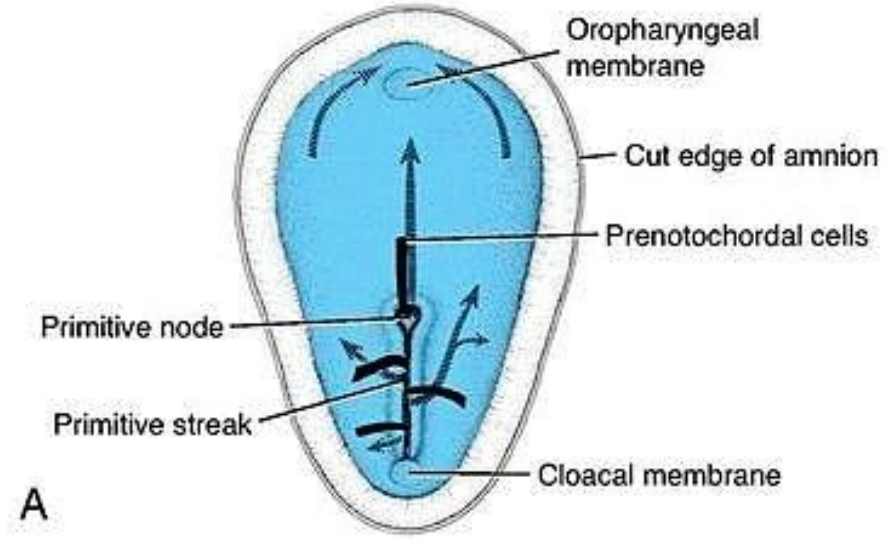
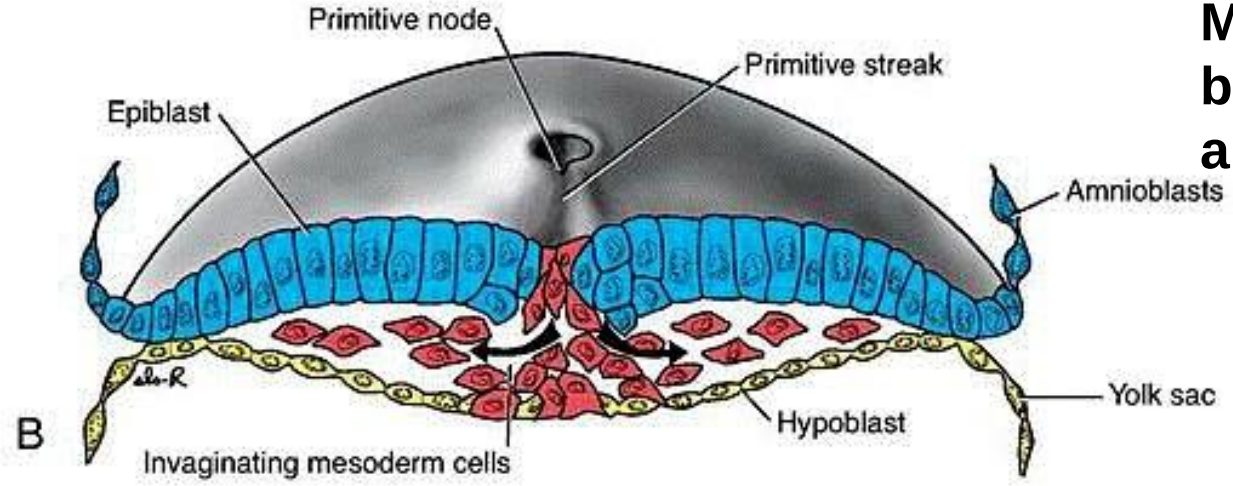
Development of the Gastrointestinal System

DR SHAHAB

Gastrulation:





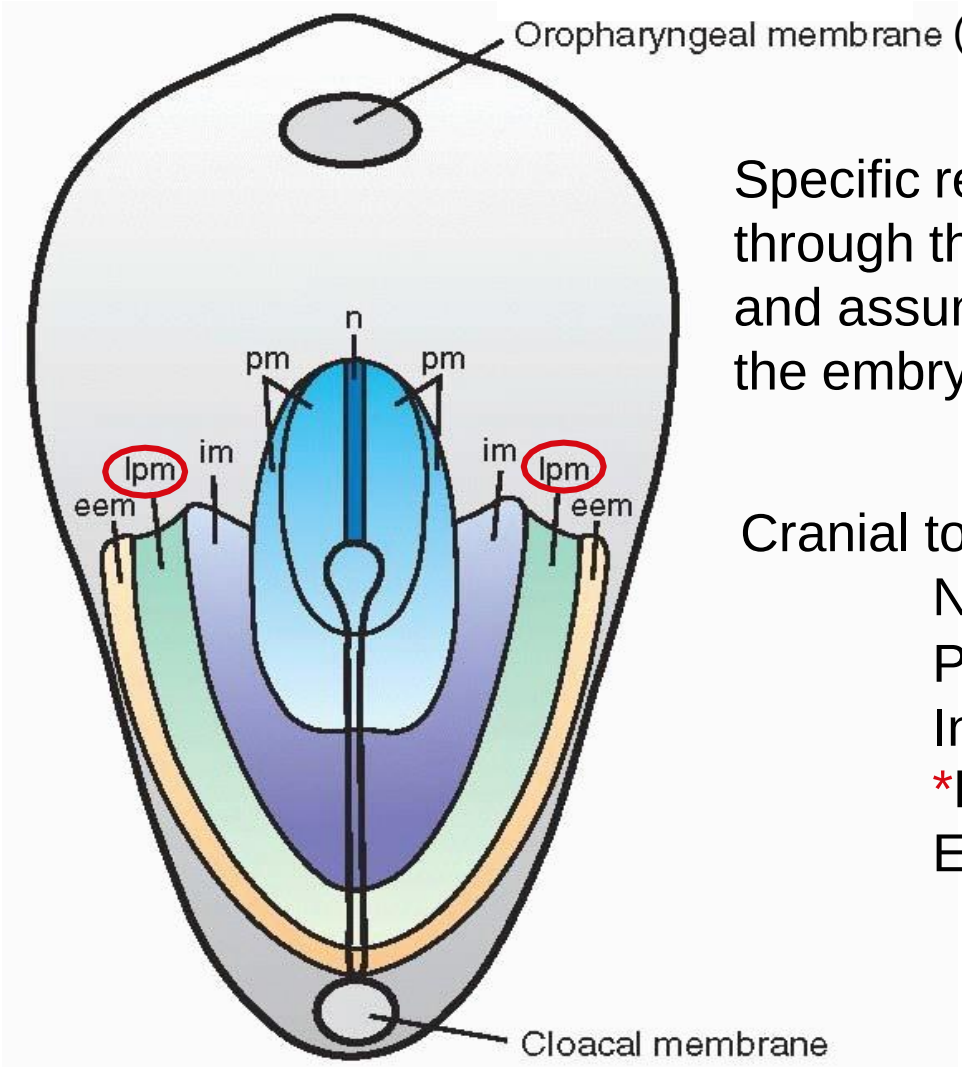
Epiblast cells migrate through the primitive streak.

Definitive (embryonic) endoderm cells displace the hypoblast.

Mesoderm spreads between endoderm and ectoderm.

 Langman's Medical Embryology, 9th ed. 2004.

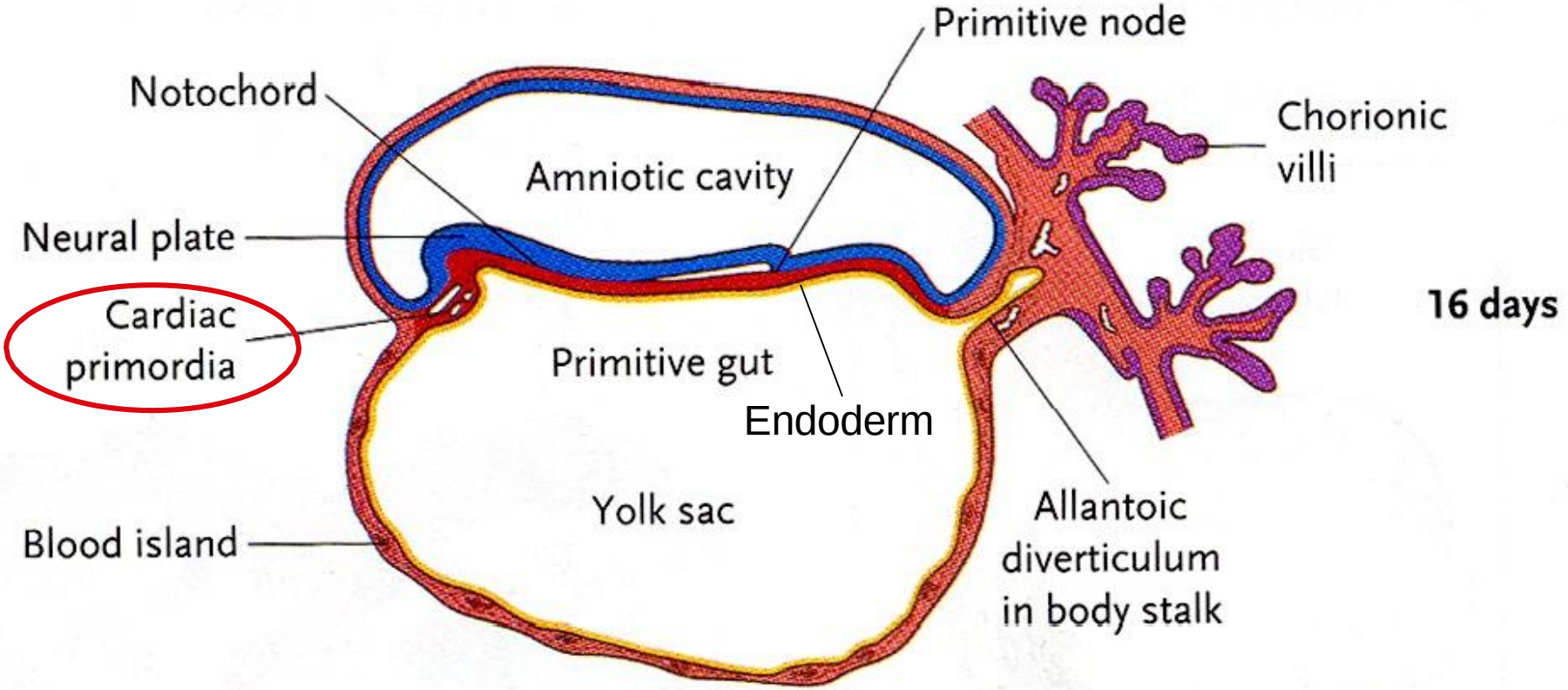
Early mesodermal patterning:



Specific regions of the epiblast migrate through the streak at different levels and assume different positions within the embryo:

Cranial to caudal:

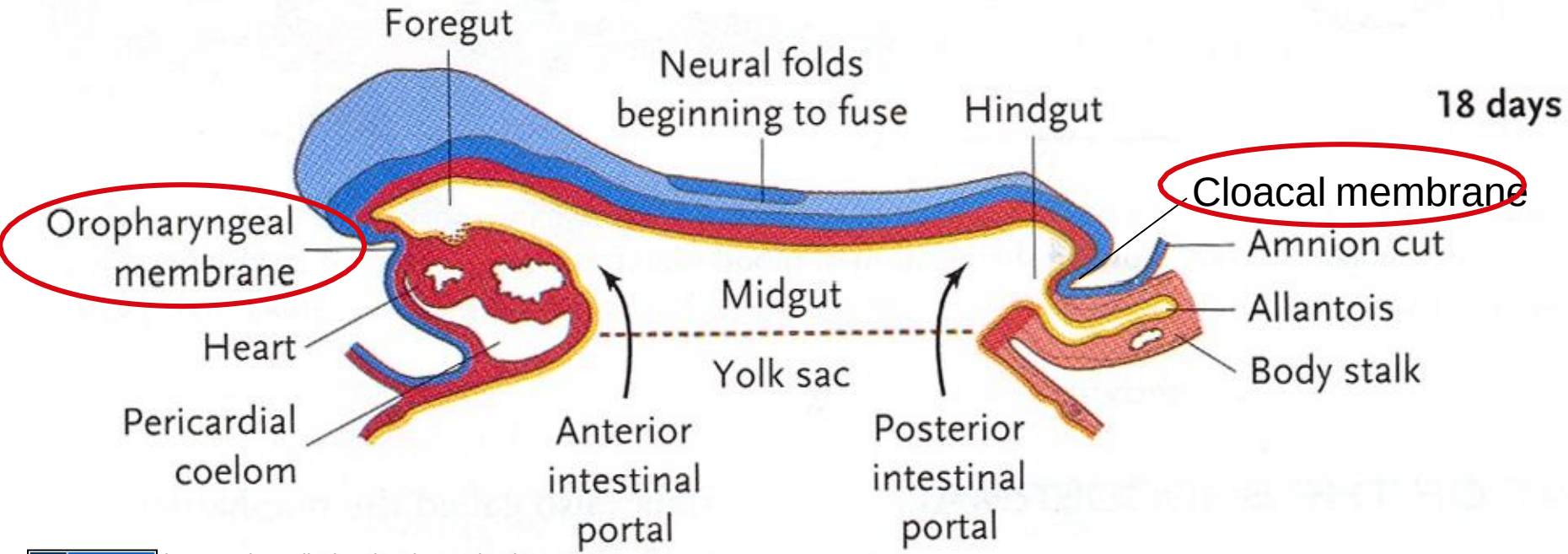
Notochord (n)
Paraxial mesoderm (pm)
Intermediate mesoderm (im)
*Lateral plate mesoderm (lpm)
Extraembryonic mesoderm (eem)



 Langman's Medical Embryology, 9th ed. 2004.

The developing endoderm (yellow) is initially open to the yolk sac (the cardiac region is initially most anterior)…

Longitudinal folding at both ends of the embryo and lateral folding at the sides of the embryo bring the endoderm inside and form the gut tube.



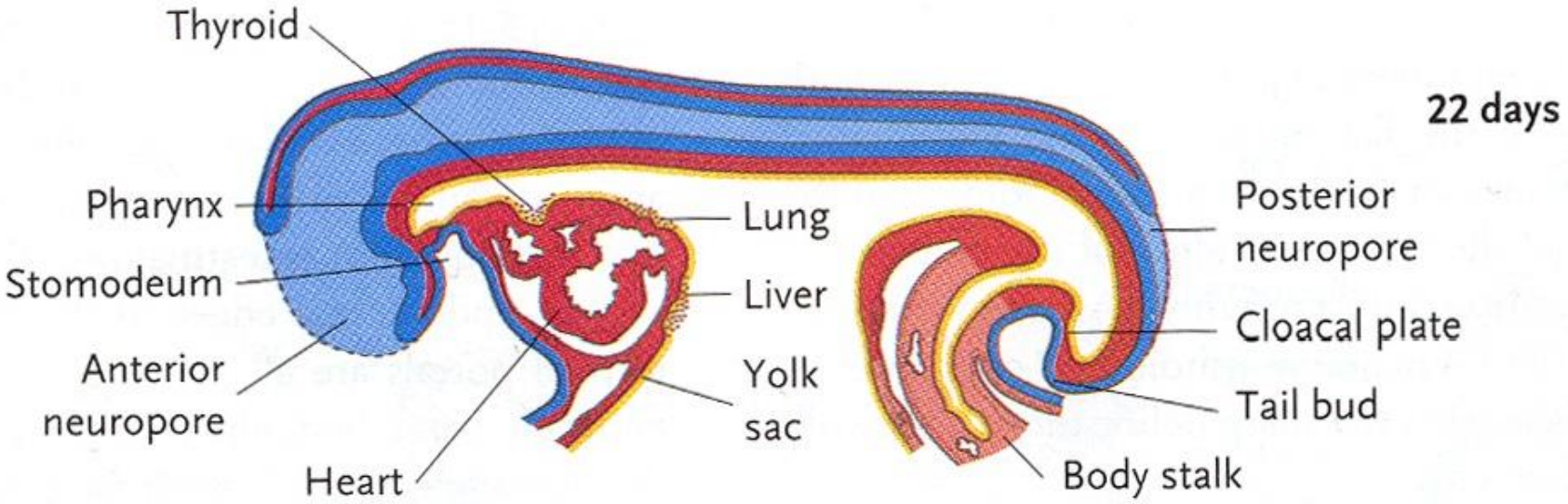
 Langman's Medical Embryology, 9th ed. 2004.

Folding creates the anterior and posterior intestinal portals (foregut and hindgut, respectively)

The cardiac region is brought to the ventral side of the developing gut tube.

Juxtaposition of ectoderm and endoderm at:

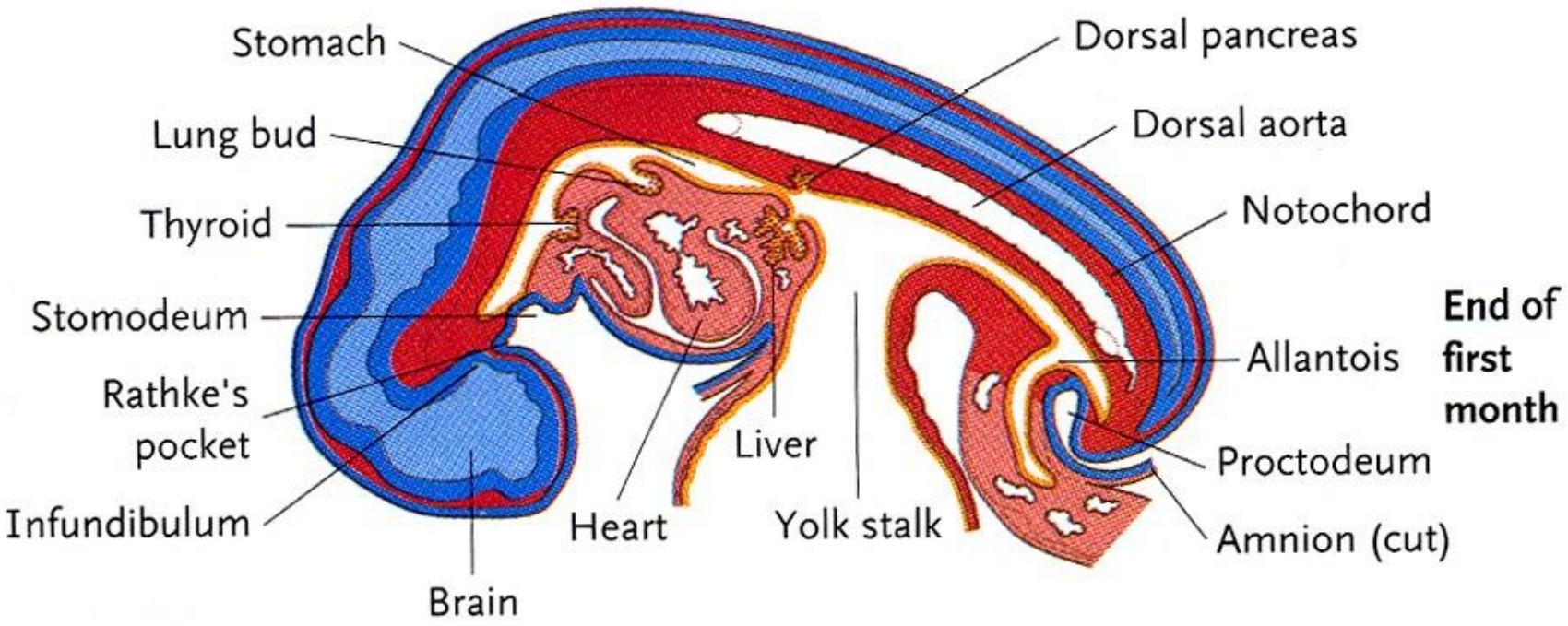
Oropharyngeal (buccopharyngeal) membrane - future mouth
Cloacal membrane - future anus



 Langman's Medical Embryology, 9th ed. 2004.

Gut-associated organs begin to form as buds from the endoderm: (e.g., thyroid, lung, liver, pancreas)

Midgut opening to the yolk sac progressively narrows



 Langman's Medical Embryology, 9th ed. 2004.

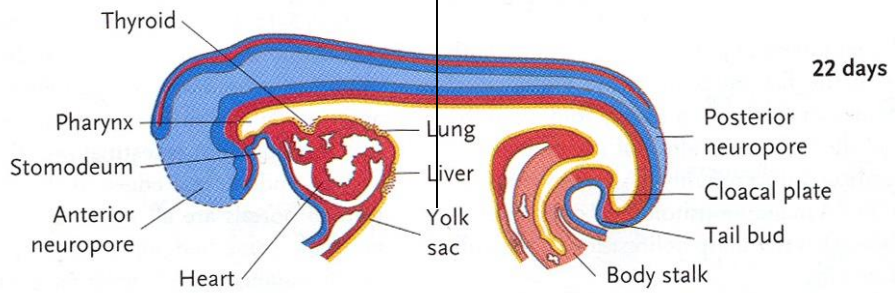
By the end of the first month:

The stomach bulge is visible,

Dorsal pancreas has begun to bud

Connection of the midgut to the yolk sac is reduced to a yolk stalk

With lateral folding, mesoderm is recruited to gut wall



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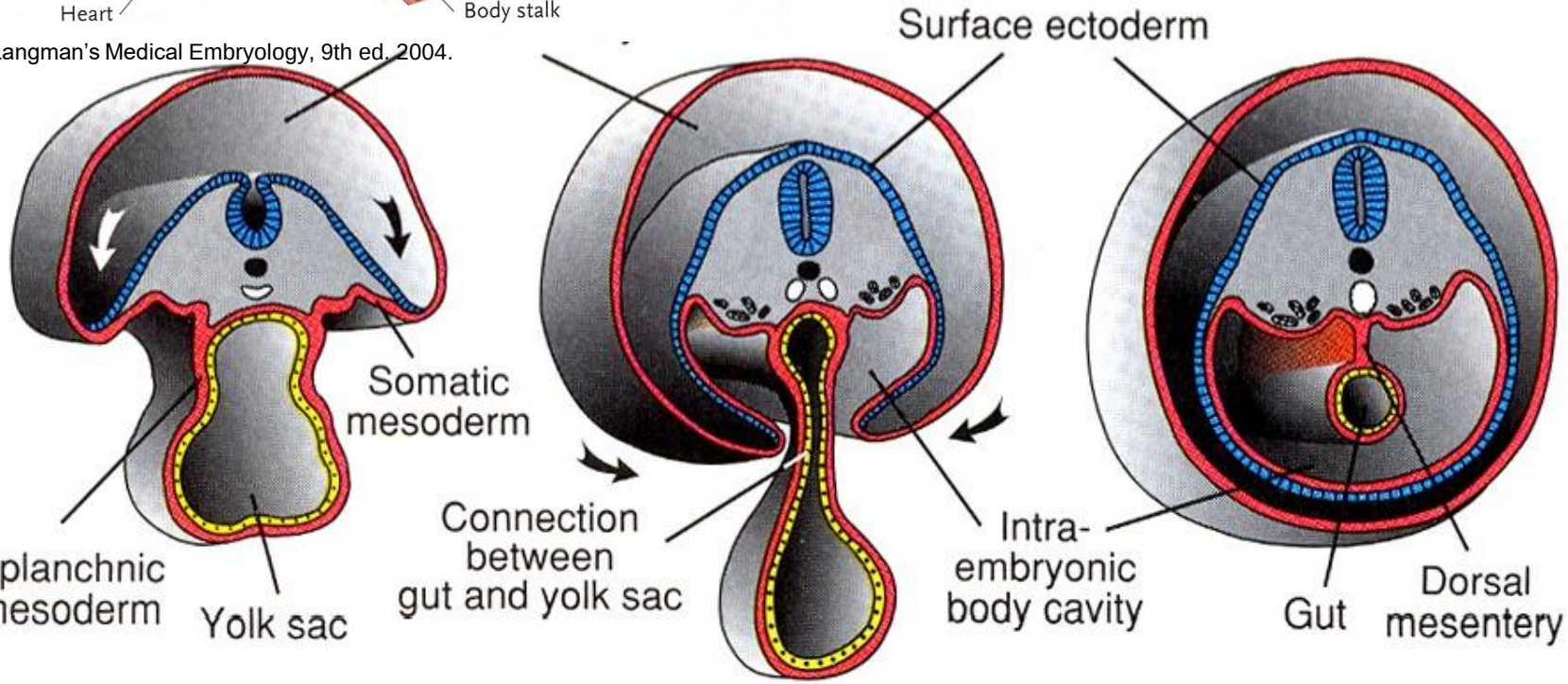

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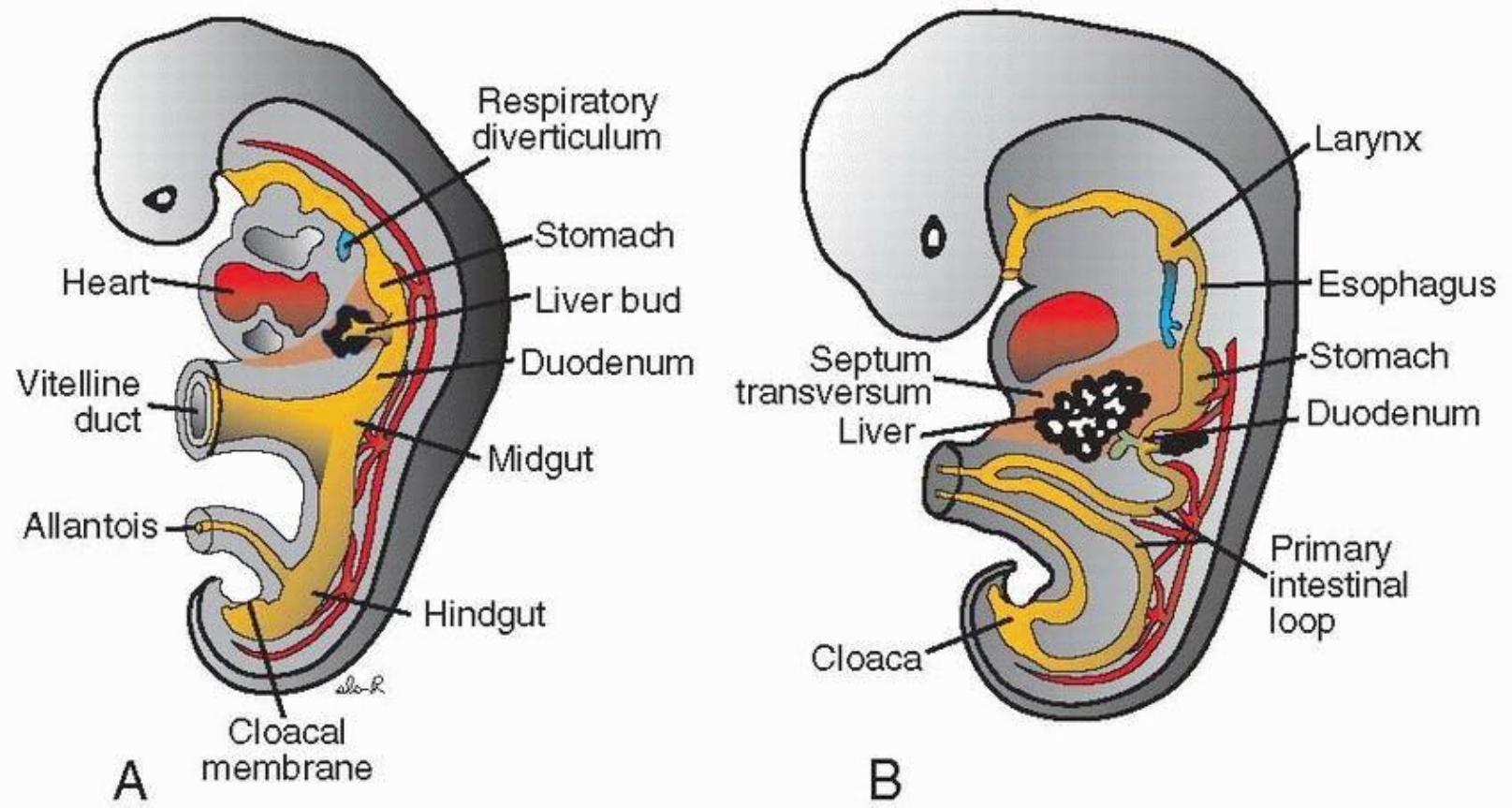
- Lateral folding of the embryo completes the gut tube
- Mesodermal layer of the gut tube is called splanchnic (visceral) mesoderm - derived from lateral plate mesoderm
- Somatic mesoderm lines body cavity

	Gut tube proper	Derivatives of gut tube
Foregut:	pharynx esophagus stomach proximal duodenum	thyroid parathyroid glands tympanic cavity trachea, bronchi, lungs liver, gallbladder pancreas
Midgut:	proximal duodenum to right half of transverse colon	
Hindgut:	left half of transverse colon to anus	urinary bladder

(These three regions are defined by their blood supply)

25 days **32 days**



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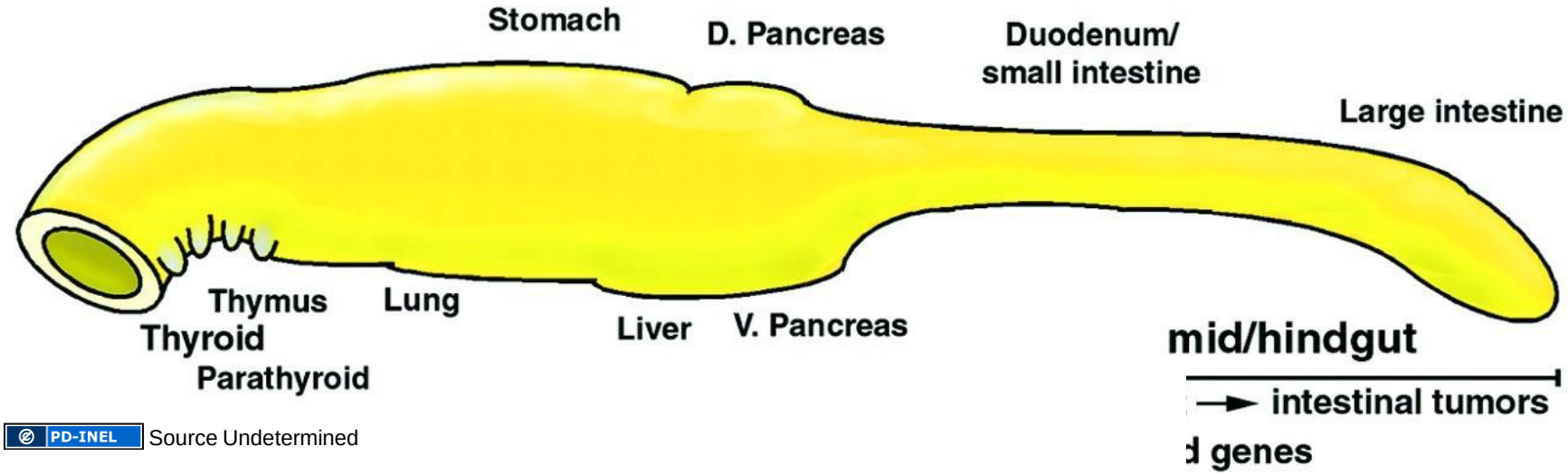
Celiac artery supplies the foregut
Superior mesenteric artery supplies the midgut
Inferior mesenteric artery supplies the hindgut

Regional patterning of the gut tube



Gut = bilayered tube (endoderm surrounded by mesoderm)

Regional gut tube patterning and organogenesis require bi-directional endoderm-mesoderm cross-talk and inductive signals from other nearby structures

Regional patterning of the gut tube - the Hox code

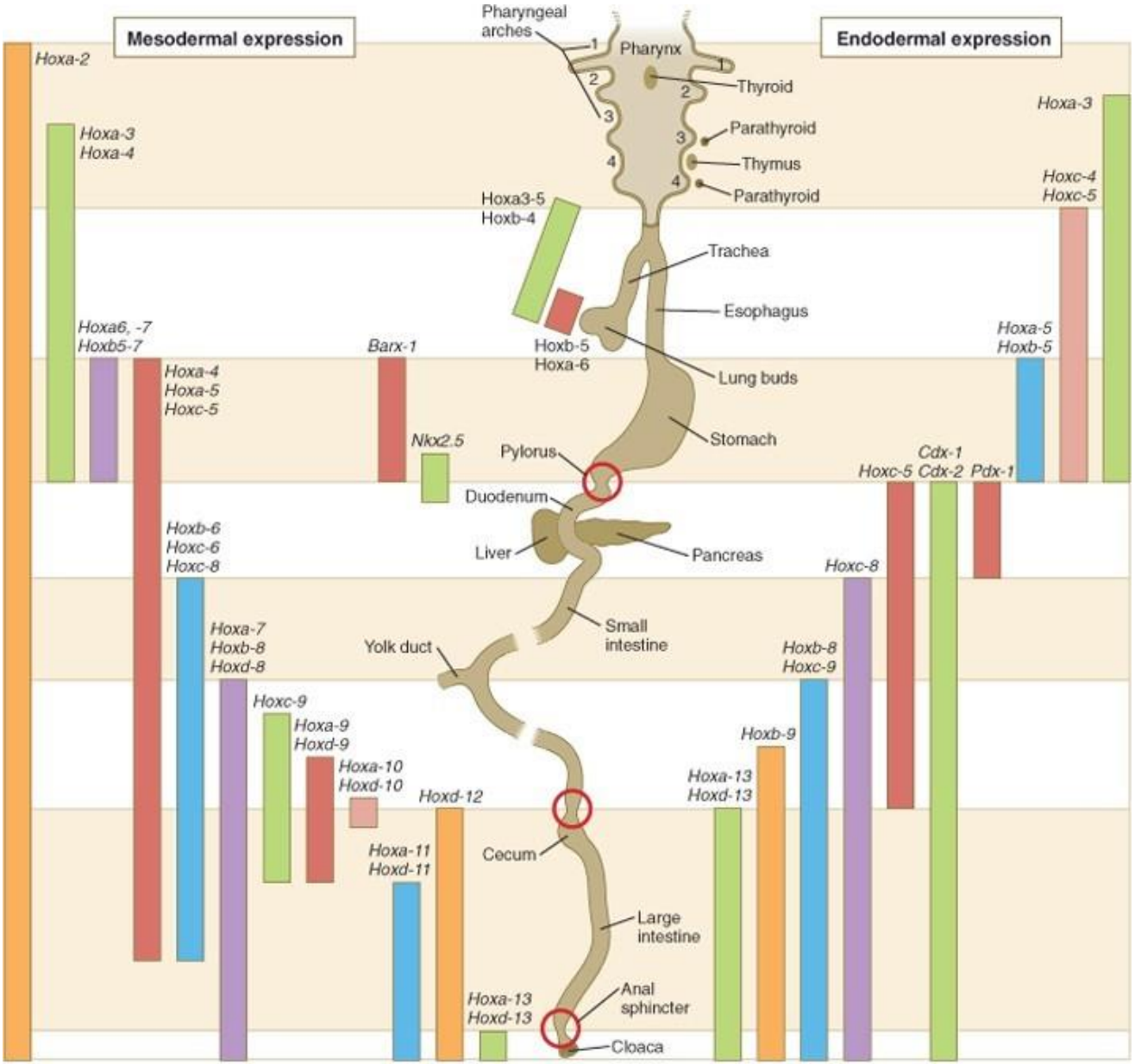
Hox genes are evolutionarily conserved transcription factors that are used in regional patterning (flies to mammals).

The gut has an cranial-caudal Hox gene expression pattern (code) similar to that seen in neural tissue.

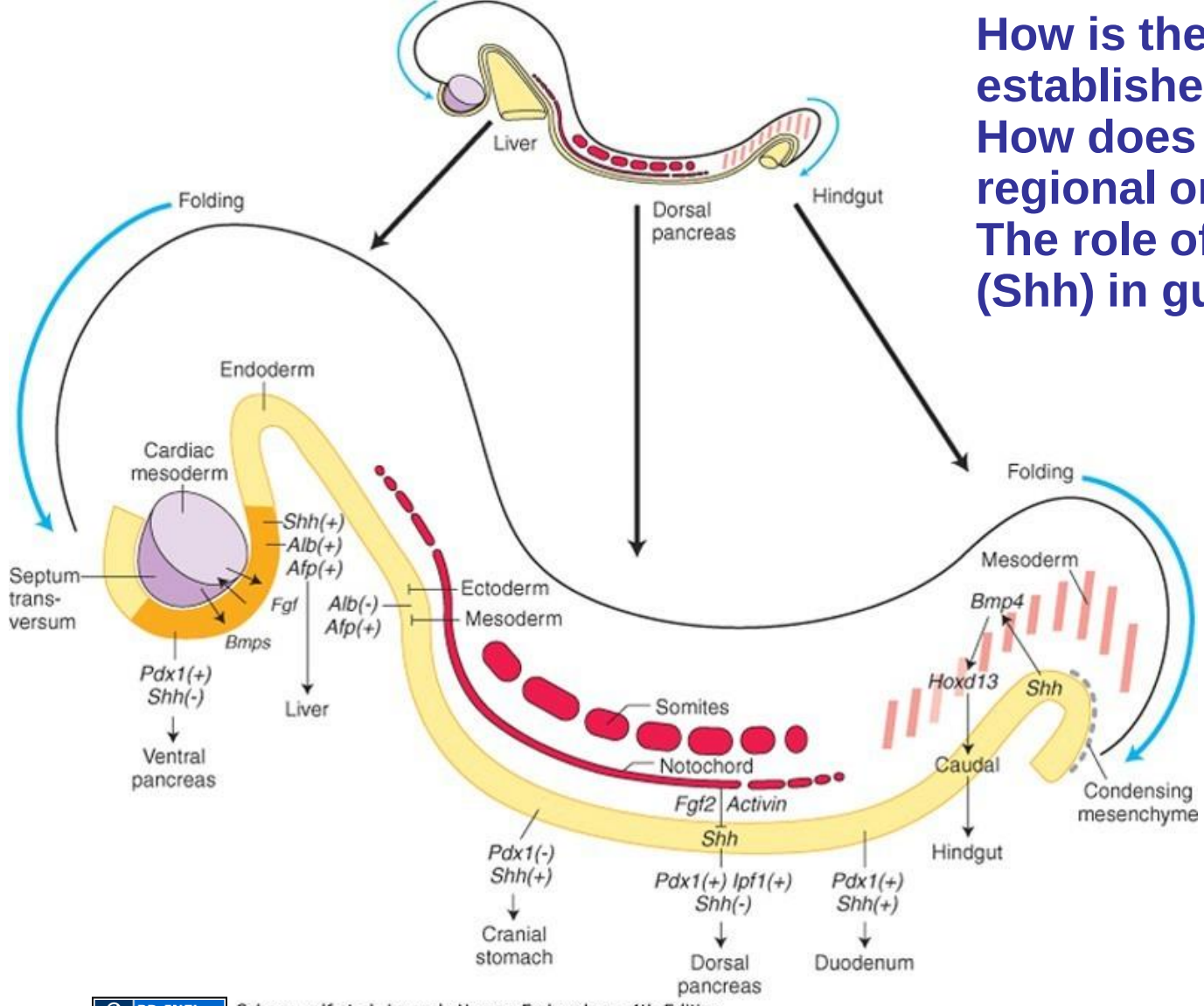
Some Hox genes are expressed in mesoderm, in overlapping patterns; some are expressed in endoderm.

Hox gene expression boundaries correspond to morphologically recognizable elements in the GI tract.

Hox gene expression is important for formation of major sphincters (red circles)



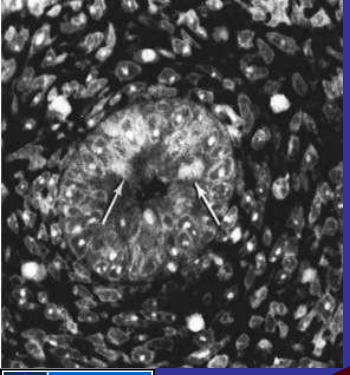
How is the patterning established?
How does it play out in regional organogenesis?
The role of Sonic hedgehog (Shh) in gut patterning….



Regulatory networks in time and space:

- Regional variation in regulatory pathways due to:
- Regional variation in competence (induction of mesodermal Hoxd-13 by Shh)
- Temporal variation in signaling (restriction of BMP from stomach mesoderm)

Hedgehog signaling is important for concentric (radial) patterning of the entire gut tube



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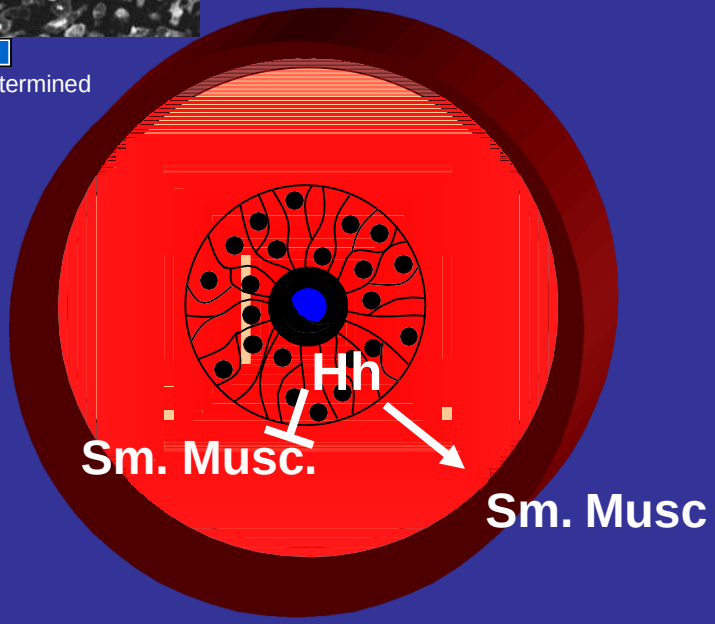
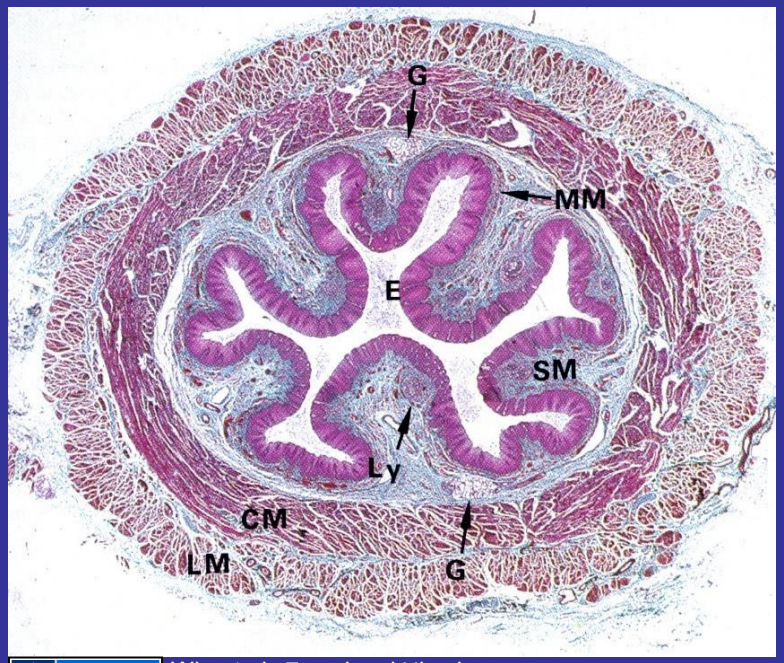


Fetus

PD-INEL M. Velkey.



PD-INEL Wheater's Functional Histology

Adult Esophagus

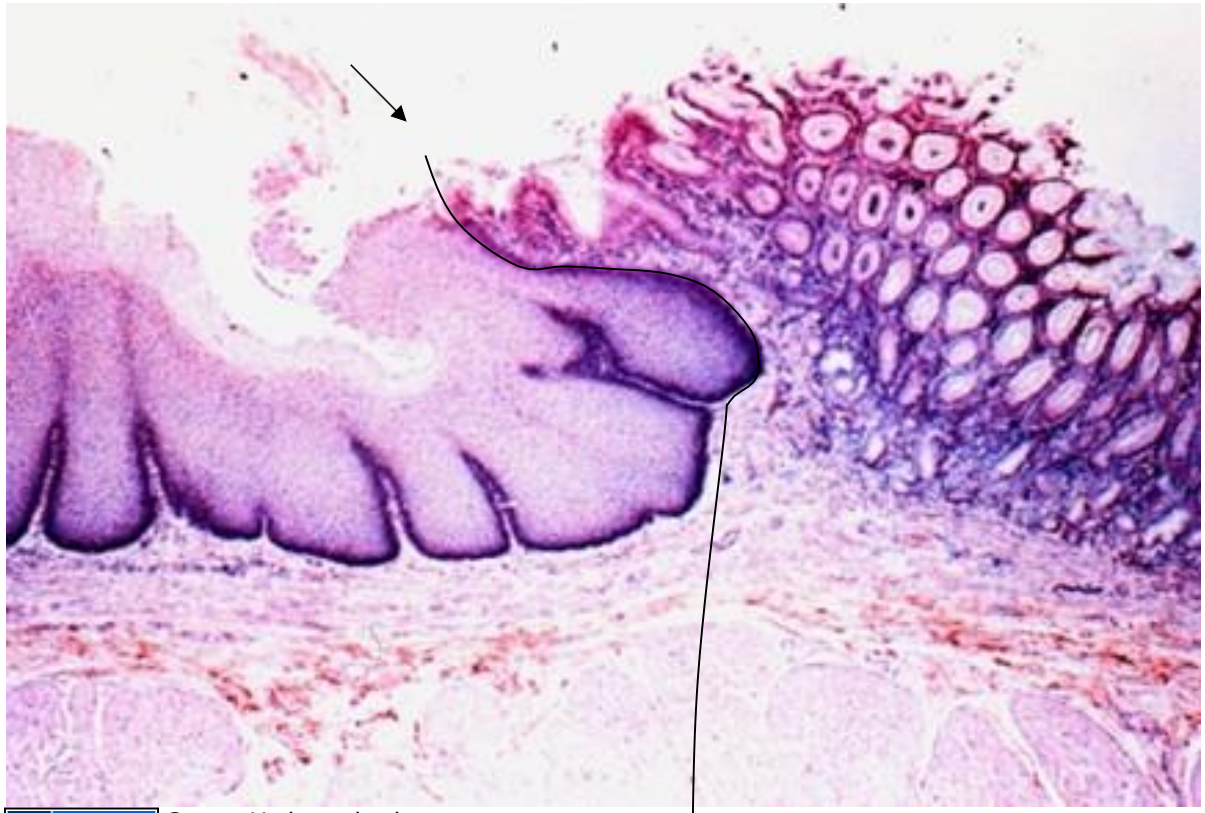
High Hedgehog concentration inhibits muscle formation;

Low Hedgehog concentration stimulates muscle differentiation

Morphogen: induces different cell fates at different concentrations of signal

Cranial-caudal pattern of the gut tube is played out as regional organ differentiation. Distinct borders form.

Esophageal/Gastric border



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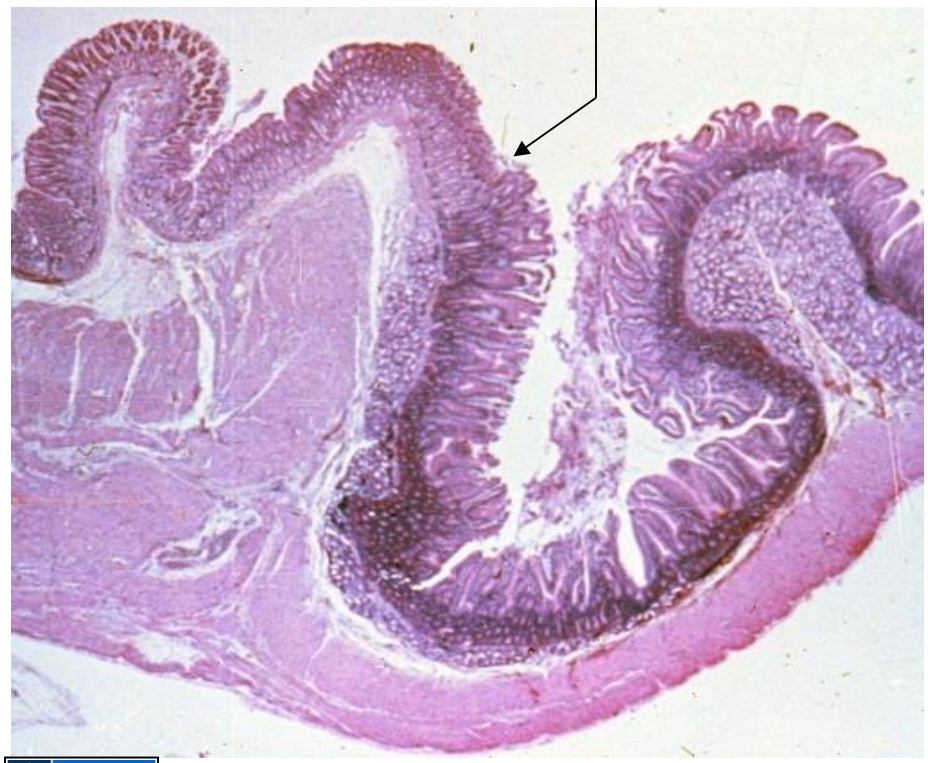
Esophagus | Stomach

CRANIO-CAUDAL PATTERNING OF THE GUT TUBE

Specific regions of the gut tube (i.e. that which will become lung vs. that which become esophagus vs. stomach, etc.) and important junctions (e.g. gastroesophageal junction) are established by a cranial to caudal pattern of segmental, combinatorial "codes" of HOX gene expression in the endoderm and mesoderm of the early embryo.

Pyloric border (gastric/duodenal)

Stomach | Duodenum



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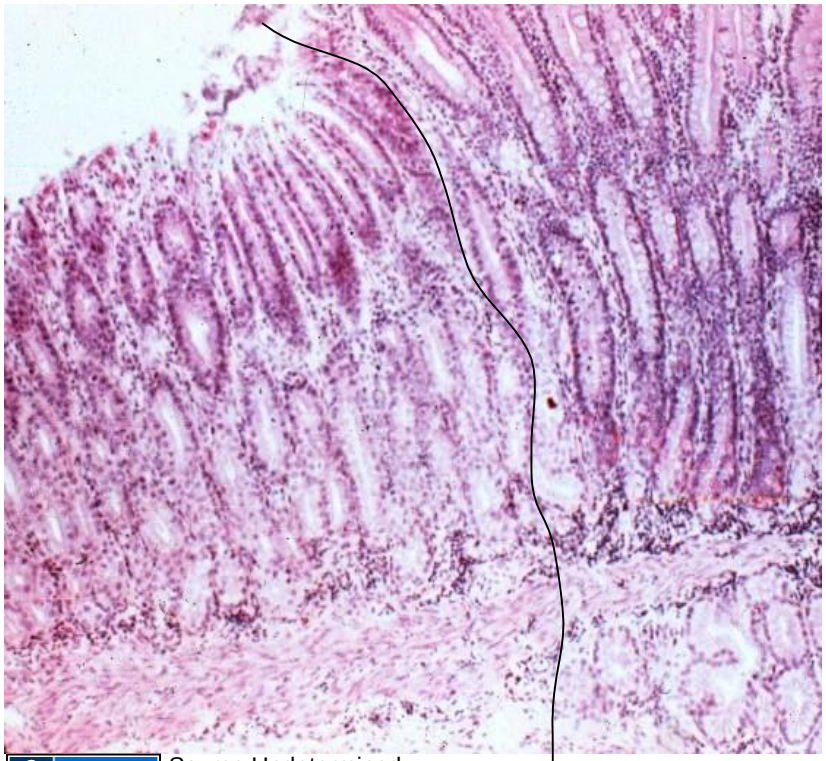

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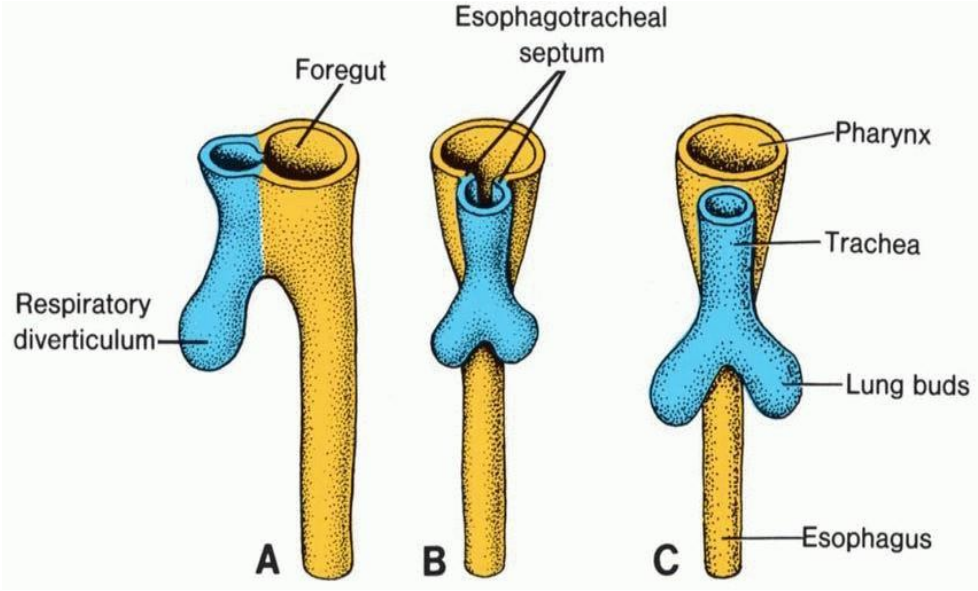
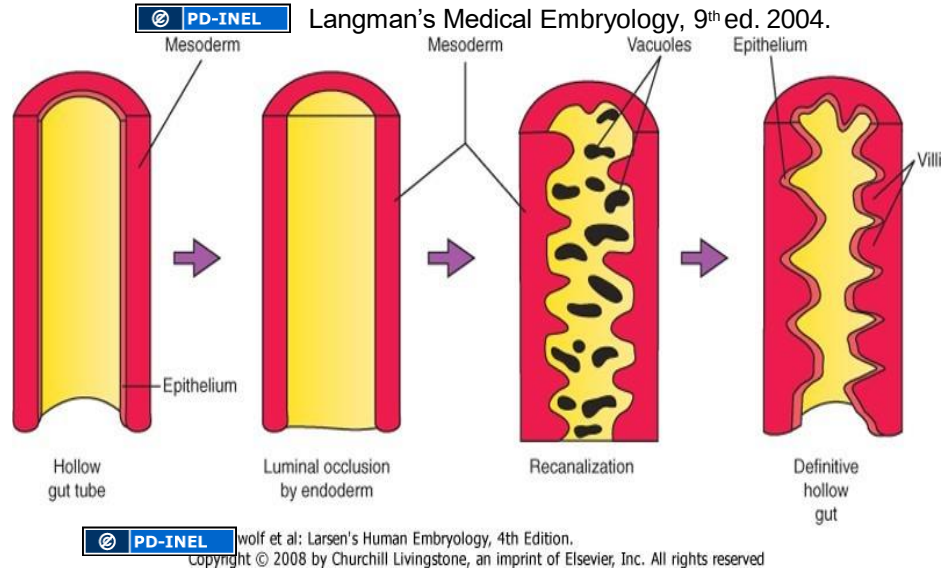
Stomach | Duod.

Regional Organogenesis: Esophagus





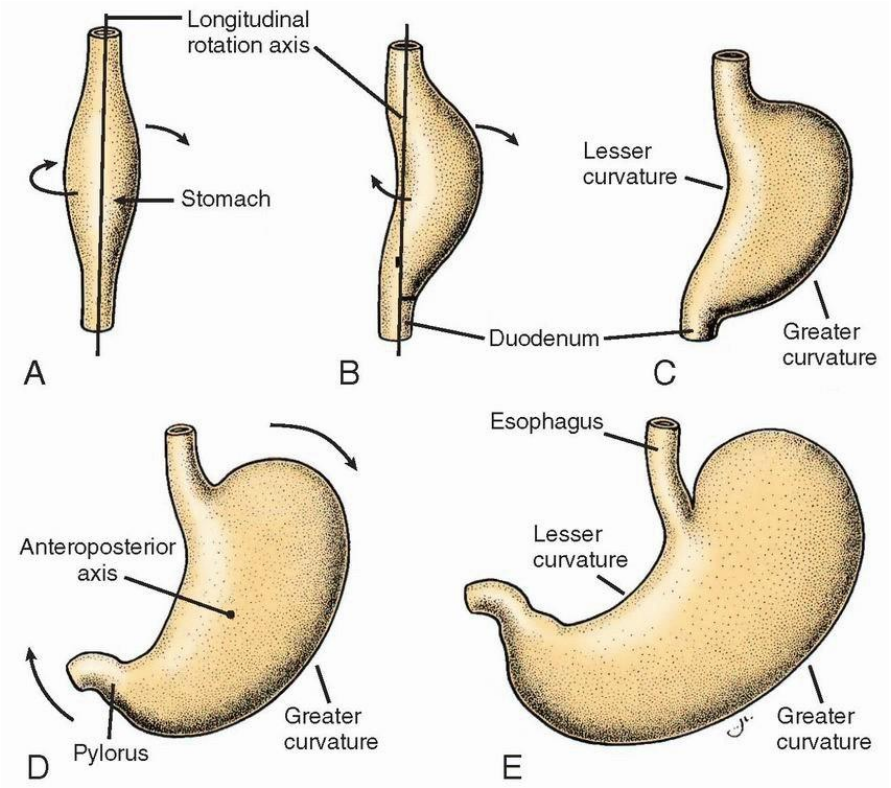
Region of foregut just caudal to lung bud develops into esophagus *–errors in forming the esophagotracheal septa and/or re-canalization lead to tracheoesophageal fistulas and/or esophageal atresia, respectively.*

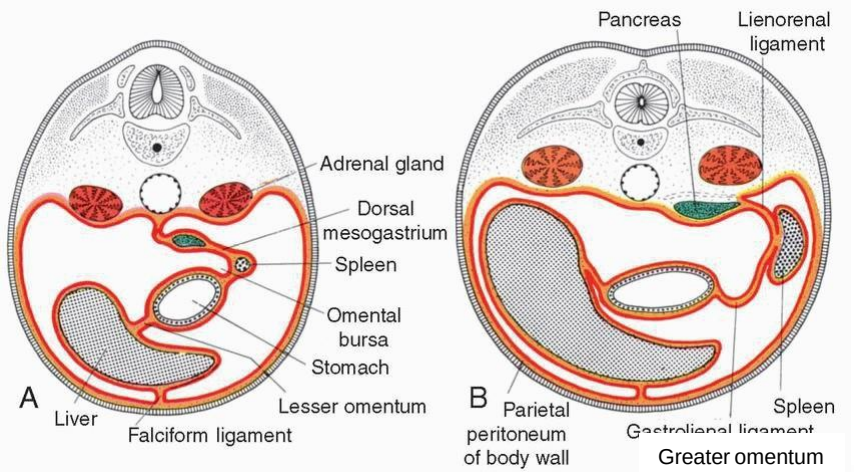
Endodermal lining is stratified columnar and proliferates such that the lumen is obliterated; patency of the lumen established by re-canalization *–errors in this process lead to esophageal stenosis*

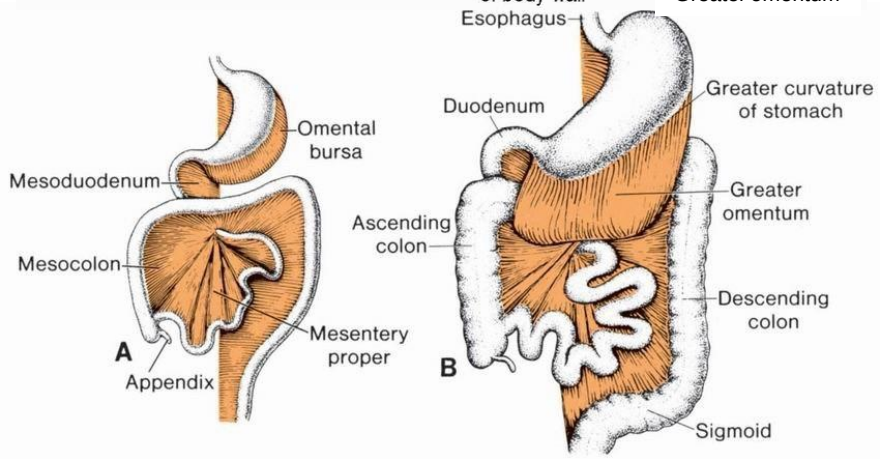
- *NOTE: this process of recanalization occurs throughout the gut tube, so occlusion can occur anywhere along the GI tract (e.g. duodenal stenosis)*

- Tube initially short and must grow in length to "keep up" with descent of heart and lungs *–failure of growth in length leads to congenital hiatal hernia in which the cranial portion of the stomach is pulled into the hiatus.*

Regional Organogenesis: Stomach







- Stomach appears first as a fusiform dilation of the foregut endoderm which undergoes a 90° rotation such that the left side moves ventrally and the right side moves dorsally (the vagus nerves follow this rotation which is how the left vagus becomes anterior and the right becomes posterior).
- Differential growth occurs to establish the greater and lesser curvatures
- Unlike other parts of the gut tube, the dorsal AND ventral mesenteries are retained to become the greater and lesser omenta, respectively
- Caudal end of the stomach separated from the duodenum by formation of the pyloric sphincter (dependent on factors such as SOX-9, NKX-2.5, and BMP-4 signaling) *–errors in this process lead to pyloric stenosis.*

Pyloric Stenosis

- Rather common malformation: present in 0.5% - 0.1% of infants

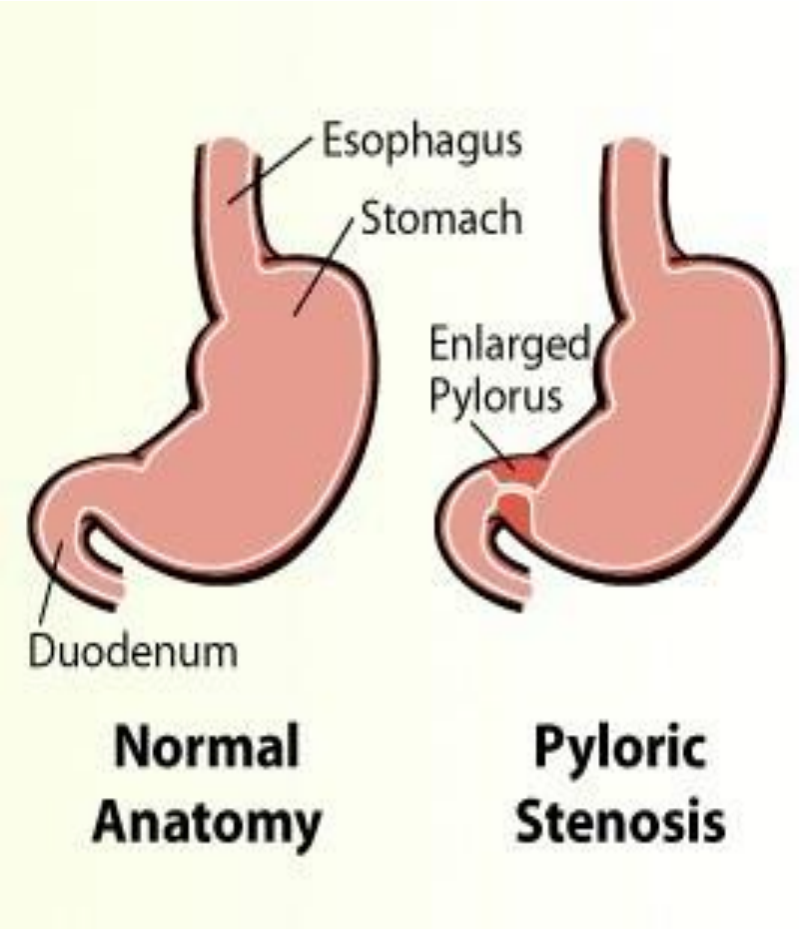
- Characterized by very forceful (aka "projectile"), non-bilious vomiting ~1hr. after feeding (when pyloric emptying would occur).

NOTE: the presence of bile would indicate POST-duodenal blockage of some sort.

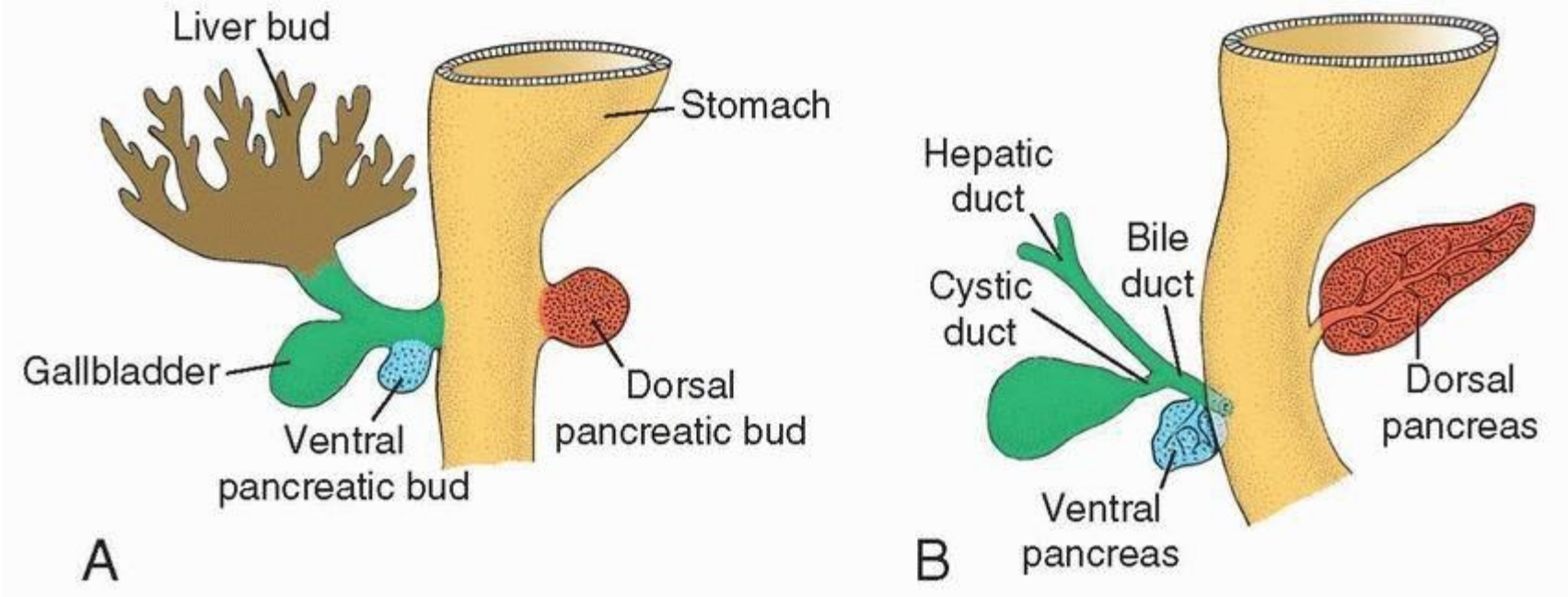
Hypertrophied sphincter can often be palpated as a spherical nodule; peristalsis of the sphincter seen/felt under the skin.

- Stenosis is due to overproliferation / hypertrophy of pyloric sphincter… NOT an error in re-canalization.

- More common in males than females, so most likely has a genetic basis which is as yet undetermined.



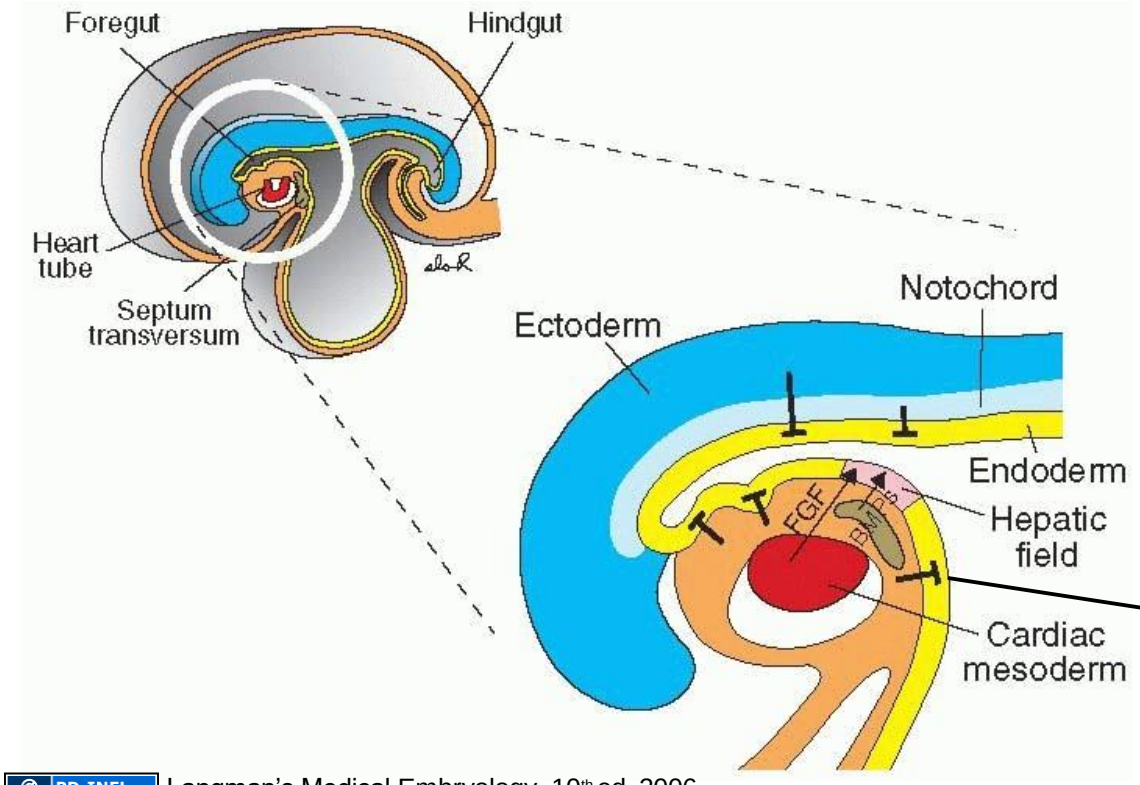
Regional Organogenesis: Liver & Pancreas



PD-INEL Langman's Medical Embryology, 10th ed. 2006.

- Liver and pancreas arise from foregut endoderm in response to signals from nearby mesoderm
- Pancreas actually has ventral and dorsal components, each specified in a different manner

Cardiac mesoderm and septum transversum specifies liver



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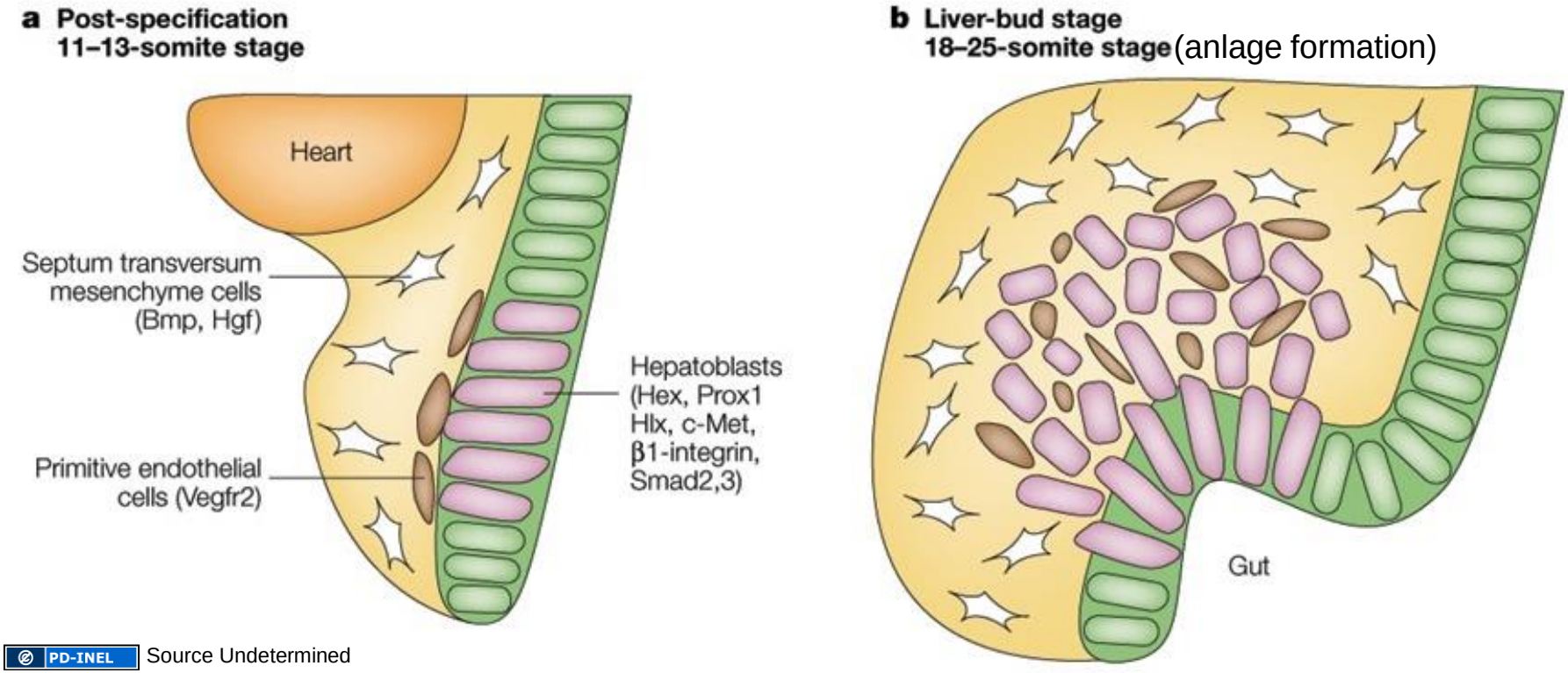
- FGFs secreted by cardiac mesoderm and BMPs secreted by septum transversum induce liver from foregut endoderm
- Endoderm just caudal to liver bud is out of reach from these signals and develops into pancreas

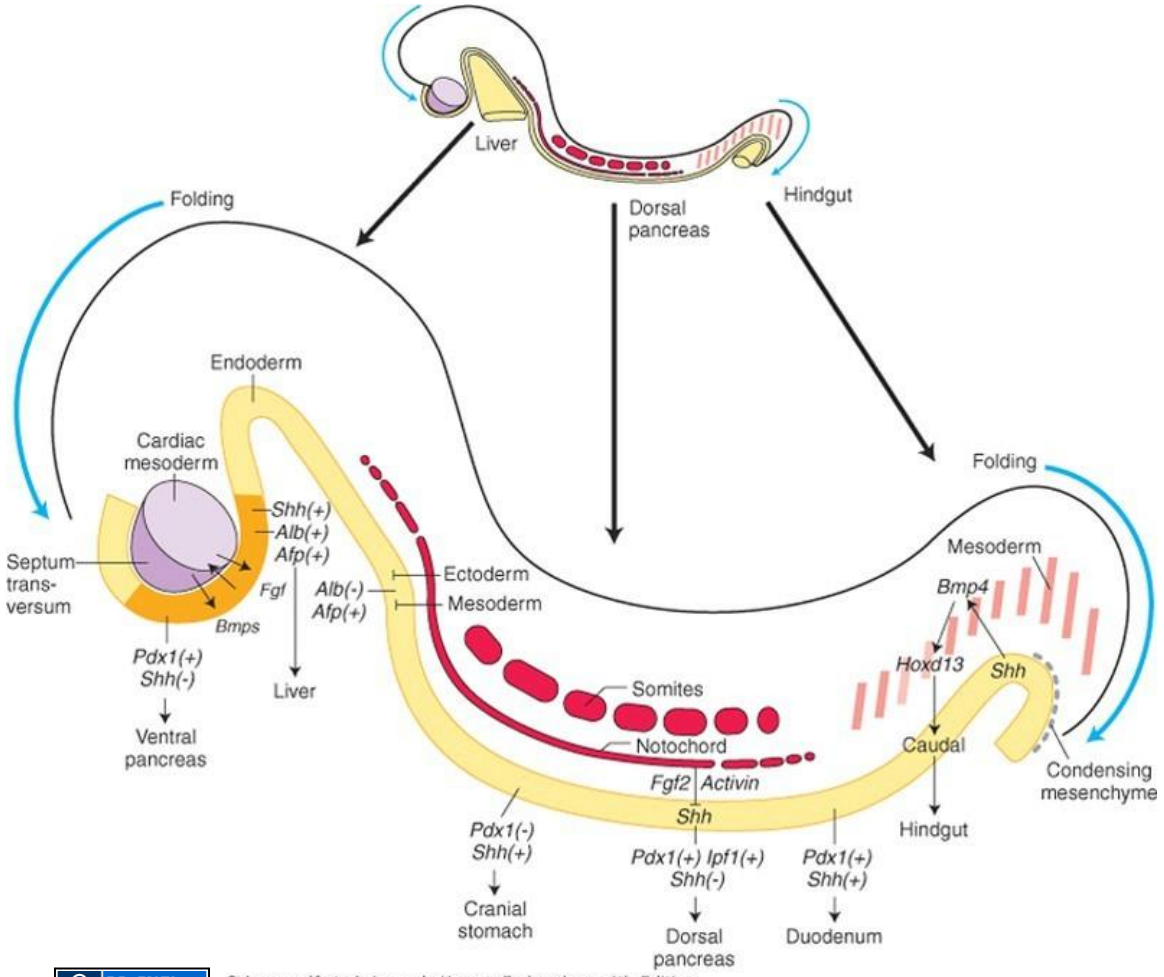
Once specified, the hepatoblasts proliferate and invade the septum transversum



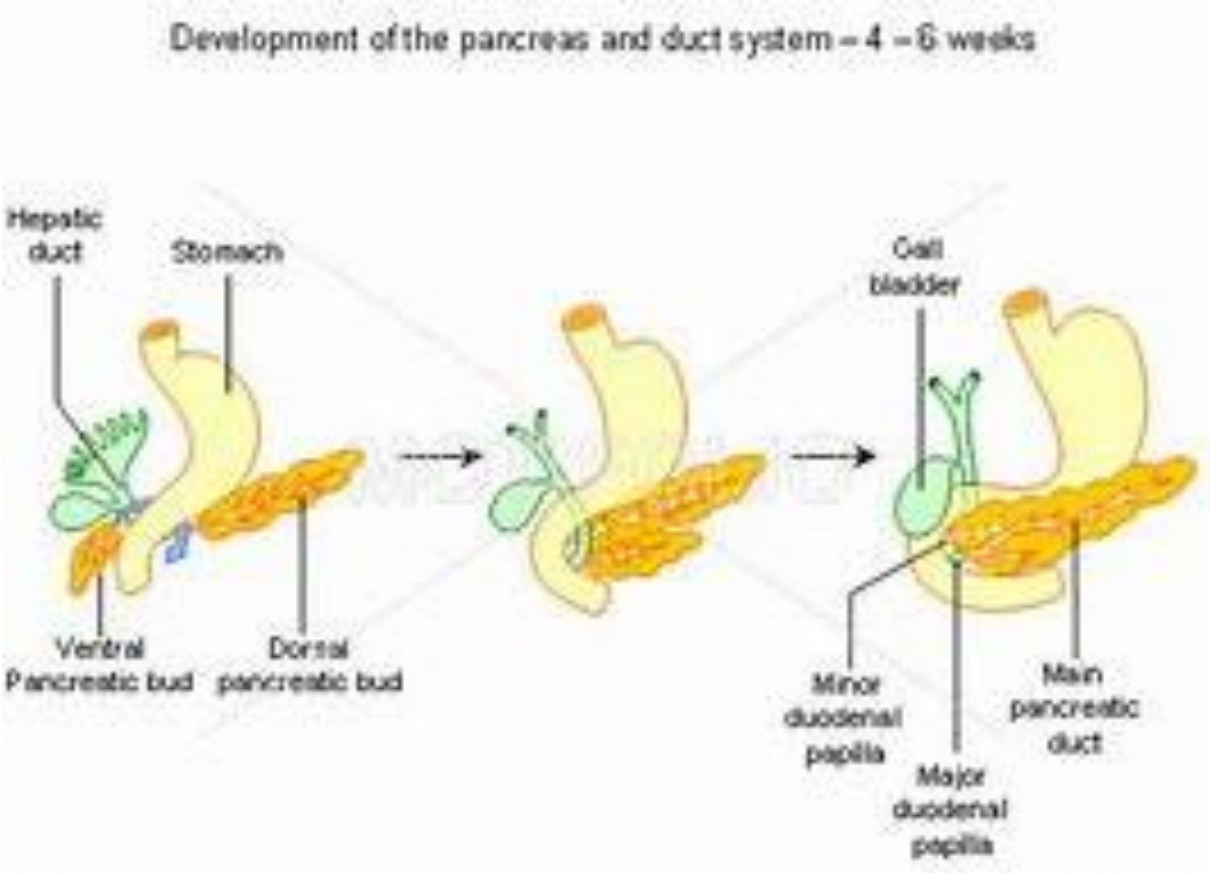
Angioblasts (endothelial cell precursors) are found next to the thickening pre-hepatic endoderm <u>before</u> invasion of the liver bud; these endothelial cells supply critical growth signals

Three signals for liver formation:
FGF from cardiac mesenchyme; BMPs from septum transversum mesenchyme, VEGF from endothelial cells

The dorsal pancreas is specified by signaling from the notochord

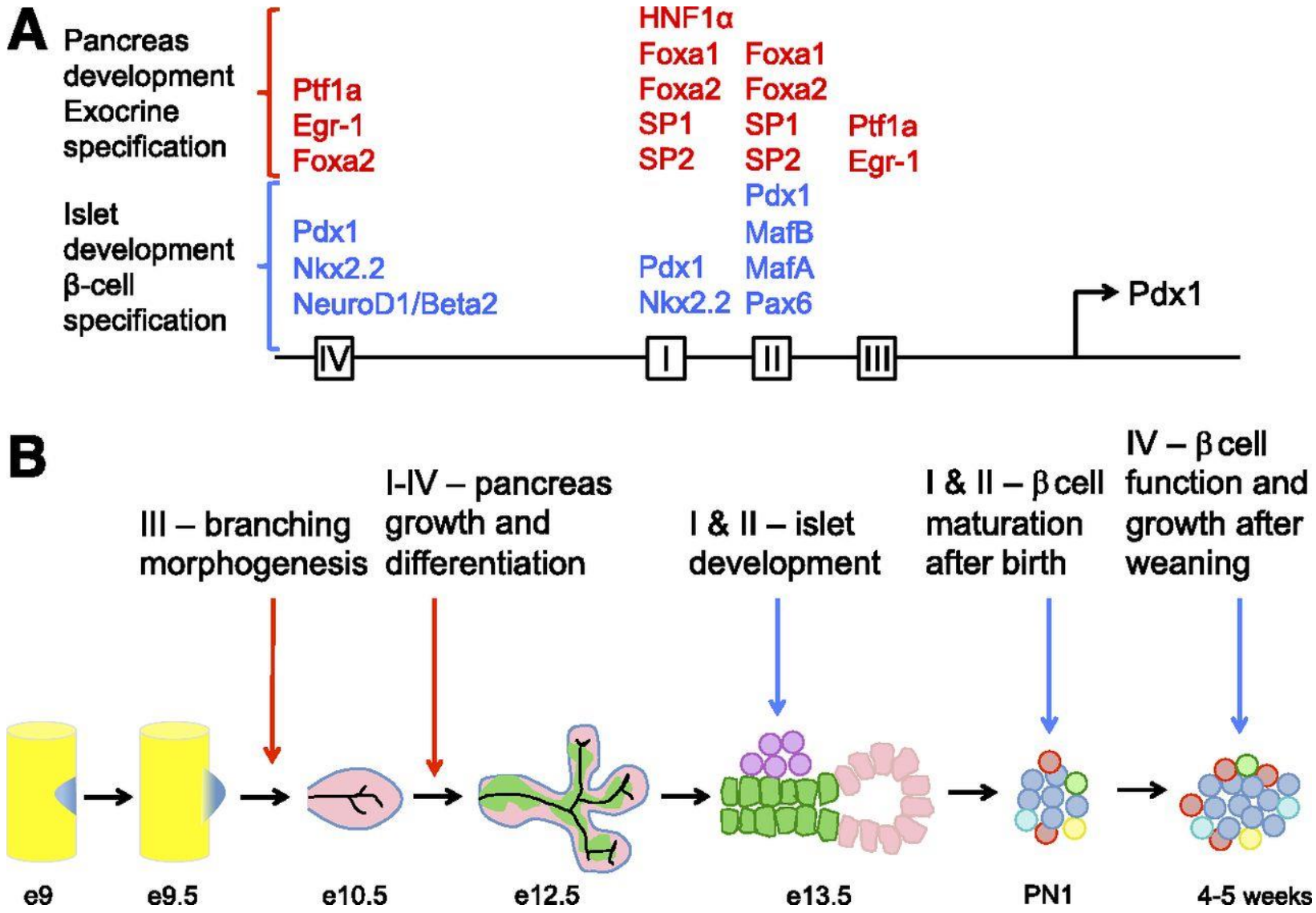


Signaling from the notochord represses Shh in foregut endoderm, which permits pancreatic differentiation.



Rotation of the duodenum brings the ventral and dorsal pancreas together

Aberrations in this process may result in an annular pancreas, which can constrict the duodenum


A
Pancreas development Exocrine specification
Islet development β-cell specification
Ptf1a
Egr-1
Foxa2
Pdx1
Nkx2.2
NeuroD1/Beta2
HNF1α
Foxa1
Foxa2
SP1
SP2
Pdx1
Nkx2.2
Foxa1
Foxa2
SP1
SP2
Pdx1
MafB
MafA
Pax6
Ptf1a
Egr-1
Pdx1
IV
I
II
III
B
III – branching morphogenesis
I-IV – pancreas growth and differentiation
I & II – islet development
I & II – β cell maturation after birth
IV – β cell function and growth after weaning
e9
e9.5
e10.5
e12.5
e13.5
PN1
4-5 weeks

Development of the midgut and colon

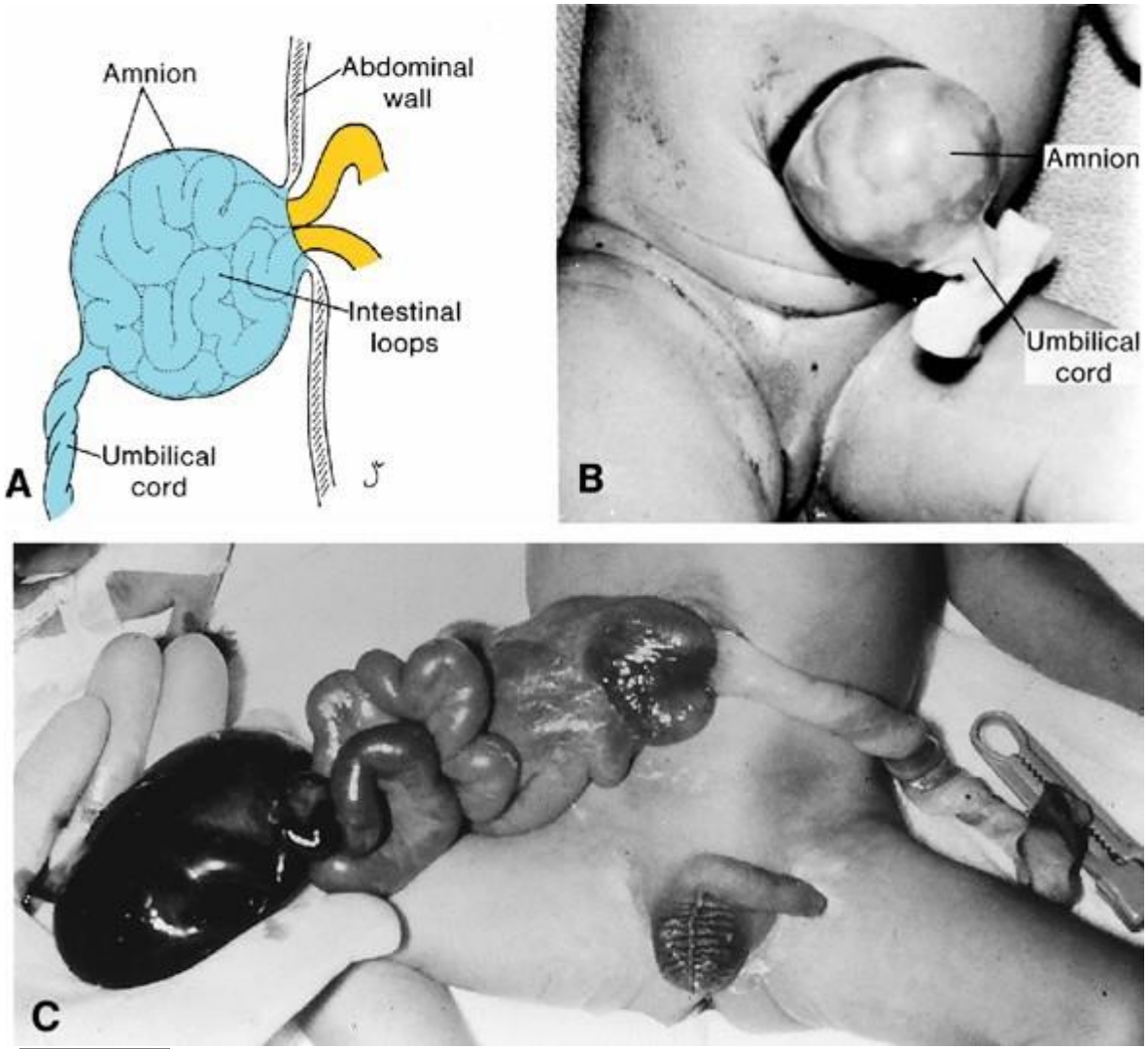
Image of development of midgut and colon removed.

Original Image: Larsen's Human Embryology, 4th Edition.

Herniation and rotation:

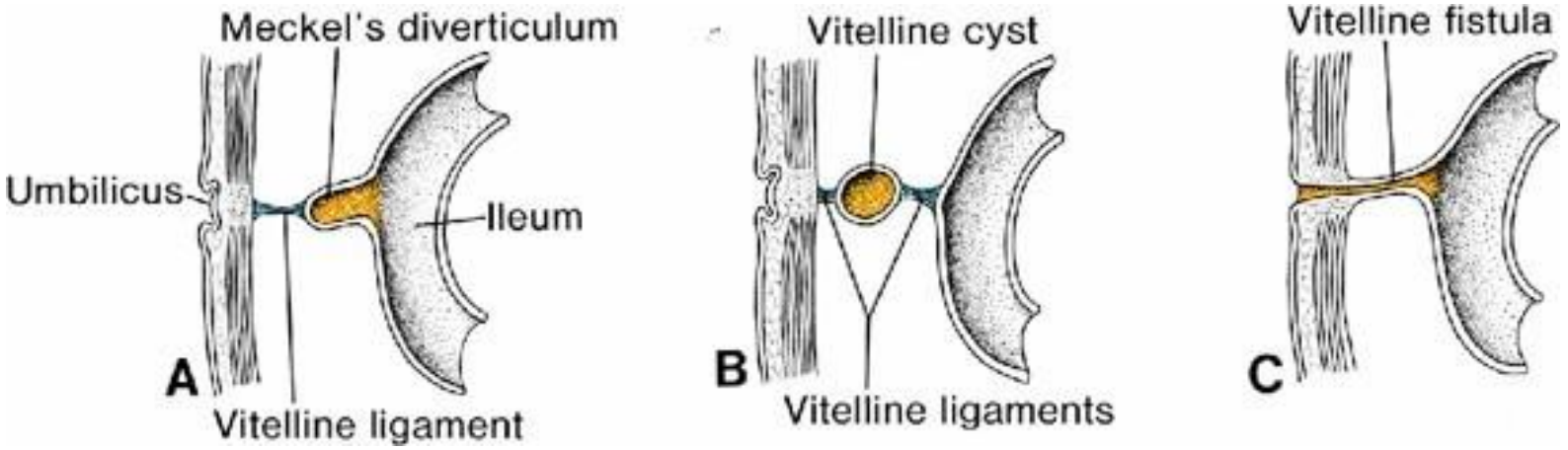
- Growth of the GI tract exceeds volume of abdominal cavity so the tube herniates through umbilicus
- While herniated, gut undergoes a primary rotation of 90° "counterclockwise" (when looking at the embryo); this corresponds with the rotation of the stomach, and positions the appendix on the left.
- With the growth of the embryo, the abdominal cavity expands thus drawing the gut tube back within the abdominal cavity and causing an additional, secondary rotation of 180° CCW (positioning the appendix on the RIGHT)
- Once in the abdominal cavity, the colon continues to grow in length, pushing the appendix to its final position in the lower right quadrant.

Defects associated with gut herniation and rotation: oomphaocoele



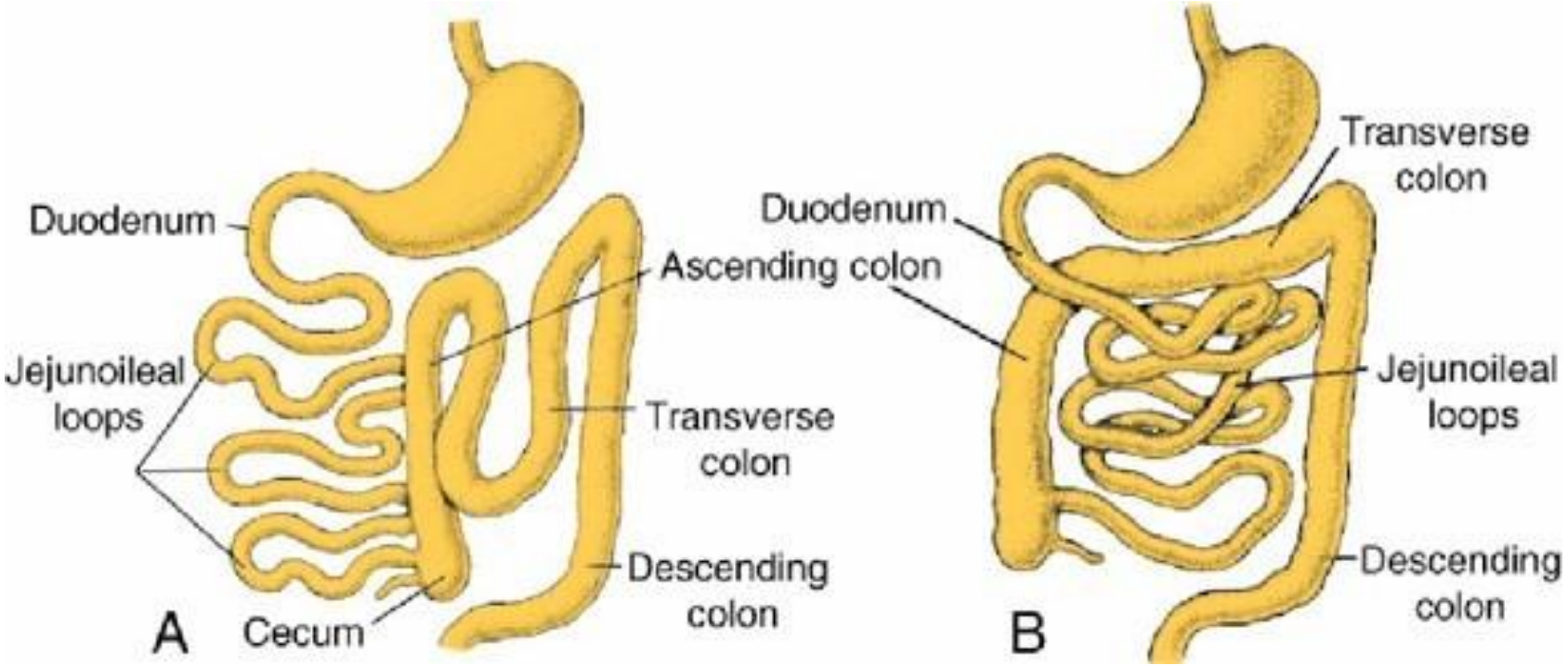
 Langman's Medical Embryology, 9th ed. 2004.

Defects associated with gut herniation and rotation: vitelline duct abnormalities



 Langman's Medical Embryology, 9th ed. 2004.

Defects associated with gut herniation and rotation: abnormal rotation



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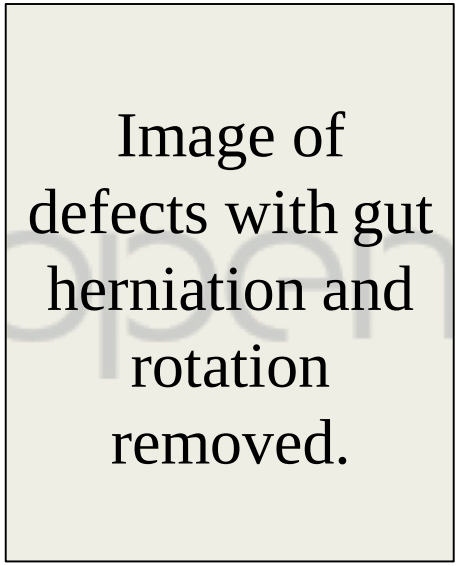
Absent or incomplete secondary rotation

Reversed primary rotation (90° CW)

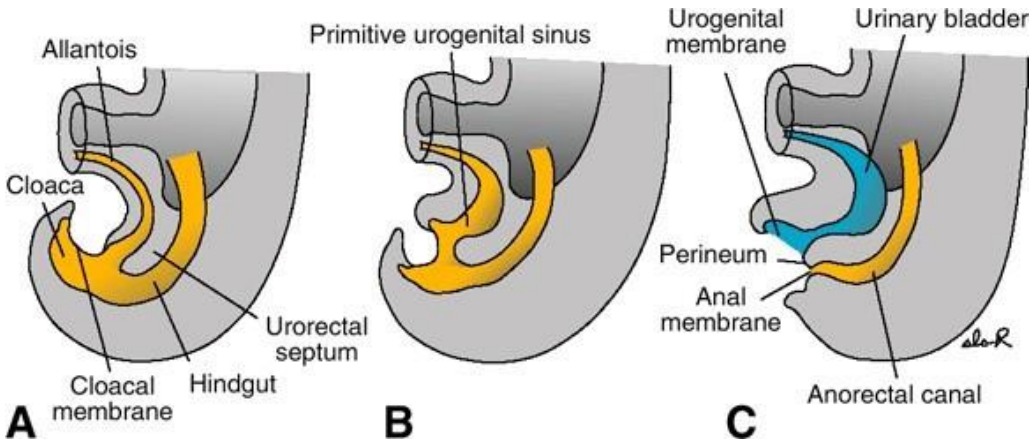
Defects associated with gut herniation and rotation: volvulus



Original Image: Carlson - Human Embryology and Developmental Biology, 4th Edition.

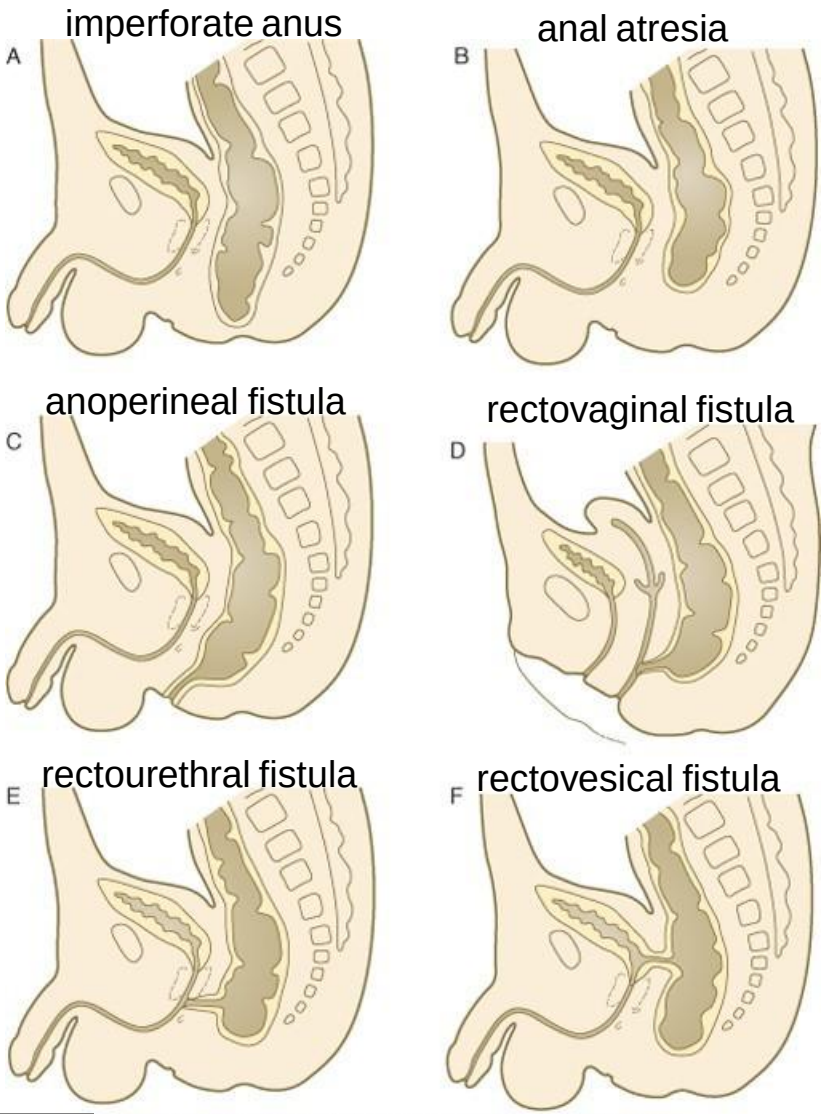
Fixation of a portion of the gut tube to the body wall; subsequent rotation causes twisting of the tube, possibly resulting in stenosis and/or ischemia.

Development of the hindgut



PD-INEL Langman's Medical Embryology, 10th ed. 2006.

- Derivatives of the hindgut include everything caudal to the distal 1/3 of the transverse colon.
- Distalmost portion (sigmoid colon and rectum) divides cloaca into the anorectal canal and urogenitial canals *–errors in this process can lead to imperforate anus ("A" on right), atresia (B), and/or fistulas (C – F)*
- As with the rest of the GI tract, enteric neurons arise from vagal neural crest. Distalmost portions of the hindgut are farthest away and therefore more sensitive to perturbations in migration (e.g. mutations in RET), resulting in congenital megacolon (Hirschspring's Disease).



PD-INEL Carlson: Human Embryology and Developmental Biology, 4th Edition.