PATHOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 6

# Chronic Inflammatory Diseases of the Intestine

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا


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# QUIZ

# Intestinal pathology, part 2

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**Each underlined term serves as a hyperlink.**

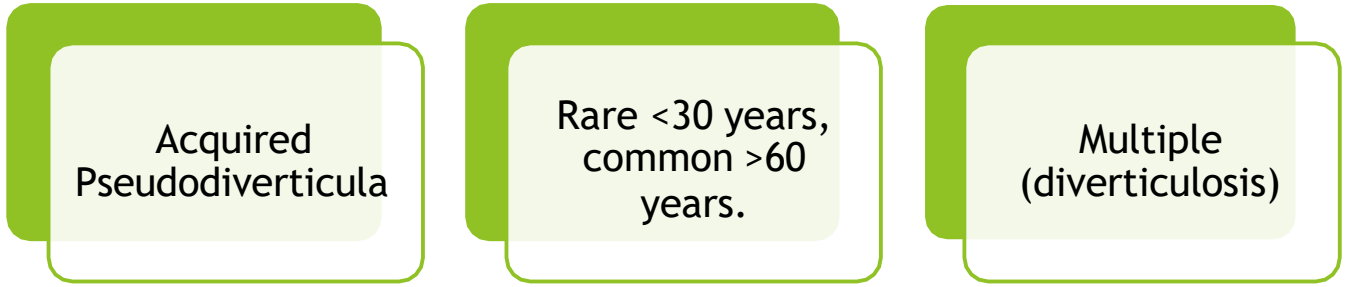
# Diseases of the intestines

- 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

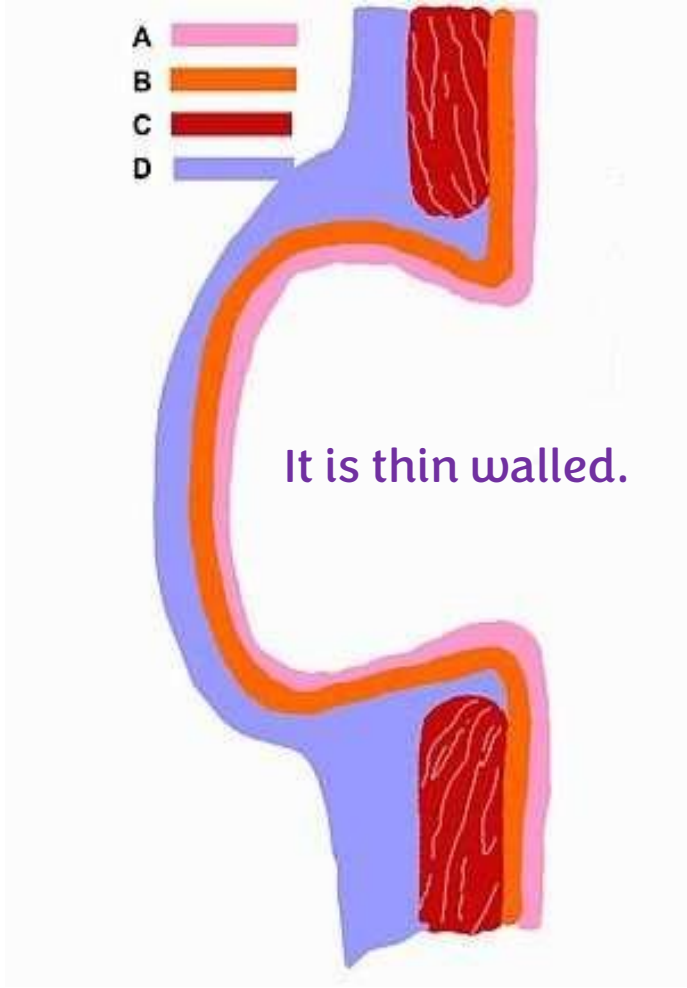
When multiple diverticula are present, the condition is called **diverticulosis**. If these diverticula become inflamed, it is known as **diverticulitis**.

- 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.

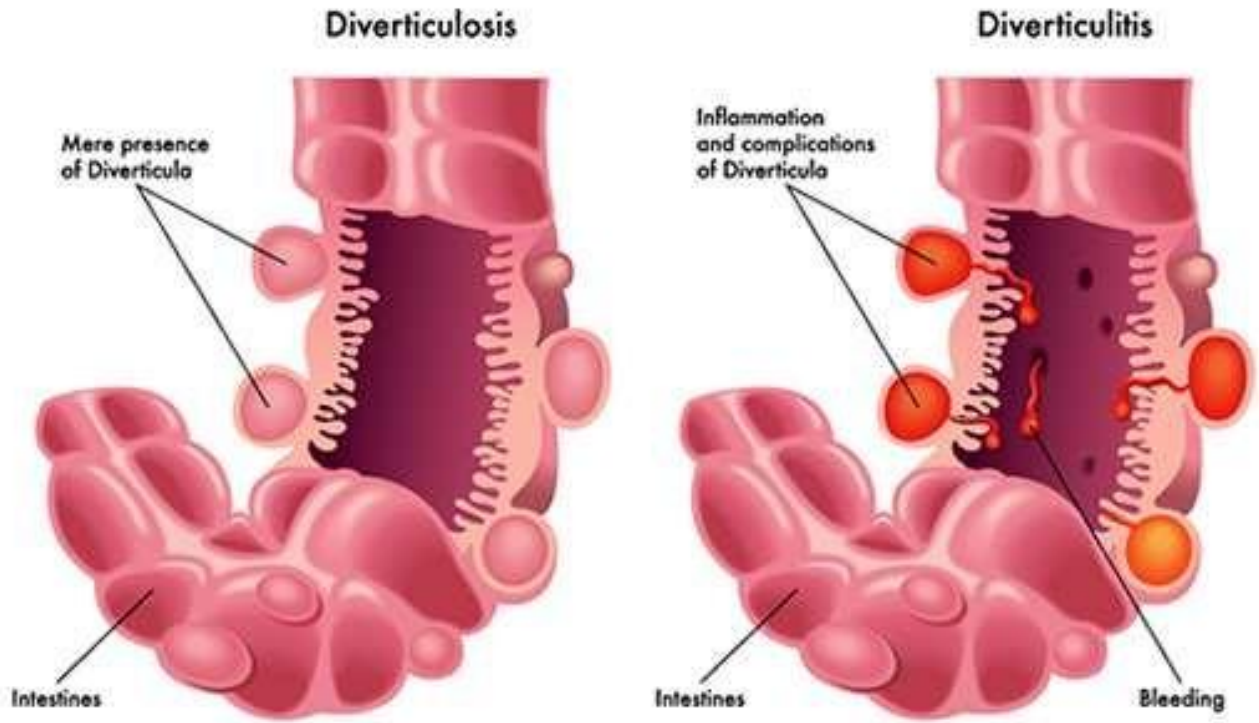
- Chronic constipation causes **exaggerated peristaltic contractions and increased intraluminal pressure**. This pressure can lead to **herniation of the mucosa and submucosa through weak areas in the muscular layer** of the colon wall.

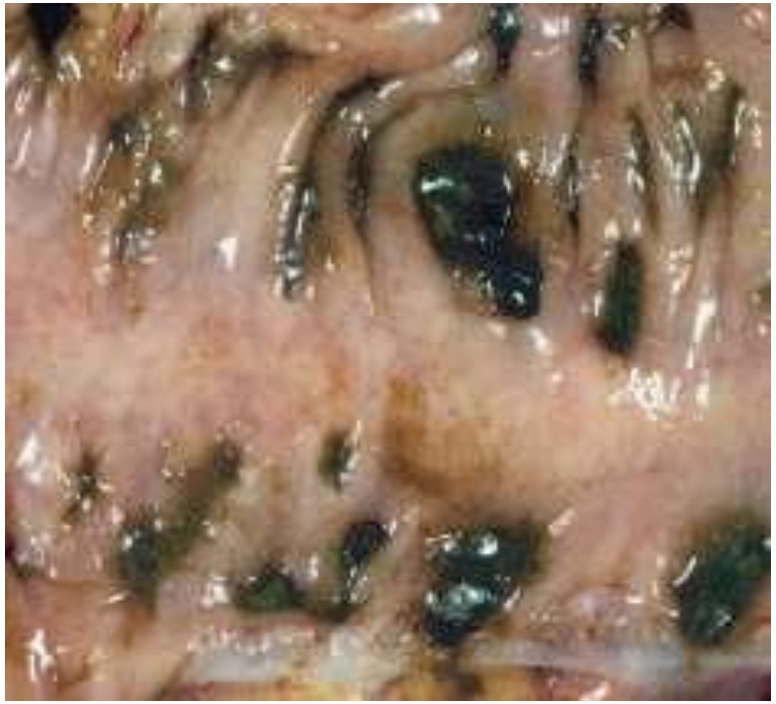
# MORPHOLOGY

- 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).




- 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

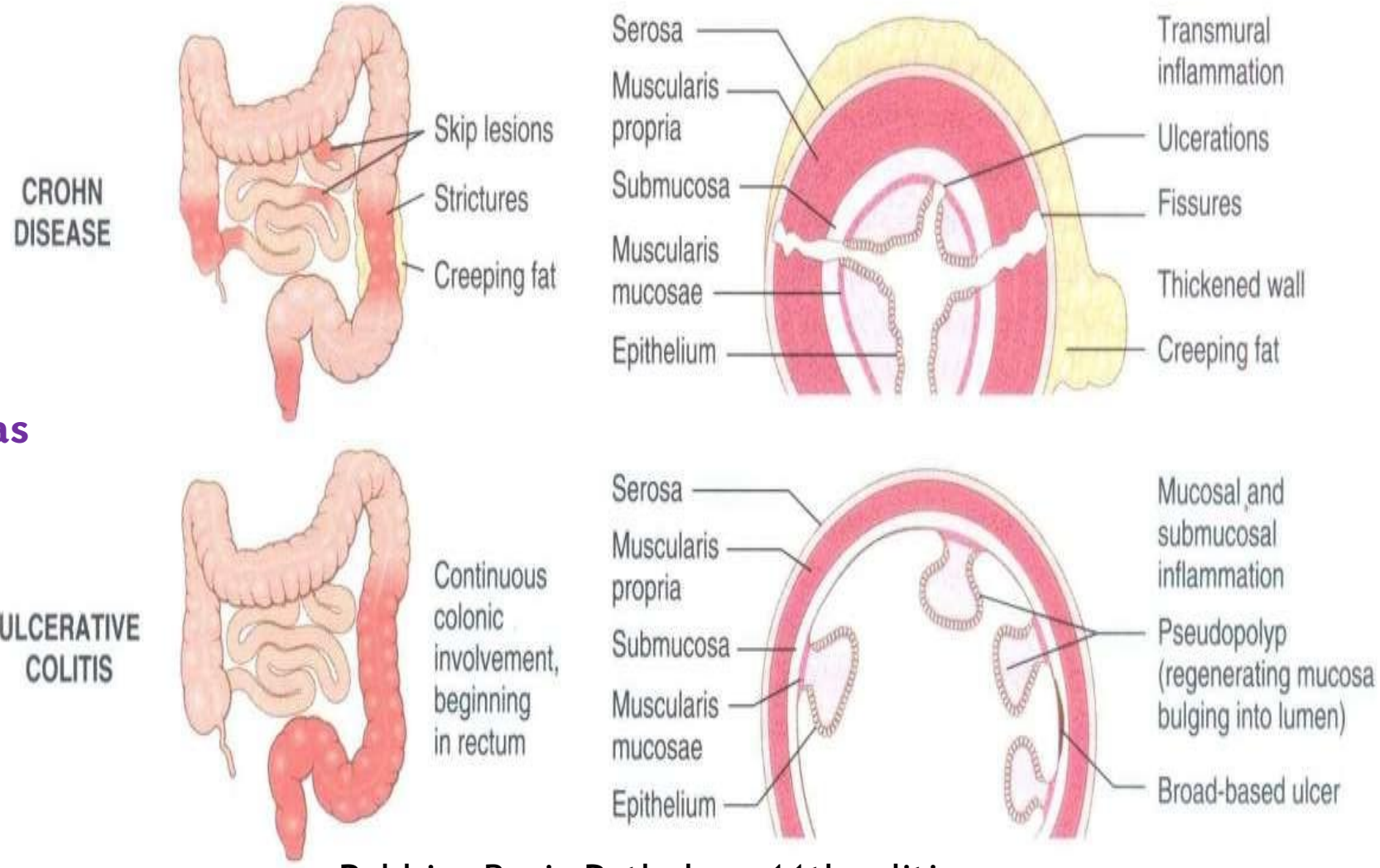
- Mostly asymptomatic.
- Intermittent lower abdominal pain
- Constipation or diarrhea.
- Patients usually **do not experience symptoms from diverticulosis itself**, they rather complain from **constipation.**
- However, if the diverticula become inflamed (**diverticulitis**), **abdominal pain** – typically 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

- 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.
  - 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, frequent ileal involvement, affect any area in GIT, frequently transmural.
  - **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** is characterized by **segmental involvement with skip lesions**. The **inflammation is transmural**, affecting **all layers of the bowel wall**.
- **Wall thickening** occurs due to **inflammation, edema, and fibrosis**. The **muscularis and serosa can be involved**, and the **mucosa may develop deep, linear ulcers known as fissures**.

- **Ulcerative colitis** always begins in the **rectum**, which is **consistently involved**, and it spreads **proximally in a continuous pattern**.
- The bowel wall remains **thin**, as the inflammation is **limited to the mucosa and submucosa**.
- The disease causes **shallow, superficial ulcers** confined to the mucosal surface.




Robbins Basic Pathology 11th edition

# Epidemiology

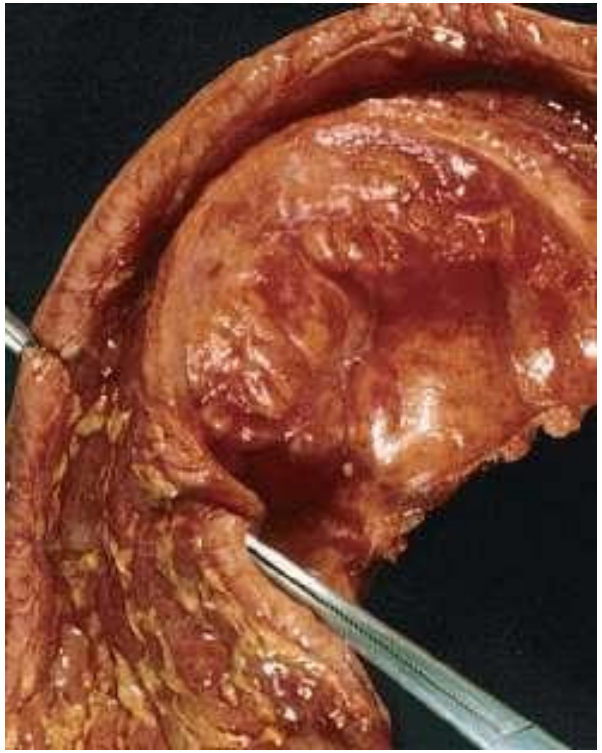
- Adolescence & young adults
- 2nd peak in fifth decade, although it is uncommon.
- Geographic variation.
- Proposed explanation:
  - **Hygiene hypothesis**: childhood exposure to environmental microbes prevents excessive immune system reactions. Firm evidence is lacking!!!.

# Pathogenesis:

- Combined effect of:
  - Altered host interaction with intestinal microbiota.
  - Intestinal Epithelial dysfunction
  - Aberrant mucosal immune responses.
    - Aberrant: Exaggerated.
      This means that *even* **commensal or low-virulence organisms** can **trigger an immune response**, due to the **abnormal immune reactivity** seen in inflammatory bowel disease.

# Crohn's Disease Morphology

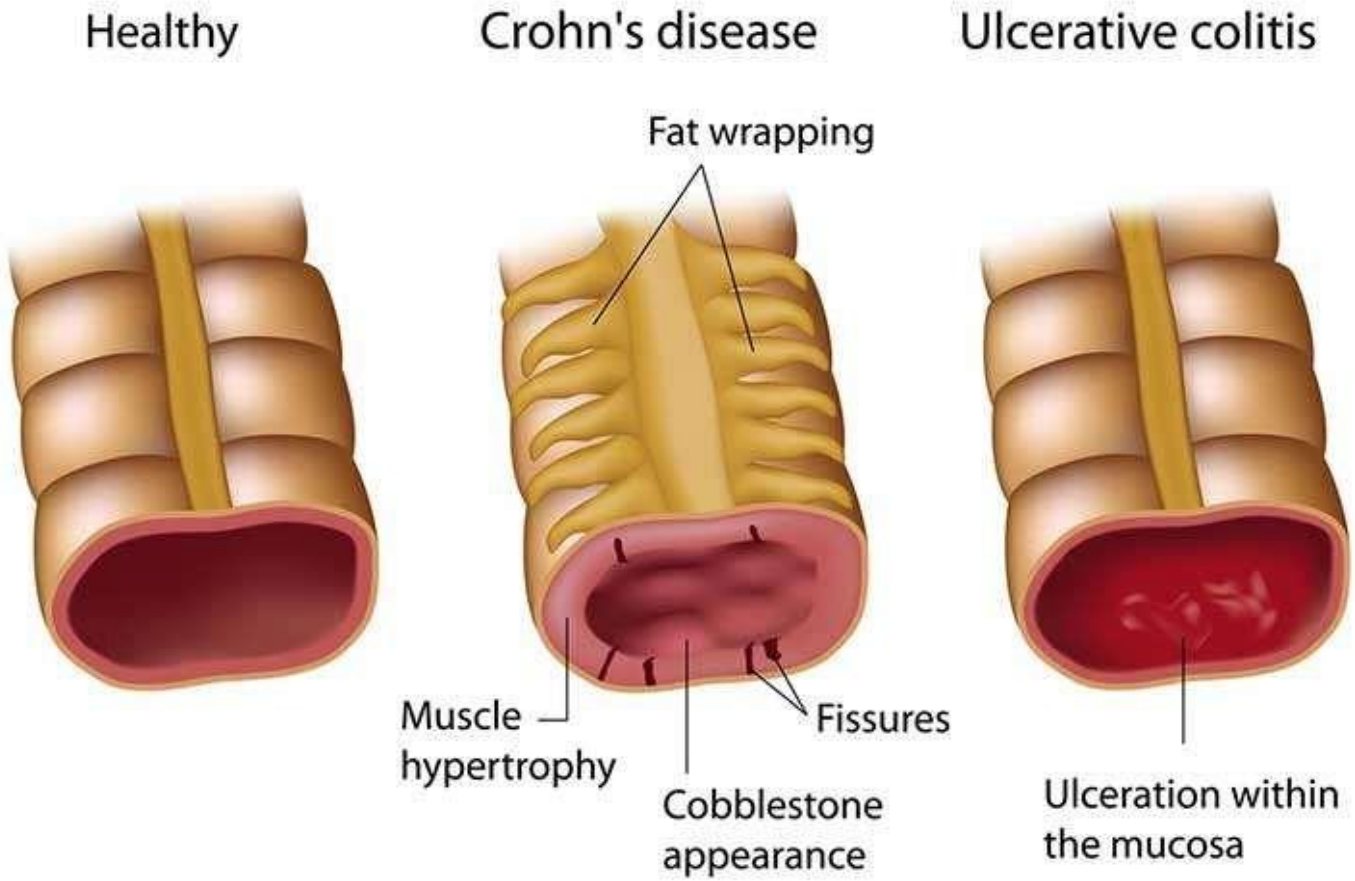
- Macroscopic:
  - Regional enteritis.
  - Any area of GIT.
  - Most common sites: right side of the bowel, terminal ileum, ileocecal valve, and cecum.
    The **initial presentation of Crohn's disease** may resemble **acute appendicitis**, particularly when the **terminal ileum is involved.**
  - Small 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**.



# Small bowel stricture.

This image shows a **fibrotic stricture of the small bowel**, a complication of **Crohn's disease**. **Surgical resection** is often required to **relieve or prevent intestinal obstruction**.

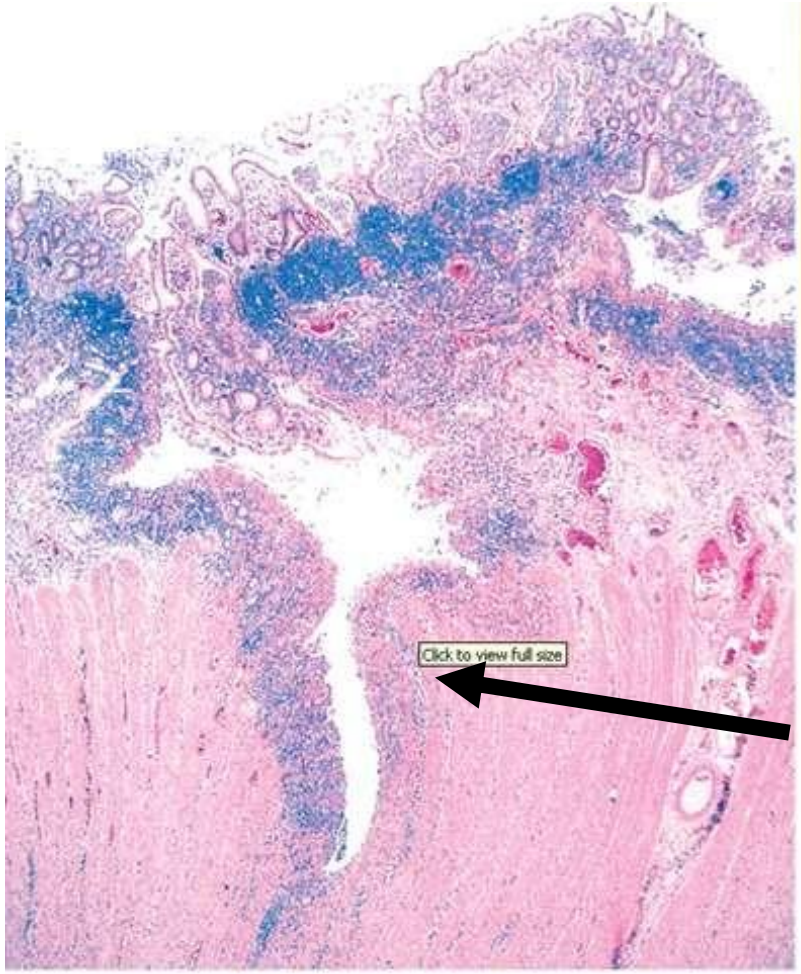
- Earliest lesion: Superficial aphthous ulcer, then:
- **Crohn's disease** is characterized by **elongated, deep serpentine ulcers**, often accompanied by **fissures**.
- These lesions may **perforate through the bowel wall**, potentially forming **abscesses** or causing **peritonitis** if bowel contents leak into the **peritoneal cavity**.
- Edema, loss of bowel folds.
- Cobblestone appearance
- 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).
- Thick bowel wall (transmural inflammation, edema, fibrosis, hypertrophic MP) >> strictures.
- Creeping fat caused by transmural inflammation, and it can reach the serosa.




Deep ulcers

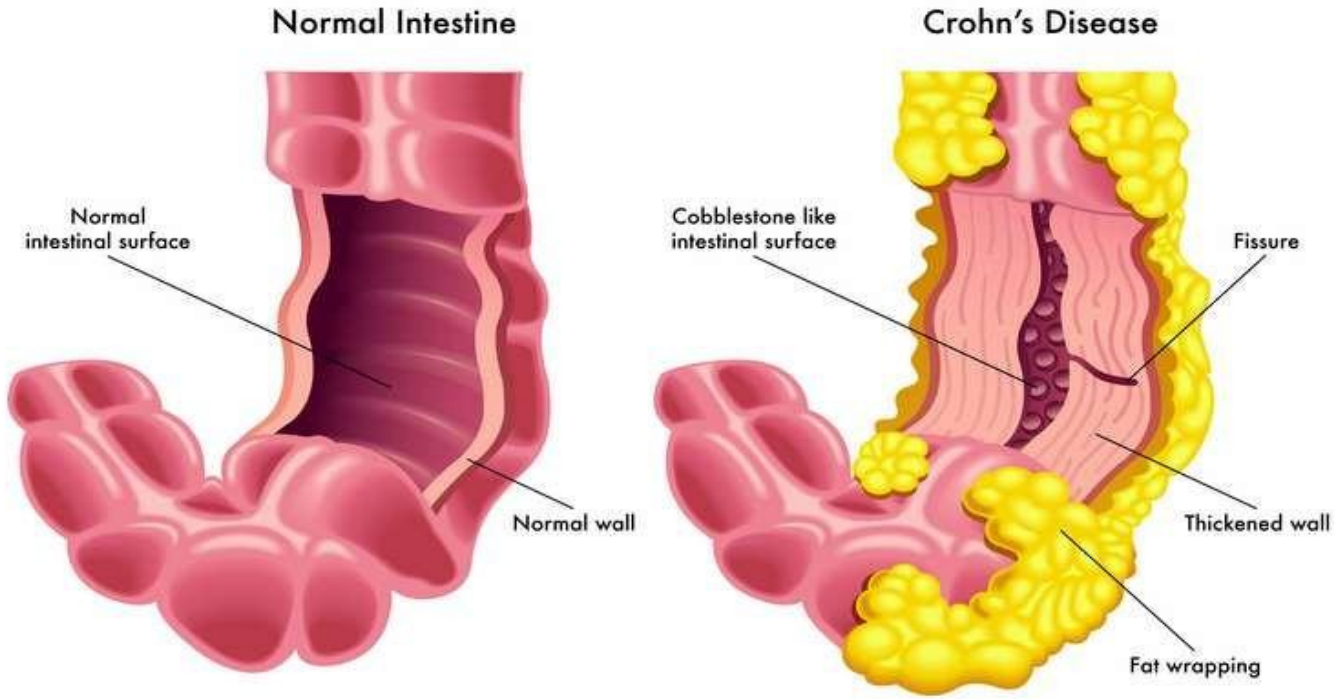
shallow ulcers

# 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

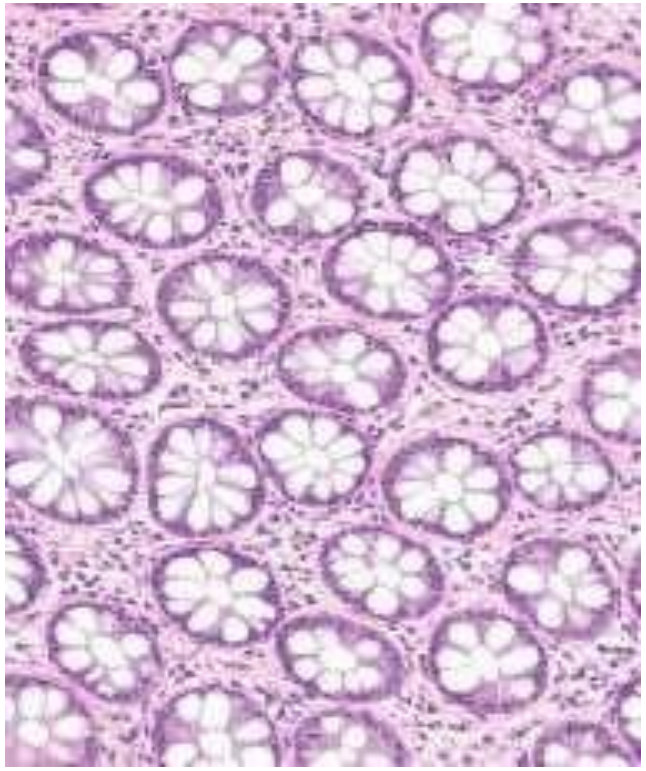
Supports Crohn's disease

ResearchGate

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

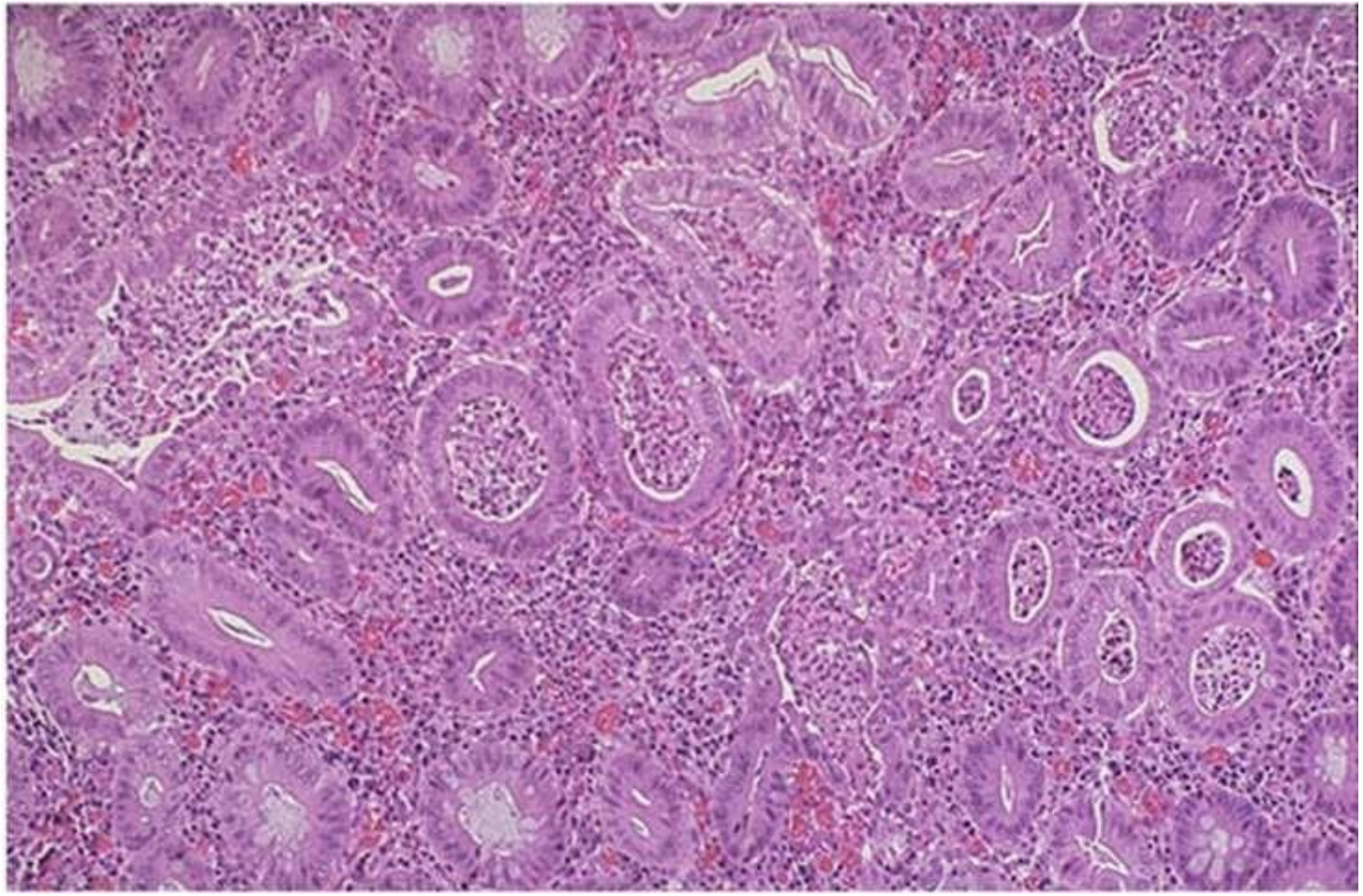
# Microscopic:

- 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

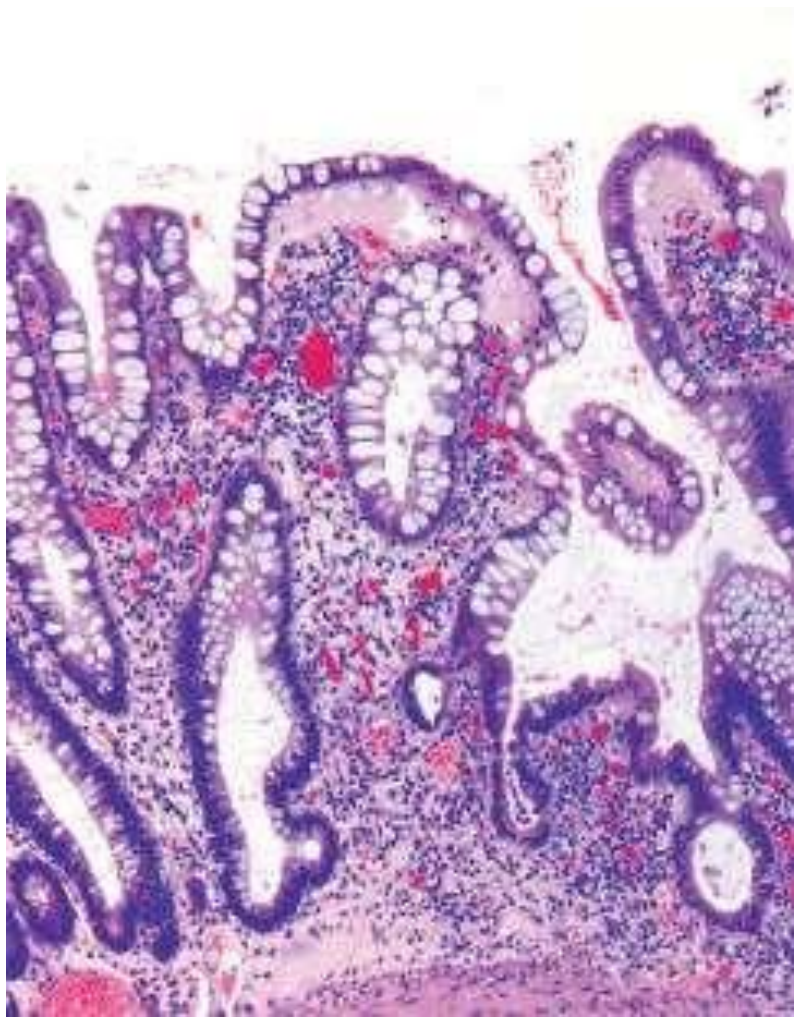
In a **normal colon**, the **crypts are closely packed, organized rounded**, and aligned vertically, extending **down to the muscularis mucosae**.



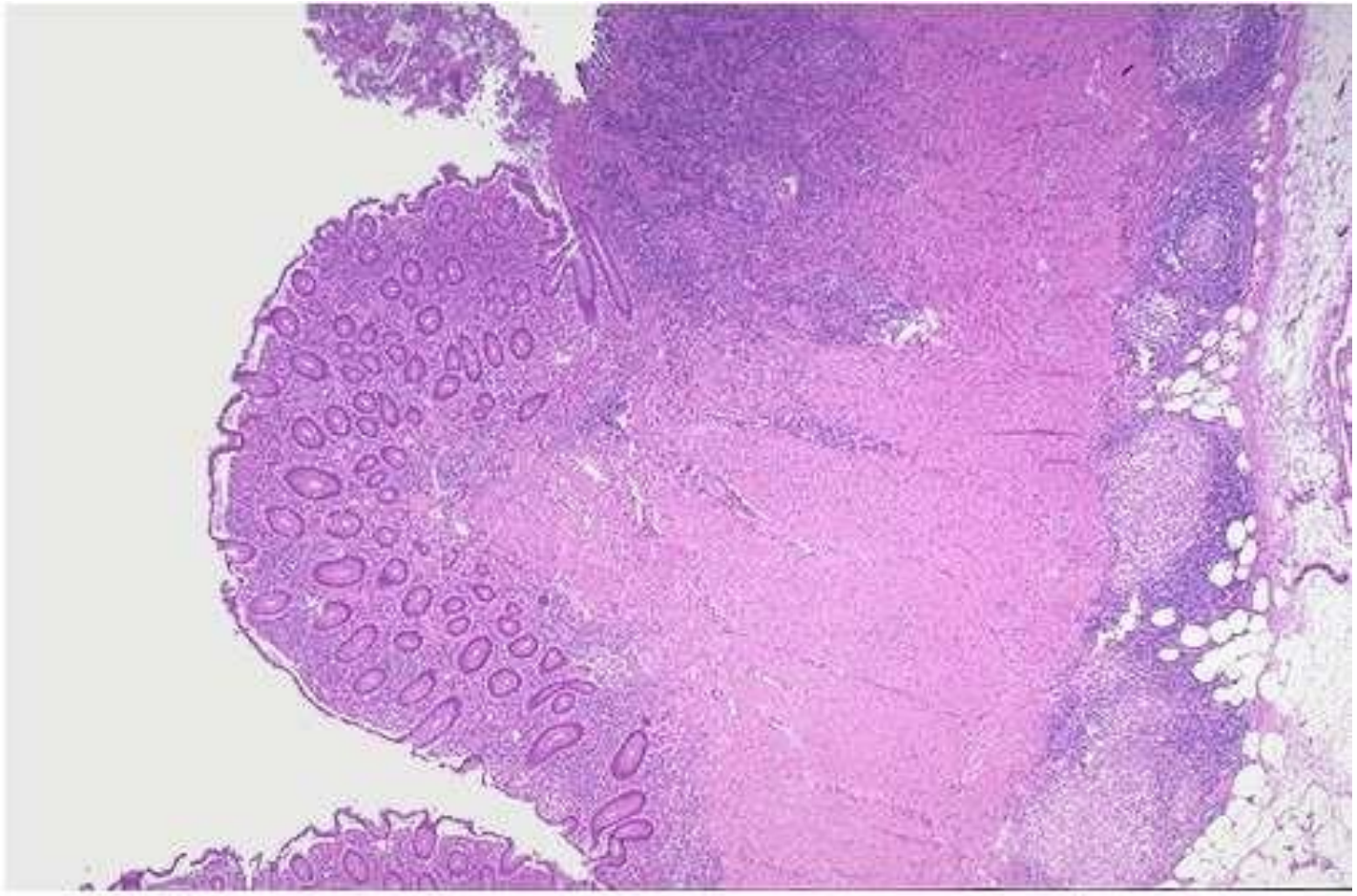
Here, we can observe **numerous neutrophils within the lumen of the crypts**, forming **crypt abscesses**. This finding indicates **active and acute inflammation**, which might be an infection.

# 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.

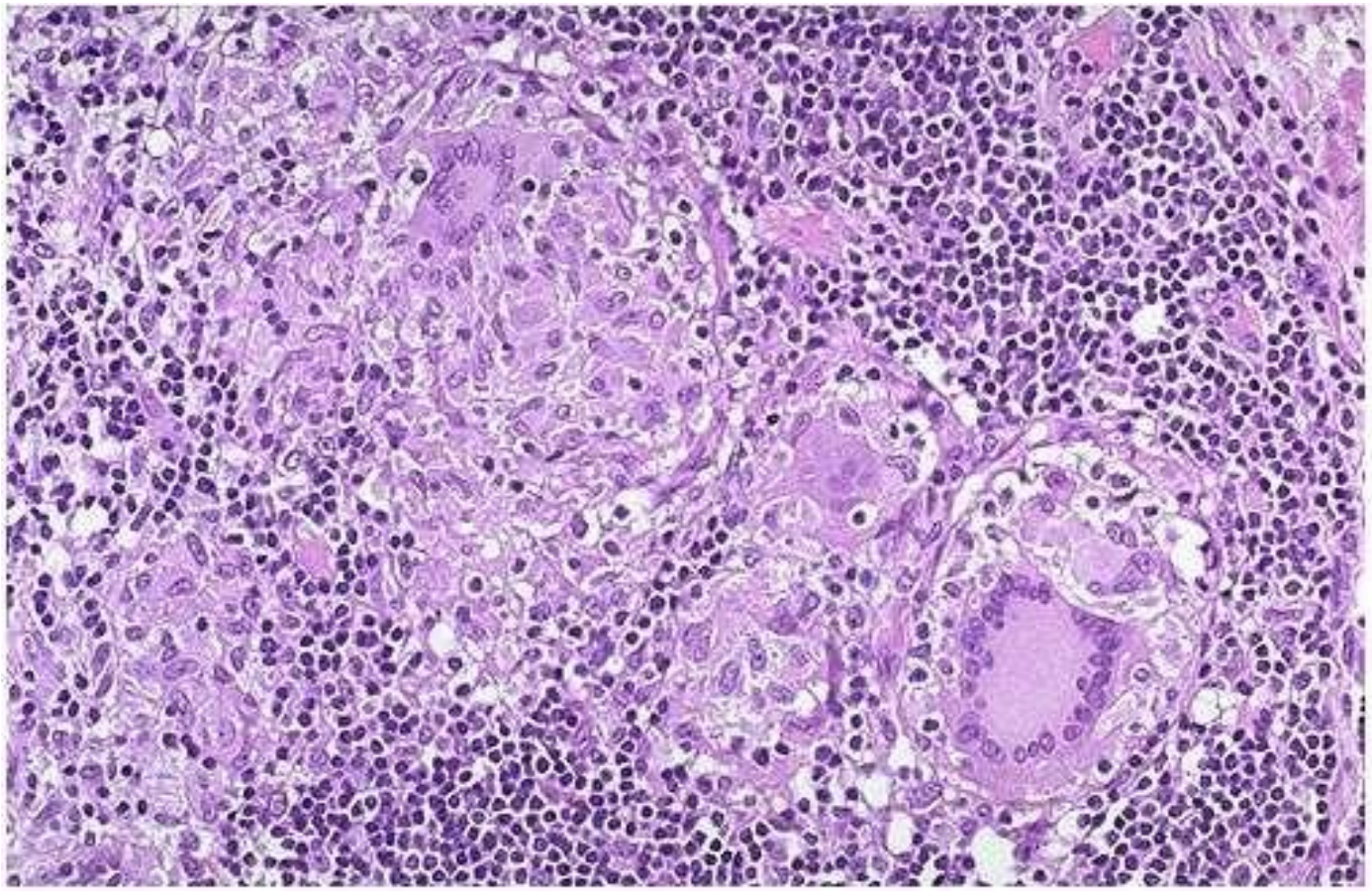


IBD = Inflammatory Bowel Disease



# 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

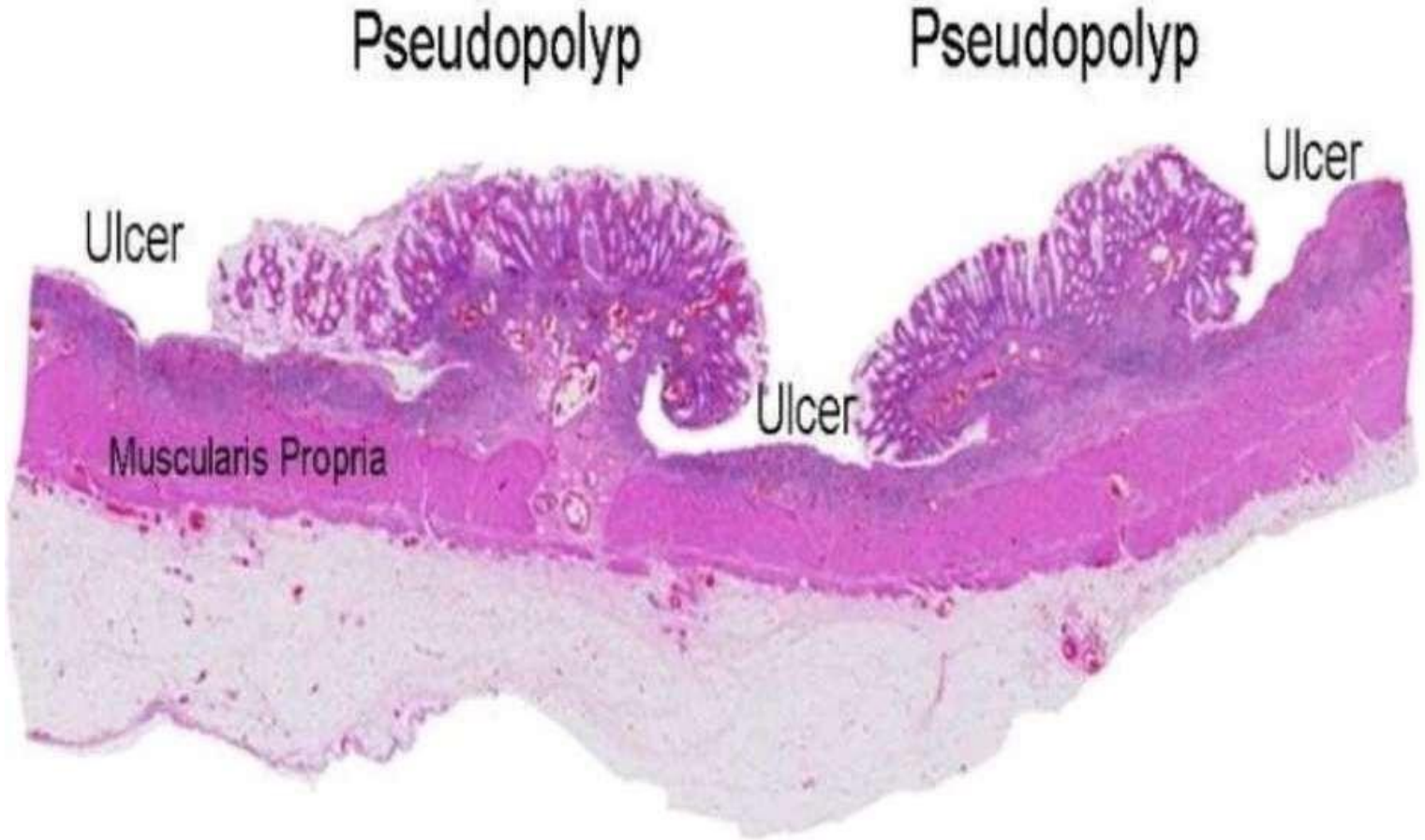
# Ulcerative Colitis Morphology

- 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

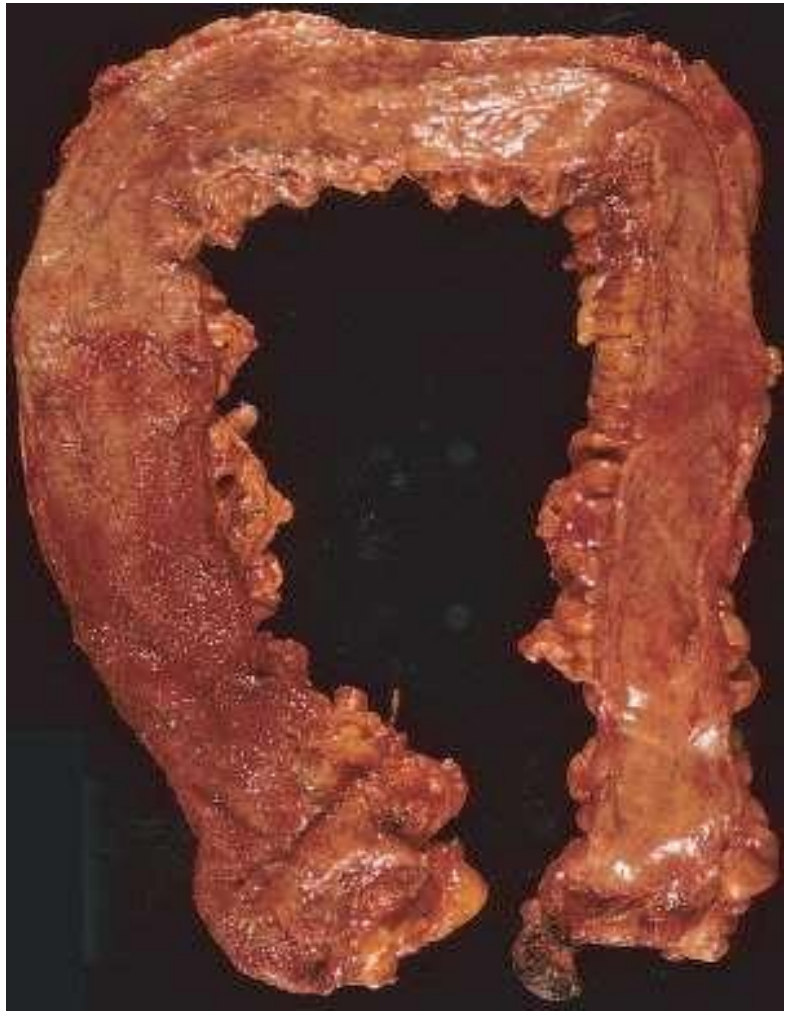
# Microscopic:
# Similar to Crohn's disease

- 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.

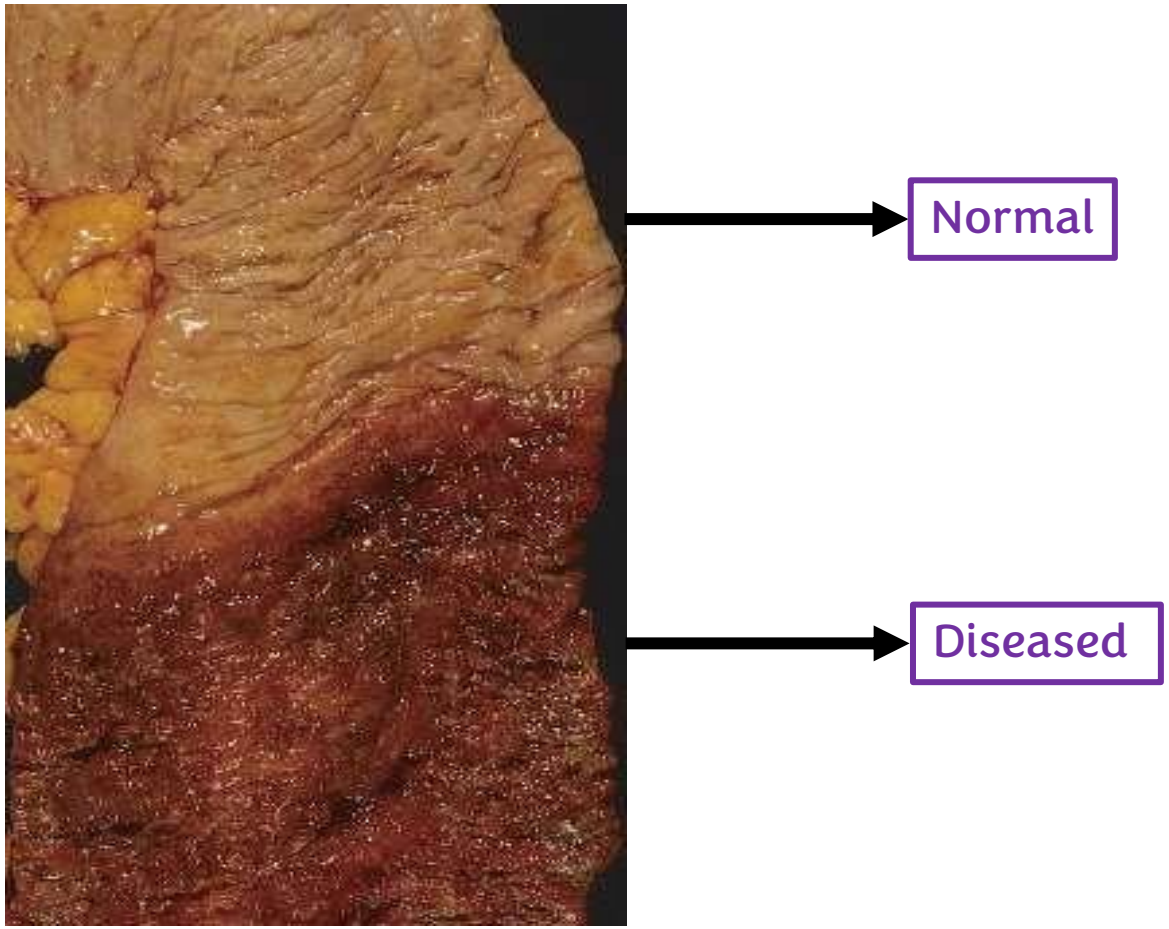
# Mucopurulent material and ulcers.

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.

# Colitis-Associated Neoplasia

- Long standing UC and CD.
- Begins as dysplasia >>>> carcinoma.
  - *Screening for dysplasia should begin after 8–10 years of disease.*
- Colonoscopy surveillance programs.
- Risk depends on:

1. **Duration of disease**: increase after 8-10 years .
2. **Extent of involvement**: more with pancolitis.
3. **Inflammation**: frequency & severity of active disease with neutrophils.

# 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 | | | |

# Additional Resources:

# رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)


1. Clubbing of the fingertips
2. Primary Sclerosing Cholangitis
3. Backwash ileitis