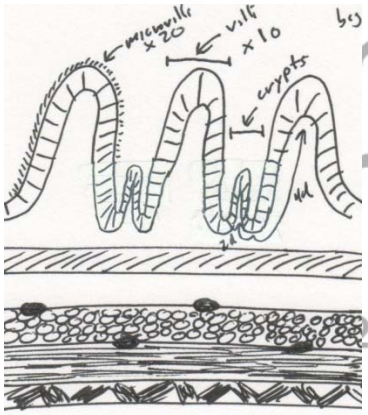
Intestine

- Embryology
  - 4th Week: alimentary track forms from the endoderm and is divided into foregut, midgut, hindgut, the alimentary track communicates w/ the yolk sac via the vitelline duct
    - NB physiologic umbilical herniation occurs in which the midgut enters the umbilical cord for a few weeks
  - 12th Week: distinct organogensis is complete
- Duodenum: 30cm ~ "12 inches" in Latin
  - 1st Part: Anterior (GB) vs Posterior (GDA, CBD, Portal Vein)
  - 2nd-4th Part are retroperitoneal
  - Remember goblet cells indicates SI (if any other part of the GI tract has goblet cells then consider intestinal metaplasia)
  - Lymphocytes, plasma cells, eosinophils are normally found in the lamina propria of the SI unlike in the stomach
  - During development the duodenal lumen is temporarily obliterated owing to proliferation of its mucosal lining subsequently luminal vacuolization and degeneration of some of the proliferating cells results in recanalization of the duodenal lumen
  - Artery: Celiac, Venous: Portal, Lymph: Pancreaticoduodenal LNs
  - Brunner's Glands (secrete bicarbonate, located in submucosa, decrease in number distally and thus mainly found in duodenum, if not present then SI is consider J/I)
  - Increased gastric contents can lead to gastric metaplasia, Brunner gland hyperplasia, increased lamina propria inflammation
  - Gastric contents triggers enterogastric reflexes via secretin/CCK/GIP that slow gastric emptying to prevent dumping syndrome
  - Plicae Circulares or Valvulae Conniventes
- Jejunum
  - Main absorptive part of the SI for nutrients, minerals, vitamins, etc in that if you just have jejunum a pt can do fine
- Ileum
  - Mainly important for water/electrolyte/VitB12 absorption



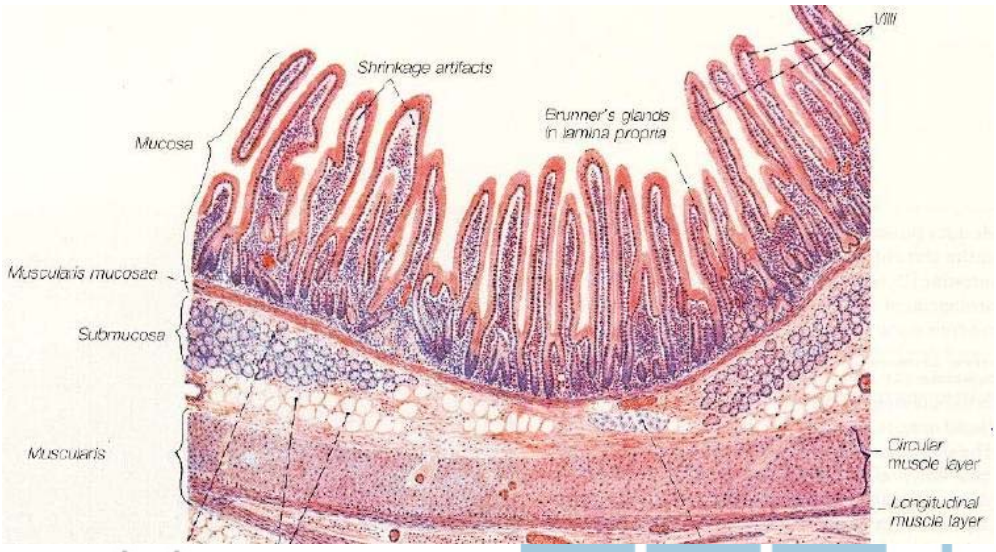
Epithelium
Lamina Propria
Muscularis Mucosa
Submucosa

Circular Muscle aka Muscularis Propria
Longitudinal Muscle aka Muscularis Propria
Serosa/Adventitia

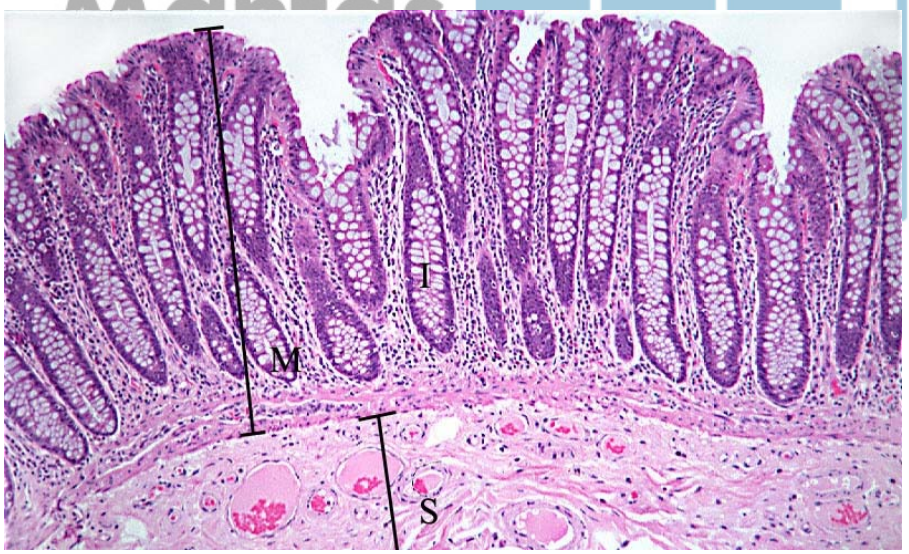
- Mucosa (composed of epithelium, lamina propria, muscularis) (Villi and Microvilli) SA ~ "Tennis Court" increasing 600x fold via plicae circularis, villi, microvilli from 3,300cm^2 to 2,000,000cm^2
  - Crypts of Lieberkuhn (Secretion)
    - Stem Cells (short cuboidal, smooth, undifferentiated cells from stem cells migrate up from crypts to villi differentiating)
  - Villous (Absorption) NB Villi change as you move down the small intestine in that they become shorter and have less nutrient absorptive capacity therefore jejunum is more important than ileum for general nutrition however the ileum can compensate while the jejunum CANNOT for specific ileal functions (bile salt and VitB12 absorption)
    - Enterocytes aka Absorptive Cells w/ Apical/Basal Polarity (Villi to Crypt Ratio 4-5:1, microvilli = brush border, columnar, sloughed off Qd w/ new villi Q5d, represent 90% of villous cells)
    - Secretory Cells
      - Enteroendocrine/Neuroendocrine/Enterochromaffin Cells (secrete hormones)
      - Goblet Cells (secrete mucin)
      - Paneth Cells (secrete various antibacterial agents including lysozyme preventing bacterial colonization of mucosa)
    - M Cells (bind, process and deliver pathogens to immune cells)
  - Lamina Propria (composed of connective tissue providing structure, vessels, nerves, immune cells)
    - **Peyer's Patches** (collections of immune cells on antimesenteric border and concentrated at TI)
    - **NB GI lymphatic vessels are called lacteals and are filled w/milky white chyle after eating**

- Muscularis Mucosa (thin layer of muscle that changes SA of villi to alter absorption)
- Submucosa (similar to lamina propria)
  - Glands
    - **Brunner's Glands** (found mainly in first part of duodenum, open into crypts secreting bicarb rich fluid to neutralize gastric chyme)
- Muscularis Propria = Inner Circular + Outer Longitudinal Muscle (mechanical movement of food)
- Serosa/Adventitia

SI



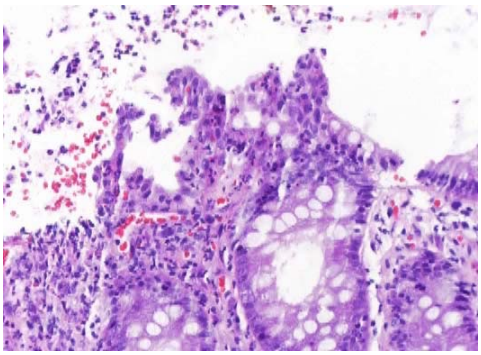
LI



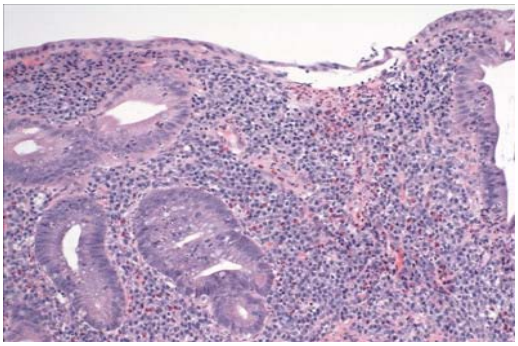
Colon/Rectum/Anus

- Anatomy
  - Three teniae coli formed by fibrotic cords
  - Haustra formed by sustained contractions of circular muscle
- Histology
  - Normal: similar to SI except flat surface w/ no real villi w/ glands that are parallel like test tubes lined and there are more Goblet cells w/ less enterocytes and secretory cells
  - Inflammation
    - Inactive vs Active (neutrophils in the crypt epithelium aka cryptitis, neutrophils in the crypt lumen aka crypt abscess, erosions/ulcers)

- Acute vs Chronic (no edema which is seen in acute inflammation, decreased mucin, crypt distortion w/ branching / loss / atrophy w/ shortening, Paneth Cell metaplasia in the left colon BUT THE BEST DISTINCTION IS the presence of basal plasmacytosis)
- UC vs CD (patchy dz and noncaseating granulomas w/ histiocytes) vs MC (no chronic changes, lymphocytosis near surface and intraepithelial, epithelial damage, thick/irregular/blurred collagen band along BM) vs Ischemia (hemorrhagic/coagulative necrosis) vs Infectious



Active Colitis



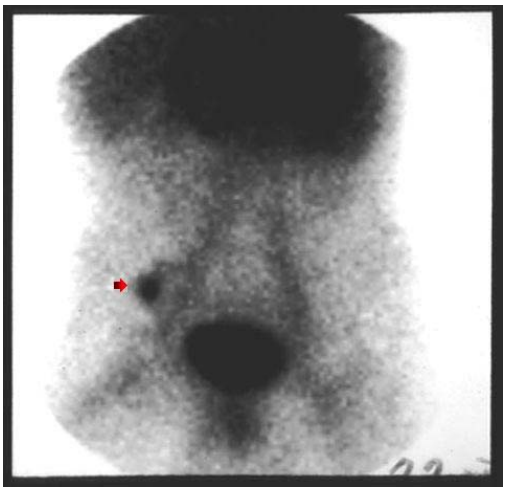
Chronic Colitis

Structural Problems

- **Ab Wall Defect**
  - **Omphalocele** (failure of intestine/liver/spleen to return w/in ab cavity after physiologic umbilical herniation, associated w/ Pentalogy of Cantrel aka DCOPS (Diaphragmatic hernia, Cardiac problems, Omphalocele, Pericardial problems, Sternal cleft) this is why umbilical cords are always cut 5cm away from baby at delivery to ensure you don't cut hidden viscera)
  - **Gastroschisis** (defect in ab wall to R of umbilicus w/ extrusion of viscera that is covered by peritoneum only, not association w/ any syndromes but atresia and malrotation can occur)
- **Atresia/Stenosis/Web**
  - Epidemiology: most common congenital abnormality
  - Associations: Down's Syndrome, Extra-GI Problems (CV, Pulm, Renal, Skeletal malformations), Other GI Problems (malrotation, volvulus, gastroschisis)
  - Etiology: likely intra-uterine ischemic insult (ergotamine/cocaine used by mother, Rubella infection, volvulus, gastroschisis, intussusception) when in jejunum/ileum while when in the duodenum it is 2/2 failed recanalization of the solid stage of duodenal development
  - 20% multiple, usually small intestine
  - Vary from blind pouch to just a membrane obstructing the lumen
  - S/S: in utero polyhydramnios, neonatal bilious vomiting
  - Dx: "double bubble" sign on KUB w/ one in stomach and another in the duodenum but no air distally from there
  - Other Problems: EA, rotation problem, imperforate anus, CV
  - Tx: always rule out rotation problems and annular pancreas as cause then perform direct anastamosis
- **Enteric Duplication Cyst**
  - Mech: defect in intestinal recanulization
  - Location: 1° Ileum, 2° Posterior to 1st/2nd portion of duodenum, Rare Stomach, Colon, Rectum
  - Types: Tubular (communicates w/ GI tract at one or both ends) vs Spherical (does not communicate)
  - Often contain heterotopic pancreatic/gastric tissue, occur on mesenteric side, have a common blood supply and muscular coat w/ the adjacent bowel
  - S/S: various including obstruction, bleeding, perforation, infection, fistulas, etc
  - Dx: Endoscopy will show extrinsic compression, US will show a cystic mass
- **Malrotation**
  - normally there is 270° counterclockwise rotation (three stages) of the midgut from duodenum to transverse colon while foregut and hindgut remain fixed, can present as a newborn or into adulthood, can cause obstruction from volvulus, ischemia, lymphagiectasia, etc, malrotations typically occur during the 2nd stage and can be described as non-rotations (SI on the right side of the abdomen and colon on the left side of the abdomen), reverse rotation (transverse colon is behind duodenum) or malrotation (most common, SI and cecum twist around the SMA causing ischemia and Ladd's Bands b/t peritoneum and malpositioned subpyloric cecum pinch the duodenum causing obstruction), NB malrotations during the 1st and 3rd stage are rare but when they occur they cause cloaca extroversion and cecal elongation in the RUQ, often coexists w/ omphalocele/gastroschisis/diaphragmatic hernia/SI-atresia/CIPO, etc, Tx: Ladd's Procedure (divide Ladd's bands, widen mesentery, appendectomy and fixation of SI/LI to normal position))
- **Volvulus/Intusseption (refer)**
- **Diverticulum/a**
  - General

- blind pouch leading off the GI tract lined by mucosa, muscularis and serosa and that communicates with lumen
- diverticulosis is many diverticulum aka diveritula (not –ae) aka "tics"

o Small Intestine
- **Extraluminal Duodenal Diverticulum**
  - Epidemiology: seen in 25% of pts undergoing ERCPs!!!
  - Mech: acquired 2/2 where vessel penetrates muscularis or where dorsal and ventral pancreas fuse during development
  - Location: 75% w/in 2cm of ampulla and are called "juxtapapillary diverticula", can be multiple
  - S/S: usually asymptomatic but sometimes perforation, diverticulitis, bleeding, acute pancreatitis, SOD, bacterial overgrowth, choledocholithiasis, cholangitis, ulceration, Dieulafoy, etc
  - Tx: only if symptomatic
- **Intraluminal Duodenal Diverticulum aka Windsock Diverticulum**
  - Epidemiology: rare w/ <100 cases
  - Mechanism: congenital problem w/ canalization of the duodenum
  - Location: second part of the duodenum, can encompass the entire circumference of the duodenum and can extend as far down as to the fourth part of the duodenum, the other end can actually recommunicate back with the duodenum!
  - S/S: can often cause obstruction by retention of food material, pancreatitis, bleeding, etc
  - Tx: only if symptomatic
- **Jejunal Diverticulum**
  - Mechanism: acquired 2/2 some underlying motility disorder
  - Location: proximal jejunum, often multiple, vary in size from small (10mm) to large (10cm), on mesenteric side
  - S/S: usually asymptomatic but sometimes ab pain, early satiety, bloating, etc, bacterial overgrowth, perforation w/ intramesentery abscess
- **Congenital aka Meckel Diverticulum**
  - REMEMBER THE "RULES of TWO"
  - Epidemiology: first 2yrs of life, 2x more common in males, 2% of population
  - Mechanism: proximal patency of the embryonic vitelline/omphalomesenteric duct (connects yolk sac with midgut thru the umbilicus and normally obliterates during the 6th week of development)
    - NB failed obliteration can result in a vitelline/omphalomesenteric diverticulum (Meckel's), cyst (rare, can get infected), cord (rare, 2/2 failed involution, can cause obstruction) or patent duct (rare, full connection b/t ileum and umbilicus, presents as foul smelling discharge from the umbilical cord upon cutting after birth)
  - Location: antimesenteric, 2in long and 2ft from ileocecal valve in ileum (fibrous cord extends from diverticulum to umbilicus)
  - S/S: only 2% symptomatic, 50% have $\geq$2 types of epithelia (ileal mucosa w/ 1° gastric 2° duodenal/bile-duct/pancreatic/colonic) resulting in unique Sx like (1) painless bleeding w/ maroon stools 2/2 PUD in heterotropic gastric mucosa, (2) obstruction 2/2 intussception or volvulus around fibrous cord remnant of the vestigial vitelline duct, (3) diverticulitis (acute inflammation can mimic appendicitis and chronic inflammation can mimic ileal Crohns)
  - Dx: Meckel's Scan (99m-technetium pertechnetate is preferentially taken up by gastric mucosa)
    - You are looking for increased activity in anterior RLQ which usually occurs at 30min-1hr
    - Pertechnetate is taken up by gastric mucosa and thus appears and fades similar to stomach
    - 85% sens and 95% spec
    - Usually you also give cimetidine to block release of pertechnetate from mucosa
  - Tx: partial small bowel resection if symptomatic



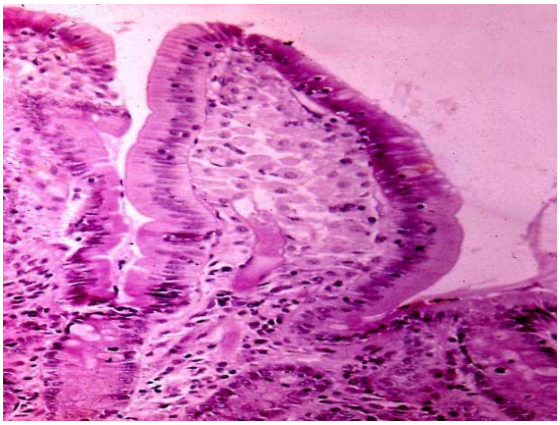
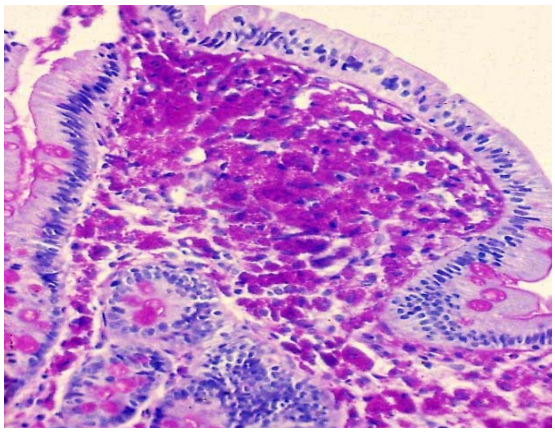
- Large Intestine
  - Epidemiology
    - b/c most pts are asymptomatic the true incidence/prevalence is hard to ascertain but often quoted numbers are 10% of 40yo, 60% of 80yo
    - M=F except M>F in terms of complications
    - RFs: industrialized countries, low fiber and high meat, CTD, age
    - NB it was recently demonstrated that NSAIDs increase r/o diverticulitis and diverticular bleed
  - Location
    - sigmoid colon (why? smallest radius of colon remember Laplace's Law P = T/R) NB in Asia the most common site is R colon
    - occur at the weakest points of the colon (4 rows b/t mesentery and teniae coli (x3 areas where the longitudinal muscle is weak) specifically where the vasa recta (neurovascular bundle) penetrate into the colon wall)
    - they are actually false diverticula (psuedodiverticula) including only mucosa/submucosa
  - Mechanism (not exactly clear)
    - (1) abnormally exaggerated segmental non-peristaltic contractions around (2) low fiber small dense stool (NB despite increase fiber intake over the last 40yrs there has been no change in diverticular incidence) in the presence of (3) altered wall structure w/ higher elastin and collagen → increased intraluminal pressure → diverticula
  - S/S
    - 80% of people w/ diverticulosis will remain asymptomatic during their lifetime suggesting that this is not a dz in and of itself but a phenomenon of aging
    - Usually asymptomatic aka "simple diverticulosis" but occasionally IBS like symptoms w/ LLQ pain worse w/ eating and relieved w/ defecation aka "Symptomatic Uncomplicated Diverticular Disease (SUDD)" 2/2 contraction of thickened colonic muscle (myochosis)
  - Dx
    - Barium Enema (the one colonic diagnosis for which enema is more sensitive than colonoscopy BUT misses other problems like cancer, IBD, etc)
    - Endoscopy (the pressures generated during colonoscopy do NOT exceed the pressures needed to perforate a diverticulum hence colonoscopy is safe except if there is diverticulitis where inflammation weakens the wall)
      - NB sometimes a diverticulum can invert and appear like a polyp and when you Bx you can perforate but suspect when overlying mucosa is nl, base is broad and it is surrounded by other diverticula (many times they can be everted w/ a forcep)
  - Px (development of Sx and/or complications)
    - High fruit/vegetable fiber diet but the studies demonstrating this benefit were not prospective randomized studies nevertheless still recommended
    - Unlike fiber there is absolutely no evidence supporting the claim that one should avoid seeds and nuts in fact some studies say that consumption is *protective*
  - Tx (if SUDD)
    - Antispasmodics
    - High fruit/vegetable fiber diet
    - 5-ASAs esp for SUDD
    - Probiotics esp for SUDD
    - Rifaximin esp for SUDD
  - Complications (Big Ones Bleed vs Small Ones Inflame)
    - **Symptomatic Uncomplicated Diverticular Disease – SUDD** (?%) refer above

- **Segmental Colitis Associated with Diverticulosis – SCAD** (1%)
  - Epidemiology: elderly men
  - S/S: diarrhea, hematochezia, ab pain (pts are generally not as toxic as in diverticulitis)
  - Mechanism: descending/sigmoid colitis (rectum is spared unlike in UC) occurring in the segment that has the diverticulum but not necessarily associated w/ diverticulitis!!!
  - Colonoscopy: erythematous patches on folds aka "Crescent Fold Disease" aka "Fawaz Spots", sometimes there are erosions (NB diverticular ostia are uniquely not inflamed unlike diverticulitis)
  - Bx: chronic changes looking just like IBD hence that is why in the past it was consider a form of UC nevertheless if pt begins to develop chronic Sx look for IBD again
  - Prognosis: spontaneous resolution often occurs if mild
  - Tx: 5-ASAs, steroids
- **Diverticular Bleed** (5%) refer to GIB notes
- **Diverticulitis** (10-25%)
  - Mech: fecalith forms → obstruction of blood supply → inflammation → microperforation (contained w/in mesentery w/ phlegmon) = "uncomplicated diverticulitis" → macroperforation (beyond mesentery w/ abscess, NB free perforation is rare b/c diverticula occur on mesenteric side) = "complicated diverticulitis"
  - S/S: Constitutional Sx, LLQ pain, C (not diarrhea!!!), occasionally N/V/anorexia, dysuria
  - Complications: abscess, peritonitis, fistulas, obstruction (acute b/c inflammation can narrow colonic lumen vs chronic b/c recurrent bouts can result in strictures)
  - Labs: leukocytosis
  - Dx
    - CT (shows colonic thickening and mesenteric stranding)
    - BE/Colonoscopy (NOT BE OR Endoscopy DUE TO RISK OF PERFORATION during acute presentation)
      - NB the practice that these pts need a colonoscopy in 2-6wks to rule out CRC as a cause is based on the fact that the diagnostic tests in the past (BE, CT-scans) were bad at finding a mass but now they are so good that colonoscopy is not needed
      - NB some do a gentle flex sig to rule out IBD, ischemia, infection
    - KUB (signs of ileus, perforation, etc)
  - Tx
    - If able to eat then out-pt: liquid diet and PO abx (Cipro + Flagyl) x7-10d and call if Sx worsen
    - If unable to eat, multiple comorbidities, etc then in-pt: NPO, IVF, decompression, IV abx (Vanc + Cefepime + Flagyl) x14d
    - If med therapy fails after >3d, free perforation, large abscess unable to be drained percutaneously, recurrent dz (1/3 risk w/ 50% occurring w/in 1yr, if a 4th attack despite medical Tx and attempted Px w/ 5-ASAs, Rifaximin, Probiotics), etc then surgery
      - if no complications then sigmoidectomy w/ direct colorectal anastomosis
      - if complications then colostomy w/ Hartmann pouch followed by reanastomosis after 10wks
  - Px
    - Recurrence of 30% after 1st episode and 50% after 2nd episode thus surgery is required

Sprue (general term for any type of mucosal flattening)

- **Other GI Dz**
  - **ZES**
  - **Cow's Milk AND Soy Protein Intolerance**
  - **Crohn's Disease**
  - **Eosinophilic Gastroenteritis**
  - **Severe Malnutrition**
- **Infections**
  - **Parasitic Infections (Giardiasis, Strongyloidiasis, Coccidiosis, Hookworm)**
  - **Viral Gastroenteritis**
  - **SIBO**
- **Genetic Conditions**
  - **Microvillus Inclusion Disease** (congenital villous atrophy w/ microvillous inclusions in enterocytes, p/w severe water diarrhea after birth, seen in Navajo/Middle Eastern females, Dx: EM of small bowel Bx, Tx: TPN then intestinal transplant)
  - **Intestinal Epithelial Dysplasia aka Tufting Enteropathy** (congenital defect in BM → tufting of epithelial cells at apex b/c they are no longer in contact w/ BM → villous atrophy, Dx: Bx, Tx: intestinal transplant)

    - **Enteric Anendocrinosis**
    - **Hyperinsulinism with Enteropathy and Deafness**
- **Immunodeficiency Syndromes**
    - **A/Hypogammaglobulinemia**
    - **GVHD**
- **Lymphatic Dz**
    - **Intestinal Lymphoma**
    - **Intestinal Lymphagiectasia**
- **Drug Induced**
    - **Olmesartan Induced Sprue** (new concept, occurs after a few years of starting medicine)
    - **Chemoradiation Enteritis**
- **Autoimmune Enteropathy**
    - Emerged as a diagnosis in 1980s
    - Well characterized in children
    - S/S: looks like severe sprue that doesn't respond to gluten free diet, other autoimmune conditions
    - Dx: sprue-like changes BUT **no IELs** (additional presence of crypt abscesses), + auto-antibodies (**anti-Goblet, anti-Enterocyte**) in tissue w/ IF and in serum but they are neither sensitive nor specific, absence of CVID (which usually has plasma cells)
    - Tx: corticosteroids ± other immunosuppressive agents
- **Whipple's Dz**
    - History: George Whipple in 1907 described a 5yr illness of a fellow physician with Sx consistent w/ Whipple's Dz but he called it "Intestinal Lipodystrophy" b/c he thought the "foam" in macrophages was lipid material
    - Epidemiology: adult white male in rural US/Europe who engage in farming/building, incidence 1/2,000,000
    - Mechanism: chronic slow-growing systemic infection w/ *Tropheryma whipplei* (GP actinomycete, oral acquisition from soil/water which subsequently invades SI and then spreads to other organ systems via lymphatic spread, lacks various metabolic capabilities making it dependent on host, large portion of its genome is dedicated to constantly changing surface proteins allowing it evade host immune system allowing for a chronic infection)
    - S/S (in order of incidence, any organ can be infected, arthralgia/fever usually precedes GI Sx by several years, if pt has Whipple's one should thoroughly examine each system that may be infected)
        - GI (90%): sprue and lymphatic obstruction at mesenteric LNs → ab pain, weight loss, malabsorptive diarrhea
        - Rheum (70%): arthralgia, fever
        - Derm (40%): hyperpigmentation
        - CNS/Psych (30%): changes in cognitive/consciousness/psych, hypothalamic (eg. polydipsia, hyperphagia, insomnia), cerebellum (eg. ataxia), CN (eg. supranuclear ophthalmoplegia)
            - "oculomasticory myorrthmia" (slow 1x/sec rhythmic oscillations of ocular/facial muscles, only occurs in 20% of Whipple's pts but very specific)
            - CNS imaging (mild atrophy, focal lesions but at no specific location which can be stereotactically biopsied)
            - CSF (mild pleocytosis, PAS+ sickle form particle containing cells, +PCR)
            - NB classically occurs during relapse after inadequate Tx w/ abx that do not penetrate CNS resulting in flourishing infection in this reservoir, unfortunately CNS infection tends to be refractory w/ abx Tx
        - Heme (30%): mesenteric/retroperitoneal/peripheral LAD (hypodense on CT, hyperechoic on US)
        - CV (10%): pericarditis, myocarditis, endocarditis (important cause of "culture negative endocarditis")
        - ID (rare): TW infection causes immune dysfunction → increased r/o opportunist infection (Giardia, PCP, TB, Crypto, Nocardia, Candida, et al)
        - Eye (rare): uveitis, viritis, retinitis, retrobulbar neuritis, papilledema
    - Dx (since GI involvement is uniform in all pts Dx is based on SI biopsy, start w/ H&E stain and if there are concerning findings then do PAS stain, rarely further confirmation is needed w/ EM and PCR, if there are extra-intestinal Sx then tissue should be obtained and examined)
        - Histology: (1) live extracellular bacteria in lamina propria that cannot be seen on LM but can be seen on EM, (2) dead intracellular bacterial remnants w/in phagolysozomes w/in macrophages in lamina propria (NB interestingly no other inflammatory cells are present which would normally be present w/ any other type of bacterial invasion!!!) that appear foamy on LM w/ H&E stain but are strongly positive w/ PAS stain b/c of the remnants are entirely glycoprotein cells walls, (3) just like celiac sprue except there are dilated lacteals aka lymphangiectasias appearing as white-yellow plaques and some degree of villous distension from the bacteria/macrophages
            - DDx: **MAI, Macroglobulinemia, Histo**
            - Sometimes you can isolate TW in various other tissues/fluids using Cx, PCR, FISH, etc
        - Labs: increased APRs, low nutrient levels, anemia

- Tx
  - Ceftriaxone IV x14d (or Streptomycin+Pen-G) then Bactrim PO x>1yr
    - NB symptoms resolve in days-weeks vs histology resolve in months-years
    - NB initial Tx w/ tetracycline was effective EXCEPT for CNS b/c tetracycline does not penetrate the BBB and sadly these pts become refractory to CNS penetrating antibiotics after Tx w/ tetracycline
    - NB uniformly fatal if untreated
    - NB Jarisch-Herxheimer Rxn is often seen a few hours after initiation of IV abx therapy
    - NB during Tx the pt should undergo periodic diagnostic testing at regular intervals to monitor improvement (one should especially evaluate the CSF for sanctuary of infection in the CNS and may be the reason for 35% relapse rate)

- **Tropical Sprue**
  - General: diarrhea in the tropics is almost 2/2 to a single infectious agent but in some cases the Sx become more chronic and no single infection is found, in addition there are sprue like changes, and this is considered tropical sprue
    - DDx of chronic tropical diarrhea: parasitic infection, SIBO, TB, lymphatic obstruction, tropical pancreatitis tropical sprue (always a DOE)
    - NB all people who live in the tropics have some degree of tropical enteropathy but they are asymptomatic though they tend to have lower BMI
  - Etiology: unknown
  - Mechanism: unknown likely 2/2 persistent inflammation following prolonged overgrowth of an unknown pathologic or non-pathologic bacteria/virus
  - Epidemiology: long term travelers from equatorial parts of the world (Central/South America, Caribbean, sub-Saharan Africa, Southern Asia), can be sporadic or epidemics (eg. there is a yearly epidemic in Puerto Rico during the winter months), incidence is declining 2/2 increased hygiene and antimicrobial use
  - S/S: malabsorptive diarrhea w/ severe nutritional deficiencies, weight loss and protein losing enteropathy
  - Dx
    - Histology: just like celiac sprue except more PATCHY, involves more of the DISTAL SI and instead of crypt cell hyperplasia there is actually degeneration suggesting that damage is done to the stem cells and not to the villus
  - Tx: correct fluids/electrolytes/vitamins (esp VitB12 and Folate) + Tetracycline 250mg PO QID x6mo
    - NB there is some evidence that folate alone can reverse atrophy
    - 20% chance of relapse rate

- **Celiac Disease aka Celiac Sprue aka Gluten Sensitive Enteropathy**
  - History
    - 1st Century: Aretaeus, a Greek doctor, described an illness that likely was sprue
    - 17th Century: Vincent Ketelaer, a Dutch doctor, coined the term "Sprouw" (later changed to "Sprue") referring to a chronic diarrheal disease accompanied by aphthous ulcers
    - 19th Century: the term "Celiac" was used
    - World War II: Willem Karel Dicke, a Dutch pediatrician, linked cereal w/ celiac dz when he noticed that celiac dz improved during the war when cereal became scarce and then worsened after the war
    - 1950: van de Kamer determined that gluten was the cause
    - 1954: Pulley described the histologic changes
  - Epidemiology
    - Incidence/Prevalence: unclear b/c there are various degrees and presentations (also what do you define as dz? HLA? AB? Histology? Sx?) nevertheless likely higher than expected
    - Location: 1° any wheat/rye/barley/oat eating regions esp Northern European Countries and US (1% of population) →→→ any rice/corn/sorghum/millet eating regions esp Asia and Africa (rare)
    - Gender: slight F>M
    - Familial: ~5% risk if 2nd degree relative → ~10% risk if 1st degree relative → ~70% concordance rate in monozygotic twin

- NB CD is specifically linked to **HLA-DQ2/Q8** (refer to immunology notes) which is found in all CD pts but 30% of the general population is also + therefore additional genes are also necessary

o Mechanism
  - Family: Gramineae (**Cereal Grain**) → Two Subfamilies: Festucoideae (**Wheat-"Gliadins", Rye-"Secalins", Barley-"Hordeins", Oats-"Avenins" = these proteins are collectively called "Glutens" which causes CD**) and Panicoideae (**Rice**-"Oryzins", **Corn**-"Zeins", **Sorghum**-"Sorghumins", **Millet**-"Pennisetins" = **these proteins do NOT cause CD**)
  - **Gluten is ingested and absorbed intact across the epithelium into the lamina propria → HLA-DQ2/8 on APCs in the lamina propria bind gluten → tissue Trans Glutaminase (tTG) enzyme is released from endomesium (connective tissue surrounding smooth muscle) and deamidates part of the gluten protein creating deamidated gliadin peptides (DGPs) (this process enhances T-cell response) → APCs presents DPGs to CD8 T-cells in lamina propria activating them → inflammation (esp via IL-15) ensues which subsequently damages enterocytes resulting in ultimate premature loss w/ compensatory increase in crypt replication (NB role of IELs is unclear)**
  - **Types**
    - **Celiac Dz (~Type IV Delayed Hypersensitity Reaction w/ an autoimmune component given the presence of Ab)**
    - **Gluten Sensitivity (~Type 1 Immediate Hypersensitivity Reaction)**
    - **Gluten Intolerant (many people have difficulty breaking down gluten protein shell that surrounds the inner carbohydrate, in these people the entire grain enters the colon where bacteria are able to effectively breakdown gluten releasing carbohydrate which enters into fermentation creating gas/bloating, hence FODMAP diet excludes gluten foods, these pts do not have CD but nonetheless are symptomatic to gluten)**

o Classification (from most common to less common, the silent form is 7x more common than symptomatic forms!!!)

	HLA-Genetics	Antibodies	Histology	Symptoms	Tx Response
Susceptible	+	-	-	-	Tx?
Latent	+	+	- (likely had changes in the past)	-	Tx?
Silent	+	+	+	-	Tx?
Atypical	+	+	+	Extra-GI	Successful
Classic	+	+	+	GI and Extra-GI	Successful
Refractory	+	+	+	+	Fail after 6mo of strict GFD

o Dx
  - Approach
    - If high probability then do both serology and biopsy and if +/- then repeat bx, if -/+ then search for other causes of sprue, if -/- then not CD and search for other cause of Sx
    - If low probability start first w/ serology and if + then do biopsy but if – then not CD and search for other cause of Sx
    - Some pts (eg. IBS pts) w/o CD can have improvement w/ GFD therefore if a pts is Dx w/ CD based on response to GFD alone (i.e. no Bx or serology) what do you do? Check HLA (if – then not CD) but if + then check serology b/c may be + and if so then Bx but if – (which occurs often) then Gluten Challenge (1/4 of a slice of bread per day then double Q3d until 4 slices of bread per day x6wks then check Ab (through-out check Sx) and if – then continue w/ Ab checks Q1-3mos (through-out check Sx) and if – at 6mo then Bx)
  - Serology (Prometheus Plus = Serology (TGA-IgA, EMA-IgA, IgA, DGP-IgA, DGP-IgG) + Genetics (HLA DQ2/DQ8))

	Sens	Spec	PPV	NPV
IgA-TGA	98	98	72	99
IgG-TGA	70	95	42	99
IgA-EMA	95	99	83	99
IgG-EMA?				
IgA-AGA	85	90	18	99
IgG-AGA	85	80	31	99
IgA-DPG	88	95	44	99
IgG-DPG	80	98	68	99

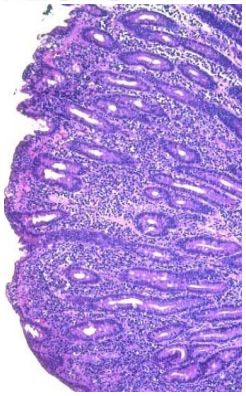
    - **anti-tissue-Trans-Glutaminase Ab (TGA) IgA** screening test b/c highest sensitivity (# value w/ nl 10.3U/mL for IgA)
    - **anti-Endo-Mesial Ab (EMA) IgA** confirmatory test b/c highest specificity, (either + or -)
    - Other
      - IgA moderately higher sensitivity but significantly higher specificity than IgG

- Sens/Spec vary based on assay and are lower in mild CD, partially Tx and children <2yo
- 2% of CD pts (vs 0.2% in the general population) have IgA deficiency therefore some (not a general recommendation) check total IgA and if low then **check IgG-DPG b/c it is the most sensitive of the IgGs**
- 20% of CD pts have –TGA and –EMA then check IgG-DPG
- **Anti-Gliadin Ab (AGA) IgA** only really used to assess GFD compliance, not really used in dx anymore however a new type of AGA is now available called **anti-Deaminated Gliadin Peptide (DGP) IgG**

▪ Other
- HLA PCR of blood or cheek swab (95% of CD pts have DQ2 and the remaining 5% have DQ8 but remember that 30% are + therefore if negative then CD is ruled out but it cannot be used to rule in disease)

▪ Endoscopy
- Often normal but there can be reduced # of folds, scalloping, mosaic fissuring but only 60% PPV
- Bx: 6 biopsies (why 6? b/c dz is patchy, unclear if biopsies from bulb should be obtained b/c architectural distortion 2/2 Brunner's glands and peptic duodenitis can make dx of CD challenging or misleading)

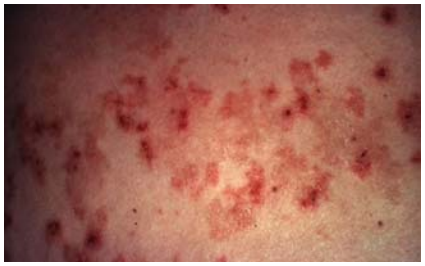
▪ Histology
- Small Intestine (affects proximal SI in early/mild dz and then progressive involvement of more distal SI in late/severe dz)
- *Modified Marsh Grading System*
  - 0: nothing
  - 1: **lamina propria mononuclear inflammation** (1° lymphocytes, plasma cells, 2° PMNs, eosinophils, mast cells) **w/ intraepithelial lymphocytes – IELs w/ >40-EILs/100-EC** (not only increased number but different type changing from CD4 helper/inducer T-cells to CD8 cytotoxic/suppressor T-cells)
  - 2: " " + **crypt hyperplasia** (increased number of cells resulting in elongation of cypts, increased mitotic activity occurs to replace mucosa that is shedding at a faster rate (6x the normal rate), otherwise crypt cells look normal on LM and EM) **w/ villous enterocyte disarray** (overall number is intact but they are shedding faster and unlike crypt cells enterocyte cells show significant changes even if the villous is overall intact, cells are more cuboidal than columnar, more basophilic cytoplasm, loss of basal nucleus polarity, brush border is attenuated, variety of degenerative intra-cellular changes seen on EM)
  - 3a/b/c: " " + **mild-4:1/mod-3:1/severe-2:1 villous atrophy** (villous blunting to flat mucosa, total thickness of mucosa is never really reduced even in Grade 3 b/c of crypt hyperplasia)
  - 4: " " + **total villous loss**
  - **NB very important to know that IELs suggest but is NOT sufficient to make the dz of CD as it is a non-specific finding seen in other conditions (SIBO, peptic duodenitis, HP, etc) hence lamina propria/crypt/villous changes are necessary to make the dx**
- **NB you can stain tissue w/ tTG-2 IgA to distinguish from other enteropathies**
- **Bx looks like colon tissue**



- S/S (very protean presentation, if you have any of the below problems and the cause is unclear then check for CD!!!)

▪ GI
- Infants
  - as child is weaned from breast milk to cereal grains Sx of **steatorrhea and ab pain** develop followed by **FTT** w/ short stature, muscle wasting, ab distension, apathetic, irritability, pallor, edema, hypotonia long eyelashes, smooth tongue, mouth sores, clubbing, peripheral neuropathy, rickets, IDA

        - NB interestingly if dz is not caught during early childhood Sx actually abate during adolescence and the return during adulthood
    - Adults
        - **Malabsorption resulting in Episodic Steatorrhea w/ Flatulence and Weight Loss and Deficiencies** (depends on location of dz but includes deficiency of iron, VitADEK, folate, zinc)
            - NB 50% are symptomatic but do NOT have diarrhea
            - NB severe dehydration from diarrhea is "gliadin shock or celiac crisis"
        - Other: **recurrent aphthous stomatitis, vague mild pain/bloating** often attributed to IBS but severe Sx should suggest complications (below)
- Extra-GI (more common in older pts 2/2 general malnutrition or specific nutritional deficiencies)
    - Derm: **follicular keratosis**, **bruising, edema**
    - Endo: **short stature, delayed menarche, amenorrhea, infertility, pregnancy complications**
    - Heme: **anemia** (low iron/folate/B12/pyridoxine), **thrombocytosis/target-RBCs/Heinz-Bodies/crenated-RBCs/Howell-Jolly-Bodies w/ increased r/o bacterial infections (therefore consider vaccination) 2/2 hyposplenism to splenic atrophy** (mechanism is unclear)
    - Liver: **isolated transaminitis** (mechanism is unclear, should completely resolve w/ GFD if not then consider coexisting autoimmune hepatobiliary dz)
    - MS: **osteopenia, atrophy, tetany, weakness**
    - Neuro/Psych: **peripheral polyneuropathy and cerebellar ataxia**
- Associated Disease
    - Genetic Syndromes: **Down's** (15% have CD), **IgA Deficiency, Turner's**
    - Autoimmune: **T1DM** (5% have CD, unexplained episodes of hypoglycemia should alert you to co-existing CD), **Hypo/Hyperthyroidism** (3% have CD), **Sjogren's, SLE, Adrenal Insufficiency**
    - GI: **Microscopic Colitis** (20% have CD), **IBD**
    - Liver: **PBC, PSC**
    - Pulm: **Bird-Fancier's Lung, Fibrosing Alveolitis, Idiopathic Pulmonary Hemosiderosis**
    - Neuro: **Epilepsy w/ Cerebral Calcifications**
    - Renal: **IgA Nephropathy**
    - CV: **Recurrent Pericarditis**
    - Neuro: **Schizophrenia, ADHD**
    - Derm: **Dermatitis Herpetiformis**
        - S/S: chronic, recurrent, very pruritic/burning/stinging vesicles/papules/wheals arranged in groups hence "herpetiformis" on symmetric extensor surfaces and scalp, neck, trunk, buttocks
        - Mech: autoimmune (not sure if it is gluten mediated?) attack on epidermal type 3 transglutaminase (not type 2 which is found in the SI in CD) but there is some cross reactivity such that some pts w/ DH get enteropathy (usually less severe form) and some pts w/ CD get skin lesions (usually less severe form)
        - Dx: granular/speckled IgA deposits in perilesional skin on IF, these pts also have similar HLA and Ab to CD pts
        - Tx: **Dapsone** 1-2mg/kg/d (remember to obtain G6PD levels before starting and check methemoglobin/CBC Qmo) heals rash but not the enteropathy which can only be reversed w/ GFD
        - NB **iodine can exacerbate** DH



- Screening
    - Mass screening is not recommended even in high risk populations in order to catch susceptible, latent or even silent dz b/c the natural course of the dz is not known (i.e. risk of converting to Sx dz or development of complications) and maintaining a GFD in an symptomatic pt is difficult
- Tx
    - Mild
        - Gluten Free Diet (GFD)
            - Dietician consult
            - GF is defined as <20ppm
            - Lifelong

        - Avoid all foods containing grains (NB even though oats contain a similar gluten many CD pts can tolerate nevertheless initially avoid oats and then reintroduce slowly after dz has abated)
        - Ok Grains: rice, corn, sorghum, millet
        - Alcohol: Bad (beers, lagers, ales, stout) vs Good (wine, liquor including whiskey, ciders, spirits)
        - Some recommended avoid lactose initially b/c bad CD likely has accompanying brush border lactase deficiency 2/2 damage to epithelium
        - Every pt is variable in their ability to tolerate gluten
        - Strict GFD decreases r/o malignancy but its role in preventing other autoimmune conditions (above) or advancing silent dz is unknown
        - Beware of hidden gluten
            - **Some processed foods (soups, gravy, sauces, imitation seafood, salad dressings, soy sauce) and precooked meals have gluten in the form of wheat flour thickener (look for gluten free symbols on packages)**
            - **Non-foods (toothpaste, lip gloss, lipstick, envelope gum, vitamins, meds, candy, communion wafers, supplements, Play-Doh)**
            - **Sometimes grains that wouldn't be a problem are b/c of contamination if processed in the same mill**
    - Identify and treat nutritional deficiencies (most just give a MVI, check a DEXA)
    - Remember that some meds will be poorly absorbed
    - Screen first degree relatives
    - Have pts join www.celiac.org
  - Severe: steroids to bring down inflammation is reserved for severe disease who p/w "gliadin shock or celiac crisis", continue until GFD diet takes effect
  - Future: glutenases from bacteria which would cleave glutens into non-toxic peptides in the stomach, larazotide acetate inhibits permeability of SI mucosa to gluten, genetic modification of wheat to delete toxic peptides, vaccine to inhibit T-cell response to gluten, tTG inhibitors, etc
- Prognosis (follow Ab to assess response and compliance, second look EGD w/ Bx is not necessary to assess response unless continued Sx or positive Ab)
  - Sx improvement w/ GFD (days-weeks)
  - Serologic Improvement w/ GFD (t1/2 is 2mo therefore follow titers therefore months)
  - Histologic Improvement w/ GFD: villous enterocyte disarray (few days), lamina propria inflammation w/ IELs, crypt hyperplasia and villous atrophy (months to yrs but can be incomplete in adult onset CD)
- **Non Responsive Celiac Disease (NRCD)** (10%, primary (never responded after initial dx) vs secondary (responded after initial dx but disease returned), defined as persistence of S/S despite GFD >6mo)
  - **1st Confirm that dx of CD was correct by checking HLA status, checking Ab status (current and in past) and reviewing biopsy specimen w/ expert pathologist if not CD then DDx should include other causes of sprue (refer above)**
  - **2nd If pt truly has CD then search for gluten exposure intentional or inadvertent gluten contamination (most common)**
    - expert dietician consult to do an extensive nutrition review for hidden glutens (refer above)
    - check Ab (specifically IgA/G AGA) and if + then suggests gluten exposure (NB –Ab does not rule it out though)
  - **3rd If pt is truly gluten free then re-biopsy duodenum and if normal then check for presence of a second disease**
    - Another sprue like illness (above)
    - Lactose Intolerance (very common)
    - MC (very common)
    - IBS (very common)
    - SIBO
    - Food Allergies
    - Pancreatic Insufficiency
  - **4th If re-biopsy of duodenum shows continued active sprue then consider other causes of sprue (refer above) and if not present then consider complications and if not present then pt likely has true refractory CD (RCD)**
    - **Complications**
      - **Collagenous Sprue**
        - Dx: sprue + subepithelial collagen band >10mm (must distinguish from collagenous colitis)
        - NB can occur alone or as a complication of CD
        - Tx: strict GFD + steroids (other: immunosuppressants, elimination diets, zinc/copper supplementation)
        - Prognosis: poor
      - **Ulcerative Jejunoileitis aka Chronic Nongranulomatous Ulcerative Enterocolitis**

        - Rare but serious
        - Ulceration w/ h/o GIB/perforation and strictures w/ h/o SBO
        - Dx: enteroscopy and enterography (diffuse deep jejunal ulcers)
        - Tx: strict GFD but surgical resection is the most effective Tx along w/ steroids and other immunosuppressants
        - Complication: EATL
        - 5yr survival is 50%
    - Cancer (2/3 EATL vs 1/3 AC)
        - **Enteropathy Associated T-cell Lymphoma** (EATL) (40x but likely much less)
            - Mech: inflammatory response triggered by gluten can result in the malignant transformation of intraepithelial T-cell lymphocytes
            - Epidemiology: M>F, ~60yo, occurs after several decades of CD
            - S/S: recurrence of severe Sx of pain, diarrhea, weight loss in previously well controlled celiac dz
            - Complications: SBO, perforation, bleeding esp during Tx (also erythrophagocytosis, cavitary mesenteric LAD)
            - Histology: bizarre large multinucleated lymphocytes w/ surrounding eosinophils (uninvolved mucosa has severe sprue like features)
            - Gross: single/multiple, solitary/diffuse, circumferential ulcers in jejunum (masses are uncommon) w/ mesenteric LAD and distant mets (BM or liver)
            - Prognosis: aggressive w/ median survival of a few months, represents the most common cause of death in Celiac pts
            - Dx: endoscopic Bx but may need full-thickness Bx via ex-lap, CT/MRI enterography and PET is helpful b/c very hard to dx
            - Tx: aggressive nutritional support and strict GFD + aggressive chemo (CODOX-M or IVAC) ± autologous HSCT → surgery
            - Prognosis: poor w/ 1/5yr survival of 31/11%
            - Px: strict GFD
        - **SI/Esophageal/Oropharyngral Adenocarcinoma** (5x but likely much less)
- **Refractory CD (RCD) (10% of NRCD pts)**
    - Epidemiology: very rare, F>M, ~50yo
    - Definition: persistent or recurrent malabsorptive Sx and villous atrophy despite strict GFD for >6-12mo in the absence of above
    - Type: determined using IHC/PCR (determine aberrant IELs) and Flow/PCR (determine TCR rearrangements) on SI biopsy
        - RCD Type 1 (**polyclonal** T-cell expansion, increased mortality 2/2 malnutrition/infection, 5yr survival 95%) and Type 2 (**clonal** T-cell expansion w/ **loss of surface CD3/4/8** and preservation of intracytoplasmic CD3 and **T-cell receptor clonal rearrangement** by PCR, increased mortality 2/2 increased r/o complications (above), 70% risk of EATL in 5yrs, 5yr survival 45%)
    - Tx: RCD-1 (strict GFD, nutritional support, steroids ± Pentasa ± Azathioprine ± cyclosporine) vs RCD-2 (" " + consider cladribine or HSCT, follow continually for development of cancer)
    - NB cavitating mesenteric LAD is a common finding w/ RCD

Inflammatory Problems

- **IBD (refer)**
    - **CD Ileitis/Colitis**
    - **UC ± Backwash Ileitis**
    - **Microscopic Colitis**
- **Cancers (refer)**
    - **CRC**
    - **Lymphoma**
    - **Carcinoid**
    - **SI Adenocarcinoma**
    - **Metastasis**
- **Chronic Infection**
    - **SI esp TI/ICV: TB, Histo, Ameba, CMV, Salmonella, Aeromonas, Actinomycosis, Yersinia**
    - **Colon: Aeromonas, Amebiasis, C.diff, Campylobacter, HSV, CMV, E.coli, TB, Salmonella, Schistosomiasis, Strongyloides, Yersinia, Giardia, Candida overgrowth**
    - **"Brainerd" Epidemic Diarrhea (refer)**

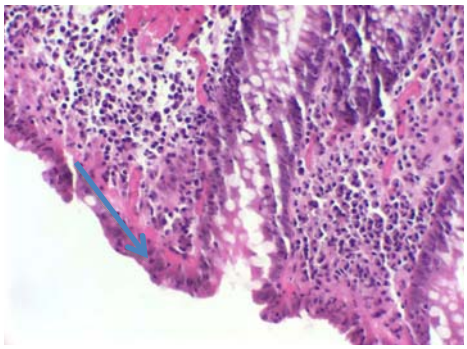
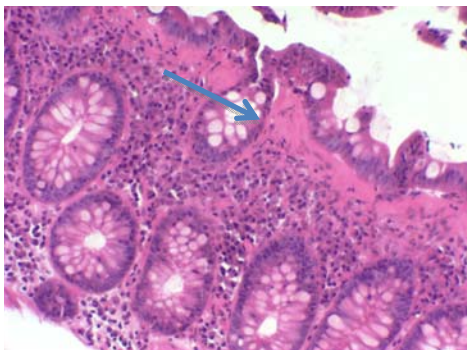
- **Also consider tropical sprue, post infectious IBS, etc**

- **Ischemia (refer)**
- **Sprues (refer above)**
- Other Systemic Diseases
  - **Endometriosis**
  - **Sarcoidosis**
  - **Any Type of CVD esp Behcet's**
  - **GVHD**
    - Consequence of allogenic BM transplant
    - Acute (<100d, 50%)
      - Mech: donor immune cells attack other tissue in the pt b/c they see it a foreign tissue
      - S/S
        - Skin: maculopapular rash to bulla
        - GI: enteritis resulting in diarrhea, bleeding, ileus
        - Liver: SOS/VOD (refer)
      - DDx: infection, radiation/chemo injury prior to BMTx, abx SEs
      - Dx: biopsy (cryptitis w/ epithelial necrosis/apoptosis)
      - Px: pre-transplant T-cell depletion of graft, early/aggressive immunosuppression
      - Tx: increase/change immunosuppression MTX/CsA
      - Prognosis: 35% morbidity and 10% mortality
    - Chronic (>100d, 30%)
      - S/S
        - Skin: scleroderma like changes, arthritis
        - GI: sicca Sx, motility problems, upper esophageal desquamation w/ rings/webs/fibrosis/strictures
        - Liver: cholestasis
        - Lung: obliterative bronchiolitis
      - Px: none
      - Tx: thalidomide, ursodiol, photopheresis of extracted WBC and reinfuse them
      - Prognosis: worse than acute GVHD
  - **Systemic Mastocytosis**
    - Abnormal proliferation and subsequent infiltration of mast cells in the skin ("bath pruritus"), BM, and visceral organs, Dx: increased urinary histamine, serum total tryptase >20ng/mL and >20 b/t Total Tryptase -Beta Tryptase
    - GI: N/V/D/ab pain, multifactorial in origin, on endoscopy (gastroduodenal ulcerations, urticaria like lesions in stomach, thickened gastric folds, circular purple pigmented lesions on colonoscopy)
  - **Amyloidosis**
    - Can result in malabsorption/rapid transit diarrhea, protein loosing enteropathy, autonomic neuropathy
  - **Immunodeficiency Syndromes**
    - Secondary
      - **AIDS Enteropathy**
    - Primary (refer, increased r/o GI infections, Celiac Dz, SI lymphoma)
      - **Selective IgA Deficiency**
      - **Common Variable Immunodeficiency (CVID)**
      - **Severe Combined Immunodeficiency (SCID)**
      - **Immune Dysregulation Polyendocrinopathy Enteropathy X-Linked Syndrome (IPEX)**
  - **Lymphangiectasia (refer to diarrhea)**
  - **Endocrine**
    - **Neurofibromatosis** (periampullary somatostatioma, pancreatic carcinoma, infiltrating mesenteric plexiform NF and vascular damage caused by nerve proliferation can lead to lymphatic/vascular obstruction)
    - **Addison's Disease** (other autoimmune conditions esp pernicious anemia and celiac dz in conjunction w/ PGA, pts also have non-specific GI complaints like ab pain and nausea and some pts have fat malabsorption the mechanism of which is unknown)
    - **Hyperthyroidism** (increased intestinal transit time)
    - **DM** (refer to diarrhea notes)
- Other GI Diseases
  - **"Non-Specific Focal Active Colitis"** (common pathology findings, ½ self limited and ½ turns into something else (below usually infection) but ~0% turns in to IBD)
  - **Segmental Colitis Associated with Diverticulitis (SCAD)**
  - **Eosinophilic Enterocolitis**
  - **Epiploic Appendigitis**
  - **Food Allergy**
  - **Alpha Chain Disease**
  - **Drug Induced Enteropathy (NSAIDs – refer below, colchicine, neomycin)**
  - **Immunoproliferative Small Intestinal Disease (IPSID)**

- **Severe Malnutrition**

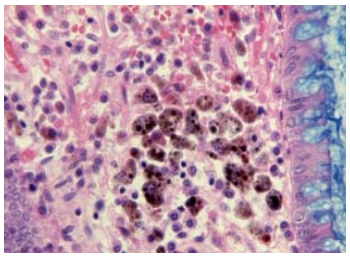
- **Diversion Colitis**
  - History: first reported by Glotzer in 1981
  - Mechanism: colitis occurring in the segment of colon that is diverted from the fecal stream
  - Etiology: diverted segment has reduced bacteria and obviously no food → luminal nutrient deficiency of SCFAs (the main energy source for colonic epithelium, 1° butyrate, 2° acetate, glutamine, ketones) which are products of carbohydrate/peptide fermentation by anaerobic bacteria → mucosal breakdown → inflammation (NB deficient SCFAs is not the sole cause though)
    - NB must distinguish from the prior condition for surgery was done (eg. IBD)
    - NB usually limited to most distal part
  - S/S: variable w/ bleeding, pain, etc
  - Endoscopy: erythema, friability, nodularity, edema, aphthous ulcers, exudates, frank bleeding, psuedopolyps, strictures
  - Histology: variable including lymphoid follicular hyperplasia, mixed mononuclear/neutrophilic infiltration to severe inflammation w/ abscesses, mucin granulomas, Paneth cell metaplasia BUT crypt architecture is preserved
  - Tx: surgical restoration of colonic continuity but if not possible then enemas (5-ASA, glucocorticoid, SCFA (60mL volume compounded containing a mixture of 60mmol/L acetate, 30mmol/L proprionate, 40mmol/L butyrate, 22mmol/L sodium chloride, BID x1mo and then 2x/wk))

- **Microscopic Colitis (MC) = Lymphocytic Colitis (LC) and Collagenous Colitis (CC)**
  - History: detailed in 1980 by Reed (collagenous colitis in 1976 by Lindstrom and lymphocytic colitis in 1980 by Lazenby)
  - Epidemiology: middle aged (female preponderance in CC vs = gender in LC), 80% LC vs 20% CC, incidence of 1-3/100,000 and prevalence of 10-16/100,000, more common than IBD but less common than IBS
  - Etiology: unknown but it is believed that there is abnormal inflammatory response to intraluminal contents which is supported by the fact that there is regression of inflammation following diversion of the fecal stream
    - Likely Intraluminal Contents
      - Meds (1° NSAIDs, SSRIs, 2° Aspirin, Lansoprazole, Acarbose, 3° Carbamazepine, Lisinopril, Simvastatin, Flutamide)
      - Autoimmune Conditions (HypoTH, Celiac Sprue, RA)
      - Infection
      - Bile Salts
      - Smoking (new RF)
  - S/S
    - **Very abrupt!!!**
    - Chronic w/ a fluctuating course
    - Watery diarrhea, mild ab cramps, rarely weight loss
    - PEx and Routine Labs are normal
    - Always consider in IBS/Celiac Dz
  - Dx (more common in R colon vs L colon nonetheless multiple L colon Bx are sufficient to make Dx in most cases)
    - Endoscopy (macroscopically normal mucosa nevertheless if your suspicion is high still Bx)
      - NB sometimes you will see "fractured mucosa" w/ erythema/edema/friability (new concept)!!!
    - Radiography (normal)
    - Stool Studies (normal except 50% will have + leukocytes)
    - Pathology (patchy)
      - epithelial disarray (flattening, decrease in number of goblet cells, Paneth cell hyperplasia) BUT NO crypt architectural distortion or neutrophilic cryptitis that is characteristic of IBD
      - intraepithelial and lamina propria inflammation w/ lymphocytes
      - ± thickened subepithelial collagen band (nl <5µm and Type IV collagen vs MC >10µm and Type VI/I/III collagen and tenascin, continuous vs patchy, R>L but multiple Bx during flexsig can make dx) = Collagenous Colitis

  - Tx (few trials, no single agent works for all pts, MC many times remits after awhile esp for LC, often abates after a few years)
    - 1st Anti-Diarrheals, Bismuth Subsalicylate, Address Underlying Problem (1/3 of pts respond, there is no change in histology)

        - 2nd Bile Acid Resins
        - 3rd Budesonide
        - 4th Probiotics, 5-ASAs, Steroids, MTX, 6-MP, Boswellia Extract
        - Last Resort: Diverting Ileostomy
    - NB no FDA approved drug
    - NB always consider sprue if diarrhea worsens after yrs of well treated disease (vice versa)
    - NB it is unclear if the two type of MC are two ends of the same spectrum or entirely different disorders
    - NB does not evolve into IBD
- **Radiation Esophagitis/Gastritis/Enteritis/Colitis**
    - When? radiation is used Tx of esophageal/gastric/rectal/cervical/uterine/prostate/bladder/testicular malignancies
    - Mechanism: radiation causes ionization aka release of an electron which then damages DNA and/or interacts w/ water forming free radicals which collectively kill the cancer cell (Why is GI tract affected? b/c mucosa has rapidly dividing cells)
    - RFs: location (colon worse than SI b/c SI constantly moves in and out of field), type (external beam worse than implant), total dose, fraction size, treatment volume, treatment techniques, additional chemo
    - S/S: early (during or shortly after radiation) vs late (months to years)
        - Oral: mucositis/stomatitis, infection, salivary gland damage w/ xerostomia, dental carries, osteoradionecrosis of the jaw, taste dysfunction, trismus
        - Esophagus: acute esophagitis (begins 2wks after initiation, lasts up to several weeks following cessation of therapy, 50% risk), stricturing (begins 3-8mo after initiation, obviously Sx can last a life time if not treated, 60% risk), dysmotility (begins 4-12wks after initiation)
        - Stomach: acute gastritis (begins 1wk after initiation, lasts 3wks following cessation), change gastric acid secretion
        - Intestine: b/c bowel moves injury is uncommon unless the pt has adhesions from prior surgeries
        - Colorectal: acute colitis (begins 3wks after initiation but can occur even a few hours after starting therapy, lasts 2-6wks following cessation), chronic radiation proctopathy (CRP, not proctitis b/c inflammation is not present rather there is ischemic obliterative endarteritis of submucosal arterioles w/ submucosal fibrosis, seen in 20% of pts who underwent radiation for prostate cancer, can occur anywhere from 9mo to 30yrs after Tx although most present at ~2yrs, S/S: bleeding, proctalgia, tenesmus, diarrhea, urgency, FlexSig: diffuse friable telengectatic lesions, 95% of cases are self-limited w/ medical Tx alone, Tx: medical (enemas using 5-ASAs, flagyl, steroids, sucralfate, SCFAs, HBO) but generally not effective → endoscopy (topical formalin, APC or Halo 90 RFA)
    - Dx
        - Histology: acute (basal epithelial layer injury w/ thinning and vacuolization) vs chronic (epithelial regeneration, fibrosis, obliterative endarteritis)
        - Endoscopy: acute (-itis) vs chronic (fibrotic strictures)
            - NB always rule out recurrence of cancer as cause of Sx as endoscopic findings are sometimes not clear
    - Px: amifostine-Ethyol (binds radicals preventing their damage), decorin-? (neutralizing antibodies to TGF-beta suppressing fibrosis)
    - Tx: very difficult to Tx, just Tx the Sx, try HBO, APC of telengiectasias, surgery if stricturing dz, consider sucralfate enemas, steroids, 5-ASAs
- **Chemical Colitis**
    - **Cathartic Colon**
        - ***** probably does not exist anymore, likely 2/2 strong laxatives that no longer exist, if you suspect laxative abuse call it "chronic laxative abuse syndrome"**
        - Def: it is an exceedingly uncommon (only 50 cases have been reported even though people use this term all the time) consequence of long term laxative abuse (difficult to know which one is the culprit)
        - S/S: constipation, fluid/electrolyte disturbance
        - Dx: BE (loss of haustrations, psuedostricturess, dilated colon w/ gaping ICV), Bx (mucosal atrophy, chronic inflammation, thickened muscularis mucosae, submucosal fatty infiltration, mild fibrosis)
        - Tx: taper of laxatives, add bulking agents, surgery
    - **Psuedomelanosis Coli**
        - History: "melanosis coli" coined by Virchow in 1857 b/c of the belief that the pigment was melanin
        - Epidemiology: ¾ of pts w/ >4mo of anthraquinone use
        - Mechanism: chronic anthraquinone use (other causes exist) → apoptosis of epithelial cells releasing organelles → deposition of lipofuscin w/in macrophages in lamina propria
        - S/S: benign w/o any Sx
        - Endoscopy: Brownish discoloration of the colonic mucosa (NB areas W/O pigment should be biopsied b/c cancers do not hold pigment!!!)
        - Tx: reverses w/in 1yr of cessation



- **NSAID Entero/colopathy** (refer below)
- **Other**
  - Enemas: any type that is done frequently, acetic acid, alcohol, ammonia, sodium hydroxide, ergotamine, formalin, glutaraldehyde, herbal medicine, henna, hydrofluoric acid, hydrogen peroxide, lye, potassium permanganate, radiocontrast agents, soap
  - Orals: chemo, KCl tablets, gold, penicillamine

- **Appendicitis**
  - Mechanism (not entirely clear)
    - 60% lymphoid hyperplasia (problem: more common in non-inflamed appendices), 35% fecalith, 5% other (eg. seeds, cancer (always rule out!!!), parasite esp *Ascaris* spp.) → obstruction of lumen → stasis → increased luminal pressure → ischemia → infection
  - Epidemiology
    - Incidence/Prevalence: 1/1000 per year (overtime has been decreasing and lower in less-developed countries)
    - more common in young adults (10-20yo, M>F) b/c of the high incidence of lymphoid hyperplasia
    - most common indication for emergent abdominal surgery
  - S/S (NB elderly, pregnant and immunosuppressed pts tend to have very atypical presentations w/ more complications)
    - "PANT": pain then anorexia (Hamburger Sign) then nausea then temp
      - initial mild visceral periumbilical pain then subsequent severe somatic pain (changes over 12-24hrs) that is variable depending on location of appendix
        - If anterior (postileal or preileal) (50%) then RLQ anterior pain at **McBurney's Point** (2/3 distance from umbilicus to R ASIS) and **Rovsing's Sign** (LLQ palpation causes referred RLQ pain)
        - If posterior (retrocecal or subcecal) or pelvic (50%) then RLQ posterior pain w/ **Psoas Sign** (extend R hip which stretches the irritated psoas muscle causing referred RLQ pain) or **Obturator Sign** (internally rotating R hip w/ R hip in flexed position which stretches the irritated obturator muscle causing referred RLQ pain)
    - Complications (if present then termed "Acute Appendicitis", risk increases w/ time esp >24hrs): gangrenous → perforation → abscess and portal pylephlebitis
  - DDx
    - *Yersinia enteroliticis* is the great mimicker of appendicitis
    - Mesenteric Adenitis
    - Crohn's Dz of the Appendix
    - Diverticula and subsequent Diverticulitis of the Appendix
    - Cancer of the Appendix (Tx: right hemicolectomy)
      - Carcinoid (rarely cause appendicitis b/c located at tip)
      - Mucinous Adenocarcinoma (produces mucin, rarely causes appendicitis)
      - Colonic Adenocarcinoma (almost always causes appendicitis)
      - Lymphoma (rare)
      - Mucocele (produced mucin which can perforate causing pseudomyxoma peritonei)
    - Any Kidney, Intestine, GU Disease
  - Dx: clinical but if uncertain then check labs and imaging
    - Labs (leukocytosis, sterile pyuria, mild increase in Amylase/Lipase)
    - CT-A/P (periappendiceal fat stranding and fluid, appendiceal diameter >6cm, appendiceal thickening, appendix that fails to fill w/ air or contrast, appendicolith)
    - US (pericecal fluid collection, shadowing appendicolith)
    - KUB (appendicolith, loss of psoas shadow, RLQ ileus)
  - Tx: appendectomy
    - NB never wait, always take it out b/c complications uniformly occur if given enough time
    - NB uncomplicated appendicitis though resolve w/ conservative Tx but 35% have a relapse
    - NB 15/5% of pts suspected to have appendicitis based on clinic picture / imaging turn out not to have it during surgery and of these 40% have some other problem to explain cause (thus 60% still have no known cause) regardless if normal still take it out
    - NB appendectomy protects against the development of UC and may improve UC
    - NB prophylactic appendectomy is not recommended but incidental (done when surgery is already being done for another reason) appendectomy is recommended if the pt is <30yo

- **Typhlitis**

- History
  - "Typhlitis" derived from the Greek word for *blind end* (τυφλός) representing the cecum
  - first described by Wagner in 1970 in a cohort of children undergoing chemotherapy for ALL
  - Various other terms: necrotizing enterocolitis, neutropenic enterocolitis, ileocecal syndrome, agranulocytic colitis, cecitis
    - "Necrotizing Enterocolitis" (NEC)
      - Necrosis of small/large bowel in premature babies
      - Etiology is unclear but RFs include early oral feeding (esp formula based), immature gut immunity and alterations in mesenteric blood flow
      - Occurs during the first few weeks of life manifesting w/ mild Sx (feeding intolerance) to severe deadly Sx (distension, bloody BMs) reflecting transumural necrosis w/ perforation
      - Prevention: NPO, TPN, antibiotics in very premature infants
      - Tx: similar ± surgery
- Etiology
  - Neutropenia (ANC <500/microL)
    - pts undergoing cytotoxic chemo (esp Taxanes w/ steroids) hematologic and solid organ malignancies
    - pts immunosuppressed s/p solid organ transplantation
    - pts w/ primary BM failure 2/2 aplastic anemia, myelodysplastic syndrome, aleukemic leukemia, myelophthisic processes
    - pts w/ HIV/AIDS
  - NB there have been cases reported in otherwise healthy adults following ingestion of food contaminated w/ *Clostridium perfringes*
- Epidemiology
  - incidence/prevalence varies in the population studied and the degree of neutropenia
    - original data in 1970s reported a prevalence of 50% in ALL children undergoing chemo classically occurring 1-2wks into induction chemotherapy corresponding to neutrophilic count nadir
    - this period clinically correlates w/ development of mucositis w/ stomatitis/pharyngitis
  - largest recent series
    - single center retrospective study of all oncologic pts b/t 1992-2002
    - 46 cases of typhlitis in 2822 in-pt oncologic pts (<2%)
    - 38% mortality
- Mech
  - mucosal injury → polymicrobial infectious cecitis → extending proximally/distally to TI/AC
    - cancer infiltration
    - stasis of bowel contents
    - mucosal ischemia from splanchnic vasoconstriction resulting from sepsis
    - directly cytotoxic chemotherapy
    - impaired host defense
    - change in colonic flora from the routine use of antimicrobials in hospitalized pts
      - Bacteria: 1° *Clostridium septicum*, 2° *Psuedomonas aeruginosa, Escherichia coli, Enterobacter taylorae, Morganella morgannii, Staphylococcus aureus, Strepococcus viridians*
      - Fungi: *Candida, Aspergillus*
- S/S
  - Sepsis Syndrome (neutropenic fever, shock, etc) + GI Sx (watery to bloody diarrhea, N/V, RLQ ab pain, distension)
    - NB b/c neutropenic presentation can be surprisingly subtle until too late
    - Complications (1) transmural infection → necrosis → perforation, (2) intra abdominal abscess, (3) GI bleeding given significant thrombocytopenia, (4) fistula, (5) ileus
- Dx
  - Clinical Picture + Imaging
  - Imaging
    - Xray (loss of psoas shadow, ileocolonic distension, decreased bowel gas pattern in RLQ)
    - US (doughnut-like hyperechoic fluid filled intestinal lumen separated from thickened hypoechoic bowel wall by a thin hyperechoic mucosa)
    - CT (fluid filled, dilated, thickened cecum ± necrosis (pneumatosis intestinalis, free air), hemorrhage, etc w/ adjacent pericolonic fat stranding and fluid)
  - Colonoscopy
    - Avoid b/c of the r/o perforation but in reported cases findings include mucosal irregularity, ulceration, friability (consider a flex sig)
  - Diagnostic Laparoscopy (occasionally is needed to make a diagnosis)
    - Gross Pathology: dilated, edematous, mucosal loss and ulceration, ecchymoses
    - Microscopy: paucity of inflammatory cells, mucosal edema, villous sloughing, hemorrhage, epithelial necrosis

        - DDx of R sided inflammation: Appendicitis, C.diff Colitis, CMV colitis, Ischemic Colitis, IBD (Crohn's or partially treated UC), Ogilvie's Syndrome, Diverticulitis, GVHD, Tubulo-Ovarian Abscess
            - Exclusion of C.diff, CMV, IBD is imperative therefore check panels
            - Usually can be differentiated via history, imaging, labs, microbiology
    - Tx
        - Principles: early recognition is imperative and management is individualized
        - Uncomplicated → Supportive Tx
            - Granulocyte Colony Stimulating Factor (G-CSF)
            - Hemodynamic Support
            - Blood Products (goal Plts >50k/microL)
            - Broad Spectrum Antimicrobials (coverage against bacteria esp C.diff and Fungi, usually regimen quoted in the literature is Vanc + Cefepime + Flagyl + Fluconazole)
            - Abdominal Decompression w/ NG Suction
            - Bowel Rest w/ Nutritional Support via TPN
            - Fluid Resuscitation
            - close in-pt observation w/ serial ab exams and imaging (pts are often critically ill prohibiting multiple CT scans, once diagnosis made pts can be followed via bedside real time high resolution US specifically following changes in bowel thickness where >10mm = surgery
        - (1) Complicated, (2) Clinical Deterioration or (3) Persistent Bleeding (despite correction of blood counts and coagulation factors) → Surgical Resection (right hemicolectomy w/ ileostomy and mucus fistula until neutropenia resolves and then secondary ileocolonic anastomosis)
    - Px
        - Recurrence has been documented in the literature in pts restarting chemo for caner → warranting investigation of prophylactic approaches (prophylactic right hemicolectomy, bowel decontamination & escalating neutropenic fever prophylaxis antimicrobials, modify chemo regimen & dosing, G-CSF, enteral glutamine to maintain gut integrity

- **Malakoplakia**
    - Malakos - "soft" plakos - "plaque"
    - History: first described by von Hansemann in 1903
    - Incidence: rare
    - Etiology: immunosuppressed state (eg. chemo, s/p transplant, HIV/AIDS), systemic illness (eg. SLE, Sarcoidosis), neoplasia (eg. CRC), genetic disorders (eg. primary hypogammaglobulinemia)
    - Mech: impaired macrophage bacterial killing → chronic multi-organ (colon (1° rectum, 2° sigmoid, 3° right colon), pancreas, lung, brain, adrenal glands, bone, GU) granulomatous disease
    - S/S: ab pain, diarrhea, hematochezia, fever, weight loss, ab mass
    - Dx
        - Endoscopy: focal/diffuse friable yellow mucosal sessile/polyploid/ulcerated plaques (look like pre-cancerous polyps)
        - Pathology: bacteria w/in macrophage cytoplasm (von Hansemann cells) w/ intracytoplasmic inclusion bodies (Michaelis-Gutmann bodies)
    - DDx: fungal infection, leprosy, Whipple's, reticulum cell sarcoma, MAC
    - Tx: reverse etiology, test immune fxn, screen for CRC, abx (Bactrim+Cipro), cholinergic agents (for some reason cholinergics reverse macrophage dysfunction)

Isolated Ulcers (absence of surrounding colitis)

- **Many of the Inflammatory Conditions Above but specifically…**
    - **Crohn's**
    - **Sprue's esp Complicated CD**
    - **Infections esp TB, Entamoeba, Strongyloidiasis, CMV, HSV, Syphilis**
    - **Systemic Dz esp GVHD, Any Type of CVD esp Behcet's, Uremia, Sarcoidosis**
    - **Cancer esp EATL**
    - **Eosinophilic/Lymphocytic/Granulomatous Enterocolitis**
    - **Endometriosis**
    - **Food Allergy**
    - **Ischemia**
    - **Radiation**
    - **Heavy Metal Poisoning**
    - **Foreign Body Ingestion**
    - **Meds esp Chemo**
- **Idiopathic/Non-Specific Benign Small/Large Bowel Ulceration**
    - Prevalence: 4/100k, wide age range
    - Etiology: unknown therefore always a DOE
    - S/S: variable (bleeding, pain, obstruction, etc)
    - Dx: most common location (ileum for SI and proximal colon for LI), antimesenteric side, most are solitary ulcers, Bx (non-specific inflammation)

- Tx: observe unless symptomatic then segmental resection w/ low risk of recurrence

- **Solitary Rectal Ulcer Syndrome (SRUS)**
  - Epidemiology
    - Prevalence: 1/100k
    - Age: young adult but reported in every age group
    - Gender: F=M
  - Mechanism (unclear in some cases)
    - (1) chronic constipation 2/2 impaired evacuation (esp paradoxic contraction of the pelvic floor) with occult or overt rectal prolapse/intussusception → prolapsed rectal mucosa rubs against anal canal during strained defecation → irritation + ischemia 2/2 high intrarectal pressure & traction of submucosal vessels (most common scenario)
    - (2) local trauma 2/2 digitations, self-instrumentation, rectal tubes, anal-intercourse, et al
    - (3) local ischemia 2/2 ergotamine-suppositories (vasoconstrictor used in aborting migraine headaches), radiotherapy, et al
  - S/S
    - passage of mucus/blood per rectum during defecation, tenesmus, urgency
      - NB 25% asymptomatic
      - NB duration of Sx b/f Dx is often long (mean 5yrs) b/c of rarity of dz and non-specific Sx
      - NB other Sx suggestive of underlying etiology (chronic constipation, rectal prolapse, dyschezia, et al)
  - Dx
    - Anoscopy (first described by French Anatomist Cruvilhier in 1829 w/ term "SRUS" coined by English Anatomist Lloyd-Davies in 1937)
      - 25% hyperemic mucosa (acute) →
      - 50% single (30% multiple, 10% circumferential) 0.5-4cm ulcer ~5-10cm above anal verge →
      - 25% polypoid lesion (chronic)
    - Bx (first described by American Pathologists Madigan and Morson in 1969)
      - Ulcer Margin Bx
        - (1) mucosal hypertrophy w/ distorted crypt architecture
        - (2) fibromuscular obliteration of the lamina propria w/ collagen deposition
        - (3) extension of hypertrophied and disorganized muscularis mucosa smooth muscle b/t crypts
        - NB no significant inflammatory cells

      - Polypoid Lesion Bx (changes similar to that seen in a hyperplastic polyp)
        - (1) epithelial and goblet cell hyperplasia resulting in a "frilly" surface and "star-shaped" dilated crypts filled w/ mucin
      - NB always should Bx to r/o cancer given similar appearance and some argue that SRUS changes can represent a change to deeper seated malignancy therefore follow-up after Tx is advocated
    - Anorectal Manometry & Defecography (to demonstrate impaired evacuation constipation and rectal prolapse/ intussusception)
  - Tx
    - Asymptomatic: no Tx as they can resolve spontaneously
    - Symptomatic
      - Conservative: 3/4 ulcers heal w/ conservative Tx by treating underlying causes (eg. biofeedback, soften and bulk up stool w/ laxatives, muscle relaxants, avoid trauma and suppositories)
      - Medical: several topical agents (eg. retention enema of 5-ASA, corticosteroid, sucralfate) have been studied but none in a prospective controlled fashion, however, anecdotally they appear to NOT be effective except sucralfate
      - Endoscopic: fibrin sealant to cover the ulcer and if bleeding then Tx similar to bleeding PUD w/ injection, thermal therapy and clips
      - Surgical (type depends on underlying anatomic pathology)
        - Rectal Prolapse → Rectopexy (suspend the rectum)
        - Rectal Redundancy → Mucosal Resection aka Delorme's Operation
        - Rectal Ulcer →
          - Ulcer Excision (NB usually not effective)
          - Colonic Diversion

        - Protectomy w/ End-to-End Anastomosis aka Altemeier's Operation
- **Stercoral Ulcers**
    - Epidemiology
        - Prevalence: unknown
        - Age: elderly (esp nursing home residents) but has been reported in all age groups
        - Gender: F=M
    - Mechanism
        - (1) chronic severe constipation w/ h/o impactions → formation of a hard fecal mass (scybalum) → local pressure ischemic necrosis
    - S/S
        - usually asymptomatic (occasionally lower ab pain) until complications: perforation and/or bleeding (has been known to occur when scybalum is removed during endoscopy or DRE 2/2 loss of tamponading effect of scybalum)
    - Dx
        - Sigmoidoscopy (single large irregular sharply demarcated ulcer along antimesenteric side of rectum/sigmoid)
        - KUB (may show calcified scybalum, fecal loading, ± perforation)
        - Bx (nonspecific acute on chronic inflammation at ulcer border)
    - Tx
        - cautious disimpaction of scybalum if present followed aggressive Tx of constipation
- **NSAID Entero/Colopathy**
    - Epidemiology
        - Prevalence: unknown, increasing w/ the development of enteric coated or delayed release or suppository NSAIDs which shifts the damage from upper to lower GI tract
        - Age: elderly
        - Gender: F=M
    - Mechanism
        - NB NSAIDs can also exacerbate IBD and cause MC
        - local contact effect NOT systemic effect (refer to stomach notes)
        - Acute Local Effect
            - Three Hit Hypothesis
                - (1) NSAIDs disrupt phospholipids on mucosal cells
                - (2) NSAIDs are uncouple mitochondrial oxidative phosphorylation → decreased ATP → mitochondrial damage w/ increased ROS, disturbed Na/K ratio, leakage of Ca into cytoplasm → loss of control of intracellular jxn w/ increased permeability
                - (3) Damaged epithelium becomes exposed to intraluminal contents (bacteria, bile acids, pancreatic secretions, etc) resulting in secondary damage
            - NB Enterohepatic circulation occurs for most NSAIDs resulting in repetitive injury (NB sulindac/aspirin do not undergo enterohepatic circulation and thus have less toxicity)
        - Chronic Systemic Effect: suppression of endogenous mucosal prostaglandin synthesis (PGE2,F2,I2) via COX-1 inhibition → decreased mucus, bicarb, blood flow, epithelial regeneration → impairment in maintaining epithelial integrity → erosions/ulcerations
            - NB COX-1 (constitutively expressed in the stomach to constantly maintain defense mechanisms) vs COX-2 (inducibly expressed in the stomach in response to cytokines generated by an inflammatory response)
    - S/S
        - non-specific isolated mucosal changes (intervening mucosa is normal, generally asymptomatic except for occasional protein loosing enteropathy, occult bleeding, unexplained IDA) → single/multiple small/large erosions/ulcers (bleeding, ab pain) → **"Diaphragmatic Strictures"** (pathognomonic thin <3mm concentric strictures w/in pinhole lumen, usually occurs in the SI and can result in obstruction)
    - Dx
        - Colonoscopy/Enteroscopy (distal ileum / proximal colon)
        - Bx (to r/o IBD, no specific finding, one can see granulation, necrosis, sclerosis of the lamina propria at ulcer margin, intervening mucosa is normal, inflammation is minimal)
        - Change in permeability w/ inflammation and bleeding has been shown with scintigraphy w/ chromium-51 labeled EDTA, technetium-99m labeled RBC, indium-111 labeled WBC in addition to stool markers (Guaiac, calprotectin, WBC)
            - NB EDTA is not normally absorbed but w/ impaired intestinal damage it is absorbed and excreted into urine which can be measured
    - Tx
        - Meds
            - NSAID Changes: avoid NSAIDs, consider Sulindac/Aspirin b/c of the lack of enterohepatic circulation, selective COX-2 inhibitors may be less injurious, PGE analogues eg misoprostol and antisecratory agents seem to not be helpful
            - Metronidazole (other antimicrobials are not effective and this is b/c it is believed that metronidazole prevents NSAID mitochondrial damage)

        - Sulfasalazine (sulfapyridine moiety appears to be the active agent NOT the 5-ASA)
    - Endoscopic dilation if stricture is present
- **Colitis Cystica Superficialis (CCS) or Colitis Cystica Profunda (CCP)**
    - Etiology
        - superficialis (various conditions including pellagra, celiac sprue, et al)
        - profunda (unknown but may be (1) congenital, (2) acquired from diseases that cause mucosal damage eg. IBD, anastomosis, colostomy, radiation exposure or (3) associated w/ adenocarcinoma esp stomach/colon as it often develops adjacent to cancer)
    - S/S
        - superficialis (no Sx)
        - profunda (dyschezia, tenesmus, obstruction, rectal bleeding, mucus discharge, palpable plaques on DRE)
    - Dx
        - Endoscopy (localized/diffuse mass w/ overlying mucosa ranging from normal → inflammation → ulceration)
        - Bx (focal/diffuse mucus filled cysts in the mucosa/submucosa of the colon (1° rectum but can occur anywhere throughout the GI tract), cysts usually communicate w/ lumen, surrounding tissue has chronic inflammation and lamina propria fibrosis)

    - Tx: similar Tx for SRUS except that surgery is effective and sometimes needed

Other

- **Pneumatosis Cystoides Intestinalis (PCI – SI) or Pneumatosis Coli (PC – LI)**
    - Definition: presence of gas psuedocysts (variable in size from a few millilmeters to centimeters) anywhere w/in wall of GI tract (usually submucosal space in the LI and subserosal space in the SI) w/ occasional extension into mesentery/LNs/peritoneum/omentum
    - Etiology
        - 15% idiopathic vs 85% 2/2 known dz
            - GI Dz
                - Infection: C.diff, TB, Typhilitis, et al
                - Mucosal Damage: IBD, Diverticulitis, Ischemia/Infarction, et al
            - Other: pulm (COPD, CF, et al), rheum (CVD, SS, et al), meds (chemo, et al)
            - Iatrogenic: endoscopy, mechanical ventilation, double contrast barium enema, post ab surgery, et al
    - Pathogenesis: poorly understood (based on underlying pathology but all theories are possible)
        - Mechanical Theory: gas dissects into bowel wall either from lumen thru mucosal breaks or from mesenteric blood vessels thru serosal breaks
            - What supports this theory? (1) it is reproduced experimentally by insufflating air into excised colon w/ mucosal incisions, (2) PCI is associated w/ disorders that disrupt mucosal integrity, (3) offers an explanation for the association of CPI w/ COPD (cough → alveolar rupture → air tracks along blood vessels → thru mediastinum → thru diaphragm → into mesenteric root → along mesenteric blood vessels → into bowel wall
            - NB gas trails are often not present and the gas in PCI does not resemble alveolar gas
        - Bacterial Theory: luminal gas-forming-bacteria gain access into submucosa thru mucosal breaks
            - What supports this theory? (1) it is reproduced experimentally by injecting *Clostridium perfringens* into bowel wall of rates, (2) some cases of PCI resolves w/ antimicrobial Tx
            - NB cysts are often sterile
        - Biochemical Theory: luminal gas-forming-forming bacteria create [high] of H_2 gas → H_2 gas enters wall
            - What supports this theory? (1) hydrogen content in cysts is very high, (2) PCI can complicate pts taking alpha-glucosidase inhibitors and lactulose, (3) microbiota profile of pts w/ PCI demonstrate low levels of hydrogen-consuming bacteria
    - S/S
        - often incidental finding on imaging/endoscopy/surgery w/o direct aside from the underlying cause
        - in some cases some pts have Sx of directly from PCI depending on the region affected and include diarrhea (~3/4), mucus discharge (~2/3), ab distention/bloating/pain (~2/3)

        - PEx can demonstrate distension, pseudo-organomegaly, palpable masses on rectal exam
- Prognosis/Complications
    - course is variable depending on the underlying disorder ranging from a benign disorder to a life threatening condition
    - rarely PCI can lead to complications of bowel obstruction, volvulus, intussusception and pneumoperitoneum (PCI is actually the most common cause of benign pneumoperitoneum 2/2 rupture of subserosal cysts therefore if you see pneumoperitoneum in an otherwise healthy/asymptomatic pt then check CT for PCI to avoid an unnecessary laparotomy)
- Dx
    - Radiology (1/3 Barium Studies +, 2/3 of plain x-rays +, CT/MRI is the gold standard)
    - Endoscopy/Laparoscopy (submucosal/serosal cysts appear as multiple rounded masses w/ overlying normal mucosa displaying a pale/bluish hue and when biopsied they rapidly deflate releasing methane, nitrogen, hydrogen (little oxygen))
    - Pathology (thin fibrotic wall lined by histiocytes and multinucleated giant cells)
- Tx
    - the critical decision is whether to treat conservatively or proceed w/ emergent ex-lap depending on the likelihood that there had been an abdominal catastrophe which sometimes can be subtle
        - Features Suggesting an Acute Abdomen: severe acute pain, lactic acidosis, elevated amylase, portal vein gas, linear cysts aka Pneumatosis Linearis (NB pneumoperitoneum does not necessarily equate to catastrophic complication)
    - Once an acute abdomen has been excluded symptomatic PCI can managed in a variety of ways
        - antibiotics to eliminate gas producing anaerobic bacteria
        - FODMAP diet to decrease gas production in the gut
        - high-flow oxygen therapy or HBO (oxygen is toxic to anaerobic bacteria and since cysts contain mainly hydrogen and nitrogen the presence of [high] oxygen promotes diffusion of nitrogen and hydrogen out of cysts, eg. FiO2 50% for 10d or HBO at 2.5 atmospheres for 2.5hrs on 2 consecutive days)
        - endoscopic cyst decompression by FNA if causing obstruction
        - Tx the underlying problem if possible
    - If asymptomatic observation alone, 50% of cysts usually resolve spontaneously over time and educate pt to avoid unnecessary work-up and surgeries