

NASPGHAN Physiology Lecture Series

Embryology and Anatomy of the Gastrointestinal Tract

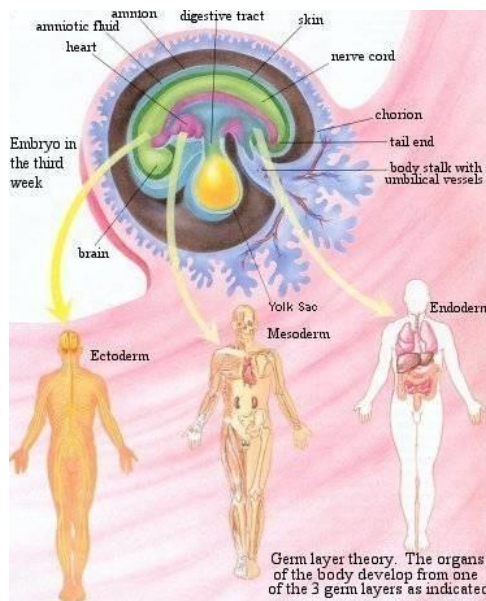
Christine Waasdorp Hurtado, MD, MSCS, FAAP
Christine.Waasdorp@childrenscolorado.org

Reviewers: Thomas Sferra, MD and Brent Polk, MD
Series Editors: Daniel Kamin, MD and Christine Waasdorp Hurtado, MD

Embryology of the GI Tract: (Slides 9-12)

Germ layers, formed during gastrulation, are present by two weeks and include endoderm, mesoderm and ectoderm. In humans, the germ tissues are the basis of all tissues and organs.

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



Images from: <http://ehumanbiofield.wikispaces.com/AP+Development+HW>

The Primitive gut tube develops during week 3-4 by incorporating the yolk sac during craniocaudal and lateral folding of the embryo. The tube is divided into 3 distinct sections; foregut, midgut and hindgut. Foregut gives rise to the esophagus, stomach, liver, gallbladder, bile ducts, pancreas and proximal duodenum. The midgut develops into the distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, and proximal 2/3 of transverse colon. The hindgut becomes the distal 1/3 of the transverse colon, descending colon, sigmoid colon and the upper anal canal.

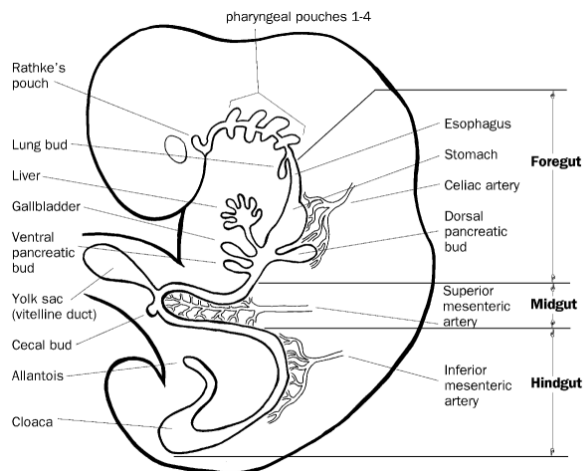


Image from <http://www.med.umich.edu/>

Proliferation of the epithelial lining of the gut tube results in obliteration of the lumen by week 6. The central cells then degenerate and the tube is recanalized by week 8. Abnormalities in this process result in: stenosis, atresia, and duplications.

Foregut Formation (Slides 13-19)

The foregut gives rise to the esophagus, stomach, liver, gallbladder, pancreas and the caudal portion of the duodenum.

Lateral grooves invaginate during week 4 on each side of the proximal foregut and fuse creating the tracheoesophageal septum. The septum separates the respiratory and digestive tracts with the ventral portion developing into respiratory system and dorsal into gastrointestinal tract. By week 16 the esophagus has

stratified squamous epithelium and swallow can appreciated. Failure of the tracheoesophageal septum development results in tracheoesophageal fistula and/or esophageal atresia.

The stomach develops from a fusiform dilation in the foregut during week 4. A 90 degree clockwise rotation creates the lesser peritoneal sac.

The liver develops from an endodermal outgrowth, hepatic diverticulum, at the cranioventral portion of the foregut. Mesoderm surrounds the diverticulum, septum transversum. Hepatic cells (hepatoblasts), both hematopoietic and endothelial precursor cells, then migrate into the septum transversum. The endothelial precursor cells, vitelline veins, are surrounded by hepatic cells forming the hepatic sinusoids. Bi-potential hepatoblasts give rise to both cholangiocytes and hepatocytes. The hepatoblasts in mesenchyme closest to the portal vein form a bi-layered structure, the ductal plate. These cells remodel to form bile ducts in the intrahepatic portal tracts.

Abnormal development of intrahepatic bile ducts due to ductal plate malformations are likely the underlying cause of congenital hepatic fibrosis and cystic kidney disease as well as ciliopathies such as Joubert syndrome, Meckel-Gruber and Ivemark syndrome.

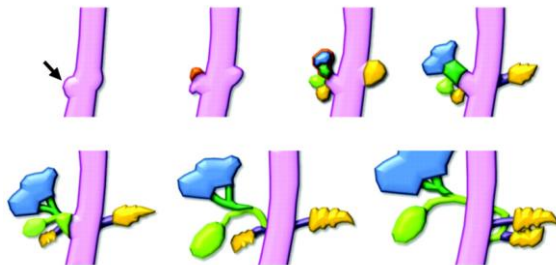


Image from: <http://www.ajronline.org>

Gallbladder and bile ducts begin as a cystic diverticulum. The gallbladder is initially solid and become cystic. Intrahepatic bile duct development starts at the hilum and progresses to the periphery of the liver. The common bile duct forms in an area of narrowing between the foregut and the hepatic diverticulum. At birth the most peripheral intrahepatic bile ducts are immature with persistence of ductal plate. Maturity of intrahepatic biliary tree is achieved by 4 weeks of life.

Pancreas development begins during the 4th-5th weeks of gestation as distinct dorsal and ventral buds arising from the endoderm of the caudal foregut, the proximal duodenum. The dorsal bud is larger than and slightly more cranial to the ventral bud. Each bud communicates with the foregut through a duct. Rotation of the duodenum causes the ventral pancreatic bud to rotate clockwise to the left of the duodenum and brings it posterior and inferior to the dorsal pancreatic bud. The two buds fuse to form the pancreas during the 7th week of gestation. The ventral bud forms the inferior part of the head of the pancreas and the uncinata process and the dorsal bud forms the superior part of the head, the body, and the tail of the pancreas. The ductal systems of the two buds fuse in the 8th week. The main pancreatic duct (duct of Wirsung) which enters the duodenum at the major duodenal papilla (ampulla of Vater) is formed by the longer dorsal duct draining into the proximal ventral duct to form. If the proximal portion of the dorsal duct remains, it forms an accessory duct (duct of Santorini) that opens into a minor accessory papilla located about 2 cm above the main duct. The accessory duct opens into a minor papilla in 33% of people and ends blindly in 8% of people. Fifty percent of people do not have an accessory duct. Endocrine cells (islets) are identifiable by the 8th week. Exocrine pancreatic development continues after birth with maturation of specific digestive enzymes.



Images from: www.netterimages.com

Abnormal development of the pancreas results in several congenital anomalies to include pancreas divisum. This is the most common variant (10%) and results from non-fusion of dorsal and ventral ducts during the second month of gestation. Annular pancreas is another congenital anomaly. A band of pancreatic tissue encircles the duodenum and is typically associated with other anomalies to include Down's syndrome and duodenal atresia.

Midgut Formation (Slides 20-22)

The distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, and proximal 2/3 of transverse colon develop from the midgut, between the 6 and 10th weeks. The midgut loop herniates through the primitive umbilical ring during umbilical herniation at week 6. By ten weeks of development the abdomen has enlarged so that the entire length of the midgut can be accommodated. Following a 270 degree counterclockwise rotation around the superior mesenteric artery, the bowel returns to the abdominal cavity. The large intestine returns following the small intestine and does an additional 180 degree counterclockwise rotation. Colonic fixation occurs after the return to the abdomen. Cecum and appendix begin as a diverticulum around the 6th week. Unequal cecal growth leaves appendix medial to the cecum.

Clinical correlations include omphalocele which results from failure of the midgut loop to return to the abdomen. Some or all of the abdominal contents remain outside the abdominal wall covered with an outer amniotic and inner peritoneal sac. Meckel's diverticulum is a persistent remnant of vitelline duct, forming a blind pouch on the antimesenteric border of the ileum. The diverticula often contain ectopic gastric, pancreatic, thyroid or endometrial tissue. Malrotation occurs if the midgut undergoes only partial rotation. Incidence is about 1 in 500 live births and has been identified in 0.5% of autopsies.

Hindgut Formation (Slides 23-25)

The distal 1/3 of the transverse colon, descending colon, sigmoid colon develop from the cranial end of the hindgut. The upper anal canal also develops from the terminal end of the hindgut with the urorectal septum dividing the upper anal canal and the urogenital sinus during the 6th week. By the 7th week, the urorectal septum fuses with the cloacal membrane, giving rise to the anal membrane and the urogenital membrane. The anal membrane ruptures during the 8th week allowing communication between the anal canal and the amniotic fluid. The superior 2/3 of the anal canal originates from hindgut and the inferior 1/3 is derived from proctodeum. The pectinate line is the junction of proctodeum ectoderm and hindgut endoderm.

Clinical correlation includes persistent cloaca resulting in fusion of rectum, vagina and urinary tract.

The mesentery develops from the mesoderm and connects the primitive gut to the body wall. The ventral mesentery is present only between the liver and the stomach, and the liver and the duodenum. It forms the lesser omentum, between

the liver and the stomach and duodenum, and the falciform ligament between the liver and the anterior body wall. The dorsal mesentery surrounds the rest of the primitive gut. It forms several organ ligaments and also becomes the greater omentum. Finally, the mesentery of the colon develops into the transverse mesocolon. During development some structures come to lie close to the posterior body wall and as the mesentery is absorbed the organ takes on a retroperitoneal position. Retroperitoneal organs include portion of the duodenum, the pancreas, the ascending and the descending colon.

Enteric Nervous System (Slides 26-31)

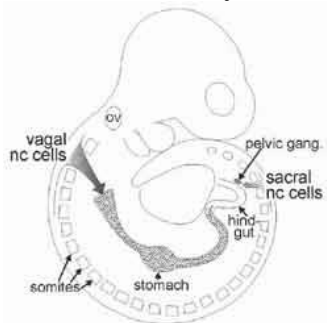


Image from: <http://www.landesbioscience.com/curie/chapter/2823/>

The enteric nervous system (ENS) originates from neural crest cells. The neural crest cells arise between the neural plate and the epidermal ectoderm along the entire rostrocaudal extent of the embryo. The ENS cells migrate to the dorsal midline forming the neural tube. The neurons of the ENS derive from these neural crest cells. Melanocytes, the sympathetic and parasympathetic ganglia all originate from the same cells as the ENS.

Neural crest cells migrate during the 5th and 12th week of gestation, down to the anal canal. Cells from the sacral segment of neural crest cells migrate from the sacral segment to the hindgut during the 6th to 12th weeks. The myenteric plexus develops first followed by the submucous plexus. As the gut lengthens and increases in diameter the ENS cells form ganglia, the functional unit of the ENS.

Interstitial cells of Cajal arise from the local gut mesenchyme and not from the neural crest cells. These cells are related to intestinal motility.

Hirschsprung's Disease (Slides 32-38)

Hirschsprung's Disease (HD) is a congenital disorder of the ENS affecting 1:5000 live births. HD is due to failure of neural crest cell colonization and migration resulting in tonic constriction of the affected bowel due to the aganglionic zone. There are two general types, short and long. Short segment is more common accounting for 80% of cases with a 4:1 male to female ratio. Typically HD is an isolated anomaly. Other anomalies are present in 30% of HD cases. Recent studies have identified multiple genes and modifier genes identified. The identified genes encode members of the Glial cell neurotrophic factor family, and are involved in either signaling pathways or are transcription factors.

Genes identified

- Ret
- GDNF
- EDNRB
- Sox10

Ret is a receptor tyrosine kinase with a strong association with HD. Ret dimerizes when activated by a member of the GDNF family and a glycoposphatidylinositol-anchored co-receptor. Ret stimulates enteric neural crest-derived cells to migrate, survive and differentiate. 70% of HD cases are associated with a Ret mutation. The severity of HD is variable. This is an indication of incomplete penetrance suggesting modifier genes, which have been identified. Gene Interactions have been identified in isolated Mennonite populations and in mouse models. The mechanisms remain unknown, but are thought to reflect downstream signaling. Identified interactions include: Ret-Ednrb, Ret-Et-3, and Sox10 and Et-3/Ednrb. Modifier genes are mutated gene that must be coupled with another mutation to result in or enhance the effect. An example of a modifier gene is Neuregulin 1 (NRG1) which associates with Ret. NRG1 signals receptors to regulate neural crest cell development. Sox10 also associated with NRG1. Additional modifiers have also been identified for Sox10, Et-3 and Ednrb.

Glial Cell-Derived Neurotrophic Factor (GDNF) is a family of extracellular signaling molecules and is a member of TGF- β superfamily. GDNF binds to and activates receptor tyrosine kinase (Ret). Defects in GDNF/Ret signaling account for 50% familial cases and 30% of sporadic cases.

Endothelin 3 (Et-3) and Endothelin receptor B (Ednrb) have also been implicated in the development of HD. Et-3 is a secreted protein expressed by gut mesenchyme that signals via Endothelin receptor B (Ednrb), which is expressed on

migrating enteric neural crest cells. Mutations in Et-3 and Ednrb account for 5% of HD cases

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

Genes and Gastrointestinal Embryology (Slide 39)

In addition to the role of genes in diseases, such as HD, the interplay of genes in gastrointestinal embryology is increasingly understood. Homeobox-containing transcription factors (Hox genes) have been identified as critical genes in gut regionalization. These genes control cellular events, with different Hox genes found in different tissues (i.e. – Hoxa3 in foregut and Hoxc5 in hindgut). Hox genes are vital to gut patterning along the AP axis to include gross morphology and epithelial differentiation. Sonic Hedgehog (Shh) is a transcription factor that controls endodermal-mesenchymal interactions. Defects in Shh are associated with TEF and anorectal malformations. It is also proposed that Shh defects play a role in development of IBD and malignancy.

Blood Supply (Slide 43)

Appropriate blood supply to the gastrointestinal tract and enteric organs is vital to health.

Proximal Esophagus - Inferior Thyroid Artery

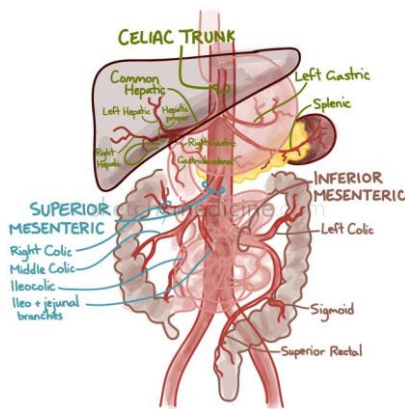
Thoracic Esophagus - Terminal bronchial arteries

Distal Esophagus - Left gastric and left phrenic arteries

Stomach - Celiac artery

Small intestine - Superior mesenteric artery

Large intestine - Superior and Inferior mesenteric arteries



<http://sketchymedicine.com/2012/04/blood-supply-of-the-gi-tract>

Stomach (Slides 44-49)

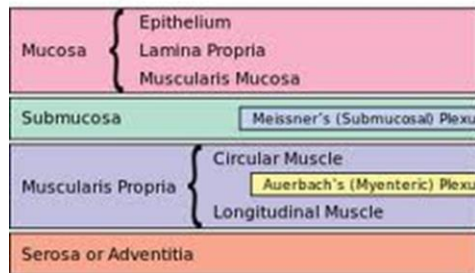
Gastric Features

The stomach serves as a reservoir, mixes and emulsifies food, secretes acids and digestive enzymes and regulates the release of gastric chyme into the duodenum. The fundus acts a reservoir for food. The body is a mixing chamber. The muscular antrum releases small volumes intermittently into the duodenum. Total gastric volume ranges from 30 ml in newborn to 2 L in adults.

Gastric Structure

The stomach muscle layers include an outer longitudinal layer, a middle circular layer, and an inner oblique layer. The inner lining consists of four layers: the serosa, the muscularis, the submucosa, and the mucosa. Gastric glands are densely packed in the mucosa. The glands contain cells that produce digestive enzymes, hydrochloric acid, and mucus.

General Organization of the Gastrointestinal Tract



http://en.wikipedia.org/wiki/Enteric_nervous_system

Gastric cells and their specific functions.

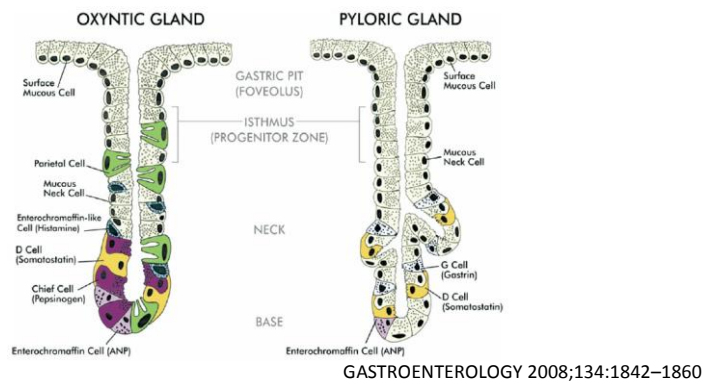
Parietal (oxyntic) cells - Secrete intrinsic factor and gastric acid
 Chief (zymogen) cells - Secrete Pepsinogen I and II
 Pyloric Glands - secreting gastrin and mucus.
 Mucous cells - Secrete mucus layer
 G cells - gastrin
 Enterochromaffin-like (ECL) cells - histamine
 Enterochromaffin cells - atrial natriuretic peptide and melatonin
 Gastric D cells - Somatostatin

Gastric pits cellular make-up varies by region

Cardia contains shallow pits with many mucous cells. Few parietal and chief cells.

Fundus contains deep, branched pits with mucous cells at the apex. Parietal cells located in the body. Chief and neuroendocrine cells are at the base. Chief cells are only present in the fundus.

Antrum contains deep pits with mucus, parietal and neuroendocrine cells.



Gastric Acid Hypersecretion

The majority of acid hypersecretion states result in gastroesophageal reflux and peptic ulcer disease. Acid hypersecretion can also result in diarrhea and

malabsorption of nutrients, particularly vitamin B12 and iron. The differential diagnosis includes Hypergastrinemia due to Zollinger Ellison syndrome, antral G cell hyperplasia, *H. pylori* infection, gastric outlet obstruction and short bowel syndrome. Hyperhistaminemia also results in gastric acid hypersecretion and can be due to mastocytosis and basophilic granulocytic leukemia. There are other etiologies that are not as clearly understood to include non-gastrin secreting tumors, rebound hypersecretion and other less common etiologies.

Gastrin, secreted by antral and duodenal G cells, regulates acid secretion as well as parietal cell maturation and gastric epithelial organization. Gastrin receptors are located on the surface of parietal cells and enterochromafin-like (ECL) cells. Stimulation of ECL results in histamine release stimulating parietal cells to release HCL. (See GI Secretion Module for full discussion)

Summary of events (Slide 54)

- 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

References

Faure S, Santa Barbara P. Molecular Embryology of the Foregut. JPGN, 2011.

Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fortran's Gastrointestinal and Liver Disease. 9th ed. Philadelphia, PA: Elsevier Health Sciences; 2010.

Goyal RK, Hirano I. Mechanism of Disease: The Enteric Nervous System. NEJM, 17, 1996.

Grand RJ, Watkins JB, Torti FM. Development of the human gastrointestinal tract. Gastroenterology, 1976.

Kleinman RE, Goulet OJ, Mieli-Vergani G, et al. Walker's Pediatric GI Disease. 5th edition ed. Hamilton, Ontario: BC Decker, Inc; 2008.

Lees C, Howie S, Sartor R, Satsangi J. The hedgehog signaling pathway in the gastrointestinal tract: implications for development, homeostasis and disease. Gastroenterology, 2005.

Newgreen D, Young H. Enteric Nervous System: Development and Developmental Disturbances—Part 1. Pediatric and Developmental Pathology 5, 2002.

Newgreen D, Young H. Enteric Nervous System: Development and Developmental Disturbances—Part 2. Pediatric and Developmental Pathology 5, 2002.

Osefo N, Ito T, Jensen RT. Gastric acid hypersecretory ~~states: recent~~states: recent insights and advances. Current Gastroenterology Reports, 2009.

Sri Paran T, Rolle U and Puri P. Enteric nervous system and developmental abnormalities in childhood. Pediatric Surgery International, 2006.

Wallace AS, Anderson RB. Genetic interactions and modifier genes in Hirschsprung's disease. World J Gastroenterology, 2011.

Watson SA, Grabowska AM, El-Zaatari M, Takhar A. Gastrin – active participant or bystander in gastric carcinogenesis. Nature Reviews Cancer 6, 2006

Review Questions:

1. 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:
 - A. Nuclear medicine gastric emptying study
 - B. Upper gastrointestinal series with contrast
 - C. Magnetic resonance imaging of the abdomen
 - D. Left lateral decubitus radiograph
 - E. Abdominal ultrasound

Answer: Upper GI series to confirm gastric outlet obstruction.

2. 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, ~~toxin~~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?
 - A. Hereditary pancreatitis genetic panel
 - B. Computerized Tomography of abdomen
 - C. Magnetic resonance cholangiopancreatography

- D. Endoscopic Retrograde cholangiopancreatography
- E. IgG4 level

Answer: MRCP is the most appropriate next test to evaluate the anatomy of the pancreas looking for pancreas divisum, which isare the most common congenital anomaly of the pancreas and a cause of recurrent pancreatitis.

Please contact Daniel Kamin or Christine Waasdorp Hurtado with questions.