DEVELOPMENT OF DIGESTIVE SYSTEM

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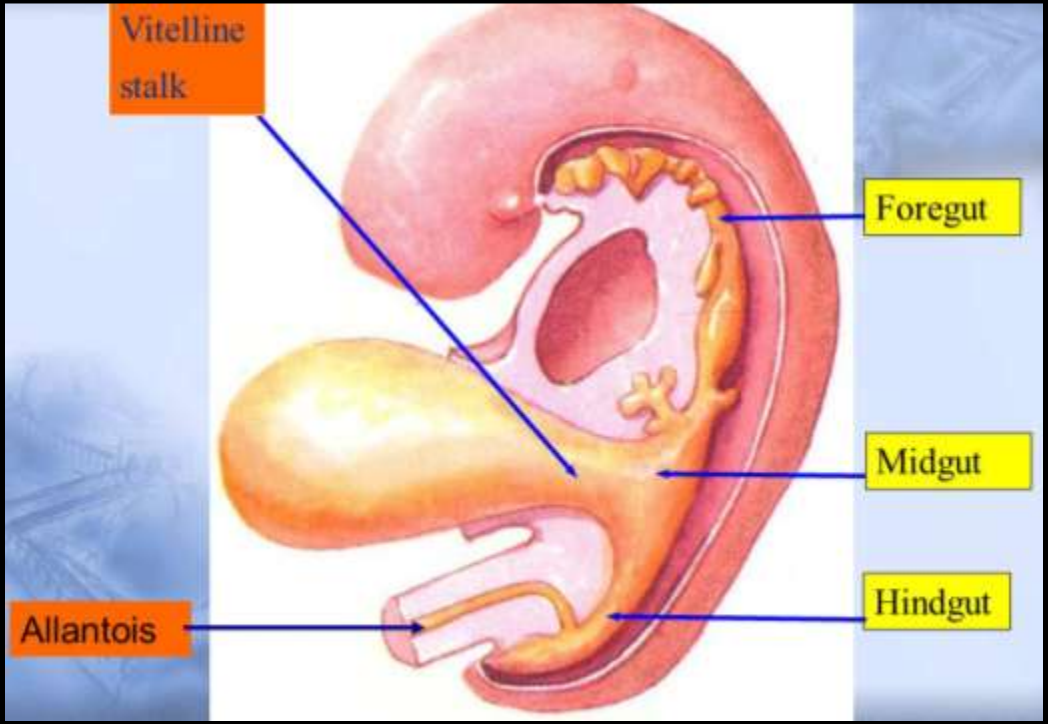
LEARNING OBJECTIVES

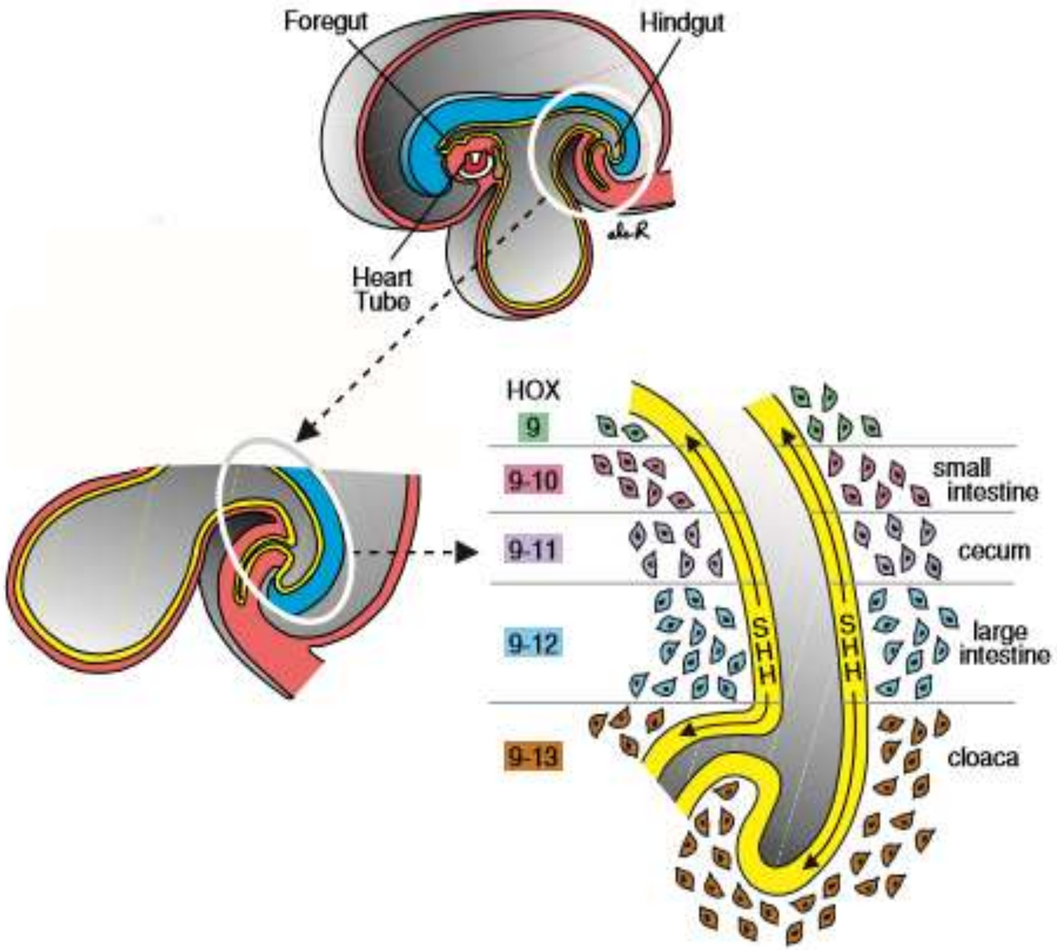
- Origin of GI Tract
- Formation of Primitive Gut
- Mesentery development
- Foregut development
- Midgut development
- Hindgut development



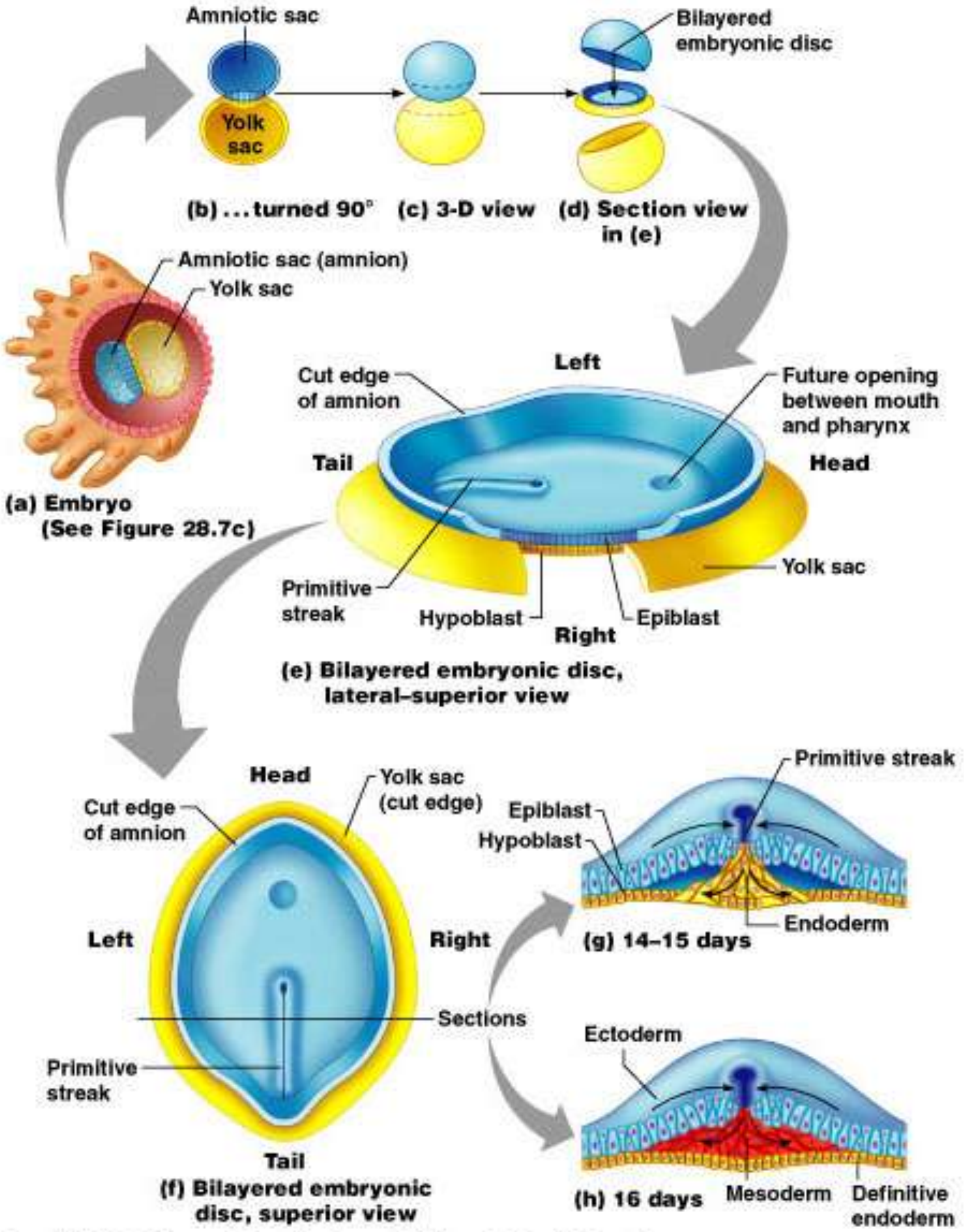
ORIGIN OF DIGESTIVE SYSTEM

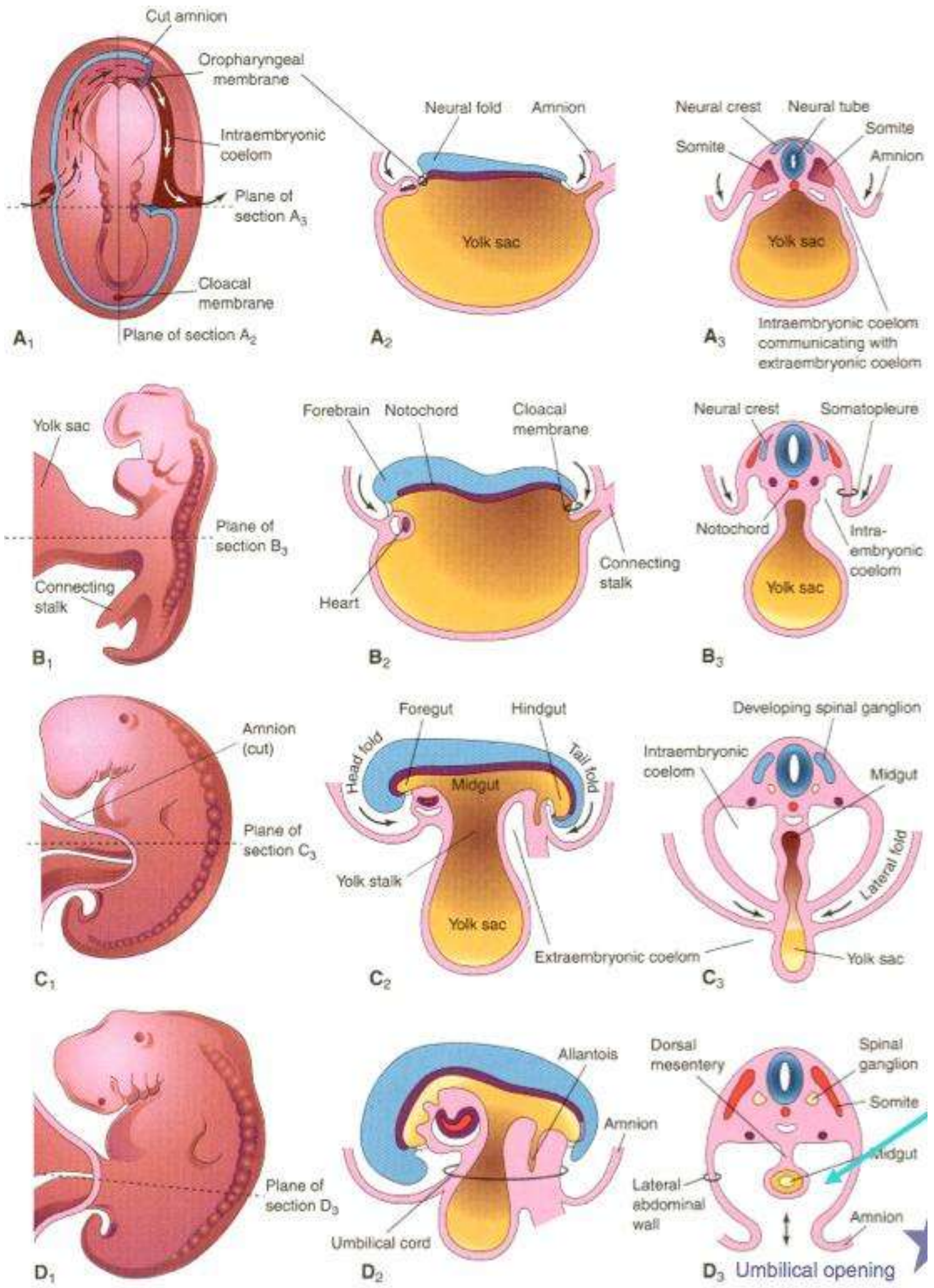
- Epithel lining the GI tract (digestive system) and parenchyma of the glands derived from **endoderm**
- Muscle, connective tissue, and peritoneal components of the wall of the gut are derived from **splanchnic mesoderm**
- ***The development of specific organs depend of the reciprocal interaction between endoderm and splanchnic mesoderm. The expression of morphogen Sonic hedgehog (SHH) in endoderm will induce the HOX code in mesoderm → encode mesoderm types of structure that will form.***

Molecular basic of GIT formation

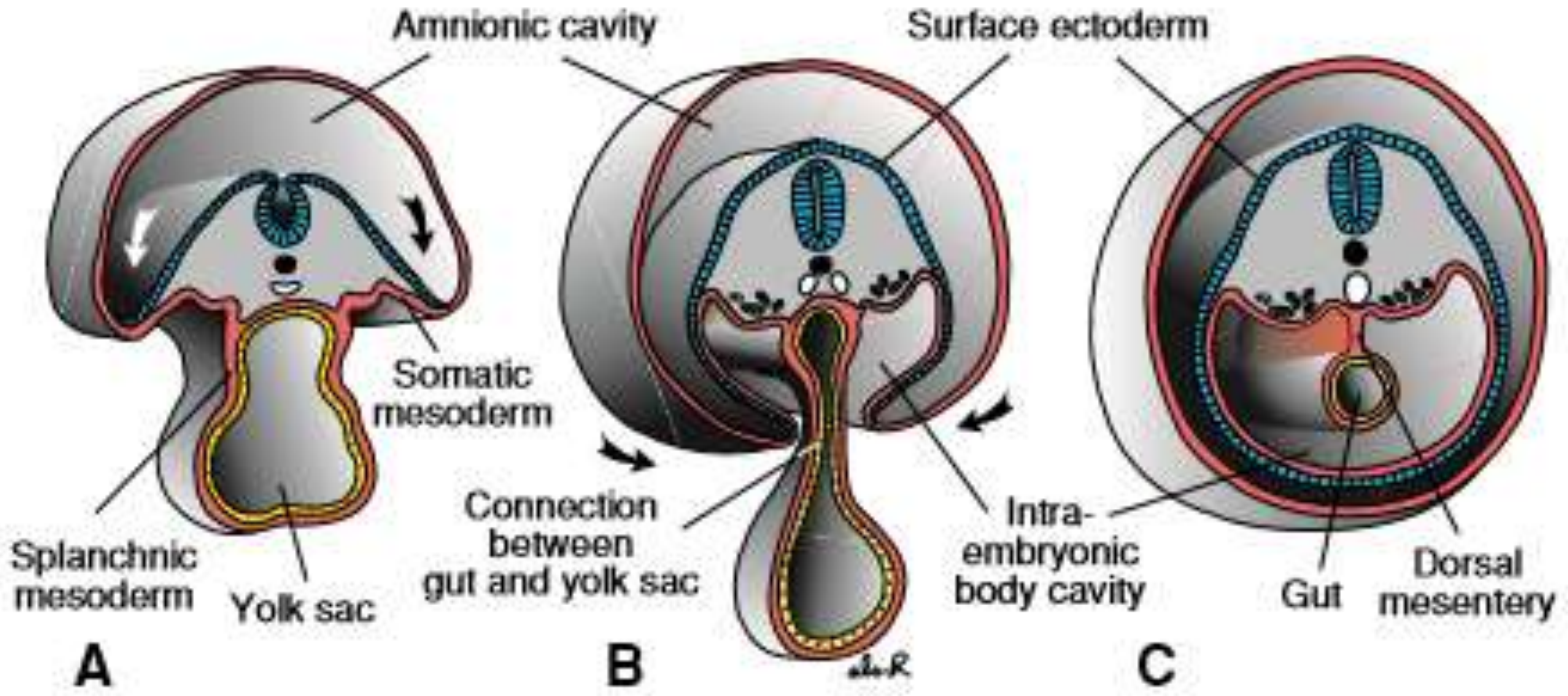


The morphogen sonic hedgehog (SHH) is secreted by gut endoderm and induces a nested expression of HOX genes in surrounding mesoderm. HOX expression then initiates a cascade of genes that “instruct” gut endoderm to differentiate into its regional identities. Signaling between the two tissues is an example of an epithelial-mesenchymal interaction


Amniotic sac
Bilayered embryonic disc
Yolk sac
(b) ... turned 90°
(c) 3-D view
(d) Section view in (e)
Amniotic sac (amnion)
Yolk sac
(a) Embryo (See Figure 28.7c)
Left
Cut edge of amnion
Future opening between mouth and pharynx
Tail
Head
Yolk sac
Primitive streak
Hypoblast
Right
Epiblast
(e) Bilayered embryonic disc, lateral–superior view
Head
Cut edge of amnion
Yolk sac (cut edge)
Left
Right
Sections
Primitive streak
Tail
(f) Bilayered embryonic disc, superior view
Primitive streak
Epiblast
Hypoblast
Endoderm
(g) 14–15 days
Ectoderm
(h) 16 days
Mesoderm
Definitive endoderm


Cut amnion
Oropharyngeal membrane
Intraembryonic coelom
Plane of section A3
Cloacal membrane
Plane of section A2
A1
Neural fold
Amnion
Yolk sac
A2
Neural crest
Neural tube
Somite
Somite
Amnion
Yolk sac
A3
Intraembryonic coelom communicating with extraembryonic coelom
Yolk sac
Plane of section B3
Connecting stalk
B1
Forebrain
Notochord
Cloacal membrane
Heart
Connecting stalk
B2
Neural crest
Somatopleure
Notochord
Intra-embryonic coelom
Yolk sac
B3
Amnion (cut)
Plane of section C3
C1
Foregut
Hindgut
Head fold
Tail fold
Midgut
Yolk stalk
Yolk sac
Extraembryonic coelom
C2
Developing spinal ganglion
Intraembryonic coelom
Midgut
Lateral fold
Yolk sac
C3
Plane of section D3
D1
Allantois
Amnion
Umbilical cord
D2
Dorsal mesentery
Spinal ganglion
Somite
Midgut
Lateral abdominal wall
Amnion
D3 Umbilical opening

Various stages of embryo development
(transverse section)



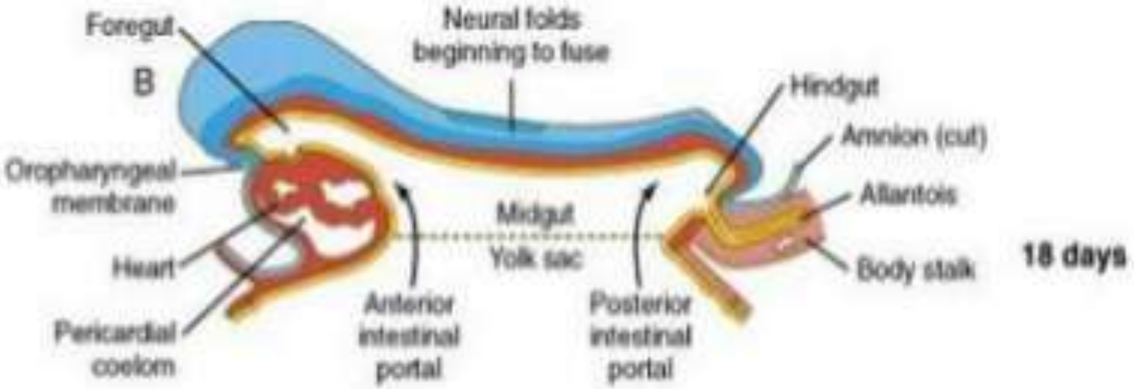
FORMATION OF PRIMITIVE GUT

- Cephalocaudal and lateral folding of embryo → formation of blind end tube from cephalic until caudal portion of embryo → **Primitive Gut**
- 4 sections of primitive gut:

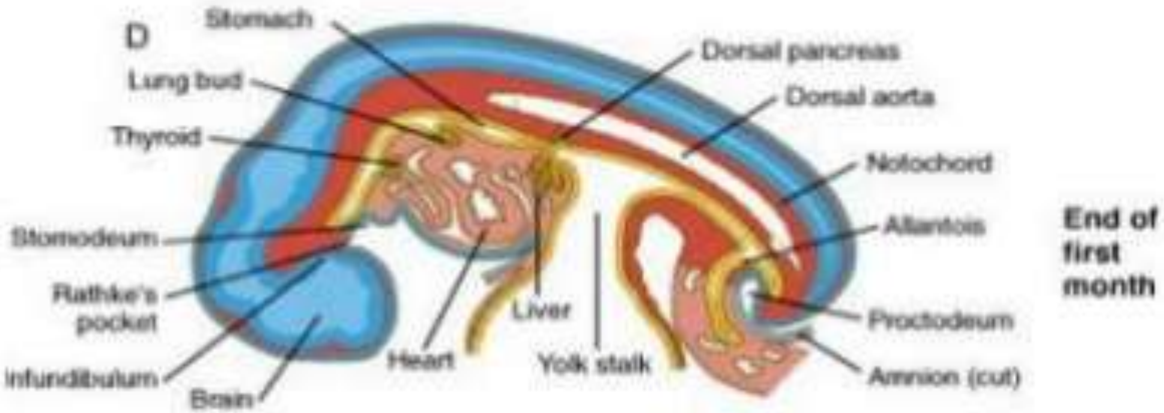
1. Pharyngeal gut
2. Foregut
3. Midgut
4. Hindgut

Formation of the Primitive Gut

- The 'cephalocaudal' and 'lateral' foldings of the embryo will lead to partial incorporation of endoderm lined cavity into the embryo to form the "primitive gut tube".

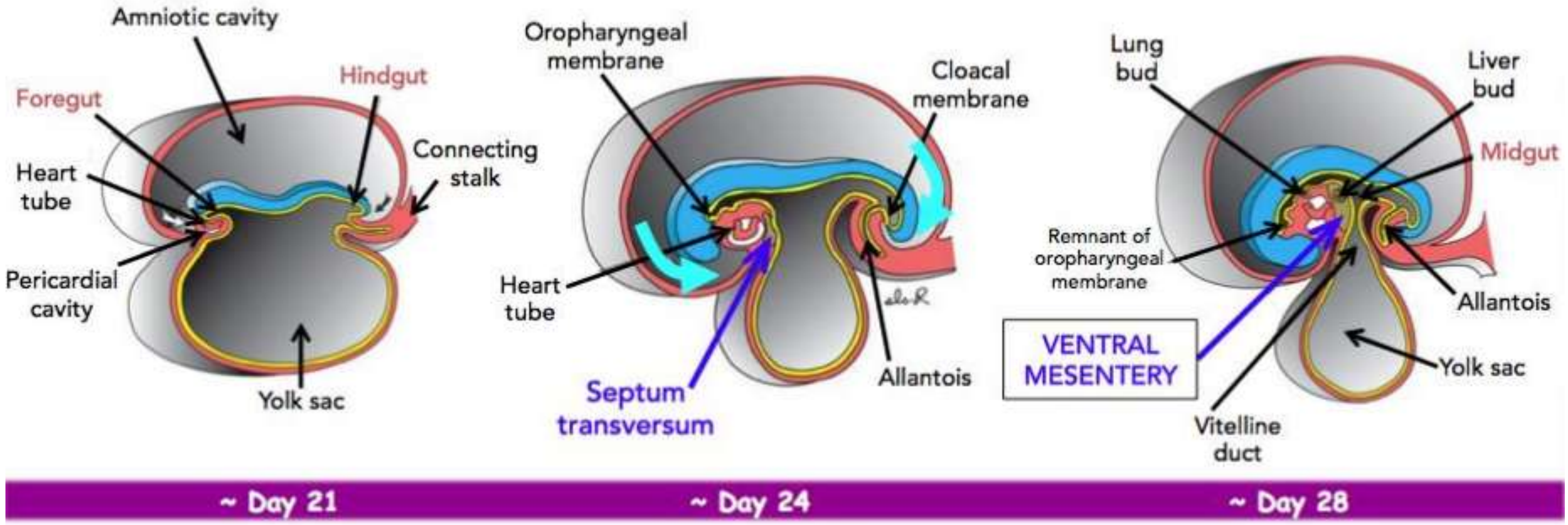


- In the cranial & caudal ends of the embryo the primitive gut forms a blind ending tube, the **'foregut'** & **'Hindgut**', respectively.



- The middle part of the tube, **'Midgut'** remains temporarily connected to the yolk sac by means of a vitelline duct/yolk stalk.

Development of the Gut Tube



Endoderm Development of GIT

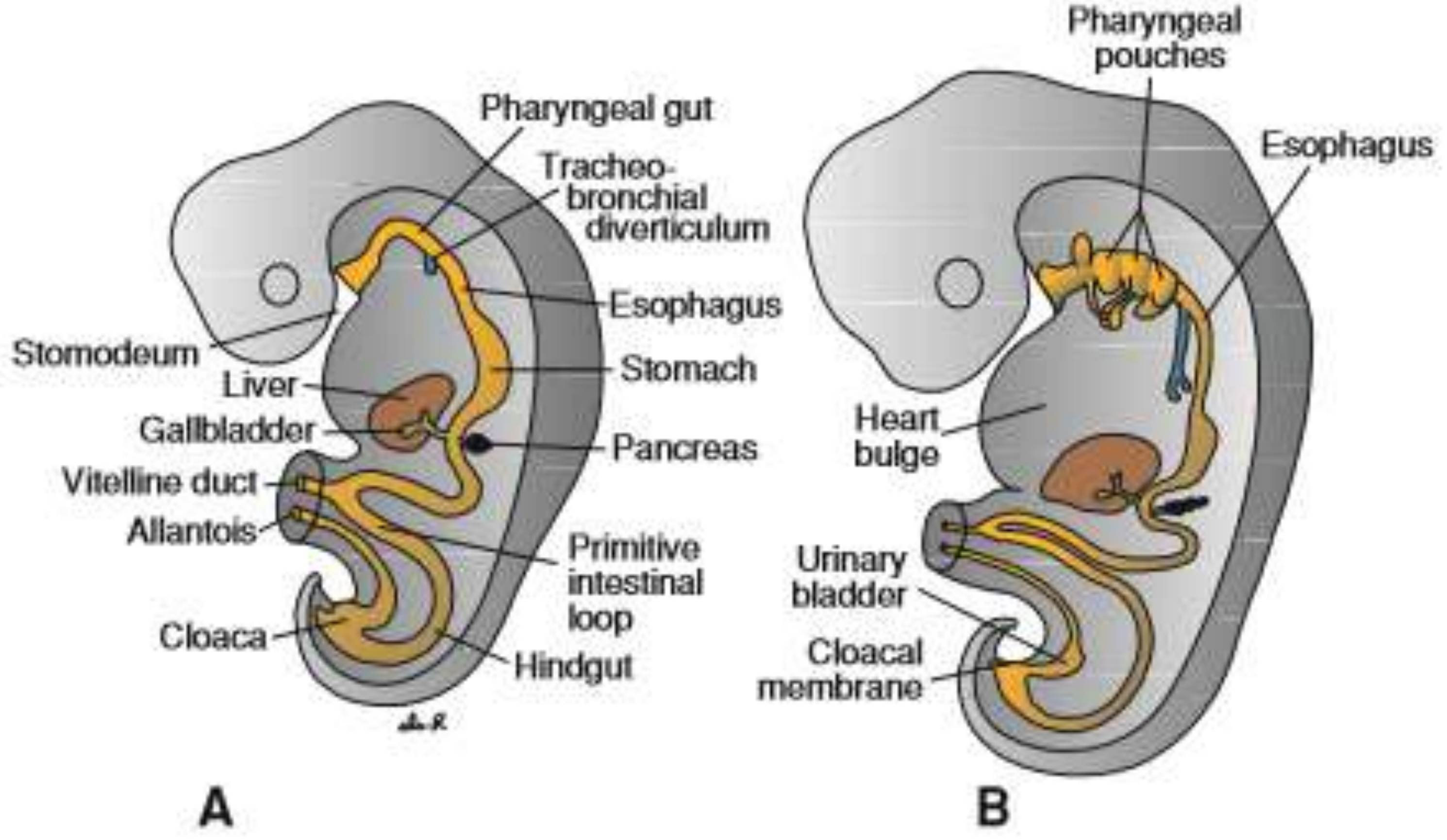
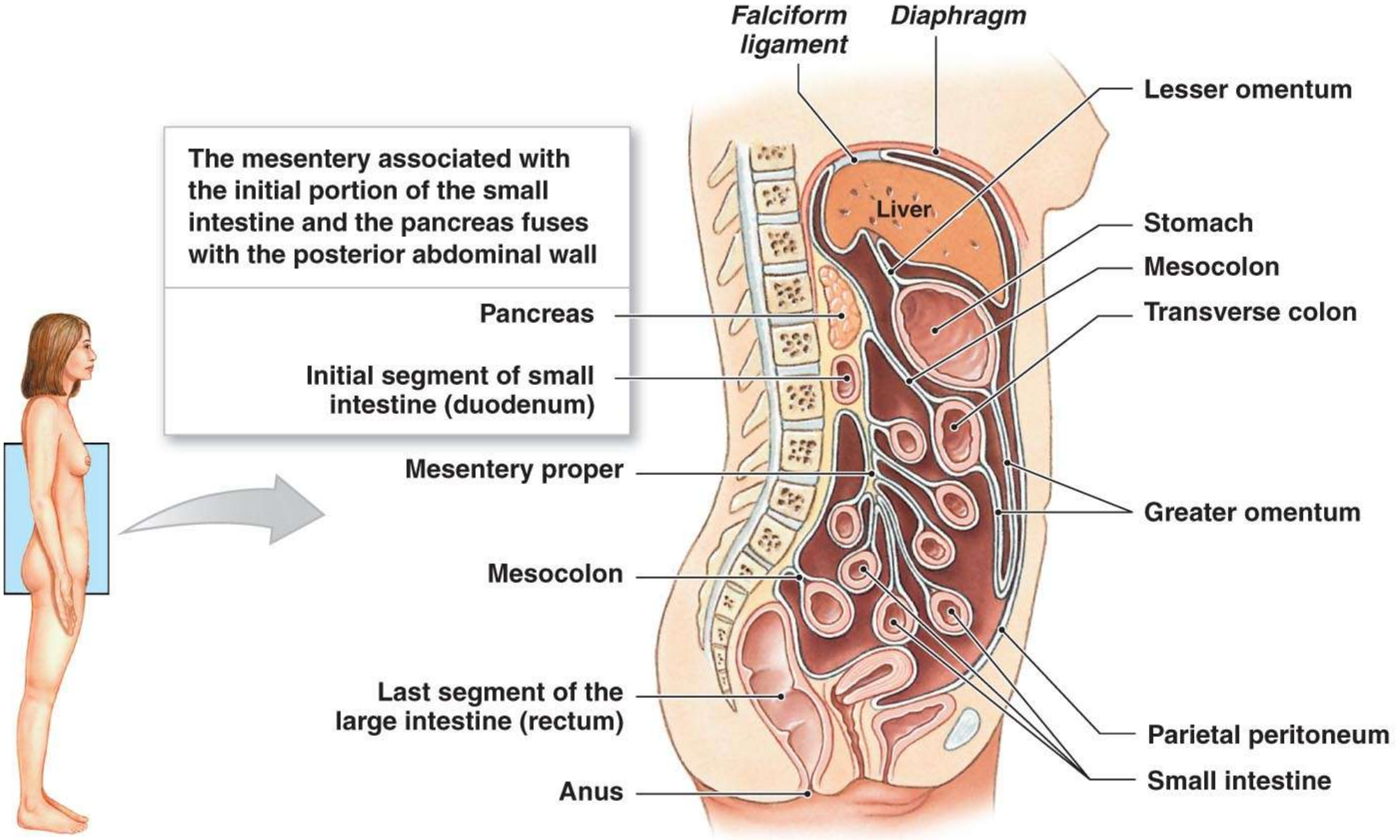


Figure 13.5 Embryos during the fourth **(A)** and fifth **(B)** weeks of development showing formation of the gastrointestinal tract and the various derivatives originating from the endodermal germ layer.

MESENTERY

- Is double layered peritoneum that cover some particular organs and connect them to the body wall
- Gut tubes and their derivation are fixed to ventral and dorsal body wall by mesentery
- Organs that are fully covered by mesentery → **intraperitoneal organs**
- Organs that are directly attached in posterior body wall and covered by mesentery only on their anterior part → **retroperitoneal organs**

A sagittal section showing the orientation of the mesenteries in an adult



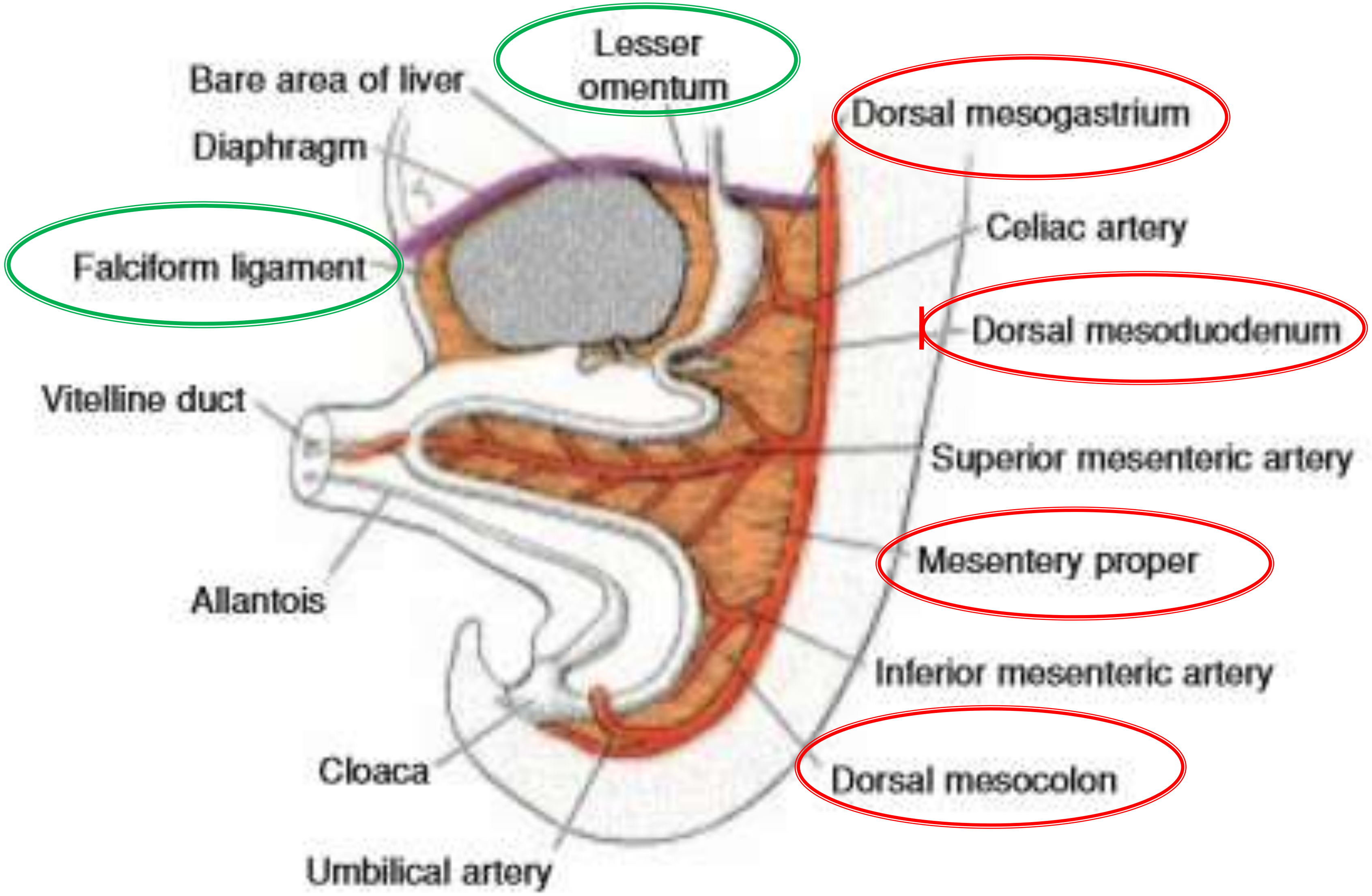
Dorsal mesentery

- passes from distal part of esophagus to cloacal region.
- When it passes :
  - ✓ the stomach → dorsal mesogastrium or major omentum
  - ✓ Duodenum → dorsal mesoduodenum
  - ✓ Jejenum ileum → mesenterium propius
  - ✓ Colon → dorsal mesocolon

Ventral Mesentery

- In terminal part of esophagus, stomach and proximal part of duodenum
- derived from transversal septum
- Liver bud growth in transversal septum will divide the ventral mesentery into 2 parts → lesser omentum and falciform ligament

Primitive Mesentery



FOREGUT DEVELOPMENT

- Lies from pharyngeal tube until liver bud
- Organs: **esophagus, trachea, lung bud, stomach, upper part of duodenum, liver and biliary ducts, pancreas, spleen**

FOREGUT DEVELOPMENT

1. ESOPHAGUS

- 4^{TH} WEEK → respiratory diverticulum appears in ventral wall of foregut, right after pharyngeal gut → slowly separated from foregut by esophageal septum

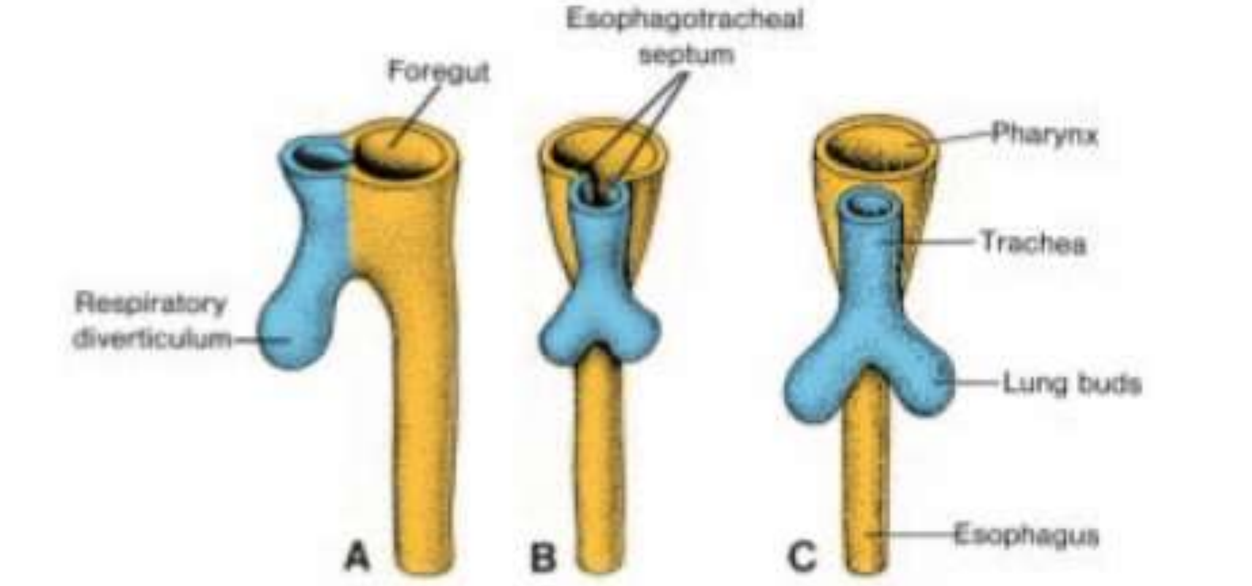


Figure 13.6 Successive stages in development of the respiratory diverticulum and esophagus through partitioning of the foregut. **A.** At the end of the third week (lateral view). **B** and **C.** During the fourth week (ventral view).

- Clinical Correlation
  - ✓ **Esophageal Atresia / Fistula** →*due to esophageal septum deviation, etc*
  - ✓ **Stenosis Esophagus** (usually 1/3 distal part) → *incomplete recanalization, abnormal bloodflow, etc*
  - ✓ **Hernia hiatus congenital** → *esophagus fails to lengthen, stomach is pulled upward*

Esophageal atresia / fistula

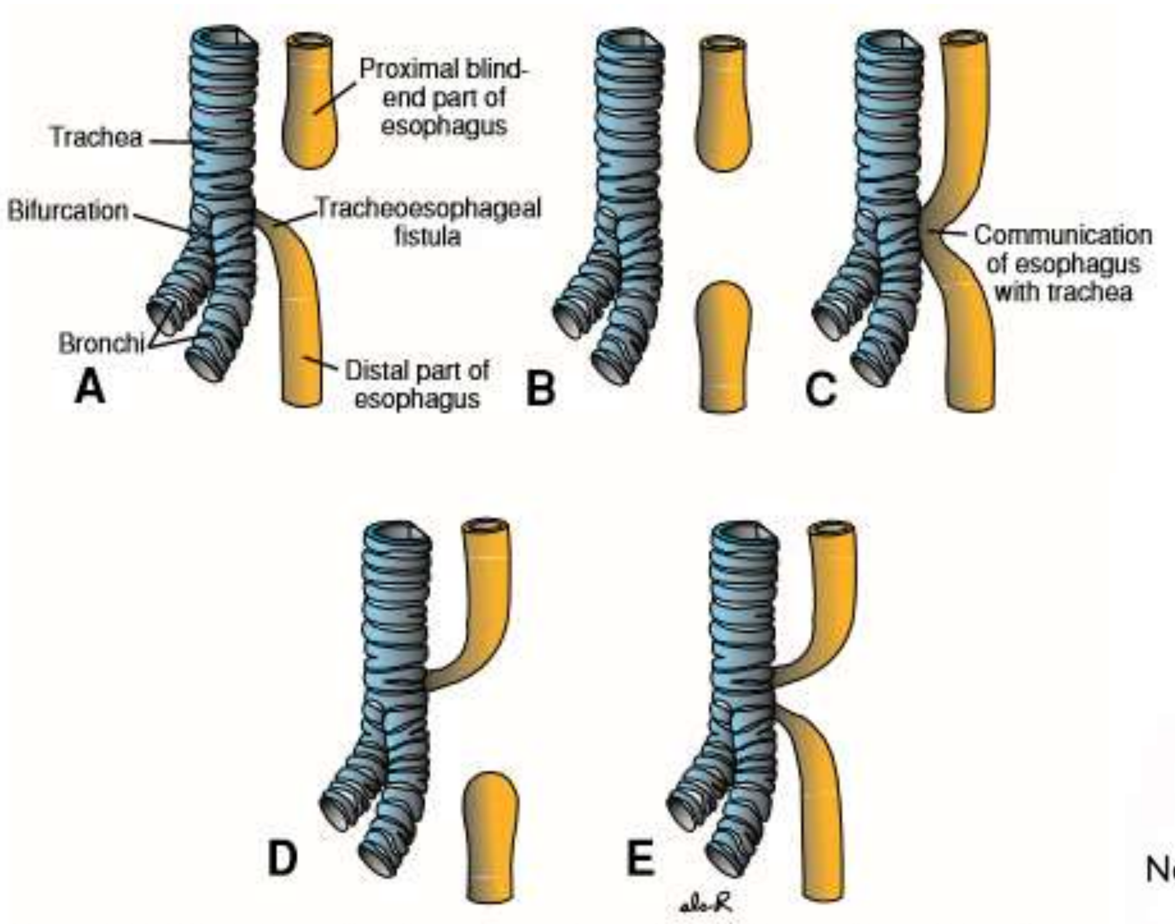
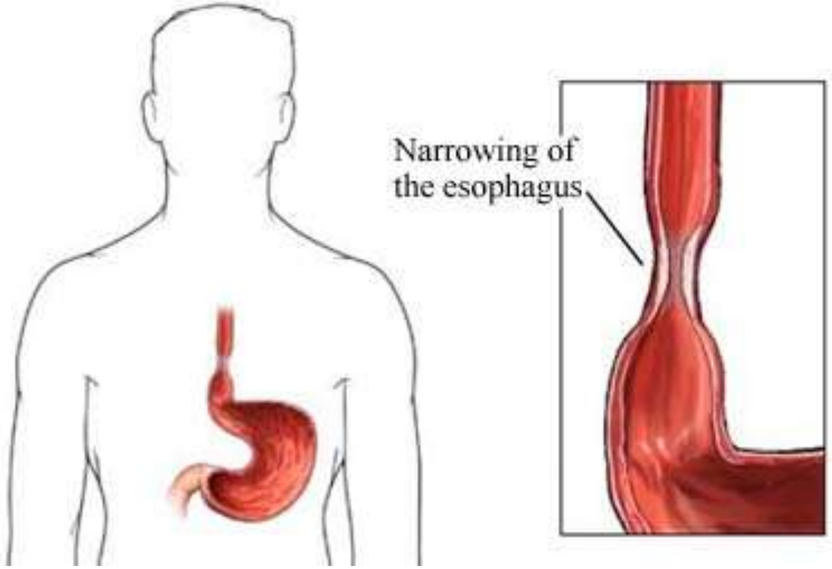
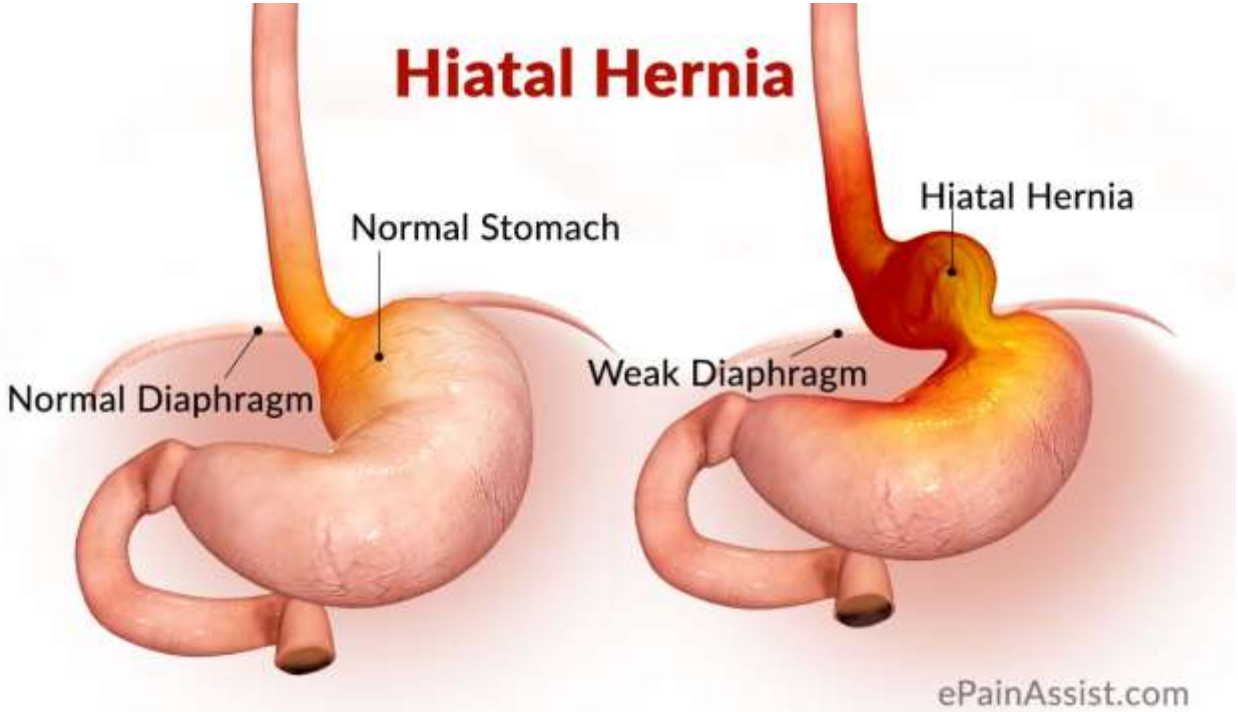


Figure 13.7 Variations of esophageal atresia and/or tracheoesophageal fistula in or of their frequency of appearance: A, 90%; B, 4%; C, 4%; D, 1%; and E, 1%.





FOREGUT DEVELOPMENT

2. STOMACH (GASTER / VENTRICULUS)

- **4 WEEKS :** due to different growth speed of each part of its wall and the development of surrounding organs → stomach change in its shape and positon

STOMACH ROTATION

- in longitudinal axis → change position of dorsal and ventral mesentery → formation of **bursa omentalis**
- in anteroposterior axis → dorsal mesogastrium protruded distally, covering transverse colon and gut loop (Like an apron)→ slowly difuses, 2 layers becomes 1

Stomach rotation

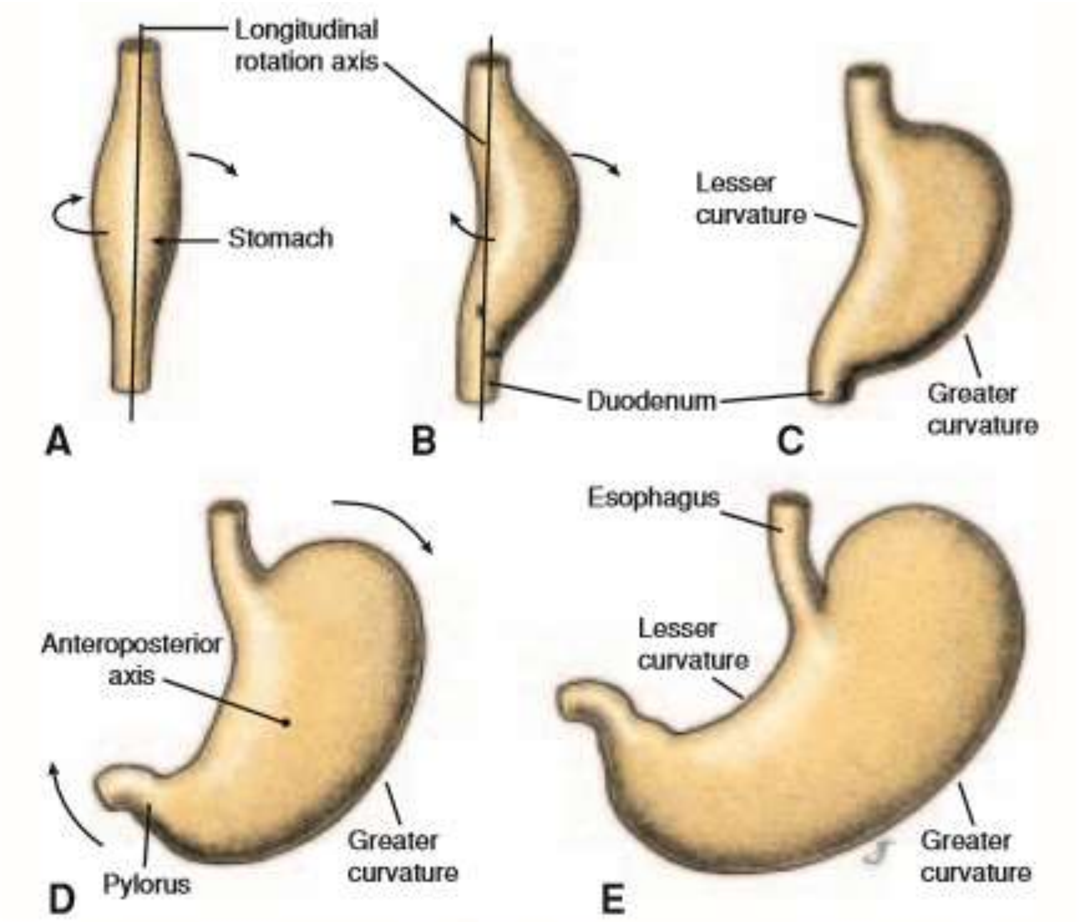


Figure 13.8 A, B, and **C.** Rotation of the stomach along its longitudinal axis as seen anteriorly. **D** and **E.** Rotation of the stomach around the anteroposterior axis. Note the change in position of the pylorus and cardia.

Mesogastrium change in position durung stomach rotation

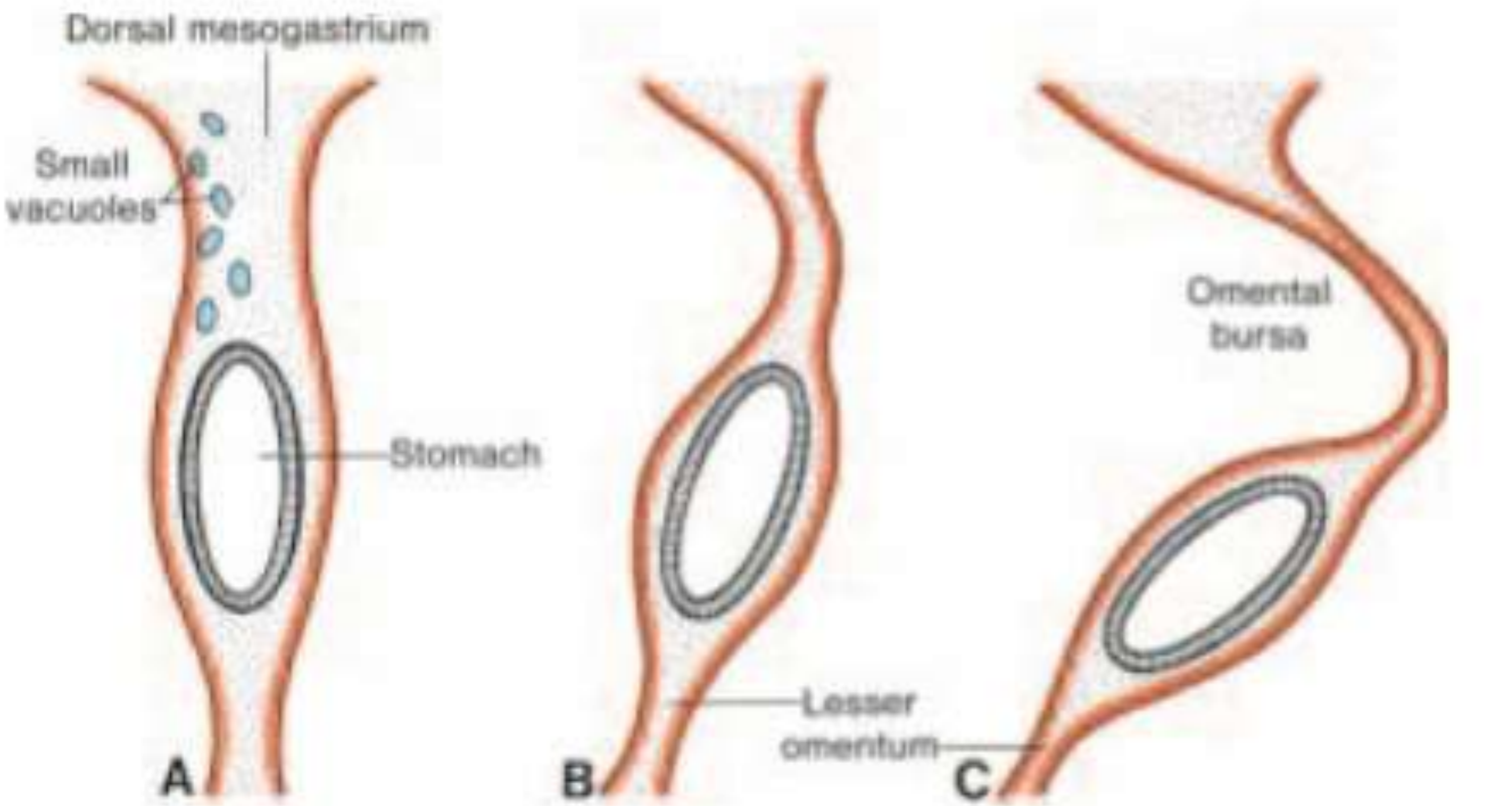


Figure 13.9 A. Transverse section through a 4-week embryo showing intercellular clefts appearing in the dorsal mesogastrium. **B** and **C.** The clefts have fused, and the omental bursa is formed as an extension of the right side of the intraembryonic cavity behind the stomach.

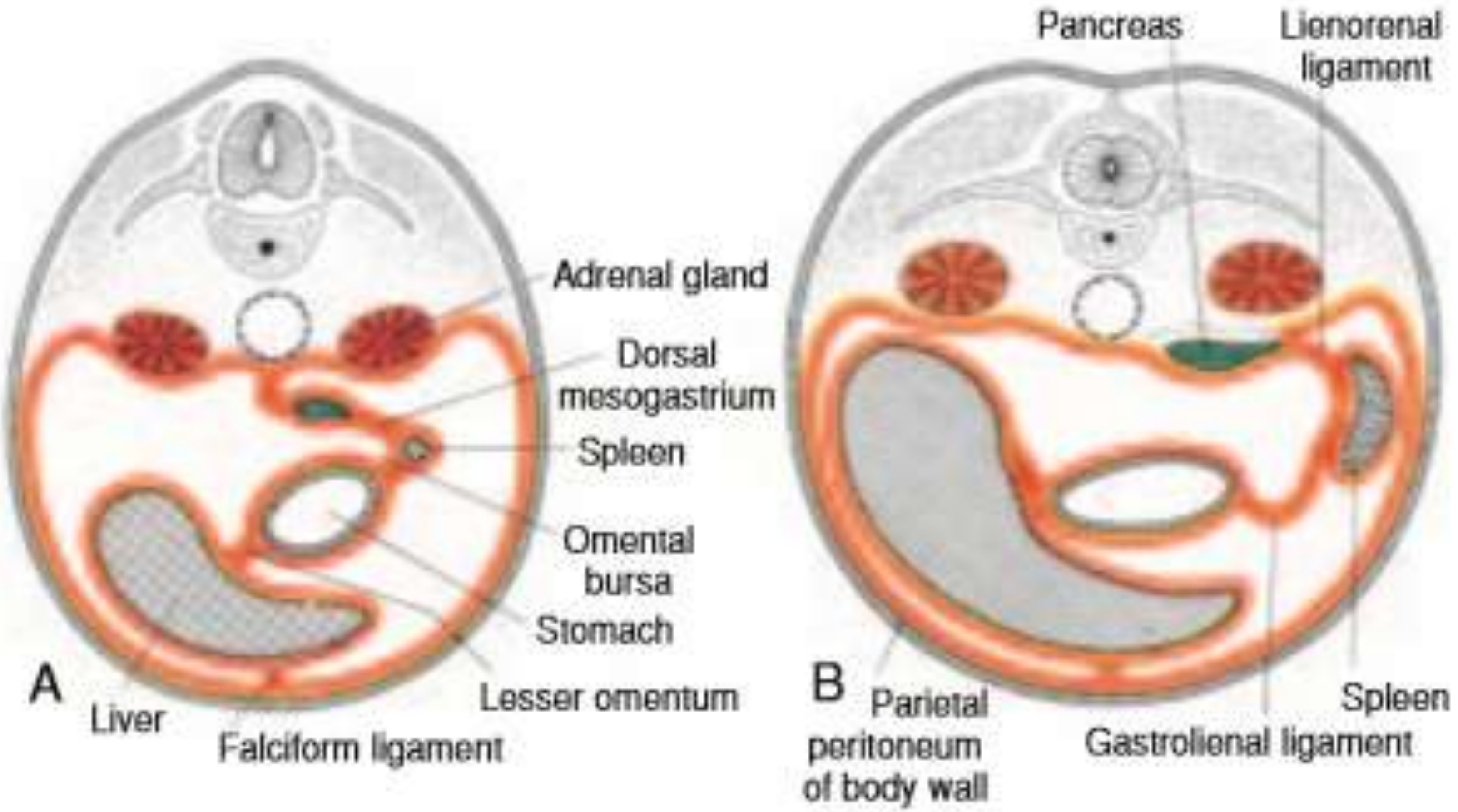
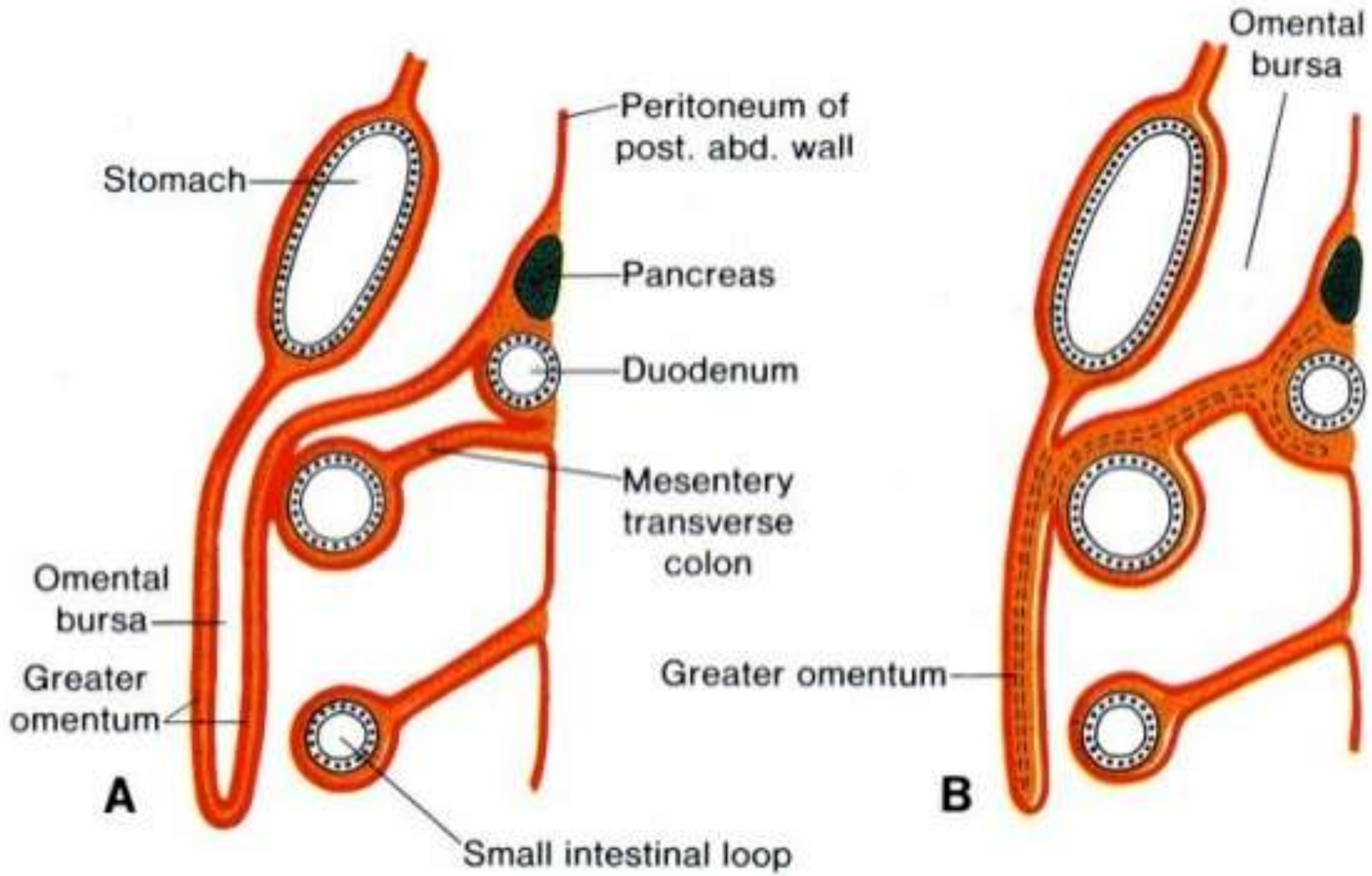


Figure 13.11 Transverse sections through the region of the stomach, liver, and spleen, showing formation of the lesser peritoneal sac, rotation of the stomach, and position of the spleen and tail of the pancreas between the two leaves of the dorsal mesogastrium. With further development, the pancreas assumes a retroperitoneal position.

DORSAL MESOGASTRIUM – GREATER OMENTUM



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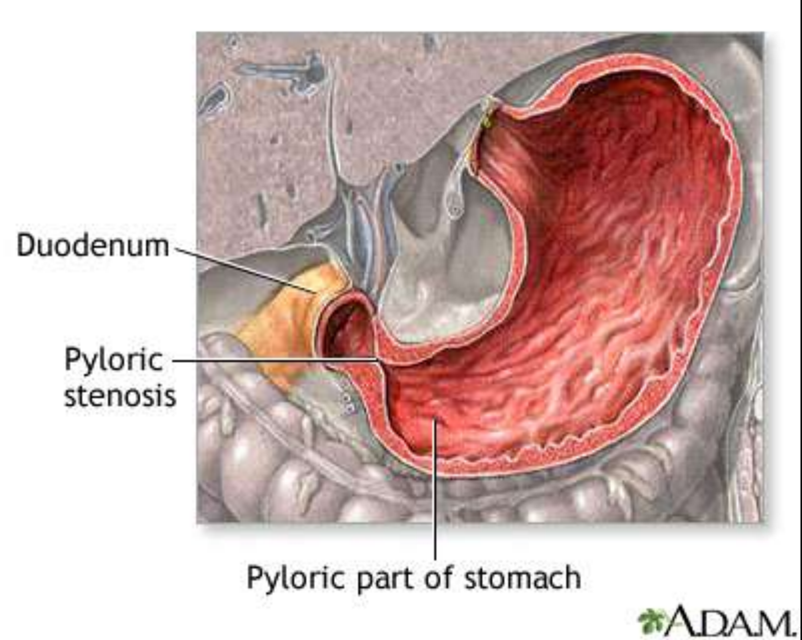
FOREGUT DEVELOPMENT

CLINICAL CORRELATION

✓**Pyloruc Stenosis →** longitudinal muscle hypertrophy and slow growing of circular muscle



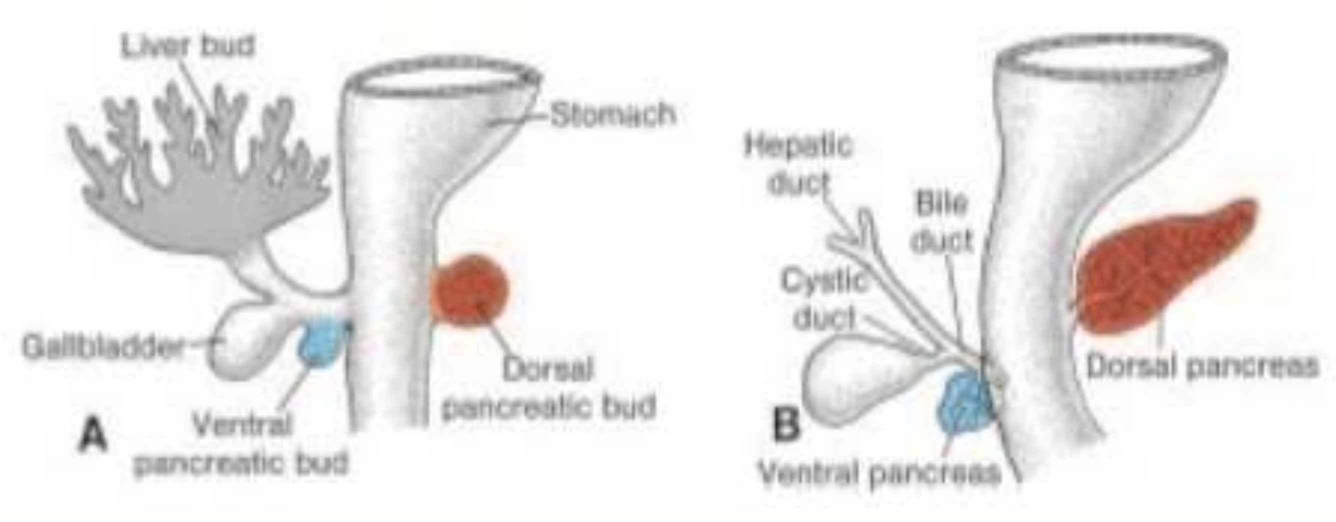
SPLEEN

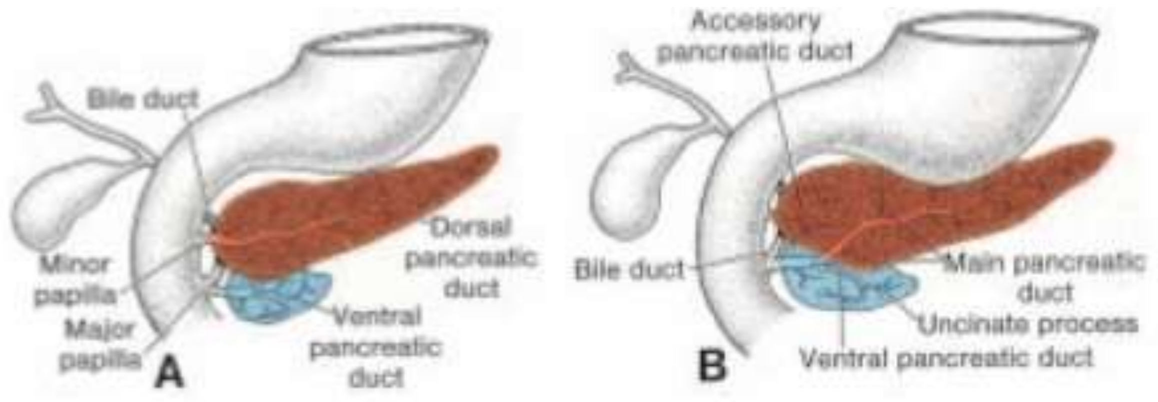
- **Spleen bud** appears in dorsal mesentery → change position due to stomach rotation
- connected with kidney → renolienalis ligament
- Connected with stomach →gastrolienalis ligament

PANCREAS

- The pancreas is formed by two buds originating from the endodermal lining of the duodenum → dorsal bud (from dorsal mesentery) and ventral bud
- When the duodenum rotates to the right and becomes C-shaped → the ventral pancreatic bud moves dorsally in a manner similar to the shifting of the entrance of the bile duct → ventral bud comes to lie immediately below and behind the dorsal bud
- The ventral bud forms: the uncinate process and inferior part of the head of the pancreas.
- The remaining part of the gland is derived from the dorsal bud.

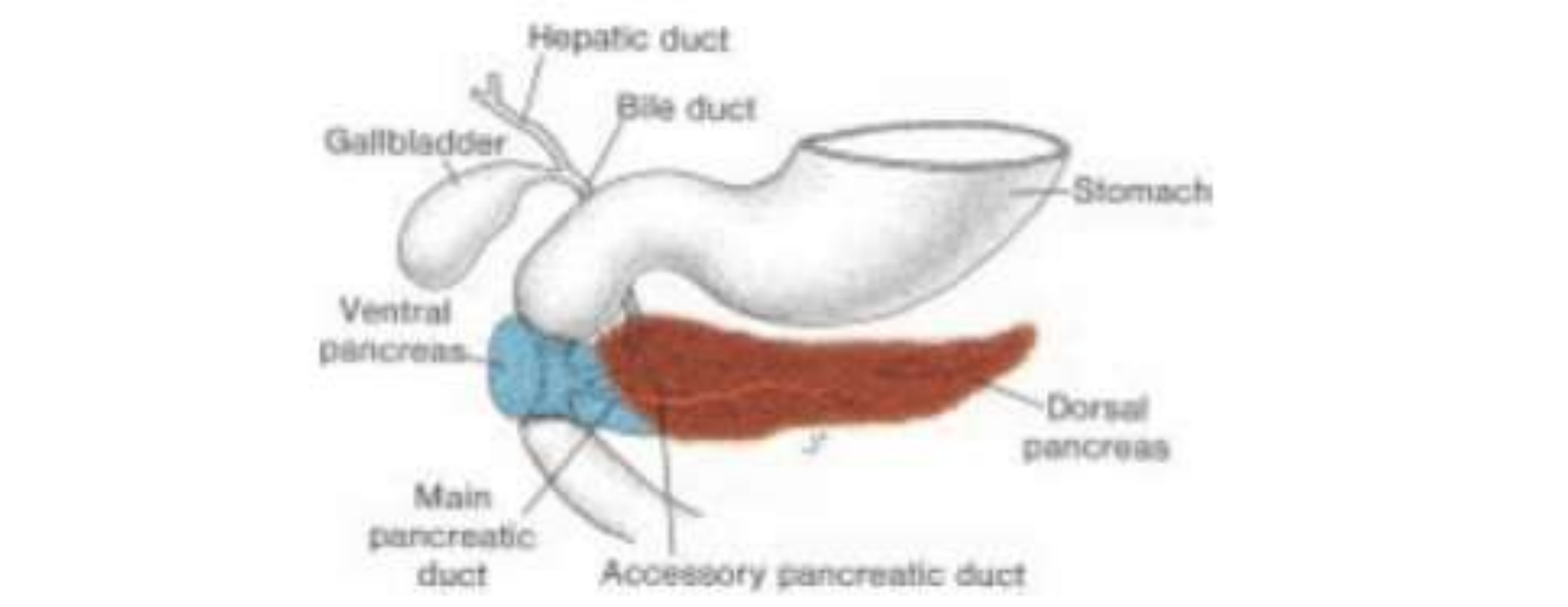
Pancreas Formation





Clinical Correlation

- **Annular Pancreas**



THE LENGTHEN AND DIFUSION OF DORSAL MESOGASTRIUM TO THE DORSAL BODY WALL → CAUSE PANCREAS THAT IS PREVIOUSLY LOCATED IN DORSAL MESOGASTRIUM REACH ITS FINAL POSITION IN POSTERIOR BODY WALL, COVERED BY PERITONEUM ONLY ON ITS ANTERIOR PART → **SECONDARY RETROPERITONEAL**

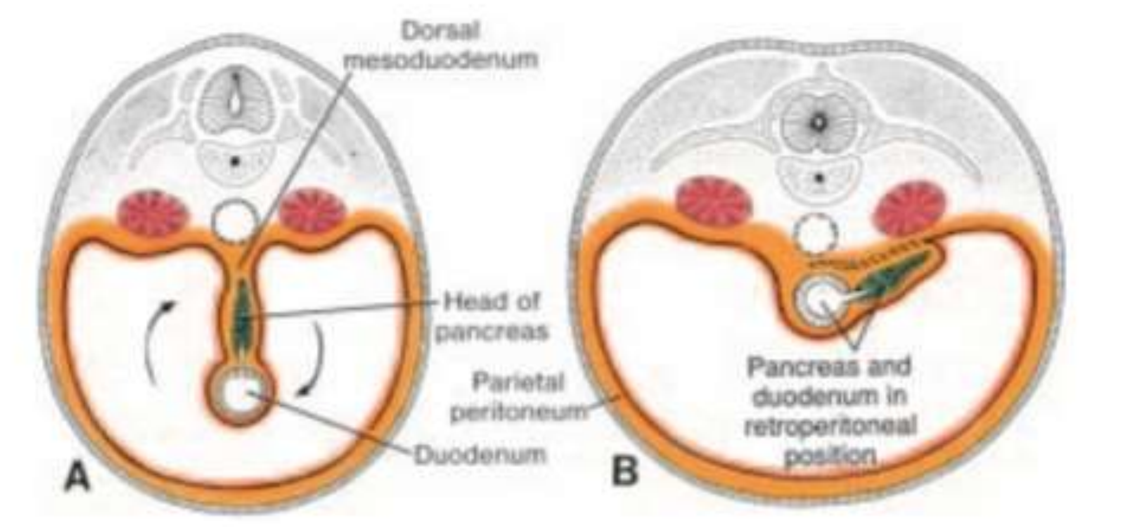


Figure 13.17 Transverse sections through the region of the duodenum at various stages of development. At first the duodenum and head of the pancreas are located in the median plane (**A**), but later they swing to the right and acquire a retroperitoneal position (**B**).

FOREGUT DERIVATION

LIVER and BILLIARY DUCTS

- Transverse Septum : mesoderm pate between pericardium cavity and yolk stalk
- Liver bud grows into the transverse septum, will split the ventral mesentery into:

➢ liver peritoneum

➢ Falciform ligament (inside: umbilical vein → degenerated → lig. Rotundum / lig. Teres hepatis)

➢ Omentum minus → connects liver and duodenum → hepatoduodenalis ligament (inside: portal triad)

- Liver bud grows into transverse septum → connection between liver and duodenum is narrowed → becomes billiary ducts
- Small buds grow in the connection tissue → vesical fellea and cystic duct

Liver Bud Growth

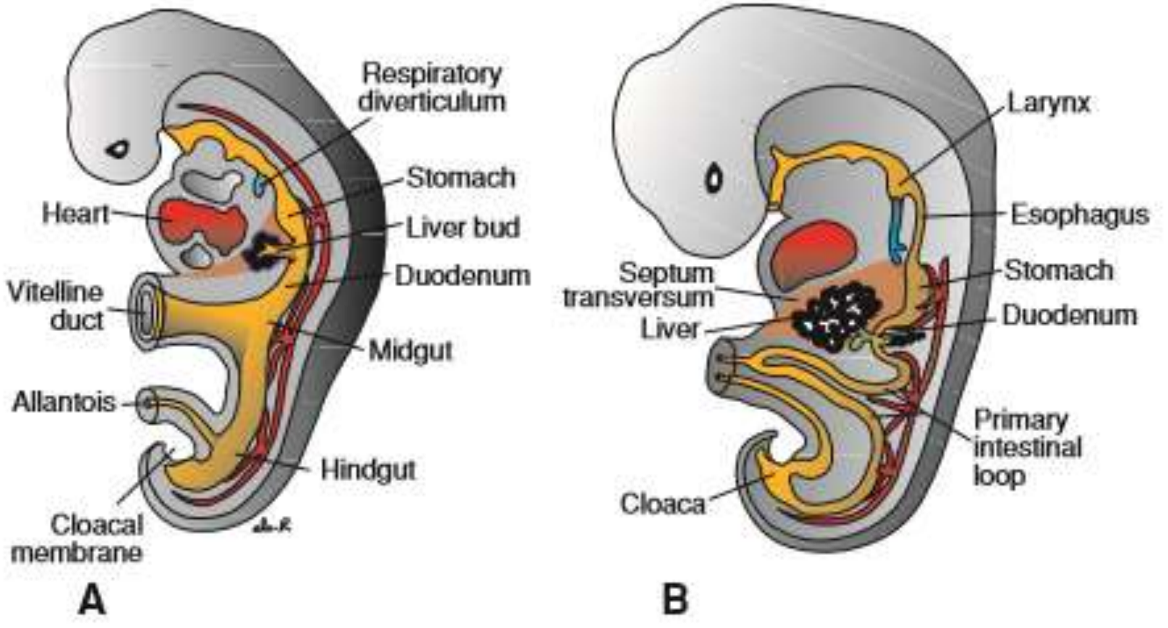


Figure 13.14 A. A 3-mm embryo (approximately 25 days) showing the primitive gastrointestinal tract and formation of the liver bud. The bud is formed by endoderm lining the foregut. **B.** A 5-mm embryo (approximately 32 days). Epithelial liver cords penetrate the mesenchyme of the septum transversum.

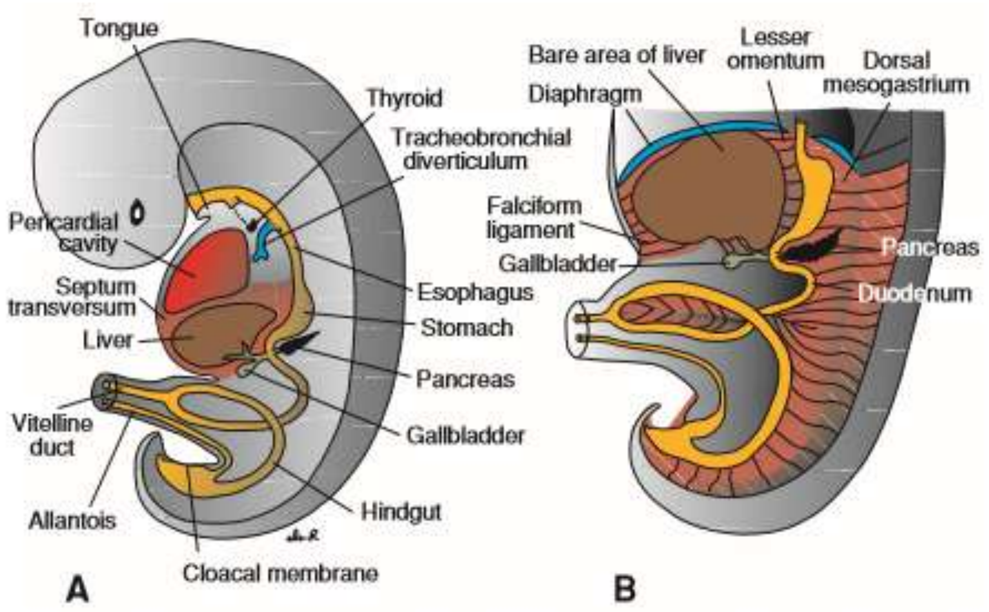


Figure 13.15 A. A 9-mm embryo (approximately 36 days). The liver expands caudally into the abdominal cavity. Note condensation of mesenchyme in the area between the liver and the pericardial cavity, foreshadowing formation of the diaphragm from part of the septum transversum. **B.** A slightly older embryo. Note the falciform ligament extending between the liver and the anterior abdominal wall and the lesser omentum extending between the liver and the foregut (stomach and duodenum). The liver is entirely surrounded by peritoneum except in its contact area with the diaphragm. This is the bare area of the liver.

FOREGUT DEVELOPMENT

- Hepatic cord epitel entangled around vitelline vein → umbilical vein → hepar sinusoid
- Hepatic cords differentiate into parenchyme tissues and tissues that will cover biliary ducts
- Hemopoetic and Kupffer, stroma → derived from mesoderm tissues in transverse septum
- 10th week : liver weight 10% from total body weight → hemopoetic function
- 12th week: bile salt production

MOLECULAR INDUCTION OF LIVER GROWTH

- All of the foregut endoderm has the potential to express liver-specific genes and to differentiate into liver tissue.
- However, this expression is blocked by factors produced by surrounding tissues, including ectoderm, non-cardiac mesoderm, and particularly the notochord
- The action of these inhibitors is blocked in the prospective hepatic region by **fibroblast growth factors (FGFs)** secreted by cardiac mesoderm.
- The cardiac mesoderm "instructs" gut endoderm to express liver specific genes by inhibiting an inhibitory factor of these same genes → cells in the liver field differentiate into both hepatocytes and biliary cell lineages,
- a process that is at least partially regulated by hepatocyte nuclear transcription factors **(HNF3 and 4).**

FOREGUT DEVELOPMENT

- **Clinical case**

✓ atresia of extrahepatic biliary ducts

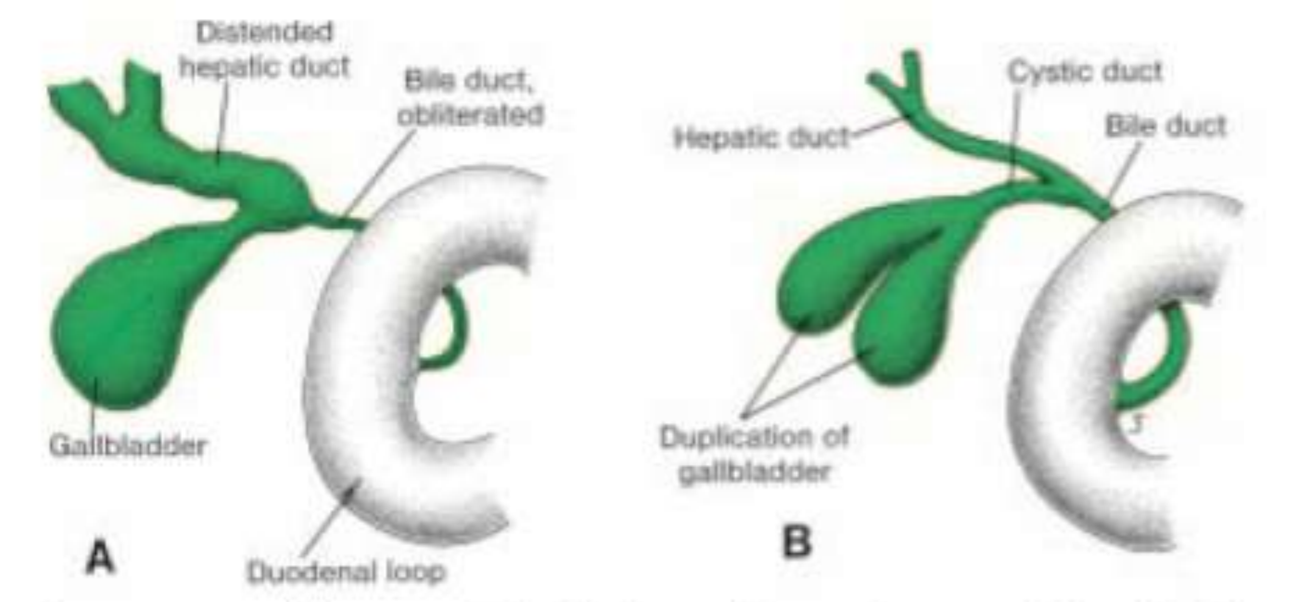


Figure 13.20 A. Obliteration of the bile duct resulting in distention of the gallbladder and hepatic ducts distal to the obliteration. **B.** Duplication of the gallbladder.

FOREGUT DEVELOPMENT

DUODENUM

- Derived from caudal part of foregut and cranial part of midgut
- Due to stomach rotation → duodenum becomes C-shaped and rotates to the right direction (along with caput pancreas growth) → duodenum turns from its center position to the left portion of abdomen → duodenum and pancreas are pressed to the dorsal body wall → secondary retroperitoneal
- Duodenum vascularization: branches of celiac trunk and superior mesentery artery

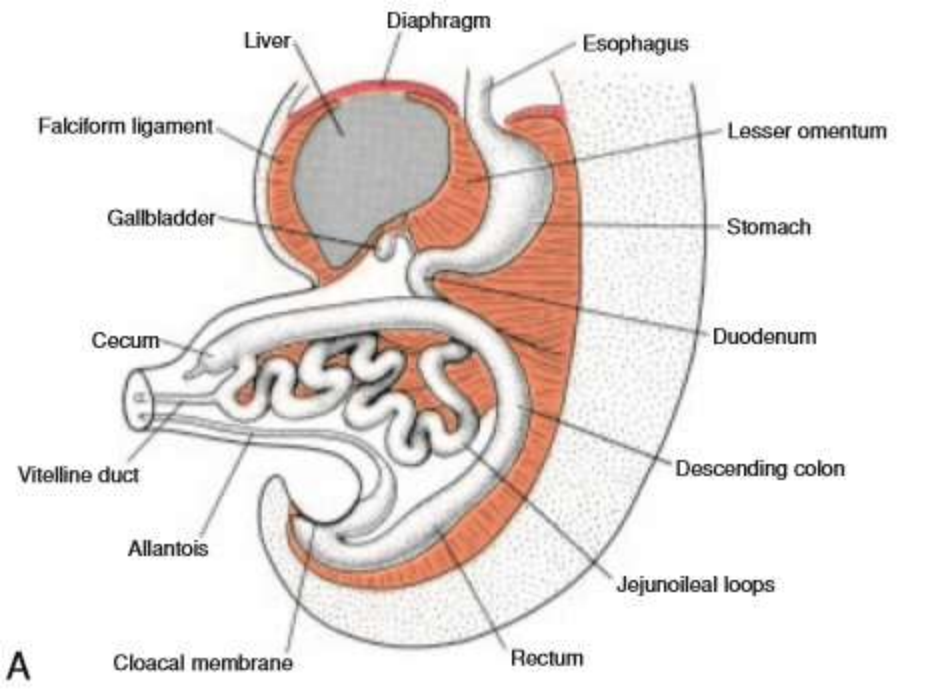
MIDGUT DEVELOPMENT

- Start from distal part of biliary ducts until 2/3 proximal transverse colon
- Fast growing gut and its mesentery → **gut loop**
- Cranial part → still connected with yolk sac through **vitelline duct**
- Cranial part of midgut derives : duodenum (distal part),cranial part of jejenum
- Caudal part of midgut derives: ileum distal, coecum, appendix, ascending colon and 2/3 transverse colon

MIDGUT DERIVATION

PHYSIOLOGIC HERNIA

- 6th week: Primary gut loop grows fast especially in cranial part → loops enter the extraembryonic coelom in umbilical cord (temporarily)
- 10th week gut loops back into the abdominal cavity



MIDGUT DERIVATION

MIDGUT ROTATION

- Axis of Rotation→ superior mesentery artery
- **270°** counter clockwise: 90° → During herniation
- 180° → in the abdomen
- 10th week: herniated gut back into abdomen
- Jejenum comes in first, follows by other parts of the loops and finally part comes in is coecum
- **Coecum** firsty located in right upper quadrant → rotate caudally → right lower quadrant
- During coecum rotation, distal end of coecum forms a amall diverticle -> **primitive appendix**

MIDGUT DERIVATION

GUT MESENTERY

- Change position due to gut rotation
- In ascending and descending part of colon, mesentery are pressed to the posterior body wall → becomes retroperitoneal organs
- Intraperitoneal organs → transverse colon, coecum, appendix

Mesentery attachment to the posterior body wall

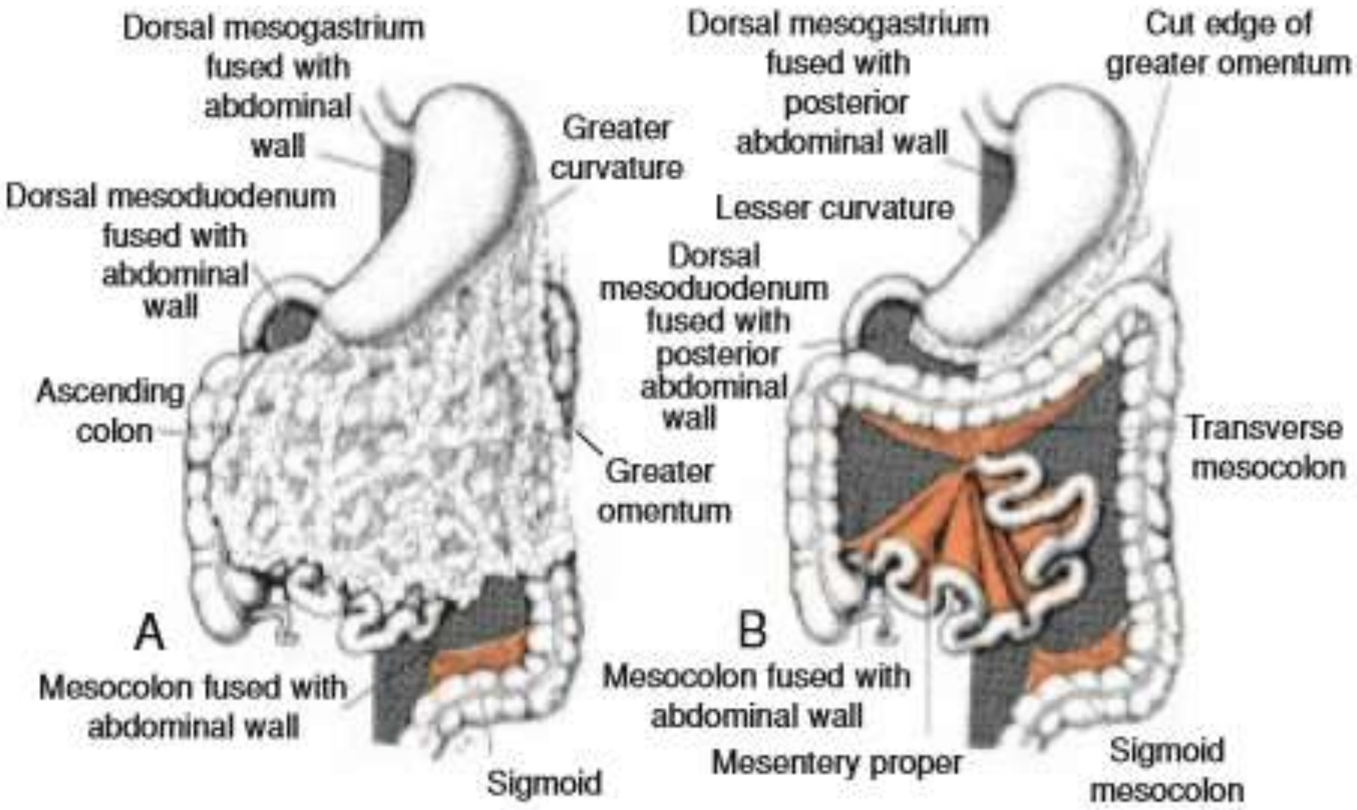


Figure 13.30 Frontal view of the intestinal loops with (**A**) and after removal of (**B**) the greater omentum. *Gray areas*, parts of the dorsal mesentery that fuse with the posterior abdominal wall. Note the line of attachment of the mesentery proper.

MIDGUT DERIVATION

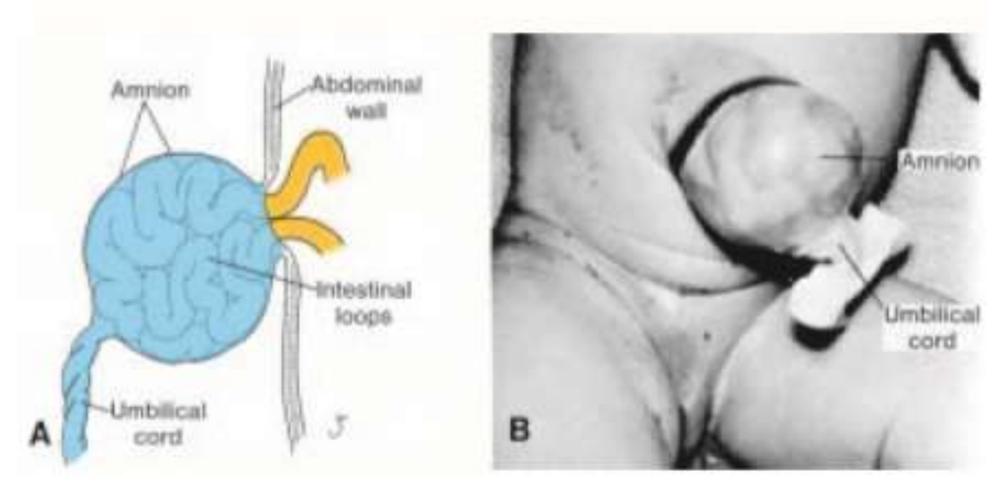
- **CLINICAL Correlation**

✓OMPHALOCELE:

herniation of abdominal viscera through an enlarged umbilical ring. The viscera, which may include liver, small and large intestines, stomach, spleen, or gallbladder, are covered by amnion

✓GASTROSCHISIS

Herniation of abdominal contents through the body wall directly into the amniotic cavity. It occurs lateral to the umbilicus usually on the right, through a region weakened by regression of the right umbilical vein, which normally disappears



MIDGUT DEVELOPMENT

- ✓MECKEL DIVERTICLE
- ✓VITELINE CYST
- ✓VITELINE FISTULE

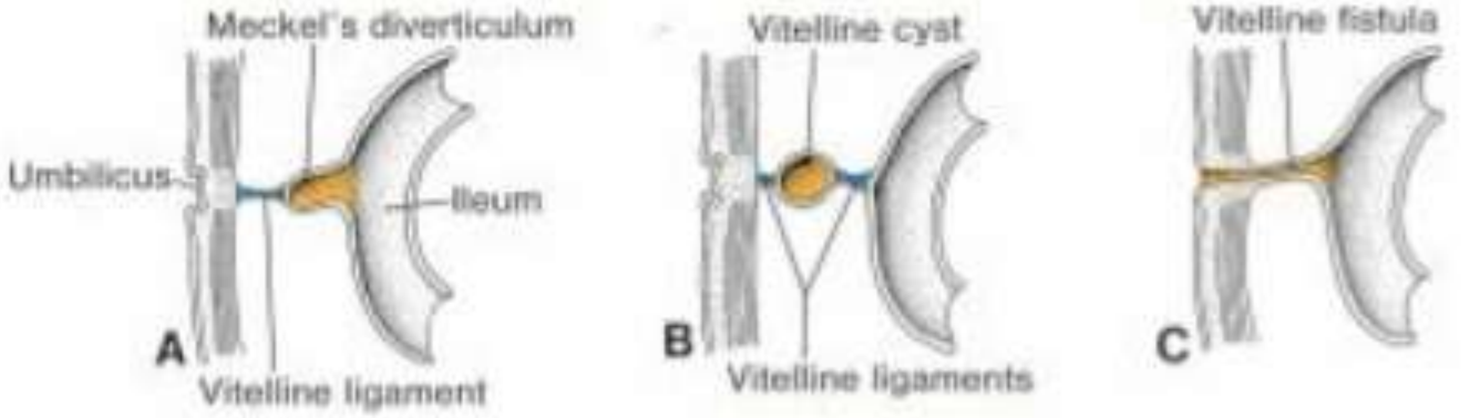


Figure 13.32 Remnants of the vitelline duct. **A.** Meckel's, or ileal, diverticulum combined with fibrous cord (vitelline ligament). **B.** Vitelline cyst attached to the umbilicus and wall of the ileum by vitelline ligaments. **C.** Vitelline fistula connecting the lumen of the ileum with the umbilicus.

- Gut Rotation Defects

✓ Abnormal rotation of the intestinal loop may result in twisting of the intestine (**volvulus**) and a compromise of the blood supply

✓ **Reversed rotation** of the intestinal loop occurs when the primary loop rotates 90◦ clockwise

✓ Duplications of intestinal loops and cysts

HINDGUT DEVELOPMENT

- Give rises to : **2/3 transverse colon, descending colon, sigmoid colon and upper part canal anal**
- The terminal portion of the hindgut enters into the posterior region of the cloaca, the primitive anorectal canal;
- the allantois enters into the anterior portion, the primitive urogenital sinus
- cloaca itself is an endoderm-lined cavity covered at its ventral boundary by surface ectoderm. This boundary between the endoderm and the ectoderm forms the cloacal membrane

HINDGUT DERIVATION

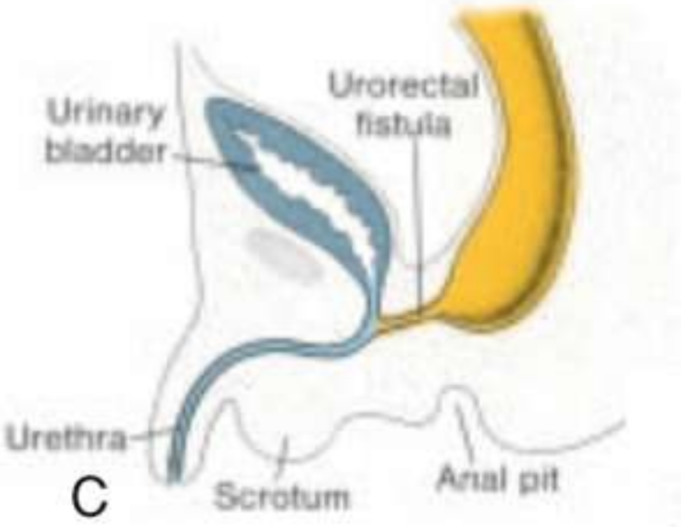
- A layer of mesoderm,the **urorectal septum**, separates the region between the allantois and hindgut
- 7th week: , the **cloacal membrane ruptures**, creating the anal opening for the hindgut and a ventral opening for the urogenital sinus
- the caudal part of the anal canal originates in the ectoderm, and it is supplied by the inferior rectal arteries, branches of the internal pudendal arteries
- The cranial part of the anal canal originates in the endoderm and is supplied by the superior rectal artery, a continuation of the inferior mesenteric artery
- The junction between the endodermal and ectodermal regions of the anal canal is delineated by the pectinate line

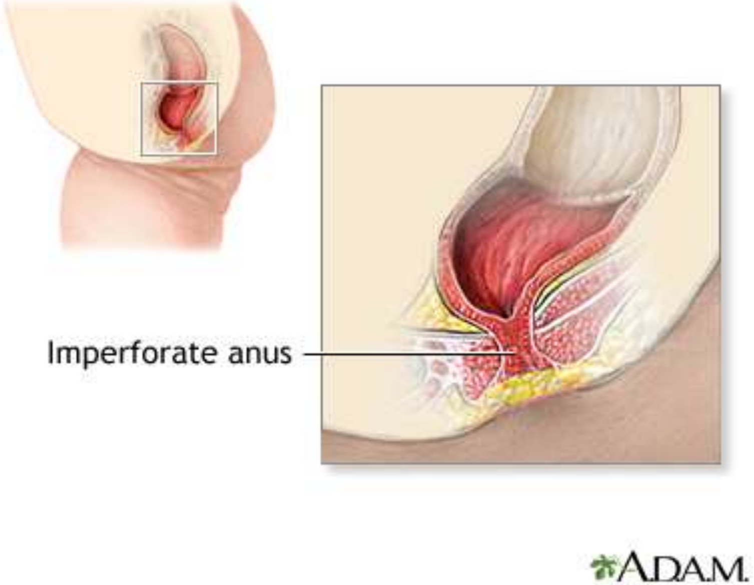
HINDGUT DERIVATION

- **Rectoanal atresias**, and **fistulas**, abnormalities in formation of the cloaca, due to ectopic positioning of the anal opening
- **imperforate anus**, no anal opening lack of recanalization of the lower portion of the anal canal
- **Congenital megacolon** is due to an absence of parasympathetic ganglia in the bowel wall (aganglionic megacolon or **Hirschsprung disease**)

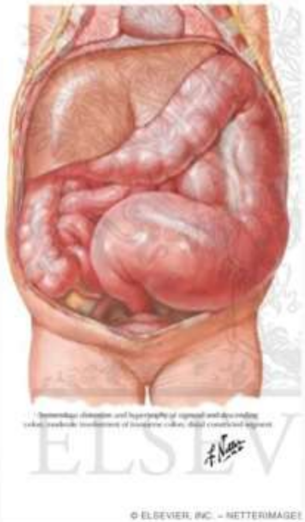
→ *Mutations in the RET gene, a tyrosine kinase receptor involved in crest cell migration*

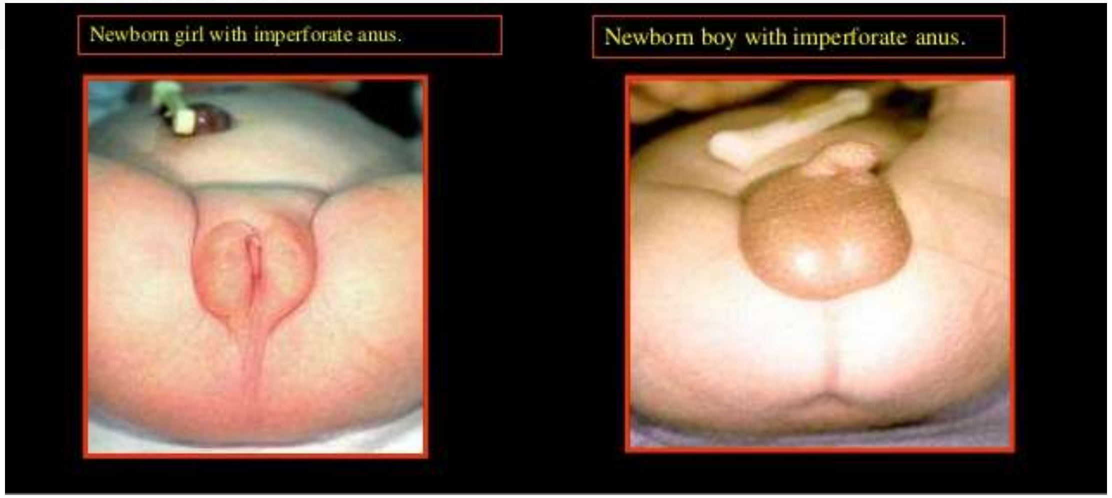
Urorectal fistula





Hirschsprungs Disease





GIT Development and Vascularization

- **Foregut**
  - The abdominal esophagus
  - The stomach
  - Proximal half of the duodenum
  - The spleen
  - The liver, gallbladder
  - Pancreas

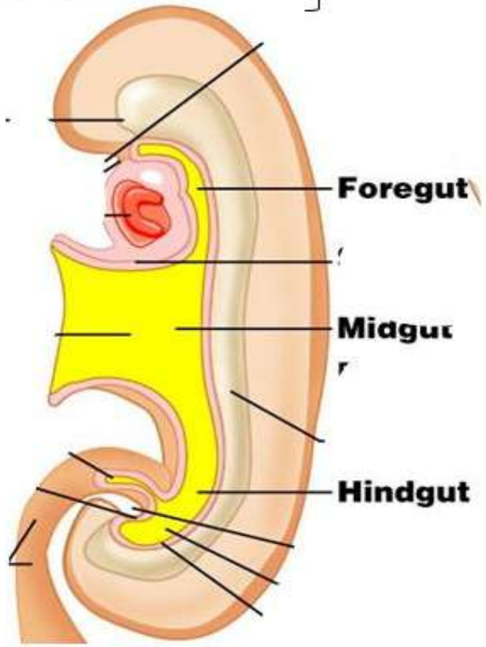
Celiac trunk

- **Midgut**
  - Second half of the duodenum
  - Jejunum, ileum
  - Cecum, appendix
  - Ascending colon
  - Transverse colon (proximal 2/3)

SMA

- **Hindgut**
  - Left portion of the tranverse colon
  - Descending colon
  - Sigmoid colon
  - The rectum

IMA



SUMMARY

- The epithelium of the digestive system and the parenchyma of its derivatives originate in the endoderm;
- connective tissue, muscular components, and peritoneal components originate in the mesoderm
- The gut system extends from the buccopharyngeal membrane to the cloacal membrane divided into the pharyngeal gut, foregut, midgut, and hindgut
- The **foregut** gives rise to the esophagus, the trachea and lung buds, the stomach, and the duodenum proximal to the entrance of the bile duct
- liver, pancreas, and biliary apparatus develop as outgrowths of the endodermal epithelium of the upper part of the duodenum

SUMMARY

- The **midgut** forms the primary intestinal loop gives rise to the duodenum distal to the entrance of the bile duct, and continues to the junction of the proximal two-thirds of the transverse colon
- The **hindgut** gives rise to the region from the distal third of the transverse colon to the upper part of the anal canal; the distal part of the anal canal originates from ectoderm

END OF TODAY'S LECTURE,

ANY QUESTION…?