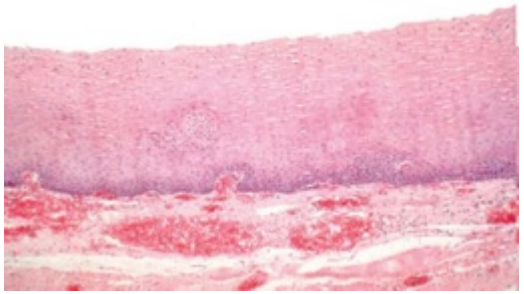
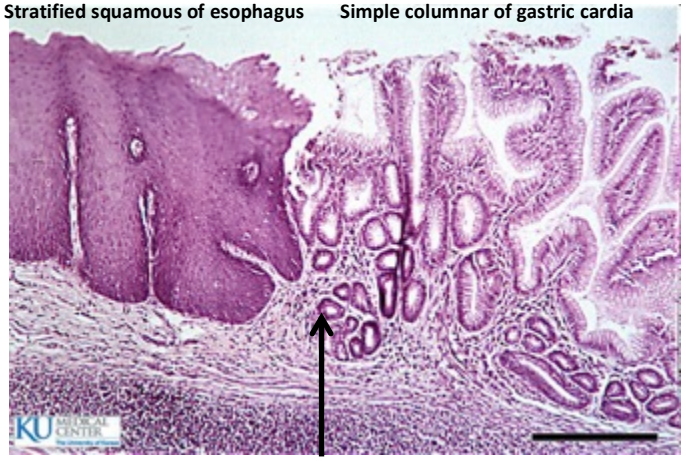
GI Path

ESOPHAGUS: Normal Anatomy & Histology

- Muscular tube connecting pharynx to stomach
- Upper (cricopharyngeal) & Lower (gastroesophageal) Muscular Sphincters: passage of food is stopped by muscular contraction & allowed to pass by muscular relaxation
- Histology: stratified squamous mucosa resting on loose lamina propria, containing supporting vasculature & scattered inflammatory cells

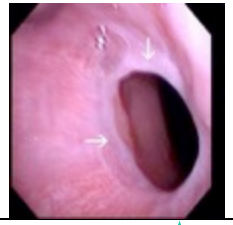
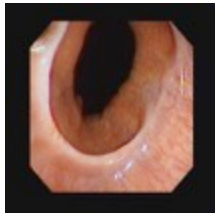


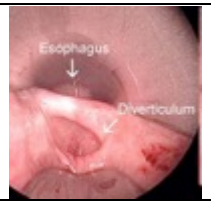
- Endoscopic Landmarks of Gastroesophageal Junction
  - **GEJ**: junction between tubular esophagus & proximal stomach (rugal folds)
  - SCJ: Z-line; mucosal junction of squamous & columnar tissue
    - *May not correspond with GEJ – meaning there is columnar metaplasia between the 2 points*

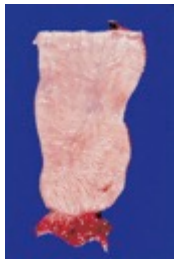


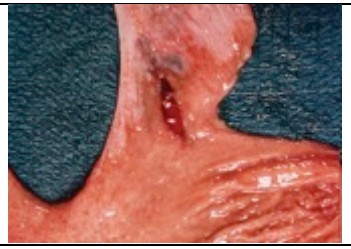
Normal Gastroesophageal (squamocolmnar) Junction

	1. ESOPHAGEAL ATRESIA & TRACHEOESOPHAGEAL FISTULA ***Congenital***
DEFINITION	*Upper esophageal atresia (blind pound) with the distal esophageal segment forming a fistula (connection) with the trachea*
CLINICAL	**Presents shortly after birth with regurgitation after feeding** **Aspiration**, pneumonia, fluid & electrolyte imbalances 50% have associated congenital anomalies: **VATER Syndrome** (**V**ertebral defects, **A**nal atresia, **T**racheo**E**sophageal fistula, & **R**enal dysplasia)
PATHOGENESIS	Exact defect is unknown

	2. ESOPHAGEAL WEB	**3. ESOPHAGEAL RING (Schatzki's Ring)**
DEFINITION	***ECCENTRIC***, thin membrane of tissue in the esophagus Most commonly in **PROXIMAL region** *Includes the esophageal **mucosa ONLY*** 	***CONCENTRIC***, thin diaphragm of tissue in the distal esophagus Most commonly at **GE junction (DISTAL region)** *May include **all 3 layers**: mucosa, submucosa, m. propria* 
CLINICAL	**PLUMMER-VINSON SYNDROME**: Upper Esophageal Web + Iron Deficiency Anemia + Glottitis + Cheilosis *(inflammation of corners of mouth)*	
	May cause **dysphagia** *(difficulty swallowing)* & **aspiration**	
TREATMENT	Responds to iron supplementation	

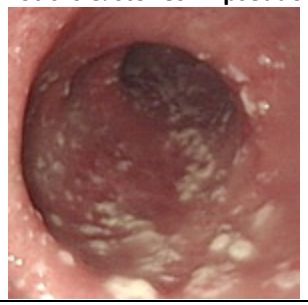
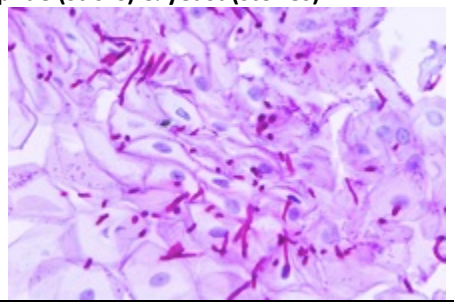
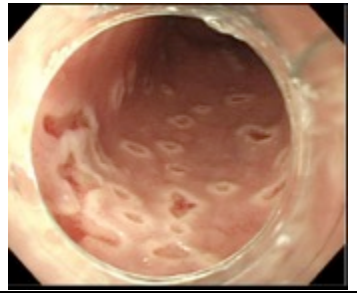
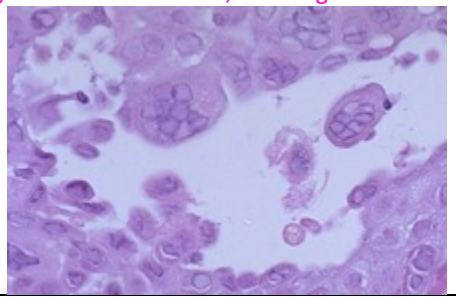
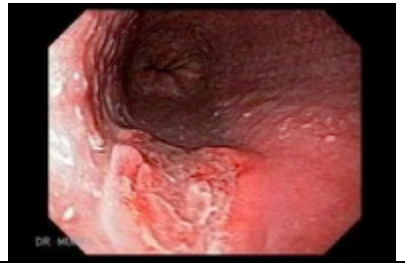
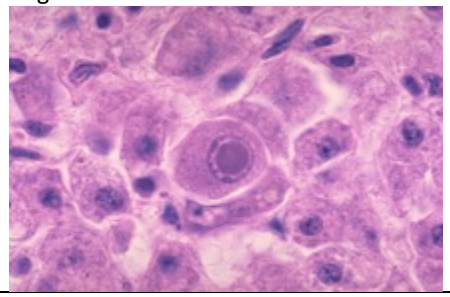
	4. ESOPHAGEAL DIVERTICULUM (Zenker Diverticulum)
DEFINITION	Out-pouching of esophageal wall **above the upper esophageal sphincter** *"Pseudodiverticulum"* 
CLINICAL	Food can collect within diverticulum causing **halitosis** *(bad breath)*, **regurgitation**, & **aspiration**
RISKS	***Increased risk for SQUAMOUS CELL CARCINOMA***

5. ACHALASIA	
DEFINITION	Inability of the **LES to relax** after swallowing, resulting in periodic esophageal obstruction
CLINICAL	**Dysphagia,** odynophagia, regurgitation
PATHOGENESIS	Impaired smooth muscle relaxation due to reduction or absence of **myenteric inhibitory neurons** **PRIMARY ACHALASIA:** due to degeneration of distal inhibitory ganglian cells; unknown cause **SECONDARY ACHALASIA:** variety of causes – Chagas Disease (*Trypanosoma cruzi*), Diabetic Autonomic Neuropathy, Malignancy, Amyloidosis, Sarcoidosis; *associated with Down Syndrome* (& possible autoimmune associated)
PATHOLOGICAL FINDINGS	 **BARIUM SWALLOW:** **"Bird's beak"** appearance  **Esophageal dilation**
CLINICAL COURSE/ RISKS	***Increased risk for SQUAMOUS CELL CARCINOMA***

6. MALLORY-WEISS LACERATION	
DEFINITION	Longitudinal mucosal tear near/across **GEJ** (usually on gastric side) associated with **severe vomiting due to alcohol intoxication**. Forceful vomiting/retching forces proximal stomach through diaphragm.
CLINICAL	*Abdominal pain, hematemesis, bloody stools*
PATHOGENESIS	Failure of LES to relax – *a normal reflex mechanism that occurs during vomiting*
GROSS	
CLINICAL COURSE/ RISKS	Usually heal on their own without surgical intervention Can cause **BOERHAAVE'S SYNDROME** (Acute Esophageal Rupture: Transmural perforation of distal esophagus + severe CP + tachypnea) – *surgery*

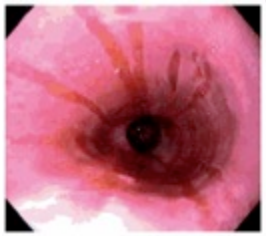
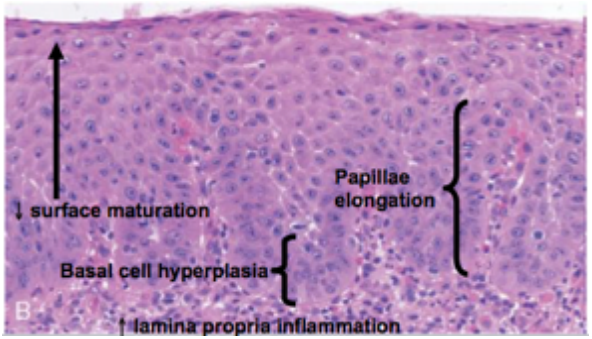
7. INFECTIOUS ESOPHAGITIS

Elderly or Immunocompromised Patients

ESOPHAGEAL CANDIDIASIS	Immunocompromised, Diabetics, Recent Antibiotics **"Sticks & stones" – pseudohyphae (sticks) & yeast (stones)**  
HERPES SIMLEX VIRUS (HSV) ESOPHAGITIS	Immunosuppressed patients ***LATERAL* aspect of the Ulcers:** **Cowdry A** internuclear "ground glass" inclusions **3 M's –** Multinucleation, Margination of chromatin, Molding of nuclei  
CMV ESOPHAGITIS	Immunosuppressed patients ***BASE* of the Ulcers:** Large (cytomegalo) cell with single large intranuclear inclusion with small intracytoplasmic inclusions  

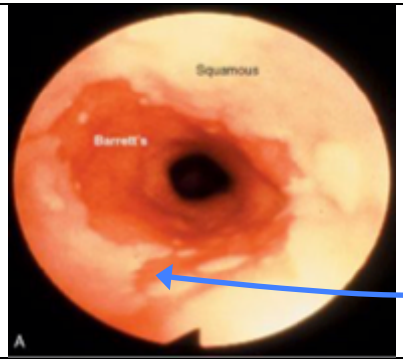
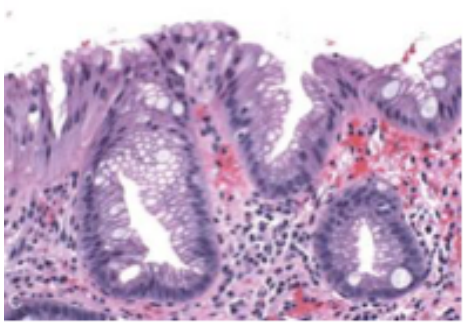
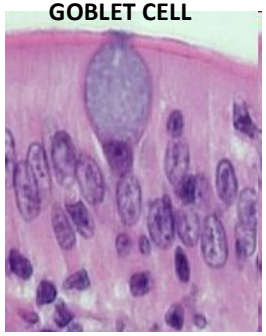
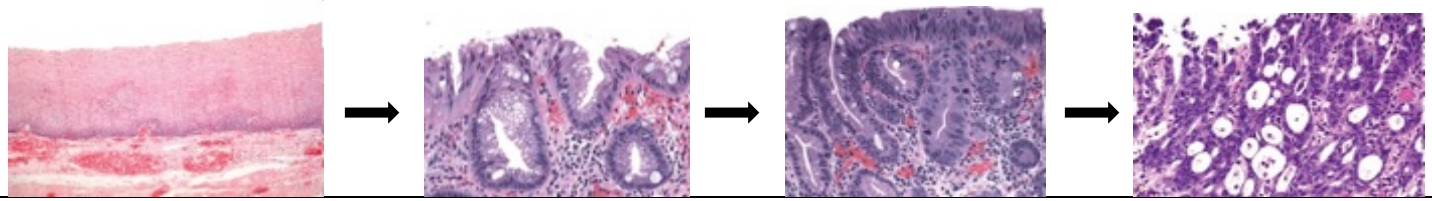
8. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

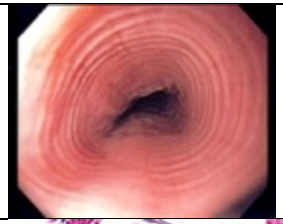
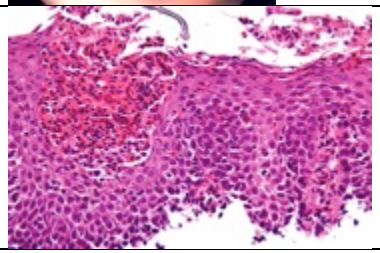
RISK FACTORS: Age, EtOH, Tobacco

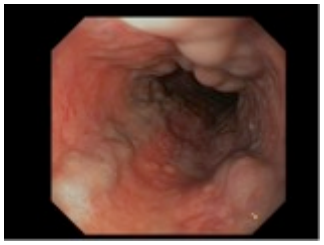
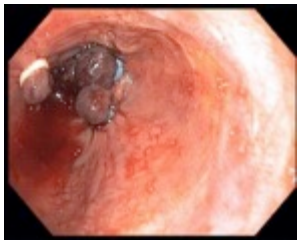
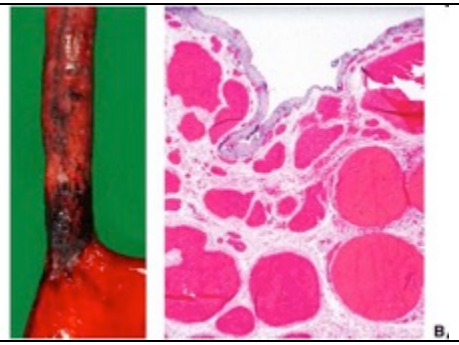
DEFINITION	Reflux of gastric acid into the esophagus **with mucosal damage**
CLINICAL	Heartburn, acid regurg, dysphagia, globus sensation, chronic sore throat
PATHOGENESIS	**GERD is the most common outpatient GI diagnosis in the USA caused by *transient relaxation of the LES, allowing reflux of gastric acid*** **Contributing Factors:** hiatal hernia, weak LES, impaired esophageal peristalsis, delayed gastric emptying, ↑gastric acid production
ENDOSCOPY	 Hyperemia, vertical linear streaks representing superficial mucosal erosions/ulcers
HISTO-MORPHOLOGY	*Basal zone hyperplasia, elongation of the lamina propria papillae, increased inflammatory cells (lymphocytes, eosinophils, neutrophils)*  **BIOPSY FINDINGS ARE NOT CONCLUSIVE OF GERD WITHOUT A CLINICAL HISTORY**
CLINICAL COURSE/ RISKS	COMPLICATION OF CHRONIC GERD: **BARRETT'S ESOPHAGUS**

9. BARRETT'S ESOPHAGUS

RISK FACTORS: Age, EtOH, Tobacco

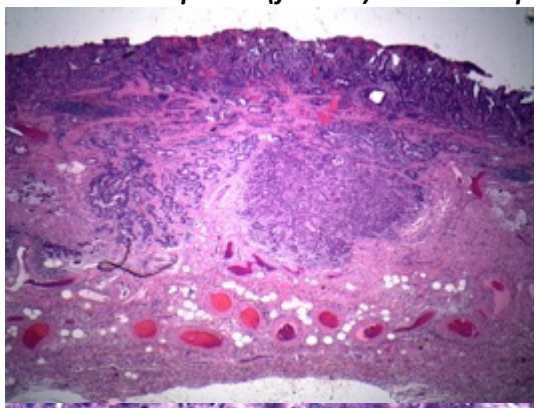
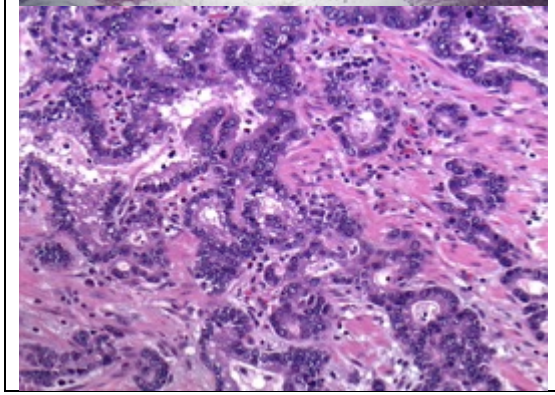
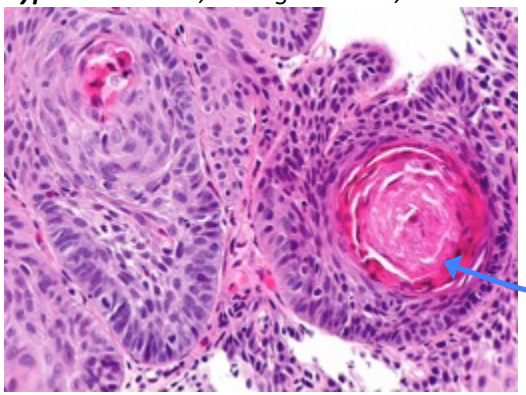
DEFINITION	***Endoscopically*** recognized **columnar metaplasia** of the esophageal mucosa that is confirmed ***pathologically*** to have **intestinal metaplasia**, defined by **GOBLET CELLS** – *both the endoscopic & pathologic components are required to diagnose Barrett's Esophagus* **GOBLET CELLS + COLUMNAR METAPLASIA = INTESTINAL METAPLASIA = BARRETT'S ESOPHAGUS**
CLINICAL	
PATHOGENESIS	Complication of Chronic GERD
ENDOSCOPY	 **SALMON-PINK TONGUES of metaplastic mucosa extending up into the esophagus**
HISTO-MORPHOLOGY	*Presence of **GOBLET CELLS** within mucosa **specified to have been taken from the GEJ***  **GOBLET CELL** 
CLINICAL COURSE/ RISKS	Normal epithelial → Barrett's Intestinal **Metaplasia** → Barrett's **Dysplasia** → Esophageal Adeno**carcinoma** 

10. PRIMARY EOSINOPHILIC ESOPHAGITIS History of ALLERGIES (Asthmatics, Dermatitis, Rhinitis)	
DEFINITION	An **ALLERGIC** disease (NOT related to acid refux), in which the esophageal mucosa has significantly increased **eosinophils** **BY DEFINITION –** Patients have **normal pH monitoring levels & fail anti-reflux therapy (i.e. PPIs)**
CLINICAL	**DYSPHAGIA**, food impactation – *Mimics GERD*
ENDOSCOPY	 **"Ringed (Feline) Esophagus"**
HISTO-MORPHOLOGY	 **EOSINOPHILIC MICROABSCESSES**
TREATMENT	Treatment includes dietary modification (elimination of cow milk), corticosteroids

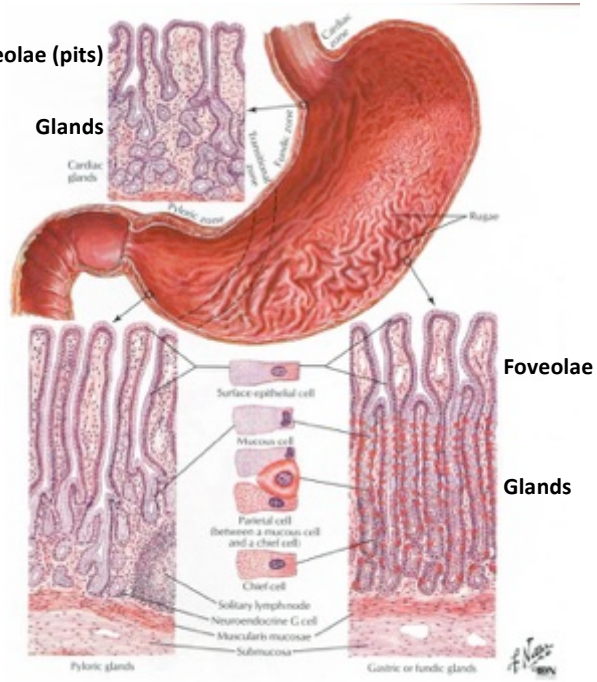
11. ESOPHAGEAL VARICES	
DEFINITION	Dilation of esophageal submucosal veinous plexus
CLINICAL	*Varices can rupture & bleed – Medical Emergency (30% of patents with variceal hemorrhage die)*
PATHOGENESIS	Anything that causes impairment of blood flow from Portal V. through the liver (cirrhosis) resulting in **PORTAL HTN**
ENDOSCOPY/ HISTO-MORPHOLOGY	  
TREATMENT	Sclerotherapy & banding (ligation of the vein)

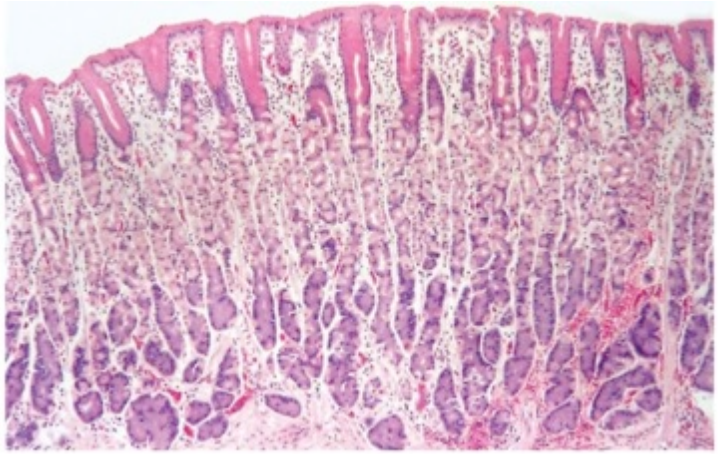
ESOPHAGEAL CANCER

(Depth of Invasion >>> Size)

12. ADENOCARCINOMA	13. SQUAMOUS CELL CARCINOMA
WHITE MALES, 60s	**AFRICAN-AMERICAN MALES**, 60s
High incidence in US – *80% of all esophageal tumors*	Low incidence in US but *most common esophageal carcinoma worldwide*
GERD **BARRETT'S ESOPHAGUS** Obesity Alcohol	**CHRONIC IRRITATION** **ALCOHOL + SMOKING** **Achalasia** **Zenker's Diverticulum**
DISTAL ESOPHAGUS	**PROXIMAL ESOPHAGUS**
GLANDS** with **nuclear hyperchromasia** & enlargement growing back-to-back with a **desmoplastic (fibrotic) stromal response;** Possibly **SIGNET RING CELLS	*Squamous epithelium, recognized due to **intercellular bridges**, with **nuclear hyperchromasia**, enlarged nuclei, & architectural disorganization; **+/-keratin***
 **Barrett's Esophagus** **Invasive Adenocarcinoma**  **GLANDULAR Differentiation**	 **Keratin Production**

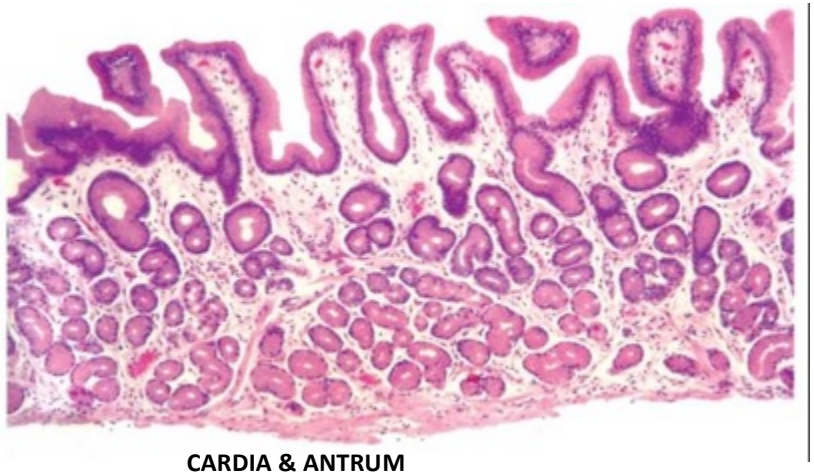
STOMACH: Normal Anatomy & Histology





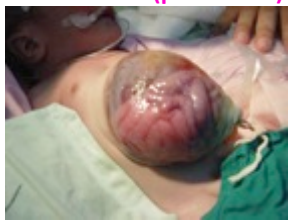
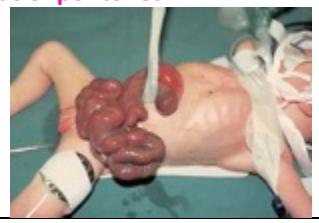
FUNDUS, BODY
Surface Foveolar Cells
Deeper Glands:
- **PINK = Parietal Cell**
- **BLUE/PURPLE = Chief Cell**

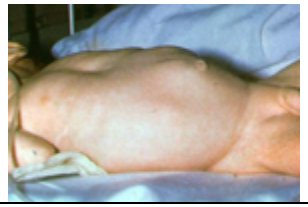
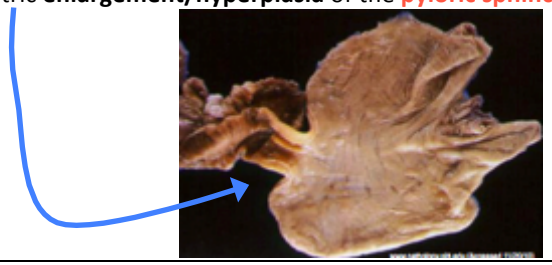
PARIETAL CELLS: HCl, Intrinsic Factor
CHIEF CELLS: Pepsinogen



CARDIA & ANTRUM
Surface Foveolar (Mucus) Cells
Deeper Mucus Glands

1. CONGENITAL DIAPHRAGMATIC HERNIA *Congenital*	
DEFINITION	When abdominal organs (**stomach**) herniate upward through **diaphragmatic defect** into the thoracic cavity; occurs *in utero*
CLINICAL	May result in **pulmonary hypoplasia**
PATHOGENESIS	Pulmonary hypoplasia is due to the fact that space is taken up in thoracic cavity by abdominal organs, preventing normal pulmonary development

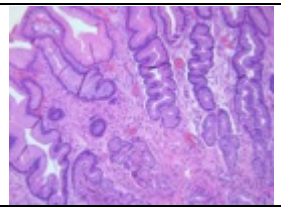
2. OMPHALOCELE	3. GASTROSCHISIS
Incomplete closure of abdominal muscular wall allows herniation of abdominal organs outside of body into a ventral **membranous (peritoneal) sac** 	Herniation through **all layers** of the abomdinal wall *(not just muscular defect)*, including the peritoneum; thus, abdominal content are completely outside the body & **NOT contained within a sac of peritoneum** 

4. CONGENITAL HYPERTROPHIC PYLORIC STENOSIS ***Congenital* – Males > Females & Caucasian**	
DEFINITION	Hyperplasia of the **pyloric muscularis propria** causing ***gastric outlet obstruction***
CLINICAL	Presents at 3-6 weeks of life with regurgitation, ***projectile vomiting after feeding**, + **firm olive shaped abdominal mass** **on PE*** 
PATHOGENESIS	Unknown
GROSS	Concentric **enlargement/hyperplasia** of the **pyloric sphincter** & **narrowing** of the **pyloric canal** that ***obstructs the gastric outlet*** 

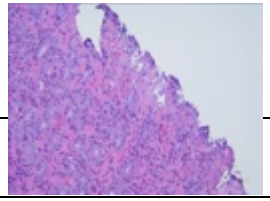
GASTRITIS VS. GASTROPATHY

PATHOGENESIS of GASTRITIS & GASTROPATHY

- Protective factors, including mucus secretion, bicarb, mucosal blood flow, & **elaborate prostaglandins**, normally protect from damaging factors such as gastric acidity or peptic enzymes
- Anything that injuries any of these protective measures will result in pathology
  - **NSAIDs** disrupt prostaglandins; **Tobacco** effects blood vessels; **Alcohol** is a direct irritant

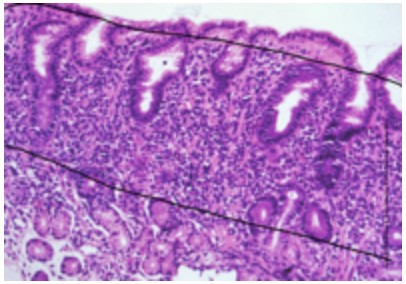
5. REACTIVE GASTROPATHY	
DEFINITION	Reactive changes with **little/no inflammation**
HISTO-MORPHOLOGY	**"CORK-SCREWING"** of glands due to **foveolar hyperplasia** 

6. ACUTE GASTRITIS	
DEFINITION	Mucosal inflammatory process; **SHORT-TERM**
CLINICAL	Abrupt onset of abdominal pain and bleeding
PATHOGENESIS	Breakdown of mucosal barrier by: Direct irritant (**ASA, NSAID, ETOH),** Drug MOA (**Steroids, ASA, NSAID**), Hypoperfusion (**post-operative state**)

7. ACUTE EROSIVE/HEMORRHAGIC GASTRITIS (AKA Stress Gastritis)	
DEFINITION	Mucosal inflammatory process; **SHORT-TERM**
CLINICAL	Abrupt onset of abdominal pain and bleeding
GROSS	**Petechiae**, erosions, ulcers  
HISTO-MORPHOLOGY	***Limited to mucosa***: superficial lamina propria hemorrhage, mucosal sloughing/necrosis, & neutrophils
TREATMENT	Acid-suppression (histamine blockers, PPs)

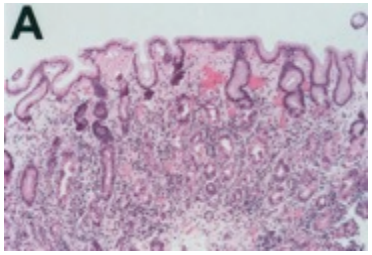
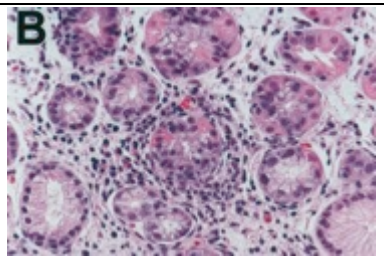
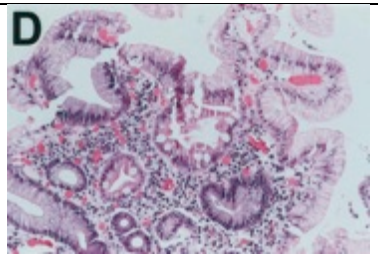
8. *HELICOBACTER PYLORI* GASTRITIS (Antral Gastritis)

#1 cause of Chronic Gastritis

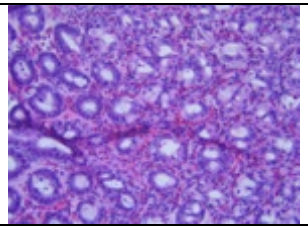
DEFINITION	Chronic **ANTRAL-predominant** gastritis caused by *H. pylori*
CLINICAL	
PATHOGENESIS	*H. pylori* is **UREASE+** organism that produces ammonia, creating a "basic force field" & allowing it to adapt to acidic environments. Infection with *H. pylori* has more than 1 outcome: 1. **Antral-predominant gastritis**: ↑ gastric acid production → *Duodenal Ulcers* 2. **Pan-gastristic:** Inflammation spreads & destroys all the parietal/glandular cells → **MULTIFOCAL ATROPHIC GASTRITIS** → *Increased risk of Intestinal Metaplasia, Dysplasia, & Adenocarcinoma*
HISTO-MORPHOLOGY	 © Elsevier 2005 Spiral-shaped organisms identified in the **mucus layer** just above the foveolar epithelium *(H. pylori is **NON**-invasive)*  Marked **LYMPHOPLASMACYTIC inflammation** admixed with **NEUTROPHILS** **(chronic 'active' gastritis)** in the *superficial lamina propria* of the gastric antrum
CLINICAL COURSE/ RISKS	**Complications**: **Peptic Ulcer Disease** Multifocal Atrophic Gastritis leads to increased risk of **Intestinal Metaplasia, Dysplasia, & Adenocarcinoma**

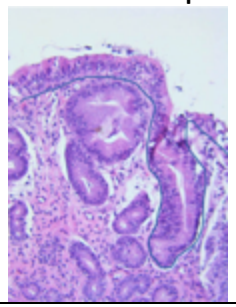
9. AUTOIMMUNE GASTRITIS (Fundus Restricted Atrophic Gastritis)

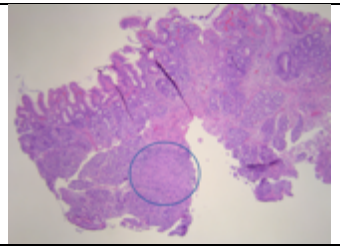
Older Females (60s)

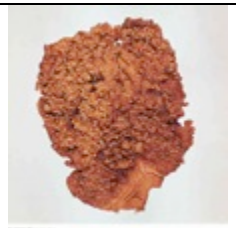
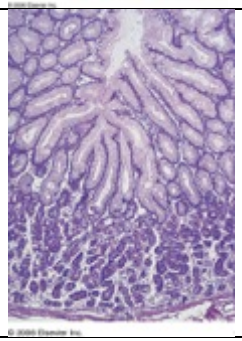
DEFINITION	Autoimmune mediated chronic gastritis characterized by the ***destruction of parietal cells in the gastric body/fundus*** ***NOTE:** Autoimmune Gastritis is limited to the **BODY/FUNDUS** because this is the only place where parietal cells are found!
CLINICAL	**Achlorhydria** (↓acid production), **HYPERGASTRINEMIA**, **Pernicious/Megaloblastic Anemia** (Vitamin B12 deficiency) *Can also have peripheral neuropathy, demyelination of spinal cord, cerebral dysfunction, etc.*
PATHOGENESIS	**Anti-parietal cell** & **anti-intrinsic factor antibodies**: – **Loss of IF** leads to decreased absorption of B12 → Megalobalstic Anemia – **Loss of parietal cells** leads to achlorhydria **& stimulates G cells in antrum to produce more gastrin** in efforts to produce more acid. With the loss of acid-producing cells, the result is hypergastrinemia.
HISTO-MORPHOLOGY	 Inflammation is deeper than in Antral/H. pylori Gastritis   Fundic gland damage by **patchy lymphocytic infiltrates** → Loss of glands → **ATROPHIC GASTRITIS (B)** → **INTESTINAL METAPLASIA w/ GOBLET CELLS (D)** ***Note**: 'active' or acute inflammation is not typically seen*

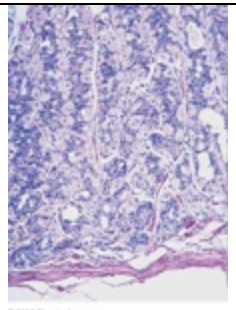
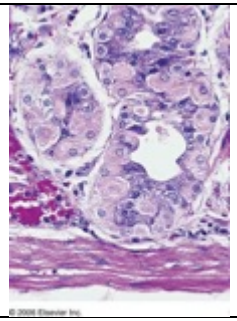
	***H. Pylori* Gastritis**	**Autoimmune Gastritis**
Etiology	*H. pylori infection*	Immune-mediated
Sex	NO sex predilection	Females
LOCATION*	**ANTRUM w/ extension into Body, Multifocal**	**BODY & FUNDUS ONLY**
Anti-parietal cell Ab	–	+
Anti-intrinsic factor Ab	–	+
Vitamin B12 level	Normal Vitamin B12	↓Vitamin B12 **(Pernicious Anemia)**
Serum gastrin	Normal/↑ Gastrin	↑↑↑Gastrin **(Hypergastrinemia)**

10. EOSINOPHILIC GASTRITIS	
DEFINITION	Chronic gastritis associated with significantly increased eosinophils in gastric lamina propria
PATHOGENESIS	CHILD: **Allergy** ADULT: **Parasite**
HISTO-MORPHOLOGY	

11. LYMPHOCYTIC GASTRITIS	
DEFINITION	Chronic gastritis associated with significantly increased intraepithelial lymphocytes
PATHOGENESIS	Mostly idiopathic, but 40% associated with **CELIAC DISEASE** & tend to be refractory to a gluten-free diet
HISTO-MORPHOLOGY	Increased **intraepithelial lymphocytes** in surface foveolar epithelium 

12. GRANULOMATOUS GASTRITIS	
DEFINITION	Chronic gastritis with granulomas
DDx	Crohn's, sarcoidosis, *Mycobacteria* infection
HISTO-MORPHOLOGY	

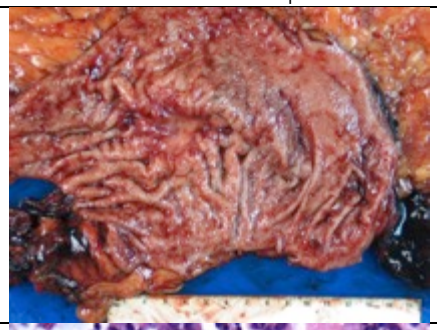
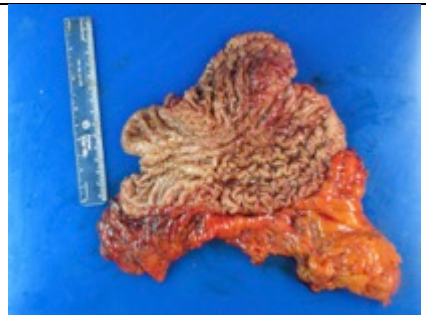
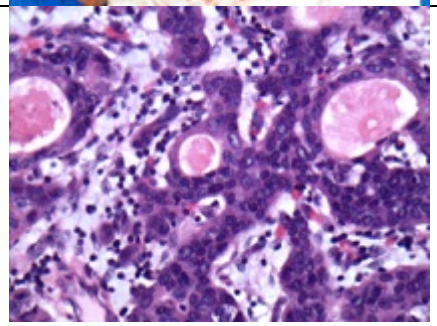
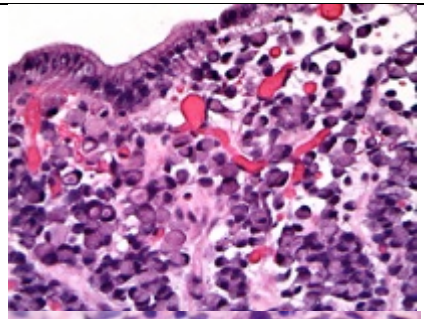
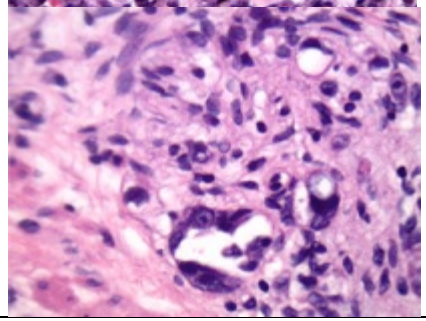
13. MENETRIER'S DISEASE *Hypertrophic Gastropathy*	
DEFINITION	**Body & Fundus**-restricted hyperplasia of **foveolar (MUCUS CELL) epithelium** with **HYPOPROTEINEMIA** due to ***protein-losing enteropathy***
CLINICAL	Loss of plasma proteins through gastric mucosa → **PERIPHERAL EDEMA**
PATHOGENESIS	TGF-α overexpression
GROSS	 Enlarged, **cerebriform rugal folds** limited to fundus/body (antrum is spared – *seen at bottom right of image*)
HISTO-MORPHOLOGY	 **Foveolar** (mucus cell) **hyperplasia**

14. ZOLLINGER-ELLISON SYNDROME *Hypertrophic Gastropathy*	
DEFINITION	Diffuse hyperplasia of **Fundic-Body PARIETAL CELLS** in response to **hypergastrinemia**
CLINICAL	
PATHOGENESIS	Usually due to a **GASTRINOMA (gastrin-secreting tumor)** in either the pancreas, duodenum, or antrum
GROSS	**Grossly mimics Menetrier's Disease! – They look EXACTLY the same***
HISTO-MORPHOLOGY	 

15. GASTRIC ADENOCARCINOMA

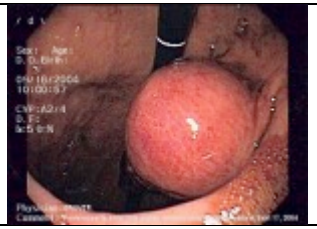
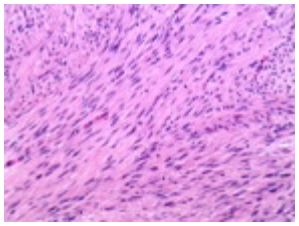
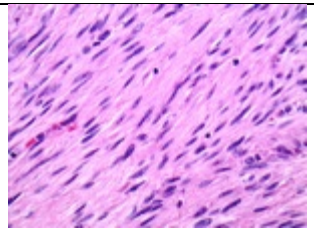
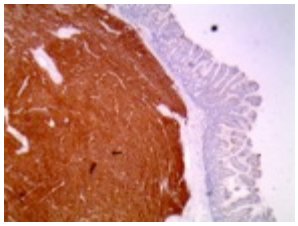
2nd most common cancer worldwide

***Developing countries; Japan, Costa Rica, East Asia, E. Europe* & Males (70s)**

↑ RISK	**DIET –** nitrites, nitrates, salt & salted foods, smoked foods **(Japanese)**; **Smoking; CHRONIC ATROPHIC GASTRITIS*;* CHRONIC *H. PYLORI,* EBV**
PATHOGENESIS	**SPORADIC (Most Common):** Chronic Gastritis → Atrophic Gastritis → Intestinal Metaplasia → Dysplasia → Adenocarcinoma **HEREDITARY:** germline **E-Cadherin/CDH1 gene mutation** – **~37 y/o** at diagnosis – Associated with ↑risk for lobular breast cancer
GROSS	 **INTESTINAL TYPE** **Produces an ulcer**  **DIFFUSE TYPE** *"Hard & crunchy feel on biopsy with lack of distention of gastric walls despite continuous air insufflation)* **LINITUS PLASTICA** ***Desmoplasia***
HISTO-MORPHOLOGY	 **INTESTINAL TYPE** **Gland forming** ***Into the ulcer*** ***No intervening stroma***
	 **DIFFUSE TYPE**  **SIGNET RING CELLS**: *intracytoplasmic mucin droplet displacing nucleus*
CLINICAL COURSE	Dependent on **DEPTH OF INVASION**, **NOT size**
MET SITES	**Virchow's Node** = L supraclavicular; **Sister Mary Joseph's Nodule** = periumbilical (intestinal); **Krukenberg tumor** = bilateral ovarian (diffuse); **Blumer Shelf** = Pouch of Douglas,

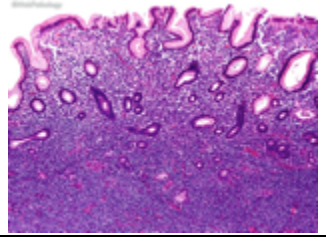
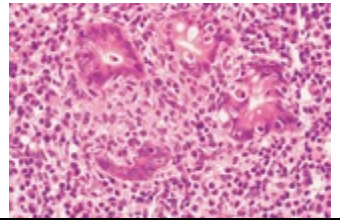
16. GASTRO-INTESTINAL STROMAL TUMORS (GIST)

Most common mesenchymal tumor of abdomen

DEFINITION	Mesenchymal tumor derived from **interstitial cells of Cajal** **(pacemaker cells of the GI tract)**
CLINICAL	Carney Triad: syndrome in young females of GIST, paraganglioma, pulmonary chondroma *(not in slides)*
PATHOGENESIS	**C-KIT** (RTK) positive in 85%
GROSS	 **Submucosal mass**
HISTO-MORPHOLOGY	  **SPINDLE CELL Neoplasm** ***Forms fascicles***  **C-KIT +**
PROGNOSTIC INDICATORS	**Site, SIZE, Mitotic Index**
TREATMENT	**Imatinib**

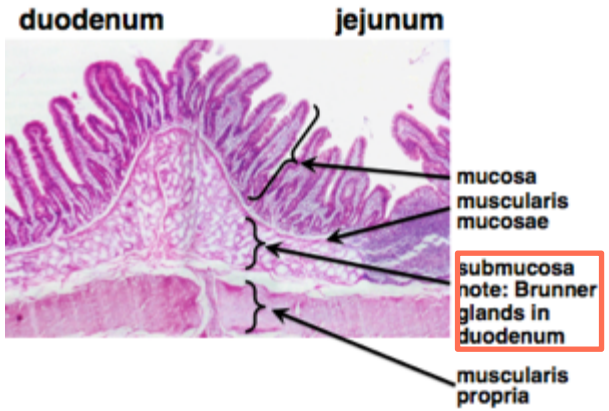
17. GASTRIC MALT LYMPHOMA

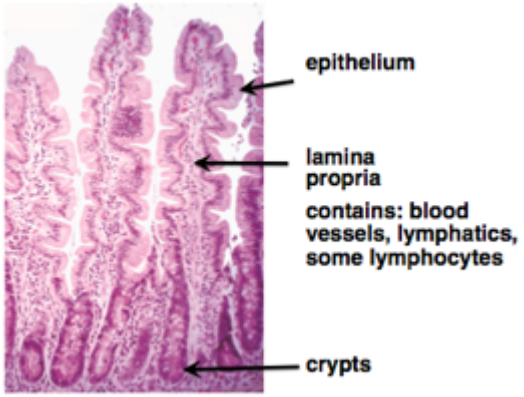
Most common primary gastric B-cell lymphoma

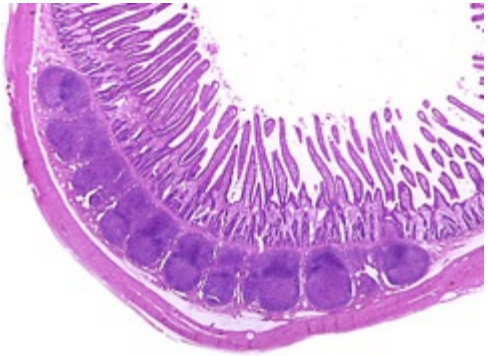
PATHOGENESIS	Most commonly arises from **Chronic *H. Pylori* Gastritis** Tumor can undergo genetic translocation, t(11;18)
HISTO-MORPHOLOGY	***Increased lamina propria*** *+ chronic inflammation*   **LYMPHEPITHELIAL LESIONS:** glands with intraepithelial lymphocytes + destruction
CLINICAL COURSE	Treatment of *H. pylori* can lead to lymphoma remission (unless possesses a translocation)

SMALL BOWEL: Normal Anatomy & Histology

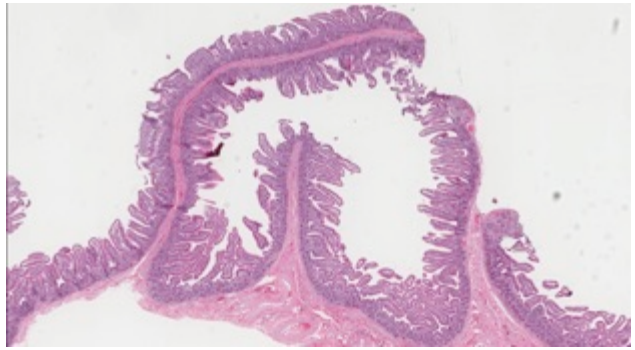
- **Epithelium:** apical cytoplasm is very pink & clear with basally oriented nucleui
  - **NOTE:** *there are NO intraepithelial lymphocytes!* ***You WILL see these in Celiac's!*



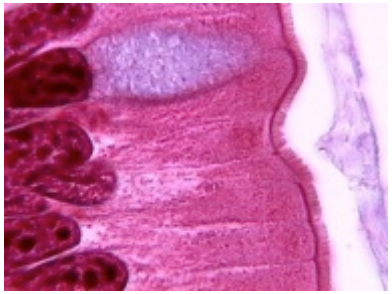




NORMAL ILEUM – resembles jejunum but has more lymphoid tissue in submucosa **(Peyer's Patches)**



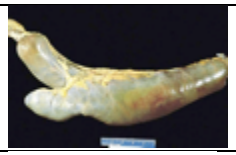
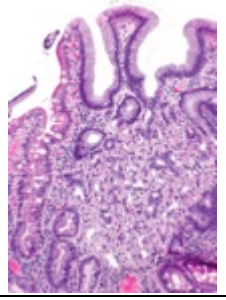
NORMAL JEJUNUM – **Plicae circulares**
Site of absorption & maximal surface



NORMAL JEJUNUM – Microvilli*

1. MECKEL DIVERTICULUM

Most common cause of intussusception in a young child

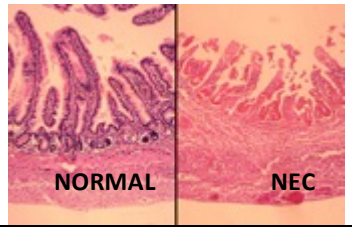
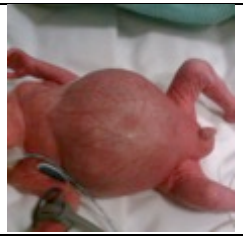
DEFINITION	A *true diverticulum* of the **ileum** (goes through all layers of the bowel) caused by ***failure of vitelline duct to involute*** **RULES OF 2's:** – 2% of population, **Within 2 feet of ileocecal valve*,** 2" long, 2x more common in **males,** Symptomatic by age of 2
CLINICAL	Abdominal pain, bloody stool – *"Previously normal 2 year old all of a sudden doesn't want to eat."*
GROSS	
HISTO-MORPHOLOGY	 SMALL BOWEL CONTAINS **HETEROTROPHIC GASTRIC MUCOSA**** ***Potential to cause ulceration/bleeding in neighboring ileal mucosa**

2. SMALL INTESTINAL OBSTRUCTION

PATHOGENESIS	**Herniation**: *protrustion of peritoneal cavity through a weakness/defect of abdominal wall; most common cause of intestinal obstruction worldwide* **Adhesions:** *fibrous bridges adhere to segments of bowel due to prior surgery, infection, or inflammation; most common cause of obstruction in US* **Volvulus:** *twisting of a loop of bowel that can cause ischemia/infarcton due to vascular compromise; sigmoid > cecum > small bowel* **INTUSSUSCEPTION** ***(Most common cause of obstruction in children <2 years)***

3. NEONATAL NECROTIZING ENTEROCOLITIS (NEC)

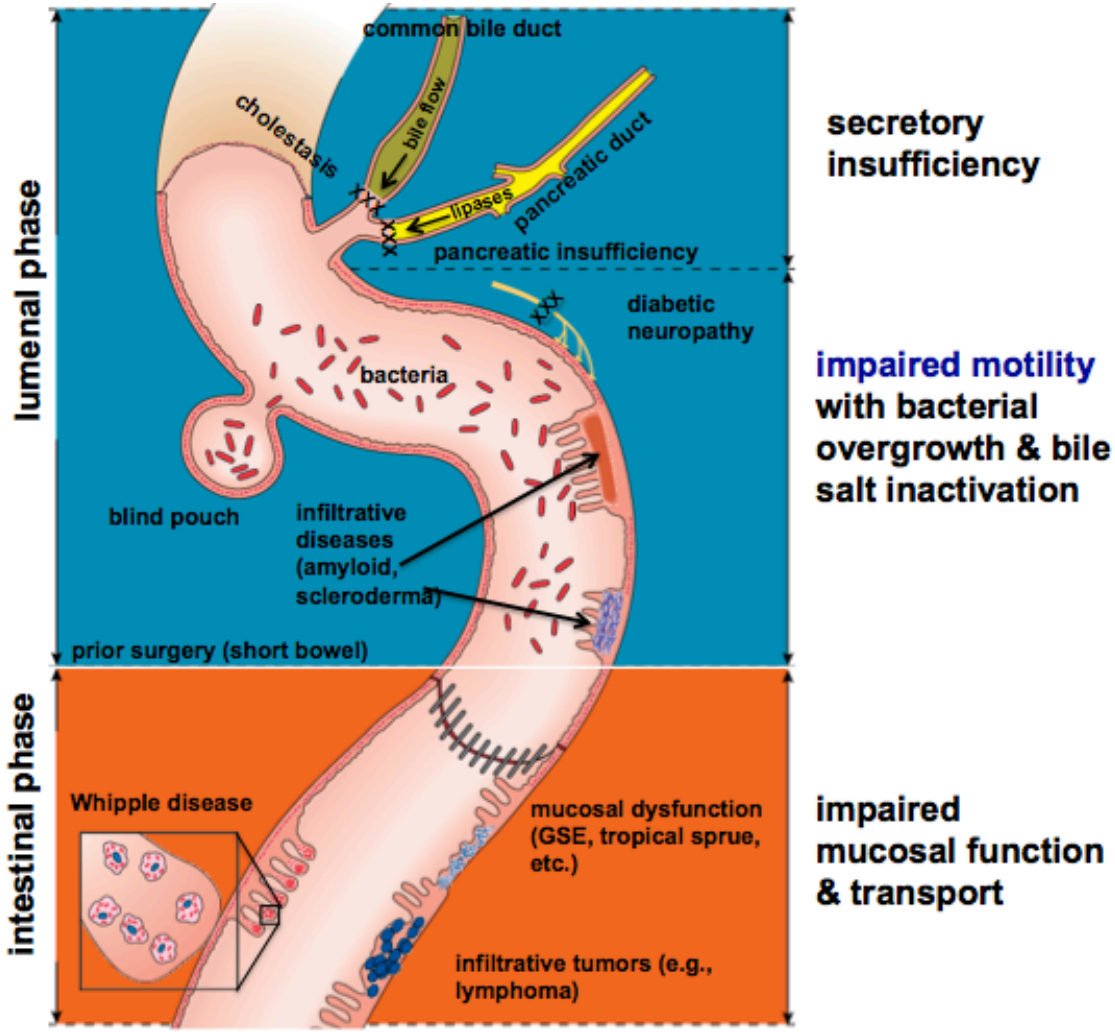
Premature Babies

DEFINITION	Acute vascular compromise that results in **transmural necrosis** in neonates upon starting oral feeds; likely due to *bowel immaturity*
CLINICAL	**Abdominal distension**, bloody stool, perforation... possible death
HISTO-MORPHOLOGY	 

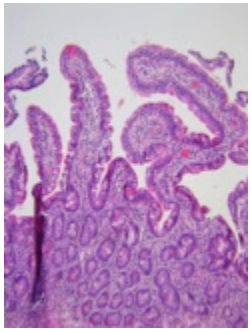
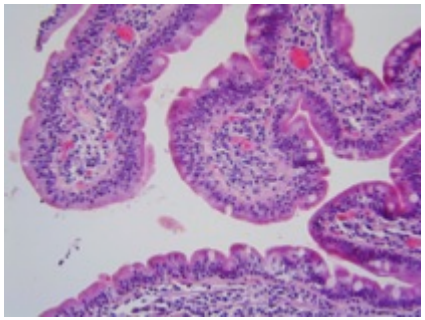
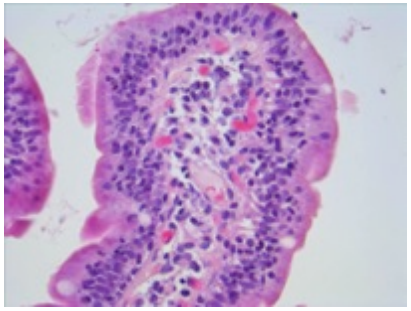
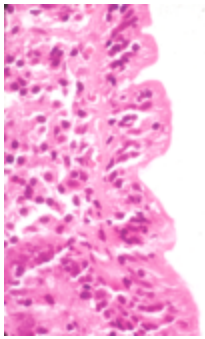
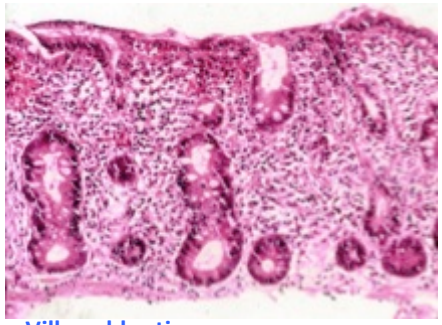
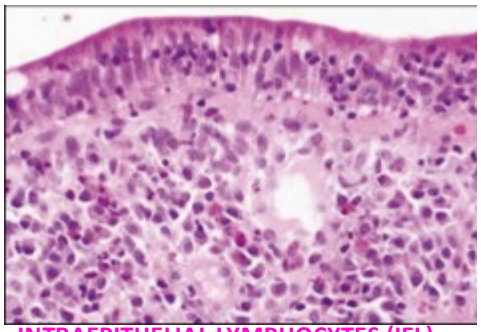
DISEASES OF MALABSORPTION

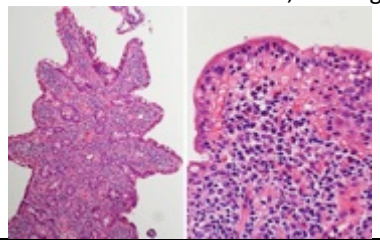
Chronic malabsorption may reflect a defect in luminal or intestinal phases of digestion

- LUMINAL phase defects mostly affect digestion & processing of food in the small intestine lumen; *within the tube of the gut*
- INTESTINAL phase defects often reflect altered villous cells or structures that absorb & transport nutrients; *the gut lining cells*

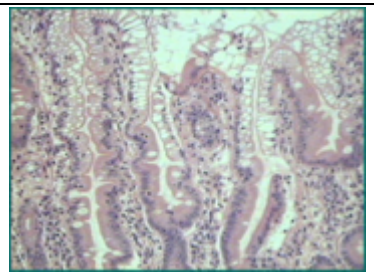
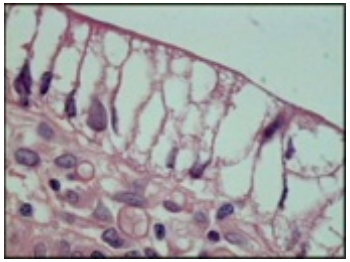
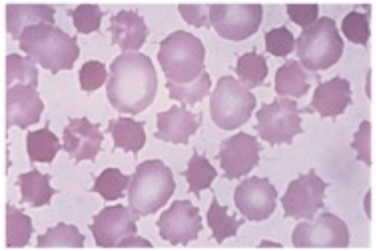


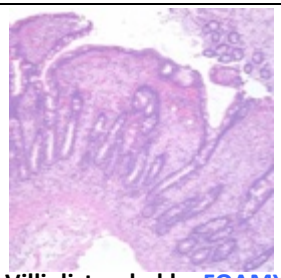
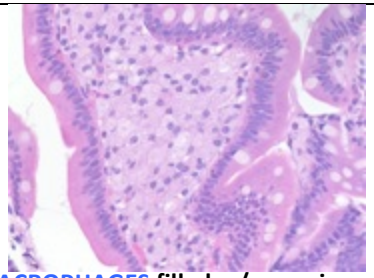
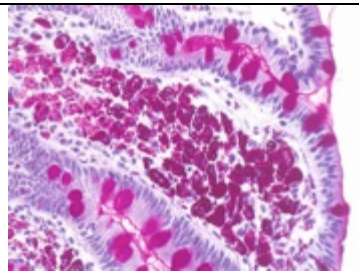
4. CYSTIC FIBROSIS & MALABSORPTION	
DEFINITION	Defect in CFTR gene leading to defective chloride (& thus, water) secretion → defective **LUMINAL** hydration (**intestinal obstruction**) & defective hydration of pancreatic ducts → pancreatic intraductal mucus & concretions with obstruction → **pancreatic autodigestion** with ***insufficiency of pancreatic enzyme secretion***
CLINICAL	
PATHOGENESIS	Mutation in CFTR gene (chr7), encoding protein involved in Cl^- transport across epithelia

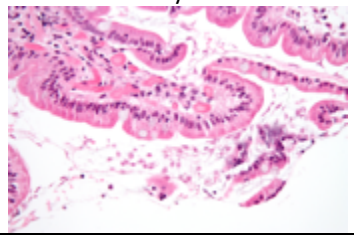
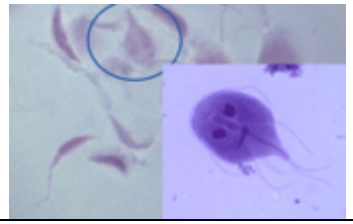
5. CELIAC DISEASE (Gluten-Sensitive Enteropathy – GSE)	
DEFINITION	**IMMUNE-MEDIATED enteropathy triggered by foods containing GLUTEN in *genetically-susceptible individuals***
PATHOGENESIS	GLUTEN is a protein that contains a component called **GLIADIN**. **Gliadin digestion induces inflammation** in Celiac patients. **HLA-DQ2** or **HLA-DQ8** on APC cells found in most patients.
SEROLOGY	**Anti-tissue transglutaminase IgA**, anti-endomysial IgA
HISTO-MORPHOLOGY	***IF ADHERING TO A GLUTEN-FREE DIET, BIOPSY MAY BE NORMAL!*** ***Varies with disease severity:*** *Chronic inflammation, loss of* ***brush border****, villous blunting,* ***intraepithelial lymphocytes*****     Chronic inflammation Loss of brush border  Villous blunting  INTRAEPITHELIAL LYMPHOCYTES (IEL) Loss of brush border

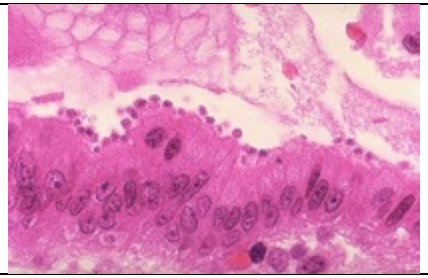
6. TROPICAL SPRUE (Environmental Enteropathy)	
DEFINITION	Malabsorption disease in ***regions with poor sanitation***
CLINICAL	
PATHOGENESIS	Cause is unknown but likely infectious on top of impaired mucosal barrier function in impoverished/malnourished children
HISTO-MORPHOLOGY	**SAME AS CELIAC DISEASE**, although thought to affect entire small bowel (rather than just proximal)  **Increased IELs + villous blunting**
TREATMENT	Antibiotics + Folic Acid + Vitamin B12

7. LACTASE DEFICIENCY	
DEFINITION	Congenital (rare) or acquired (adult) deficiency of lactase, & thus inability to digest lactose
CLINICAL	**ACQUIRED: diarrhea + flatulence** due to fermentation of lactose by colonic bacteria **CONGENITAL**: explosive diarrhea upon milk ingestion w/ resolution once milk is withheld
PATHOGENESIS	**ACQUIRED:** down-regulation of lactase gene expression; *diseases that affect brush border enzymes (Celiac) may cause secondary loss of lactase* **CONGENITAL** (AR): mutation in gene encoding lactasae

8. ABETALIPOPROTEINEMIA	
DEFINITION	***Inability to secrete triglyceride-rich lipoproteins due to genetic mutation in a transporter***
CLINICAL	Presents in infancy with diarrhea, steatorrhea, deficiency of fat-soluble vitamins, lipid-membrane defects
PATHOGENESIS	Autosomal recessive mutation in **lipoprotein transporter** gene → ***accumulation of lipids within enterocyte cytoplasm***
HISTO-MORPHOLOGY	 **Accumulation of lipids in enterocyte cytoplasm**  **VACUOLATED ENTEROCYTES:** *lipids can't get assembled into chylomicrons & out of enterocyte*  **RBC Burr Cells (Acanthocytes):** *due to loss of membrane lipids*

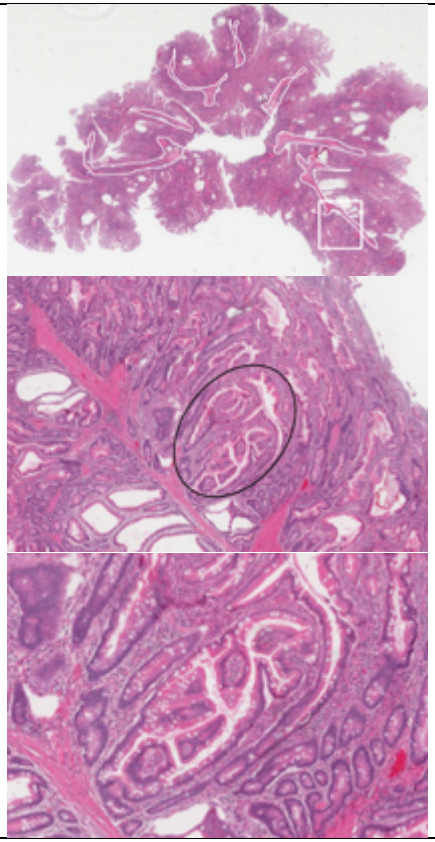
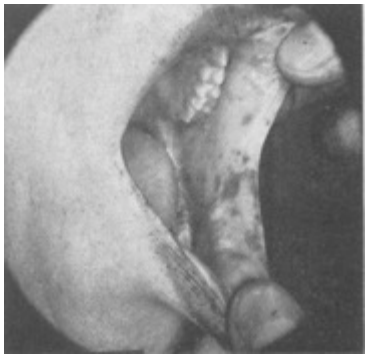
9. WHIPPLE DISEASE	
DEFINITION	Infectious disease by gram-positive rod ***Tropheryma whippelii***
CLINICAL	**WHIPPLE'S TRIAD:** *diarrhea, weight loss, arthralgia*
PATHOGENESIS	Macrophages filled with organism accumulate in **small intestine** lamina propria, mesenteric **lymph nodes**, & **joints** → **LYMPHATIC OBSTRUCTION** **Malabsorption** due to impaired lymphatic transport occurs → *Diarrhea*
HISTO-MORPHOLOGY	  **Villi distended by FOAMY MACROPHAGES filled w/ organisms**  **PAS Stain +**

10. INFECTIVE ENTERITIS: *Giardia lamblia* ***Most common parasite in humans*** *(fecal-oral transmission:* ***Campers****)*	
DEFINITION	Parasitic infection causing **microvillus** damage & apoptosis of **intestinal epithelial cells**
CLINICAL	Symptoms range from asymptomatic to diarrhea
HISTO-MORPHOLOGY	Most commonly seen in **DUODENAL** biopsies   **Pear-shaped trophozoites** with 2 nuclei of equal size found at **brush border** *without invasion*

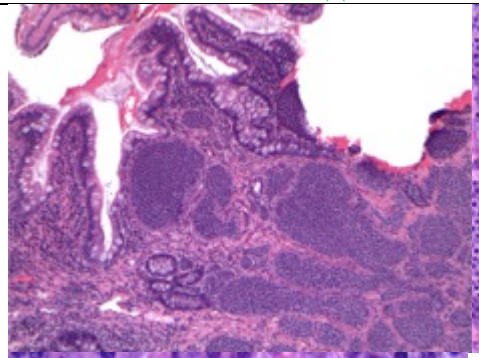
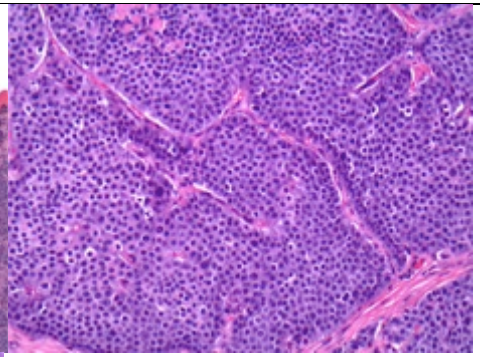
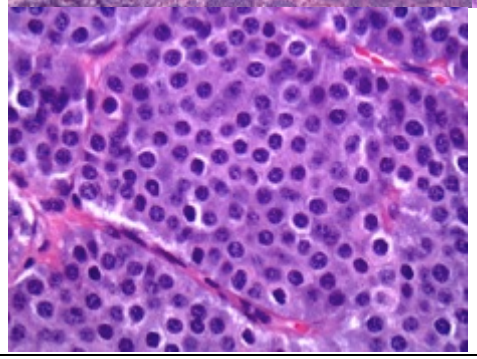
11. INFECTIVE ENTERITIS: *Cryptosporidium*	
DEFINITION	Parasite acquired from fecally-contaminated water; especially prevalent in ***AIDS*** ***patients w/ watery*** *diarrhea*
PATHOGENESIS	Parasite resides in endocytic vacuole within apical enterocyte cytoplasm (microvillus) & causes Na^+ malabsorption, Cl^- secretion (w/ water)
HISTO-MORPHOLOGY	

12. PEUTZ-JEGHERS SYNDROME (Hamartomatous Polyps)

*****Prof diagnosed a patient with this based off of hyperpigmentation of buccal mucosa*****

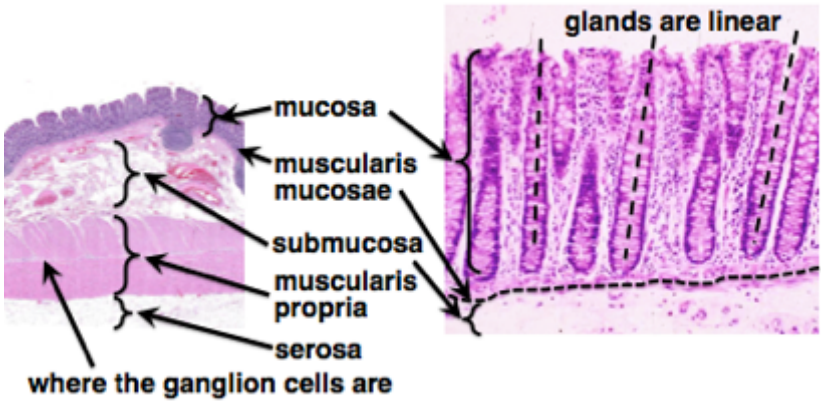
DEFINITION	Autosomal dominant condition consisting of multiple GI hamartomatous polyps (throughout GI tract) & **mucocutaneous hyperpigmentation** *(**Hamartoma** = benign disorganized overgrowth of cells normally found in that tissue)*
CLINICAL	**Small Bowel Intussusception is often cause of the initial presentation**
PATHOGENESIS	**AUTOSOMAL DOMINANT** germ line **STK11** mutation (TSG – requires 2nd hit)
HISTO-MORPHOLOGY	 **"ARBORIZING" smooth muscle** **Lobulated "pin-wheel" glands** 
CLINICAL COURSE/ RISKS	PJS patients have greatly **increased risk of malignancy** throughout the body (colon, breast, pancreas, etc.) – **Sertoli Cell Tumor of the Testes in Males** – **Sec-cord Tumor with Annular Tubules (SCTAT) in Females**

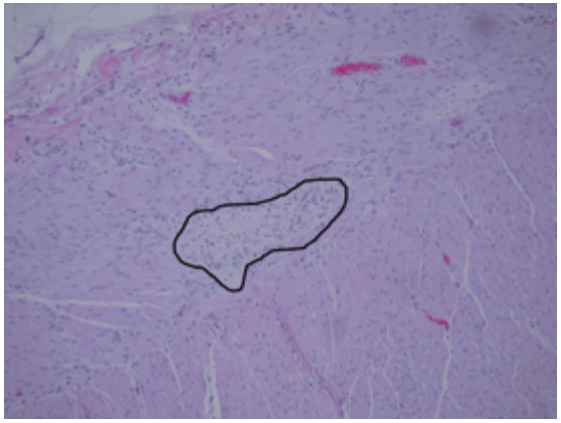
13. NEUROENDOCRINE 'CARCINOID' TUMOR
(Well-differentiated Neuroendocrine Tumor)

DEFINITION	A neuroendocrine tumor that can arise anywhere in the GI tract, but **most commonly in the SMALL INTESTINE** ***Small bowel NETs are more aggressive than those at other sites!**
CLINICAL	**These tumors may secrete hormones causing clinical symptoms:** – **Zollinger-Ellison Syndrome (Gastrinoma)** – *associated with ulcers from too much acid production, diarrhea* – **Carcinoid Syndrome (SEROTONIN)** – *cutaneous flushing, sweating, bronchospasm, abdominal pain, diarrhea, R cardiac valvular fibrosis* ○ This is rare!! **Presence of Carcinoid Syndrome suggest that tumor has metastasized to other sites, i.e. LIVER** – **VIPoma** – *watery diarrhea, achlorhydria, etc.* – **Glucagonoma** – *hyperglycemia unresponsive to fasting, rash (MNE), anemia, hypoaminoacidemia, weight loss, thromboembolism* – **Insulinoma** – *hypoglycemia unresponsive to food intake, neuroglycopenia, sympathetic overdrive*
PATHOGENESIS	**Associated with MEN1**
HISTO-MORPHOLOGY	  **"Insular" architecture = ISLANDS**  **Monophormic bland cytology** **"Salt & Pepper" chromatin**
CLINICAL COURSE/ RISKS	Possible behavior is determined by ***depth of invasion, size, site, & lymphovascular invasion***

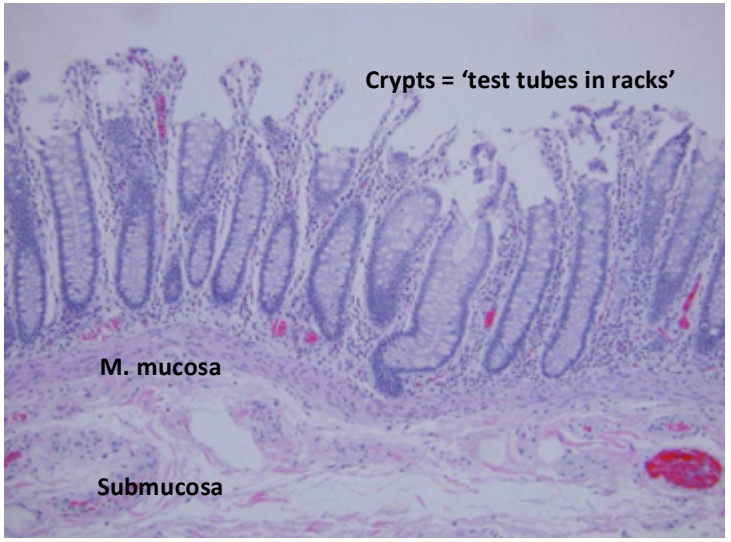
COLON: Normal Anatomy & Histology

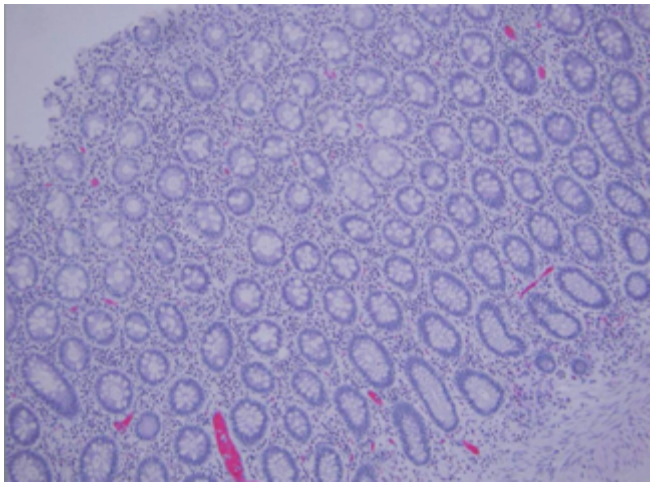
- The colon has no villi
- Glands are linear & perpendicular to the surface + close together
- Lamina propria has few cells
- All mitotic activity occurs in the lower 1/3 of the colonic glands



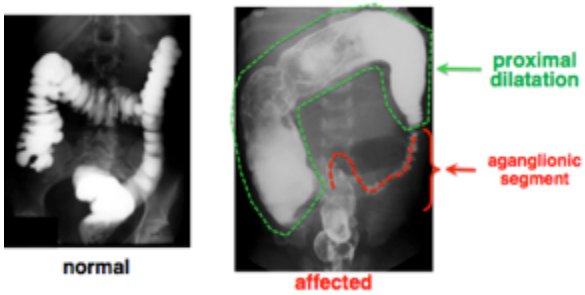
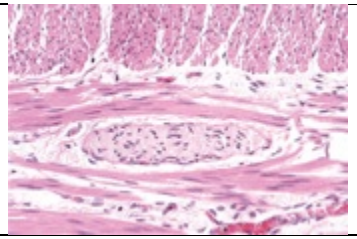


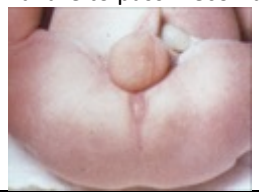
Muscularis propria with myenteric plexus (ganglion cells)





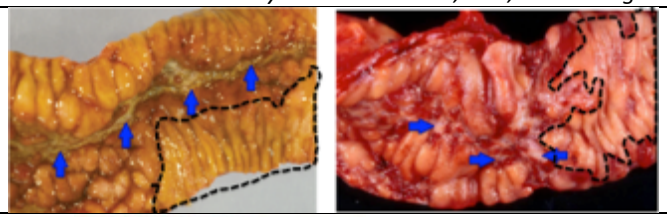
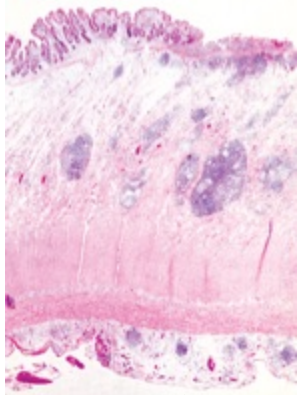
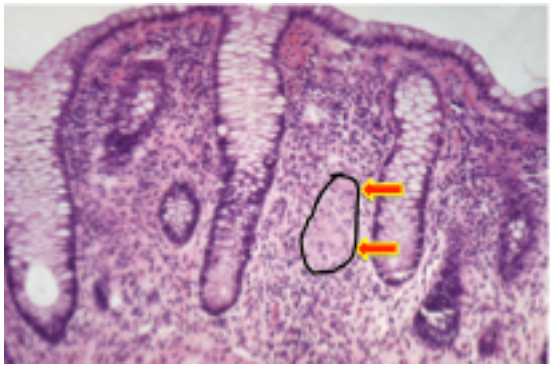
Crypts cut in cross section

1. HIRSCHSPRUNG DISEASE (Congenital Aganglionic Megacolon)	
DEFINITION	Failure of neural crest cells to fully migrate from cecum to rectum → distal colon without innervation → failure of peristalsis to travel full length of bowel → ***functional* obstruction** at affected segment & **dilation of proximal colon;** begins at **anal sphincter** & extends variable distance proximally
CLINICAL	Failure to pass meconium in the first few days of life followed by abdominal distention 
HISTO-MORPHOLOGY	 **Absence of ganglion cells**

2. IMPERFORATE ANUS ***Most common form of congenital intestinal atresia***	
DEFINITION	Failure of cloacal diaphragm to involute
CLINICAL	Failure to pass meconium with abdominal distension 

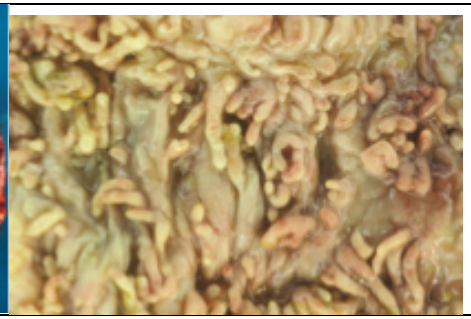
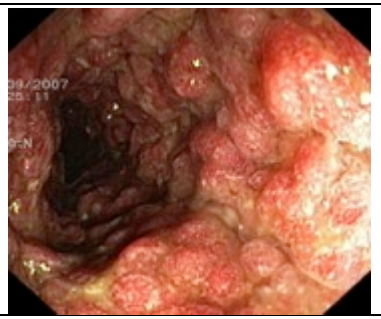
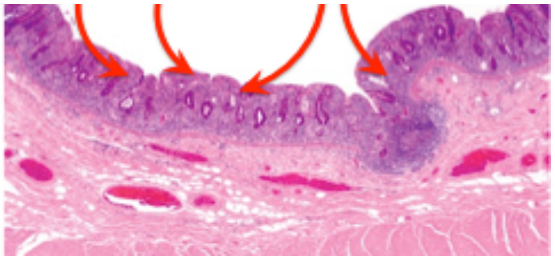
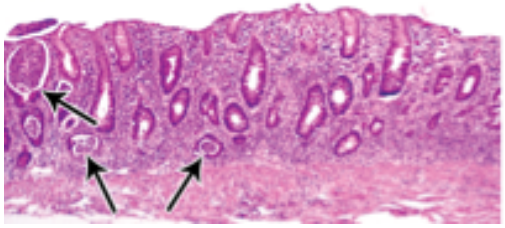
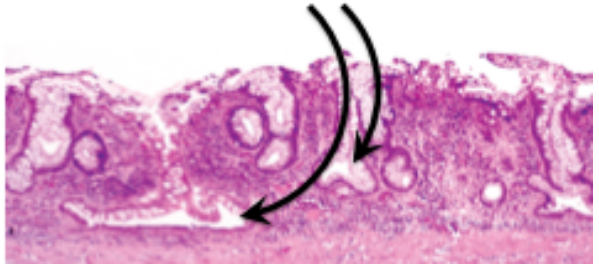
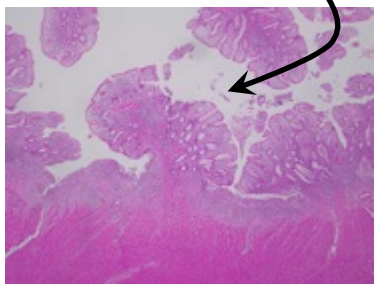
INFLAMMATORY BOWEL DISEASE: CROHN DISEASE vs. ULCERATIVE COLITIS

- *Chronic inflammatory condition resulting from dysfunctional mucosal immune activation*
- **Early teens-20s; Caucasians & Ashkenazi Jews**
- **Idiopathic;** *Suggestion of* ***epithelial defects in tight junctions*** *allowing microbial components to activate an altered immune response*
- **RISK FOR ADENOCARCINOMA:**
  - **Duration of disease:** *risk starts at >10 years*
  - **Extent**: *how much surface of the GI tract is affected*
  - **Severity**: *more severe inflammation = more risk*
- **IBD patients get frequent colonoscopic biopsies to detect *dysplasia, the premalignant lesion***

4. CROHN DISEASE	
DEFINITION	May affect **any segment** of the GI tract from **mouth to anus**; *most common presentation in* **terminal ileum & cecum**
CLINICAL	Diarrhea, ***fever***, abdominal pain, +/- malabsorption with nutritional deficiencies **Fistulas (abdominal connections)**– *perianal fistula, enterocutaneous fistula, colovesicle fistula* **Perforation** **Extraintestinal manifestations:** *uveitis, arthritis* *Disease reactivation may be due to stress, diet, & smoking*
GROSS	 ***Thickened wall in affected segments*** **DISCONTINUOUS INVOLVEMENT: "SKIP LESIONS"** *Note surrounding & intervening normal areas* ***Blue arrows: longitudinal ulcers***
HISTO-MORPHOLOGY	 **Edema & expansion of submucosa with abundant LYMPHOID AGGREGATES, including in SUBSEROSAL SOFT TISSUES;**  **GRANULOMAS, non-necrotizing** **1. Skip Lesions** **2. Granulomas** **3. Transmural inflammation** **4. Lymphoid aggregates** **5. Thickened wall** **6. Ulcerations**
CLINICAL COURSE/ RISKS	*Increased risk of* ***ADENOCARCINOMA***

5. ULCERATIVE COLITIS

Associated with Primary Sclerosing Cholangitis

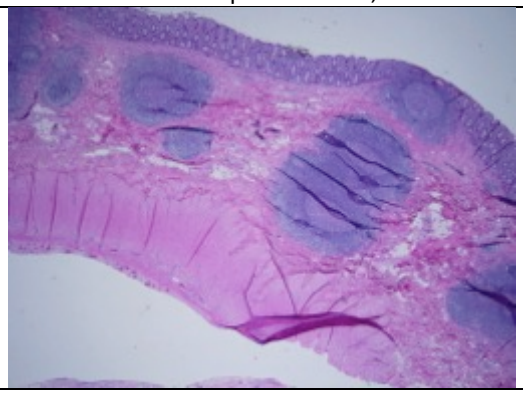
DEFINITION	***Limited to the COLON & RECTUM in continuous fashion, distal to proximal, WITHOUT skip regions***
CLINICAL	Relapsing attacks of *bloody diarrhea, abdominal pain* ***relieved by defecation***
GROSS	  **PSEUDOPOLYPS: Nodules of regenerating mucosa with inflammation; surrounded by ulcerated mucosa** 
HISTO-MORPHOLOGY	**MUCOSAL INFLAMMATION**   **1. Continuous disease** **2. Mucosal & submucosal inflammation only** **3. Crypt architectural distortion** **4. Active cryptitis** **5. NO GRANULOMAS** ***Crypt abscesses*, consisting of AGGREGATES OF PMNs & DEBRIS (arrows)**  **(Chronic UC) *Crypt architectural distortion***  **PSEUDOPOLYP** 
CLINICAL COURSE/ RISKS	*Increased risk of* ***ADENOCARCINOMA***

6. IRRITABLE BOWEL SYNDROME (IBS)

Female, 20-40s

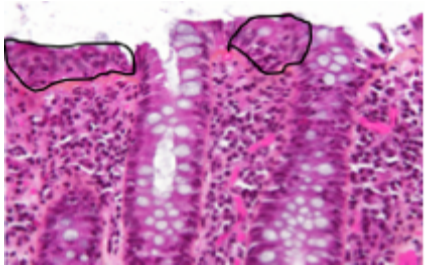
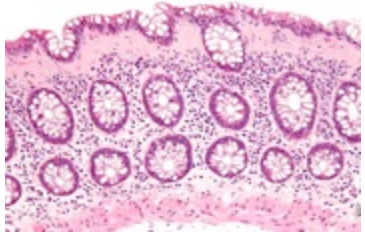
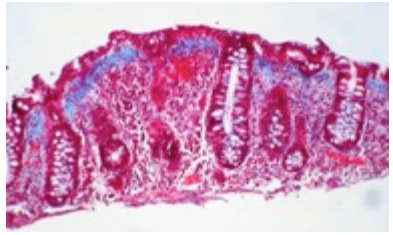
DEFINITION	Chronic, *relapsing abdominal pain, bloating, & changes in bowel habits*, ***despite NORMAL biopsy findings of GI tract***
CLINICAL	**CRITERIA**: Abdominal pain 3 days/month over 3 months without improvement after defecation & change in stool frequency or form *Diagnosis of exclusion*

7. DIVERSION COLITIS

DEFINITION	Colitis that occurs in portion of colon that has been surgically made to be a blind pouch & excluded from the normal fecal stream
PATHOGENESIS	***Results from lack of normal fecal flow to the blind segments.*** Normally, bacterial digestion of fecal material produces SCFAs, an energy source needed for colonic epithelial cells; with diversion of the fecal flow, these Fas are not produced, resulting in colitis
HISTO-MORPHOLOGY	 **Normal mucosa** **Submucosa with increase lymphoid follicles** **(LYMPHOID HYPERPLASIA)**
TREATMENT	Treated with SCFA enemas to the blind segment

MICROSCOPIC COLITIS

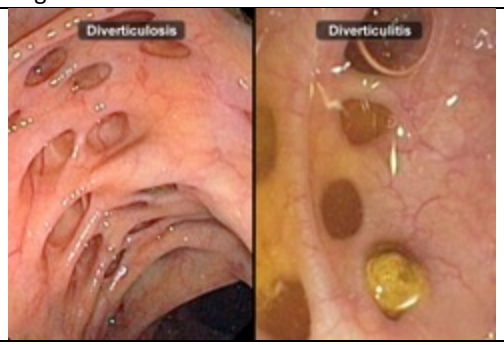
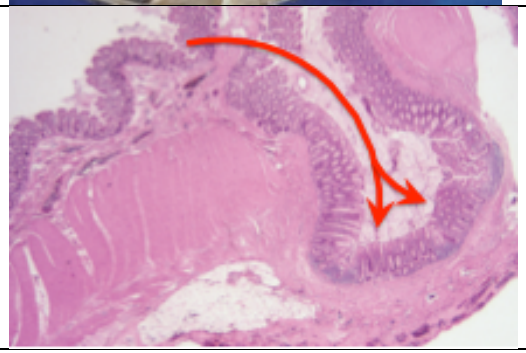
Associated with Celiac Disease, Autoimmune Disease, NSAIDs

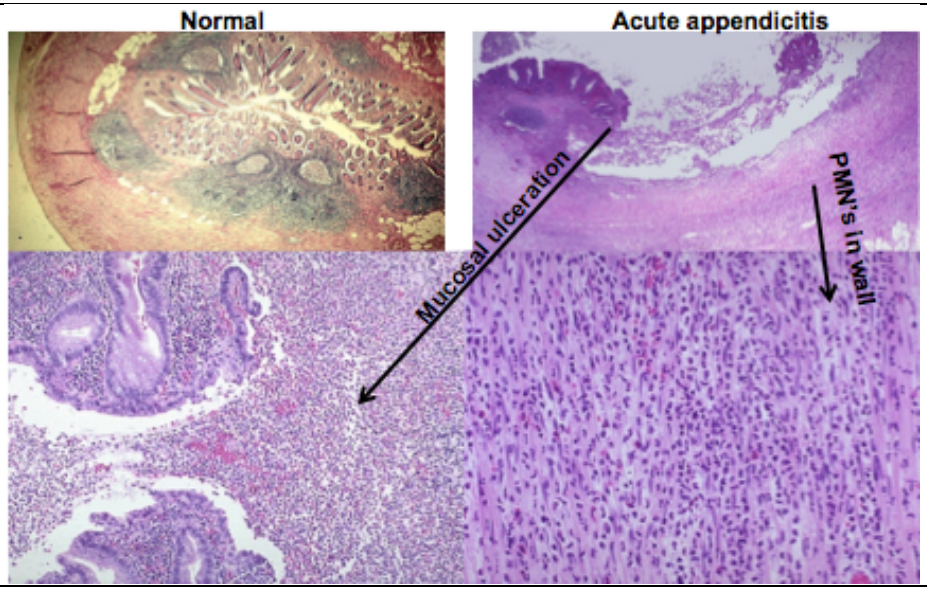
DEFINITION	Idiopathic diseases that present with *watery diarrhea* & **normal findings on colonoscopy**	
2 TYPES	**8. LYMPHOCYTIC COLITIS**  **↑ Intraepithelial Lymphocytes**	**9. COLLAGENOUS COLITIS**  **Thickened subepithelial collagen**  **Trichrome stain – blue collagen**

10. DIVERTICULOSIS/DIVERTICULITIS

>50% of patients 70+ in Western countries

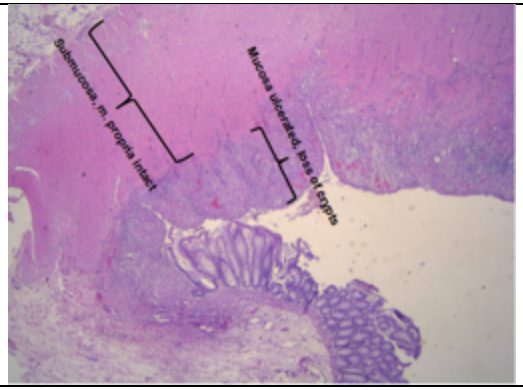
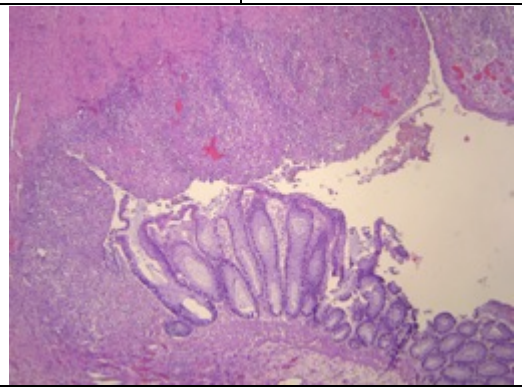
Most common cause of lower GI bleeding

DEFINITION	Outpouchings of the colonic mucosa/submucosa, typically in the **sigmoid colon**
CLINICAL	***LLQ cramping***, constipation/diarrhea, sensation of never being able to empty rectum
PATHOGENESIS	Due to *segmental weaknesses (gaps) in the colonic muscularis propria*, where nerves & arterial vasa recta penetrate the inner circular muscle coat; increased intraluminal pressure can cause ***outpouchings of the mucosa/submucosa*** at these sites. Obstruction of diverticula by stool/mucus → stasis → bacterial overgrowth → inflammation → ***diverticulitis***
GROSS	  **Stricturing fibrosis** **Perforation & fistula formation** **Adhesions**
HISTO-MORPHOLOGY	 **FLASK-SHAPED protrusion of mucosa + muscularis mucosae through musclaris propria**

11. ACUTE APPENDICITIS **Adolescents, Young Adults**	
DEFINITION	Acute inflammation of the appendix with ***neutrophilic infiltration*** of the appendiceal wall (*muscularis propria)*
CLINICAL	Initial *periumbilical pain* that later localized to **RLQ** **McBURNEY'S SIGN:** tenderness locatied 2/3rds of distance from umbilicus to R ASIS
PATHOGENESIS	Increased intraluminal pressure (*due to obstruction by a fecalith)* → stasis → bacterial proliferation → inflammation, edema, neutrophilic infiltration *All of which* ***thicken the muscular wall*** → ***compromises venous outflow***
HISTO-MORPHOLOGY	
CLINICAL COURSE/ RISKS	Can rupture – medical emergency

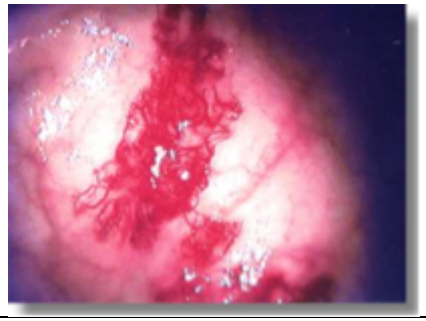
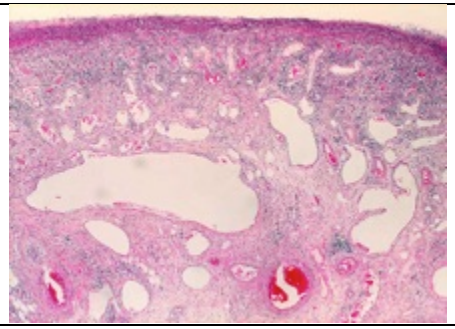
12. ISCHEMIC BOWEL DISEASE

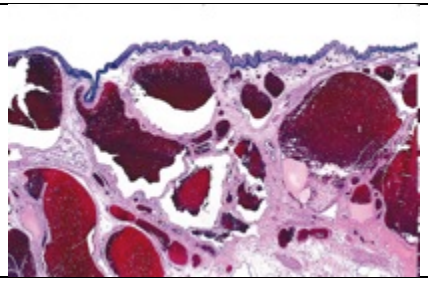
Adults

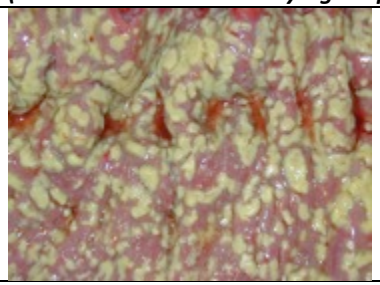
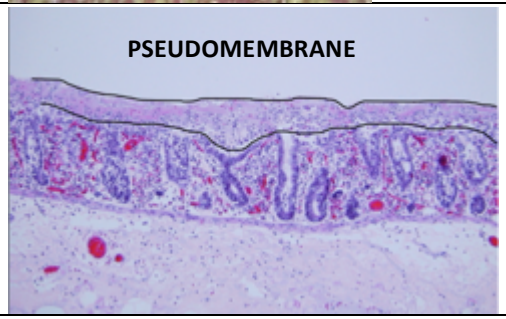
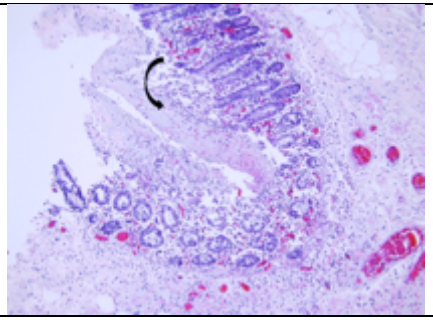
DEFINITION	Acute vascular compromise of any major branch of Celiac, SMA, or IMA causing **acute intestinal ischemia w/** ***transmural ischemic necrosis*** **of bowel.**	
CLINICAL	Abrupt pain, bloody diarrhea, vomiting, distention, death	
PATHOGENESIS	Occlusion of major blood vessels from **atherosclerosis**, **hypercoagulable states**, **aortic aneurysm**, **volvulus,** or, **shock (hypotension)**	
	SMALL INTESTINAL ISCHEMIA – SMA + anastomosing arcuate arteries – Blood supply is most vulnerable to interruption at or near source – Pancreatitis, tumor, lympohadenopathy, atherosclerosis, thrombus, or embolus	**COLONIC ISCHEMIA** – **SMA** (up to SPLENIC FLEXURE) – **IMA** (splenic flexure to sigmoid) – ***"Watershed" areas*** *by* ***SPLENIC FLEXURE*** *= most vulnerable*
HISTO-MORPHOLOGY	  **Ischemia = superficial mucosa necrosis**	
CLINICAL COURSE	**MUCOSA most susceptible to ischemic injury,** with musculature the least susceptible. If cause is addressed, mucosa may regenerate. **Chronic Ischemia – "withering" atrophy of surface epithelium** that may progress to ulceration, but *submucosa & muscularis propria are spared.*	

13. ANGIODYSPLASIA

2nd leading cause of lower GI bleed

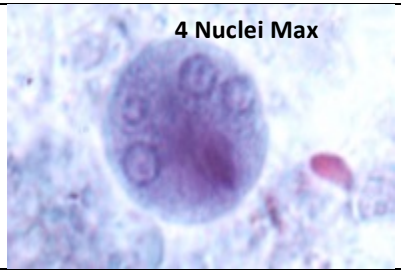
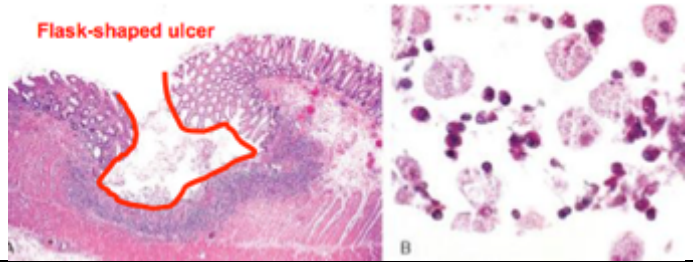
DEFINITION	Tortuous focus of mucosal & submucosal vessels, usually located in **cecum/RIGHT COLON**
CLINICAL	Incidence increases with **age**
HISTO-MORPHOLOGY	 

14. HEMORRHOIDS	
DEFINITION	Swelling of internal or external perianal tissue due to ***persistently elevated venous pressure*** within hemorrhoidal plexus
PATHOGENESIS	**Causes**: *straining at defecation, pregnancy, portal HTN, sedentary lifestyle of prolonged sitting*
HISTO-MORPHOLOGY	 Dilated thin-walled submucosal vessels with overlying normal squamous/ columnar epithelium

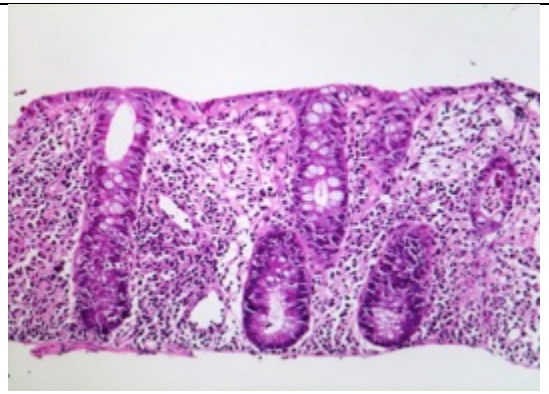
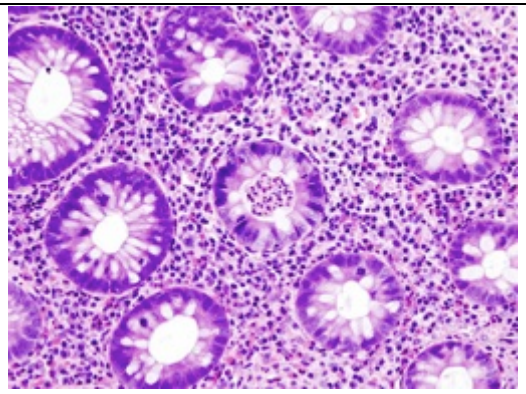
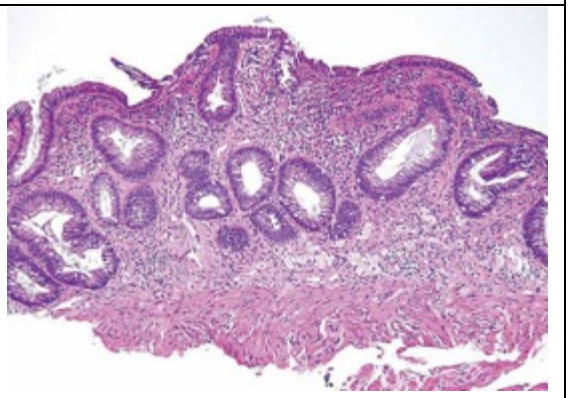
15. PSEUDOMEMBRANOUS COLITIS (Antibiotic-Associated Colitis; *C. difficile* Colitis) Hospitalized Patients	
DEFINITION	Caused by bacterial overgrowth of *C. difficule* due to **long-term antibiotic use** causing eliminating of other beneficial colonic flora that normally keep *C. diff* in check
CLINICAL	Watery diarrhea
PATHOGENESIS	Overgrowth of *C. diff* → *C. diff* releases TOXIN → loss of epithelial cell tight junctions → sloughing of epithelilum → pseudomembrane formation ***(AKA a necrotic exudate lying atop the mucosa)***
GROSS	
HISTO-MORPHOLOGY	  **TOXIN causes loss of cell adhesion → sloughing of cells, PMNs, mucus into pseudomembrane**

16. *ENTAMOEBA HISTOLYTICA* COLITIS (Amebiasis)

Developing countries with poor sanitation

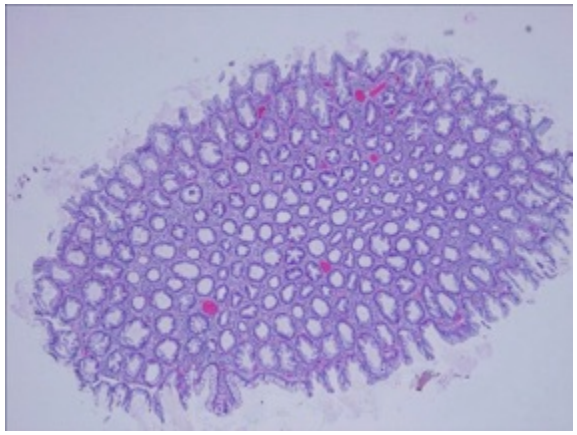
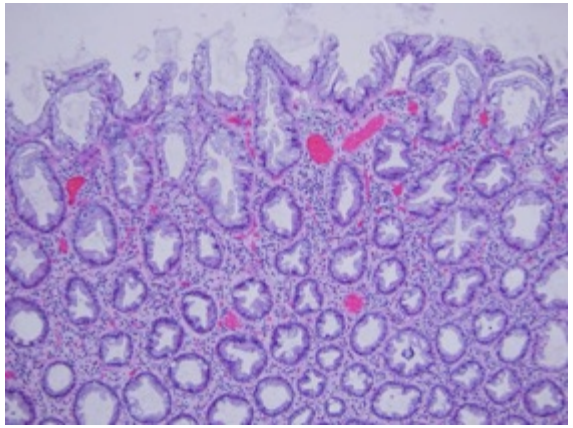
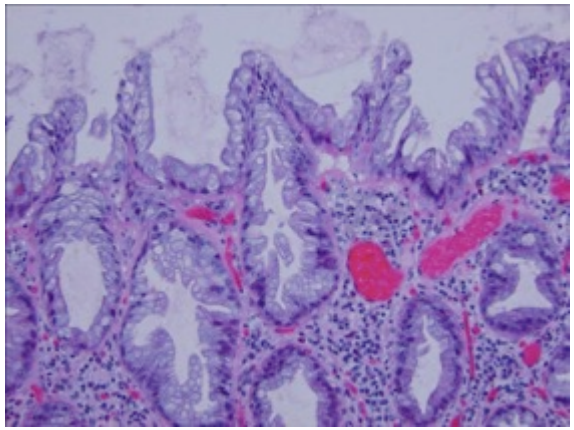
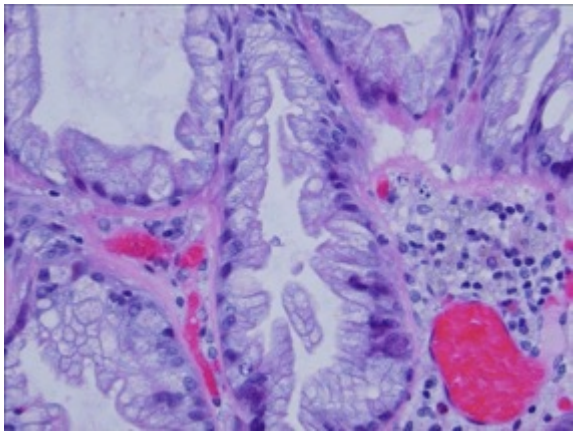
DEFINITION	Protozoal infection that may cause colitis; *fecal-oral transmission*
PATHOGENESIS	Cysts resistant to gastric acid → pass to colon where they release **trophozoites**, which may either: 1. Remain in the colonic lumen → *asymptomatic (90%)* 2. Invade & cause tissue destruction → *bloody diarrhea (10%)*
HISTO-MORPHOLOGY	  
CLINICAL COURSE/ RISKS	Trophozoites may invade vessels & embolize to the liver & form liver abscesses (40% of infected patients)

17. ACUTE SELF-LIMITED (INFECTIOUS) COLITIS

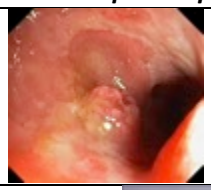
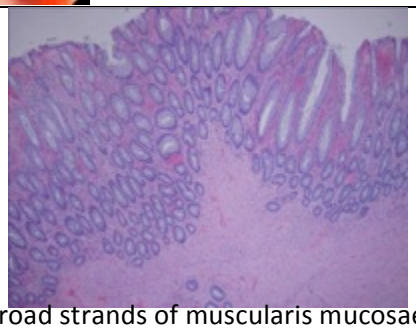
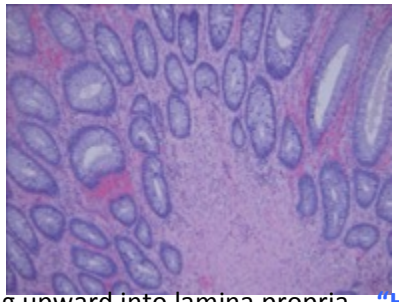
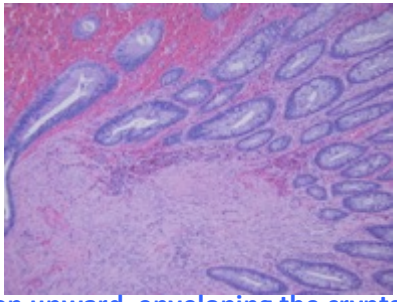
DEFINITION	Transient, presumably infectious colonic inflammation that presents with acute-onset diarrhea (sometimes bloody)
CLINICAL	Diarrhea (+/- blood), *may be explosive*; usually resolves in 2-4 weeks
PATHOGENESIS	Ingestion of **pre-formed toxin** causing symptoms within hours Infection by toxogenic organisms Infection by enteroinvasive organisms, which invade & destroy mucosal epithelium Infection by viral organisms
HISTO-MORPHOLOGY	 **'Active' Cryptitis: INTRAEPITHELIAL NEUTROPHILS** *No signs of crypt architectural distortion (branching) means process isn't chronic*  **Crypt Abscesses:** Neutrophils in lumens  **Crypts are not oriented perpendicular to muscularis mucosa** – *this is architectural distortion so this is NOT ACUTE colitis!*

18. HYPERPLASTIC POLYPS

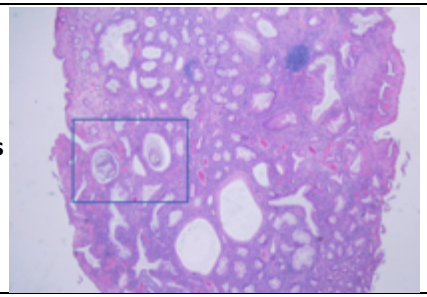
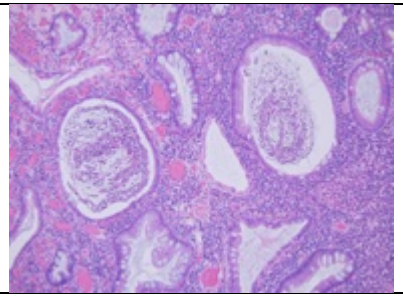
Non-neoplastic polyps

DEFINITION	BENIGN epithelial proliferation, with ***NO malignant potential*; commonly occurs in the LEFT COLON**
HISTO-MORPHOLOGY	**NORMAL CYTOLOGY + NORMAL ARCHITECTURE = HYPERPLASTIC (non-malignant) POLYPS**     **Crowding epithelial cells → SERRATIONS** **"STAR SHAPES"** **NO cytologic atypia:** ***small nuclei, no hyperchromasia*** ***= NO DYSPLASIA*** ***Must be distinguished from sessile serrated adenomas (which have malignant potential)***

19. MUCOSAL PROLAPSE (INFLAMMATORY) POLYPS

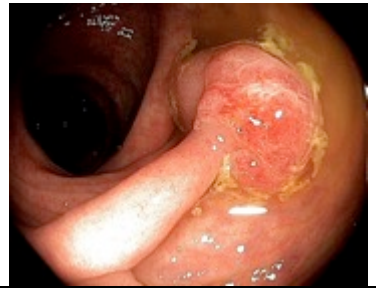
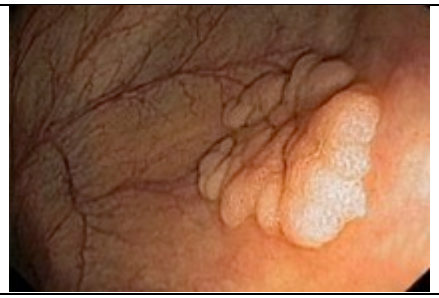
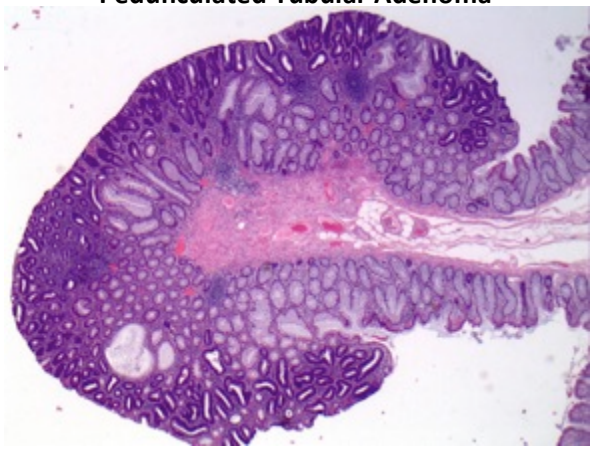
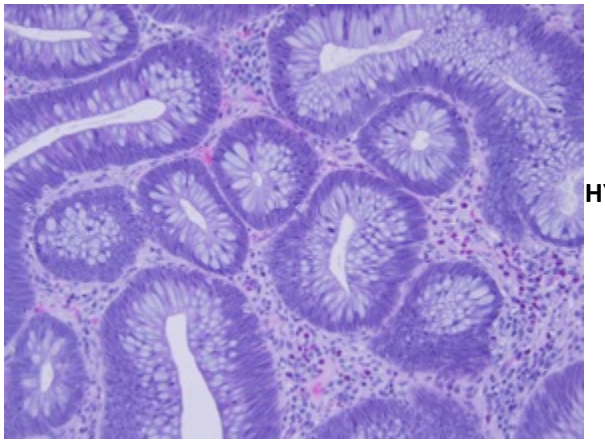
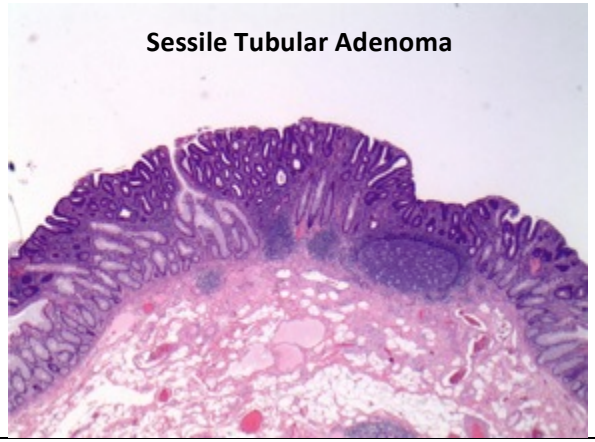
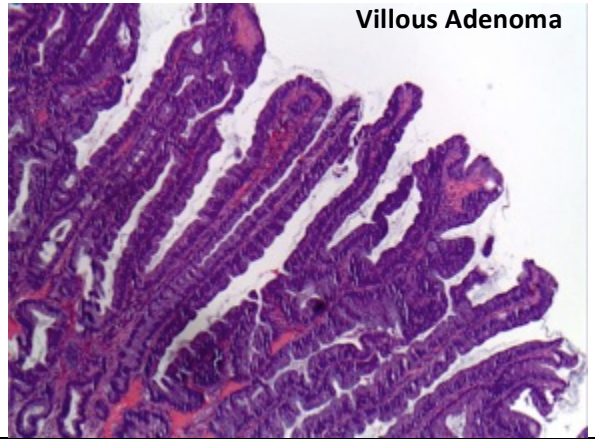
DEFINITION	***Non-neoplastic polyps;*** Typically seen in the **RECTUM**, resulting from impaired relaxation of anorectal sphincter with recurrent abrasion
GROSS	
HISTO-MORPHOLOGY	   Broad strands of muscularis mucosae pushing upward into lamina propria – **"Herniation upward, enveloping the crypts"** Accompanying inflammatory cells & possible epithelial hyperplasia

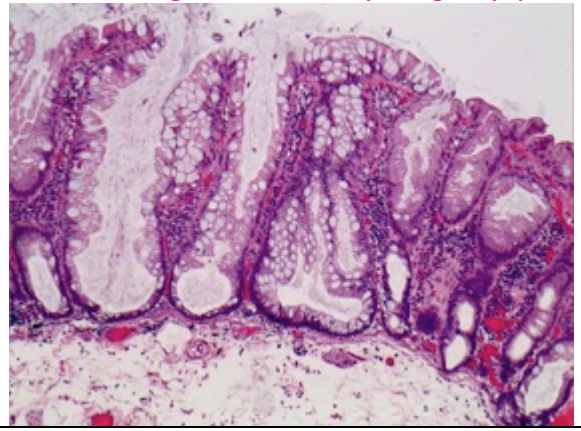
20. JUVENILE POLYPS

DEFINITION	***Non-neoplastic polyps***; Must occur **<5 years old**; in the **RECTOSIGMOID**
PATHOGENESIS	**JUVENILE POLYPOSIS SYNDROME:** Autosomal dominant **SMAD4 or BMPR1α** mutation; up to 100 hamartomatous polyps
GROSS	
HISTO-MORPHOLOGY	**GLOBOID SHAPE** **Lots of dilated & branching cysts**   **Stromal inflammation** **Dilated mucin-filled crypts**
RISKS	***Increased risk of cancer throughout GI tract***

21. COLONIC ADENOMAS

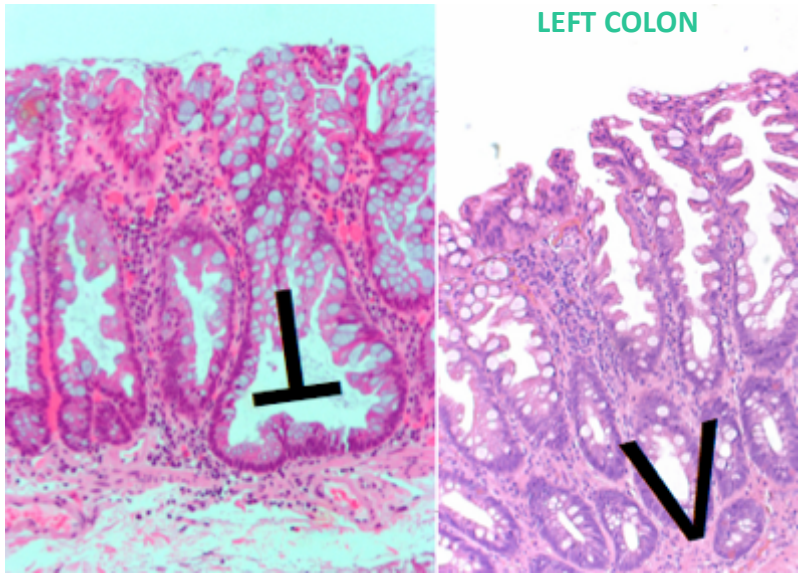
This is the reason for screening colonoscopies in adults 50+

DEFINITION	A ***dysplastic polyp***, & thus a **precursor to malignancy;** Can either be ***tubular adenoma, villous adenoma,*** **or** ***tubulovillous adenoma***
GROSS	**PEDUNCULATED POLYP**   **SESSILE POLYP**
HISTO-MORPHOLOGY	**Pedunculated Tubular Adenoma**  **Tubules**  **CIGAR-SHAPED** **HYPERCHROMATIC NUCLEI** **PSEUDOSTRATIFIED** **= DYSPLASIA!**  **Sessile Tubular Adenoma**  **Villous Adenoma**
PROGNOSIS	**SIZE MATTERS!!!** – Size is the most important prognostic factor correlating with malignancy!

22. SESSILE SERRATED ADENOMA	
DEFINITION	A special type of polyp that most commonly occurs in the **RIGHT COLON** & *resembles a hyperplastic polyp*, but has **MALIGNANT POTENTIAL**
PATHOGENESIS	Defects in DNA mismatch repair gene **MLH1** *Even though there is no cytologic dysplasia, there is **architectural dysplasia!***
HISTO-MORPHOLOGY	*Even though there is no cytologic dysplasia, there is **architectural dysplasia! (distinguishing it from hyperplastic polyps)***  **BASAL DILATION OF CRYPTS** – ***Inverted 'T'*** **Serration extending into crypt base** ***Crypts growing horizontally***
CLINICAL COURSE/ RISKS	Precursors of ***RIGHT-SIDED COLON CANCER***

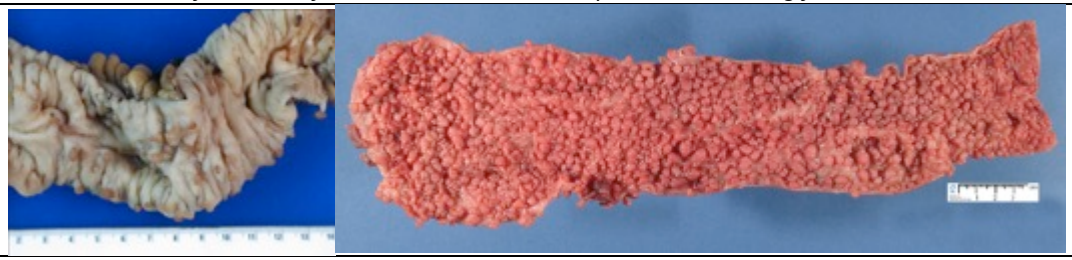
SESSILE SERRATED ADENOMA
RIGHT COLON

HYPERPLASTIC POLYP
LEFT COLON



CRITERIA FOR COLON CANCER

- Tumors are only staged as malignant when they have **INVADED THROUGH THE MUSCULARIS MUCOSA & INTO SUBMUCOSA**
- *There is a paucity of lymphates in lamina propria of the colon. Thus, invasion confined to the lamina propria & muscularis mucosae is not associated with lymph nodes & thus has no metastatic potential.*

	23. FAMILIAL ADENOMATOUS POLYPOSIS (FAP) **35-40 years old**
DEFINITION	Innumerable colorectal adenomas ***(at least 100 polyps for diagnosis)*** with **100% risk of colonic adenocarcinoma** before 30 years old
CLINICAL	**Wide Extracolonic Manifestations:** – **PERIAMPULLARY ADENOMAS & Adenocarcinomas**; *#1 cause of mortality in FAP patients who have undergone prophylactic colectomy*
PATHOGENESIS	Autosomal dominant mutation in **APC** (TSG) *Adenomas result from loss of 2nd allele within colonic epithelium allowing for additional mutations in KRAS, TP53*
GROSS	 **Tubular Adenomas**
TREATMENT	**Prophylactic colectomy –** *after treatment patient's are still at risk for adenomas at other sites, particullary* ***Ampulla of Vater*** *& stomach*

VARIANTS OF FAP – *All have APC mutation*

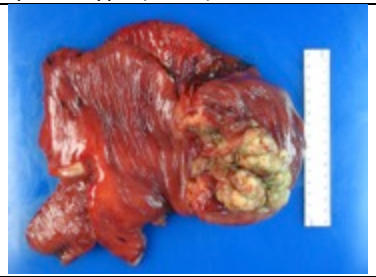
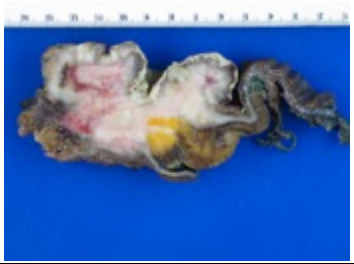
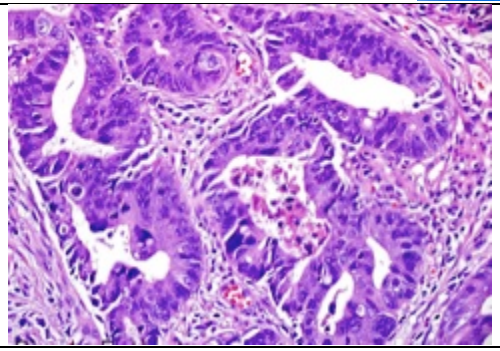
24. ATTENUATED FAP	Similar to conventential FAP, but with **<100 polyps & later onset (50 years old)**
25. GARDNER'S SYNDROME	Syndrome with 100+ adenomatous polyps (FAP) + osteomas, skin cysts, dental abnormalities, & desmoid tumors **& later onset**
26. TURCOT'S SYNDROME	Syndrome with 100+ adenomatous polyps (FAP) + CNS tumors (medulloblastoma) **& later onset**

	27. HEREDITARY NON-POLYPOSIS COLON CANCER (HNPCC) (AKA Lynch Syndrome) ***Most common cause of hereditary colon cancer (5% of all colon cancers)***
DEFINITION	Cancer occurs at ***younger age*** than sporadic colon cancer; it is most often **RIGHT SIDED**
PATHOGENESIS	Autosomal dominate mutation in one of the **DNA mismatch repair enzymes (MLH1, MSH2, MSH6, PMS2)** Leads to ***microsatellite instability*** in promoter & encoding regions → rapid accumulation of somatic mutations in genes that control tumor progression
MORPHOLOGY	**TUMOR-INFILTRATING LYMPHOCYTES, CROHN'S LIKE LYMPHOCYTE REACTION, MUCINOUS/SIGNET RING DIFFERENTIATION, or MEDULLARY GROWTH PATTERN**
CLINICAL COURSE/ RISK	Increased risk of cancer in other organs: **ENDOMETRIAL**, ovary, small bowel, stomach, urinary tract, brain ***Woman with colon cancer at age 50. What should you screen her for next? #1 ENDOMETRIAL CANCER!!***

28. COLORECTAL ADENOCARCINOMA

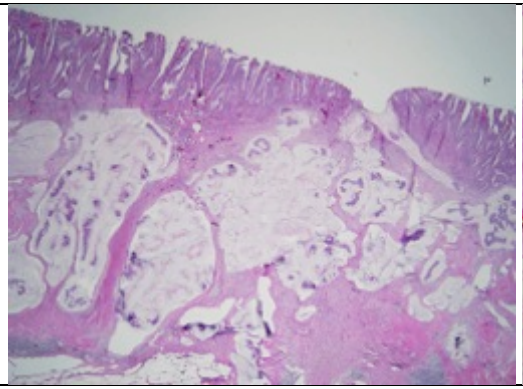
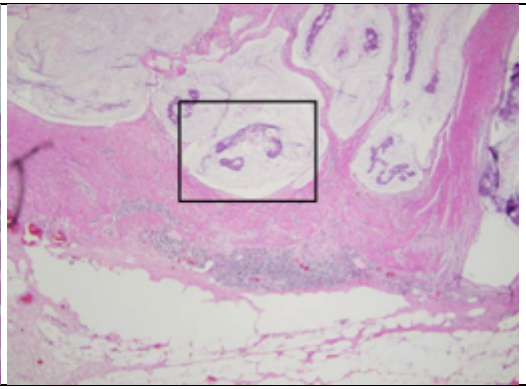
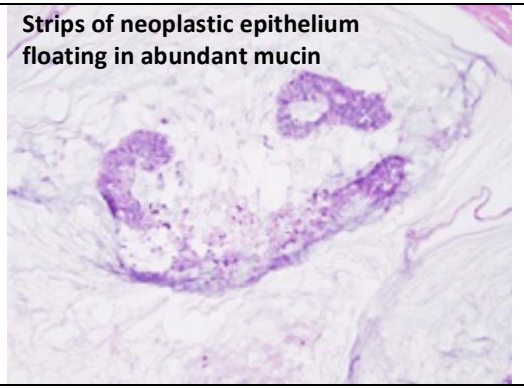
60 years old

3rd most common & 3rd leading cause of cancer death in the USA

RISK FACTORS	FAMILY HISTORY of colorectal cancer, **IBD**, HNPCC, FAP, etc.
CLINICAL	***Classic presentation is unexplained iron-deficiency anemia in an older man or postmenopausal woman due to occult bleeding from a colonic mass***
PATHOGENESIS	1. APC/β-catenin Pathway aka Chromosomal Instability 2. Microsatellite Instability Pathway – *associated with sessile serrated adenomas as precursor lesion* – Mutation in MLH1, MSH2 (Lynch Syndrome) – CpG island hypermethylation phenotype (CIMP): *associated with BRAF mutation*
GROSS	**Invasive Colorectal Adenocarcinoma, NOS** **LEFT SIDED**  
HISTO-MORPHOLOGY	 **TYPICAL COLORECTAL ADENOMACARCINOMA** ***Highly atypical cells forming glands*** ***"Dirty Necrosis"***
PROGNOSTIC	2 most important prognostic factors: **DEPTH OF INVASION & PRESENCE OF LYMPH NODE METASTASIS**

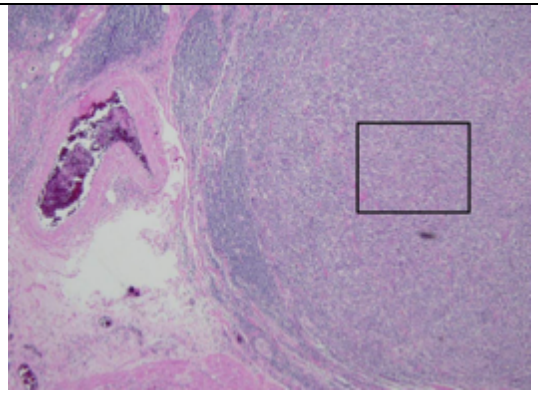
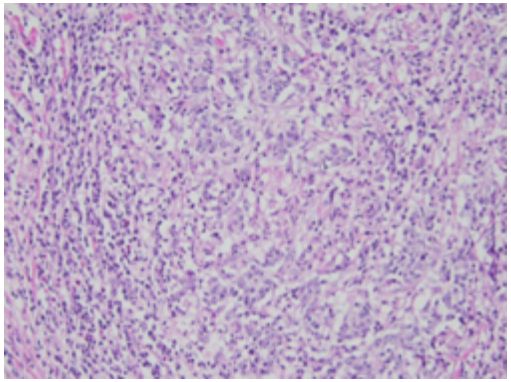
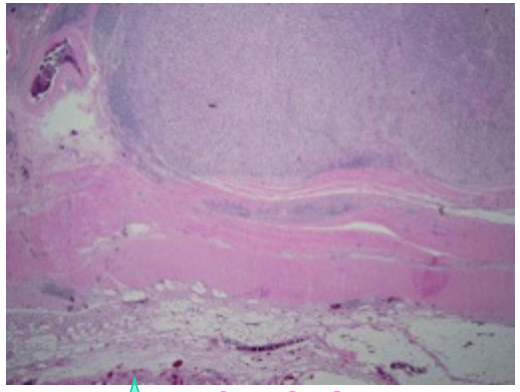
29. MUCINOUS ADENOCARCINOMA: *Subtype of colonic adenocarcinoma*

Associated with HNPCC & loss of DNA mismatch repair enzymes

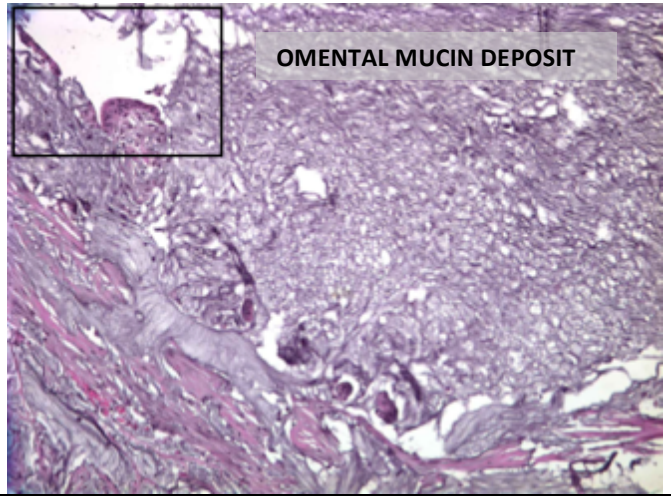
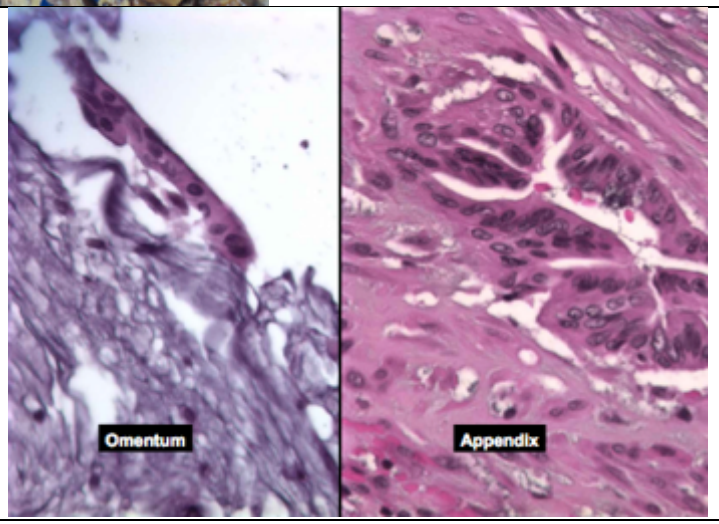
DEFINITION	>50% extracellular mucin present;
HISTO-MORPHOLOGY	   **Strips of neoplastic epithelium floating in abundant mucin**

30. MEDULLARY CARCINOMA: *Subtype of colonic adenocarcinoma*

Females

DEFINITION	**RIGHT COLON PREDOMINANT; MORE FAVORABLE PROGNOSIS**
PATHOGENESIS	Often possess ***defects in DNA mismatch repair***;
HISTO-MORPHOLOGY	 **Peritumoral lymphocytic response = "CROHN'S LIKE REACTION"**  **TUMOR INFILTRATING LYMPHOCYTES (TILs)** **"Medullary" growth pattern = islands of polyglonal cells with prominent nucleoli, syncytial growth**  **PUSHING BORDER** *As opposed to infiltrating*

31. APPENDICEAL ADENOCARCINOMA + PSEUDOMYXOMA PERITONEI

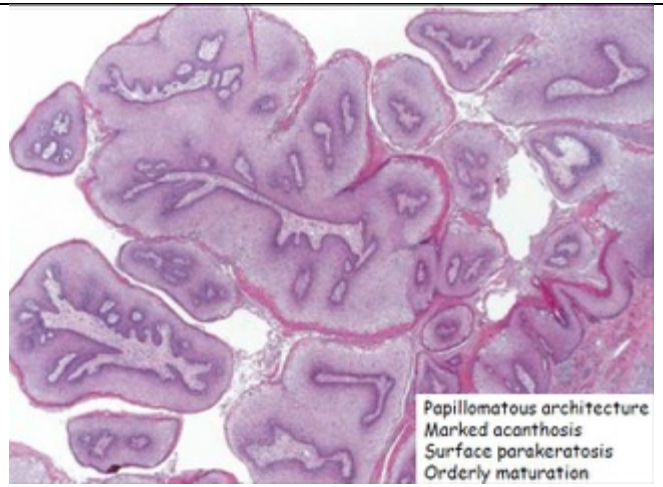
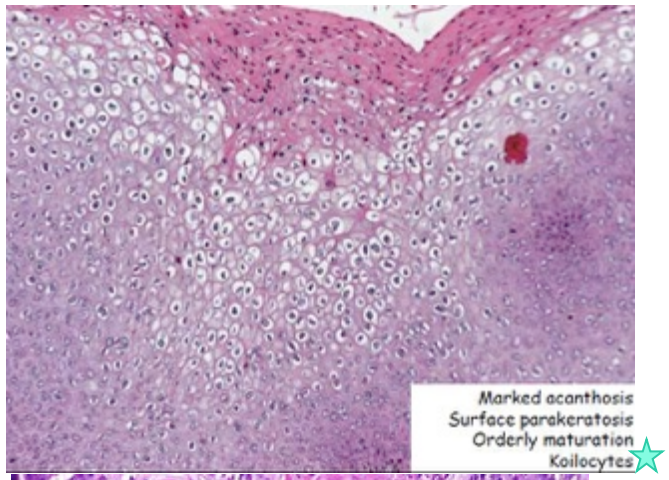
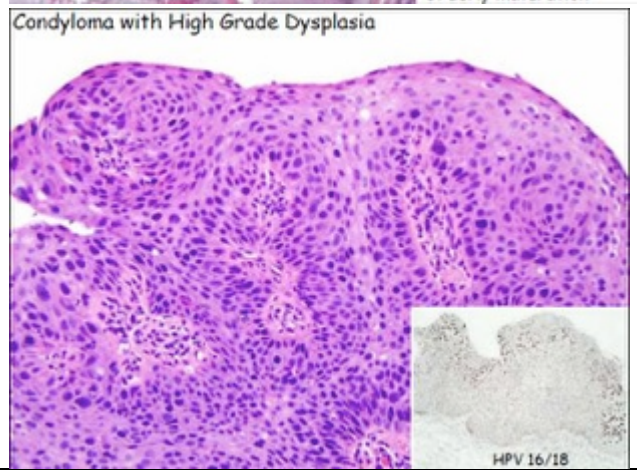
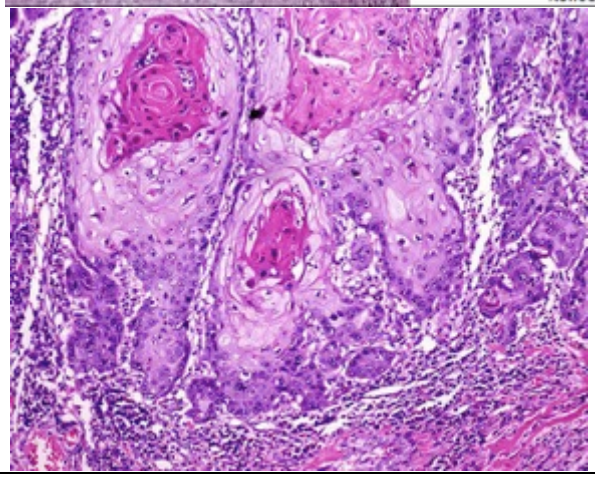
CLINICAL	**PSEUDOMYXOMA PERITONEI:** ↑abdominal girth, inguinal hernia in males or R ovarian mass in females, appendicitis (even after appy)
PATHOGENESIS	When adenocarcinoma invades through the wall of the appendix → Appendiceal Perforation → Seeding & spread of tumor cells throughout abdomen → continued production of mucus by the tumor cells → **MUCIN FILLS ABDOMEN** → **Pseudomyxoma Peritonei**
GROSS	
HISTO-MORPHOLOGY	 

ANAL SQUAMOUS CELL CARCINOMA: *Invasive malignant neoplasm demonstrating* ***squamous differentiation***

- **Females, HIV+ Young Males, African Americans**
- **RISK FACTORS:** Anal intercourse, heavy smokers, Hx of STDs, HIV+, immunosuppression, cervical dysplasia/cancer in females, low SES
- **HPV is the cause of all of these tumors!**

32. CONDYLOMA ACUMINATUM *(THINK: Cauliflower!)*

Most common tumor of the anal & perianal region

DEFINITION	Exophytic, papillomatous lesion of the squamous epithelium caused by **HPV**
PATHOGENESIS	HPV blocks **p53 & Rb** tumor suppressor genes **Most associated with HPV 6/11 (LOW RISK SEROTYPES)** **High grade dysplasia in condyloma associated with HPV 16/18 (HIGH RISK SEROTYPES)**
GROSS	*I'll save you the site* ☺
HISTO-MORPHOLOGY	    **Well-defined cell borders** **BASKET WEAVE PATTERN** **Dyskeratotic cells** **+/- Keratin production**

	CONGENITAL	NON-NEOPLASTIC	NEOPLASTIC
ESOPHAGUS (13)	Esophageal Atresia + Tracheoesophageal Fistula	Esophageal Web Esophageal Ring (Schatski Ring) Zenker Diverticulum Achalasia Mallory-Weiss Syndrome (Boerhaave Syndrome) Infectious Esophagitis: *Candida*, HSV, CMV Reflux Esophagitis Barrett Esophagus Eosinophilic Esophagitis Esophageal Varices	Esophageal Adenocarcinoma Esophageal Squamous Cell Carcinoma
STOMACH (17)	Diaphragmatic Hernia Omphalocele Gastroschisis Congenital Hypertrophic Pyloric Stenosis	Reactive Gastropathy Acute Gastritis + Acute Erosive/Hemorrhagic Gastritis Chronic Gastritis: *H. pylori* Gastritis Autoimmune Gastritis Eosinophilic, Lymphocytic, & Granulomatous Gastritis Hypertrophic Gastropathies: Menetrier Disease Zollinger-Ellison Syndrome	Gastric Adenocarcinoma Gastrointestinal Stromal Tumor (GIST) Gastric MALT Lymphoma
SMALL BOWEL (13)	Meckel Diverticulum	Small Intestinal Obstruction Neonatal Necrotizing Enterocolitis (NEC) Malabsorption Diseases: Cystic Fibrosis Celiac Disease Tropical Sprue Lactase Deficiency Abetalipoproteinemia Whipple Disease Infectious Enteritis: *Giardia lamblia* *Cryptosporidium* Peutz-Jeghers Syndrome	Well-differentiated Neuroendocrine Tumor
COLON (33)	Hirschprung Disease Imperforate Anus	Inflammatory Bowel Disease (IBD): Crohn Disease Ulcerative Colitis (+ Inflammatory Pseudopolyp) Irritable Bowel Syndrome (IBS) Diversion Colitis Microscopic Colitis: Lymphocytic Colitis & Collagenous Colitis Diverticulosis/Diverticulitis Acute Appendicitis Vascular Pathology: Ischemic Bowel Disease Angiodysplasia Hemorrhoids Infectious Colitis: Pseudomembranous Colitis *Entamoeba histolytic* Colitis Acute Self-Limited Infectious Colitis Non-Neoplastic Polyps: Hyperplastic Polyps Inflammatory Polyps (AKA Mucosal Prolapse Polyps) Juvenile Polyps	Neoplastic Polyps: Colonic Adenomas (Pedunculated or Sessile) Sessile Serrated Adenoma Colon Cancer Syndromes: Familial Adenomatous Polyposis (FAP) Attenuated FAP Gardner's Syndrome Turcot's Syndrome Hereditary Nonpolyposis Colon Cancer (HNPCC) Colorectal Adenocarcinoma Subtypes of Colonic Adenocarcinoma Mucinous Adenocarcinoma Medullary Carcinoma Appendiceal Adenocarcinoma & Pseudomyxoma Peritonei Anal Squamous Cell Carcinoma Condyloma Acuminatum Giant Condyloma of Buschke-Lowenstein

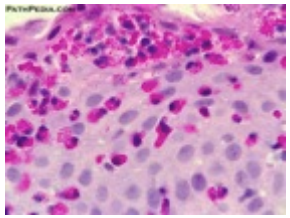
IN-CLASS QUESTIONS

1. In the esophagus, if the Z-line does NOT correspond to the gastroesophageal junction, what has occurred between the two points?
    a. Adenocarcinoma
    b. Inflammation
    c. Columnar metaplasia
    d. Intestinal metaplasia
    e. Squamous metaplasia

2. The pathogenesis of achalasia involves which of the following?
    a. Failure of the lower esophageal sphincter to relax
    b. Failure of the lower esophageal sphincter to contract
    c. Failure of the lower esophageal muscular valve to open
    d. Congenital absence of excitatory esophageal neurons

3. Barrett's esophagus is defined as the presence of what type of cell within the luminal esophagus?
    a. Paneth cell
    b. Goblet cell
    c. Squamous cell
    d. Islet cell
    e. Endocrine cell

4. A patient with this esophageal biopsy finding likely has what associated condition?



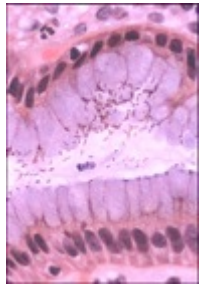
    a. Autoimmune disease
    b. Gastroesophageal reflux disease
    c. Parasitic infection
    d. Eosinophilic leukemia
    e. Allergies

5. A patient with a long-standing esophageal Zenker diverticulum is at risk for developing which of the following:
    a. Adenocarcinoma
    b. Squamous cell carcinoma
    c. Leiomyoma
    d. Lymphoma
    e. Infection

6. What is the main difference between omphalocele and gastroschisis?
    a. In omphalocele, the abdominal contents are contained within a sac; in gastroschisis, they are not.
    b. In gastroschisis, the abdominal contents are contained within a sac; in omphalocele, they are not.

7. NSAIDs contribute to acute gastritis through what mechanism?
    a. Recruitment of inflammatory cells
    b. Inhibition of prostaglandin synthesis
    c. Inhibition of bicarbonate secretion
    d. Activation of acid secretion

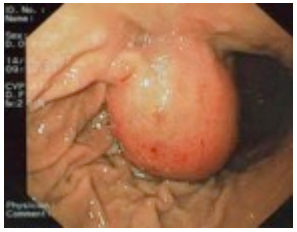
8. A patient has a gastric antral biopsy for abdominal pain, the slide of which is pictured to right. How does this organism survive in the acidic stomach?



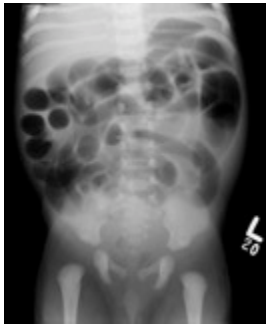
    a. Ammonia production
    b. Hydroxide production
    c. Bicarbonate production
    d. Sulfate production

9. A 62 year-old woman is diagnosed with a autoimmune gastritis and pernicious anemia. Which of following laboratory findings is likely?**
    a. High vitamin B12
    b. Hypergastrinemia
    c. Elevated hematocrit
    d. Low serum iron

10. A 42 year-old woman has this stomach mass resected – the diagnosis is a gastrointestinal stromal tumor. She later develops metastases. Assessing the tumor for overexpression of what protein has therapeutic implications?
    a. C-KIT
    b. KRAS
    c. EGFR
    d. BRAF



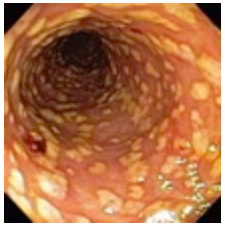
11. This is a radiograph of a newborn, taken after he failed to pass meconium and developed abdominal distention. A biopsy of his rectum is taken. What is the leading entity on your differential diagnosis?
    a. Imperforate anus
    b. Esophageal atresia with tracheoesophageal fistula
    c. Hirschsprung's disease
    d. Hypertrophic pyloric stenosis



12. A 17 year-old male with abdominal pain and long-standing intermittent bloody diarrhea gets a colon biopsy. All of the following favor ulcerative colitis over Crohn disease EXCEPT:
    a. Perianal fistulas
    b. Inflammation limited to the mucosa
    c. Inflammatory pseudopolyps
    d. Continuous disease from rectum to sigmoid colon

13. Which portion of the colon is most likely to be affected in a patient with systemic hypotension?
    e. Cecum
    f. Ascending colon
    g. Transverse colon
    h. Splenic flexure
    i. Rectum

14. This is a colonoscopic image from a patient with diarrhea. What medication is the patient most likely taking long term?
    j. An immunosuppressive agent
    k. An antibiotic agent
    l. A cholesterol-lowering agent
    m. A anti-hypertensive agent



15. What is the major histologic clue to distinguish an acute from a chronic colitis?
    n. Presence of neutrophils
    o. Presence of crypt architectural distortion
    p. Presence of lymphocytes
    q. Present of mucosal granulomas

1. C
2. A
3. B
4. E
5. B
6. A
7. B
8. A
9. B
10. A
11. C
12. A
13. D
14. B
15. B

Eccentric + Proximal	Esophageal Web	Interstitial cells of Cajal	Gastrointestinal Stromal Tumor (GIST)
Concentric + Distal	Esophageal (Schatzki's) Ring	Linitus Plastica	Diffuse type Gastric Adenocarcinoma (desmoplasia)
Plummer Vinson Syndrome (4)	Esophageal web, Fe-deficiency anemia, glottitis, cheilosis	Lymphepithelial lesions + *H. pylori*	MALT Lymphoma
3 M's of HSV Esophagitis	Multinucleation, Margination of chromatin, Molding of nuclei at *lateral aspect of ulcers*	Carney Triad (3)	Young female: GIST + paraganglioma + pulmonary chondroma
No myenteric inhibitory neurons	Achalasia (inability of LES to relax)	Cerebriform rugal folds of fundus	Menetrier's Disease; ZES
Severe vomiting + ETOH	Mallory Weiss laceration	Intracytoplasmic mucin droplet	Signet ring cells (adenocarcinoma)
Chagas Disease	Achalasia	c-Kit +	GIST
Boerhaave's Syndrome (3)	Perforation of esophagus, severe CP, tachypnea	t(11;18)	MALT Lymphoma
Infectious Esophagitis bugs (3)	*Candida*, HSV, CMV	Signet ring cells	Diffuse type Gastric Adenocarcinoma
Pseudohyphae	*Candida*	Young child + intussusception	Meckel Diverticulum
Goblet cells + columnar metaplasia	Barrett's Esophagus	Neonate + abdominal distension	Necrotizing Enterocolitic (NEC), Hirschprung
Zenker Diverticulum (3)	Halitosis, regurgitation, aspiration	Heterotrophic gastric mucosa	Meckel Diverticulum
Birds beak	Achalasia	Failure of vitelline duct involution	Meckel Diverticulum
Ringed esophagus	Eosinophilic Esophagitis	Gluten Sensitive Enteropathy	Celiac Disease
Eosinophilic microabscesses	Eosinophilic Esophagitis	Diarrhea + Flatulence	Lactase deficiency
Salmon pink tongues	Barrett's Esophagus	Characteristic of Celiac Disease	Intraepithelial lymphocytes, loss of brush border
Cowdry A internuclear inclusions	HSV	Steatorrhea in infancy	Abetalipoproteinemia
Esophagitis in atopic patients	Eosinophilic Esophagitis	Anti-tissue transglutaminase IgA	Celiac Disease
Prognostic, esophageal cancer	Depth of invasion	Apoptosis of intestinal epithelium	*Giardia lamblia* (Infective enteritis)
↑Risk Esophageal SCC (5)	Chronic irritation, ETOH+Tob, Zenker Diverticulum, Achalasia	HLA-DQ2, HLA-DQ8	Celiac Disease
↑Risk Esophageal Adenocarcinoma (4)	Barrett's, GERD, obesity, ETOH	Defected lipoprotein transported	Abetalipoproteinemia
Esophageal CA, White male	Adenocarcinoma	RBC burr cells (acanthocytes)	Abetalipoproteinemia
Esophageal CA, Black male	SCC	Common location for *Giardia*	Duodenum
Esophageal CA, distal 1/3	Adenocarcinoma	Lipid accumulation in enterocytes	Abetalipoproteinemia
Esophageal CA, proximal	SCC	Whipple Triad	Diarrhea, weight loss, arthralgia
Secrete HCL, IF	Parietal cells (fundus)	Foamy macrophages + PAS+	Whipple Disease
Secrete pepsinogen	Chief cells (fundus)	Vacuolated enterocytes	Abetalipoproteinemia
Omphalocele	Within peritoneal sac	Whipple Disease locations (3)	Small intestine, lymph nodes, joints
Gastroschisis	Not within peritoneal sac	Pear-shaped trophozoites	*Giardia lamblia* (Infective enteritis)
Projectile vomiting + Olive	Pyloric Stenosis	AIDS patient + watery diarrhea	*Cryptosporidium* (Infective enteritis)
Foveolar hyperplasia "corkscrew"	Reactive Gastropathy	Hyperpigmented buccal mucosa	Peutz-Jeghers Syndrome
Acute Erosive Gastritis (4)	Petechiae, erosions, ulcers; *mucosa only*	"Insular" architecture/Islands	Neuroendocrine Tumor
Duodenal ulcers	Antral Gastritis	STK11 mutation	Peutz-Jeghers Syndrome
Hyperplasia of pyloric *m. propria*	Pyloric Stenosis	Associated with MEN1	Neuroendocrine Tumor
Antral Gastritis	*H. pylori* Gastritis	Peutz-Jeghers Syndrome	Hamartomatous Polyps
Fundic Gastritic	Autoimmune Gastritis	Salt & pepper chromatic	Neuroendocrine Tumor
H. pylori gastritis (2 types)	Antral Gastritis OR Multifocal Atrophic Gastritis	"Arborizing" smooth muscle	Peutz-Jeghers Syndrome
Celiac Disease	Lymphocytic Gastritis	Common site for NET	Small intestine
Autoimmune Gastritis (4)	Anti-IF/Anti-parietal cell, achlorhydria, hypergastrinemia, megaloblastic anemia	Lobulated "pin-wheel" glands	Peutz-Jeghers Syndrome
Foveolar hyperplasia + hypoproteinemia	Menetrier's Disease (Hypertrophic Gastropathy)	Common site of Crohns	Terminal ileum & cecum
Hyperplasia of parietal cells	Zollinger-Ellison Syndrome (Hypertrophic Gastropathy)	Common site of Ulcerative Colitis	Colon & Rectum
E-Cadherin/CDH1 mutation	Gastric Adenocarcinoma	Flask-shaped protrusion	Diverticulitis
↑Risk Gastric (2)/Colonic Adenocarcinoma (2)	*H. pylori* Multifocal Atrophic & Autoimmune Gastritis Crohn's & Ulcerative Colitis	Crohn's Morphology (6)	Skip lesions, granulomas, transmural inflammation, lymphoid aggregates, thickened wall, ulcerations

Skip lesions	Crohn's	LLQ cramping	Diverticulitis
Ulcerative Colitis Morphology (4)	Continuous lesion, mucosal/submucosal inflammation, crypt architectural distortion, active cryptitis	'Herniation upward, enveloping crypts'	Mucosal prolapse polyps
Most common cause lower GI bleed	Diverticulitis	Most vulnerable area to ischemia	Splenic flexure
Tortuous focus of vessel; RIGHT COLON	Angiodysplasia	Flask-shaped ulcer	*Entamoeba histolytica* colitis (Amebiasis)
Ingested RBC	*Entamoeba histolytica* colitis (Amebiasis)	Acute vs. Chronic Colitis	Chronic has architectural distortion
Polyp of LEFT COLON	Hyperplastic polyps	Polyps <5y/o in rectosigmoid	Juvenile polyps
Pseudopolyps	Ulcerative Colitis	Prognostic, Colonic Adenomas	SIZE
Reason for colonoscopy	Colonic adenomas	Polyp in the RIGHT COLON	Sessile serrated adenoma
'Inverted T' shape of crypts	Sessile serrated adenoma	SMAD4	Juvenile Polyposis Syndrome
Criteria for colon cancer	Invasion through muscularis mucosae	FAP Extracolonic manifestation	Periampullary adenomas
MLH1 mutation	HNPCC	Most common hereditary colon CA	HNPCC
Gardner Syndrome (4)	FAP + osteomas + desmoid tumors + late onset	Turcot's Syndrome (3)	FAP + CNS tumors + late onset
Microsatellite instability	HNPCC	Right sided colon cancer	HNPCC
Common CA associated with HNPCC	Endometrial cancer	<100 polyps; >50 y/o	Attenuated FAP
Iron-deficiency anemia + occult bleeding	Colorectal Adenocarcinoma	APC mutation	Familial Adenomatous Polyposis
R colon + Pushing border	Medullary Colon Adenocarcinoma	R colon + Crohn's-like reaction	HNPCC, Medullary Colon Adenocarcinoma
Most common tumor of anal region	Condyloma acuminatum	High risk HPV	HPV 16, 18
Koilocytes	HPV	Low risk HPV	HPV 6, 11
Basket-weave pattern	Condyloma acuminatum		