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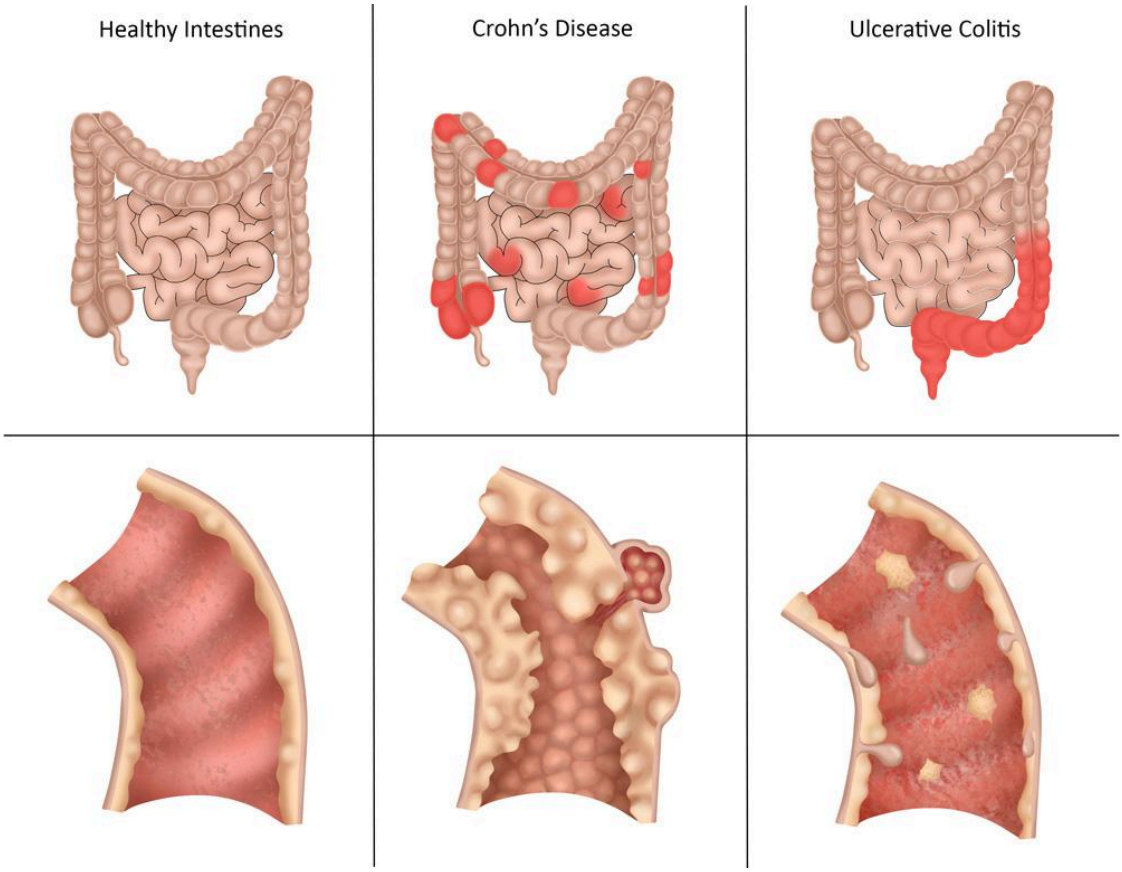
Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) involves ongoing inflammation of parts or all of the digestive tract. It is divided into two main types: **Crohn's disease** and **ulcerative colitis (UC)**. Both types of IBD cause inflammation and diarrhea and have a pattern of familial occurrence. Systemic manifestations of IBD include arthritis, skin lesions, inflammatory conditions of the eye like uveitis, and blood disorders including anemia and hypercoagulability. IBD can stunt a child's growth because of its effects on the absorption of vital nutrients. Genetics, deranged mucosal immune responses, epithelial defects, and the intestinal microbiome all play a role in the pathogenesis of IBD.



Crohn's Disease vs. Ulcerative Colitis *Image by Becky T. F19*

Crohn's Disease

Crohn's disease has sometimes been referred to as an autoimmune disorder. However, this categorization is a bit controversial because, like other autoimmune conditions, we don't find adaptive immunity specifically targeting self antigens. Rather, with Crohn's disease, we find a type of "auto-inflammatory" condition that arises when inflammation gets out of control and the ability to regulate this inflammation is compromised. Symptoms and damage arising from a

dysregulation of the innate immune system might categorize this disease as an immune mediated condition rather than an autoimmune condition. The inflammation can affect the GI lining on any part of the digestive tract from the mouth to the anus. However, inflammation most commonly occurs in the small intestine and colon. This inflammation can occur in a continuous or patchy pattern. Crohn's disease most typically affects individuals in their 20s.

Granulomatous lesions or granulomas are common in Crohn's disease. A **granuloma** is a localized swelling composed of an aggregation of immune cells (mostly macrophages). These structures form when the immune system perceives something as foreign but has been unsuccessful at getting rid of it. The immune system attempts to "wall off" the substance by surrounding it with these immune cells.

Crohn's disease is also known for skip lesions that can be transmural (meaning they affect all the layers of the GI tract). **Skip lesions** are patchy areas of inflammation or even wounds that represent intestinal tissue damage. This tissue damage can extend through all the layers of the GI tract and create **fistulas** (or openings) from the lumen of the GI into the peritoneal cavity, or into other organs (e.g. the bladder), or into other areas of the intestine, or even onto the skin. Between the two types of IBD, skip lesions are characteristic of Crohn's disease but not ulcerative colitis.

Cobblestone mucosa is another feature of Crohn's disease. The "cobblestone" appearance arises because of longitudinal and circumferential fissures that develop in the mucosa. These fissures together with associated ulcerations, submucosal inflammation, granulomas, and wall thickening gives the mucosa an appearance that resembles cobblestones. Strictures, which are narrowing of the gut lumen, can also develop. The submucosal layer is affected more than the mucosal layer with Crohn's disease, which means there is less bloody diarrhea with Crohn's disease compared to ulcerative colitis.

NOD2 (nucleotide oligomerization domain 2) mutations are strongly correlated with Crohn's disease. NOD2 codes for an intracellular protein that binds to bacterial PAMPs and activates signals that trigger an innate immune response, for example, the secretion of defensins and lysozyme. In its mutated form, these secretions fail to occur leading to a dysbiosis between the gut bacterial flora and the intestinal epithelium. Without NOD2, this dysbiosis means there are increased populations of bacteria in the gut, many of which are harmful to gut epithelial cells and trigger a strong, chronic inflammatory response leading to increased Peyer's patches and mesenteric lymph node granulocyte and lymphocyte recruitment. These pro-inflammatory responses involve the activation of helper T-cells of the adaptive immune system, specifically TH1 and TH17. Recall that these helper T-cells release cytokines that recruit macrophages, neutrophils, and cytotoxic T-cells to the area and can exacerbate inflammation and tissue damage. It is known that IL-23, secreted by APCs like macrophages of the gut is a potent activator of TH17 cells. Interestingly, those with defects in the IL-23 receptor have reduced risk for developing both Crohn's disease and UC since they have decreased activation of TH17 cells.

Endoscopy, stool cultures, and CT scans are all useful in the diagnosis of Crohn's disease. Stool cultures are taken to test for a protein called calprotectin, which is secreted by white blood cells. Calprotectin is a common protein secreted by white blood cells such as neutrophils. This protein sequesters zinc which many bacteria need for normal metabolic functioning. The production of this protein is upregulated during periods of inflammation. Stool samples that show elevated calprotectin suggest intestinal inflammation and can serve as a marker for IBD. Increased calprotectin can help distinguish between IBS and IBD, but it cannot help distinguish between Crohn's and UC.

A nutritious diet is especially important in the treatment of Crohn's disease because patients may experience nutrition deficiencies due to diarrhea, steatorrhea (fatty stool), and other malabsorption problems. It is necessary for those with Crohn's disease to avoid excessive consumption of fats because fat aggravates the diarrhea. Elemental diets may be used during times of acute flare up. An **elemental diet** includes foods that are nutritionally balanced while being bulk and residue free. It is usually composed of amino acids, fats, sugars, vitamins, and minerals. This diet, however, may lack whole or partial protein due to the possibility of these proteins triggering an allergic reaction in some people. In more severe cases, an elemental nutritional supplement may be delivered via a gastric feeding tube or intravenous line.

The following medications reduce the inflammation associated with Crohn's disease: 5-aminosalicylic acid agent (5-ASA) like mesalamine (Asacol), corticosteroids like budesonide (Entocort EC), immunosuppressant drugs like

methotrexate (Trexall), alpha-4-integrin inhibitors like natalizumab (Tysabri), and TNF-alpha blockers like certolizumab pegol (Cimzia). Metronidazole (Flagyl) is an antibiotic used to treat bacterial overgrowth in the small intestine.

Ulcerative colitis

Ulcerative colitis (UC) involves ulcerative inflammation of only the colon and rectum where it spreads proximally without any skip lesions. Peak incidence for UC occurs in people's 30s. UC primarily affects the mucosal layer. In UC, the damage to the mucosa is continuous and exudative (which means it weeps or leaks fluid onto the damaged epithelial surface). For this reason, bloody diarrhea is more common with UC. **Pseudopolyps**, which are tongue-like projections in the mucosal layer that resemble polyps, may develop due to the inflammation process. UC is also induced by genetic factors that alter the relationship between the gut microbiota and epithelium, however, skip lesions and cobblestone mucosa do not occur. Granulomatous inflammation is also not a characteristic.

There are a few different categories of UC:

- **Ulcerative proctitis:** affects only the rectum
- **Proctosigmoiditis:** affects the rectum and sigmoid colon
- **Pancolitis:** affects the entire colon

Diagnosis of UC includes colonoscopy, biopsy, and stool examinations to rule out infections. The stool of UC patients normally contains blood and mucus. Nocturnal diarrhea occurs more often when the daytime symptoms are severe. Other complications include severe anemia, hypovolemia, and impaired nutrition with hypoalbuminemia.

Treatment for UC involves lifestyle modifications and medication. UC patients should avoid caffeine, lactose, spicy foods, fatty foods, and gas-forming foods. UC patients also have a relatively high risk for developing cancer, so it is highly recommended that patients have annual or biannual colonoscopies. The medications for UC are similar to those used for Crohn's disease. For those that do not respond to medications and more conservative treatments, surgery can be done to remove the rectum and entire colon.

Characteristic	Crohn's Disease	Ulcerative Colitis
Type of Inflammation	Granulomatous	Ulcerative and exudative
Tissue Involvement	Primarily submucosa with presence of skip lesions	Primarily mucosa and continuous without skip lesions
Areas Involved	Primarily the ileum, but can be anywhere in GI tract	Primarily the descending colon and rectum
Diarrhea	Common	Common and more likely to be bloody
Rectal Bleeding	Rare	Common
Fistulas	Common	Rare
Strictures	Common	Rare
Development of	Less common	More common

Cancer