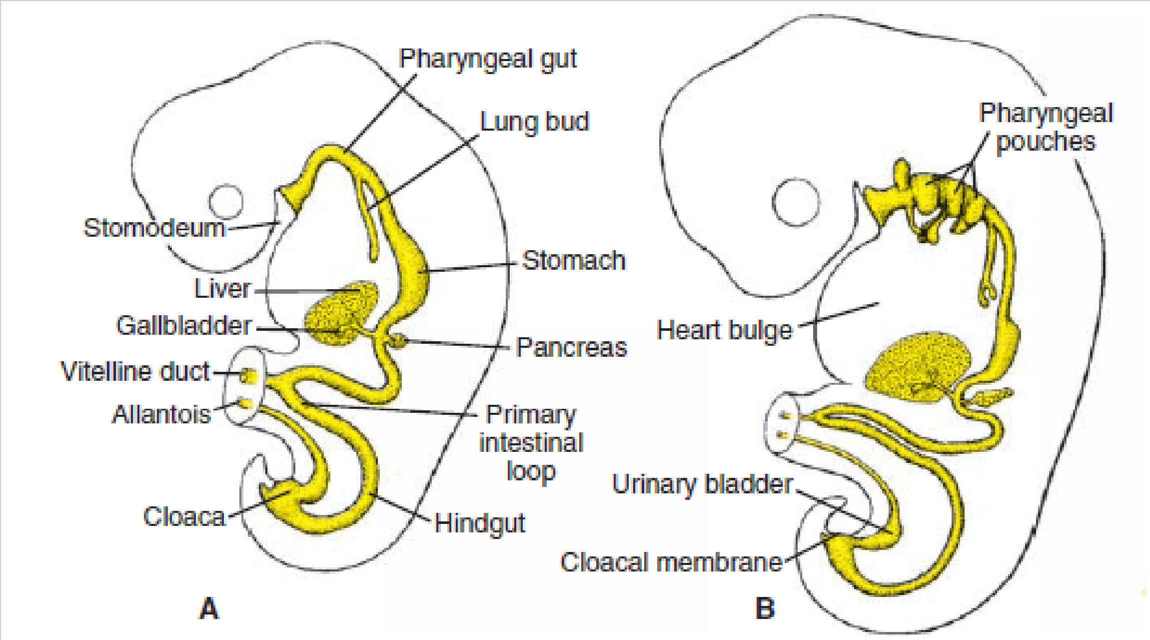
- **cloaca**
- allantois incorporation, body folding

- 5^{th} week,

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

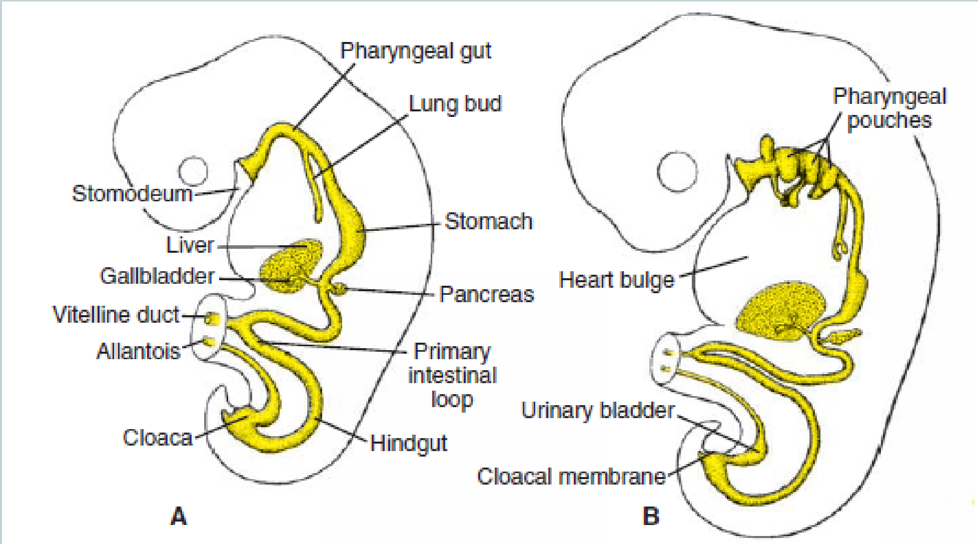
The yolk sac role:

- nutritive organ
- first blood cells
- 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)

- somites
- pharyngeal arches

Age in the second month

- 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
(4^{th} cervical to the first thoracic somites)

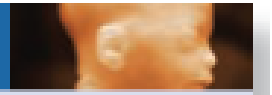
- brachial plexus

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