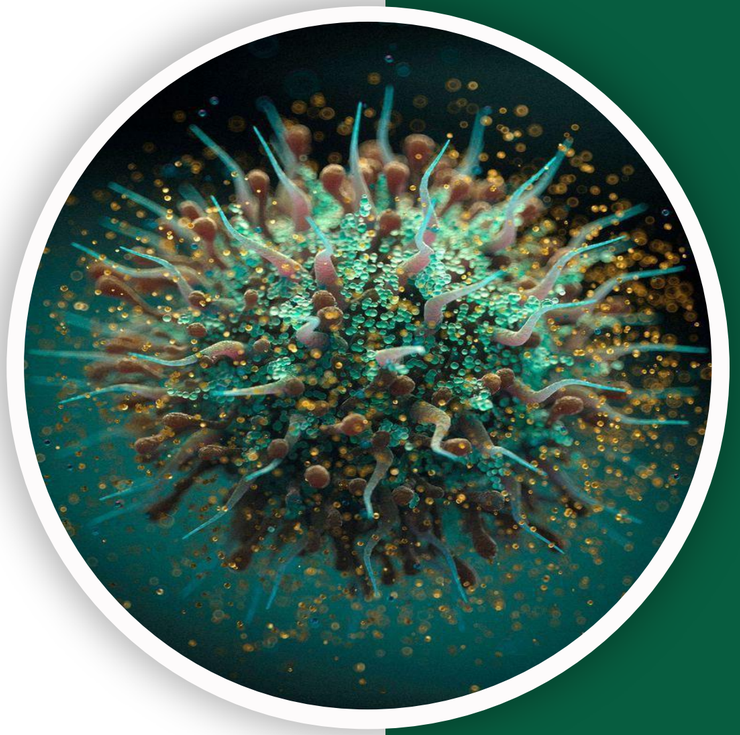
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | MID 6

Intestinal Diseases pt.2



Written by : DST

Reviewed by : Rawan Okour

Hashem Al-Halalmeh

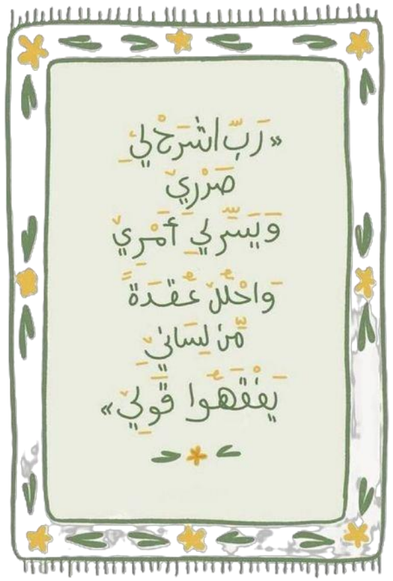
Lactase (Disaccharidase) Deficiency

Deficient enzyme responsible for the digestion of lactose which is present on the terminal brush border.

- Osmotic diarrhea because the lactose in the bowel will absorb water.
- Lactose remains in the gut lumen.
- Lactase found at apical brush border membrane.
- Normal biopsy findings.

Continuous diarrhea can impair intestinal absorption, particularly in the pediatric age group, and may lead to **failure to thrive**.

- Three types:
- ***Congenital*** : AR, genetic mutation, rare, explosive diarrhea, watery, frothy stools & abdominal distention, after milk ingestion. Treatment include lactose free milk.
- ***Acquired*** : very common, downregulation of gene (Lactase is present but in decreased amount, so if patient consumes more milk than the amount of enzyme they have, they will experience symptoms), after weaning. Affects 2/3 of world's population (50% of USA population).
- **Transient**: caused by injury after infectious or inflammatory insults (reversible). In inflammation of the bowel like viral enterocolitis or gastroenteritis causes the brush border to get damaged. The patient will experience symptoms for a short period of time that is until the brush border regenerates.



Abetalipoproteinemia

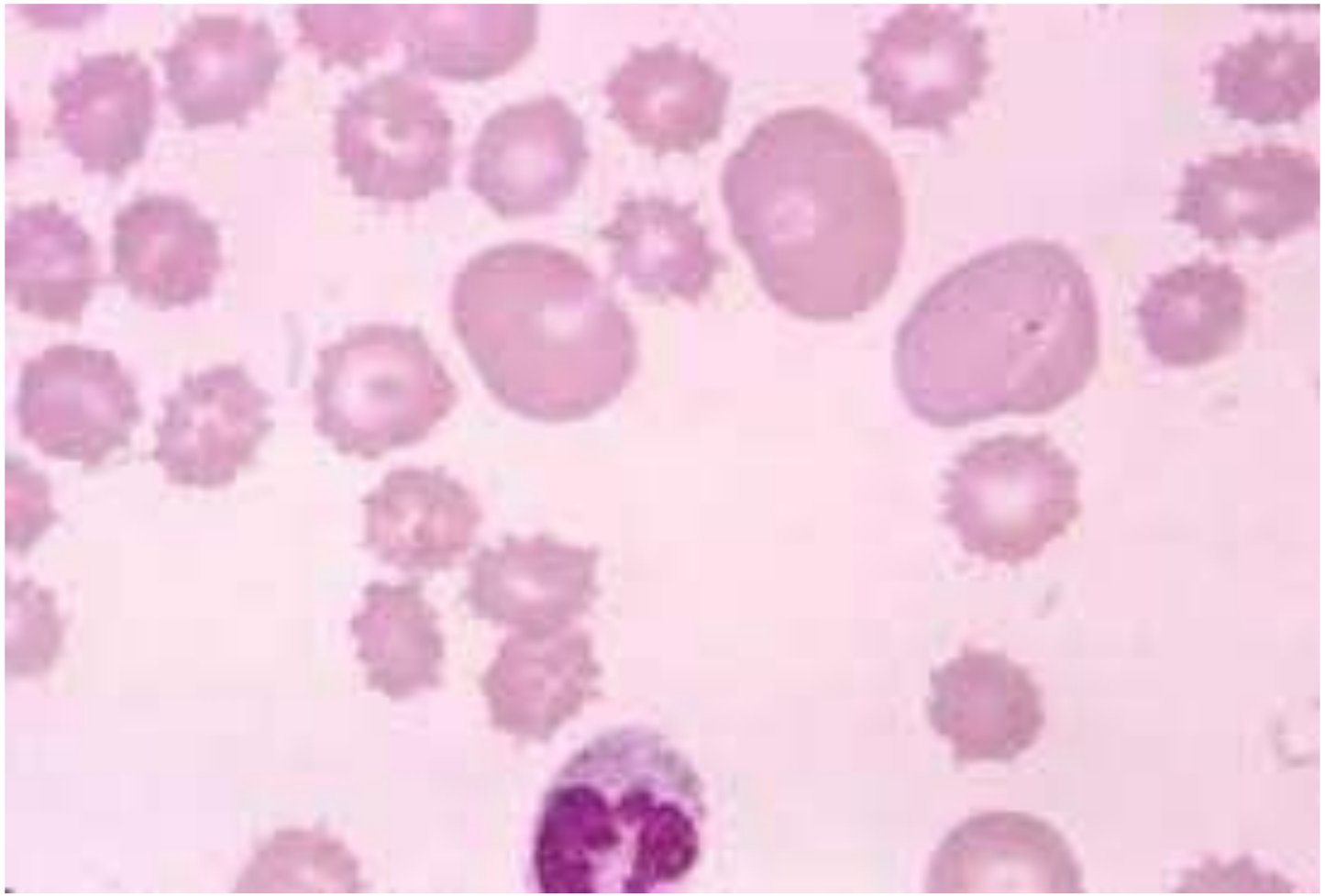
Absence of lipoproteins due to malabsorption

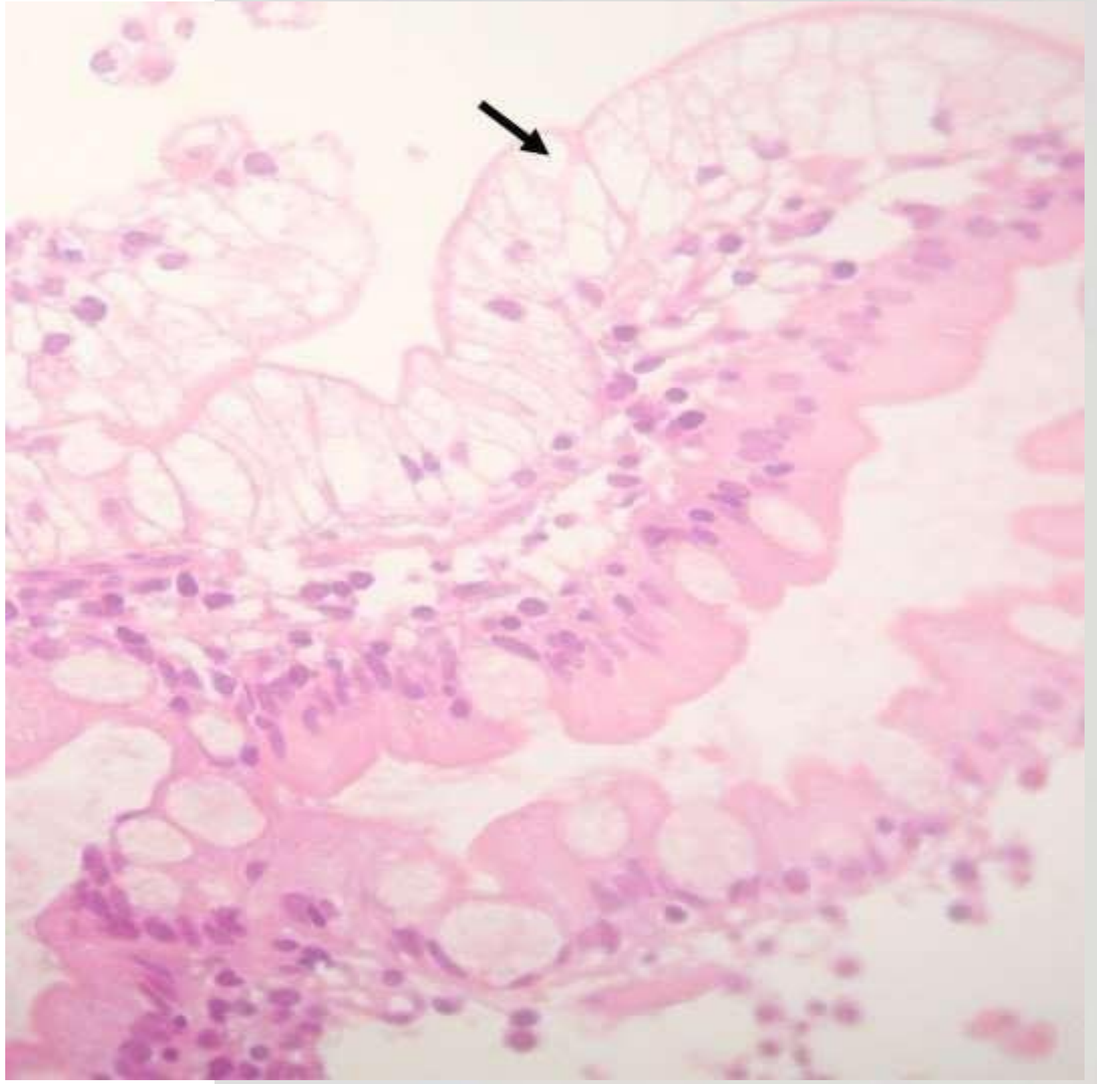
Lipoproteins enter the enterocytes but can't be transported to lymphatics due to a defect in the transport. Lipoproteins, FA, and fat-soluble vitamins will accumulate in the enterocytes which results in a white color in the cytoplasm of the enterocytes under the microscope.

- Autosomal recessive, rare.
- Inability of enterocytes to secrete triglyceride-rich chylomicrons.
- Lack of absorption (Transepithelial transport defect of lipoproteins, FAs and fat-soluble vitamins).
- Usually effects Infants' w/ failure to thrive, diarrhea, and steatorrhea.
- Vitamin K deficiency (Symptoms include anything affected by the fat-soluble vitamins "AKED"; Vit A effects skin and retina, Vit D might cause rickets), skeletal CNS and retinal abnormalities.
- Spur cells in peripheral blood because FAs are needed to produce the phospholipids in the wall of the all cells including RBCs. We use RBCs because they can be easily seen on peripheral blood smear.
- Monoglycerides and triglycerides accumulate in epithelial cells, and don't reach circulation.

Spur cells in peripheral blood

Notice the star-like appearance due to the disruption of the plasma membrane of the cells.





Micrograph showing enterocytes with a clear cytoplasm (due to lipid accumulation) characteristic of abetalipoproteinemia.

Intestinal pathology, part 2

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Each underlined term serves as a hyperlink.

The next 8 slides are not required for the exam

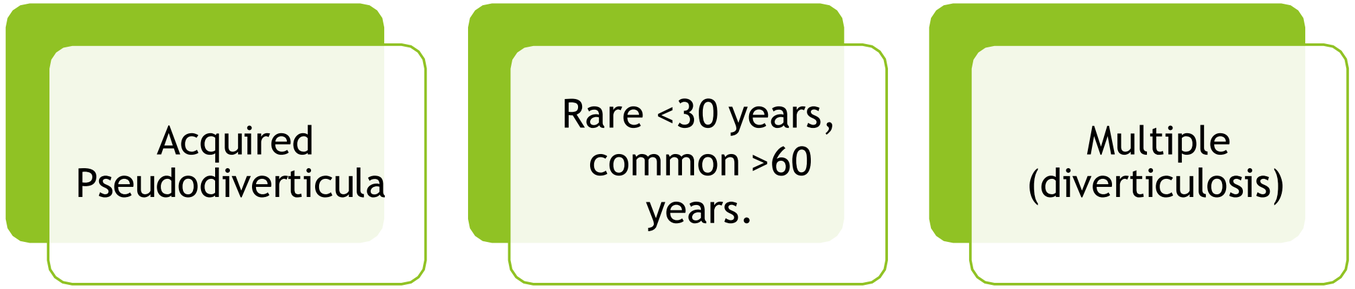
Diseases of the intestines

- Intestinal obstruction
- Vascular disorders
- Malabsorptive diseases and infections
- **Inflammatory intestinal disease.**
- Polyps and neoplastic diseases

INFLAMMATORY INTESTINAL DISEASE

- **Sigmoid Diverticulitis**
- **Chronic Inflammatory bowel diseases (CIBD)**
  - Crohn disease
  - Ulcerative colitis

Sigmoid Diverticulitis



Sigmoid diverticula differ from Meckel's diverticulum in several ways: they are **pseudodiverticula involving** herniation of **the mucosa and submucosa** through the muscularis propria, are typically acquired rather than congenital, usually appear after the age of 60, and are often multiple rather than solitary.

Pathogenesis

When multiple diverticula are present, the condition is called **diverticulosis**. If these diverticula become inflamed, it is known as **diverticulitis**.

- Chronic constipation causes:
  - **Elevated intraluminal pressure.**
  - Unique location (discontinuous muscle layer at points of nerve and vessels entry).
  - Longitudinal muscle layer is discontinuous in colon (taeniae coli)
  - Area of weakness: outward herniation of the mucosa and submucosa, where there is discontinuous muscle layers.
  - Most common in sigmoid (narrowest part)
  - Exaggerated peristaltic contractions.
  - Low fiber diet, constipation, sedentary lifestyle, obesity, and smoking.

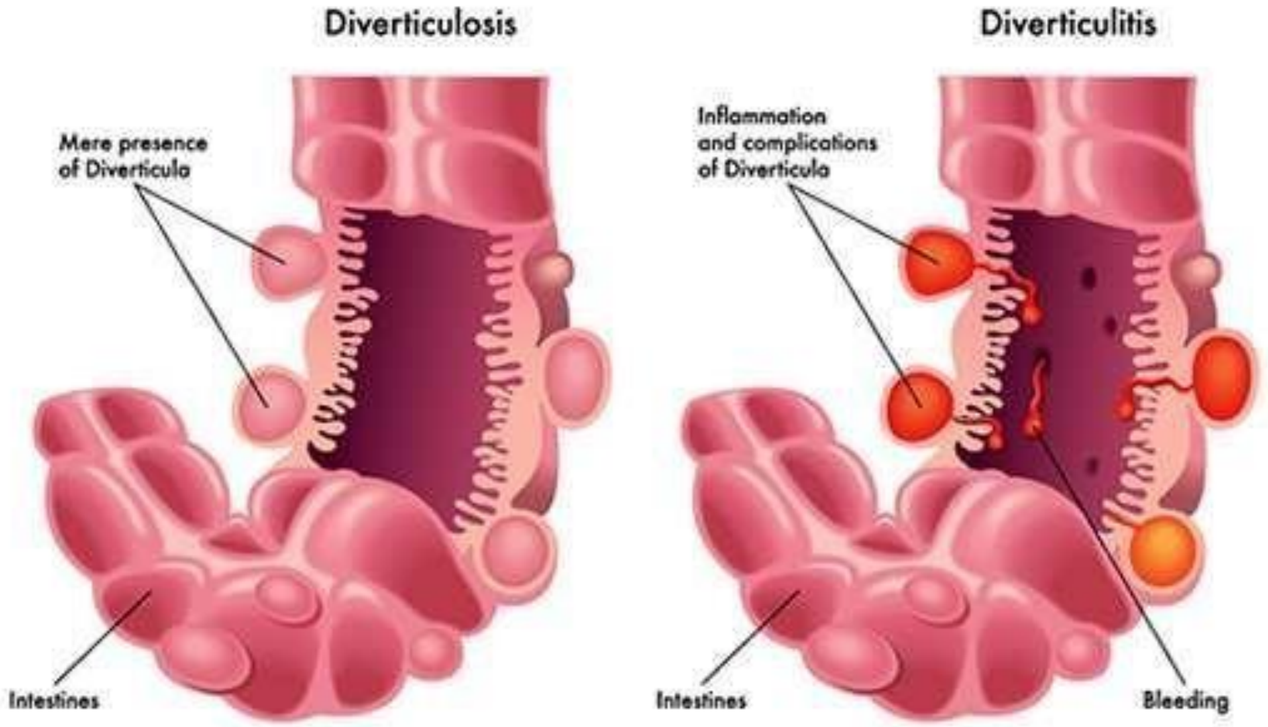
- Chronic constipation causes **exaggerated peristaltic contractions and increased intraluminal pressure**. This pressure can lead to **herniation of the mucosa and submucosa through weak areas in the muscular layer** of the colon wall.

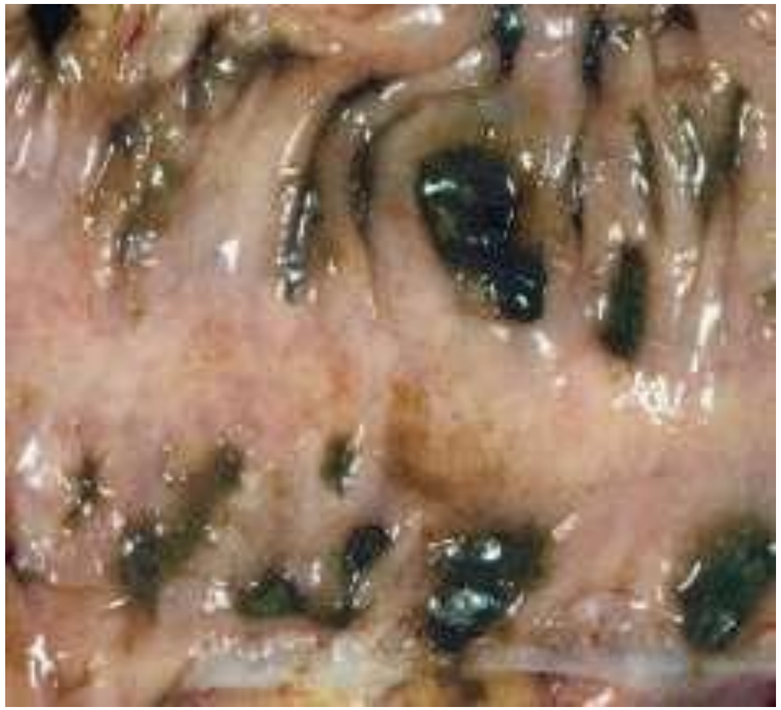
MORPHOLOGY

- Flask-like outpouchings
- Between taeniae coli.
- Thin wall (atrophic mucosa, compressed submucosa)
- Attenuated or absent muscularis propria.
- Obstruction leads to diverticulitis.
- Risk of perforation.
- Recurrent diverticulitis leads to fibrosis (strictures).

It is thin walled.

- The region that opens into the lumen is called the **neck of the diverticulum**. It is often **obstructed by stool**, leading to **inflammation**. Repeated inflammation can cause **fibrosis**, which may eventually lead to **stricture formation** and contribute to **constipation**.
- This process most commonly occurs in the **sigmoid colon**.


Diverticulosis
Mere presence of Diverticula
Intestines
Diverticulitis
Inflammation and complications of Diverticula
Intestines
Bleeding



Inner colonic lumen (outpouchings).

Clinical Features

- Mostly asymptomatic.
- Intermittent lower abdominal pain
- Constipation or diarrhea.
- Patients usually **do not experience symptoms from diverticulosis itself**, they rather complain from **constipation.**
- However, if the diverticula become inflamed (**diverticulitis**), **abdominal pain** –typically in the **left lower quadrant** –and **bloody diarrhea** may occur.
- Treatment (Tx):
  - High fiber diet, to treat constipation.
  - Antibiotics in diverticulitis.
  - Surgery.

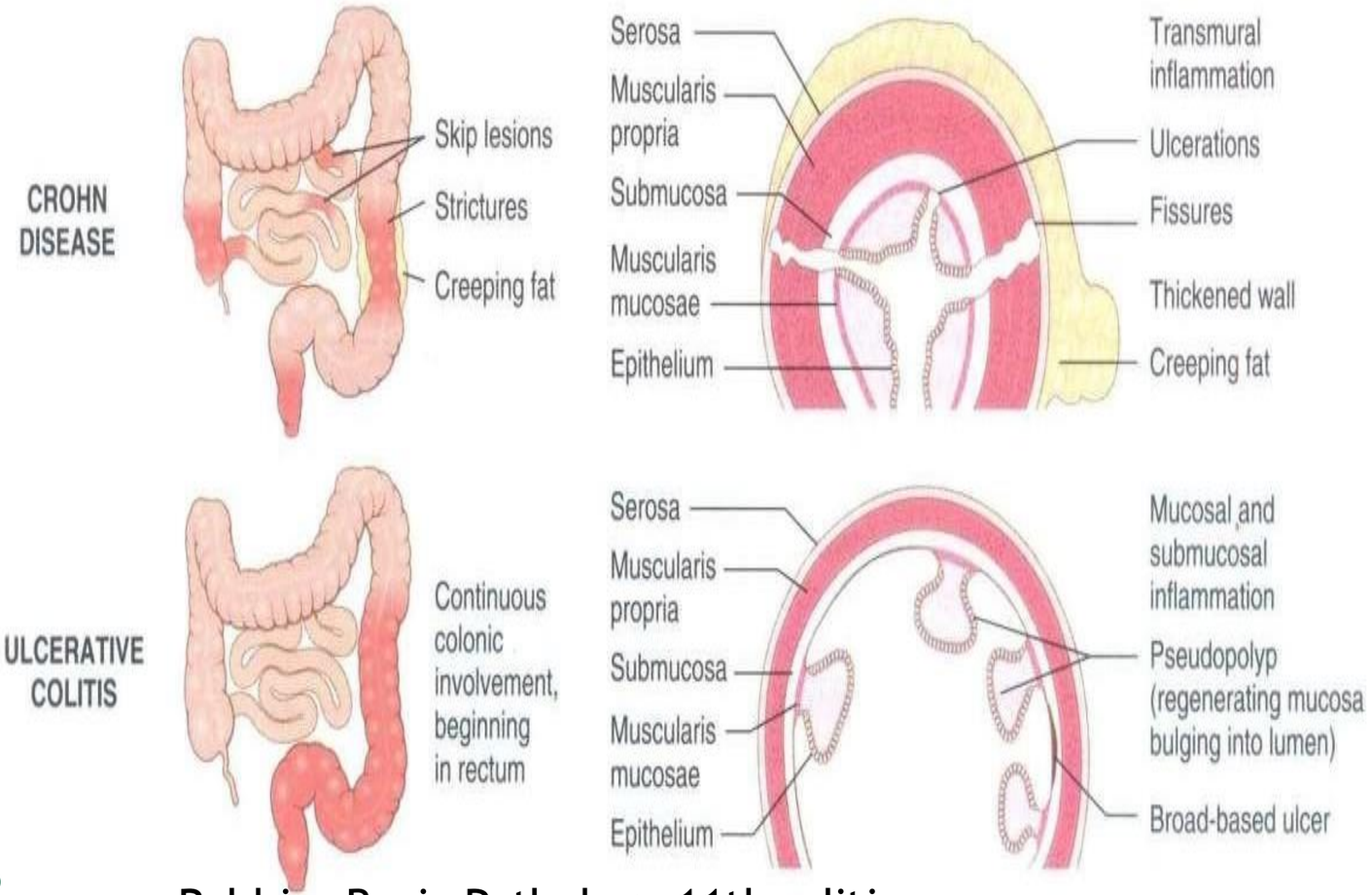
Chronic Inflammatory Bowel Disease

The Dr. started from here

- Genetic predisposition
- **Exaggerated** immune response to intestinal microbes, **including microbiota.**
- Inappropriate mucosal damage.
- **Ulcerative colitis**: limited to the colon and rectum, extends only into mucosa and Submucosa, **while muscularis & serosa are normal.**
  - A clear **demarcation between inflamed and non-inflamed mucosa** is often observed in **ulcerative colitis**.
  - The disease may be limited to the **rectum** (**proctitis**), extend to the **sigmoid colon**, or involve the **entire colon** (**pan colitis**). As a result, the **severity and clinical presentation** of ulcerative colitis can **vary significantly between individuals.**

- **Crohn disease**: regional enteritis with skip area in between , frequent ileal involvement, affect any area in GIT from mouth to anus, frequently transmural (**the whole wall of the bowel affected: mucosa, muscularis, submucosa & serosa).**
  - **Regional involvement** refers to the pattern seen in **Crohn's disease**, where inflammation can begin in **any part of the gastrointestinal tract**, not necessarily the rectum.
  - The disease is **not continuous**, and areas of inflammation are often **separated by normal segments**, a pattern known as **skip lesions**.

•**Crohn's Disease (CD)** has a more **regional and discontinuous distribution**, meaning that different segments of the gastrointestinal tract may be affected. It can involve not only the **colon**, but also the **small intestine**, **stomach**, **oral mucosa**, and **esophagus**.
•Crohn's disease is characterized by **deep ulceration**, which may progress to **perforation** or the formation of **fistulas** (abnormal connections between the bowel and adjacent organs).
•Unlike ulcerative colitis, Crohn's disease affects the **entire bowel wall thickness**, leading to **bowel wall thickening**. This thickening results from **fibrosis (scarring)** that develops secondary to chronic inflammation and fissuring ulceration.



Robbins Basic Pathology 11th edition

- **Ulcerative Colitis** is a disease limited to the **colon**. It **always begins in the rectum** and extends proximally in a continuous manner to a variable extent. In some patients, involvement is limited to the **sigmoid colon**, while in others it may extend to the **left side of the colon**, the **distal transverse colon**, or involve the **entire colon (pancolitis)**.
- The inflammation in ulcerative colitis is confined to the **mucosa and submucosa** and is associated with **shallow ulceration**. These ulcers do not penetrate the full thickness of the bowel wall.

Epidemiology

- Adolescence & young adults
- 2nd peak in fifth decade, **although it is uncommon.**
- Geographic variation.
- Proposed explanation:
  - ***Hygiene hypothesis****: childhood exposure to environmental microbes prevents excessive immune system reactions. Firm evidence is lacking!!!.*

According to this hypothesis, **childhood exposure to environmental microbes** may help regulate the immune system and reduce the likelihood of exaggerated immune responses later in life. In contrast, highly protective environments with reduced microbial exposure may limit the development of normal immune tolerance, increasing susceptibility to abnormal immune reactions.
This remains a **hypothesis**, and there is **no firm evidence** confirming it.

Pathogenesis:

- The pathogenesis of inflammatory bowel disease is complex and beyond the current scope in full detail. However, it is understood to result from a Combined effect of:
  - Altered host interaction with intestinal microbiota.
  - Intestinal Epithelial dysfunction
  - Aberrant mucosal immune responses.
    - *Aberrant: Exaggerated.*

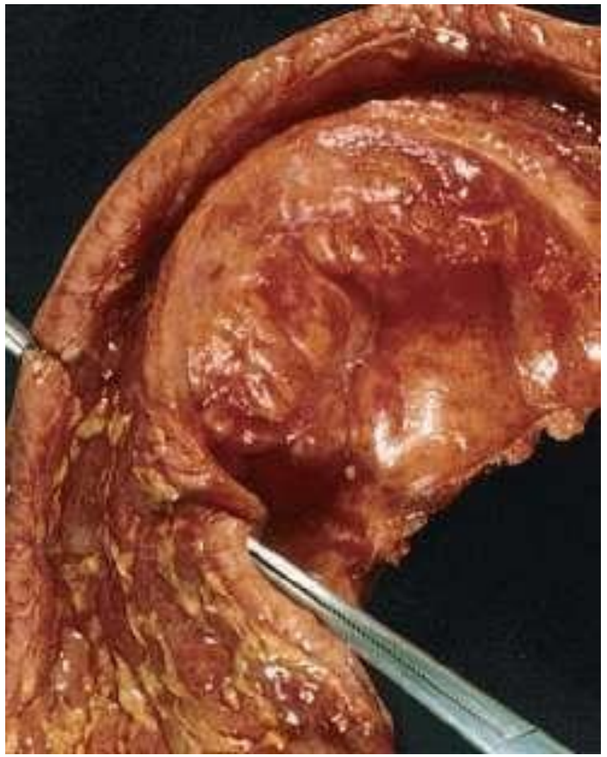
The central concept in inflammatory bowel disease is **immune dysregulation**. For this reason, these conditions are considered **immune-related disorders** and are commonly treated with **immunosuppressive therapy** and **steroids**.

Inflammatory bowel disease is not classified as a classic autoimmune disease in which specific antibodies are consistently identified. Rather, it is considered an **immune-mediated disease**.

Crohn´s Disease Morphology

Crohn's disease is a **chronic inflammatory bowel disease** that may sometimes be clearly distinguished from **ulcerative colitis** by macroscopic and microscopic features. However, in some cases there is an area of overlap, creating a **gray zone** in which definite classification may be difficult.

- Macroscopic:
  - Regional enteritis,characterized by alternating areas of **normal bowel** and **diseased bowel**. This discontinuous pattern may involve different parts of the gastrointestinal tract..
  - Any area of GIT.
  - Most common sites: right side of the bowel, terminal ileum, ileocecal valve, and cecum. The **initial presentation of Crohn's disease** may resemble **acute appendicitis**, particularly when the **terminal ileum is involved.**
  - Small intestine alone 40%
  - Small intestine and colon 30%
  - Colon only 30%.
    These 30% are hard to be distinguished from ulcerative colitis.
  - Skip lesions
  - Strictures common.
    They develop when **transmural inflammation** is followed by **fibrotic healing**, which leads to **narrowing of the affected bowel segment**



This finding represents a **stricture**, which is a recognized complication of **Crohn's disease**. In this condition, chronic transmural inflammation leads to **fibrosis and thickening of the bowel wall**, causing narrowing of the **intestinal lumen**.
Grossly, the affected segment may show:

- Marked **luminal narrowing**
- Thickened bowel wall
- **Yellowish discharge** or a yellowish membrane-like inflammatory material on the surface

Strictures may impair the passage of intestinal contents and can result in **partial or complete mechanical obstruction**.
This complication is characteristic of **Crohn's disease** and is **not typically seen in ulcerative colitis**.
Surgical resection is often required to **relieve or prevent intestinal obstruction**.

Small bowel stricture.

- Earliest lesion: Superficial aphthous ulcer, then:
- **Crohn's disease** is characterized by **elongated, deep serpentine ulcers**, often accompanied
  by **fissures**.
- These lesions may **perforate through the bowel wall**, potentially forming **abscesses** or causing **peritonitis** if bowel contents leak into the **peritoneal cavity**.
- Edema, loss of bowel folds.
- Cobblestone appearance produced by elevated areas of relatively normal mucosa separated by intervening linear ulcerated areas. The "stones" are preserved mucosa, while the depressed areas represent ulcers. This is characteristic of Crohn's disease and not seen in ulcerative colitis.
- Toxic megacolon (before fibrosis). It is a condition marked by **massive colonic dilation** with a high risk of **perforation**. It occurs more commonly in **ulcerative colitis**, where the **colonic wall is thin and inflamed**. In contrast, the **fibrosis and wall thickening** seen in **Crohn's disease** may reduce the risk of perforation in such cases.

•Fissures (fistulas, perforations),transmural ulcers may penetrate the bowel wall causing perforation, adhesions, or fistula formation.

•Fistulas may occur between:

Different bowel segments

Bowel and urinary bladder

Bowel and uterus.

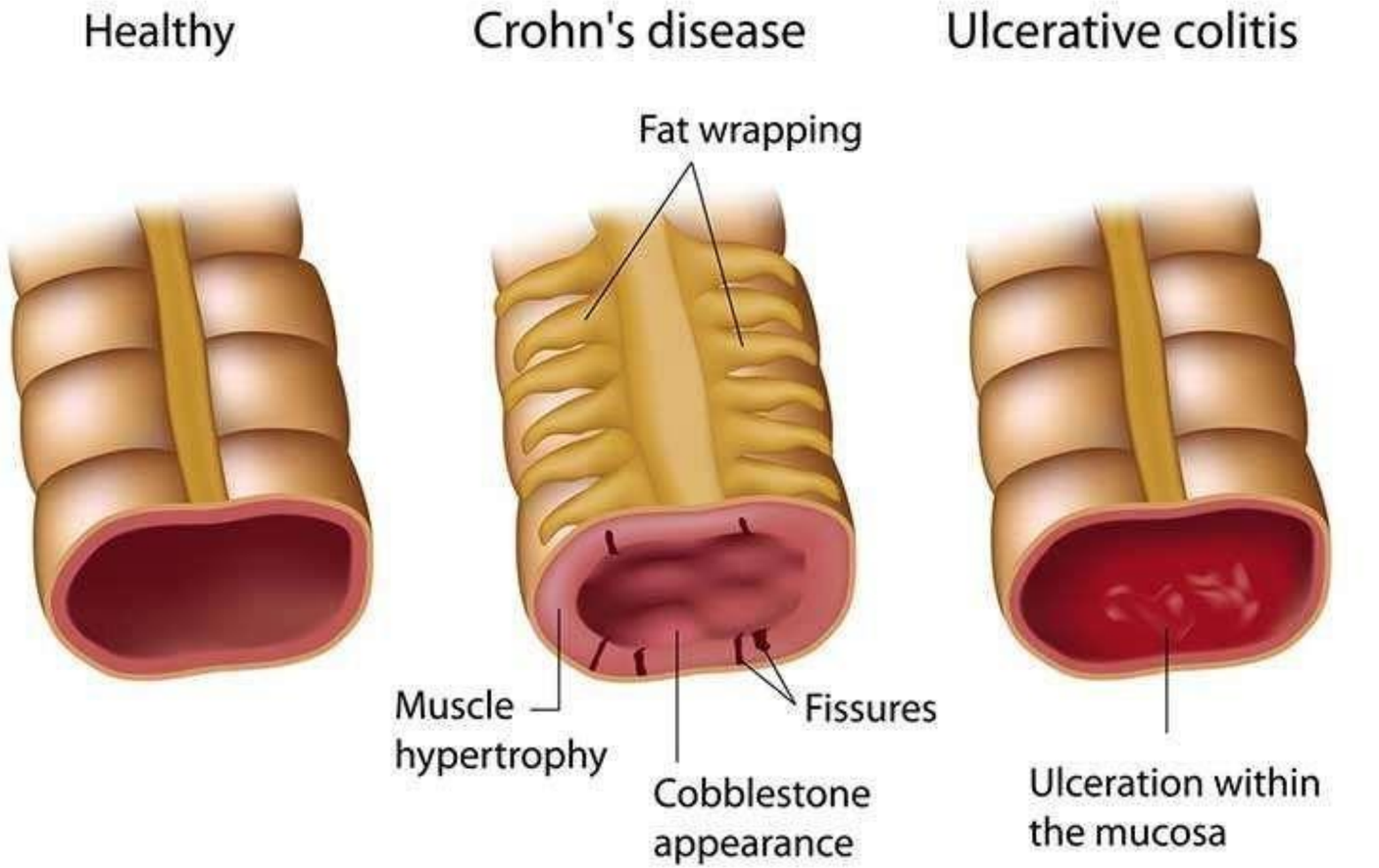
- Thick bowel wall ,which is much more prominent than in ulcerative colitis, (due to transmural inflammation, edema, fibrosis, hypertrophic MP) >> This thickening may contribute to **stricture formations.**
- Creeping fat caused by transmural inflammation, and it can reach the serosa.

Supports Crohn's disease

Cobblestone appearance

ResearchGate

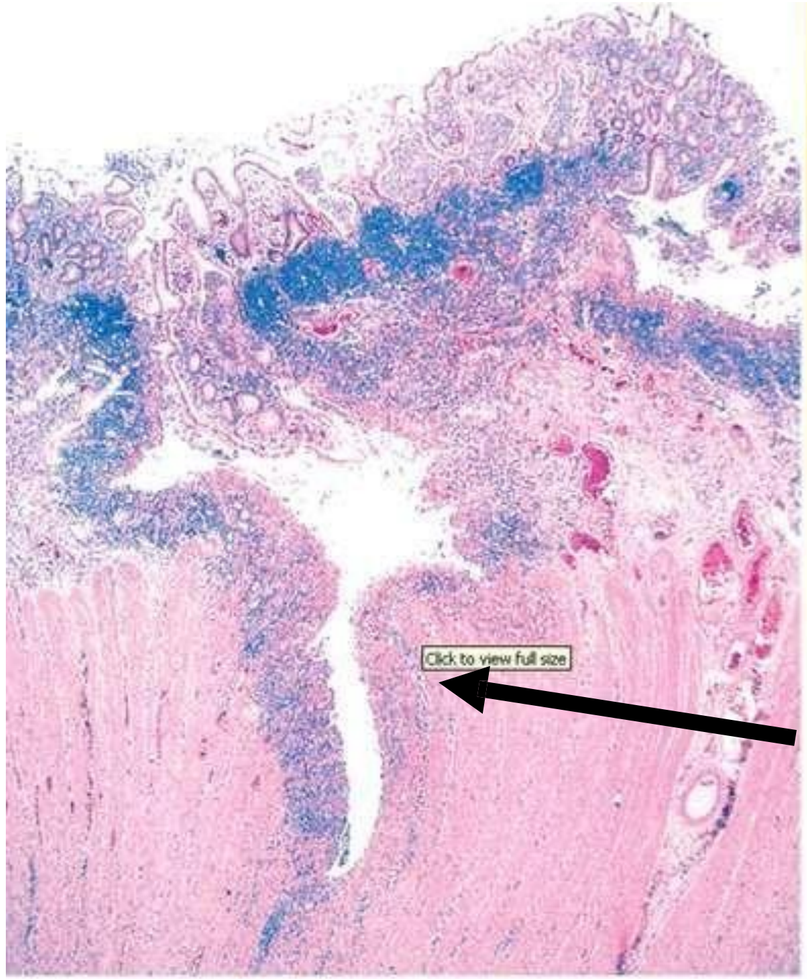
Cobblestone appearance: the elevated areas are normal and depressed are ulcers, usually seen with colonoscopy.



Deep ulcers

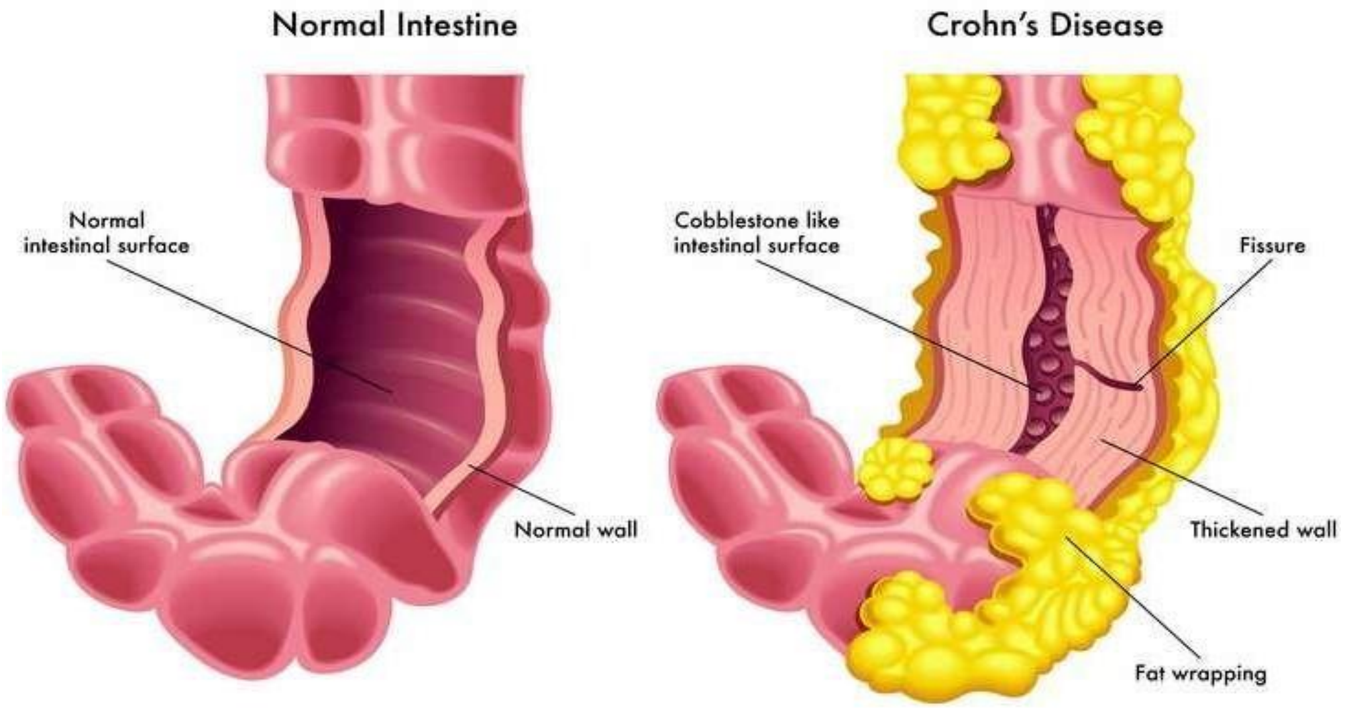
shallow ulcers

fissure



Crohn disease of the colon showing a deep fissure extending into the muscle wall, a second, shallow ulcer (upper right), and relative preservation of the intervening mucosa. Abundant lymphocyte aggregates are present, evident as dense blue patches of cells at the interface between mucosa and submucosa

Notice how the fissure is deep and reaches the muscles which can cause perforation then peritonitis and peritoneal abscess.



Creeping fat

This illustration shows the characteristic **"cobblestone" appearance** of the mucosa and a markedly **thickened, fibrotic bowel wall** due to **transmural inflammation** in **Crohn's disease**.

Cobblestone appearance

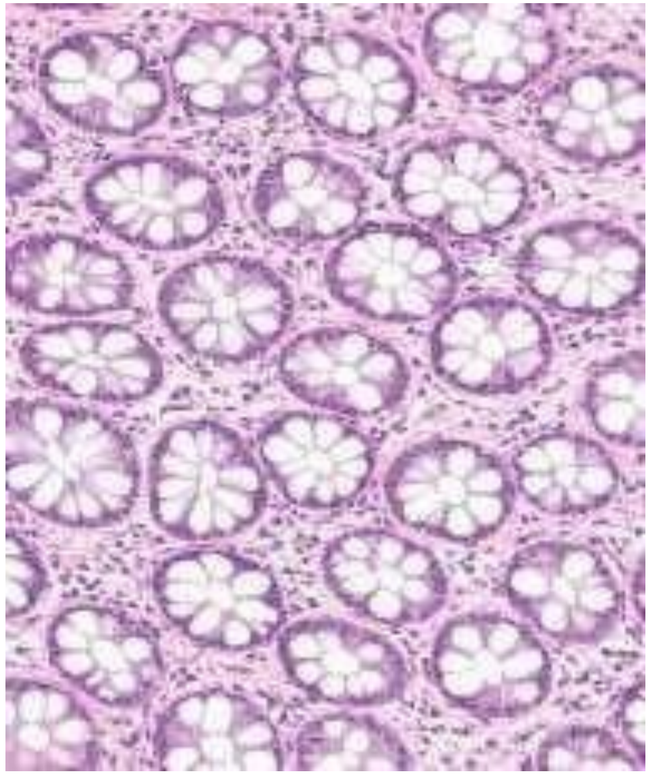
Supports Crohn’s disease

ResearchGate

Cobblestone appearance: the elevated areas are normal and depressed are ulcers, usually seen with colonoscopy.

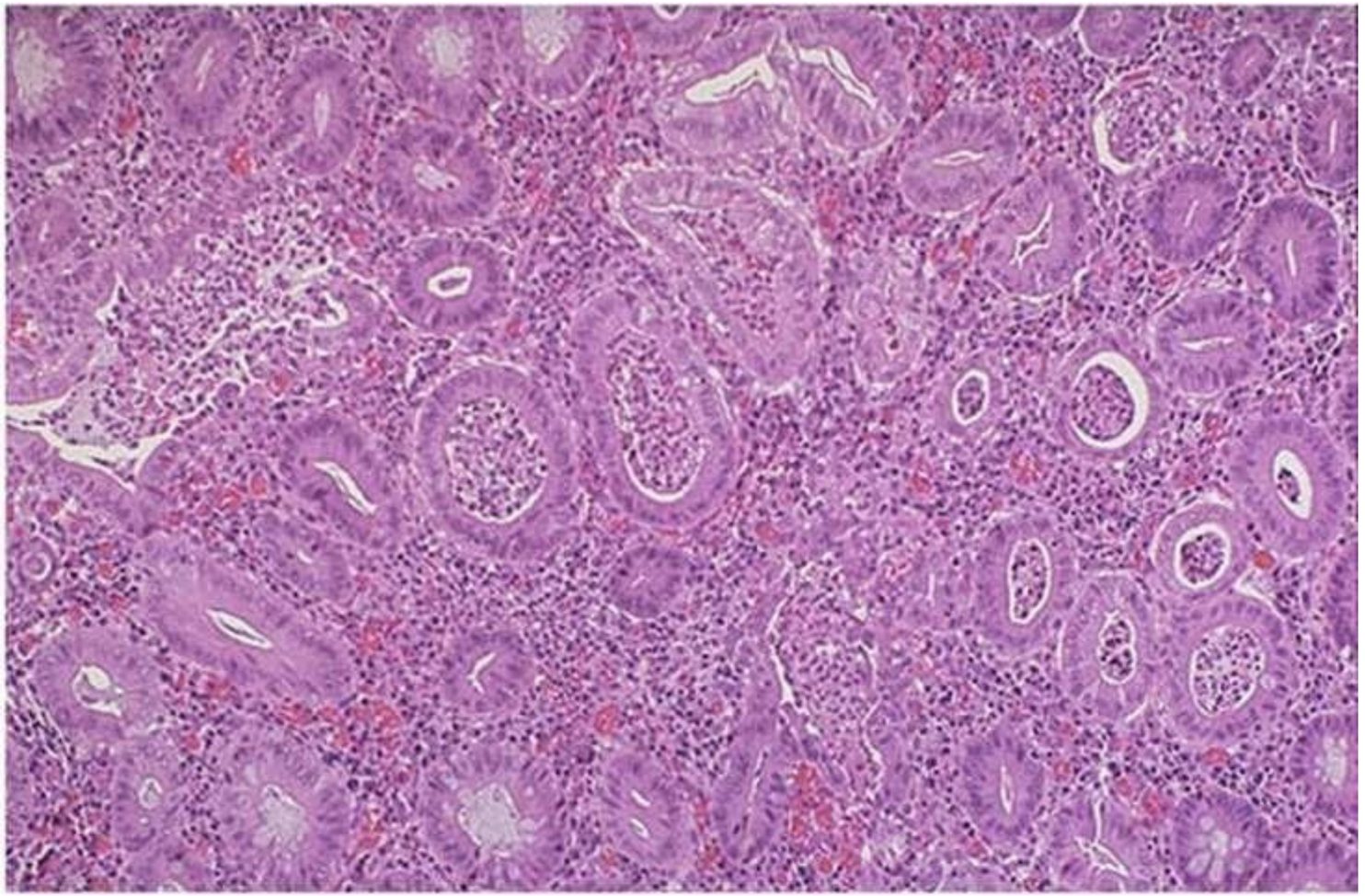
Microscopic:

- Neutrophils in active disease.
- Crypt abscesses.
- Ulceration.
- Distortion of mucosal architecture (repeated cycles)
  This is the **most important feature to observe**, as the diagnosis of **chronic inflammatory bowel disease** requires **evidence of chronicity**, such as **architectural distortion** of the crypts.
- Paneth cell metaplasia in left colon
  Normally, Paneth cells are found in the **small intestine** and extend only up to the **transverse colon**. If Paneth cells are seen in a **rectal or sigmoid biopsy**, this indicates **chronic inflammation**, as they are **not normally present** in this region. Their appearance reflects **metaplasia** —a chronic adaptive response in which **Paneth cells develop in an abnormal location**.
- Mucosal atrophy.
- Non-caseating granulomas (hallmark) only in 35% of cases. Can be seen anywhere, even in normal GIT tissues or lymph nodes draining the colon and small bowel!!



Normal colon

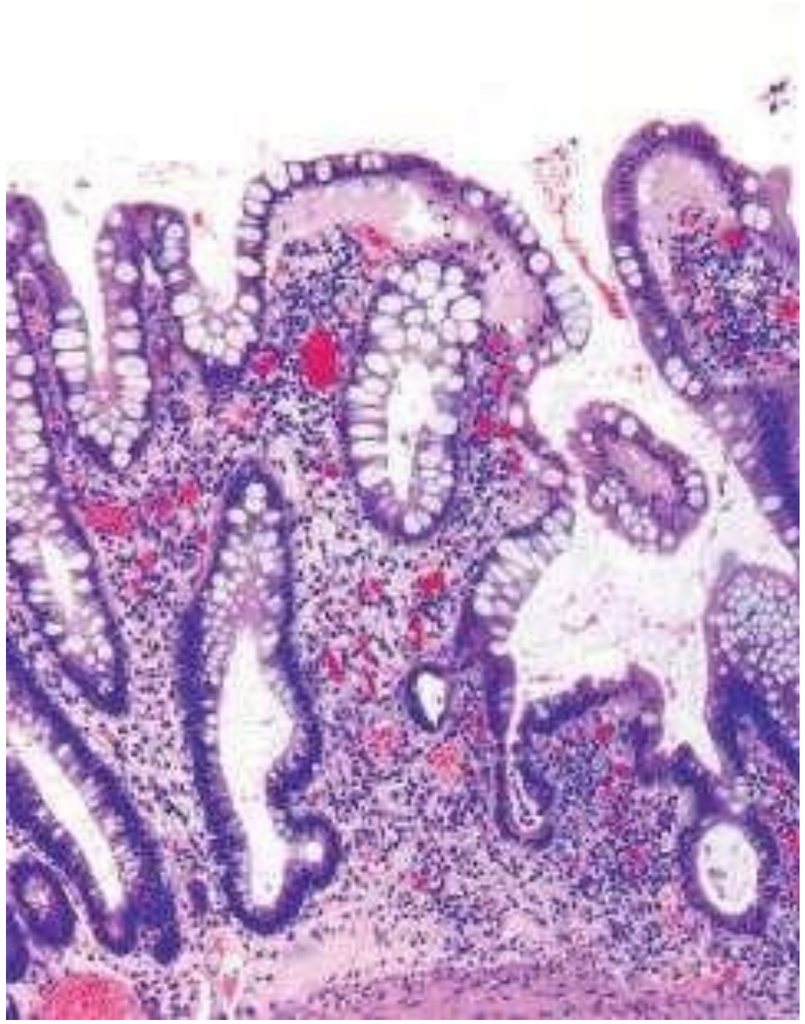
In a **normal colon**, the **crypts are closely packed, organized rounded, and aligned vertically**, extending **down to the muscularis mucosae**.



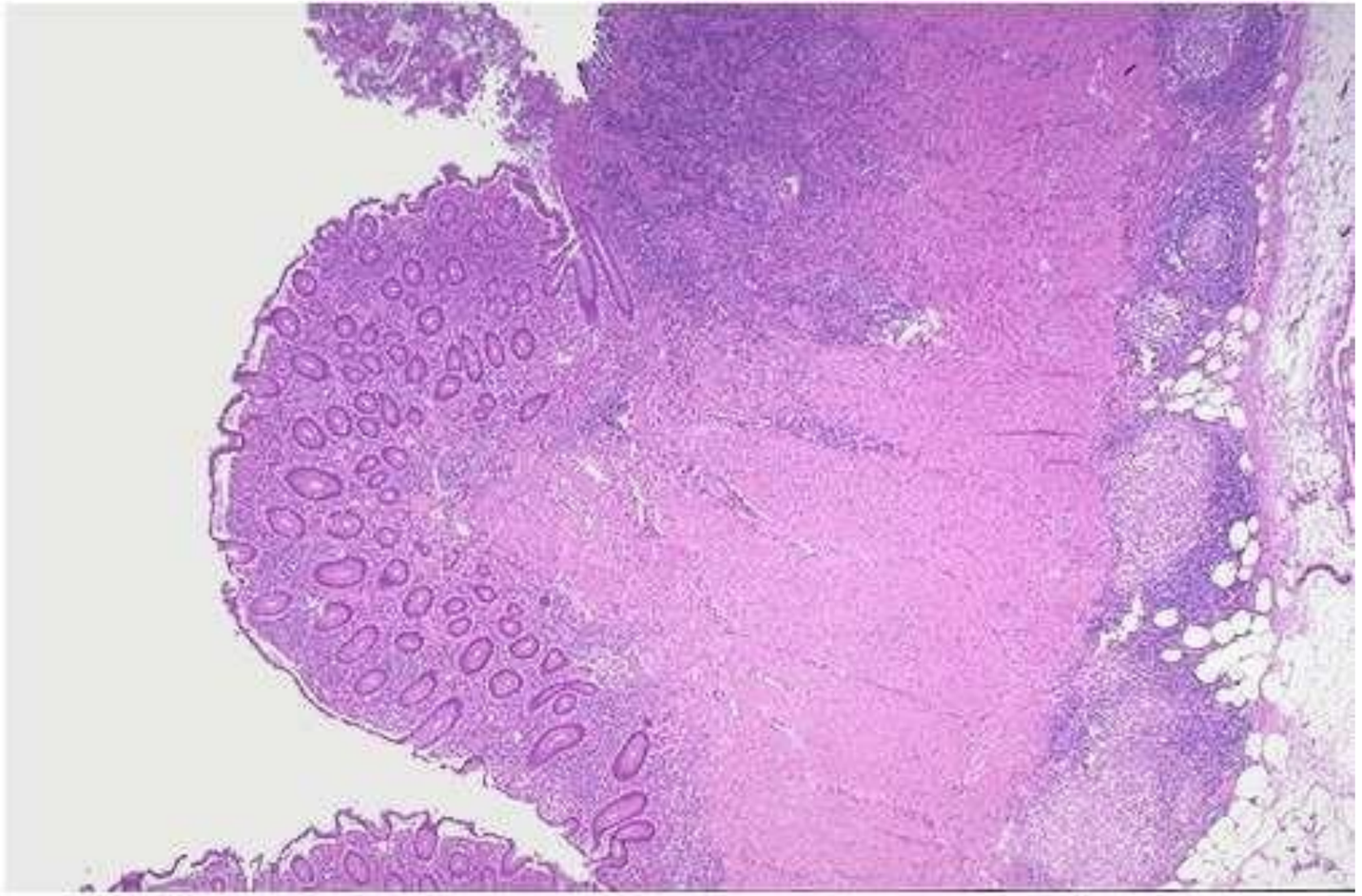
Here, we can observe **numerous neutrophils within the lumen of the crypts**, forming **crypt abscesses**. This finding indicates **active and acute inflammation**, which might be an infection.

Haphazardly arranged crypts

- In **chronic inflammatory bowel disease**, the **crypts of the colonic mucosa appear haphazardly arranged.**
- This feature is **characteristic and supportive** of IBD.

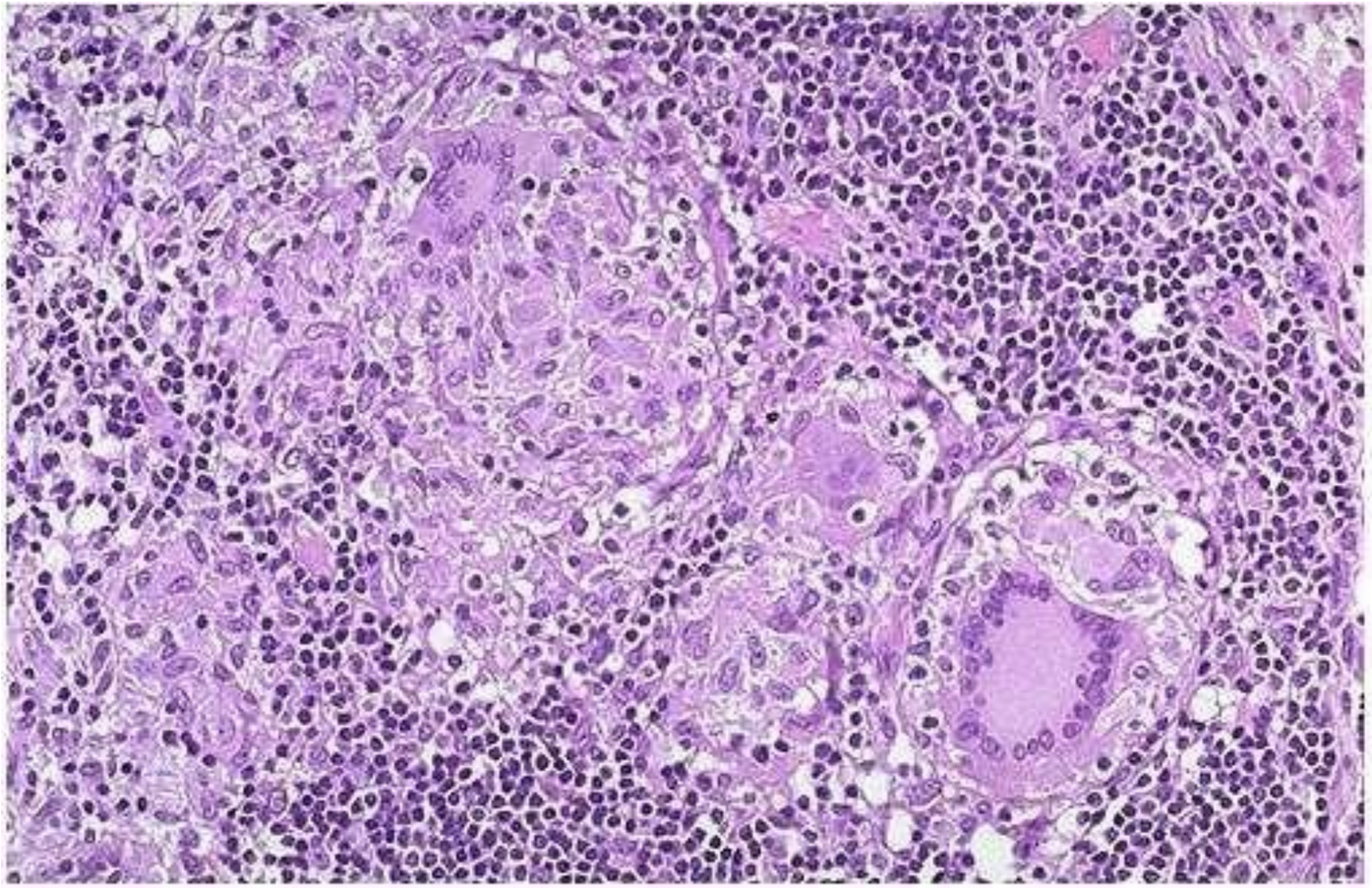


IBD = Inflammatory Bowel Disease



Transmural inflammation.

This section shows transmural inflammation, with inflammatory infiltrates extending from the lymphoid aggregates to the serosal surface.



Non-caseating granuloma.

A **granuloma** is a collection of **epithelioid histiocytes**, often containing **multinucleated giant cells**. In **Crohn's disease**, these granulomas are typically **non-caseating**.
Reminder: The presence of a **caseating granuloma** should raise suspicion for **tuberculosis**.

Clinical Features

- Intermittent attacks of mild diarrhea, fever, and abdominal pain.
- Asymptomatic intervals between attacks (weeks to months).
- In approximately **20% of Crohn's disease cases**, the disease involves the **terminal ileum, ileocecal region, and cecum**, presenting with symptoms that **mimic acute appendicitis**, such as acute right lower-quadrant pain and fever (20%).
- Bloody diarrhea and severe abdominal pain (colonic disease).
- Triggers: Infections, physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking.

Complications:

- Colonic: Iron-deficiency anemia, happens due to ulcerations and bleeding.
- Small bowel: Hypoproteinemia and hypoalbuminemia, malabsorption of nutrients, vitamin B12, folate and bile salts
- Fistulas, peritoneal abscesses, strictures:
  - A **fissure** (deep mucosal ulcer) can **extend and perforate**, forming a **fistula** — an abnormal connection between two bowel loops (**enteroenteric**) or between the bowel and other structures, such as the **skin** (**perianal fistula**).
    Perianal fistulas are particularly common in Crohn's, and any patient presenting with one should be **evaluated for Crohn's disease**.
  - A **peritoneal abscess** may form if a fissure or ulcer **perforates** and leaks bowel contents into the peritoneal cavity.
  - These complications **do not occur in ulcerative colitis**, as its inflammation is **limited to the mucosa and submucosa**.
- Risk of colonic and small intestinal Adenocarcinoma, Usually after 8-10 years of diagnosis, so we must do screenings for these patients.

Extra intestinal manifestations

Immune-mediated disease → immune-mediated symptoms

- Uveitis
- Migratory polyarthritis,
- Sacroiliitis of sacroiliac joint.
- Ankylosing spondylitis (immune mediated rheumatological disorder)
- Erythema nodosum: tender (painful with touch) red elevated region
- Clubbing of the fingertips. It refers to an **increased convexity of the nail** at the fingertips.
- Primary sclerosing cholangitis (more with Ulcerative Colitis [UC])
  - It is inflammation of the bile ducts in the liver.
  - Patients may present with jaundice as well.

Erythema nodosum

Neurology Advisor

Clubbing

Wikipedia

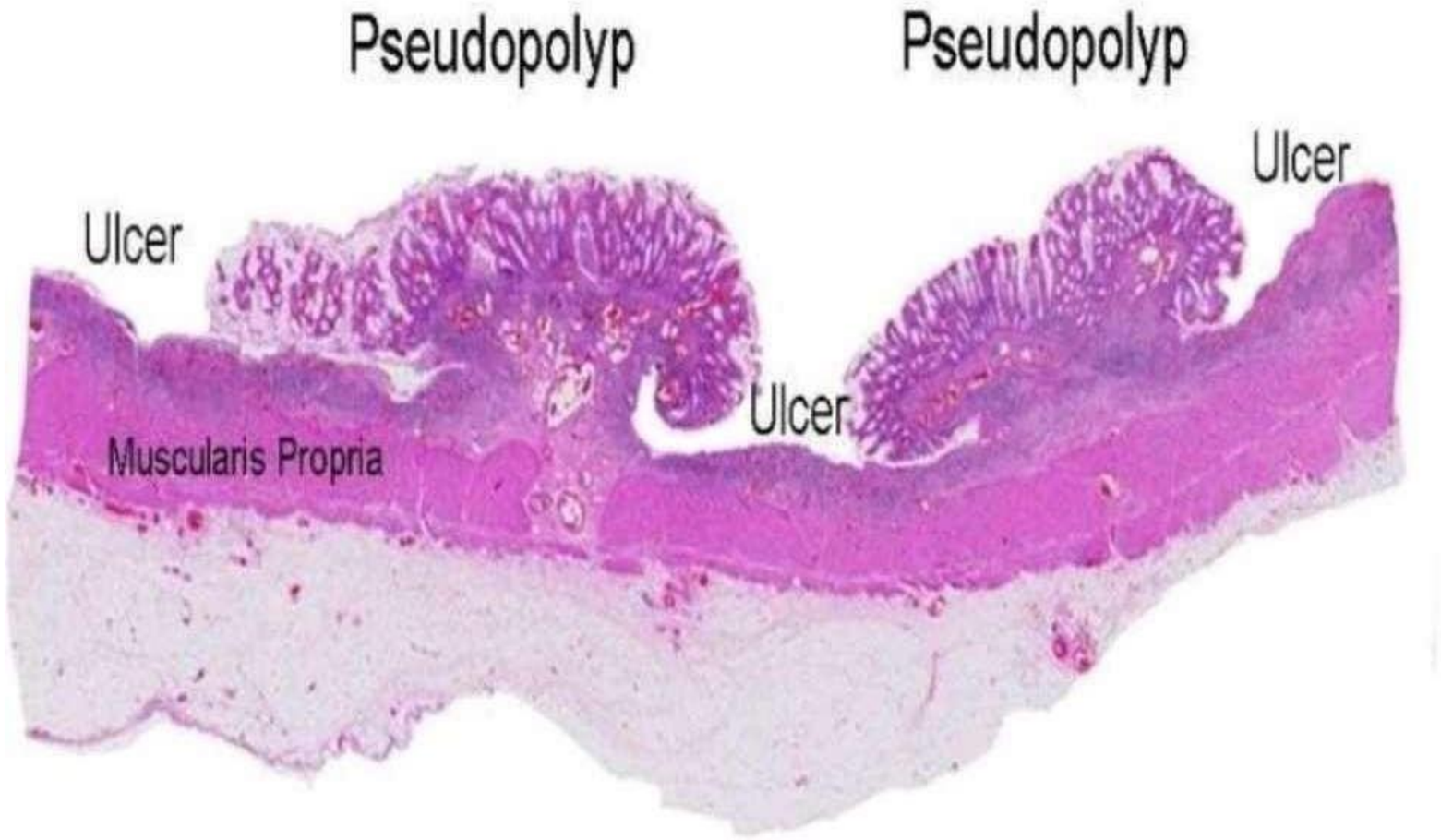
Ulcerative Colitis Morphology

- Only affects the colon & always involves the rectum.
- Extends proximally in continuous pattern.
- No skip lesions. They may present in severe cases of **pan colitis**.
- Pan colitis. Refers to inflammation involving the entire colon.
- Occasionally focal appendiceal or cecal inflammation.
- In some patients with **pan colitis**, the inflammation may also involve the **terminal ileum**, a condition known as **backwash ileitis**.
- Limited diseases: Ulcerative proctitis (rectum) or ulcerative Proctosigmoiditis (rectum and sigmoid)
- Small intestine is normal (except mild backwash ileitis, a feature of UC, not Crohn's disease. In contrast, **Crohn's disease commonly involves a larger portion of the terminal ileum**, with **more extensive and transmural changes**.)

Ulcerative Colitis Morphology

- Macroscopic: opposite to Crohn's disease
- No fissures, fistulas, perforations, strictures, granulomas or transmural inflammation.
- Broad-based ulcers.
- Pseudo polyps (due to regenerating mucosa)
- Mucosal atrophy in long standing
- Mural thickening absent
- Serosal surface normal
- No strictures
- Toxic megacolon (damage of MP, disturbed neuromuscular function) associated with UC due to atrophied/thin wall and leads to a higher risk of perforation.

It is **not a true polyp**, but a **pseudopolyp**, which appears elevated because the **surrounding mucosa is ulcerated**. The **remaining intact or regenerating mucosa** stands out between ulcers, creating a **polyp-like appearance**.



Toxic megacolon

Microscopic:

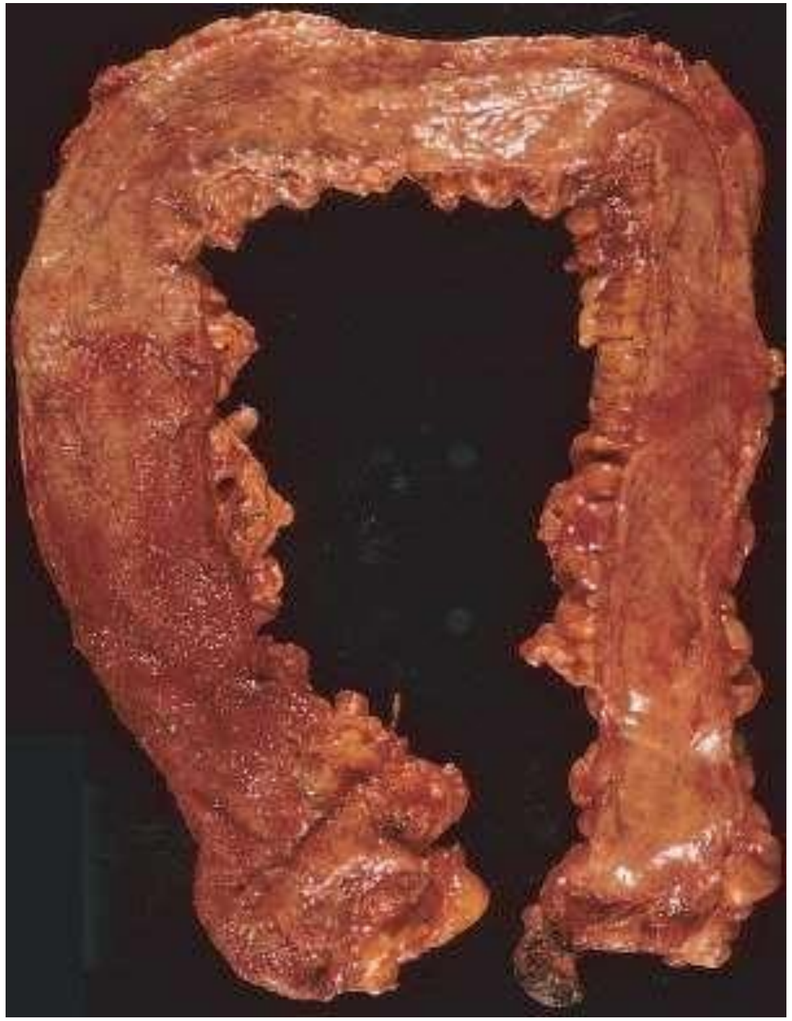
Similar to Crohn's disease

- Chronic inflammatory changes
- Ulcerations
- Inflammatory infiltrates, neutrophils in acute attacks.
- Crypt abscesses
- Crypt architecture distortion
- Epithelial metaplasia
  - Paneth cell metaplasia in the left side of the colon.
- Submucosal fibrosis
- Inflammation limited to mucosa and submucosa.
- No skip lesions
- No granulomas. Only in Crohn's disease.

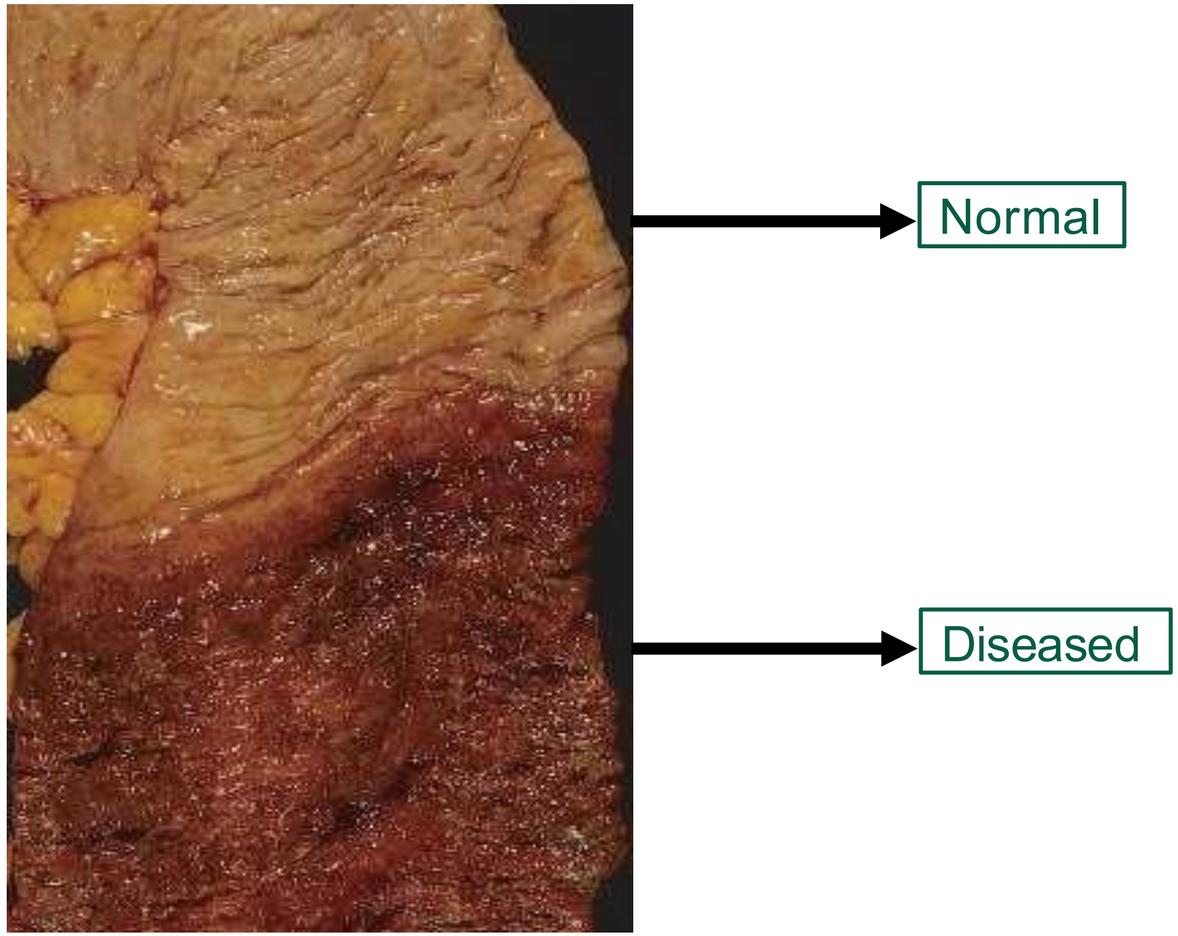
Mucopurulent material and ulcers.

In a colonoscopy we see mucus, purulent material

Pancolitis.



Abrupt transition between normal and diseased segment.



Clinical Features

- It is often **difficult to differentiate clinically between Crohn's disease and ulcerative colitis**, as both can present with **acute flares** triggered by factors such as **infections, viral gastroenteritis, or stress**. Patients are typically **asymptomatic between attacks**.
- In **ulcerative colitis**, there are **always colonic manifestations**, since the disease is limited to the **colon and rectum**. Symptoms may include **abdominal pain, fever, diarrhea**, and **bloody diarrhea**.
- **Malabsorption is not a feature** of ulcerative colitis, as the **small intestine is not involved.**
- Relapsing remitting disorder
- Attacks of bloody mucoid diarrhea +lower abdominal cramps
- Temporarily relieved by defecation
- Attacks last for days, weeks, or months.
- Asymptomatic intervals.
- Infectious enteritis may trigger disease onset, or cessation of smoking. The reason is not well understood.
- **Colectomy**, performed for complications such as **toxic megacolon, dysplasia, or carcinoma**, can **cure the intestinal disease** of **ulcerative colitis only**. However, **extraintestinal manifestations** may **persist** after surgery.
- Anti-inflammatory and biologic agents, immune-modulating drugs like steroids or some immunotherapy.

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			