Inflammatory Bowel Diseases

Crohn's Disease and **Ulcerative Colitis.**

Although their causes are still not clear, the two diseases probably have an immunologic ***hypersensitivity*** basis.

Pathophysiology

- The pathogenesis of IBD involve:

1. genetic susceptibility **<< names are for understanding only**

   (according to dr.)

2. failure of immune regulation

3. triggering by microbial flora

Genetic susceptibility

- First-degree relatives are 3 to 20 times more likely to develop the disease,
- **Both** Crohn disease and ulcerative colitis have been linked to specific major histocompatibility complex class II alleles.

30% of Crohn disease with *HLA-DR7* and *DQ4* alleles

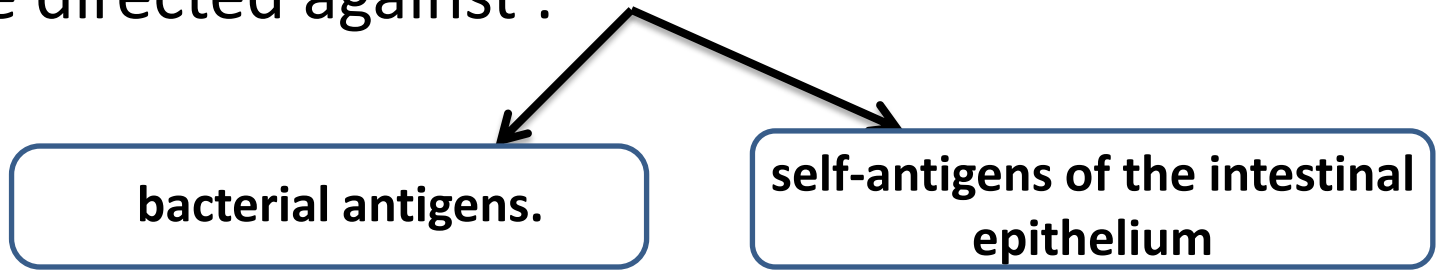
Ulcerative colitis with *HLA-DRB1*

- A gene called *NOD2* (or *CARD15*) is mutated in as many as 25% of Crohn disease patients in some ethnic populations.

- mutant form of the *IL-23 receptor* (*IL-23R*) gene. IL-23 is a cytokine that promotes the production

Immunologic Factors

- It is not known whether the immune responses in IBD are directed against :



- In <u>both</u> Crohn disease and ulcerative colitis the primary damaging agents appear to be **<u>CD4+ cells.</u>**

- IL 17
- TNF

Pathophysiology: understand main picture

Genetics: mutation in
***NOD2*, *ATG16L1* and *IRGM*…….** susceptibility gene in Crohn disease.
……. Abnormal recognition and response to intracellular pathogens

Less effective at recognizing and combating luminal microbes

***Mucosal immune responses*.**

Abnormal intestinal epithelial tight junction barrier function

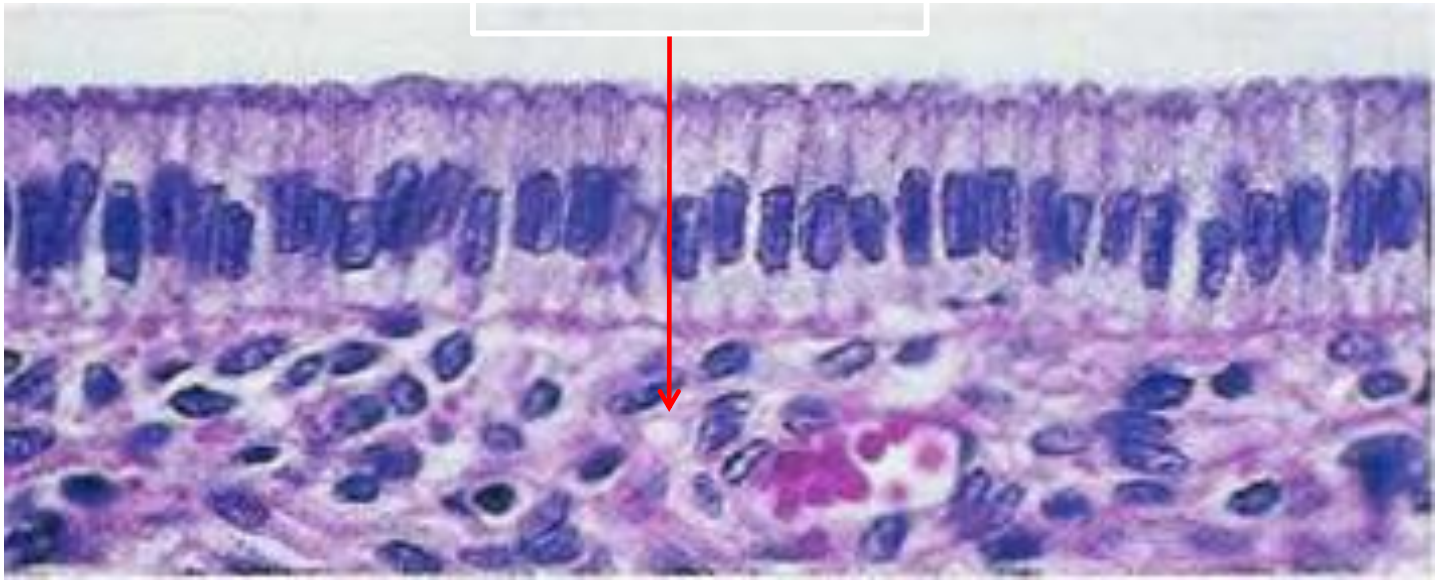
Transepithelial flux of luminal bacterial components activates innate and adaptive immune responses

Immunosuppression is the mainstay of IBD therapy.

Inflammation

***NOD2* encodes a protein that binds to intracellular bacterial peptidoglycans**

luminal bacteria



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,
=not all crohn’s disease caused by mutation .

so mutations in *NOD2* are neither necessary nor sufficient for the development of Crohn's disease
= person who has this mutation my not develop crohn’s disease.

Pathophysiology

An *idiopathic disorder*

The pathophysiology of IBD is under active investigation.

Persons with IBD have a genetic predisposition for the disease.

Most investigators believe that the two diseases result from a combination of

1. ***defects in host interactions with intestinal flora***
2. ***intestinal epithelial dysfunction***
3. ***aberrant mucosal immune responses*.**

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

Clinical

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

Colon	Small intestine	Extraintestinal manifestations
bloody diarrhea, **tenesmus** (not easy to pass)	abdominal pain Intestinal obstruction Steatorrhea	Arthritis Eye manifestation Skin manifestation

Crohn's disease

Is a chronic inflammatory disorder. Also called "***regional*** entritis", because:
It 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.**

Clinical Features

- Occurs at Any age but has its highest incidence in **young adults**
- Extremely ***variable clinical feature***.

➢ **Acute phase:**
- Fever
- Diarrhea
- right lower quadrant Pain

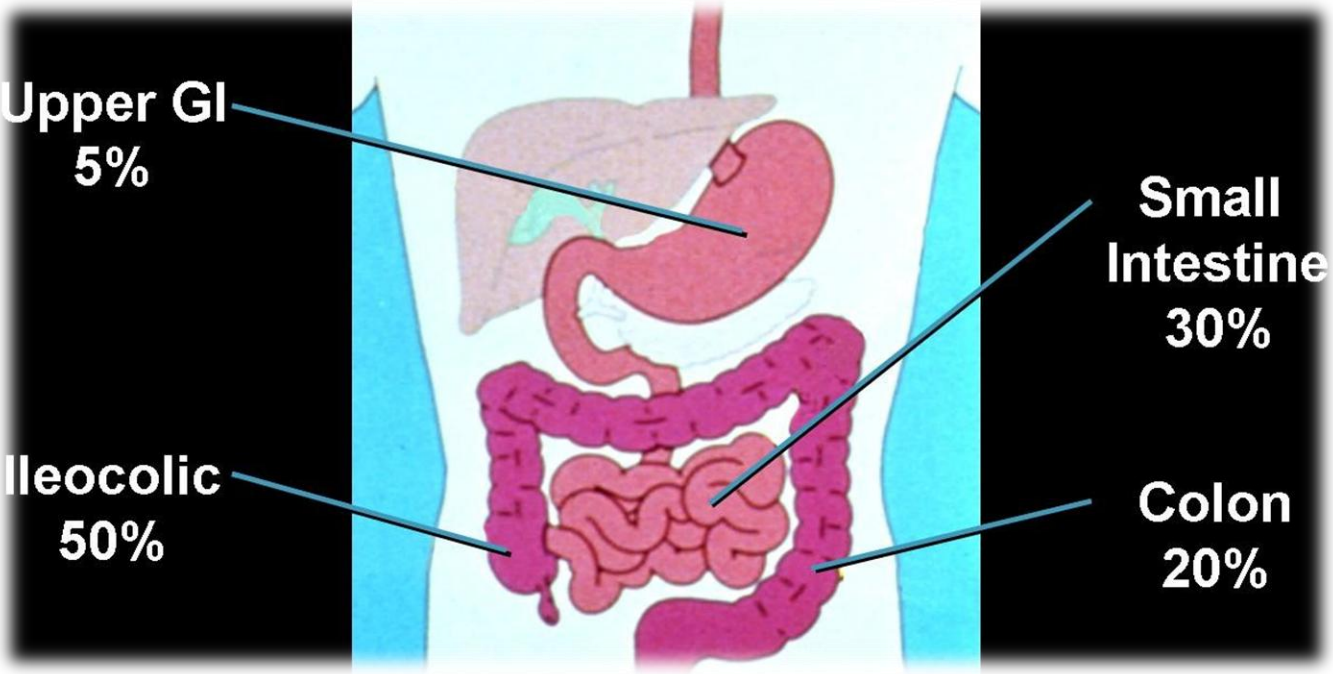
((may mimic acute appendicitis)).

➢ **Chronic disease:**
Remissions and relapses over a long period of time.

➢ **Thickening of the intestine** may produce an ill-defined mass in the abdomen. (felt under abdominal mass)

Sites of Involvement

- Any part of the GIT. Mouth→Anus.
- ileum (30%) colon (20%).
- Most commonly terminal ileum.
- Commonly (75%) have perianal lesions (around the anus) such as abscesses, fistulas (abnormal duct resulting from injury), and skin tags.



Morphology

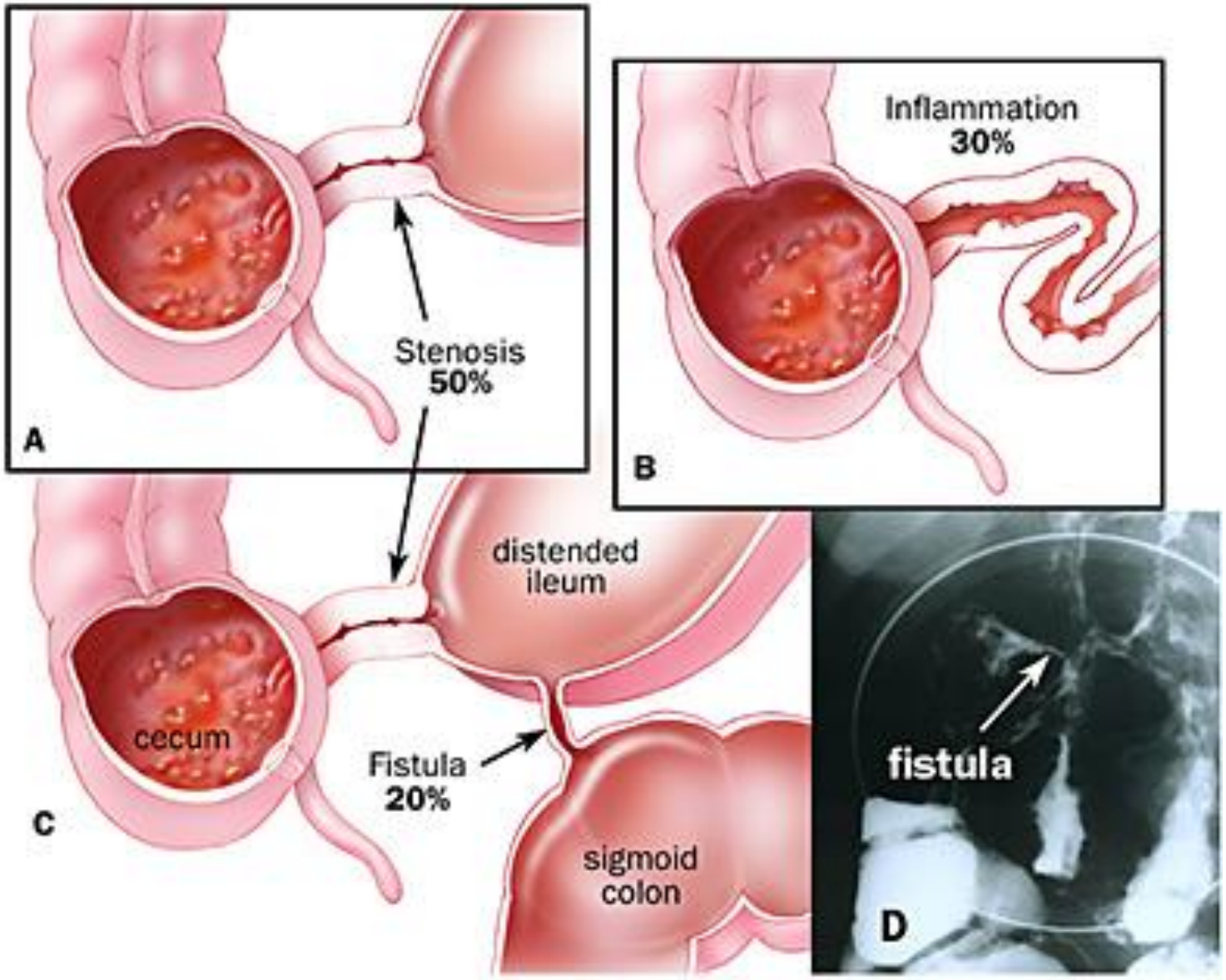
❖ Gross Appearance:

- Involvement is typically **segmental**, with ***skip areas*** of normal intestine between areas of involved bowel.

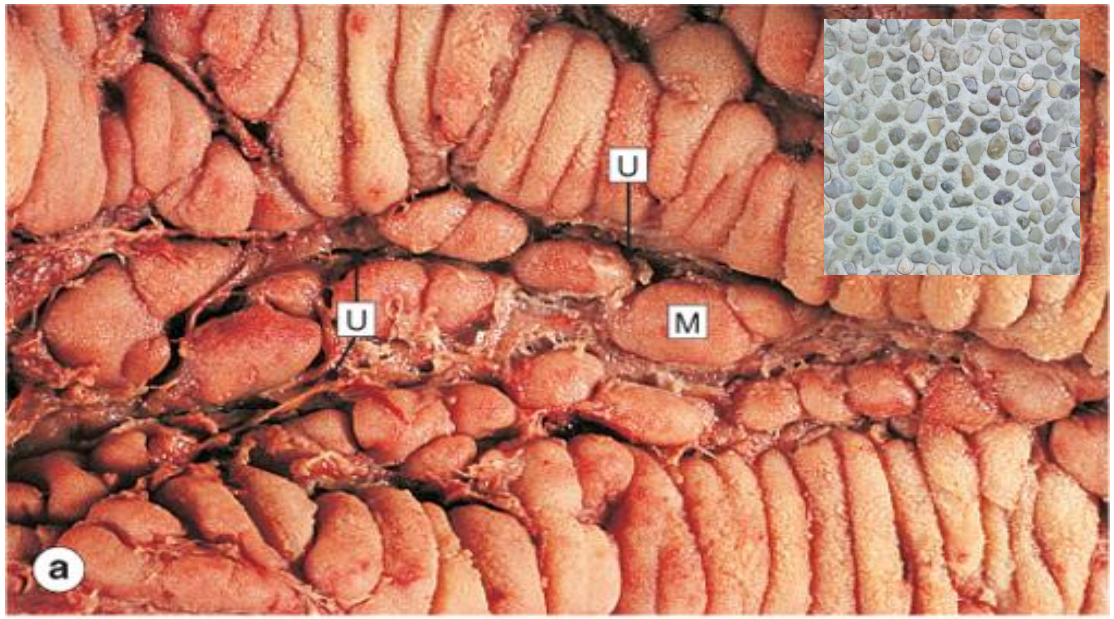
- **Marked fibrosis** causing **luminal narrowing** with intestinal **obstruction (stenosis)**.

- **Fissures** (deep and narrow ulcers that look like stabs with a knife that penetrate deeply into the wall of the affected intestine)

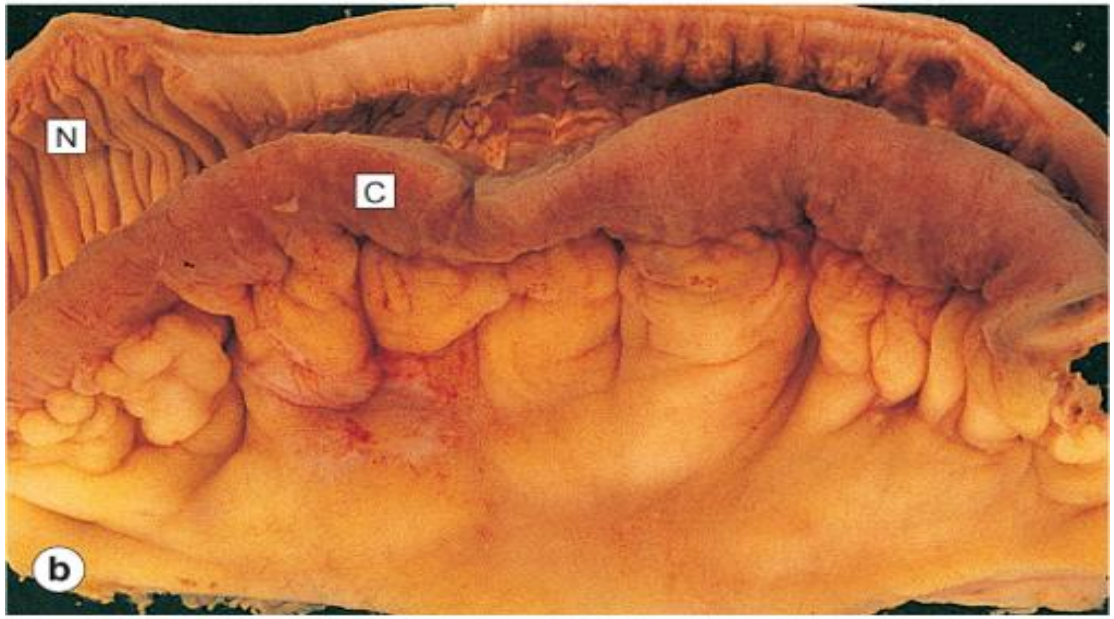
- **fistulas** (communications with other viscera).


Stenosis
50%
A
Inflammation
30%
B
distended
ileum
cecum
Fistula
20%
C
sigmoid
colon
fistula
D

Mucosa:
longitudinal ***serpiginous (wavy)*** ***ulcers*** separated by irregular islands of edematous mucosa. This results in the typical **cobblestone effect.**
((cobblestone: rounded stones**))**



FAT: **The mesentric fat** in the *involved* ileal segments, creeps from the mesentery to surround the bowel wall **(creeping fat)**



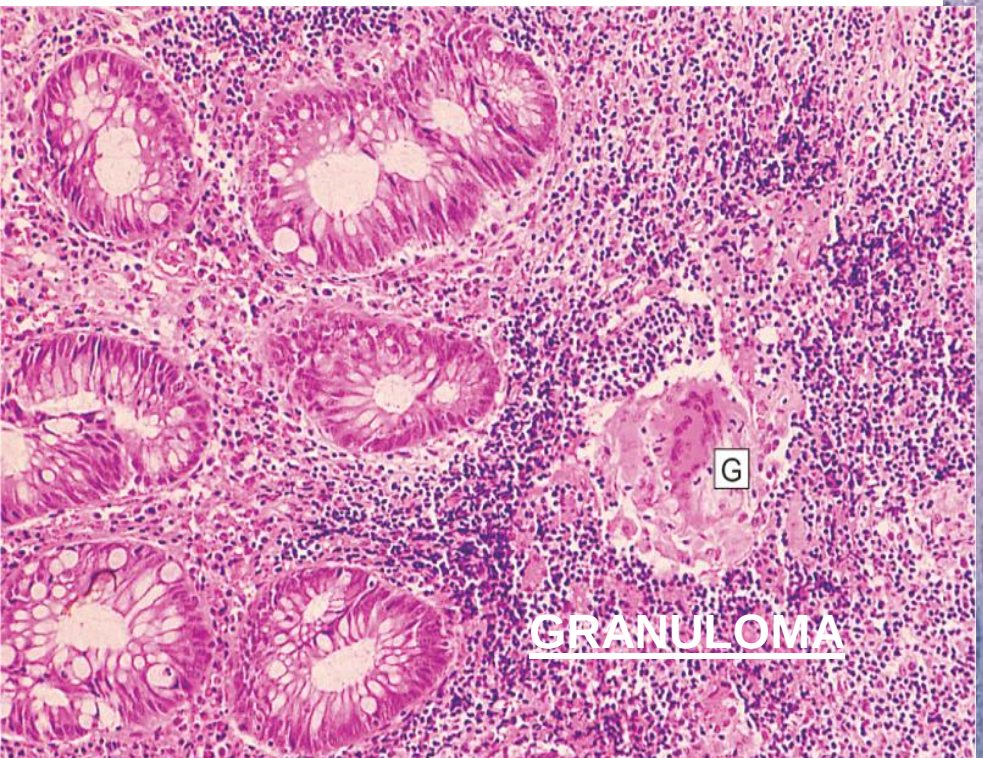
Morphology cont'd

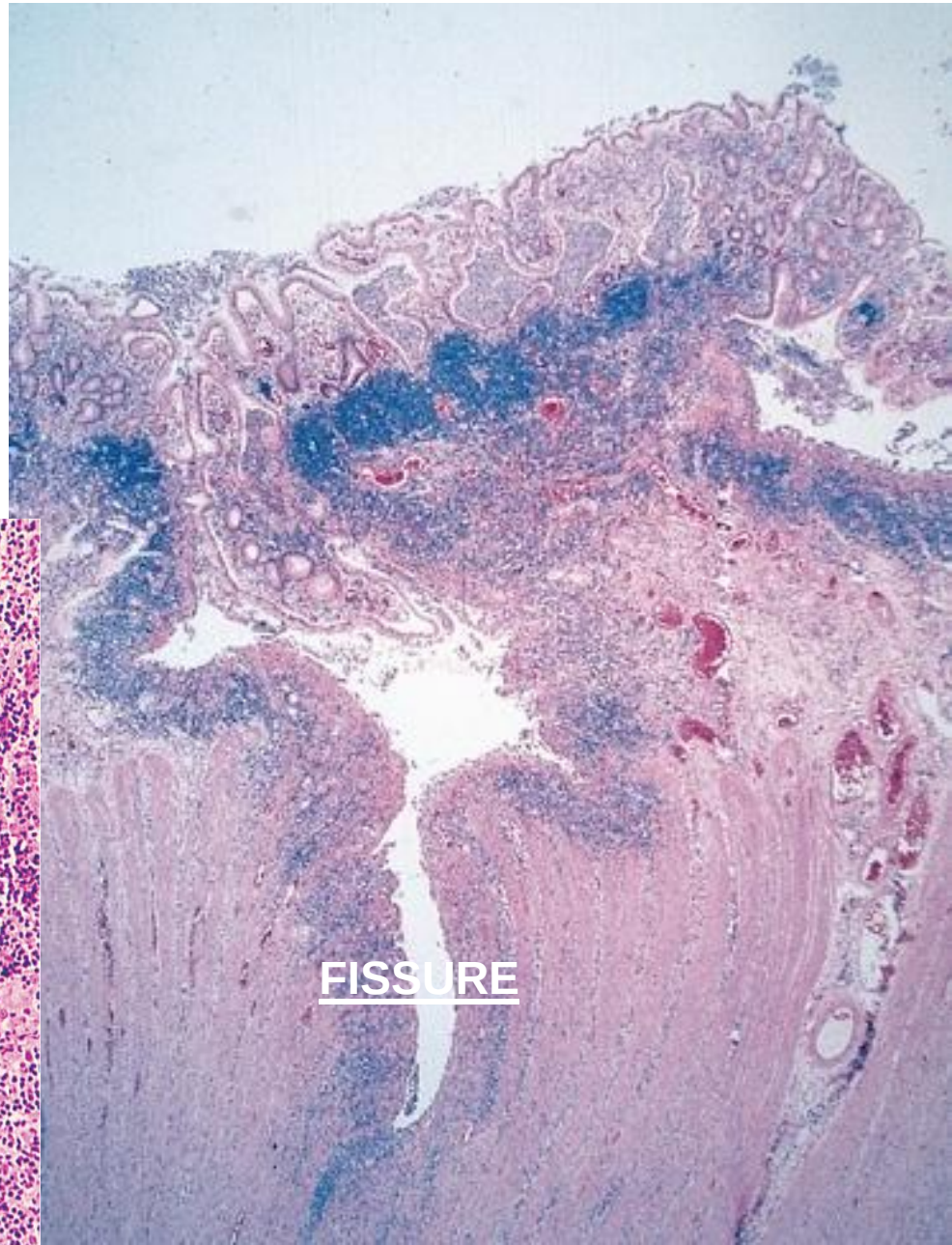
❖ Microscopic Features

1. Distortion (change in chape) of mucosal crypt architecture.
2. Transmural inflammation (through the wall of the organ) .
3. Epithelioid granulomas [60%].

Fissure-ulcers *and* ***fistulas*** *can be seen microscopically.*
(as previously mentioned)

Crohn's Disease





Complications

1. **Intestinal obstruction**
2. **Fistula formation :**

a) **between the ileum and the colon** → result in → malabsorption

b) **Enterovesical fistulas (between organs)** → lead to → urinary infections and passage of gas and feces with urine.

c) **Enterovaginal fistulas (to vagina)** → produce → fecal vaginal discharge.

3. **Extraintestinal manifestations** (arthritis and uveitis: inflammation of middle layer of the eye).
4. **Slight** increased risk of development of **carcinoma** of the colon—more in ulcerative colitis.

Summary Points of Crohn's Disease

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

ULCERATIVE COLITIS

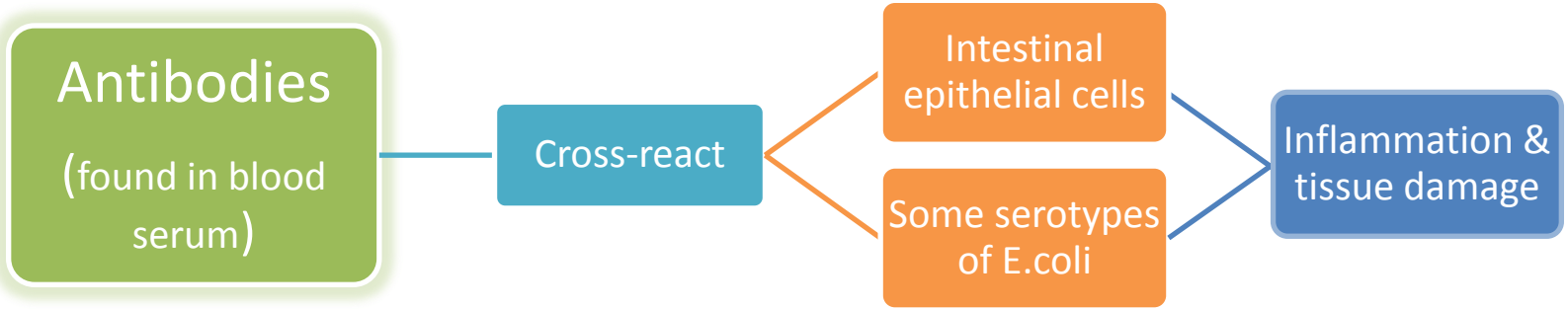
Inflammatory disease of uncertain cause

- Is a disease of the rectum, and the colon
- Rectum is involved in almost all cases
- The disease extends proximally from the rectum in a continuous manner without skip areas.
- The ileum is not involved as a rule
- Age group: 20-30 years (but could occur at any age)

ULCERATIVE COLITIS: Etiology

- Cause is unknown,

  but in some patients:



ULCERATIVE COLITIS: Clinical Features

- It has a chronic course characterized by remissions and relapses = patient experiences attacks (symptoms) then symptom-free periods
- During relapse (attack) patient experiences:
  - Fever
  - Leukocytosis (↑ WBC count)
  - Lower abdominal pain
  - Diarrhea with blood and mucus in the stool

ULCERATIVE COLITIS: Pathology

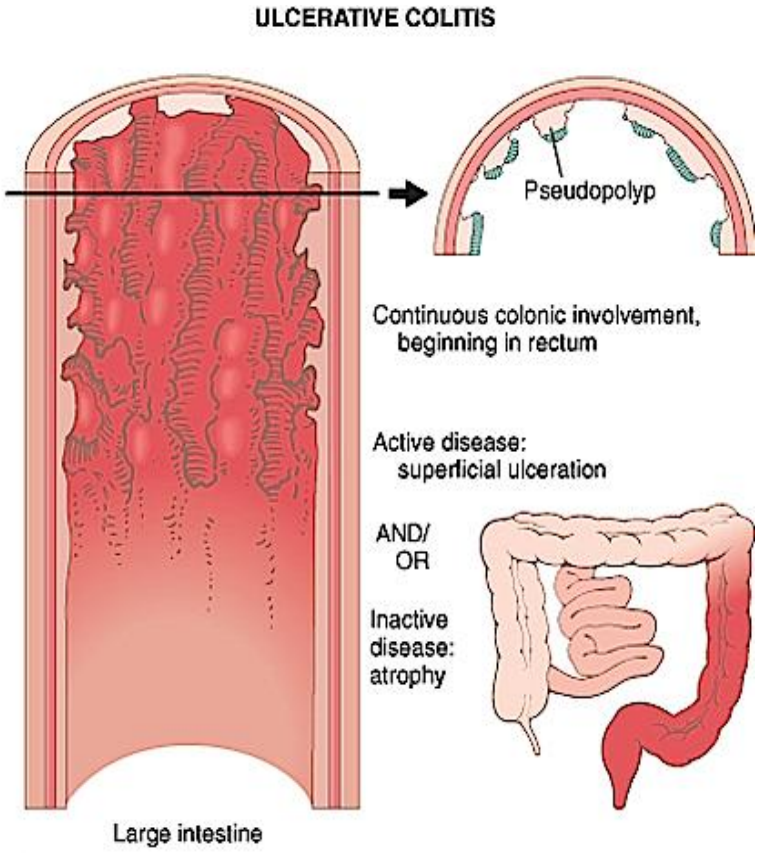
- **Gross Features**

  Involves mainly the mucosa

  – Acute phase; active (ongoing inflammation & tissue destruction):
    - Diffuse hyperemia
    - Numerous superficial ulcerations

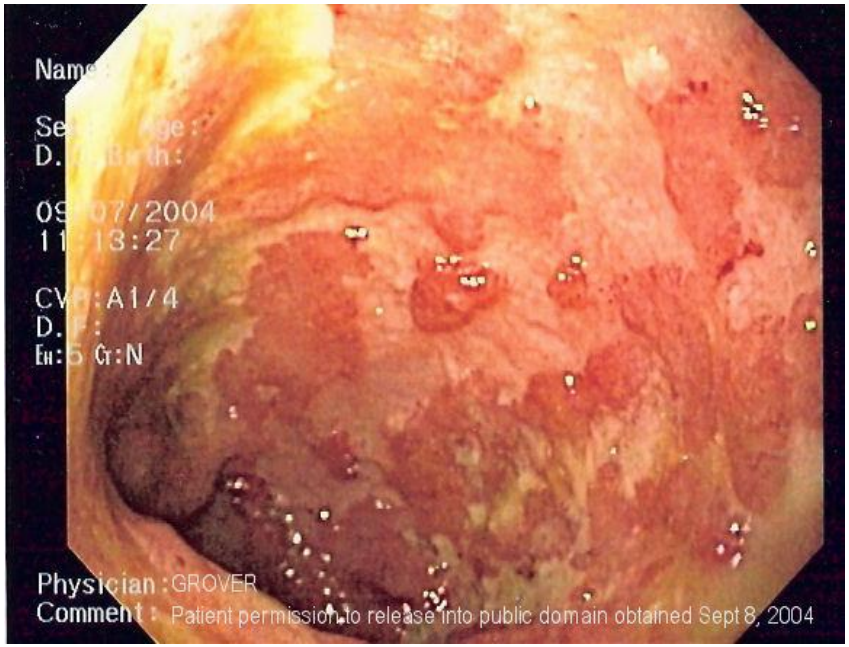
  – Inactive disease
    - Atrophic areas (the entire colon appears narrowed and shortened)

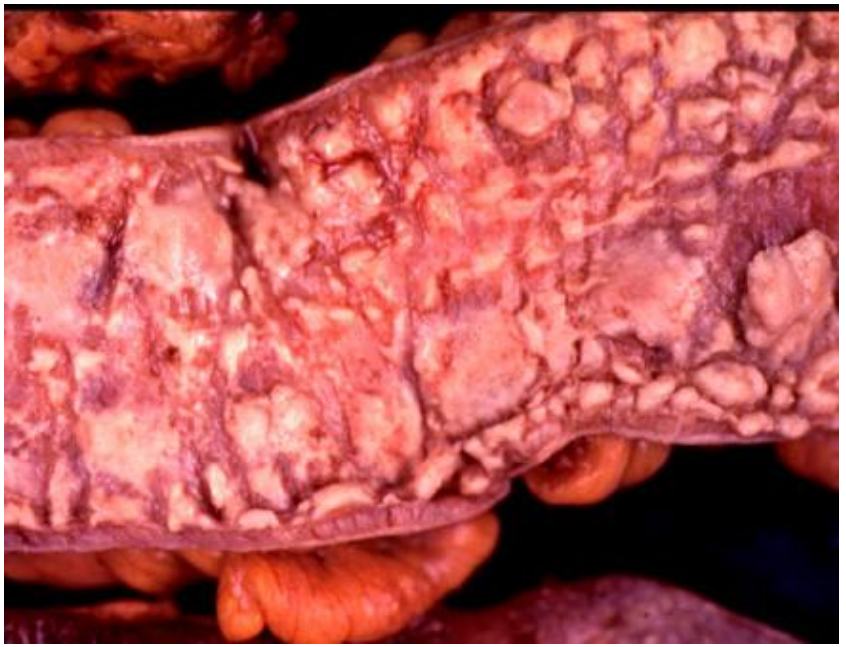
  – Regenerated (non-ulcerated) mucosa → forms polypoid (polyp-like) structures: pseudopolyps



ULCERATIVE COLITIS: Pathology

Summary:





Mild: erythematous, granular surface
Severe: hemorrhagic, edematous, ulcerated
Long-standing (chronic): pseudopolyps, atrophic areas

ULCERATIVE COLITIS: Pathology

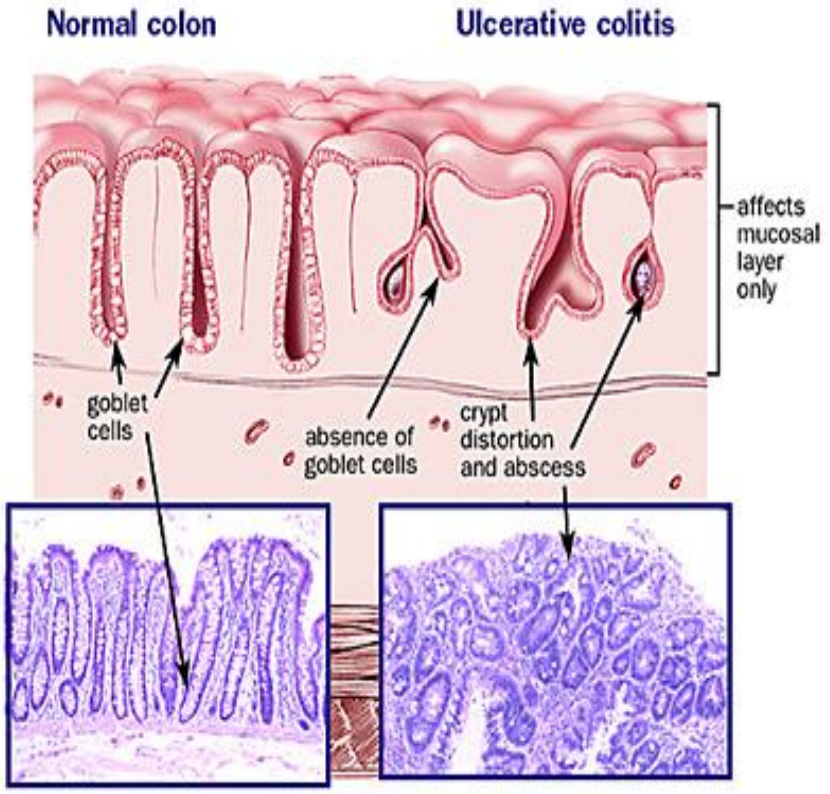
- **Microscopic Features**

  Inflammation restricted to mucosa

  – Active phase → neutrophils (usually invade crypt epithelium → cryptitis → crypt abscess)

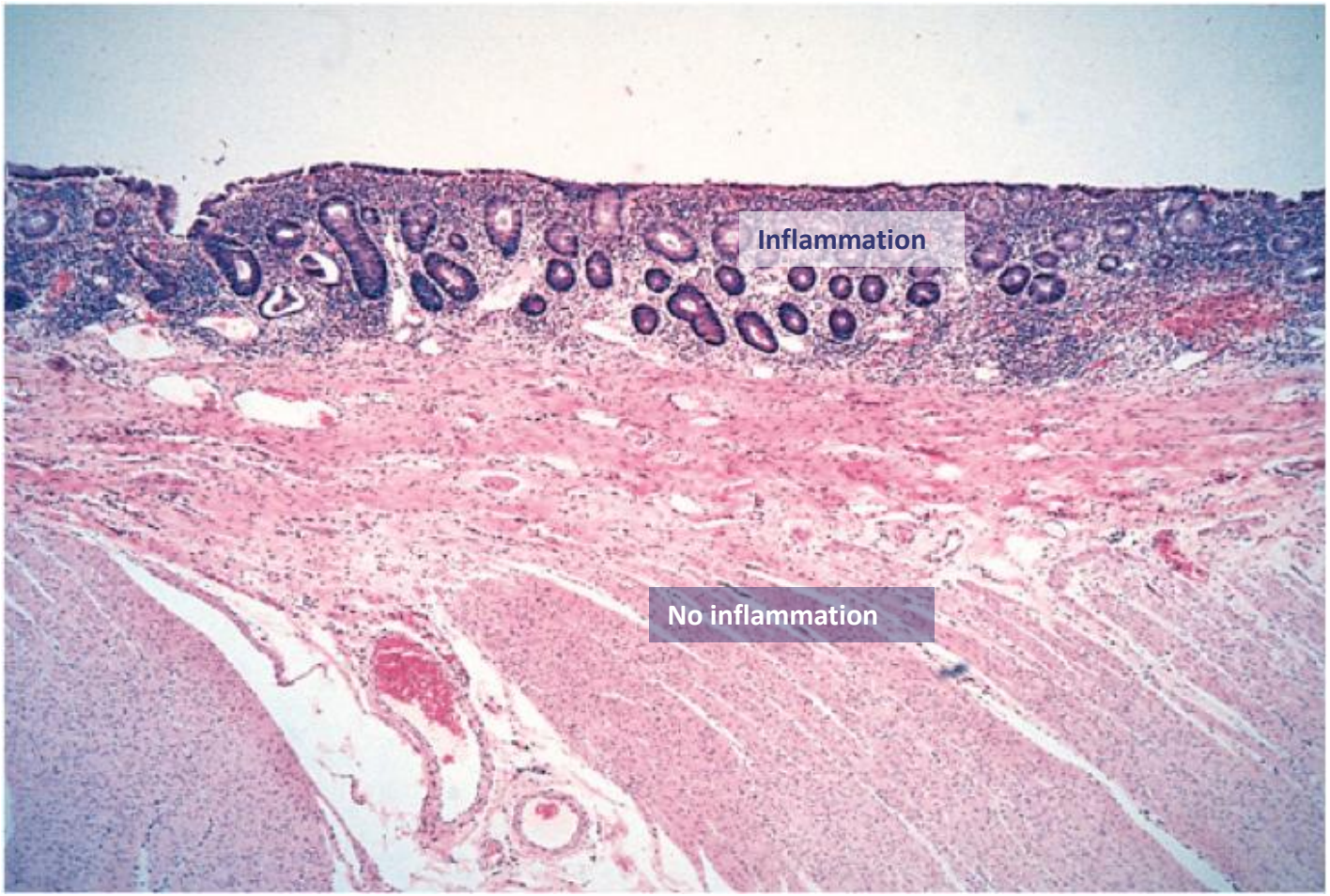
  – Vascular congestion w/edema & hemorrhage

  – Chronic (inactive) phase → crypt atrophy & distortion



Crypt distortion & lymphoid aggregates of mucosa suggest chronicity

ULCERATIVE COLITIS: Pathology

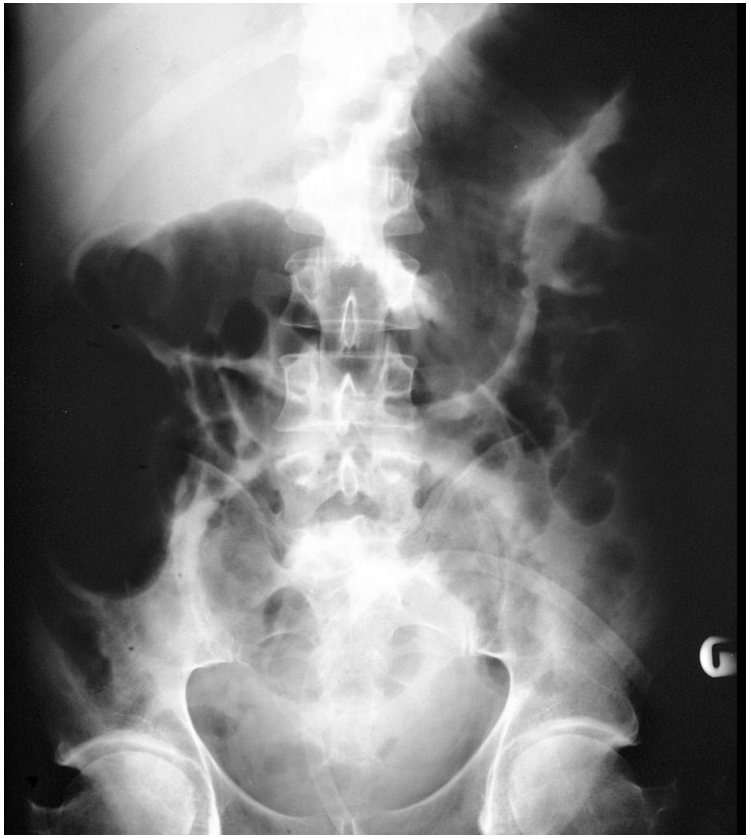


Marked chronic inflammation of the mucosa with atrophy of colonic glands, moderate submucosal fibrosis, and a normal muscle wall

ULCERATIVE COLITIS: Complications

- Acute Phase

1. **Severe bleeding**
2. Severe diarrhea and electrolyte derangements
3. **Toxic megacolon**: a form of acute colonic distension. Colon is dilated & thin-walled.
   - Perforation is the most dangerous of complications → peritonitis



ULCERATIVE COLITIS: Complications

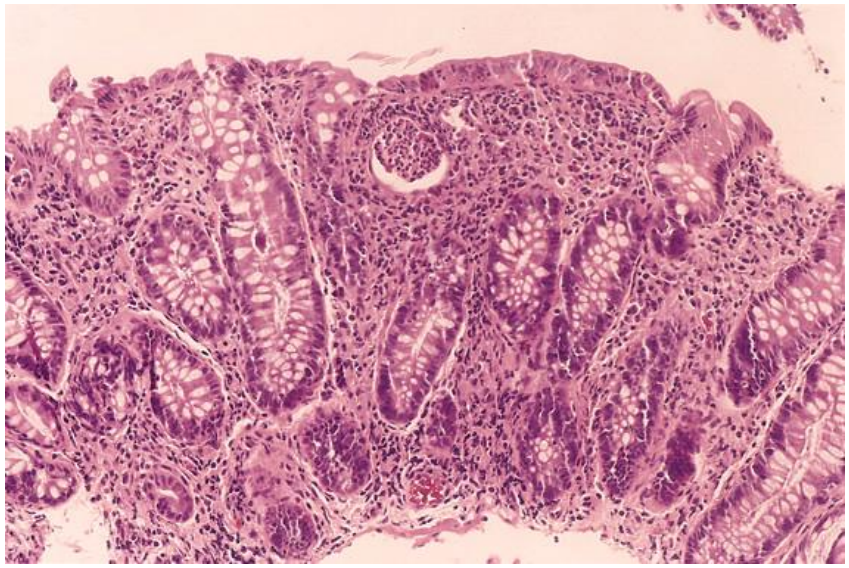
- Chronic Phase

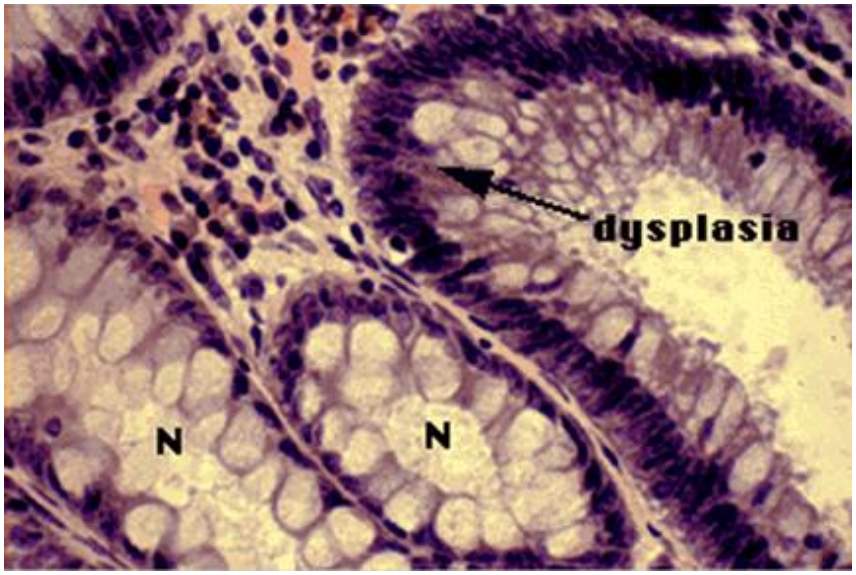
Increased risk of developing colon carcinoma

  - UC is characterized by DNA damage with microsatellite instability (DNA damage due to errors in normal repair processes)
  - Depends on duration and anatomic extent of the disease; patient with pancolitis (UC involving the entire colon) for 10 years has x20 risk of developing cancer

✓ Dysplasia = high risk of developing cancer → colectomy is indicated

ULCERATIVE COLITIS: Complications



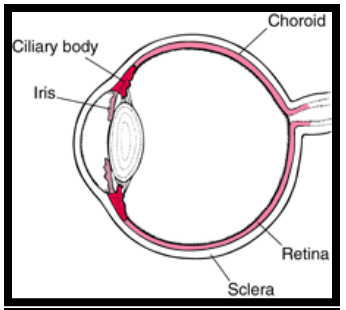


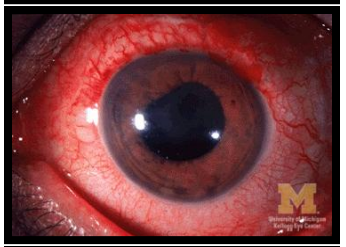
N = normal glands with small basally placed nuclei and large amounts of mucin
Dysplastic cells have cigar shaped hyperchromatic nuclei.

ULCERATIVE COLITIS:
Extraintestinal Manifestations

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

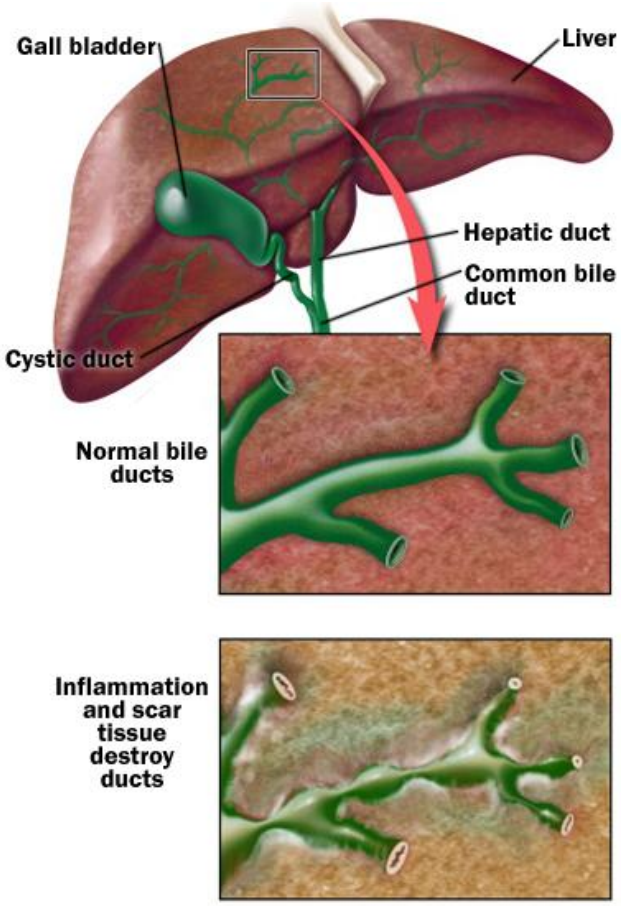
1. **Arthritis**; *migratory polyarthritis:* inflammation of a number of joints that usually settles in the large joints
2. Ocular
   - **Uveitis**: inflammation of the uvea
     - Uvea: vascular layer of the eye = iris, ciliary body and choroid
   - The inflammation could involve the iris and anterior chamber, the vitreous cavity, or the choroid
3. Dermatologic
   - **Pyoderma gangrenosum**: a condition that causes tissue to become necrotic, with deep ulcers (usually in the leg)





ULCERATIVE COLITIS:
Extraintestinal Manifestations

- Hepatobiliary
  - **Sclerosing pericholangitis**: Fibrosis around bile ducts in the liver → obstructive jaundice
    - May also lead to liver cirrhosis and liver cancer



Other extra-intestinal manifestations: Urologic (stones, ureteral obstruction), metabolic bone disorders (↓ bone density → ↑ risk of fractures), thromboembolic disorders (venous and arterial thrombosis)