

Embryology and Anatomy of the Gastrointestinal Tract

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NASPGHAN

Physiology Education Series

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Objectives

- Understand the normal development of the foregut (esophagus, stomach, duodenum, liver, and gallbladder), midgut (intestines, colon), and hindgut (rectum)
- Identify the anatomic features of the stomach (gross, microscopic, neuromuscular)
- Understand normal blood supply
- Understand the normal development of the enteric nervous system
- Understand common congenital anomalies

Case #1



- 3yo male with:
 - 1 to 2 days of right sided abdominal pain
 - Maroon colored stools
 - No fever, dysuria, rash
 - No recent travel
- Physical exam
 - HR 135 bpm, RR 25 bpm
 - Pale
 - Good bowel sounds
 - Slight tenderness to abdomen, no rebound, no guarding

Case #1

- CBC
 - WBC – 11,000/ μ L
 - HCT 28%
 - Plts 350×10^9 /L
- Hemocult – Positive
- Other tests?
 - Labs?
 - Radiology?

Case #1

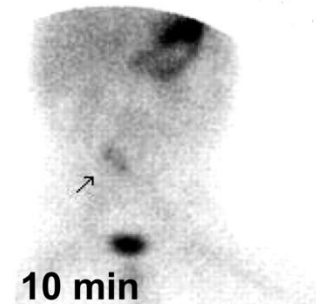
- Meckel's Scan
(technetium- 99m
pertechnetate scintiscan)
- Meckel's Diverticulum =
Persistence of the
omphalomesenteric duct.
True diverticulum of the
intestine with all layers of
the intestinal wall present.



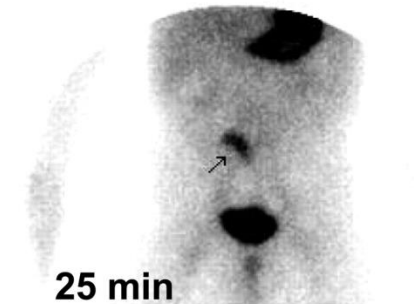
2-3 min



5 min



10 min



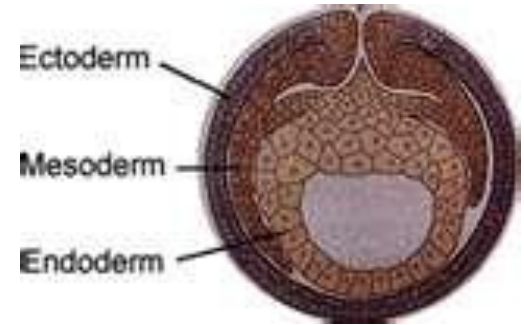
25 min

Meckel's Diverticulum

- 2% of population
- 2 feet from the ileocecal valve
- 2 inches long
- 50% present before 2 years
 - 60% present before 10 years
- Present
 - Painless bleeding, obstruction, inflammation
 - Symptoms due to mucosal ulceration

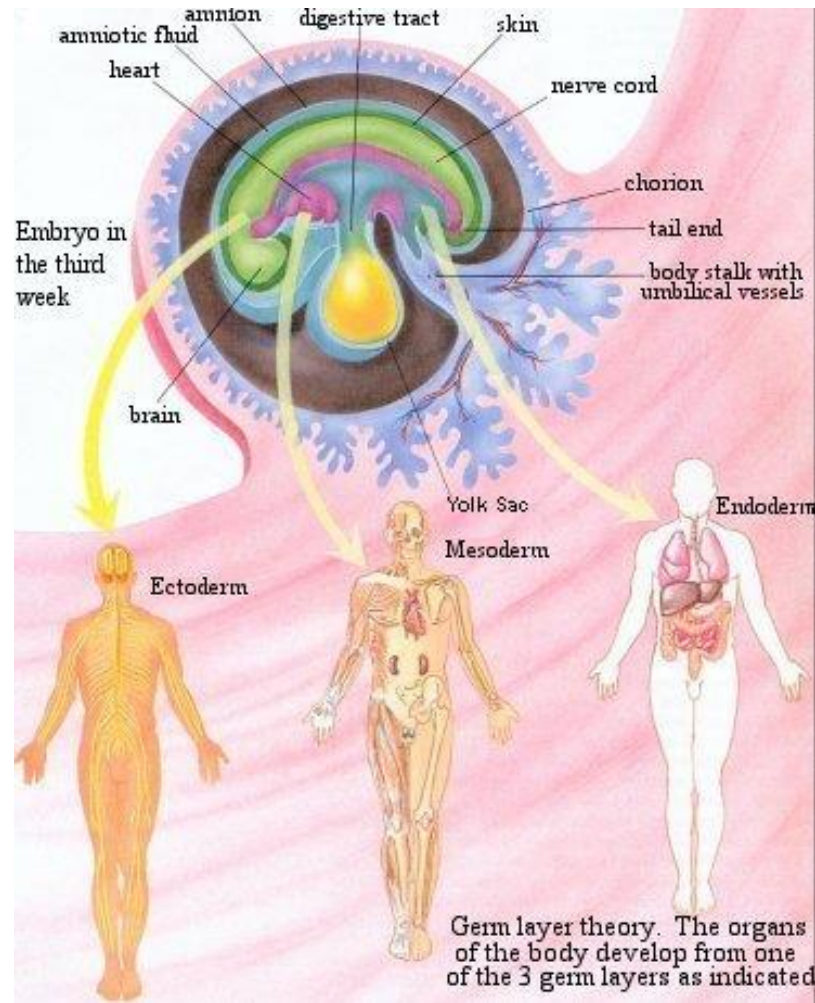


Normal Embryology



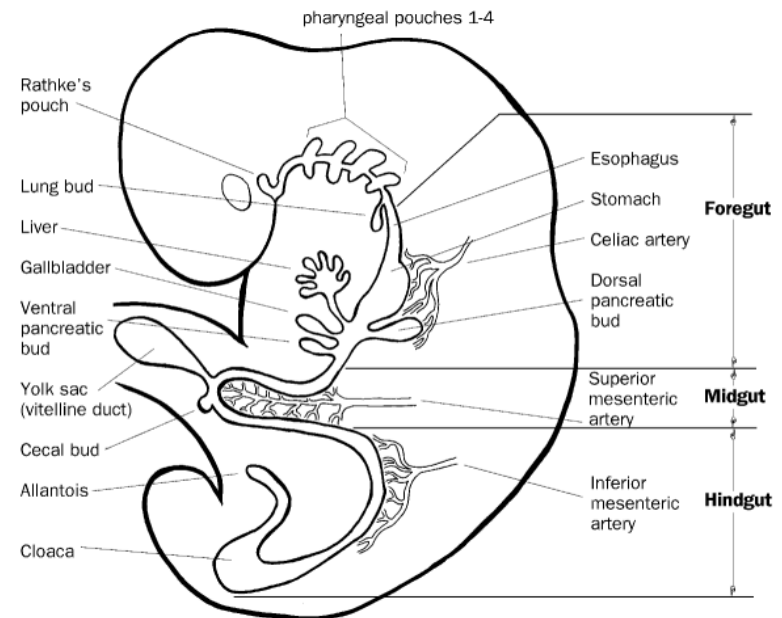
- Endoderm
 - Epithelial lining and glands
- Mesoderm
 - Lamina propria, muscularis mucosa, submucosa, muscularis externa and serosa
- Ectoderm
 - Enteric nervous system and posterior luminal digestive structures

Normal Embryology



Normal Embryology

- Primitive Gut Tube –
 - Incorporation of the yolk sac during craniocaudal and lateral folding of the embryo.
- Foregut
- Midgut
- Hindgut



Canalization

- Canalization
 - Week 5 - Endoderm portion of GI tract proliferates
 - Week 6 - Occlusion of the lumen
 - Week 8 - Recanalization due to cell degeneration
 - Abnormalities in this process
 - Stenosis/Atresia
 - Duplications

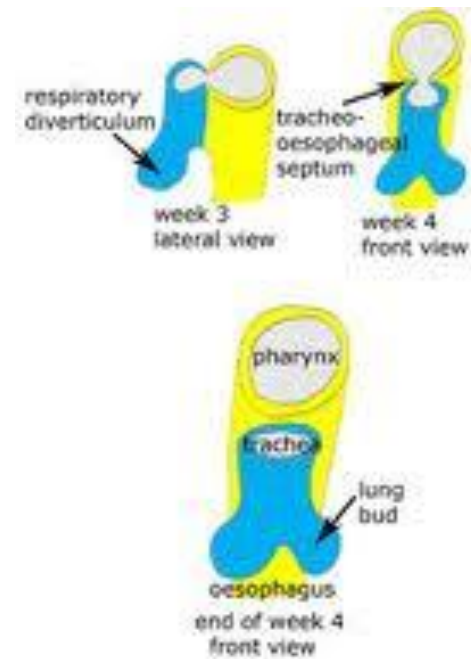
Foregut

- Foregut gives rise to:
 - Esophagus
 - Stomach
 - Liver
 - Gallbladder and bile ducts
 - Pancreas
 - Upper Duodenum

Foregut

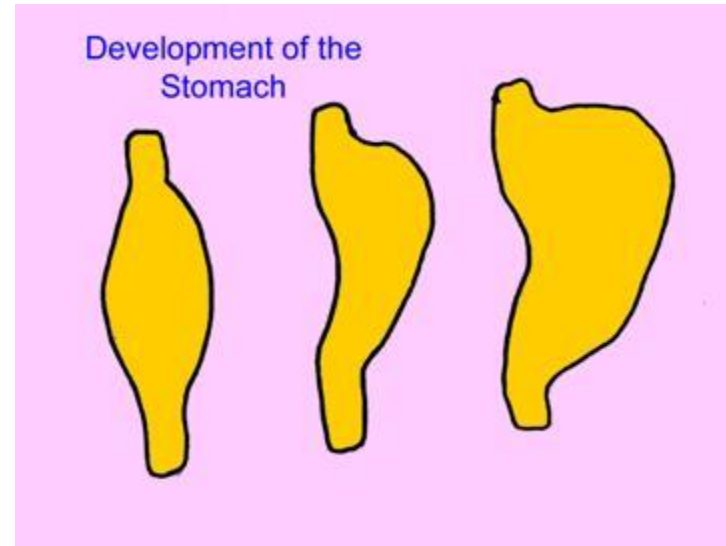
- **Esophagus** – The tracheoesophageal septum divides foregut into the esophagus and trachea

- **Clinical Correlation**
 - Esophageal atresia
 - Tracheoesophageal fistula



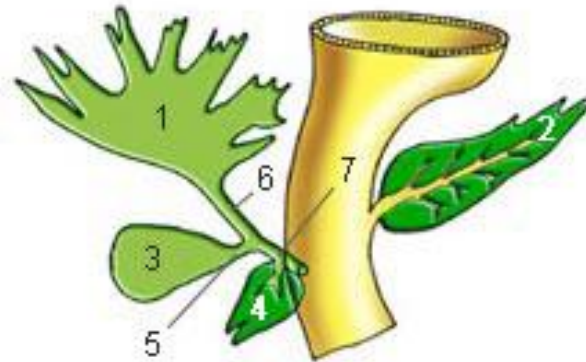
Foregut

- **Stomach** – A fusiform dilation in the foregut occurring during the 4th week. 90 degree clockwise rotation, creates the lesser peritoneal sac.



Foregut

- **Liver** – Develops from an endodermal outgrowth at cranioventral portion of the foregut (hepatic diverticulum).
- Mesoderm surrounds the diverticulum (septum transversum).



Foregut

- Hepatic cells (hepatoblasts) migrate into the septum transversum.
- The migrating cells are both hematopoietic and endothelial precursors.
- The hepatic cells surround the endothelial precursor cells, vitelline veins, to form the hepatic sinusoids.

Foregut

- Gallbladder and bile ducts –
 - Cystic diverticulum develops into gallbladder and cystic duct.

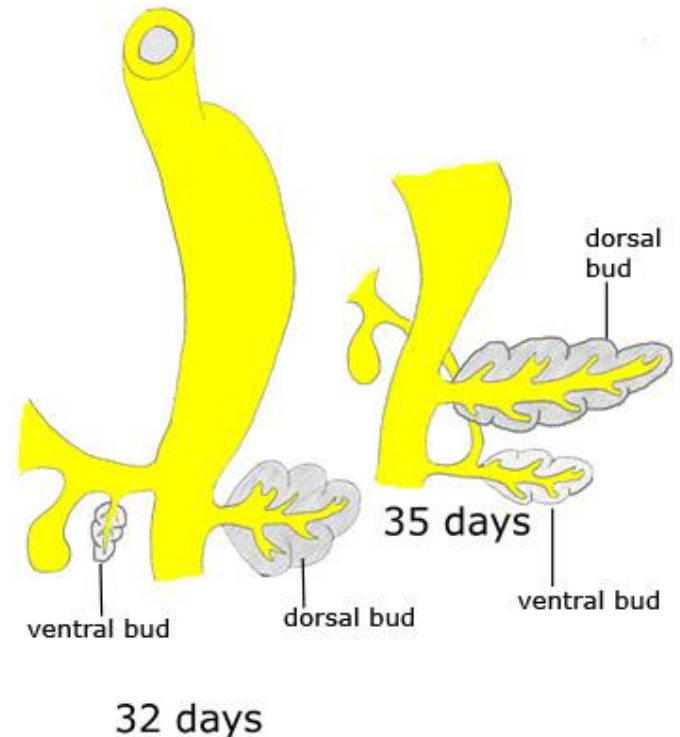


Foregut

- **Pancreas** – Develops from 2 pancreatic buds (weeks 4-5).
 - Ventral pancreatic bud forms the uncinate process and the head of the pancreas.
 - The larger dorsal pancreatic bud forms the remaining head, body and tail.

Foregut

- Pancreas continued
 - The ventral pancreatic bud rotates clockwise with the rotation of the duodenum. During 7th week the 2 buds fuse.
- **Clinical Correlation:**
 - Failure of this rotation and fusion results in pancreas divisum.



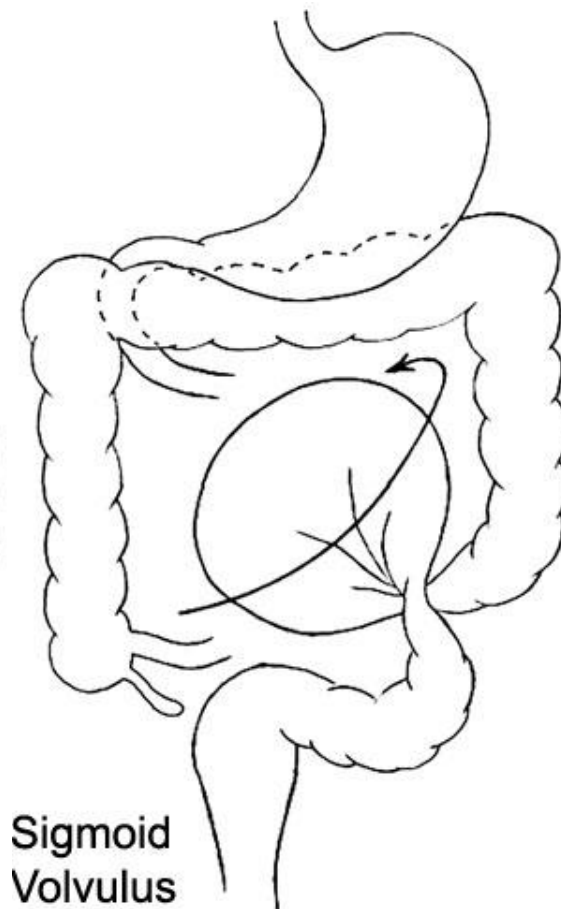
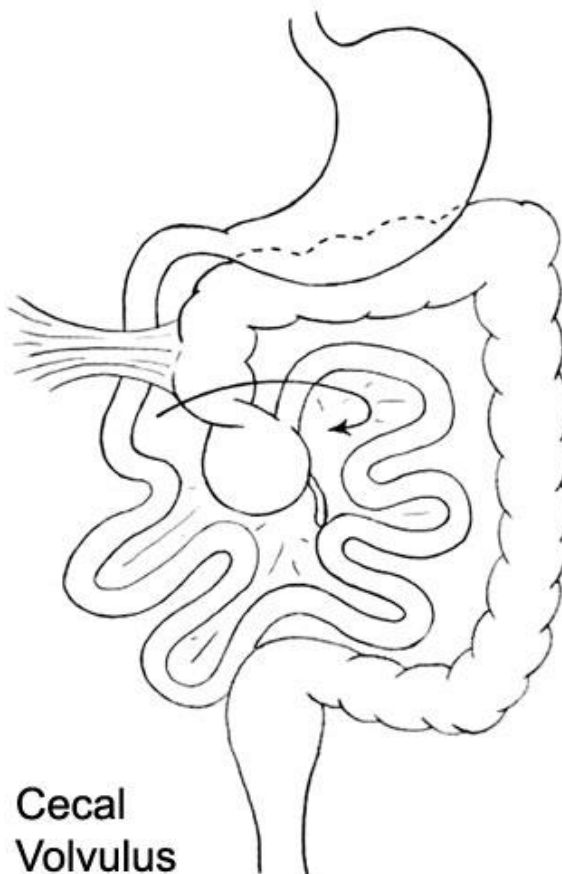
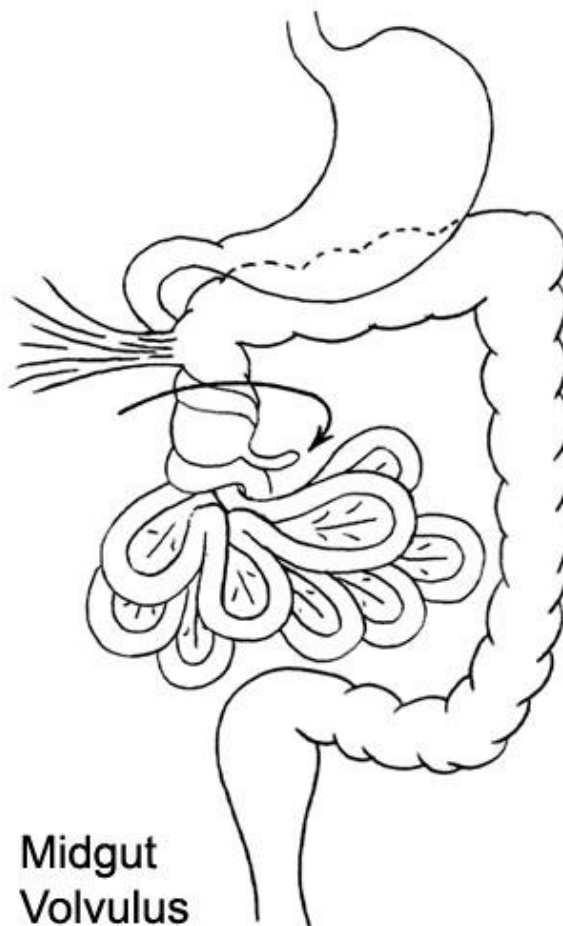
Midgut

- Lower Duodenum – Cranial portion of the midgut.
- Jejunum, ileum, cecum, appendix, ascending colon, and proximal 2/3 of transverse colon – Develop as the midgut loop herniates through the primitive umbilical ring during umbilical herniation at week 6.
 - The loop then rotates 270 degrees counterclockwise around the superior mesenteric artery and returns to the abdominal cavity.

Midgut Anomalies

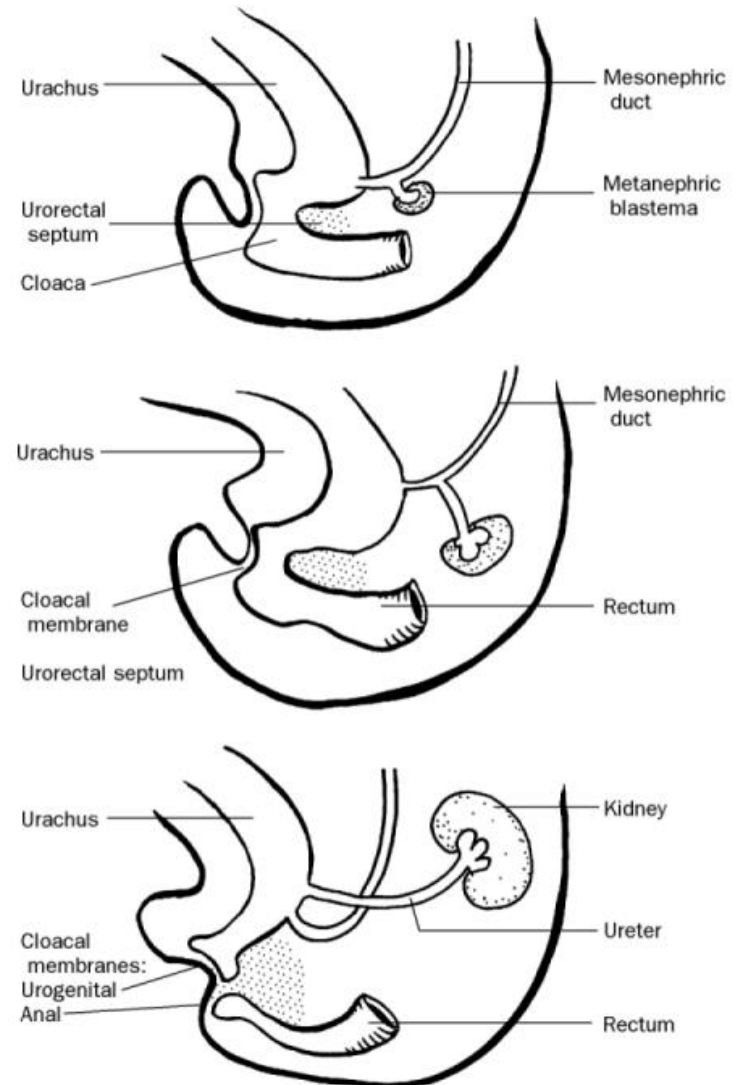
- **Clinical correlation –**
 - Duodenal atresia is due to failed canalization.
 - Omphalocele results from failure of the midgut loop to return to the abdomen.
 - Meckel's diverticulum occurs when a remnant of the yolk sac (Vitelline duct) persists.
 - Malrotation occurs if the midgut does not complete the rotation prior to returning to the abdomen.

Malrotation



Hindgut

- Distal 1/3 of the transverse colon, descending colon and sigmoid colon develop from the cranial end of the hindgut.
- Upper anal canal develops from the terminal end of the hindgut with the urorectal septum dividing the upper anal canal and the urogenital sinus.



Hindgut Anomalies

- **Clinical Correlation**

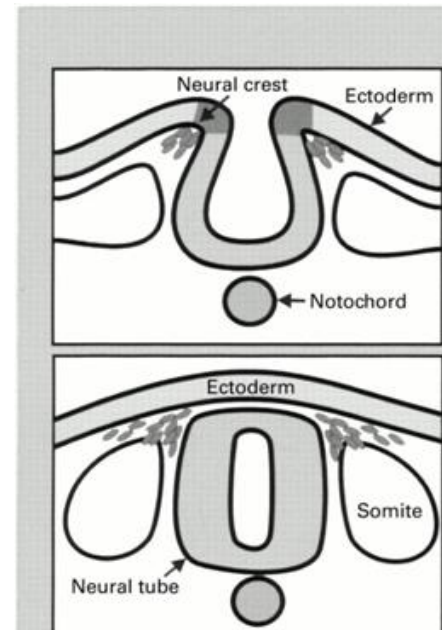
- Anorectal agenesis occurs if the urorectal septum does not develop appropriately.
- VACTERL Association
 - Vertebral anomalies, anal defects, cardiac defects, TEF, Renal and Limb defects
- Hirschsprung disease – failure of the neural crest cells to form the myenteric plexus (see Enteric Nervous System).

Proctodeum

- The posterior ectodermal portion of the alimentary canal is formed in the embryo by invagination of the outer body wall.
 - Becomes the lower 1/3 of the anal canal

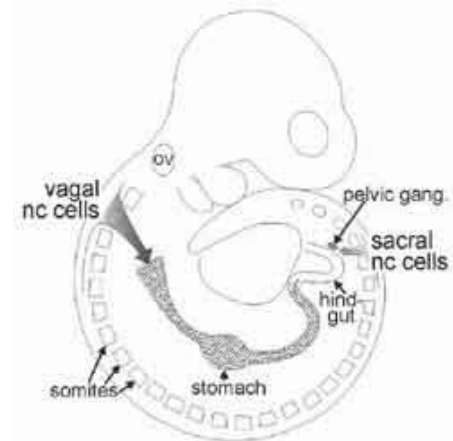
Enteric Nervous System

- Collection of neurons in the GI tract.
- Controls motility, exocrine and endocrine secretion and microcirculation.
- Regulates immune and inflammatory process.
- Functions independent of CNS.



Development of Enteric Nervous System

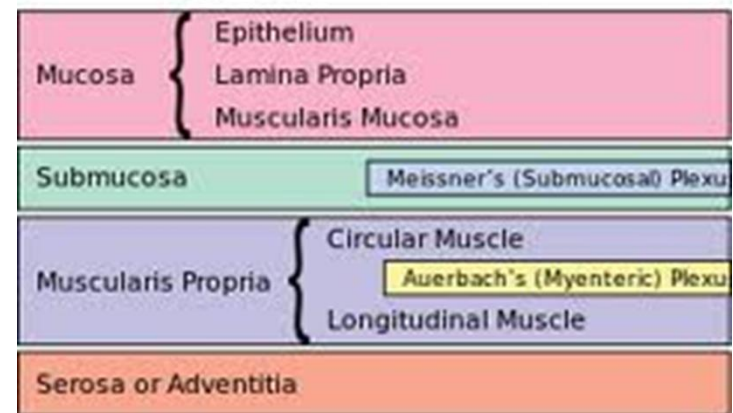
- Primarily derived from the vagal segment of neural crest cells.
- Cells initially migrate to the cranial section and then caudally
- Hindgut ganglia receive contributions of cells from the cranial and sacral segments of the neural crest cells
- Interstitial cells of Cajal arise from the local gut mesenchyme



Development of the Enteric Nervous System

- Nerve cell bodies are grouped into ganglia
- Ganglia are connected to bundles of nerves forming two plexus
 - Myenteric (Auerbach's)
 - Submucosal (Meissner's)

General Organization of the Gastrointestinal Tract



Enteric Nervous System

- Myenteric plexus
 - Lies between the circular and longitudinal muscles
 - Regulates
 - Motility
 - Secretomotor function to mucosa
 - Connections to
 - gallbladder and pancreas
 - sympathetic ganglia
 - esophageal striated muscle

Enteric Nervous System

- Submucosal plexus
 - Lies between circular muscle layer and the muscularis mucosa
 - Regulates:
 - Glandular secretions
 - Electrolyte and water transport
 - Blood flow
 - Similar structure found in gallbladder, cystic duct, common bile duct and the pancreas

Enteric Nervous System

- **Clinical Correlations:**
 - Motility
 - Achalasia
 - Psuedo-obstruction
 - Hirschsprung's disease
 - Secretions
 - Cholera
 - *E. Coli*

Hirschsprung's Disease

- Congenital disorder
- 1:5000 live births
- Failure of neural crest cells to colonize the entire gut resulting in an aganglionic zone
 - Tonic constriction of aganglionic section
- Long (20%) and Short Segment (80%)
 - Short segment 4:1 male:female
- Isolated anomaly in 70% of cases
- Multiple genes and modifier genes identified
 - Not mendelian

Genetics of Hirschsprung's Disease

- Associated genes encode members of the glial cell neurotrophic factor family
 - involved in signaling pathways
 - transcription factors
- Genes identified
 - GDNF
 - Ret
 - EDNRB
 - Sox10

Genetics of Hirschsprung's Disease

- Glial Cell-Derived Neurotrophic Factor (GDNF)
 - Member of TGF- β superfamily
 - Binds to and activates receptor tyrosine kinase (Ret)
 - Defects on GDNF/Ret signaling account for
 - 50% familial cases
 - 30% of sporadic cases

Genetics of Hirschsprung's Disease

- Endothelin 3 (Et-3) is a secreted protein expressed by gut mesenchyme.
- Et-3 signals via Endothelin receptor B (Ednrb)
- Ednrb is expressed on migrating enteric neural crest cells
- Mutations in Et-3 and Ednrb account for 5% of cases

Genetics of Hirschsprung's Disease

- Sex determining region Y – box 10 (Sox10) is a high mobility group transcription factor.
- Expressed on migrating enteric neural crest cells
- Mutations of Sox10 account for 5% of cases

Genetics of Hirschsprung's Disease

- Gene Interactions have been identified in isolated Mennonite populations and mouse models.
 - Ret and Ednrb
 - Ret and Et-3
 - Sox10 and Et-3/Ednrb
- Mechanisms are unknown –
 - ?Downstream signaling

Genetics of Hirschsprung's Disease

- Modifier Genes = Mutated gene that must be coupled with another mutation to result in or enhance the effect.
 - Neuregulin 1 (NRG1) - associates with Ret
 - NRG1 signals receptors to regulate neural crest cell development. The receptor is also associated with Sox10
- Modifiers have also been identified for Sox10 and Et-3 and Ednrb

Genes in Gastrointestinal Embryology

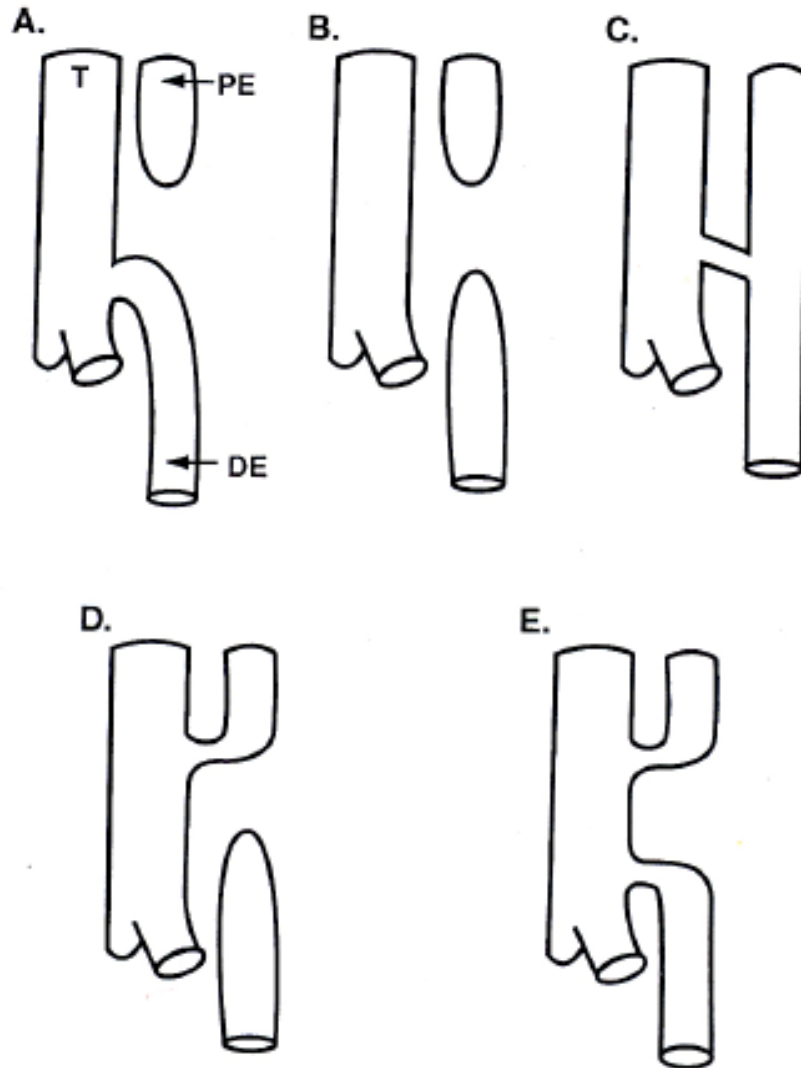
- Homeobox-containing transcription factors (Hox genes) – play a role in gut regionalization
- Sonic Hedgehog (Shh) – transcription factor controls endodermal-mesenchymal interactions
 - Defects associated with TEF and Anorectal malformations
 - Possible role in IBD and Malignancy

Case #2

- Newborn presents with feeding intolerance and drooling.
- Polyhydramnios was noted in the third trimester.
- KUB with small gastric bubble
- A nurse was unable to pass an NG tube following delivery



Tracheoesophageal Fistula



A. 85%

B. 8% Esophageal atresia

C. 4% H or N type

D. 1%

E. 1%

TEF

- Occurs in 1 in ~ 3000 births
- Highest incidence in caucasians
- 50% have associated congenital anomalies
- Diagnosis
 - Prenatal Ultrasound – polyhydramnios
 - CXR – absence of gastric bubble, tracheal deviation
 - CT
 - Feeding difficulties with respiratory symptoms
- Etiology
 - Canalization defect
 - Defect with tracheoesophageal septum development

Blood Supply to the GI tract

Proximal Esophagus

Inferior Thyroid Artery

Thoracic Esophagus

Terminal bronchial arteries

Distal Esophagus

Left gastric and left phrenic arteries

Stomach

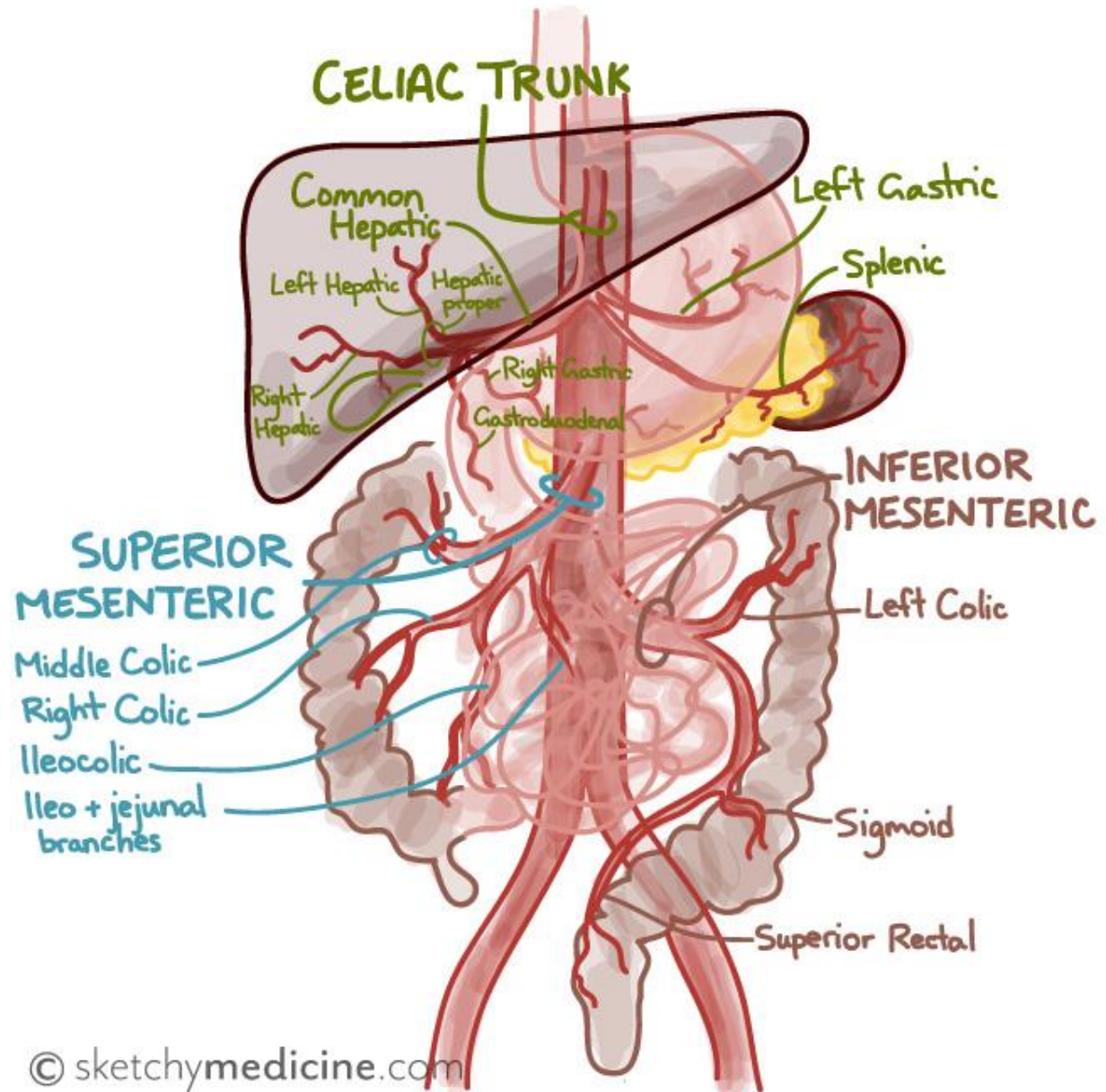
Celiac artery

Small intestine

Superior mesenteric artery

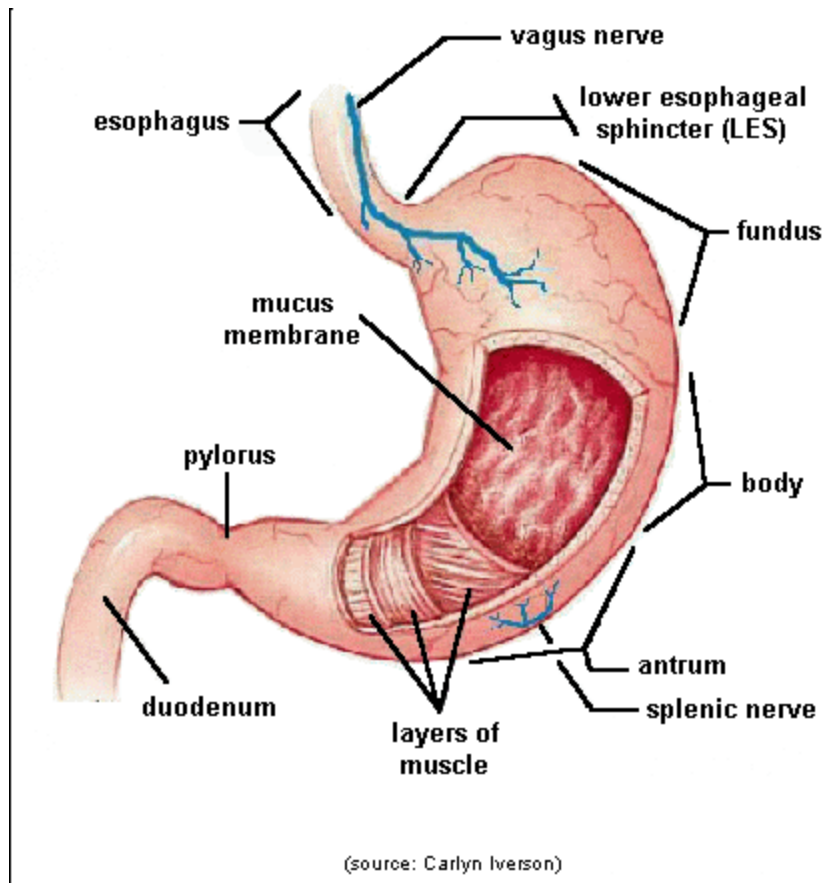
Large intestine

Superior and Inferior mesenteric arteries



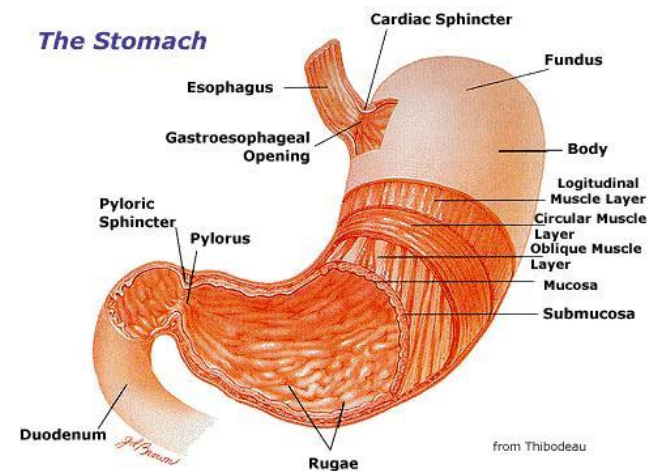
The Stomach

- Understand the features of the stomach



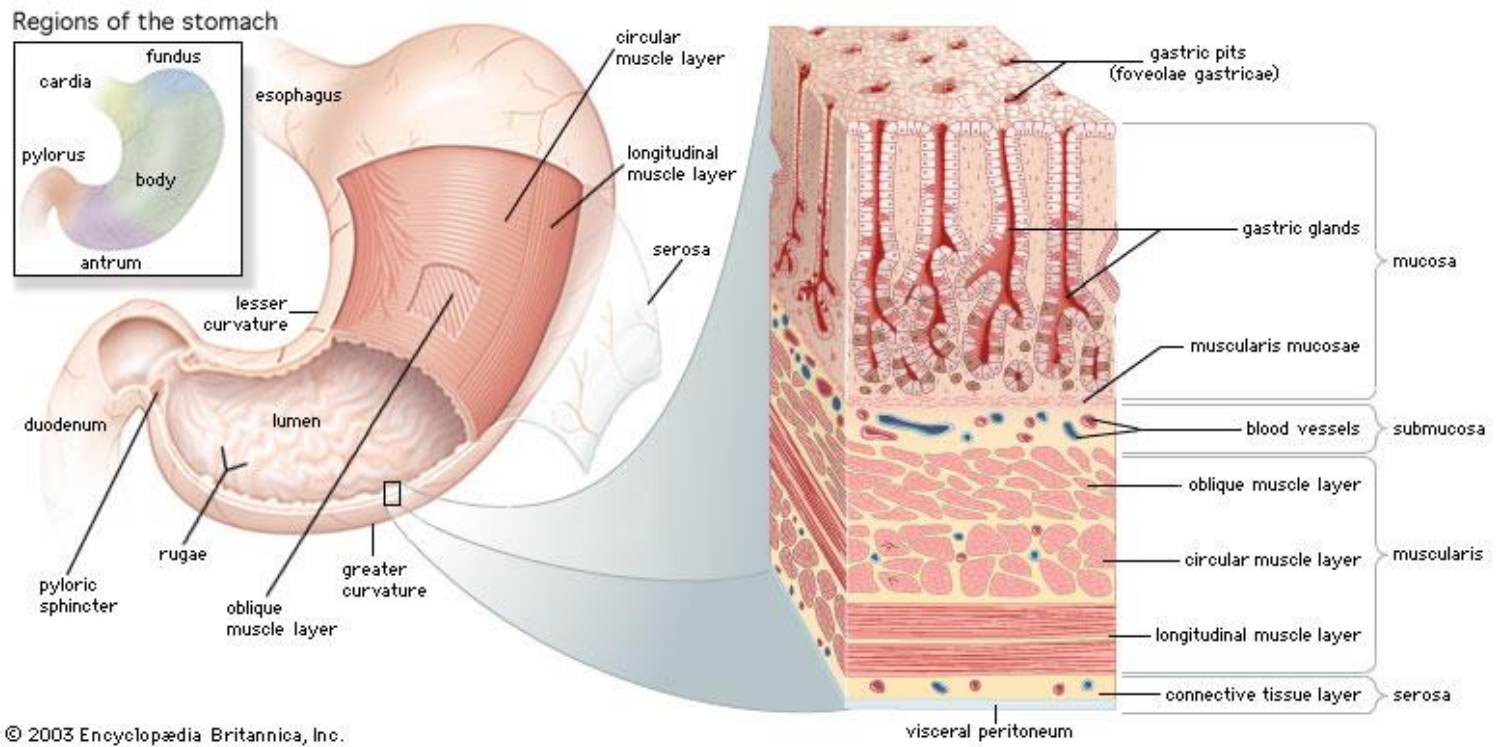
Gastric Features

- Mixes and Emulsifies
- Reservoir
- Secretes
 - Acid → Host Defense and Digestion
 - Digestive Enzymes → Pepsin, Lipase
 - Intrinsic Factor → Vitamin B₁₂ absorption
- Regulates release of gastric chyme
- Prevents acid reflux - (LES)



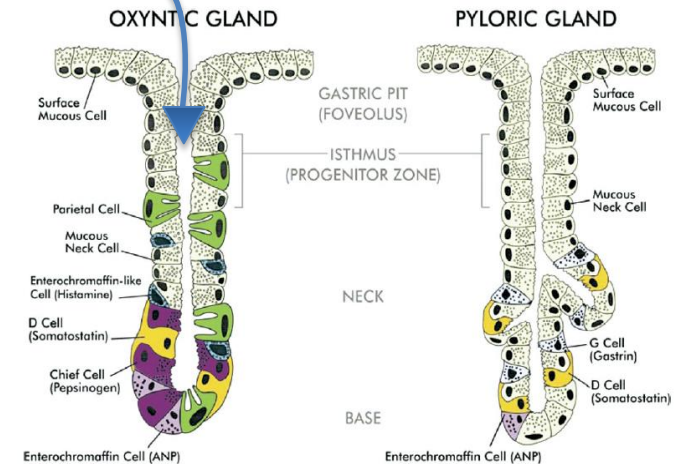
Gastric Anatomy

- Neuromuscular



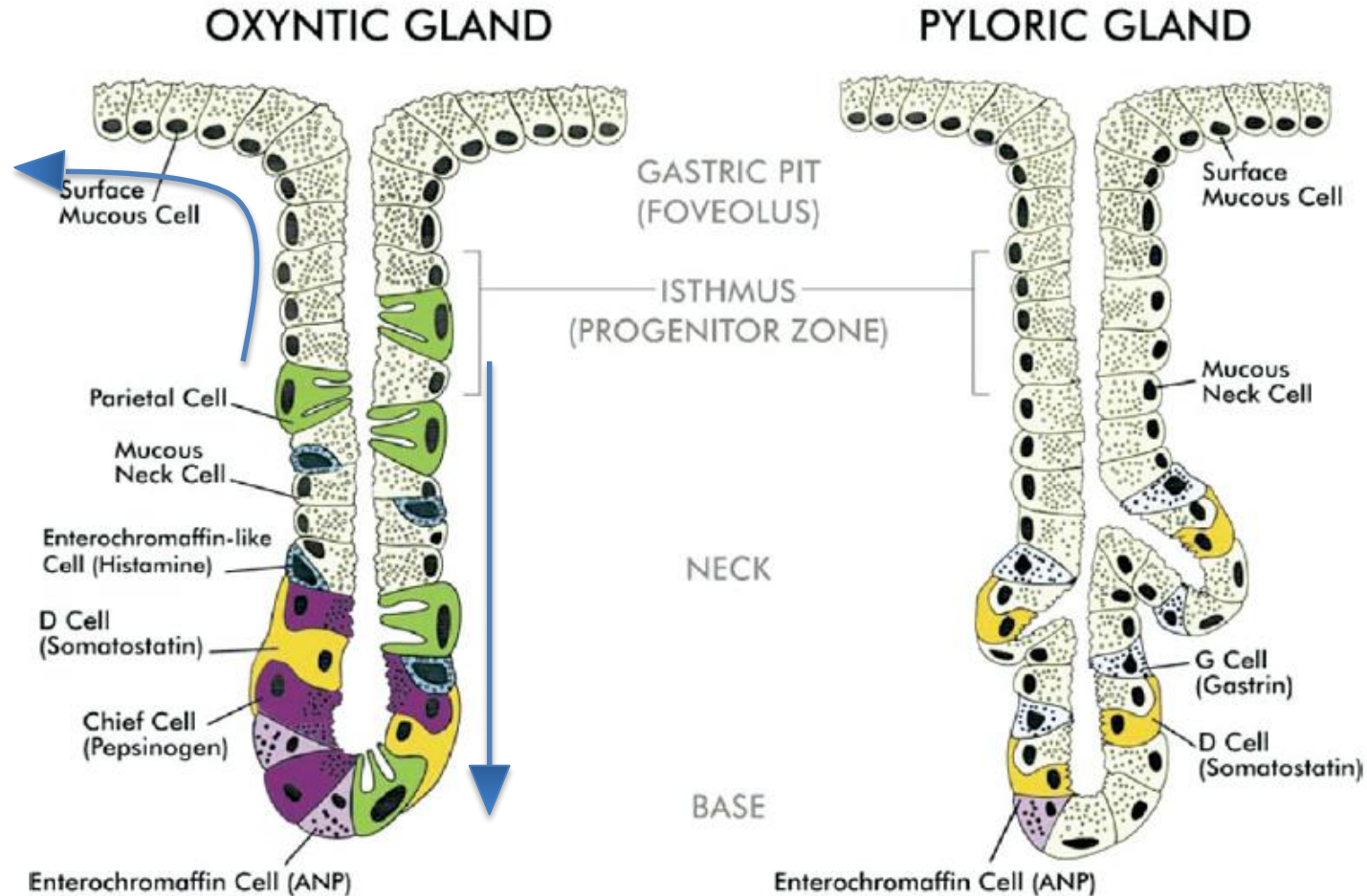
Gastric Glands

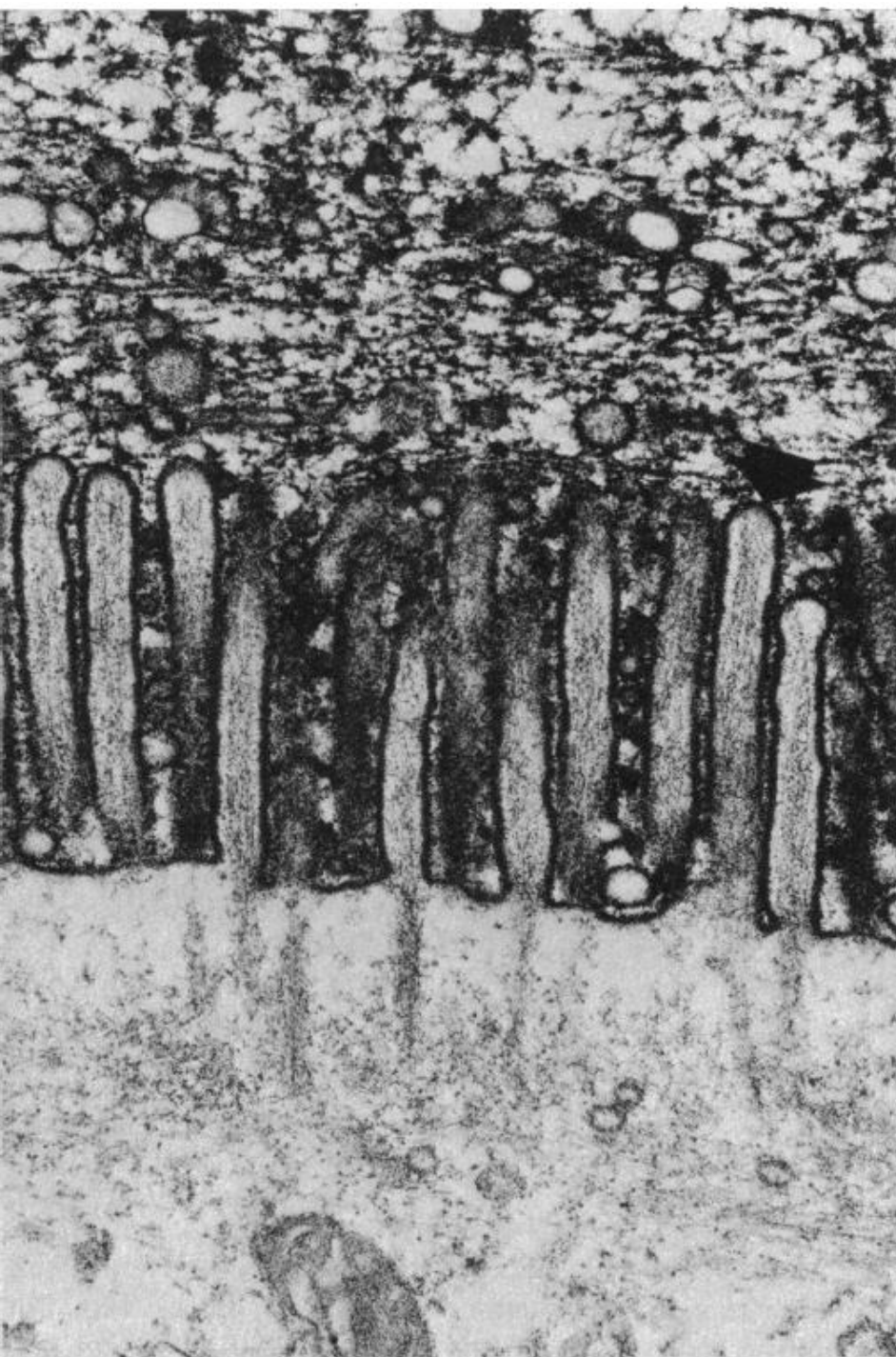
- Cells line the gastric pits with differing products
 - Acid secretion
 - Mucus secretion
 - Bicarbonate secretion
 - Hormone secretion



Endocrine Cells of Stomach

(Located in the stomach body)





Extrinsic barrier- The Mucous Layer

Mucous layer thickness
 $4.3 \pm 1.0 \mu\text{m}$

Microvilli height
 $1.6 \pm 0.2 \mu\text{m}$

Mucus

- Mucin glycoproteins
- Negatively charged
- 95% water (hygroscopic)
- Small amount of phospholipid, IgA

Case #3

- 15yo female presents with 6 months of abdominal pain, weight loss, GER and diarrhea.
- Laboratory evaluation
 - H. Pylori IgG – Negative
 - Celiac and RAST panels – Negative
 - Hemocult - Positive
- Minimal improvement with 1 month of PPI (20mg daily)

Case #3 Continued

- EGD –
 - Prominent gastric folds
 - Gastritis/ECL and Parietal cell hyperplasia
 - Duodenal ulceration
- What's your differential diagnosis?

Zollinger-Ellison Syndrome

- Gastric acid hyper-secretion secondary to gastrinoma
- Presentation
 - Pain – 83%
 - Diarrhea – 70%
 - Ulcerations (90% with duodenal ulcers)
- Diagnosis
 - Elevated fasting Gastrin (>1000 pg/ml) (+ gastric pH < 2)
 - Somatostatin receptor scintigraphy or PET scan
 - Secretin stimulation test – Elevated gastrin in ZES

Zollinger-Ellison Syndrome

- Prevalence is 1-3 per million
- 80% de novo mutation, 20% familial
- Gastrinoma
 - Duodenum 70%, Pancreas 20%, Lymph nodes 10%

Embryology Summary

- Week 1-2 - Germ Layers develop
- Week 3-4 – Primitive gut tube forms
- Week 4 – Foregut organs begin to form
- Week 5 – Neural crest cells start migration to form ENS
- Week 6 – Midgut herniation
- Week 7 – Urorectal septum begins to form
- Week 7-8 - Primitive gut has re-canalized
- Week 12-14- Appearance of primitive crypts
- Week 13- Completed development of both circular and longitudinal muscle layers
- Week 16- Epithelium develops along with muscularis mucosa
- Week 16 – Esophageal swallowing can be appreciated
- Week 20- Presence of well developed villi and crypts, along with lamina propria and specialized connective tissue

Review Questions

- A term male infant has non-bilious emesis after each feed since birth. A NG tube was passed and an abdominal radiograph shows a dilated stomach with a coiled gastric tube. The best diagnostic test to order next is:
 - Nuclear medicine gastric emptying study
 - Upper gastrointestinal series with contrast
 - Magnetic resonance imaging of the abdomen
 - Left lateral decubitus radiograph
 - Abdominal ultrasound

Review Question

- A 12yo previously healthy female presents with 2 days of worsening right sided abdominal pain with associated nausea and vomiting. She denies ill contacts, trauma, and toxin exposure. She is evaluated in the emergency department due to concerns of dehydration and worsening pain. Laboratory evaluation finds an elevated white blood cell count of 15 with no anemia. Transaminases and bilirubin are normal. Lipase is elevated at 2,500. Calcium is normal. Ultrasound of her abdomen appears normal. Her pancreatitis resolves after 1 week of conservative therapy. What is the most appropriate test to diagnose cause of recurrent pancreatitis?
- Hereditary pancreatitis genetic panel
- Computerized Tomography of abdomen
- Magnetic resonance cholangiopancreatography
- Endoscopic Retrograde cholangiopancreatography
- IgG4 level

Questions



Please send any questions or comments to

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