EDUCATIONAL GOALS AND OBJECTIVES

1. Define the following term:

Diverticulum
Heterotopia
Ectopia
Stenosis
Atresia
Diarrhea
Dysentery
Pseudomembrane
Malabsorption

Steatorrhea
Enteritis
Fissure
Fistula
Meconium
Meganocolon
Pseudopolyp
Polyp

Volvulus
Intussusception
Peutz-Jeghers Syndrome
Carcinoid Syndrome
Peritonitis
Villus
Mucocele

2. Describe the pathology, pathophysiology and clinical manifestations of Meckel's diverticulum and Hirschsprung's disease.

3. Compare and contrast the characteristic pathologic and clinical features, and when known, the etiology and pathogenesis of ischemic bowel disease, angiodysplasia, and hemorrhoids.

4. Define malabsorption and explain the mechanisms by which it occurs, citing examples of disease from each category (see handout).

5. Compare and contrast the characteristic pathologic and clinical features of celiac sprue, Whipple's disease and disaccharidase deficiency. If known, indicate the etiology and explain the pathogenesis.

6. Compare and contrast the characteristic pathologic and clinical characteristics of Crohn's disease, ulcerative colitis, and pseudomembranous colitis.

7. Describe the etiology, pathogenesis, pathology and characteristic clinical findings of diverticular disease and acute appendicitis.

8. Define bowel obstruction and explain the various mechanisms by which it occurs, citing specific examples. Describe briefly the pathophysiology of bowel obstruction.

9. Compare and contrast the characteristic features of benign (polyp/adenoma) and malignant (carcinoma) neoplasms of the small and large intestine. Describe the etiology, pathogenesis, pathology and clinical features of tubular adenoma, villous adenoma and colonic carcinoma. Briefly describe and explain the reason for staging colon cancers.
SMALL AND LARGE INTESTINES

I. CONGENITAL

A. ATRESIA AND STENOSIS
1. Congenital intestinal obstruction that may be complete (atresia) or incomplete (stenosis).
   a. Atresia: imperforate mucosal diaphragm or string like bowel segment
   b. Stenosis: narrowing of the bowel segment
2. Duodenal atresia is the most common; the jejunum and ileum are equally involved and the colon virtually never
3. Etiology: developmental failure, intrauterine vascular accidents or intussusception
4. Imperforate anus: failure of the cloacal diaphragm to rupture; membranous septum occluding the anal canal

B. MECKEL'S DIVERTICULUM
1. Pathology: Persistence of the intra-abdominal remnant of the omphalomesenteric duct (vitelline duct); True diverticulum.
2. Clinico-pathologic correlation: "Disease of 2's" occurs in 2% of the population, 2x as common in males as females, 2 inches in length, occurs within 2 feet of the ileo-cecal valve, contains 2 types of ectopic tissue (gastric and pancreatic), 2 major complications (pain with inflammation and hemorrhage with ulceration)
3. Of the 2% population, most patients asymptomatic or discovered incidentally

C. CONGENITAL AGANGLIONIC MEGACOLON: HIRSCHSPRUNG'S DISEASE
1. Pathology: Absence of ganglia in Meissner's submucosal and Auerbach's myenteric plexuses; generally limited to the anus and rectum. Complete bowel obstruction or partial bowel obstruction with alternating obstruction and diarrhea. Aganglionic segment causes functional obstruction because peristalsis does not pass from the normal to the abnormal bowel. Obstruction causes secondary distention of the colon proximal to the aganglionic segment.
2. Clinico-pathologic correlation: Males predominate 4:1; Associated with Down Syndrome and serious neurologic abnormalities
   a. Presents in the immediate neonatal period by failure to pass meconium or as abdominal distention
   b. Risk of perforation, sepsis, enterocolitis with fluid disturbances.
   c. *Acquired megacolon* may occur in Chagas disease, bowel obstruction, megacolon associated with inflammatory bowel disease, and psychosomatic disorders

II. ENTEROCOLITIS

A. INFECTIOUS ENTEROCOLITIS
Pathology of the Small and Large Bowel

2. Bacterial
   a. The pathologic changes are variable to the type bacteria.
   b. V. cholerae demonstrate non-mucosal changes
   c. C. difficile demonstrate classic changes discussed below

3. Parasites and Protozoa
   a. More than half of the world's population are affected by a chronic or relapsing infection
   b. Nematodes
   c. Flatworms
   d. Protozoa (Giardia lamblia is noninvasive, in contrast to Entameoba histolytica is invasive and may involve liver and CNS

B. NECROTIZING ENTEROCOLITIS
   1. An acute, necrotizing inflammation of the small and large intestine
   2. Pathogenesis: Multifactorial- immaturity of the gut's immune system; the initiation of oral feeding with gut colonization by bacterial results in release of cytokines and endotoxins that are damaging to the mucosa and/or the vascular blood supply
   3. Pathology: Primarily in the terminal ileum or the ascending colon
      a. Initially edema, hemorrhage and necrosis that leads to
      b. Full-thickness necrosis, thickening, and eventual gangrene
   4. Clinico-pathologic correlation: Most common acquired GI emergency in premature or low-birth weight neonate. This may result in mild GI symptoms or fulminant illness

C. PSEUDOMEMBRANOUS COLITIS: ANTIBIOTIC-ASSOCIATED COLITIS
   1. Pathology: Macroscopically, the mucosa is covered by a yellow green, "false membrane" composed of a mixture of mucous and neutrophils
   2. Etiology: toxin produced by Clostridium difficile; 20% of patients hospitalized for several days acquire C. difficile as a nosocomial infection
   3. Pathogenesis: Direct effect of toxin on surface epithelium; antibiotics allow overgrowth of C. difficile
   4. Clinico-pathologic correlation: sudden onset of fever and diarrhea in a patient who is seriously ill or in a post-operative state and who is receiving antibiotics; diarrhea may rapidly lead to dehydration, shock, and death

III. MALABSORPTION SYNDROMES

A. MALABSORPTION
   1. Broadly defined: a defect in assimilation of food, taking into consideration both digestion and absorption
   2. Many diseases cause malabsorption. The following is an outline of the nonnal physiologic digestive and absorptive phases to help you understand the pathophysiology of malabsorption - an example of a pathologic condition causing malabsorption is given.
   3. Intraluminal Stage
      a. Secretory Phase: Pancreatic enzymes for digestion example: Chronic pancreatitis/insufficiency
      b. Biliary Phase: Bile acids necessary for fat solubilization
5. Removal Stage
   a. Delivery Phase: Vehicle used for carrying away the final products for storage or metabolism; Lymphatics example: Whipple's disease

B. CELIAC SPRUE
   1. Pathology: Flat mucosa of the small intestine, with blunting or total disappearance of the villi. The lamina propria contains a marked increase in lymphocytes and plasma cells.
   2. Etiology: Gluten, specifically gliadin protein (from grains: wheat, oat, barley, and rye)
   3. Pathogenesis: Hypersensitivity (immunologic) reaction to gluten present; 90-95% of patients express HLA DQ heterodimer on chromosome 6
   4. Clinico-pathologic correlation: occurs in whites; rare to nonexistent in native Africans, Japanese, and Chinese
      a. Definitive diagnosis dependent on the clinical documentation of malabsorption, demonstration of the lesion on biopsy, and unequivocal improvement upon gluten withdrawal from the diet
      b. Most patients who maintain their special diet, remain well indefinitely
      c. There is a long-term risk of malignancy, particularly lymphomas (risk is still less than 2x the normal population)

C. TROPICAL SPRUE (POSTINFECTIOUS SPRUE)
   1. Limited to people living in the tropics
   2. Etiology not clear; however, treated with broad-spectrum antibiotics

D. WHIPPLE DISEASE
   1. Rare disease due to gram-positive organism called Tropheryma whippleii
   2. Diagnostic by demonstration of rod-shaped organisms present by electron microscopy and PAS positive macrophages on light microscopy
   3. Strong male predilection, ratio 10:1

E. DISACCHARIDASE (LACTASE) DEFICIENCY
   1. Congenital: rare
   3. Symptoms: Diarrhea and Gas

F. A-BETA-LIPOPROTEINEMIA
   1. Rare inborn error resulting in a defect of synthesis and export of lipoproteins from the intestinal mucosal cells
   2. Autosomal recessive disease manifesting in infancy with failure to thrive, diarrhea and steatorrhea

IV. INFLAMMATION

A. COLLAGENOUS AND LYMPHOCYTIC COLITIS
B. MISCELLANEOUS
1. Graft-vs-Host Disease
2. Drug-induced
3. Radiation enterocolitis
4. Neutropenic Colitis
5. Diversion Colitis

C. ACUTE APPENDICITIS
1. Pathology: Acute inflammation characterized by neutrophils infiltrating the wall of the appendix. The lumen contains pus and the serosal surface is covered by fibrinous exudate
2. Etiology: Bacteria
3. Pathogenesis: Fecalith impairing circulation (by compression) causing ischemia, necrosis and bacterial contamination
4. Clinico-pathologic correlation: “Acute Abdomen;” Nausea; vomiting; peri-umbilical dull ache followed by shift and localization of the pain to the right lower quadrant (RLQ) of the abdomen. The dull ache becomes a sharp, severe pain in the RLQ, associated with rebound tenderness. Pressing on the anterior abdominal wall stretched the inflamed parietal peritoneum causing tenderness. Sudden release of pressure causes vibration of the parietal peritoneum that in turn causes rebound tenderness. Fever and leukocytosis is present.

V. IDIOPATHIC INFLAMMATORY BOWEL DISEASE

A. INFLAMMATORY BOWEL DISEASE (IBD)
1. Single term to collectively refer to either Crohn's Disease or Ulcerative Colitis
2. Etiology unknown
   a. Genetic predisposition: HLA Class II locus on chromosome 6
   b. Abnormal Host Immunoreactivity

B. CROHN'S DISEASE: REGIONAL ENTERITIS
1. Pathology: Chronic inflammation involving all layers (transmural inflammation) of the small bowel wall.
   a. Inflammation, including characteristic non-caseating granulomas, spread through the bowel wall to adjacent mesentery fat and lymph nodes.
   b. Although may occur at any point along the gastrointestinal tract, it primarily affects the small intestine or colon
   c. Mucosa shows linear ulceration. The inflammation is segmental (discontinuous), involving some segments of the bowel, but sparing others
2. Epidemiology: Tends to occur in adolescents and young adults. The incidence of cancer of the small intestine or colon is
C. ULCERATIVE COLITIS

1. Pathology: Inflammation primarily involving the mucosa of the colon. In contrast to Crohn's disease, the inflammation of ulcerative colitis is diffuse (continuous).

   a. Early phase of disease: neutrophils accumulate within the depths of the crypts of Lieberkuhn forming "crypt abscesses."
   b. Later phase of disease: the mucosa ulcerates and pseudopolyps form
   c. Late phase of disease: After many years of inflammation, the mucosa may become dysplastic, increasing the risk of colon cancer

2. Clinico-pathologic correlation: Bloody diarrhea (Blood is lost from ruptured vessels located in the inflamed mucosa) crampy abdominal pain, tenesmus and fever. In some cases, toxic megacolon (extension of severe inflammation to the muscular layer causing prominent dilatation of the colon and septic shock)

VI. VASCULAR DISEASE

A. ISCHEMIC BOWEL DISEASE


2. Etiology/Pathogenesis:

   a. Embolus: most common cause of sudden complete occlusion of the superior mesenteric artery. The most common source of the embolus is the heart (mural thrombus, auricular thrombus, valvular vegetation). Fragment of thrombus breaks off the cardiac wall, travels to the mesentery and occludes the artery causing ischemia
   b. Thrombus: superimposed on atherosclerotic plaque in "mesenteric artery
   c. Hypoperfusion (nonocclusive ischemia): shock, CHF

B. ANGIODYSPLASIA

1. Pathology: Ectasia of veins. Submucosal veins are focally dilated and tortuous. Prone to rupture.


C. HEMORRHOIDS

1. Pathology: Dilated veins of the hemorrhoidal plexus.

   a. Internal Hemorrhoids: dilated veins of the superior hemorrhoidal plexus above the dentate line
   b. External Hemorrhoids: dilated veins of the
VII. OTHER NON-NEOPLASTIC BOWEL DISEASES

A. DIVERTICULAR DISEASE
   1. Pathology: Diverticulosis and Diverticulitis
      acquired herniation of mucosa and submucosa through the muscle layers of the colon
   2. May occur anywhere in the colon, but most commonly in the left colon, particularly the sigmoid colon; acute or chronic inflammation may occur
   3. Perforation can also occur and may result in peritonitis or fistula formation with an adjacent organ

B. HERNIAS
   1. A serosal lined outpouching of the peritoneum. A loop of small intestine becomes trapped (incarcerated) within an inguinal hernia sac or an umbilical hernia sac.
   2. The bowel may become compressed at the mouth of the hernia or twisted on itself, compromising blood supply and leading to infarction (strangulation).

C. ADHESIONS
   1. String-like or band-like portions of scar tissue that form during healing after surgery or peritonitis
   2. May result in obstruction due to kinking or compression of a portion of bowel

D. INTUSSUCEPTION
   1. Caused by an infolding or telescoping of one segment of bowel (proximal) into the adjacent distal segment
   2. Infants and children: spontaneous and reversible 3. Adults: tumor is usually involved

E. VOLVULUS
   1. Obstruction due to rotation or twisting of a loop of bowel around its mesenteric base of attachment
   2. Most often occurs in the sigmoid colon, followed by the cecum

VIII. NEOPLASMS OF THE SMALL INTESTINE

1. Uncommon when compared to other tumors in other segments of the GI tract
2. Only 3-6% of GI tumors

A. BENIGN
   1. Adenomas: most commonly in the Ampulla of Vater
   2. Leiomyomas
   3. Lipomas
   4. Angiomas

B. MALIGNANT (represents only 1% of GI malignancies)
Pathology of the Small and Large Bowel

- Gastric lymphomas most common with better prognosis than the small or large intestine if discovered early

3. Carcinoids
   a. arise from neuroendocrine cells and may secrete bioactive amines like serotonin resulting in diarrhea, flushing of the face, bronchospasm and cyanosis
   b. accounts for less than half of small bowel malignances; in contrast, less than 2% of colorectal malignancies c. overall 5-year survival rate is 90% :

   - uncommon
   - arise in wall of bowel (interstitial cells of Cajal)
   - protrude into lumen; ulcerate; GI bleed
   - mostly slow growing; cured by surgery
   - 30% recurrence/liver mets within 10 years
   - may progress to high grade sarcoma
   - c-kit proto-oncogene, receptor type tyrosine kinase

IX. NEOPLASMS OF THE LARGE INTESTINES

A. Polyps with no malignant potential
   1. Pseudopolyp – occasionally seen in long standing IBD: UC> Crohns
   2. Hamartomatous polypl-rare
   3. Juvenile inflammatory polyp
   4. Peutz Jeghers polyp – mostly small intestinal
   5. Hyperplastic polyps – very common
   6. Lymphoid polyps

B. ADENOMAS

All adenomas show dysplastic epithelium. All adenomas may demonstrate an intramucosal carcinoma or invasive carcinoma. Although they may occur anywhere in the large intestine, most occur in the left colon, specifically in the recto-sigmoid colon. The risk of malignant transformation is dependent on polyp size, histologic architecture and severity of the epithelial dysplasia.

1. Tubular Adenomas
   a. Pendunculated, composed of branching round/tubular glands on a stalk
   b. Can grow up to 4 cm in diameter; the larger the polyp, the greater the chance of harboring a carcinoma

2. Villous Adenomas
   a. Sessile, broad base rather than a stalk, composed of numerous, finger-like projections of epithelium
   b. Greater than 50% of the epithelium demonstrates the villous
4. Familial syndromes
   a. Familial adenomatous polyposis (F AP)
      Autosomal dominant; genetic defect is in the APC gene on chromosome 5q21; patient with 500-2500 polyps (minimum 100 polyps)
   b. Gardner syndrome autosomal dominant; similar to F AP except the additional presence of multiple bone and skin lesions
   c. Hereditary nonpolyposis colorectal cancer (HNPCC) autosomal dominant; lower numbers of polyps but occur earlier than the general adult population; women at increased risk of endometrial cancer

C. ADENOCARCINOMA

1. Pathogenesis: Described as the Adenoma-Carcinoma Sequence.
   a. Germline (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")
   b. Methylation abnormalities and inactivation of normal alleles ("second hit")
   c. Proto-oncogene mutation
   d. Homozygous loss of additional cancer suppressor genes e. Additional mutations with gross chromosomal alterations

2. Genetic alterations:
   a. APC at chromosome 5q21
   b. APC -catenin
   c. K-ras at chromosome 12p12
   d. p53 at chromosome 17p13 or loss of heterozygosity

3. Epidemiology:

   Accounts for 10% of all cancer related deaths.
   a. Peak incidence is 60-79 years old
   b. Less than 20% of cases occur before the age of 50. Found worldwide: environmental factors, dietary practices, obesity and physical activity; no causal relationship has been shown

4. Pathology
   a. Macroscopically, the right colon cancers are usually polyploid, fungating lesions whereas the left colon cancers are generally annular, encircling lesions
   b. Tumor will infiltrate wall of the colon and metastasize to regional lymph nodes and liver; Prognosis is related to size and spread of the lesion

D. Right colon tumors tend to be polyploid, non-obstructive and asymptomatic for a longer period of time that left sided lesions. The symptoms and signs of iron deficiency anemia may be the presenting clinical features because surface ulceration results in chronic blood loss.
X. NEOPLASMS OF THE APPENDIX

A. MUCOCOELE
Benign dilatation of the lumen by mucinous secretions

B. MUCINOUS CYSTADENOMA
Proliferation of benign neoplastic epithelial cells that result in dilatation of the lumen by mucinous material; may rupture

C. MUCINOUS CYST ADENOCARCINOMA
   i. Invasion of malignant neoplastic cells
   ii. Pseudomyxoma peritonei
       Term describing distention of the peritoneal cavity by the presence of semisolid, mucin-containing adenocarcinoma cells

XI. PERITONEUM

A. INFLAMMATION
   1. Sterile peritonitis due to bile or pancreatic enzymes
   2. Surgical procedures
   3. Endometriosis
   4. Rupture of GI tract i.e. appendicitis or diverticulitis or GU related as in peritoneal dialysis or acute salpingitis

B. NEOPLASMS
   1. Primary mesothelioma is rare
   2. Secondary malignancies due to extension, seeding or implantation of tumor