Inflammatory Bowel Disease
Ischemic bowel disease
Inflammatory Bowel Disease

• The two disorders that comprise IBD are: ulcerative colitis
  Crohn disease
• The distinction between ulcerative colitis and Crohn disease is based, in large part, on the distribution of affected sites and the morphologic expression of disease at those sites.

**Ulcerative colitis** is limited to the colon and rectum and extends only into the mucosa and submucosa. **Crohn disease**, which has also been referred to as regional enteritis (because of frequent ileal involvement) may involve any area of the GI tract and is typically transmural.
Figure 17-32 Distribution of lesions in inflammatory bowel disease. The distinction between Crohn disease and ulcerative colitis is primarily based on morphology.
• Epidemiology:
Ulcerative colitis and Crohn disease frequently present in the teens and early 20s, with the former being slightly more common in females. IBD is most common among Caucasians and, in the United States, occurs 3 to 5 times more often among eastern European (Ashkenazi) Jews than the general population.
• IBD incidence worldwide is on the rise,

• **The hygiene hypothesis** suggests that this increasing incidence is related to improved food storage conditions, decreased food contamination, and changes in gut microbiome composition. Apparently this results in inadequate development of regulatory processes that limit mucosal immune responses. This in turn allows some mucosa-associated microbial organisms to trigger persistent and chronic inflammation in susceptible hosts.
Pathogenesis:
Although precise causes are not yet defined, most investigators believe that IBD results from the combined effects of:
alterations in host interactions with intestinal microbiota,
intestinal epithelial dysfunction,
aberrant mucosal immune responses,
altered composition of the gut microbiome
• **Genetics.** There is compelling evidence that genetic factors contribute to IBD. Risk of disease is increased when there is an affected family member. Genetic factors are more dominant in **Crohn disease.**

3 genes strongly associated with Crohn disease: **NOD2, ATG16L1,** and **IRGM.**

These genes involved in recognition and response to intracellular pathogens.
• Mucosal immune responses: it is clear that deranged mucosal immune activation and defective immunoregulation contribute to the development of ulcerative colitis and Crohn disease.

Immunosuppressive agents remain the mainstay of treatment for these conditions.

• Epithelial defects: Defects in intestinal epithelial tight junction barrier function
Figure 17-33 One model of IBD pathogenesis. Aspects of both Crohn disease and ulcerative colitis are shown. See text for details.
Crohn Disease

- Crohn disease may occur in any area of the GI tract, but the most common sites involved at presentation are the terminal ileum, ileocecal valve, and cecum.

- Disease is **limited to the small intestine alone in about 40% of cases**; the small intestine and colon are both involved in 30% of patients; the remainder have only colonic involvement.
• The presence of multiple, separate, sharply delineated areas of disease, resulting in **skip lesions**, is characteristic of Crohn disease and may help in the differentiation from ulcerative colitis. Sparing of interspersed mucosa, a result of the patchy distribution of Crohn disease, results in a coarsely textured, **cobblestone appearance** in which diseased tissue is depressed below the level of normal mucosa.

The earliest lesion called **aphthous ulcer**
• **Fissures** frequently develop between mucosal folds and may extend deeply to become **fistula tracts** or sites of **perforation**.

• The **intestinal wall is thickened** and rubbery as a consequence of transmural edema, inflammation, submucosal fibrosis, and hypertrophy of the muscularis propria, all of which contribute to **stricture formation**.

• In cases with extensive transmural disease, mesenteric fat frequently extends around the serosal surface (**creeping fat**)
Figure 17-35 Microscopic pathology of Crohn disease. 

A, Haphazard crypt organization results from repeated injury and regeneration. B, Noncaseating granuloma. 
C, Transmural Crohn disease with submucosal and serosal granulomas (arrows).
Figure 17-34 Gross pathology of Crohn disease. A, Small-intestinal stricture. B, Linear mucosal ulcers, which impart a cobblestone appearance to the mucosa, and thickened intestinal wall. C, Perforation and associated serositis. D, Creeping fat.
• **Noncaseating granulomas**, a hallmark of Crohn disease, are found in approximately 35% of cases.
Clinical Features:
diarrhea, fever, and abdominal pain.

**Periods of active disease are typically interrupted by asymptomatic periods that last for weeks to many months.**

Disease re-activation can be associated with a variety of **external triggers**, including physical or emotional stress, specific dietary items, and cigarette smoking.

nutrient malabsorption (small bowel disease)
Iron-deficiency anemia (colonic disease)
Fistulae develop between loops of bowel and may also involve the urinary bladder, vagina, and abdominal or perianal skin.
• Extraintestinal manifestations of Crohn disease: uveitis, migratory polyarthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, clubbing of the fingertips, any of which may develop before intestinal disease is recognized.

Pericholangitis and primary sclerosing cholangitis occur in Crohn disease, but are more common in those who have ulcerative colitis.
• risk of colonic adenocarcinoma is increased in patients with long-standing IBD affecting the colon.

• **Anti-TNF antibodies** have revolutionized treatment of Crohn disease, and other biologic therapies are becoming available.
Ulcerative Colitis

• the disease in ulcerative colitis is limited to the colon and rectum.

• Common extraintestinal manifestations of ulcerative colitis overlap with those of Crohn disease (but Pericholangitis and primary sclerosing cholangitis are more in UC)
ulcerative colitis always involves the rectum (ulcerative proctitis) and extends proximally in a **continuous fashion** to involve part or all of the colon.

- Disease of the entire colon is termed pancolitis.
- The small intestine is normal, although mild mucosal inflammation of the distal ileum, termed **backwash ileitis**, may be present in severe cases of pancolitis.

- broad-based ulcers
- Isolated islands of regenerating mucosa often bulge into the lumen to create **pseudopolyps**, and the tips of these polyps may fuse to create **mucosal bridges**
• inflammation and inflammatory mediators can damage the muscularis propria and disturb neuromuscular function leading to colonic dilation and toxic megacolon, which carries a significant risk of perforation.
Figure 17-36 Gross pathology of ulcerative colitis. A, Total colectomy with pancolitis showing active disease, with red, granular mucosa in the cecum (left) and smooth, atrophic mucosa distally (right). B, Sharp demarcation between active ulcerative colitis (right) and normal mucosa (left). C, Inflammatory polyps. D, Mucosal bridges.
Figure 17-37 Microscopic pathology of ulcerative colitis. A, Crypt abscess. B, Pseudopyloric metaplasia (bottom). C, Disease is limited to the mucosa. Compare to Figure 17-36C.
Clinical Features:
Ulcerative colitis is a relapsing disorder characterized by attacks of bloody diarrhea with stringy, mucoid material, lower abdominal pain, and cramps that are temporarily relieved by defecation. These symptoms may persist for days, weeks, or months before they subside.
The initial attack may, in some cases, be severe enough to constitute a medical or surgical emergency.
Colectomy effectively cures intestinal disease in ulcerative colitis, but extraintestinal manifestations may persist.
• The factors that trigger ulcerative colitis are not known, but infectious enteritis precedes disease onset in some cases.

• In other cases the first attack is preceded by psychologic stress, which may also be linked to relapse during remission.

• The initial onset of symptoms has also been reported to occur shortly after smoking cessation in some patients, and smoking may partially relieve symptoms.
### Table 17-9 Features That Differ between Crohn Disease and Ulcerative Colitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel region</td>
<td>Ileum ± colon</td>
<td>Colon only</td>
</tr>
<tr>
<td>Distribution</td>
<td>Skip lesions</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Stricture</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Wall appearance</td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td><strong>Microscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>Transmural</td>
<td>Limited to mucosa</td>
</tr>
<tr>
<td>Pseudopolyps</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Deep, knife-like</td>
<td>Superficial, broad-based</td>
</tr>
<tr>
<td>Lymphoid reaction</td>
<td>Marked</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Marked</td>
<td>Mild to none</td>
</tr>
<tr>
<td>Serositis</td>
<td>Marked</td>
<td>Mild to none</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Yes (~35%)</td>
<td>No</td>
</tr>
<tr>
<td>Fistulae/sinuses</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perianal fistula</td>
<td>Yes (in colonic disease)</td>
<td>No</td>
</tr>
<tr>
<td>Fat/vitamin malabsorption</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Malignant potential</td>
<td>With colonic involvement</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrence after surgery</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*All features may not be present in a single case.*
Irritable Bowel Syndrome

• Irritable bowel syndrome (IBS) is characterized by chronic, relapsing abdominal pain, bloating, and changes in bowel habits.

• IBS is currently divided into several subtypes, as defined by successive revisions of the Rome criteria:
  - IBS with diarrhea (IBS-D),
  - IBS with constipation (IBS-C),
  - mixed IBS (IBS-M)
• Pathogenesis:
The pathogenesis of IBS remains poorly defined, although there is clearly interplay between psychologic stressors, diet, perturbation of the gut microbiome, increased enteric sensory responses to gastrointestinal stimuli, and abnormal GI motility. Other data link disturbances in enteric nervous system function to IBS, suggesting a role for defective brain-gut axis signaling.
Several candidate genes to IBS, including: serotonin reuptake transporters, cannabinoid receptors, TNF-related inflammatory mediators.

5-HT3 receptor antagonists are effective in many cases of diarrhea-predominant IBS. Opioids and psychoactive drugs with anti-cholinergic effects are also commonly used to treat diarrhea predominant IBS.
• A separate group of IBS patients, relate onset to a bout of infectious gastroenteritis, suggesting that immune activation or, alternatively, a shift in the gut microbiome.
Clinical Features.

The peak prevalence of IBS is between 20 and 40 years of age, and there is a significant female predominance.

Other causes, such as enteric infection or inflammatory bowel disease, must be excluded.

IBS is not associated with serious long-term sequelae.
The **Rome IV criteria** for the diagnosis of irritable bowel syndrome require that patients have had:

- recurrent abdominal pain on average at least 1 day per week during the previous 3 months that is associated with 2 or more of the following:
  * Related to defecation (may be increased or unchanged by defecation)
  * Associated with a change in stool frequency
  * Associated with a change in stool form or appearance
Ischemic Bowel Disease

- the colon is the most common site of gastrointestinal ischemia.
- The severity of vascular compromise, the time frame during which it develops, and the vessels affected are the major variables in ischemic bowel disease.
Two aspects of intestinal vascular anatomy also contribute to the distribution of ischemic damage and are worthy of note:

- Intestinal segments at the end of their respective arterial supplies are particularly susceptible to ischemia. These watershed zones include the splenic flexure, where the superior and inferior mesenteric arterial circulations terminate, and, to a lesser extent, the sigmoid colon and rectum where inferior mesenteric, pudendal, and iliac arterial circulations end.

- Intestinal capillaries run alongside the glands, from crypt to surface, before making a hairpin turn to empty into the post-capillary venules. This arrangement makes the surface epithelium particularly vulnerable to ischemic injury, relative to the crypts. Organization of the blood supply in this patterns has advantages, as it protects the epithelial stem cells, which are located within the crypts and are necessary for recovery from epithelial injury.
• **mucosal and mural infarctions** can follow acute or chronic hypoperfusion (non-occlusive), causes: cardiac failure, shock, dehydration, or use of vasoconstrictive drugs.

• **transmural infarction** is typically caused by acute vascular obstruction (occlusive), causes: severe atherosclerosis, aortic aneurysm, hypercoagulable states, oral contraceptive use, and embolization of cardiac vegetations or aortic atheromas.
• Intestinal responses to ischemia occur in two phases.
  - The initial **hypoxic injury** occurs at the onset of vascular compromise. While some damage occurs during this phase, the epithelial cells lining the intestine are relatively resistant to transient hypoxia.
  - The second phase, **reperfusion injury**, is initiated by restoration of the blood supply and it is at this time that the greatest damage occurs. In severe cases this may trigger multiorgan failure. Leakage of gut lumen bacterial products into the systemic circulation, free radical production, neutrophil infiltration, and release of additional inflammatory mediators.
• Clinical Features:
Ischemic disease of the colon is most common in patients older than 70 years of age, and occurs slightly more often in women.

**Acute colonic ischemia** typically presents with sudden onset of cramping, left lower abdominal pain, a desire to defecate, and passage of blood or bloody diarrhea.----- resemble acute abdomin.

**Chronic ischemia:** episodes of bloody diarrhea interspersed with periods of healing------ resemble IBD

Necrotizing enterocolitis (NEC): transmural necrosis--neonates