PATHOLOGY TEAM

IBD

Inflammatory Bowel Disease

Done by:

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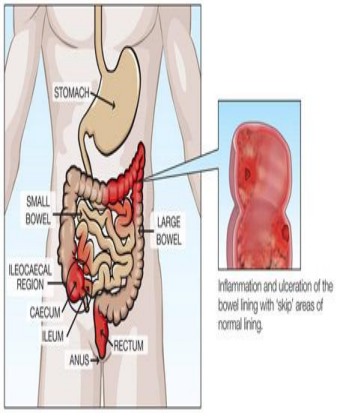
Inflammatory bowel disease

Introduction:



-Inflammatory bowel disease (IBD) is a chronic condition resulting from inappropriate mucosal immune activation(inflammation involve the intestine)
-There are two main types of (IBS)→crohn's disease and ulcerative colitis.
-Although their causes are still not clear, the two diseases probably have an immunologic hypersensitivity basis.

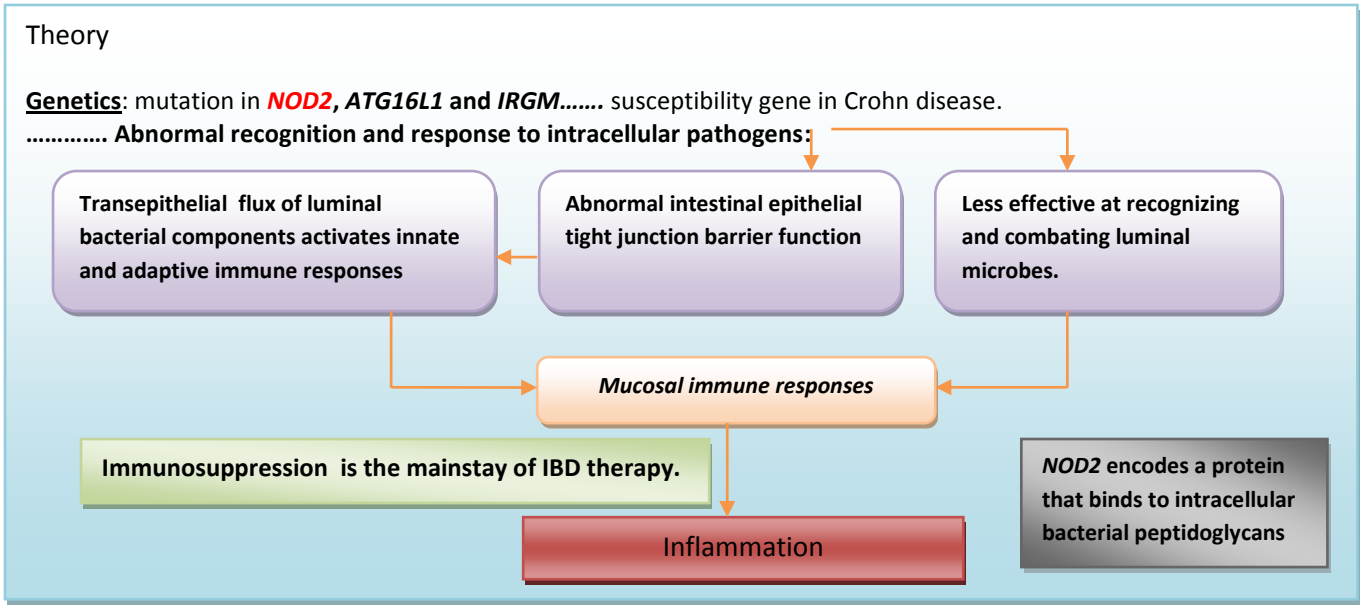
Pathophysiology:

Under active investigation(there a lot of researches that understand the pathophysiology of this disease)
It is idiopathic disorder(unknown the cause), Persons with IBD have a genetic predisposition for the disease.

There is about 50-60% family history chance to have cronh's disease but ulcerative colitis 15%.
CD>UC genetic predisposition

Most investigators believe that the two diseases result from a combination of:
1)Defects in host interactions with intestinal microbes
2)Intestinal epithelial dysfunction
3)Aberrant mucosal immune responses. →inflammation of the mucosa

**For unclear reasons, research suggests that smoking increases the risk of Crohn disease but reduces the likelihood of ulcerative colitis.

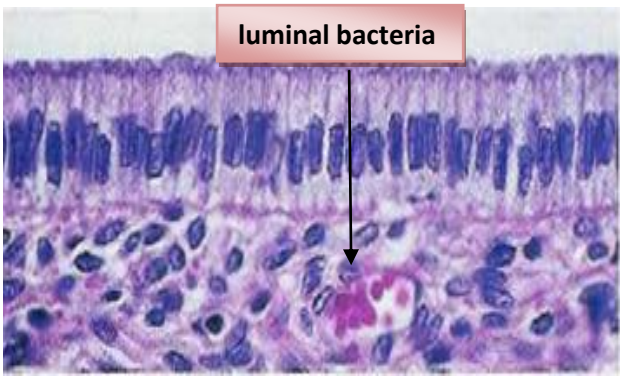


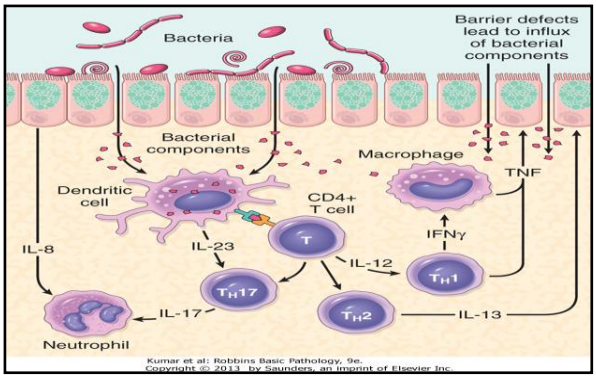
Nucleotide Oligomerization binding Domain 2

NOD2 encodes a protein that binds to intracellular bacterial peptidoglycans and subsequently activates NF-κB.

It has been postulated that disease-associated *NOD2* variants are less effective at recognizing and combating luminal microbes, which are then able to enter the lamina propria and trigger inflammatory reactions.

Mutations in NOD2 are seen in about 15% of Crohn's disease patients but are also seen in a smaller percentage of the general population, so mutations in NOD2 are neither necessary nor sufficient for the development of Crohn's disease(Not found in all patient who have crohn's disease also found in another diseases)**.**





Bacteria go to the lamina propria→ stimulate dendritic cells(Ag presenting cell)→ T lymphocyte will be stimulated→ stimulating different type of T helper. Th1→production of TNF and IFN,Th2→production of IL13 lead to destruction of the epithelium so more bacteria come to the lamina propria , Or stimulate IL23 which stimulate Th17 to recruit more neutrophil to the area and produce more injury to the epithelium

Nowadays, a lot of researches done for treatment- against TNF and against IL23 giving good result in mutation management in case of crohn's disease

Clinical Features:

The manifestations of IBD generally **depend** on the **area** of the intestinal tract **involved.**

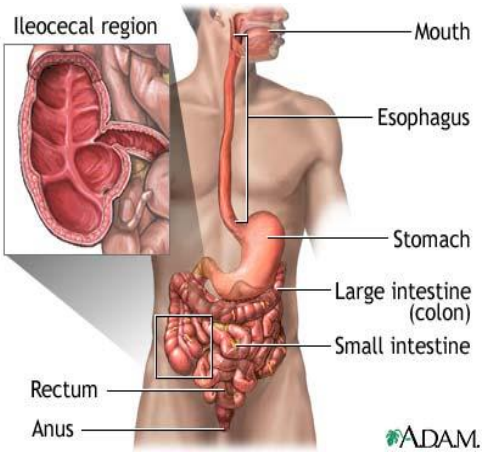
- **Colon** : Bloody diarrhea, Tenesmus, colicky pain
- **Small Intestine**: Abdominal pain, Diarrhea, Intestinal obstruction, Malabsorption.
- **Extra-intestinal manifestations (systemic manifestation)** : Arthritis , Eye and skin manifestations(erythema), uveitis and cholangitis.

Tenesmus is the feeling of constantly needing to pass stools , even if the bowels are already empty.

The term is used also with urination process.

Crohn's Disease

Crohn's Disease:

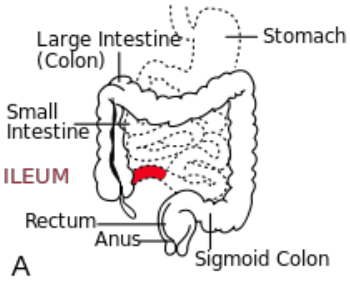


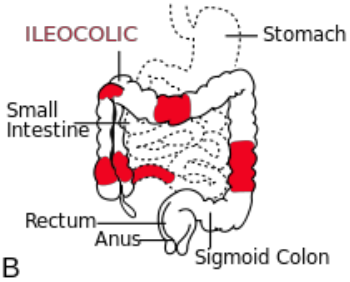
Is a *chronic inflammatory* disorder that most commonly affects the *Ileum* and *Colon* but has the potential to involve *any part* of the gastrointestinal tract from the mouth to the anus.(it has skip lesion)

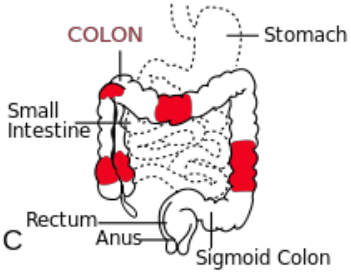
Clinical Features:

- Any age but has its highest incidence in young adults(15-35).
- Extremely variable clinical feature (according to the site which involved):
  -large bowel → tanesmus(abdominal pain) and bloody diarrhea
  -Small bowel→ obstruction
  -Stomach → epigastric pain
- Acute phase(systemic manifestation) : fever, diarrhea, and right lower quadrant pain may mimic acute appendicitis.
- Chronic disease (sometimes the patient have the disease(acute phase) and other are not)(could present with complication→ malabsorption –fistula formation, etc) : remissions and relapses over a long period of time.
- Thickening of the intestine may produce an ill-defined mass in the abdomen.

Sites of Involvement:







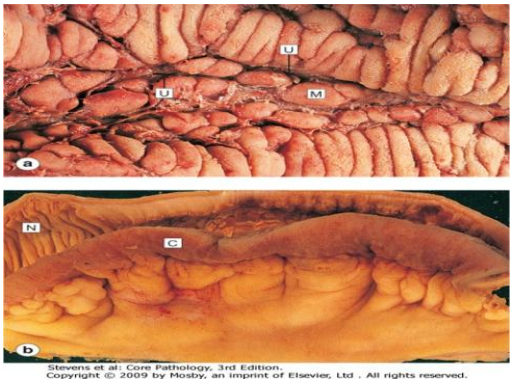
- Any part of the GIT from the mouth to the anus.
- Ileum (30%) colon (20%).
- Most commonly terminal ileum
- Commonly (75%) have perianal lesions such as abscesses, fistulas, and skin tags.

Gross Appearance:

- Involvement is typically segmental, with skip areas of normal intestine between areas of involved bowel.
- Segmental distribution discountenius (area involved and other area are normal (eg. ileum) regional ileitis- skip lesion)
- Transmural inflammation- the whole wall mucosa- submucosa -muscularis –serosa are inflamed.(with edema- wall become thicken)

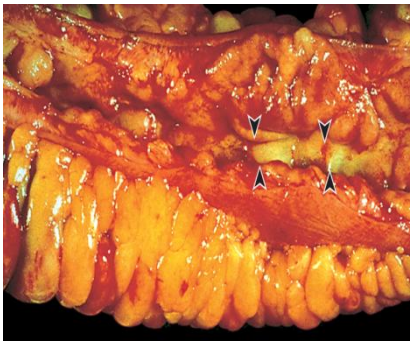
- Marked fibrosis causing luminal narrowing with intestinal obstruction.
- Fissures ulcer (deep and narrow ulcers that look like stabs with a knife that penetrate deeply into the wall of the affected intestine) could open in pretonial cavity lead to peretonotits
- Fistulas (communications with other viscera). May be between urinary bladder and intestine

Mucosa: longitudinal serpiginous ulcers separated by irregular islands of edematous mucosa. This results in the typical(Cobblestone effect)



FAT: In involved ileal segments, the mesenteric fat creeps from the mesentery to surround the bowel wall (creeping fat)

Creeping fat (Movement of fat to cover the area which have deep ulcer to prevent spread of inflammation into the peritoneal cavity)



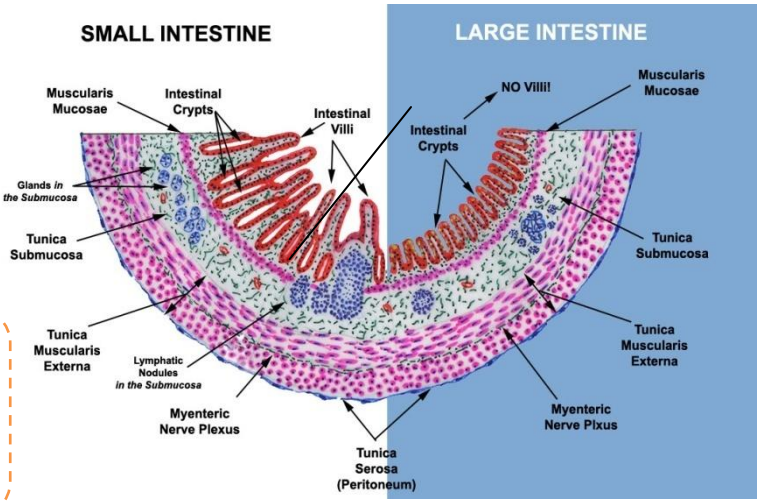
Crohn disease of the ileum showing narrowing of the lumen, bowel wall thickening, serosal extension of mesenteric fat ("creeping fat"), and linear ulceration of the mucosal surface (*arrowheads*).

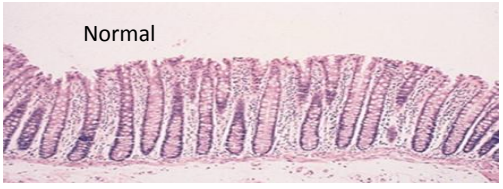
Microscopic Features:

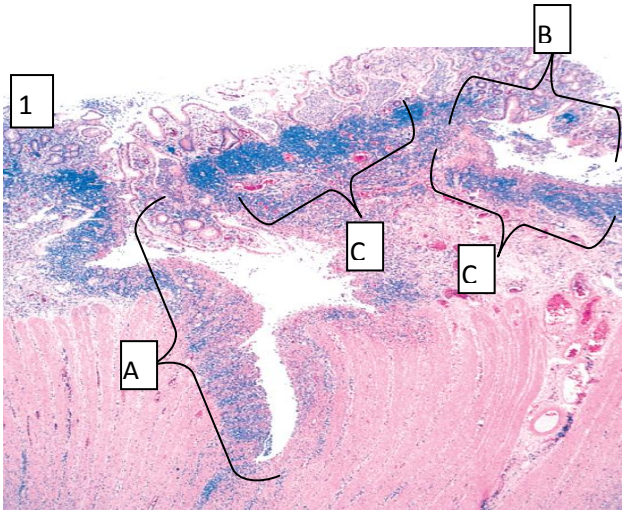
-Distortion of mucosal crypt architecture.
-Transmural inflammation.
-Epithelioid granulomas (collection of activating histiocytes) [60%].
*Fissure-ulcers and fistulas can be seen microscopically**

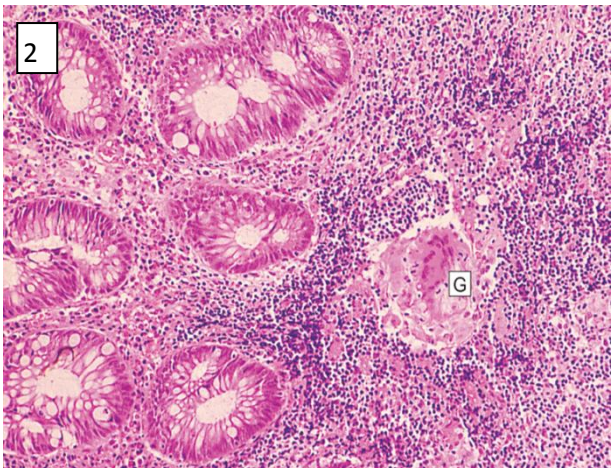
Active inflammation → increase inflammation in the lamina propria some inflammatory cells will attack crypts leading to cryptitis→ as a result distortion of crypt architecture

Normal









1- Crohn's disease of the colon showing (A) a deep fissure extending into the muscle wall, a second, (B) shallow ulcer (upper right).(C) Abundant lymphocyte aggregates are present, evident as dense blue patches of cells at the interface between mucosa and submucosa.

2- GRANULOMA (G) , Crohn's disease could be non-granulomatous.

Complications:

1-Intestinal obstruction

2-Fistula formation

a) between the ileum and the colon result in malabsorption

b) Enterovesical fistulas lead to urinary infections and passage of gas and feces with urine.

c) Enterovaginal fistulas produce a fecal vaginal discharge.

3- Extraintestinal manifestations (arthritis and uveitis)

4- Slight increased risk of development of carcinoma of the colon—much less than in ulcerative colitis.

Summary

- Involvement of discontinuous segments of intestine (skip areas)
- Can involve any part of GIT.
- Noncaseating small epithelioid cell granulomas in 60%
- Transmural (full-thickness) inflammation of the affected parts

Ulcerative Colitis

Ulcerative Colitis:

- Idiopathic inflammatory disease affecting the colon.
- Limited to the mucosa.(Crohns is transmural)
- Chronic course characterized by remissions and relapses.
- **Age Group:** mainly in 20 to 30 year olds, but may occur at any age.
- **Race:** whites > blacks.
- **Genetic Susceptibility:** linked to **MHCII HLA-DRB1.**
- No sex predilection (males and females affected equally)
- **LOWER** incidence in smokers and nicotine users.
- p-ANCA antibodies found in> 45% of cases.

Etiology

- Unknown.
- Antibodies that cross-react with intestinal epithelial cells and certain serotypes of *Escherichia coli* have been demonstrated in the serum of some patients with ulcerative colitis.
  (Antibodies cross-react with and attack epithelial cells and normal flora -E. Coli)

Clinical Features

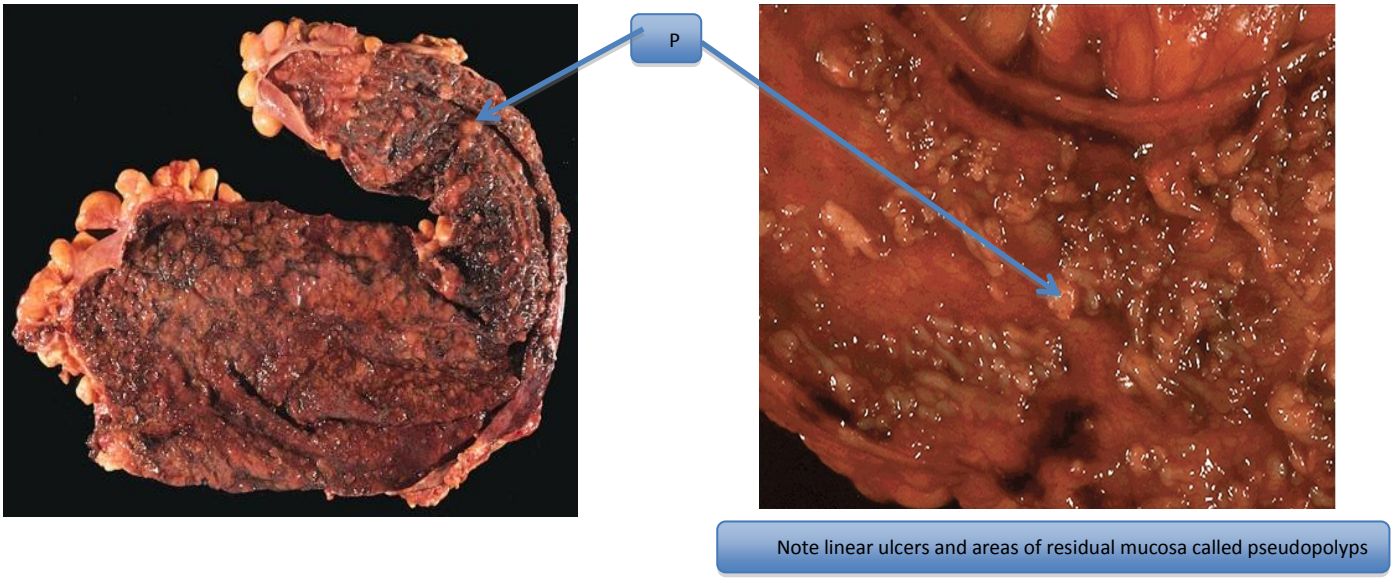
- The disease usually has a **chronic** course, with remissions and exacerbations (relapses).
- Acute phase &Relapse:
  - Fever.
  - Leukocytosis.
  - Left-sided abdominal pain/cramping.
  - Weight loss.
  - Tenesmus.(feeling of constantly needing to pass stool)
  - Diarrhea with blood and mucus and inflammatory cells.

Sites of Involvement

- Ulcerative colitis is a disease of the colon and rectum.
- The disease classically begins at the rectum and extends proximally in a continuous manner without skip areas.(Crohns can start anywhere)
- Rectum is involved in almost all cases.
- The ileum is not involved as a rule(by default), but may be afflicted.

Gross Appearance

- In the <u>acute phase</u>:<u>Diffuse</u> hyperemia(increased blood flow to the area)with numerous <u>superficial</u> ulcerations.(It appears congested and red)
- The regenerated or nonulcerated mucosa(the remaining normal colon)may appearpolypoid (inflammatory pseudopolyps[P]) in contrast with the atrophic areas or ulcers.
- <u>NO skip lesions.</u>

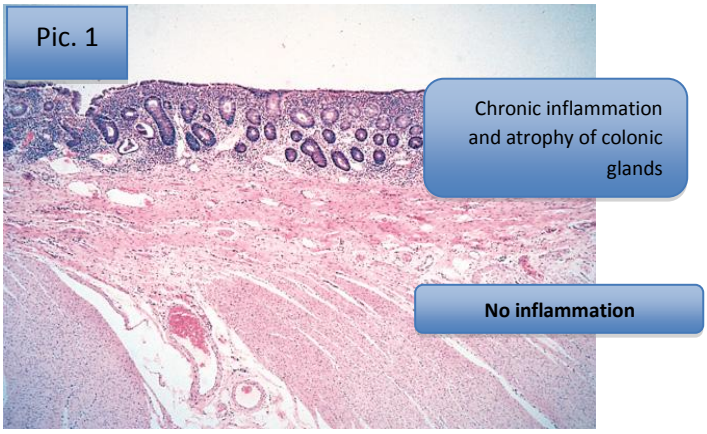


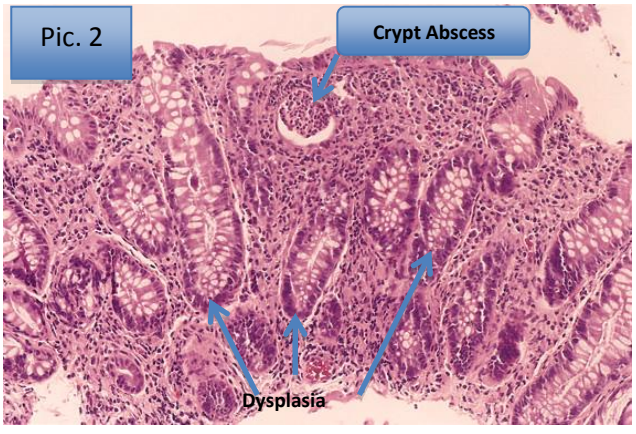
Microscopic Appearance

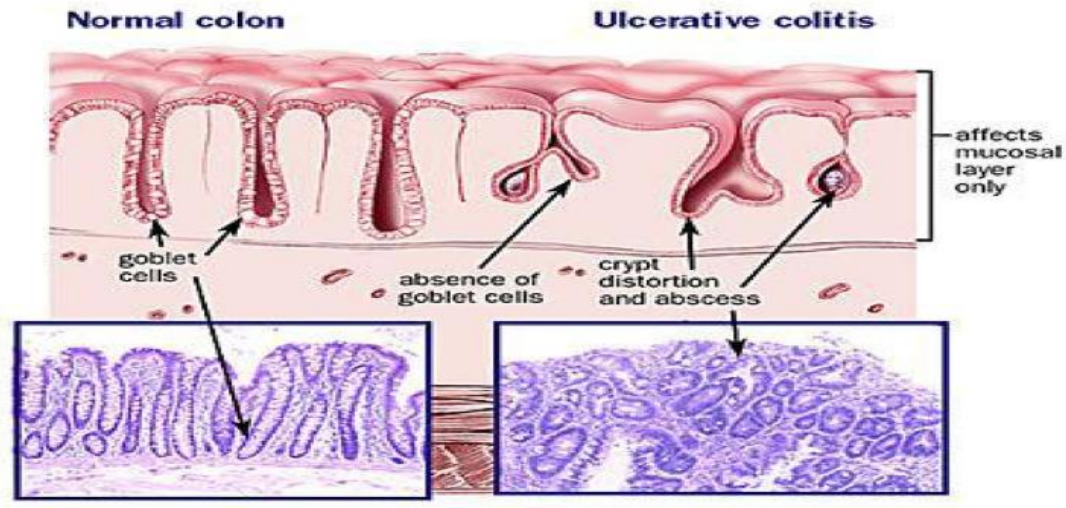
- Inflammation usually restricted to the mucosa.[Pic. 1]
- **<u>Active Phase</u>:Neutrophils**:[Pic. 2]
    1. Cryptits: neutrophilsattack epithelium.
    2. Crypt Abscess:collection of neutrophils in the crypts. (Diagnostic)
- **<u>Chronic Phase</u>**:Cryptatrophy and distortion (dilation and branching)
- Active inflammation correlates well with the severity of symptoms.

➔ Severity of symptoms ∝amount of neutrophils

-Dysplasia occurs as a result of continuous injury and repair mechanisms. After 10 years people with ulcerative colitis are at high risk of developing adenocarcinoma (aggressive and high grade). Patients need continuous follow-ups to make sure the dysplasia doesn't progress to adenocarcinoma.







Complications

- **Acute phase**
  - Severe bleeding.(As a result of inflammation)
  - Electrolyte loss.
  - Toxic megacolon. (Weakening of muscularisexterna leading to dilation of the colon, with functional obstruction)

    Toxic Megacolon:A form of acute colonic distension in which colon becomes dilated & thin-walled and could even become gangrenous; surgical removal of dilated area.

- **Chronic ulcerative colitis**
  - Increase risk of developing colon carcinoma. (>CD)
  - The presence of high-grade dysplasia in a mucosal biopsy imposes a high risk of cancer and is an indication for colectomy.
- **Extraintestinal manifestations**

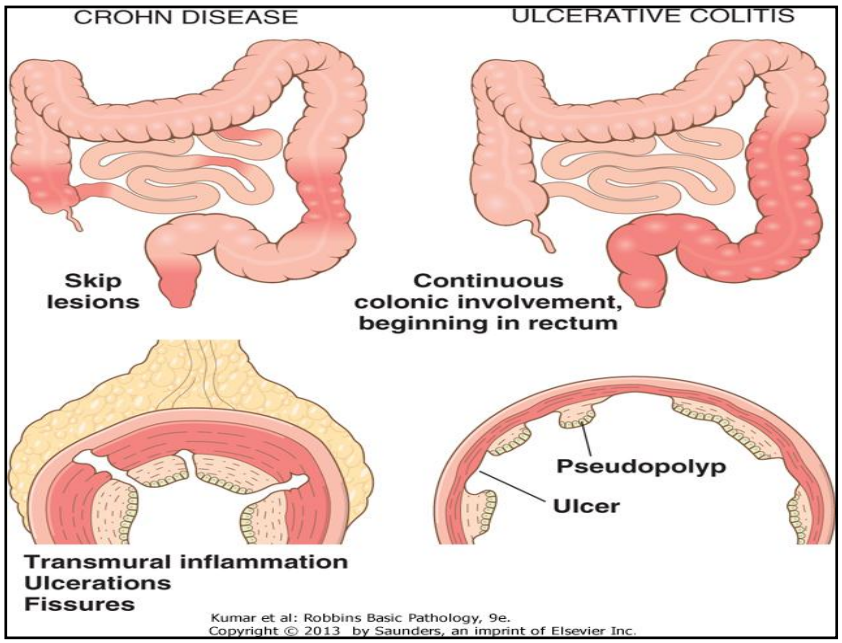
Occur more commonly in ulcerative colitis than in Crohn's disease.

- Arthritis, HLA-B27 positive.(Individuals with ulcerative colitis and Ankylosing spondylitis are HLA-B27 positive but this is related to the spondylitis not ulcerative colitis)
- Sclerosing cholangitis: fibrosis around bile ducts leading to obstructive jaundice. (> CD)
- Iritis/Uveitis.(<CD)(Swelling and irritation of the uvea, the middle layer of the eye. The uvea provides most of the blood supply to the retina)
- Skin lesions: PyodermaGangrenosum&Erythema Nodosum.
  - **PyodermaGangrenosum** is a rare condition that causes large, painful sores (ulcers) to develop on your skin, most often on your legs. With black discoloration.
  - **Erythema Nodosum** (*red nodules*) is an inflammation of the fat cells under the skin.

	Crohn's disease	Ulcerative Colitis
Site	Any part of the GIT	Colon only
Pattern	Skip areas of normal mucosa	Diffuse involvement of mucosa
Depth of the ulcer	Deep ulcers (fissure)	Superficial ulcers
Extent of inflammation	Transmural inflammation	Mucosal inflammation only
Fistula formation	Yes	No
Creeping mesenteric fat	Yes	No
Fibrous thickening of wall	Yes	No
Granulomas	Yes	No
Dysplasia	rare	Common
Carcinoma	rare	more common (10%)
Mucosal appearances	Cobblestone	Pseudopolyps
Bowel wall	Thickened wall Narrow lumen	Thin wall Dilated lumen
MHC Class II	HLA-DR1/DQw5	HLA-DR2
Complications	Short gut syndrome Fistula formation Bowel perforation Stricture formation	Haemorrhage Electrolyte loss Toxic megacolon Systemic effects

	Crohn's disease	**Ulcerative Colitis**
Epidemiology	-More common in whites than blacks, in Jews than non-Jews - No sex predilection -Age group:Majority (>75%) of cases occur between 11 and 35 years of age -Smoking is a risk factor	-More common in whites than blacks -No sex predilection -Occurs between 14 and 38 years of age -Lower incidence in smokers and other nicotine users
Clinical Features	Recurrent right lower quadrant colicky pain (obstruction) with diarrhea Bleeding occurs only with colon or anal involvement (fistulas; abscesses) Apthous ulcers in mouth Extragastrointestinal: erythema nodosum, sacroiliitis (HLA-B27 association), pyoderma gangrenosum, iritis inflammation in iris (CD > UC), primary sclerosing cholangitis (UC > CD)	Recurrent left-sided abdominal cramping with bloody diarrhea and mucus Fever, tenesmus, weight loss Extragastrointestinal: primary sclerosing cholangitis (UC > CD), erythema nodosum, iritis/uveitis (CD > UC), pyoderma gangrenosum(skinn black pigmentation), HLA-B27 positive arthritis. p-ANCA(Ab directed against neutrophil) antibodies > 45% of cases

complication	-Fistulas, obstruction -Colon cancer (UC > CD) -Calcium oxalate renal calculi (increased reabsorption of oxalate through inflamed mucosa→ forming stone in the kidney) -Malabsorption due to bile salt deficiency(problem in the terminal part of ileum) -Macrocytic anemia due to vitamin B_{12} deficiency	Toxic megacolon (hypotonic and distended bowel) Adenocarcinoma: greatest risks are pancolitis(all colon is involved), early onset, duration of disease > 10 years)



Characteristics	A or B	Disease
Colon only	B	**A. Crohn's disease**
Diffuse involvement of mucosa	B	
Superficial ulcers	B	
Any part of the GIT	A	
Skip areas of normal mucosa	A	
Mucosal inflammation only	B	
Fistula formation	A	**B. Ulcerative Colitis**
Transmural inflammation	A	
Granulomas	A	
Deep ulcers	A	
Dysplasia is common	B	
Carcinoma is more common (10%)	B	

Questions

Q1: Which of the following respondsbetter to surgery:

A- Crohns Disease of small intestine
B- Crohns Disease of colon
C- Ulcerative colitis

Q2: Positive HLA-B27 allelein individuals with ulcerative colitis is linked to:

A- Arthritis
B- Sclerosing cholangitis
C- PyodermaGangrenosum

Q3: Ulcerative colitis associated with:

A- HLADR7
B- Mutations of NOD2 GENE
C- HLA-DRB1

Q4: What are the manifestations of ulcerative colitis:

A- Superficial ulcers in the colon with granulomas
B- Chronic inflammation with granulomas
C- Superficial ulcers in the colon without granulomas

Q5: A 22-year-old women has recurrent episodes of diarrhea, crampy abdominal pain, and slight fever over the last 2 years. At first episodes, which usually last 1 or 2 weeks, were several months apart, but recently they have occurred more frequently. Other symptoms have included mild joint pain and sometimes red skin lesions. On at least one occasion, her stool has been guaiac-positive, indicating the presence of occult blood. Colonoscopy reveals several sharply delineated areas with thickening of the bowel wall and mucosal ulceration. Areas adjacent to these lesions appear normal. Biopsies of the affected areas show full-thickness inflammation of the bowel wall and several noncaseating granulomas.

What is the most likely diagnosis?

A- Ulcerative colitis
B- Crohn's disease
C-Colon cancer

Q6: A 44-year-old man present with multiple episodes of bloody diarrhea accompanied by cramping abdominal pain. A colonoscopy reseals the rectum and distal colon to be unremarkable, but x-ray studies find areas of focal thickening of the wall of the proximal colon, producing a characteristic "string sign". Biopsies from the abnormal portions of the colon revealed histologic features that were diagnostic of crohn disease. Which of the following histologic features is most characteristic of crohn disease?

A-Dilated submucosal blood vessels with focal thrombosis.
B- Increased thickness of the subepithelial collagen layer.
C-Noncaseating granulomas with scattered giant cells.
D-Numerous eosinophils within the lamina propria.

Q7: Which one of the following findings is more characteristic of ulcerative colitis rather than Crohn disease?

A-Inflammation beginning in the rectum and extending proximally without "skip lesions"
B-Pericolonic fibrosis forming "creeping fat" around the outside of the gut.
C-Intestinal obstruction resulting from pericolonic abscess.
D-Superficial noncaseating granulomas forming hamartomatous polyps.

Answers are : C , A , C , C , B , C , A