Inflammatory Bowel Disease

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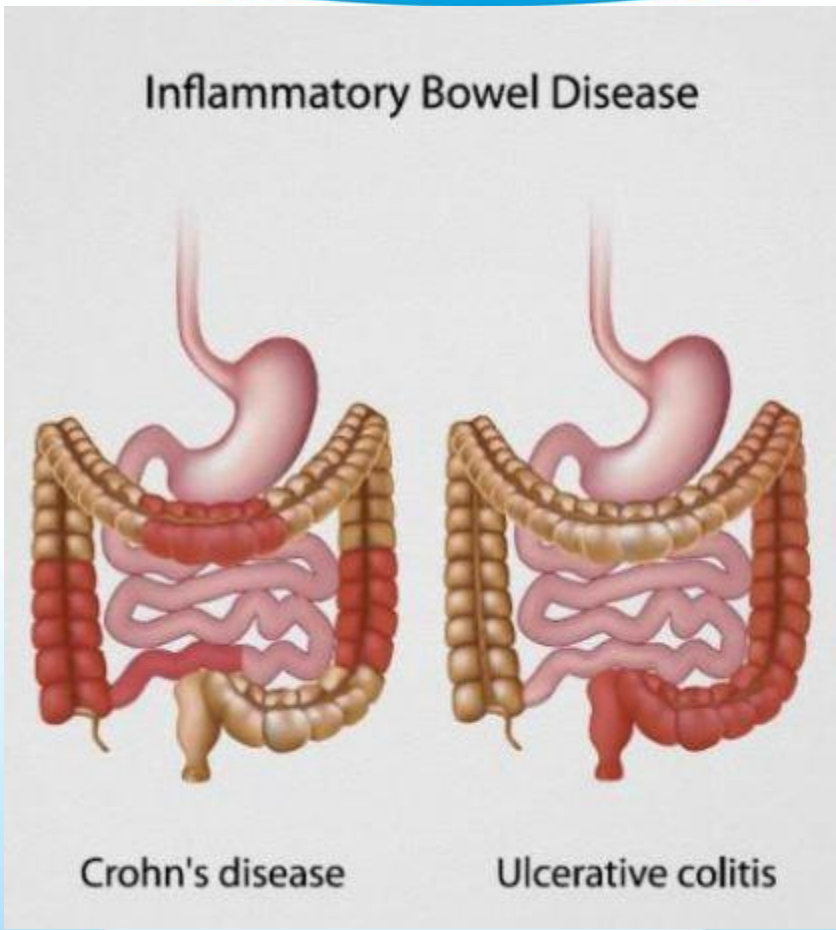
Inflammatory bowel disease (IBD)

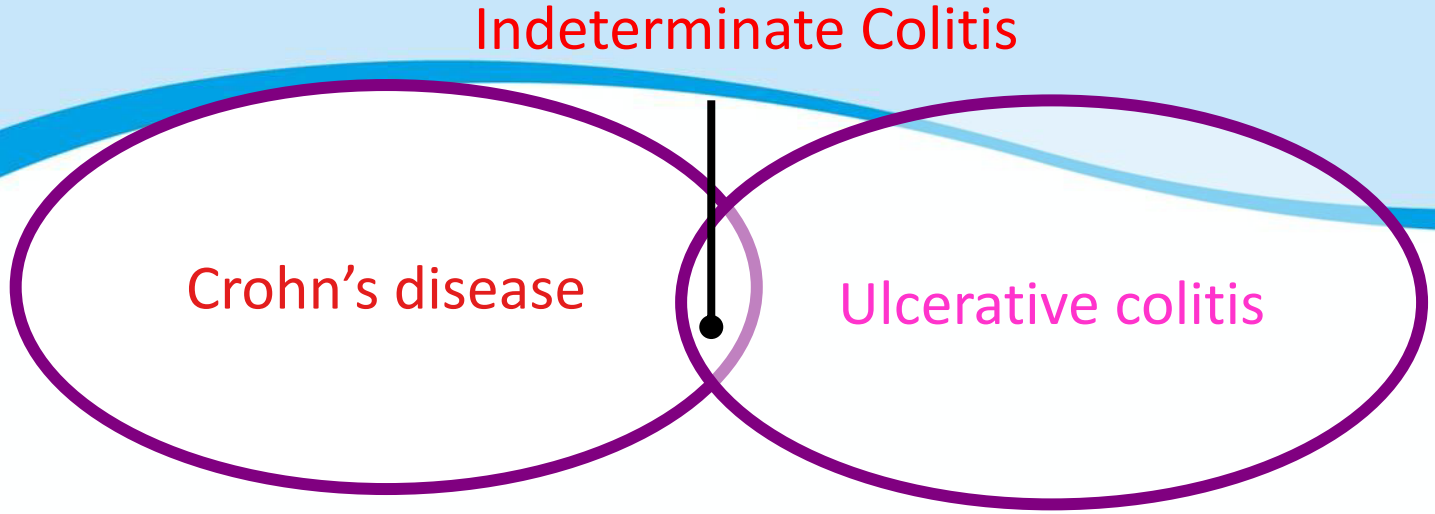
- represents a group of intestinal disorders that cause prolonged inflammation of the digestive tract.
- It is a spectrum of chronic idiopathic inflammatory condition. Introduction



Classification

- Ulcerative colitis: is a disease that causes mucosal inflammation and sores (ulcers) in the lining of the large intestine (colon).
- Crohn's disease: Crohn's disease is a chronic, relapsing and remitting inflammatory disease of the gastrointestinal tract, affecting any site from mouth to anus.

Inflammatory Bowel Disease :

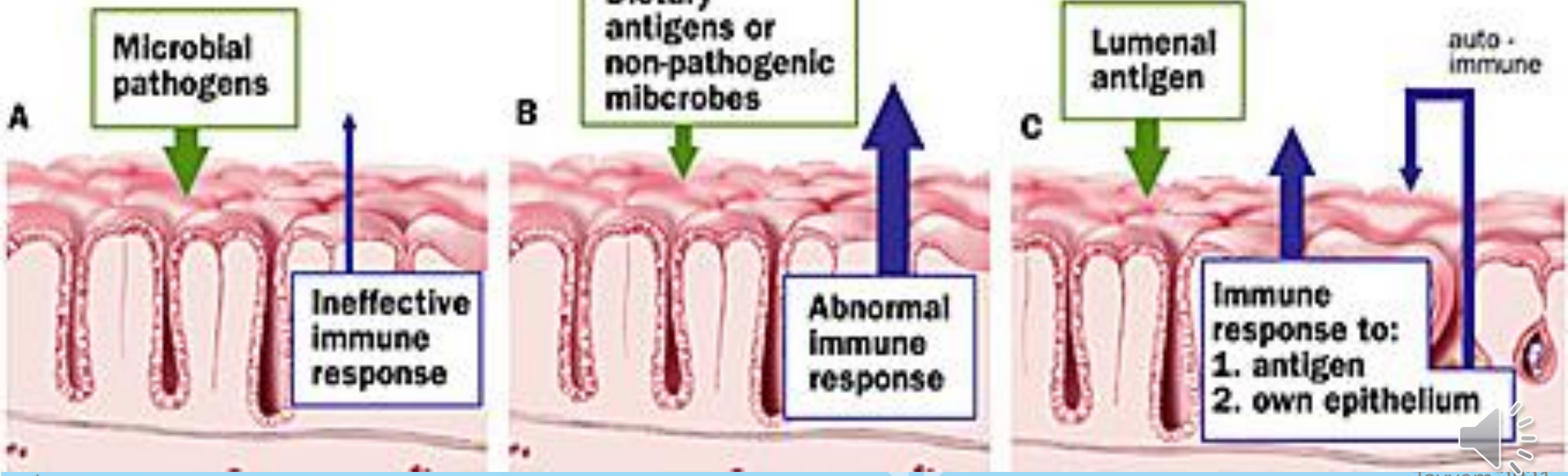


Inflammatory Bowel Disease :

Indeterminate Colitis

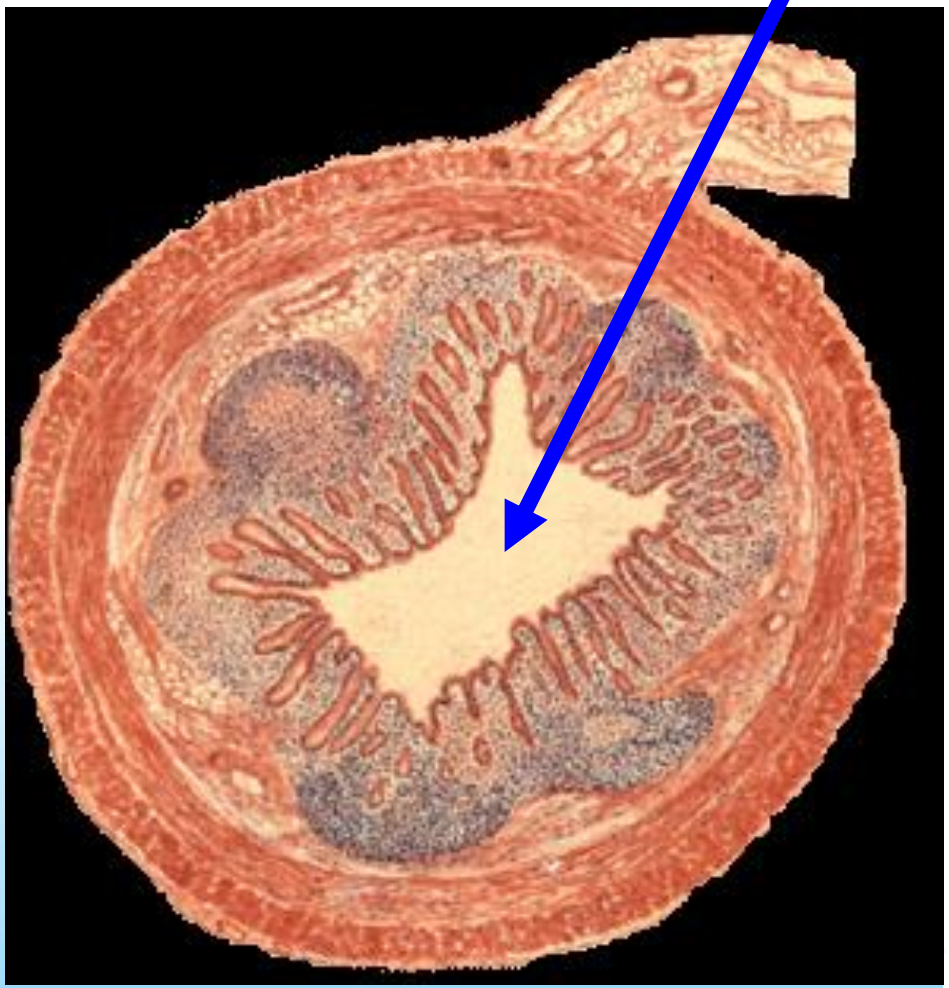
Crohn's disease

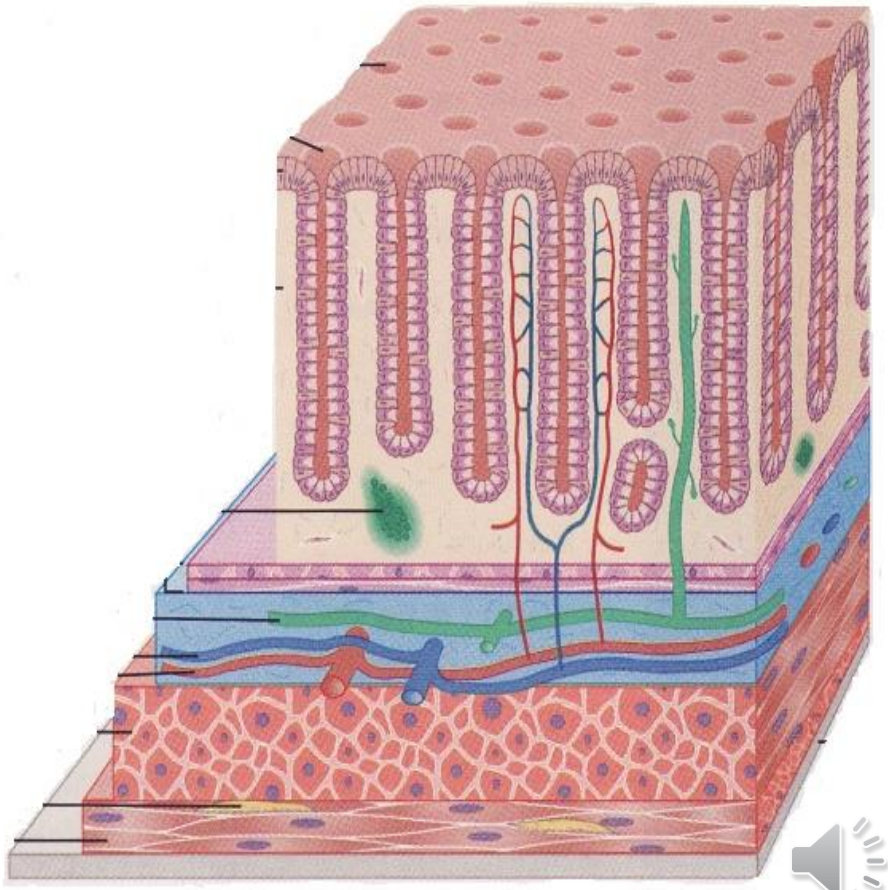
Ulcerative colitis



Layers of the Wall of the Colon

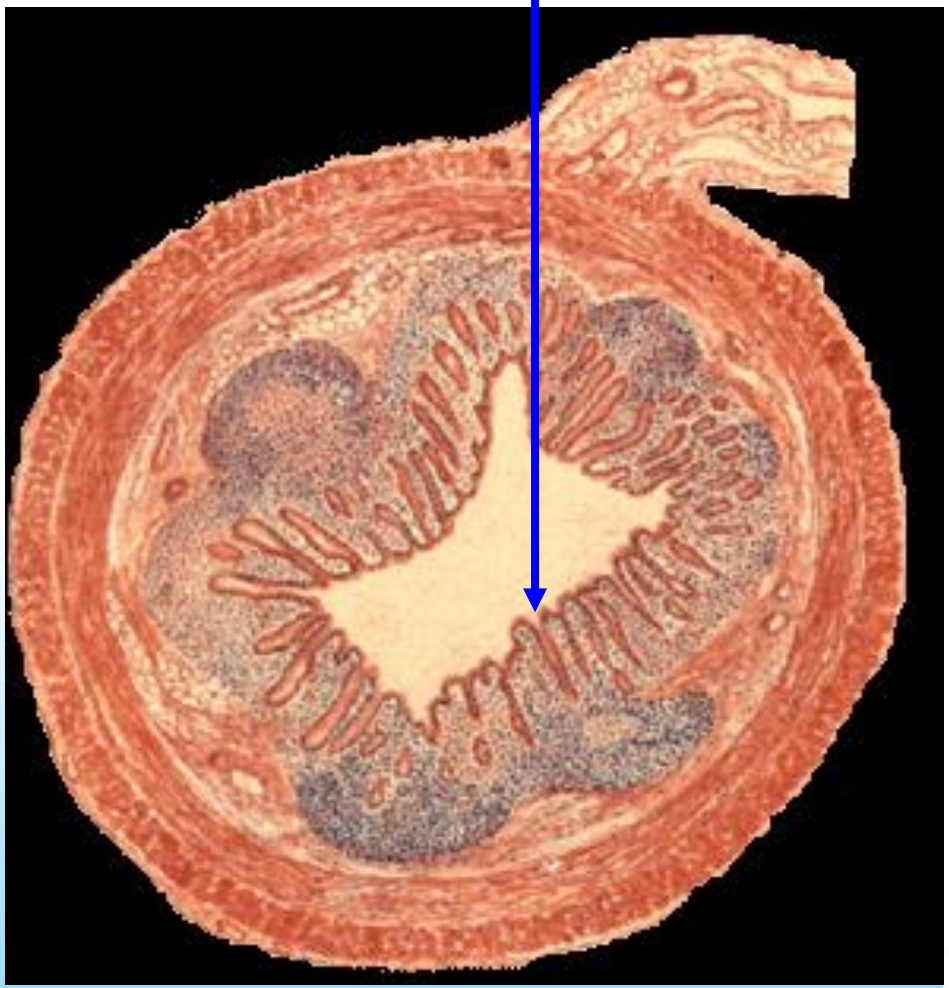
Lumen

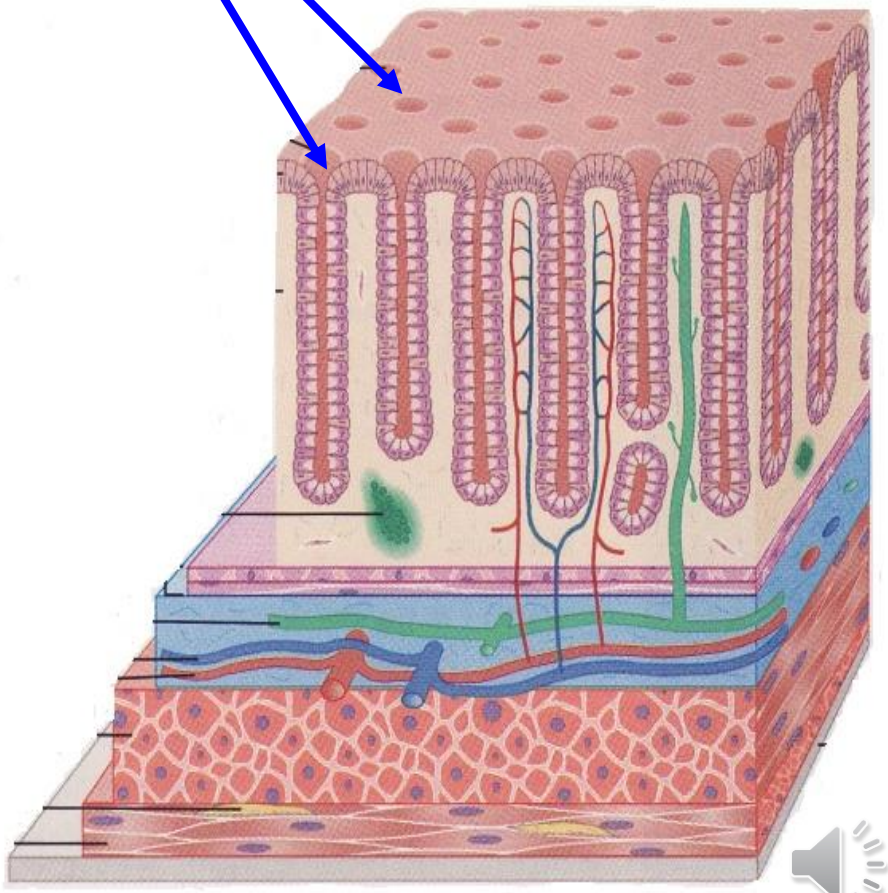




Layers of the Wall of the Colon

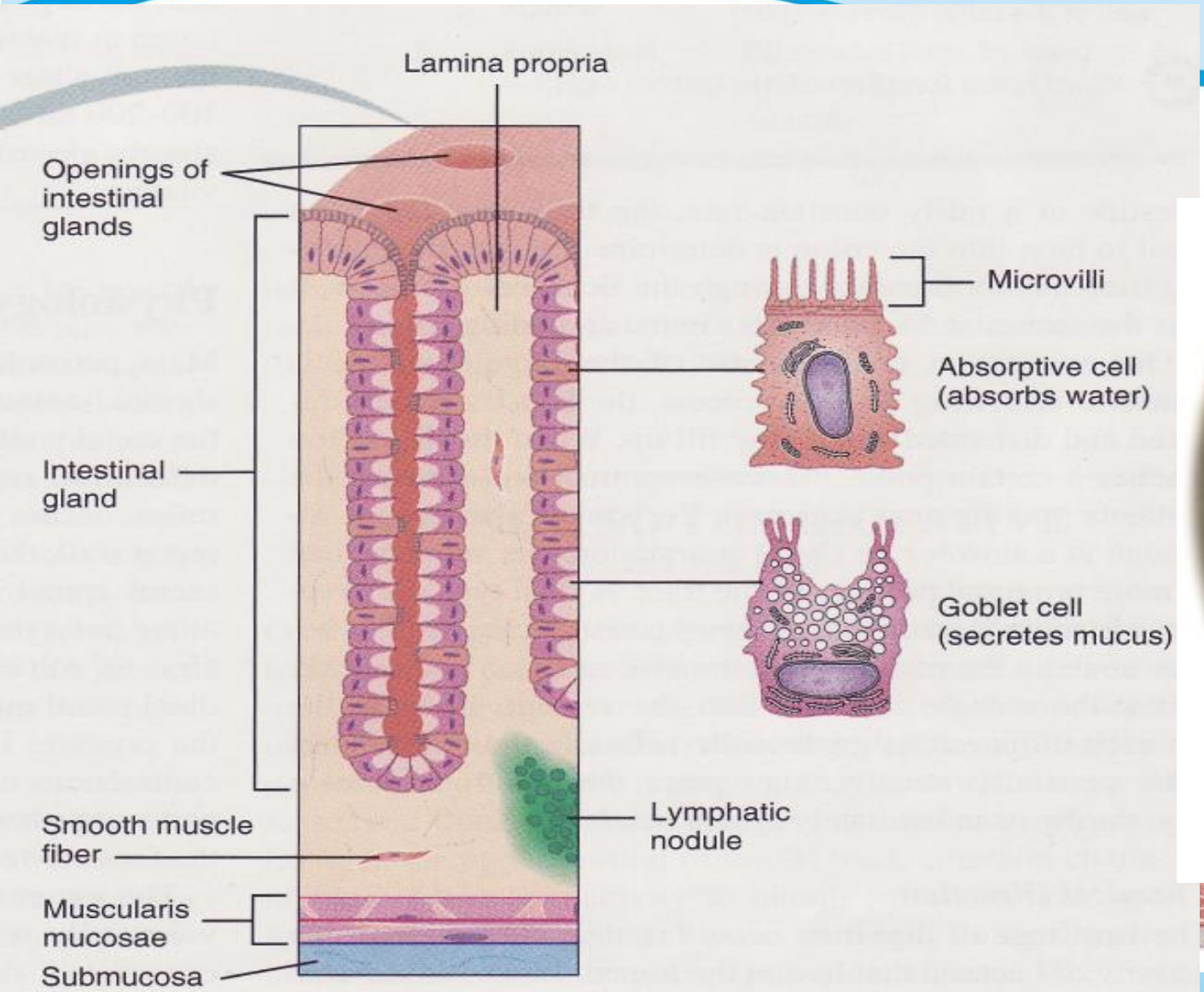
Openings of the Crypts of Lieberkuhn





Layers of the Wall of the Colon

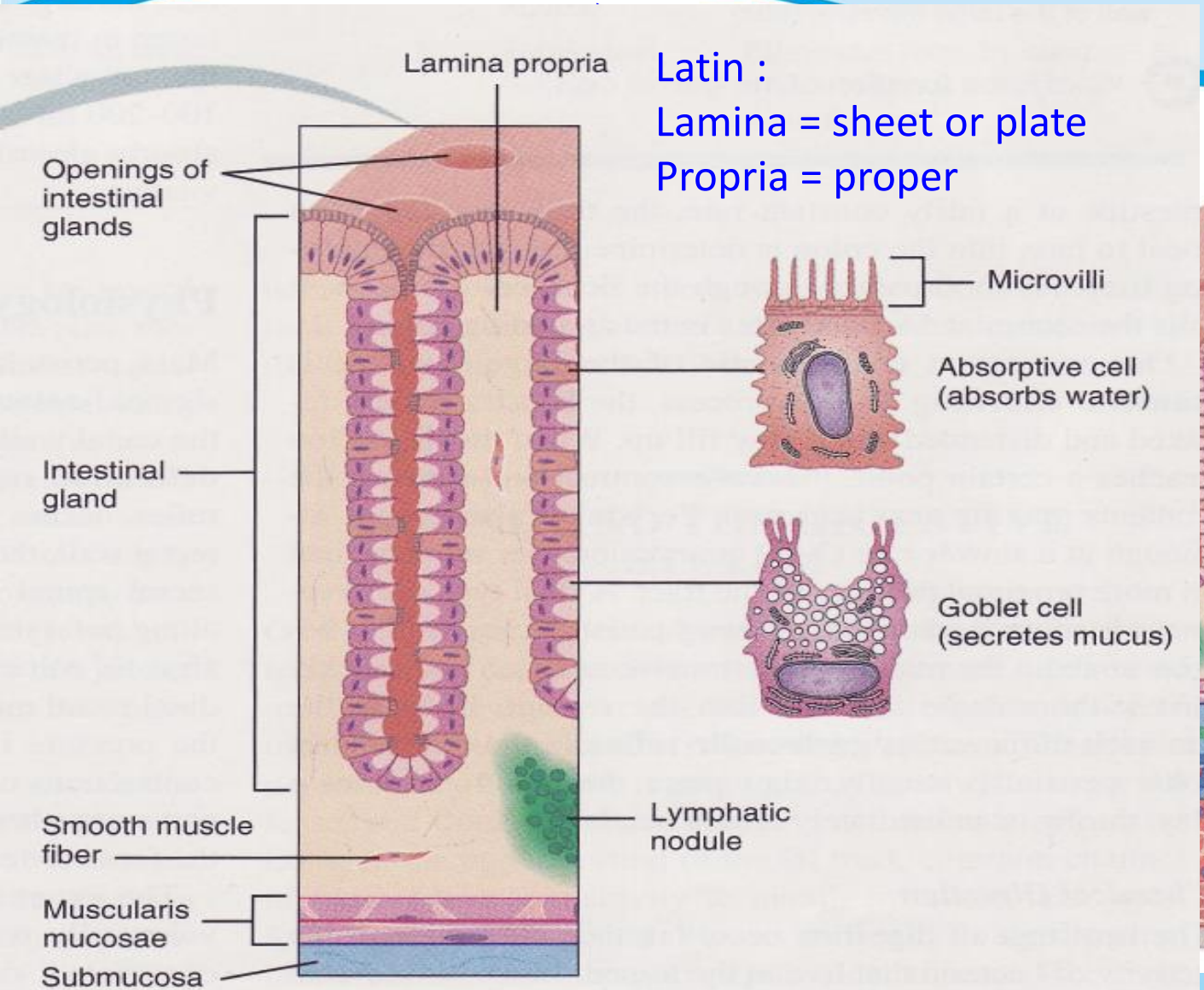
The Crypts of Lieberkuhn



Johann N. Lieberkuhn
(1711-1756)

Layers of the Wall of the Colon

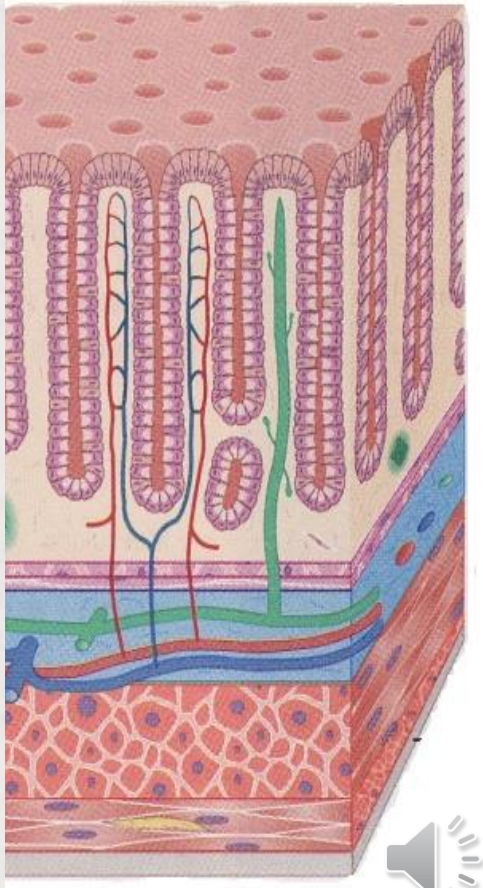
Lamina Propria



Latin :

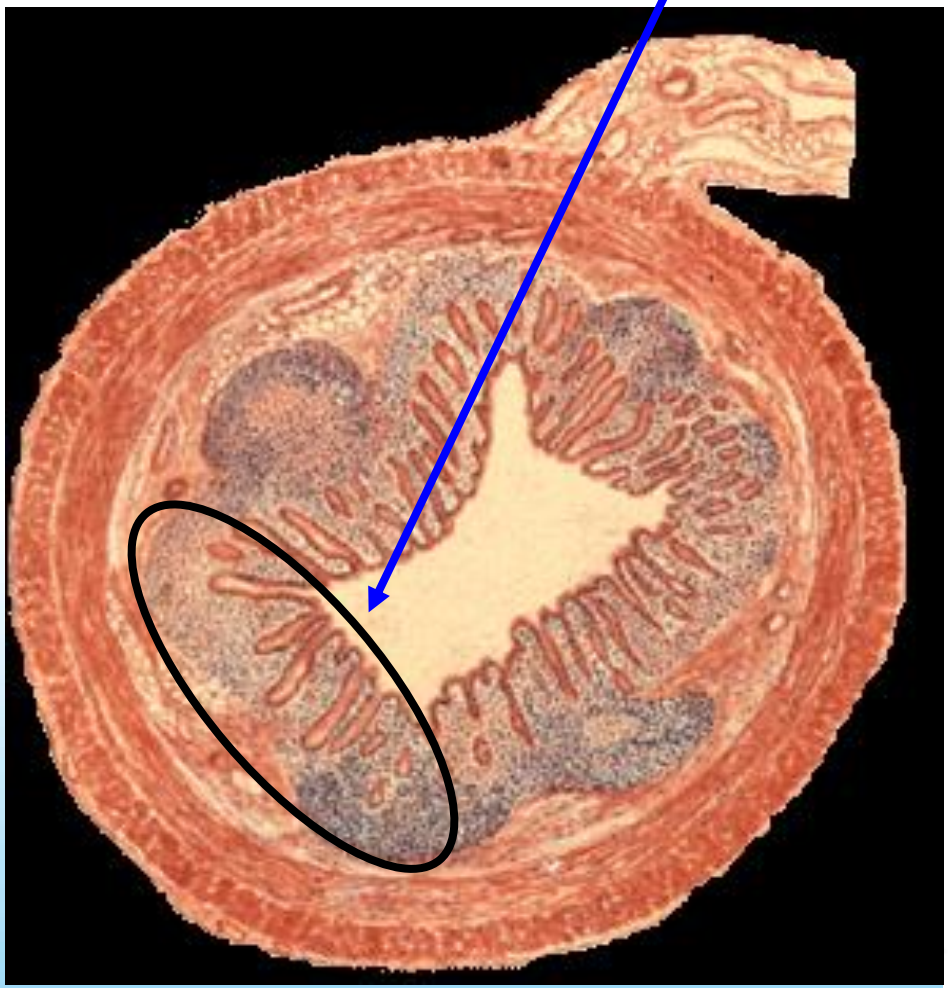
Lamina = sheet or plate

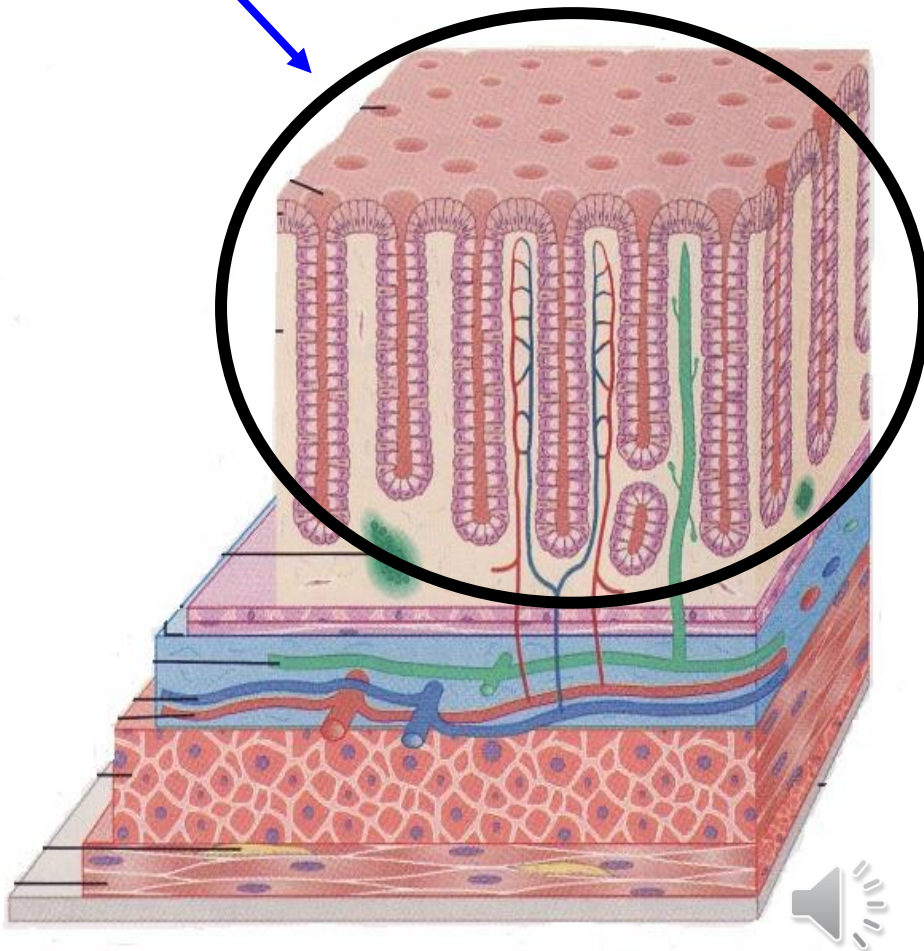
Propria = proper



Layers of the Wall of the Colon

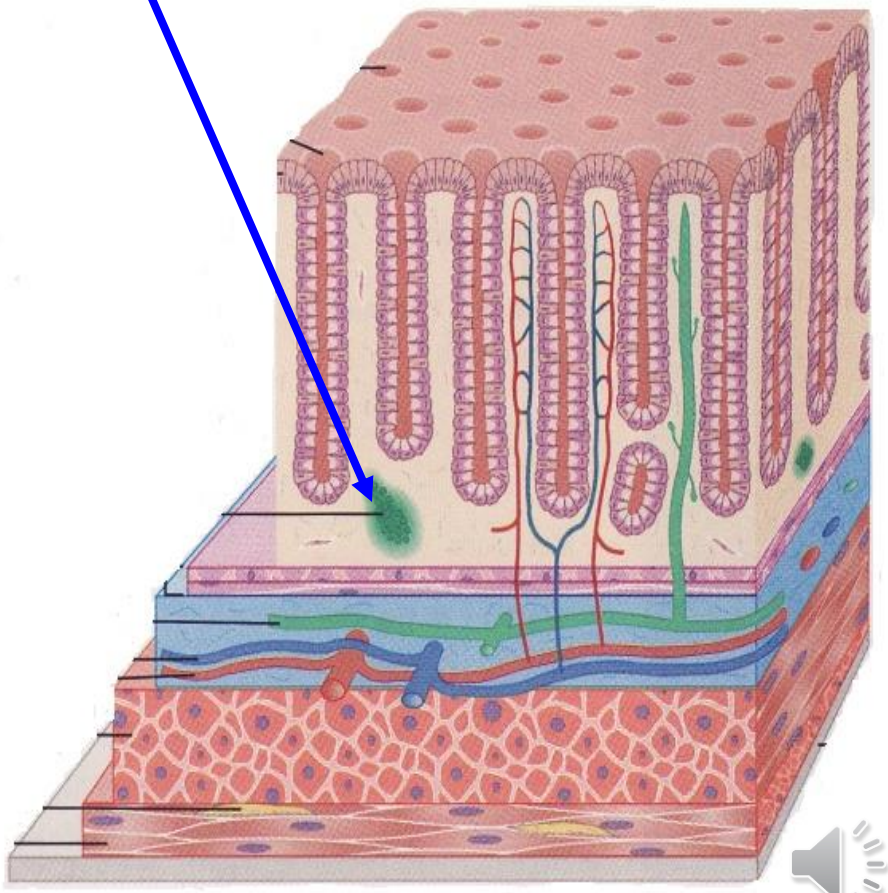
Mucosa





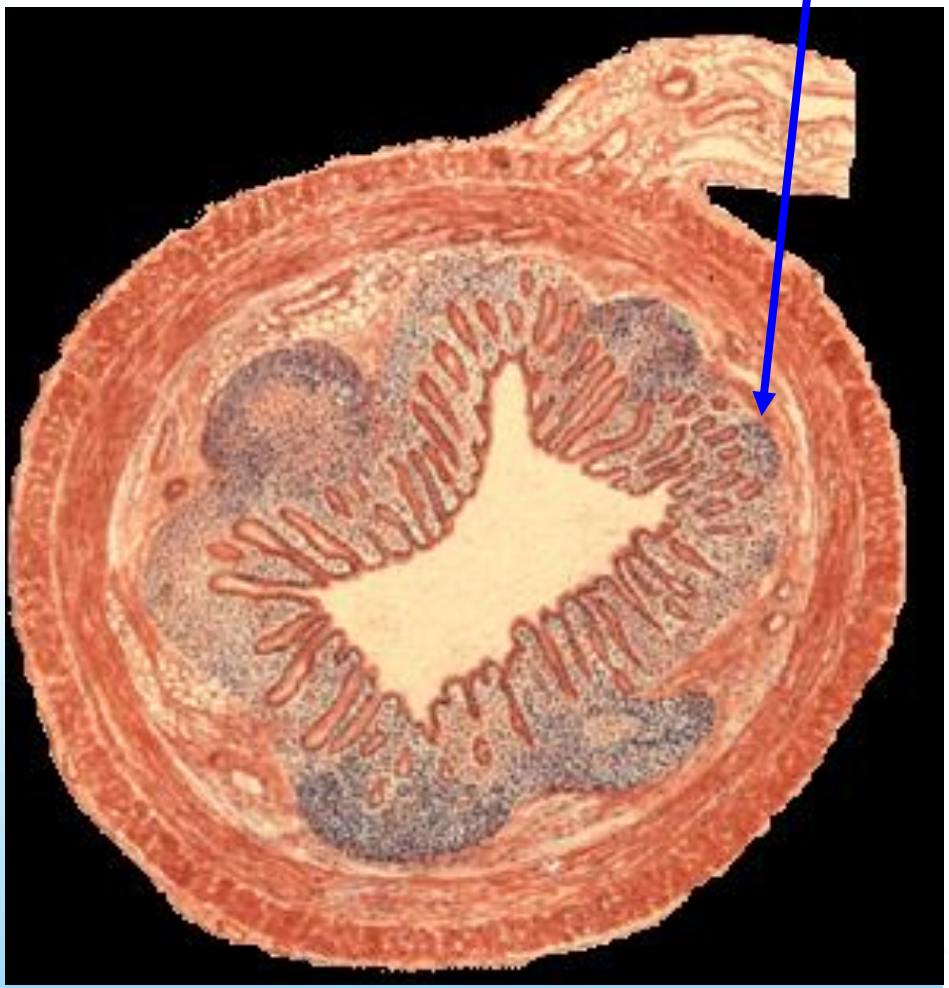
Layers of the Wall of the Colon

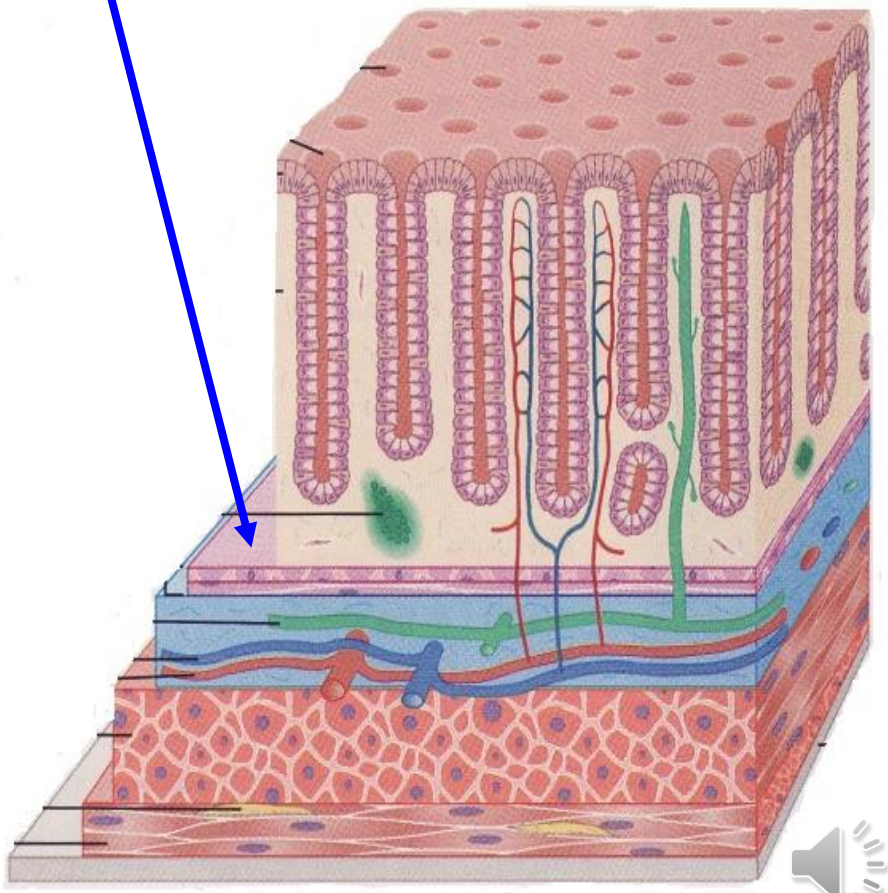
Lymphatic nodule in Mucosa



Layers of the Wall of the Colon

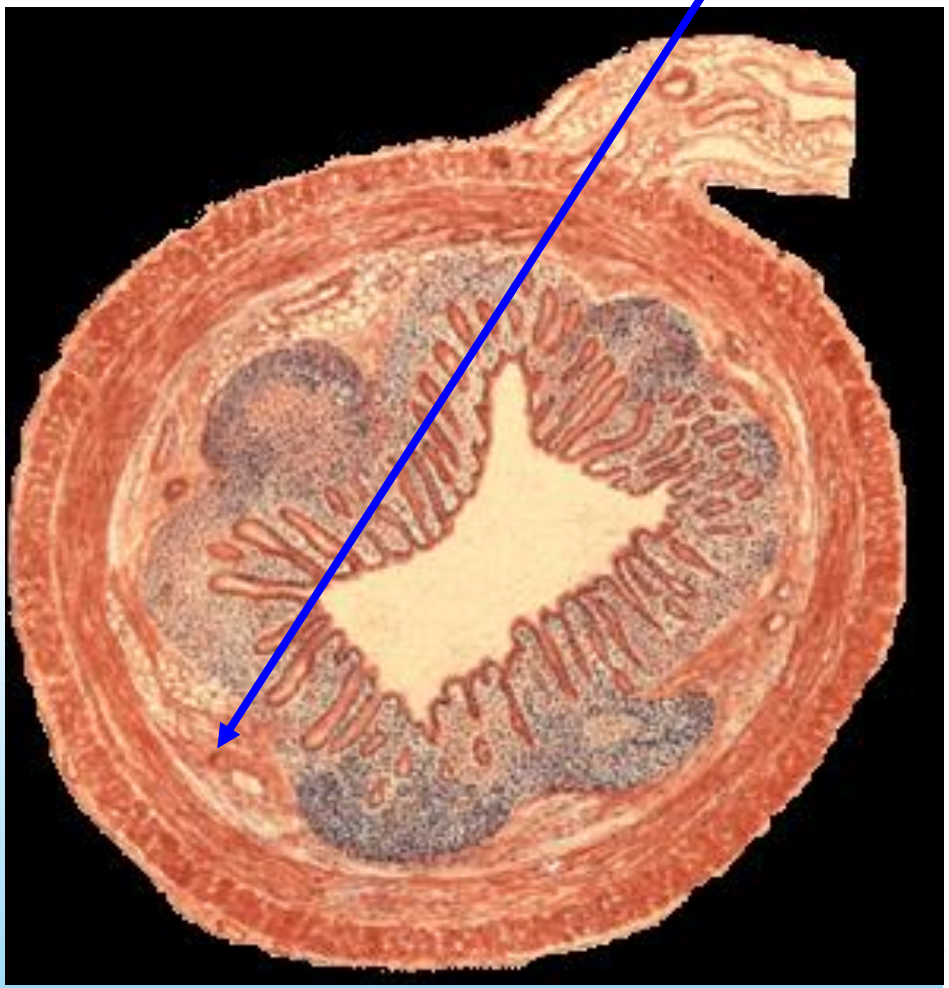
Muscularis Mucosa

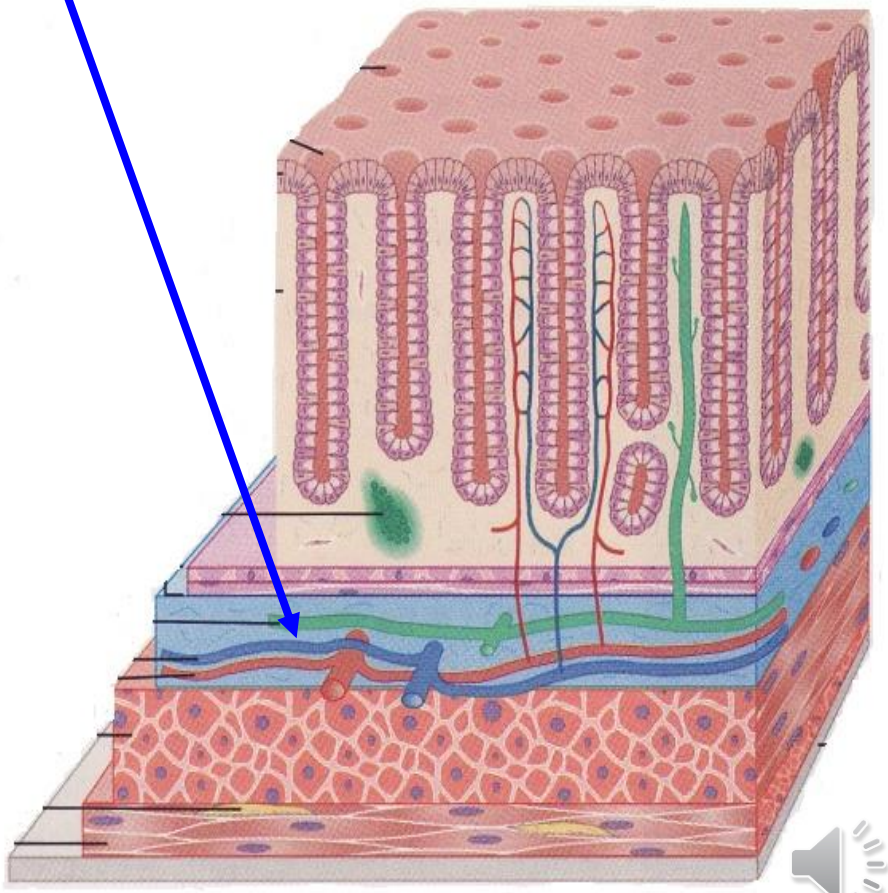




Layers of the Wall of the Colon

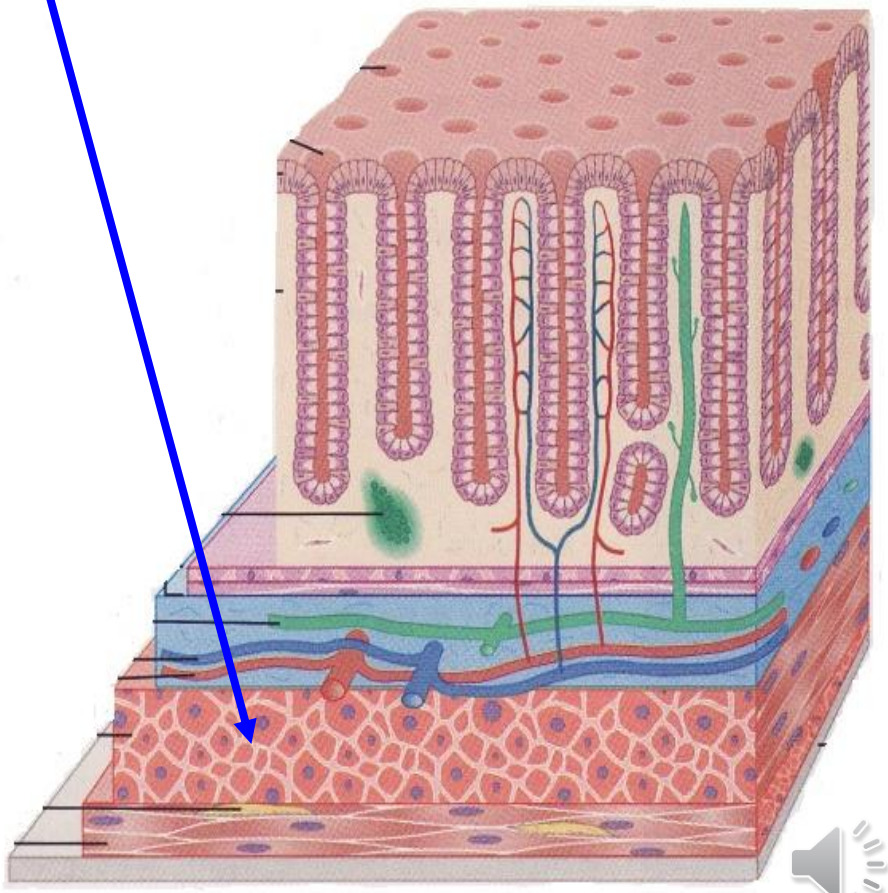
Submucosa





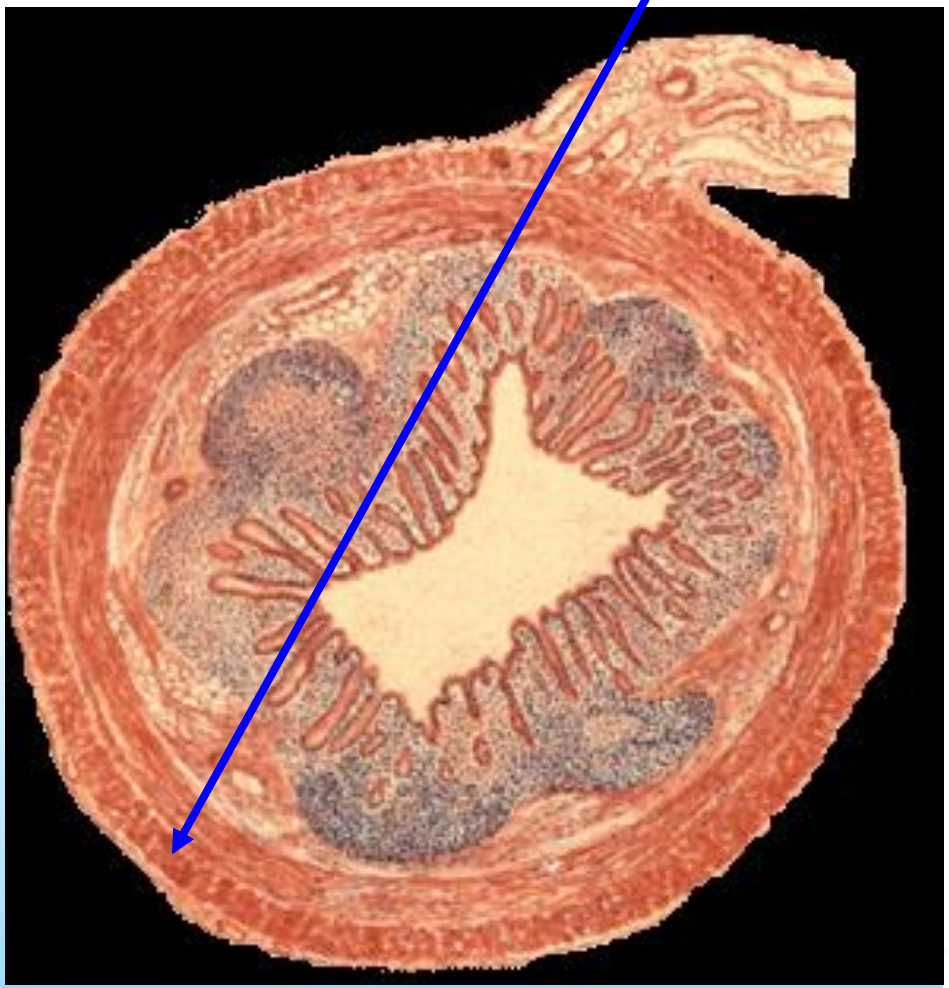
Layers of the Wall of the Colon

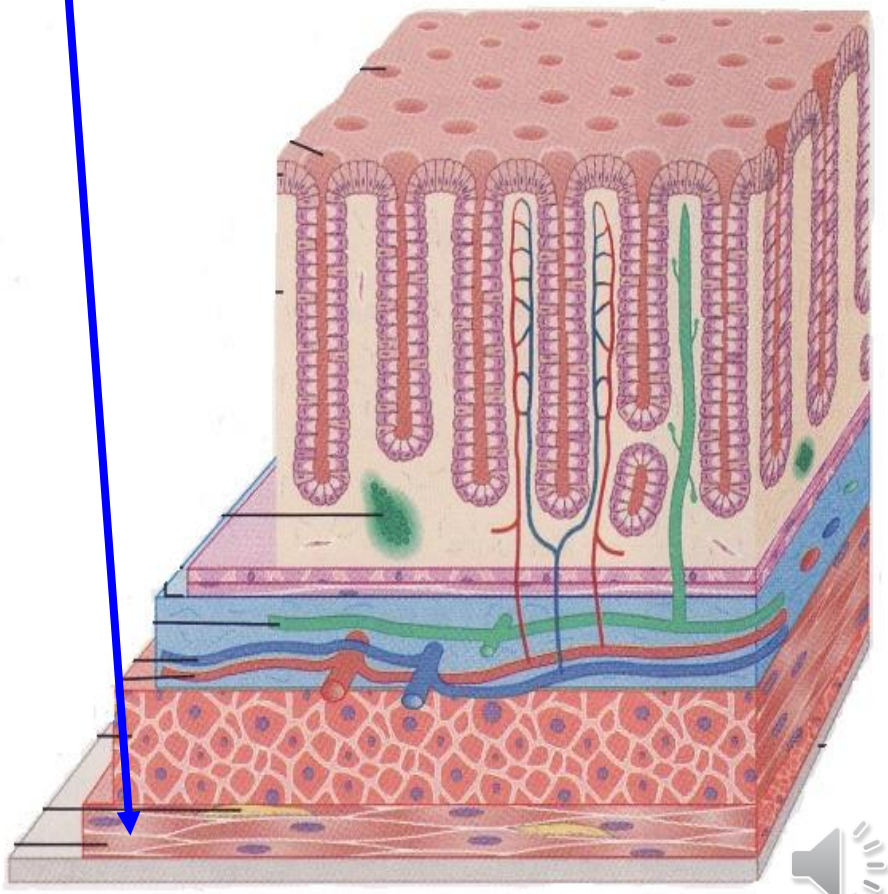
Circular layer of Muscle



Layers of the Wall of the Colon

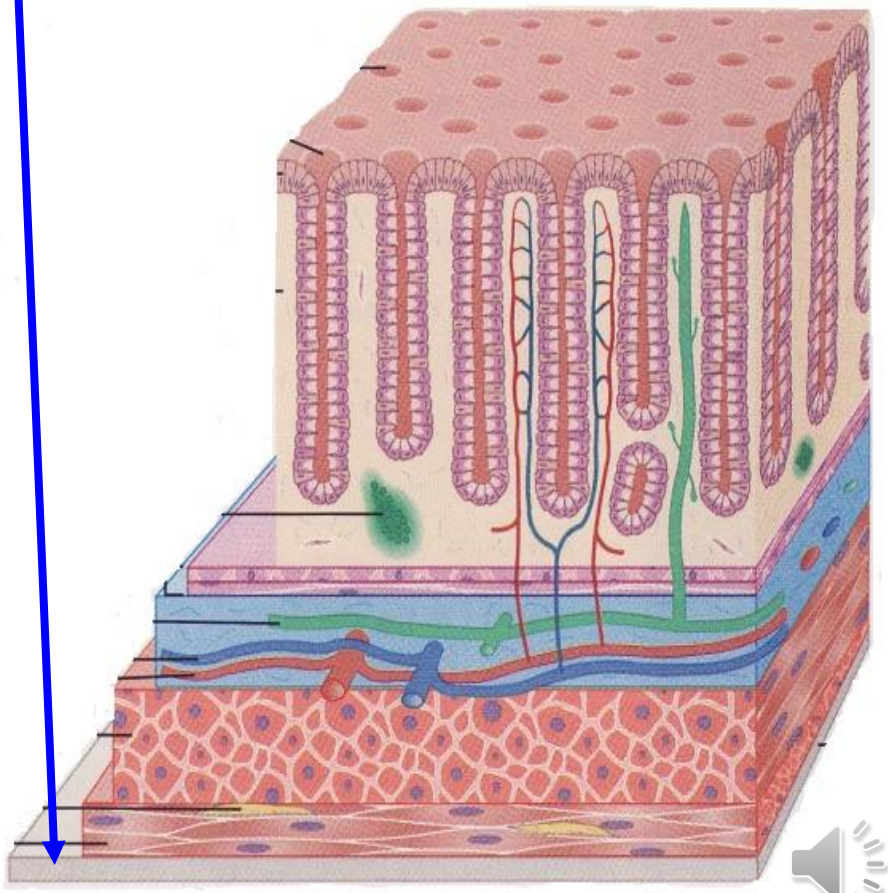
Longitudinal layer of Muscle



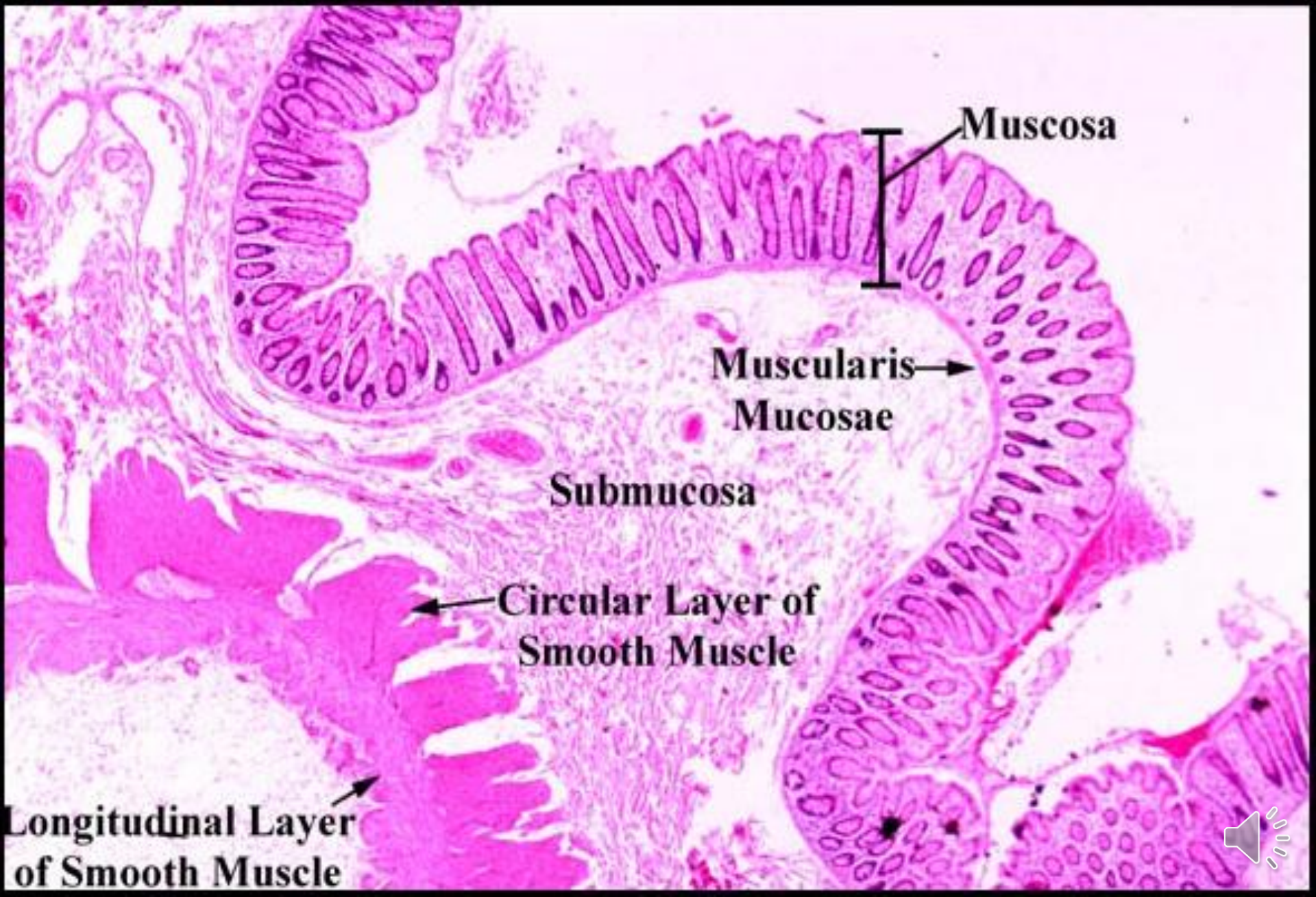


Layers of the Wall of the Colon

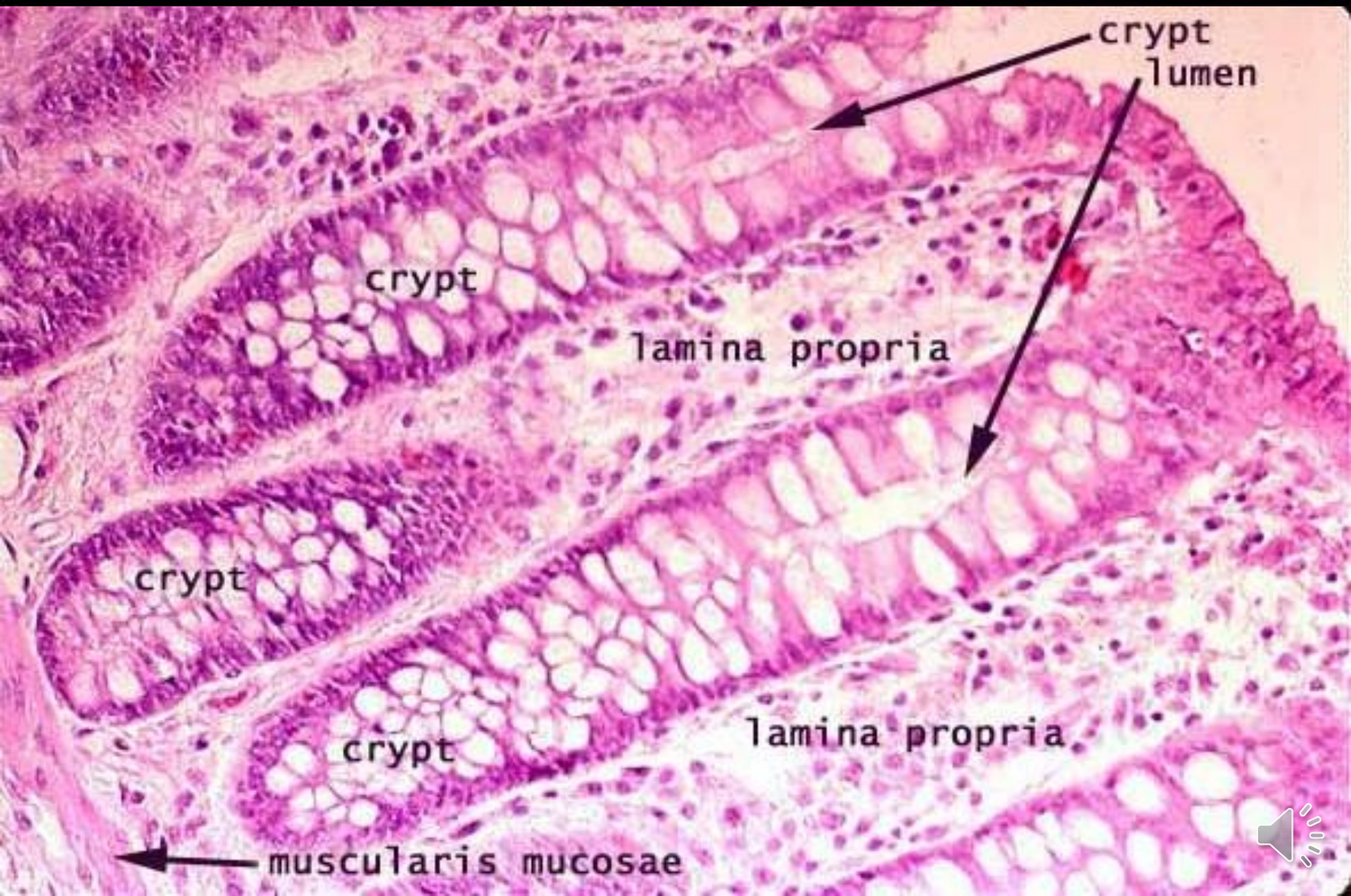
Serosa



The layers of the wall of the colon



Mucosa of the Colon



Crohn's disease

- Extends into the deeper layers of the *intestinal wall*
- and may affect the mouth, esophagus, stomach,
- Transmural inflammation and skip lesions.
- Sites:
  - In 50% cases ileocolic
  - 30% ileal
  - 20% -colic region.
- Regional enteritis

Macroscopic pathology

- Can affect any part of GIT
- Transmural
- Segmental with skip lesions
- Cobblestone appearance
- Creeping fat- adhesions & fistula

Microscopic features

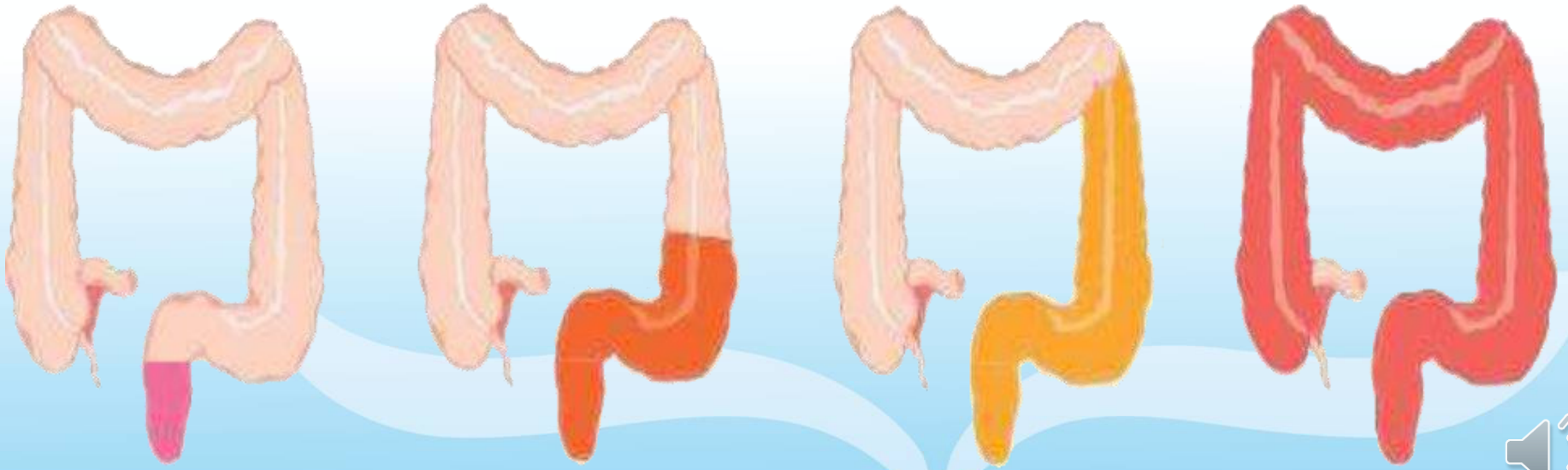
- Aphthous ulcerations
- Focal crypt abscesses
- Granuloma-pathognomic
- Submucosal or subserosal lymphoid aggregates
- Transmural with fissure formation

Ulcerative colitis

- causes ulceration and inflammation of the inner lining of the colon and rectum.
- It is usually in the form of characteristic ulcers

Macroscopic Pathology

- Ulcerative colitis
- Usually involves rectum & extends proximally to involve all or part of colon.
- Spread is in continuity.



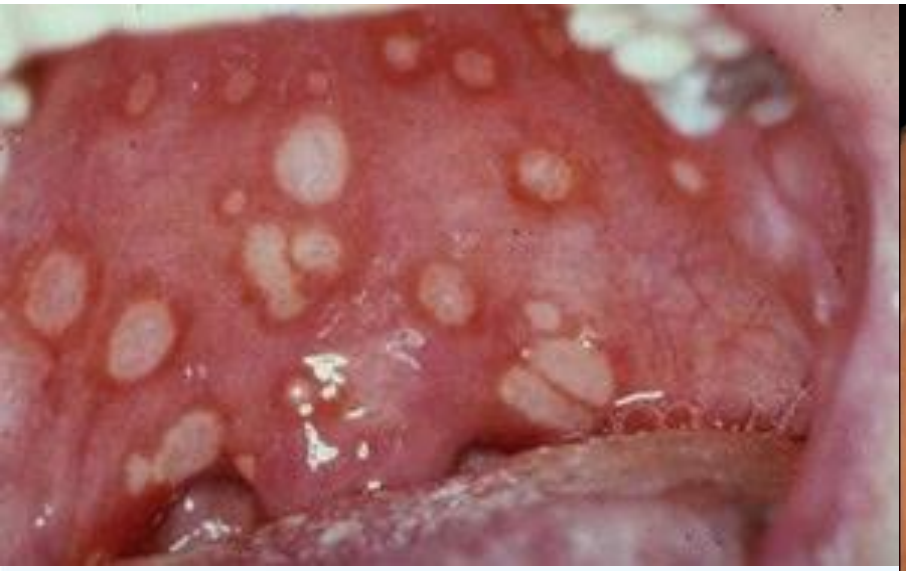
Cont

- **Mild disease- erythema & sand paper** appearance(fine granularity)
- **Moderate-marked erythema, coarse** granularity, contact bleeding & no ulceration
- **Severe- spontaneous bleeding, edematous &** ulcerated(collar button ulcer).
- **Long standing-epithelial regeneration so** pseudopolyps , mucosal atrophy & disorientation leads to a precancerous condition.
- Eventually can lead to shortening and narrowing of colon.
- **Fulminant disease-Toxic colitis/megacolon**

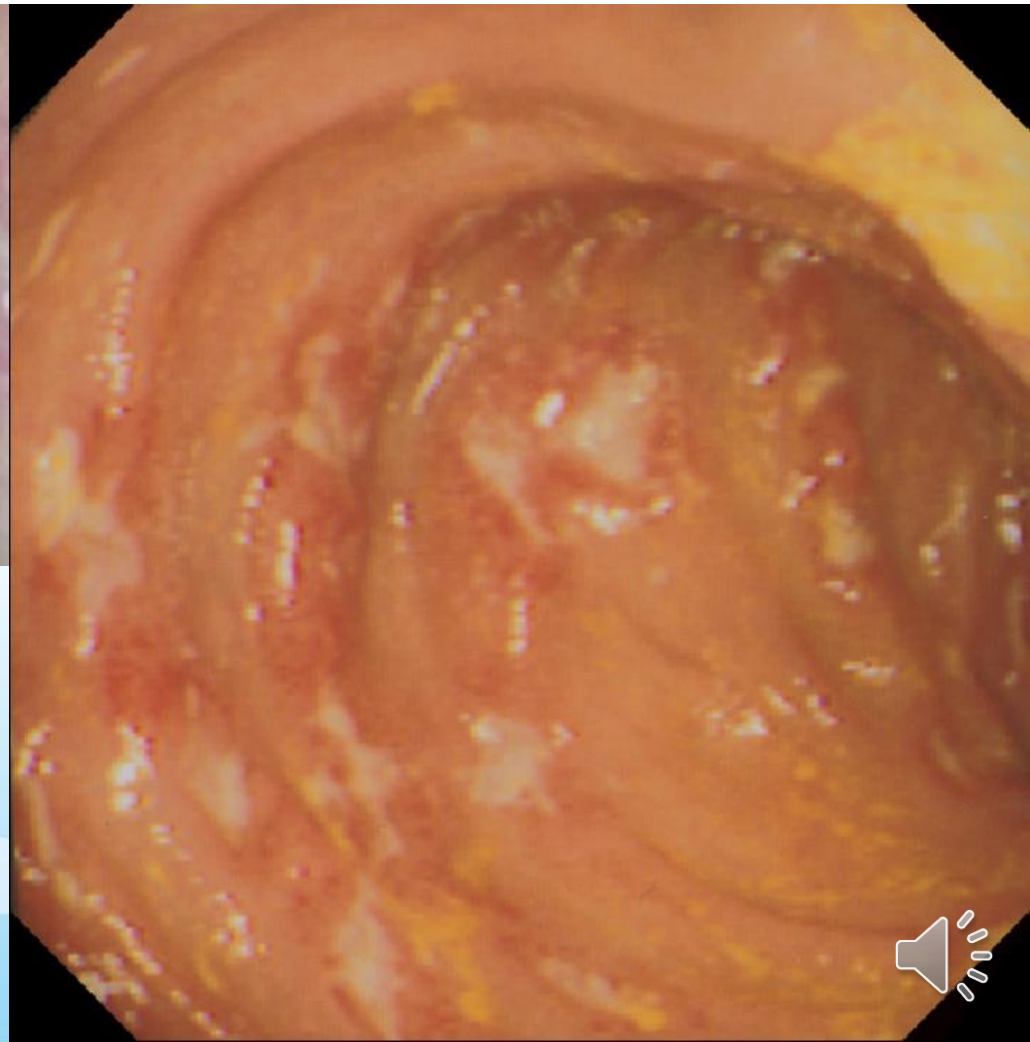
Inflammatory Bowel Disease

…the punched out oral mucosal lesion of Behcet's disease :

Behcet's



Crohn's



Aphthoid :

Greek :

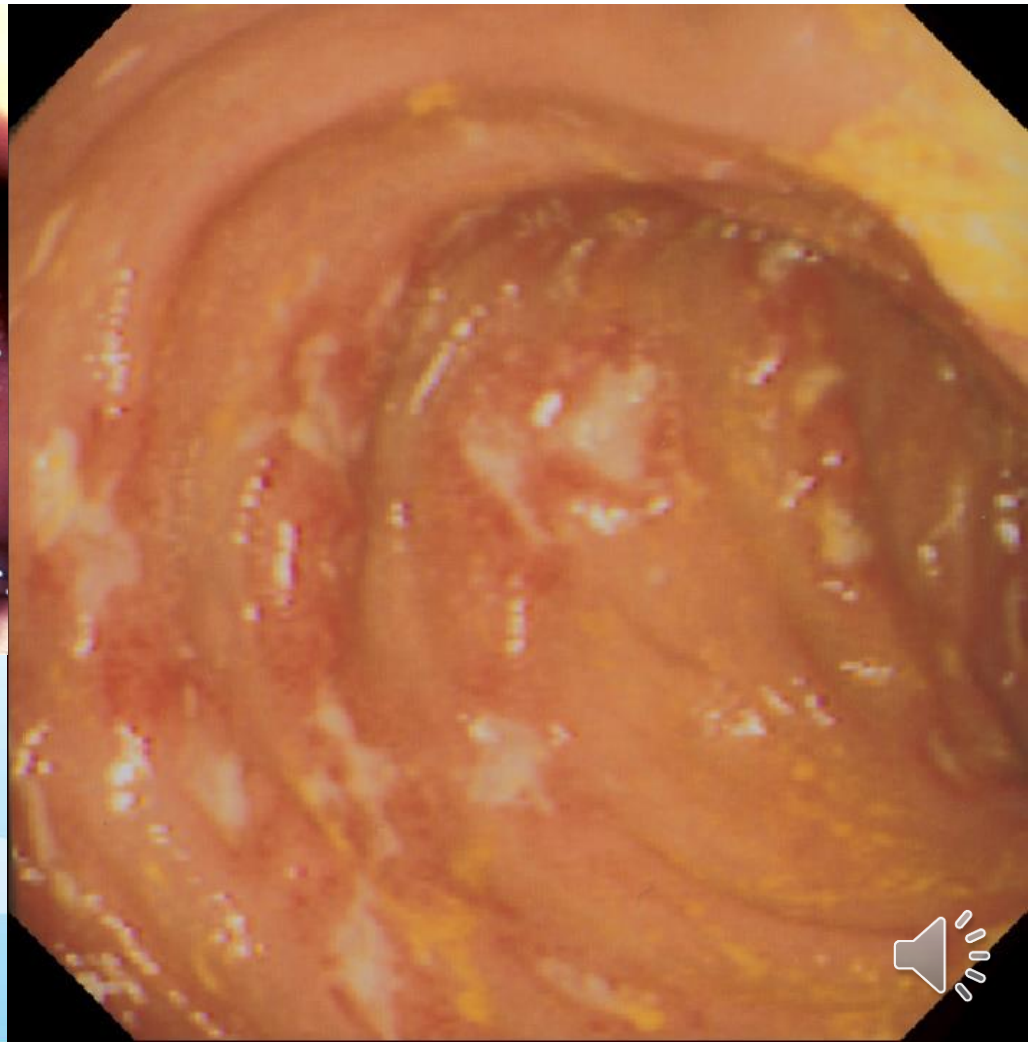
Resembling thrush

Inflammatory Bowel Disease

…the punched out oral mucosal lesion of Behcet's disease :

Behcet's

Crohn's



Aphthoid :

Greek :

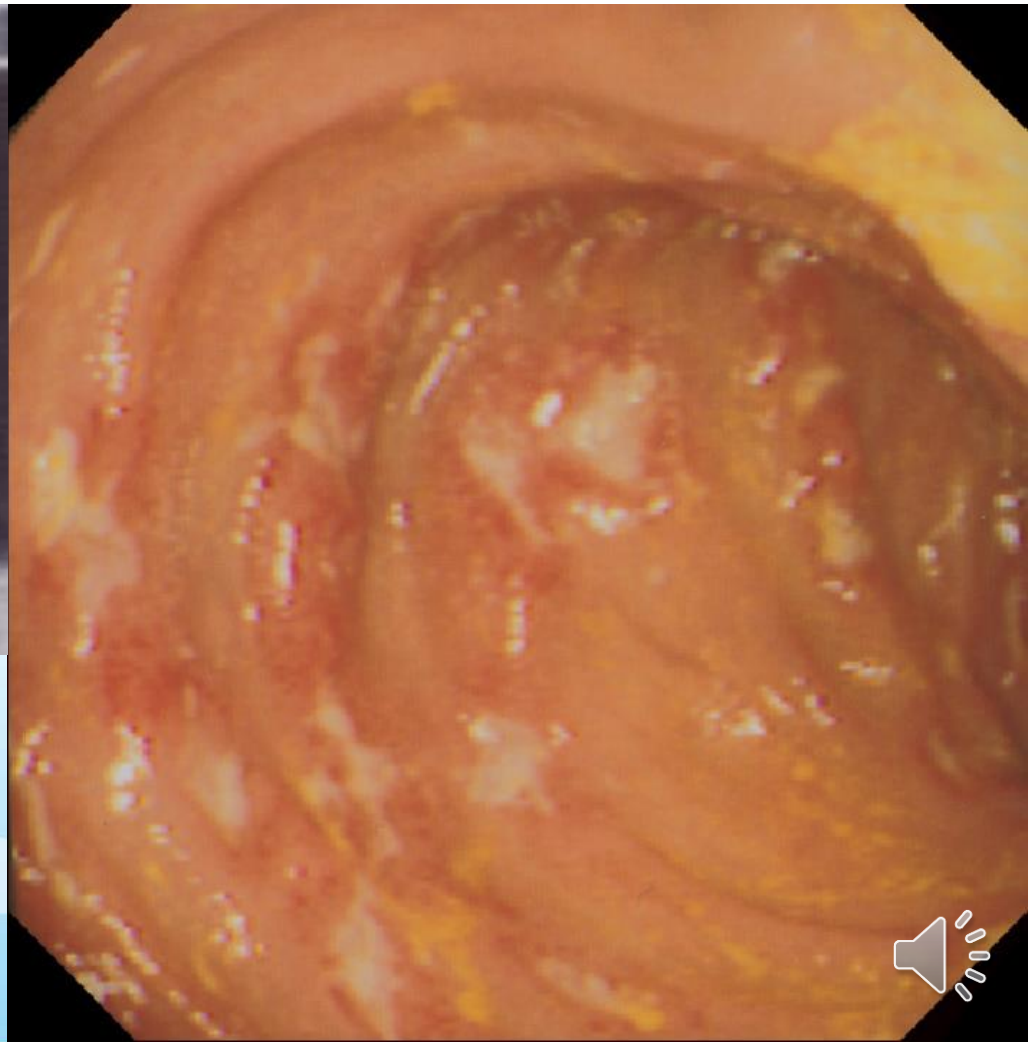
Resembling thrush

Inflammatory Bowel Disease

…the punched out oral mucosal lesion of Behcet's disease :

Barium Enema

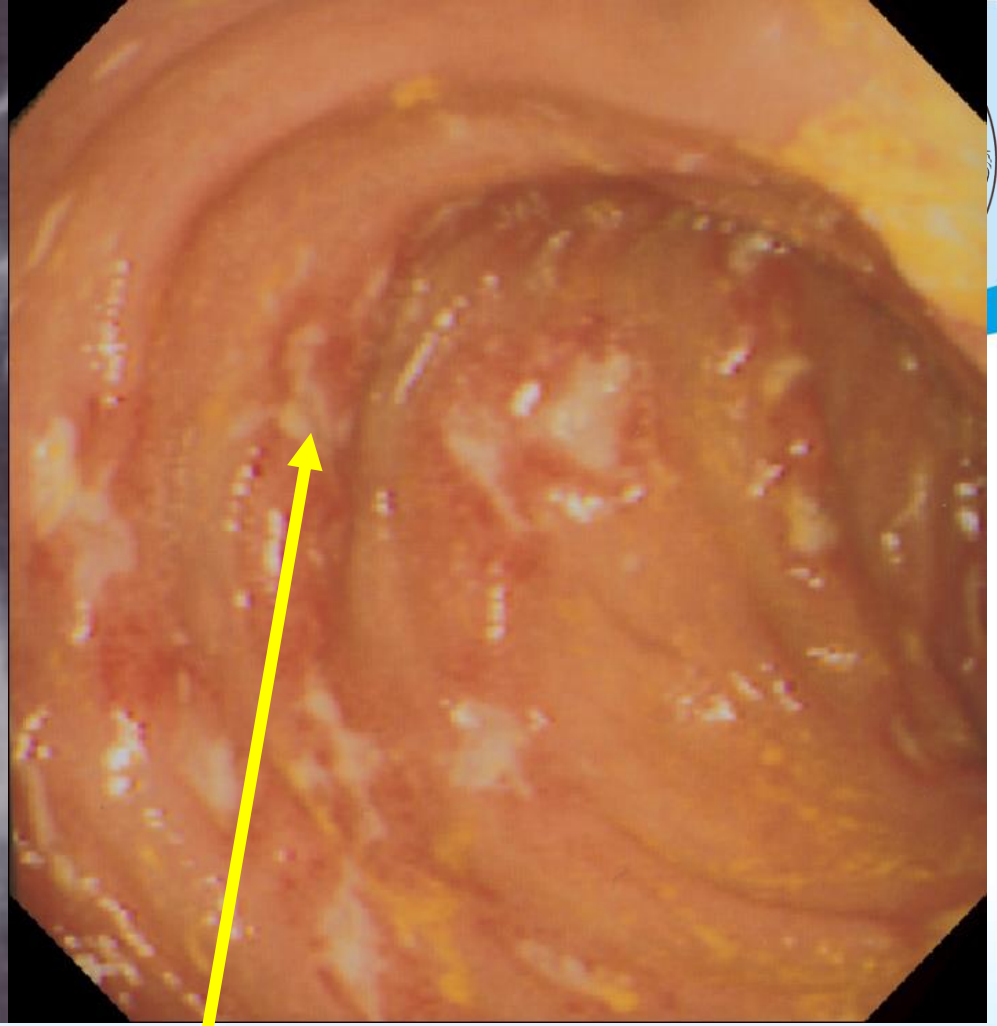
Crohn's



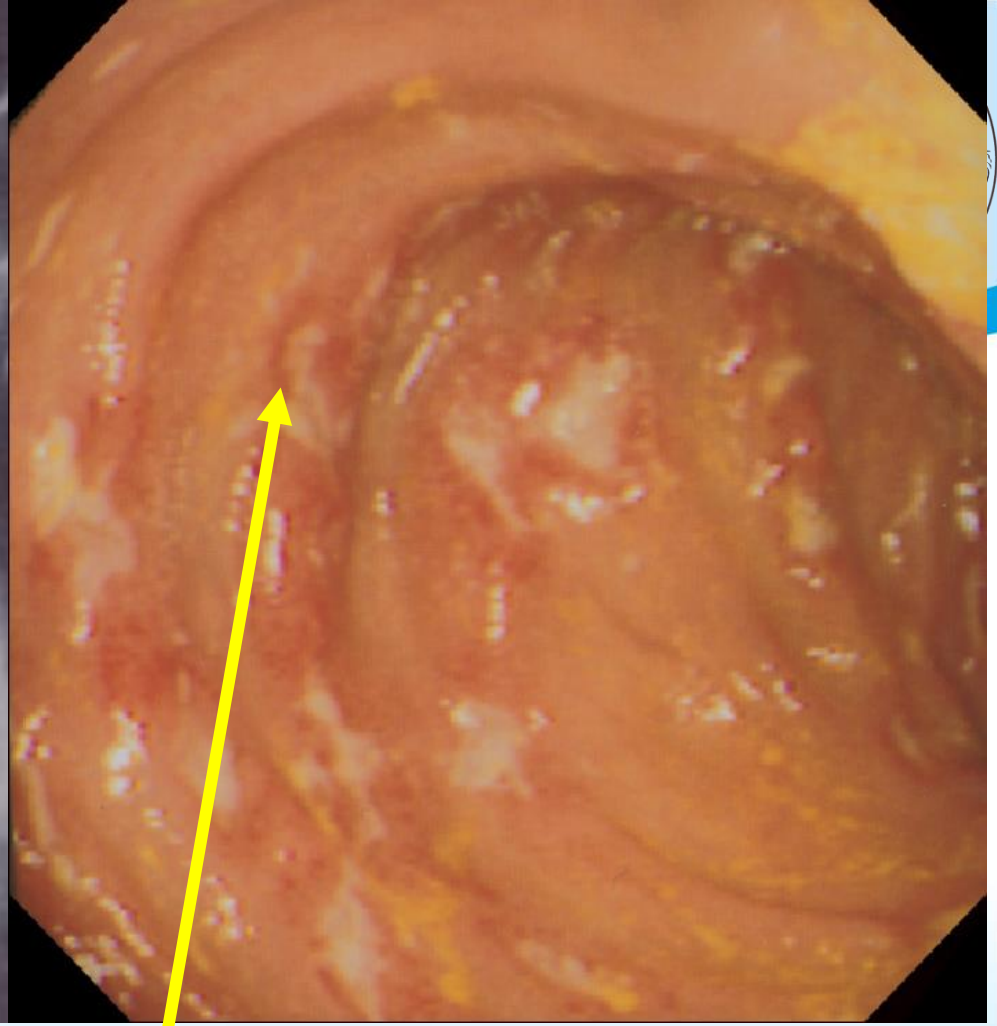
Aphthoid :

Greek :

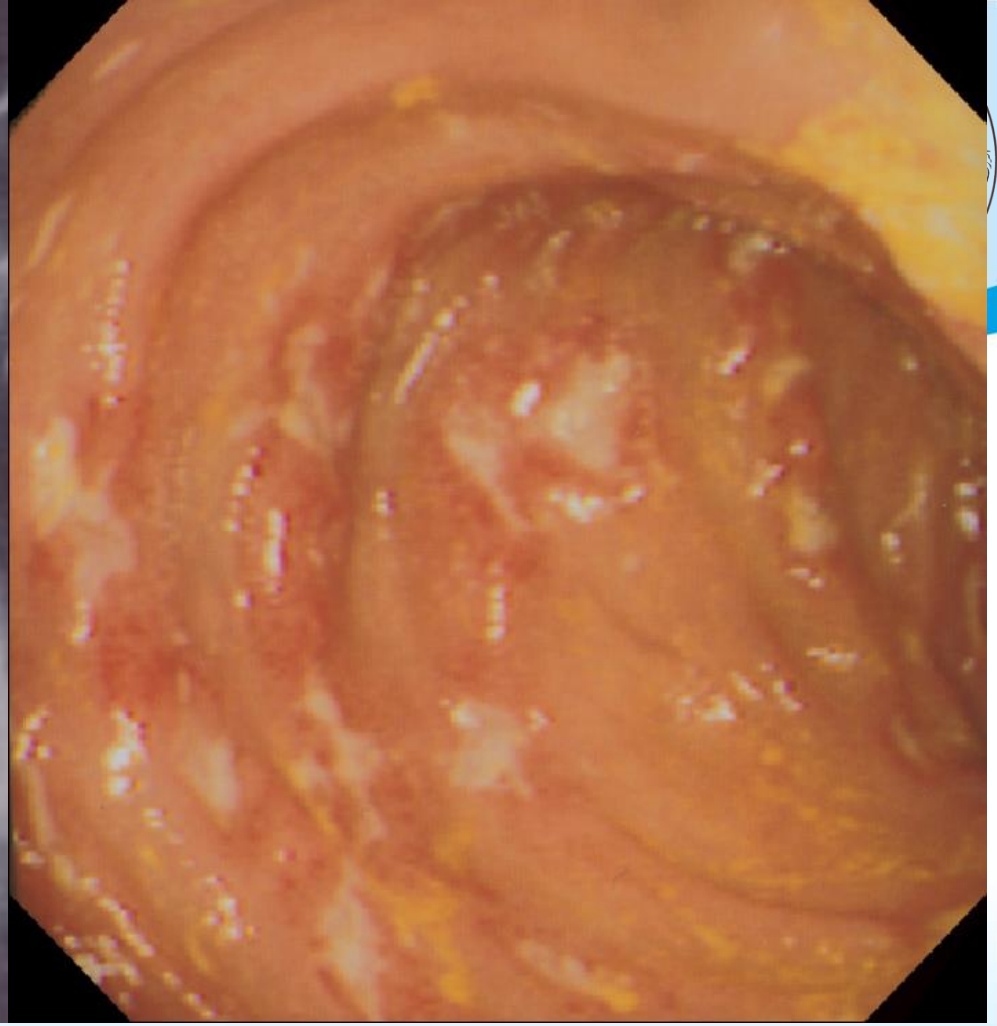
Resembling thrush



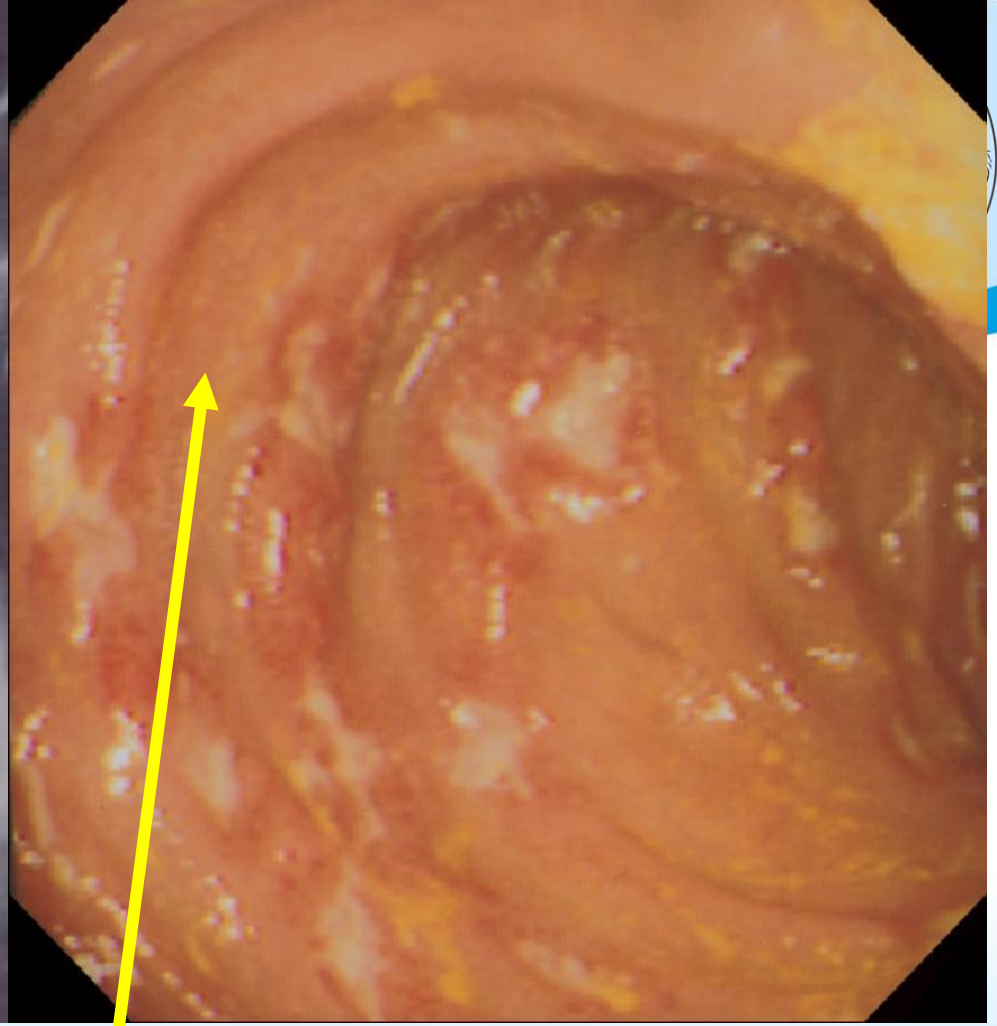
Barium adheres to the slough in the base of the ulcer, creating a dense amorphous pool



The edge of the ulcer is oedematous and slightly elevated



...and as it does not coat with barium, it creates a black halo



…and the surrounding mucosa is normal

Inflammatory Bowel Disease

Aphthoid ulcers are also seen in :

Infectious enterocolitides such as:

Yersinia enterocolitica

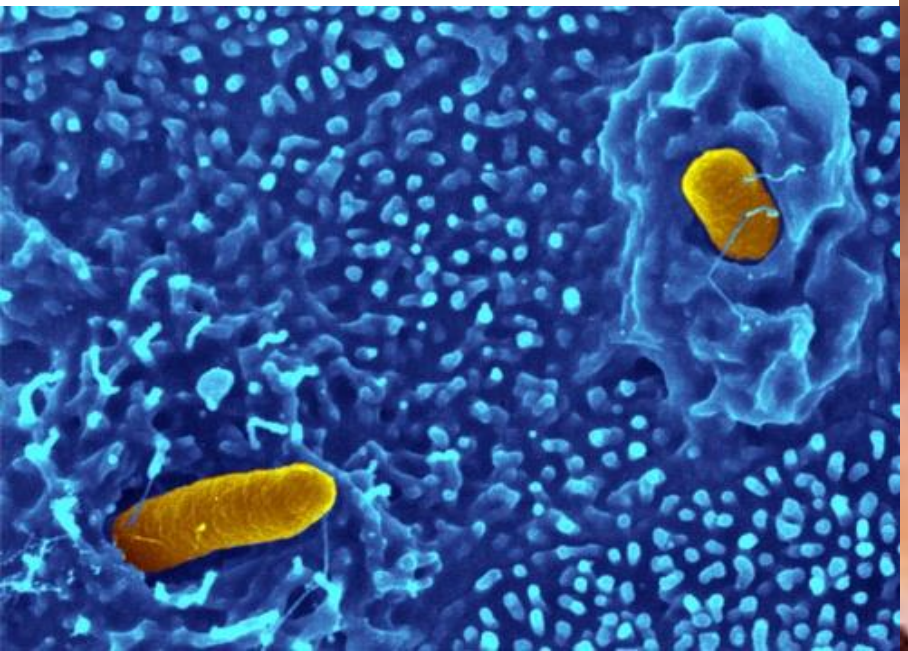
Crohn's

Inflammatory Bowel Disease

Aphthoid ulcers are also seen in :

Infectious enterocolitides such as:

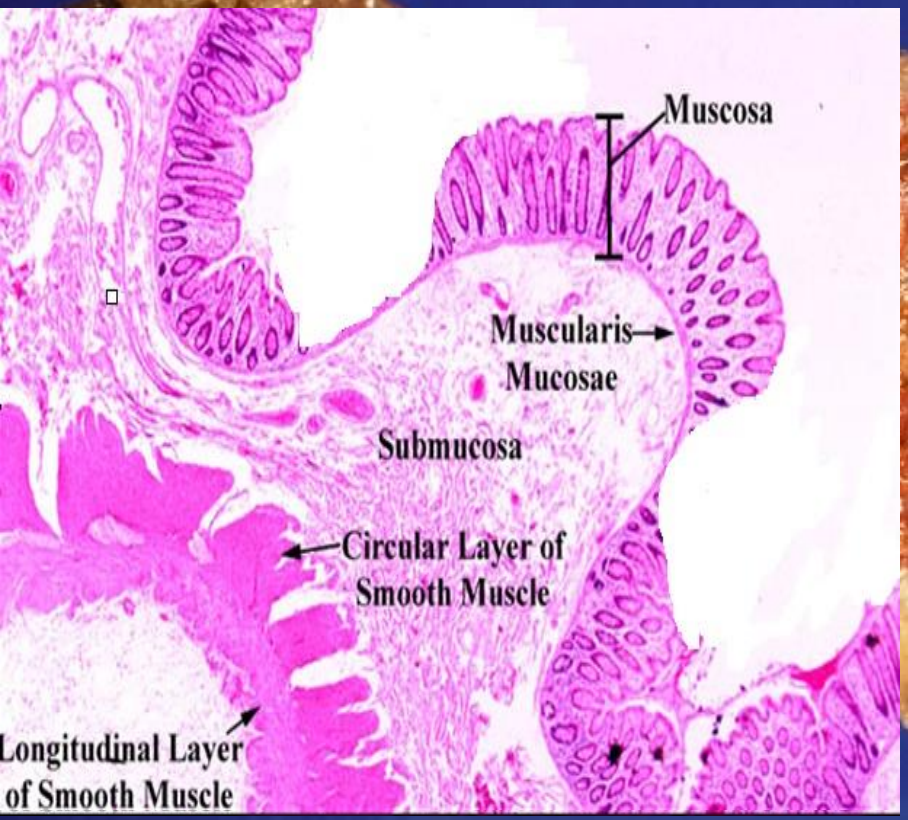
Salmonella species

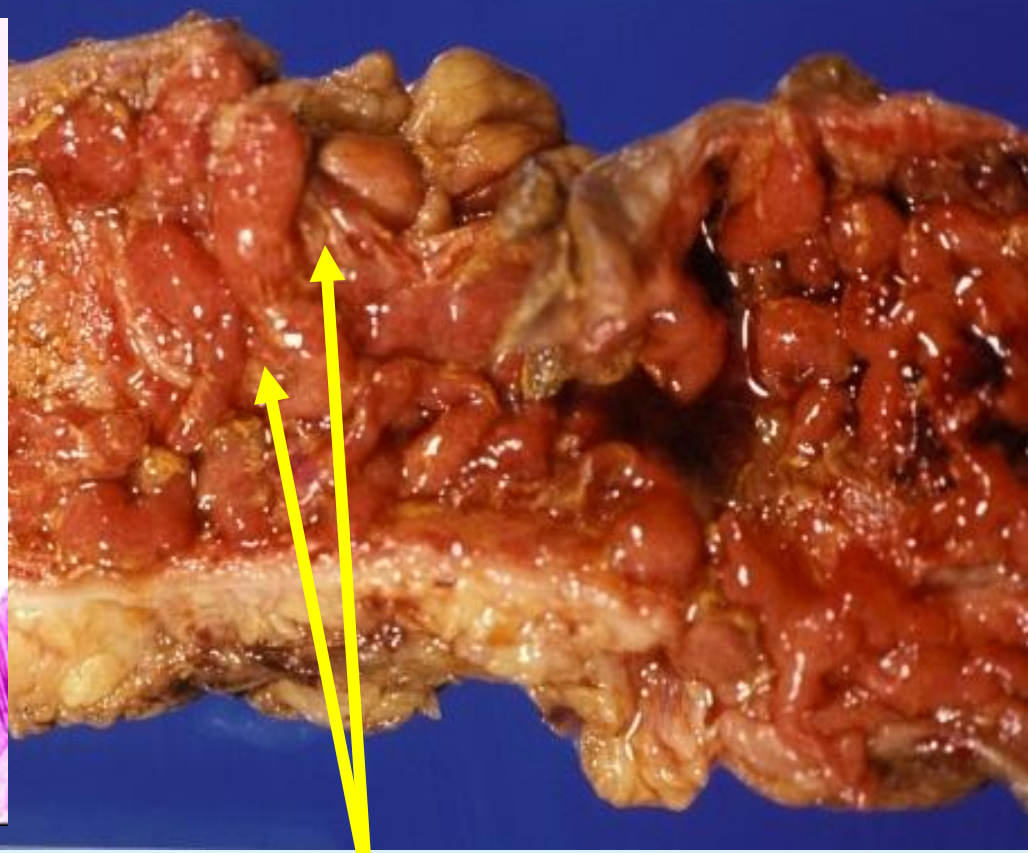


and

Crohn's

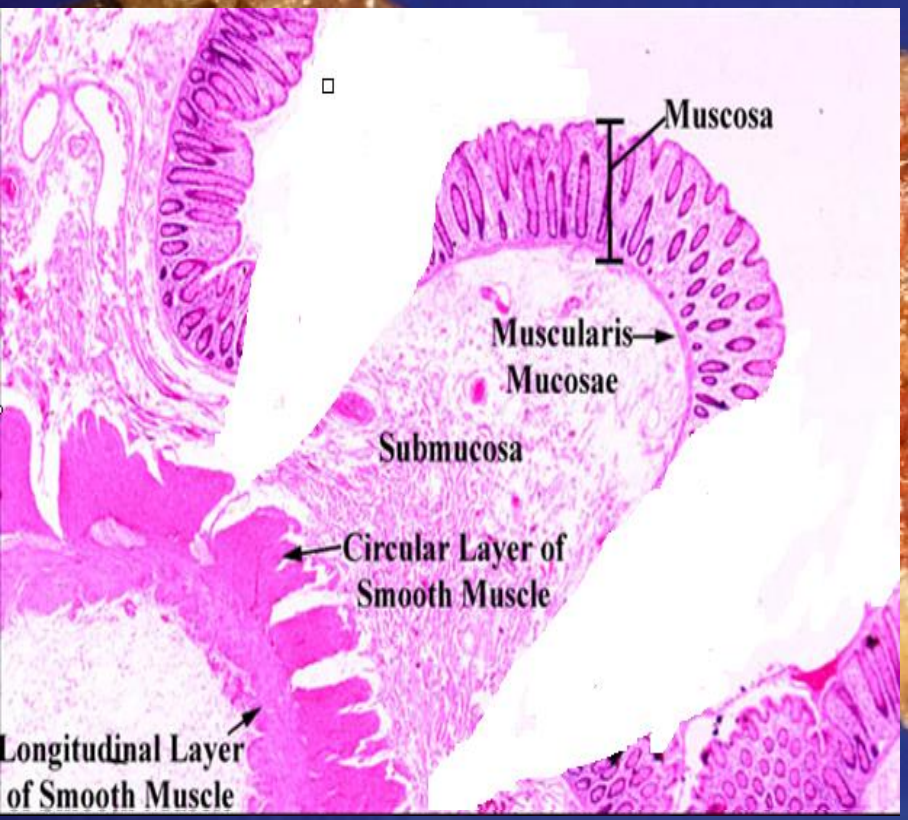
Pseudopolyps of Ulcerative Colitis

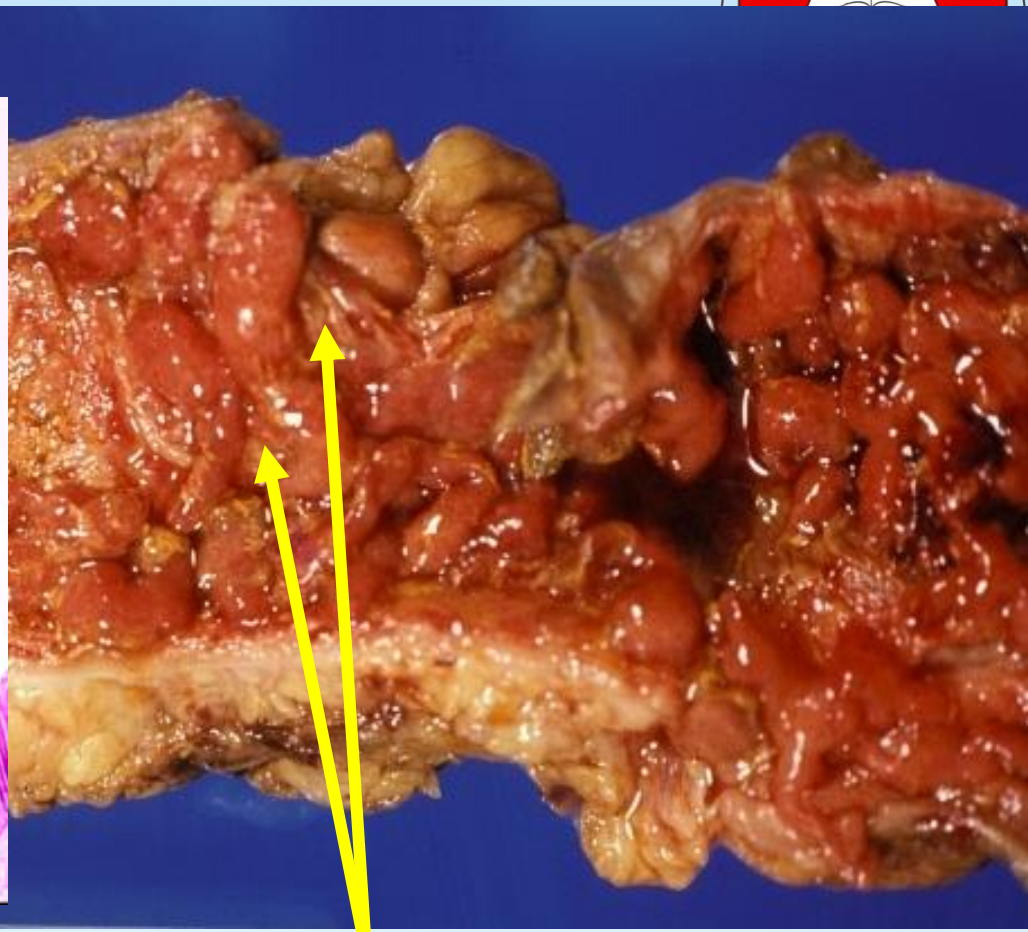




In between the pseudopolyps, the mucosa has been completely destroyed..

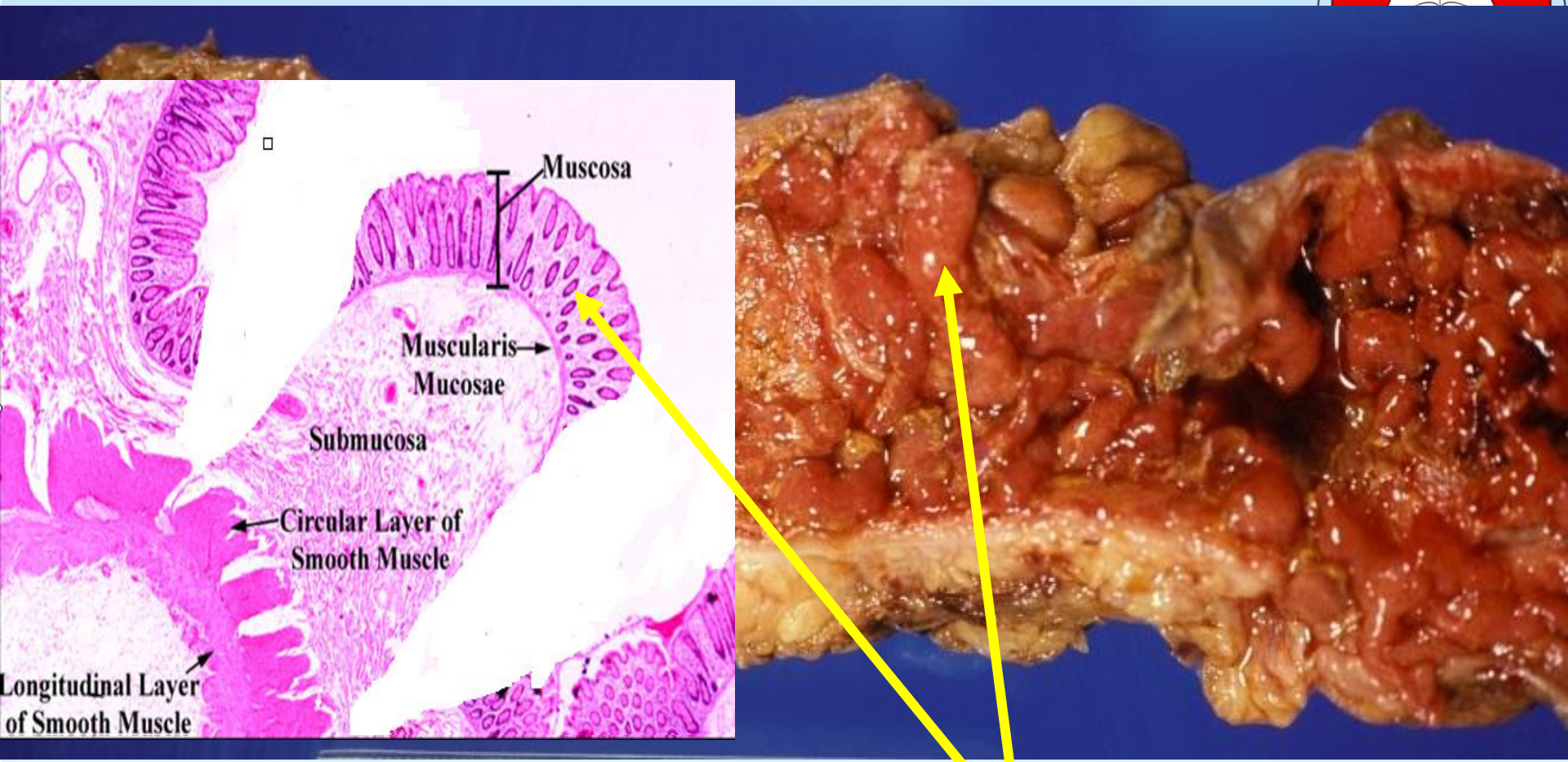
Pseudopolyps of Ulcerative Colitis





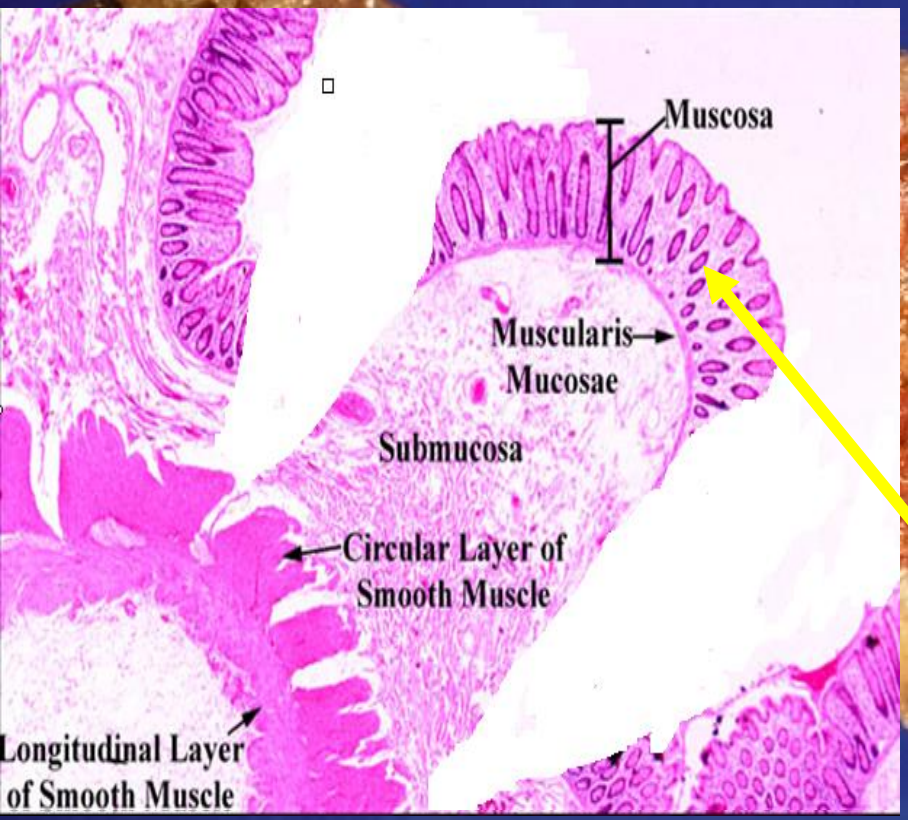
...and this continues all the way down to the muscle layers which are now macroscopically visible…

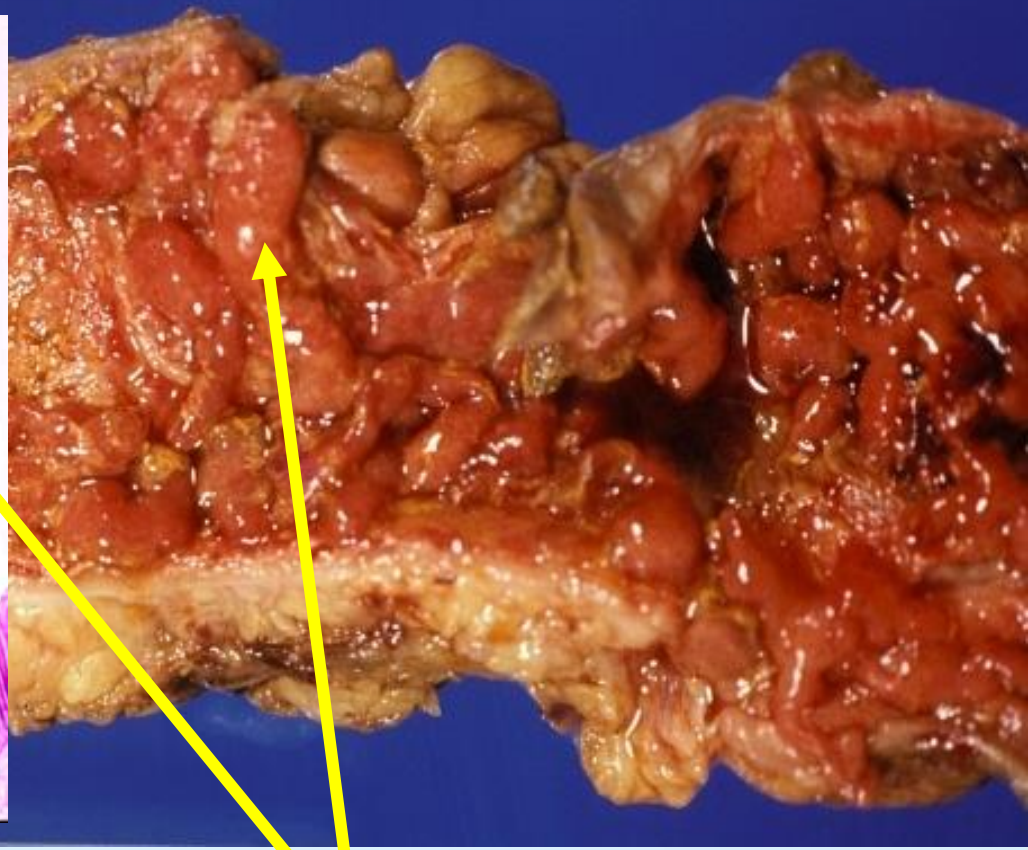
Pseudopolyps of Ulcerative Colitis



…and the remaining mucosa remains prominent forming a pseudopolyp…

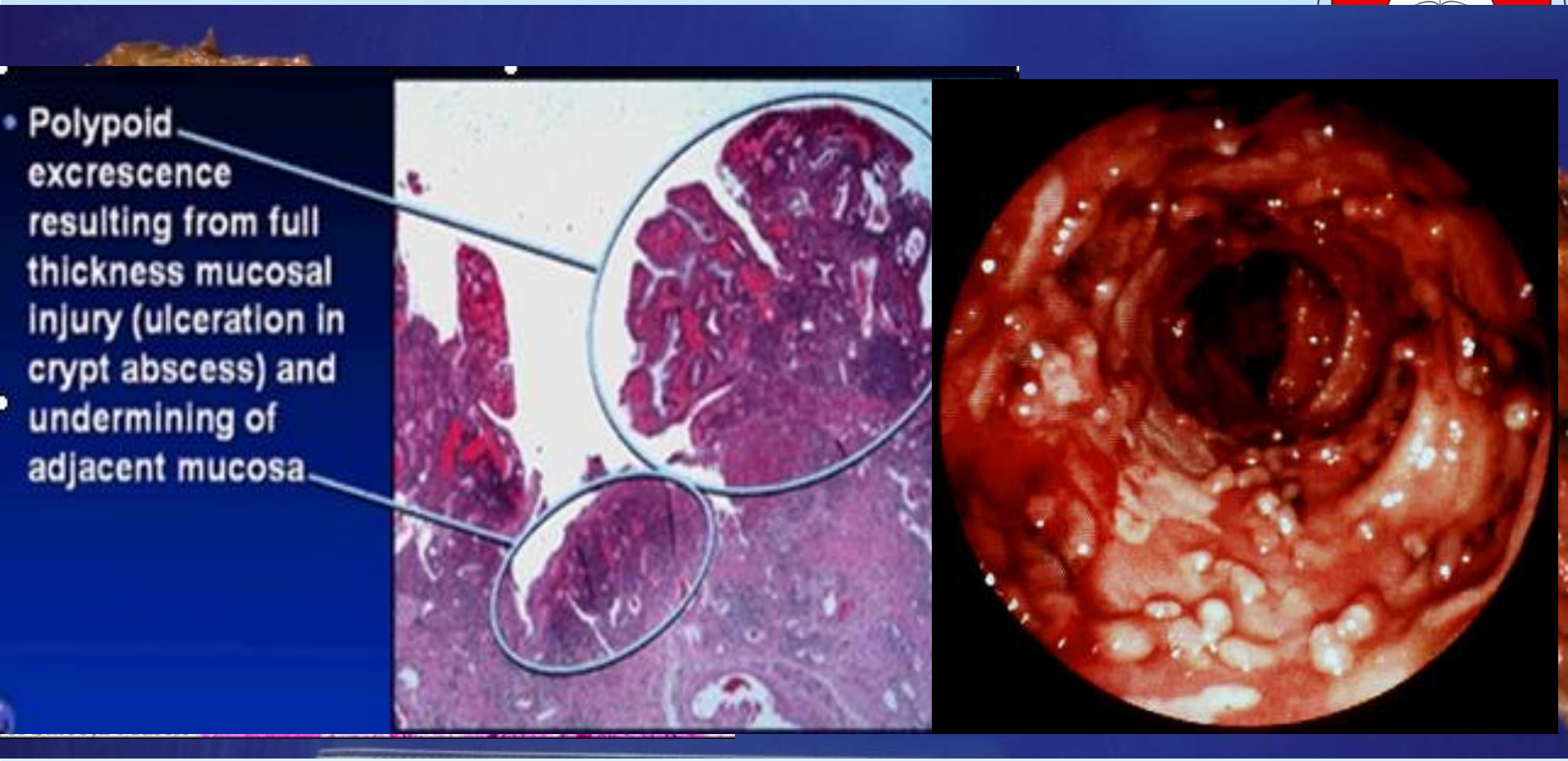
Pseudopolyps of Ulcerative Colitis





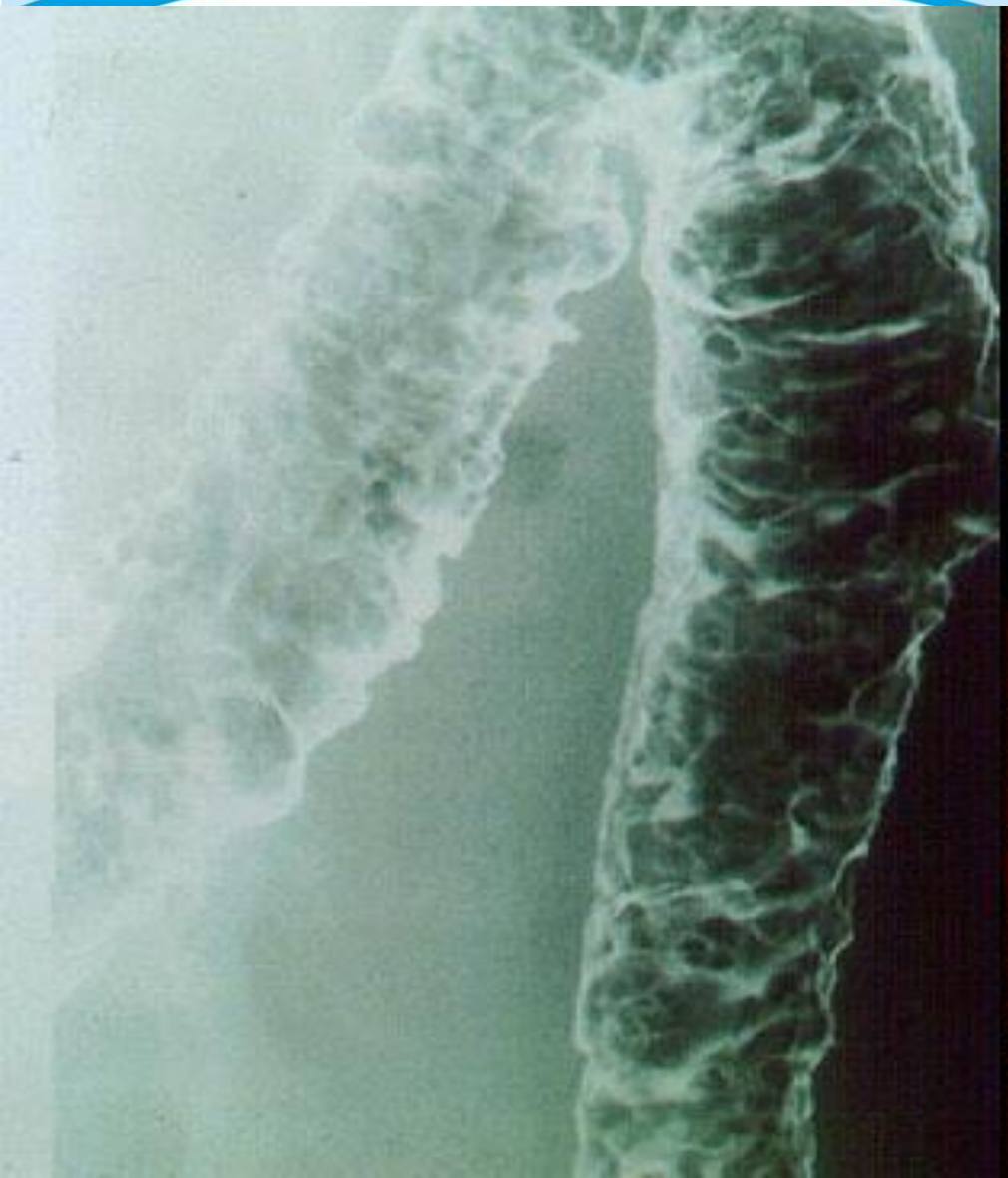
...this remaining mucosa is chronically inflammed and undergoes repair and granulation tissue is deposited within it...

Pseudopolyps of Ulcerative Colitis

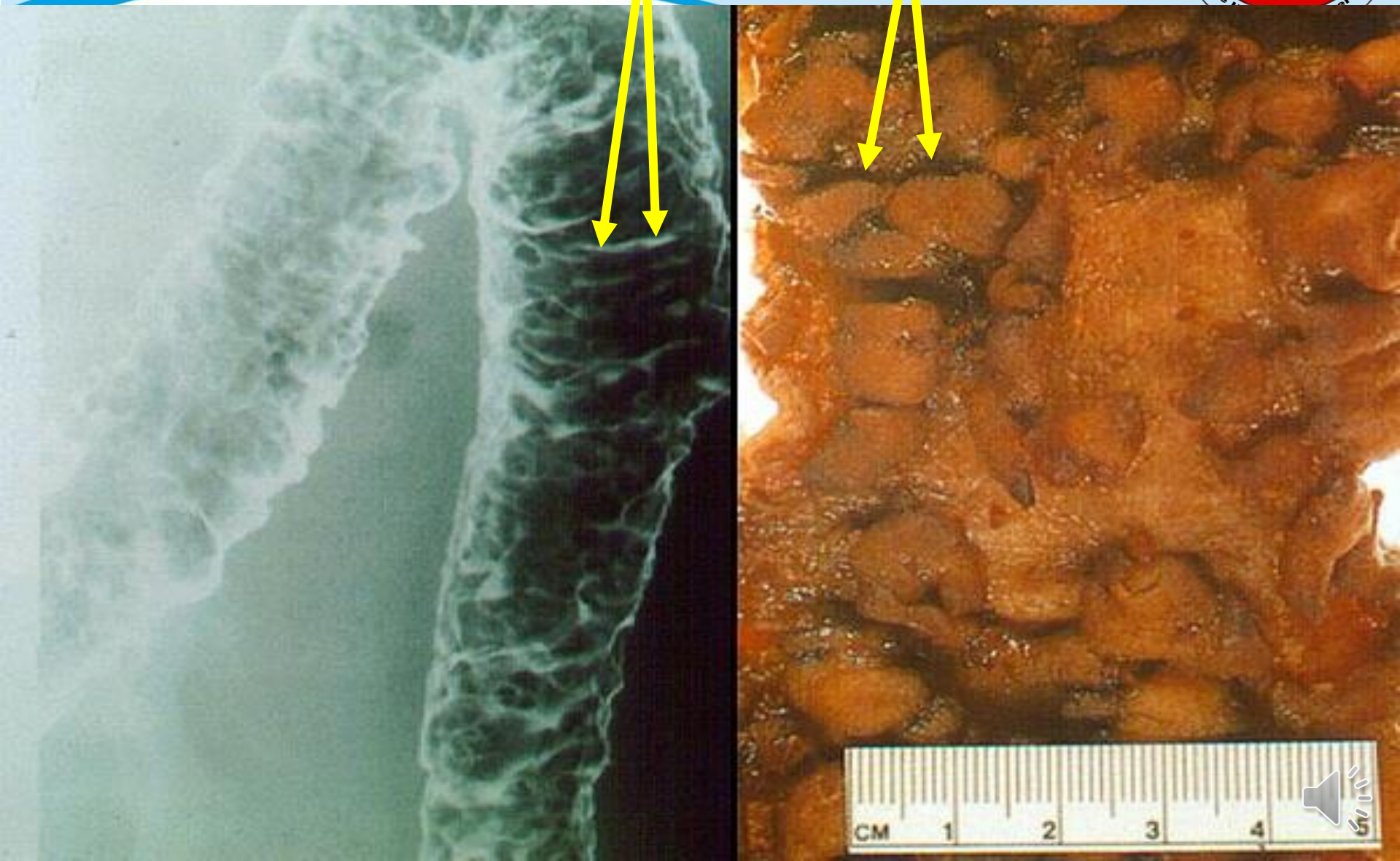


…and it is called a pseudopolyp because it does not protrude beyond the previously normal mucosal surface…

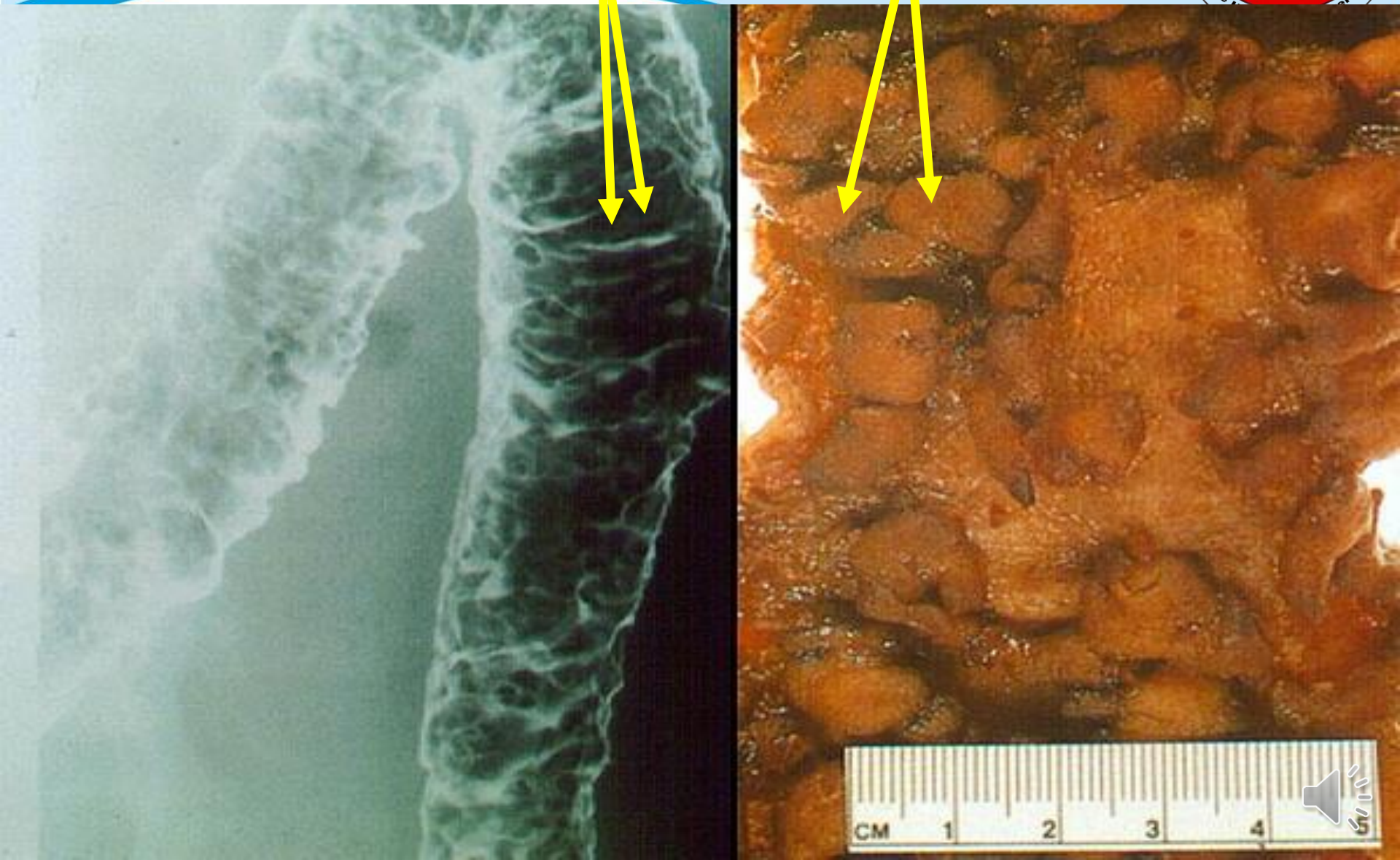
So ulceration, alternating with the deposition of granulation tissue during the healing phase, results in the development of raised areas of inflamed tissue that resembles polyps

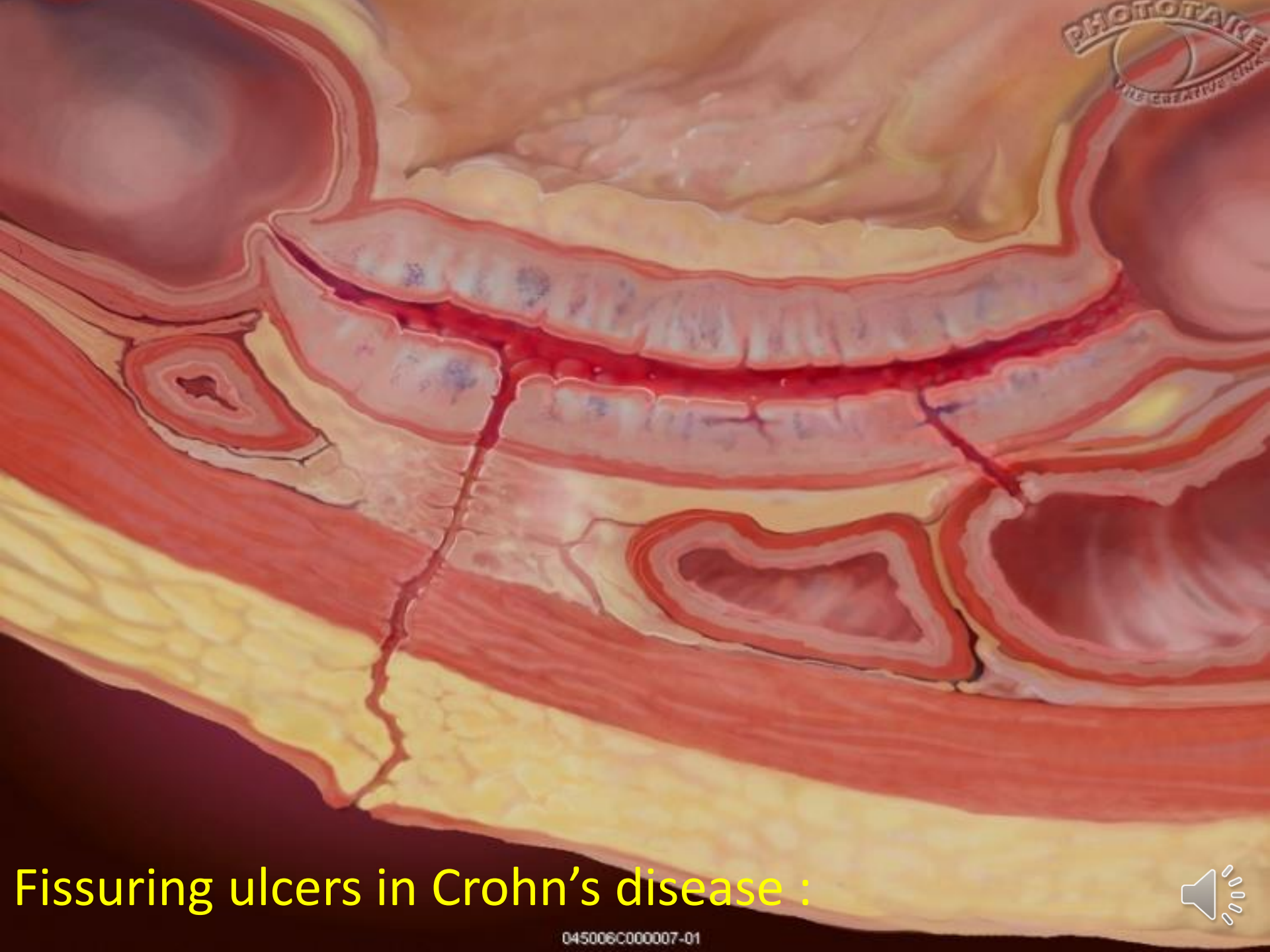


On a barium enema, barium fills the area between the pseudopolyps, which is really barium lying on the exposed muscle layer which appears as the apparent mucosal line.



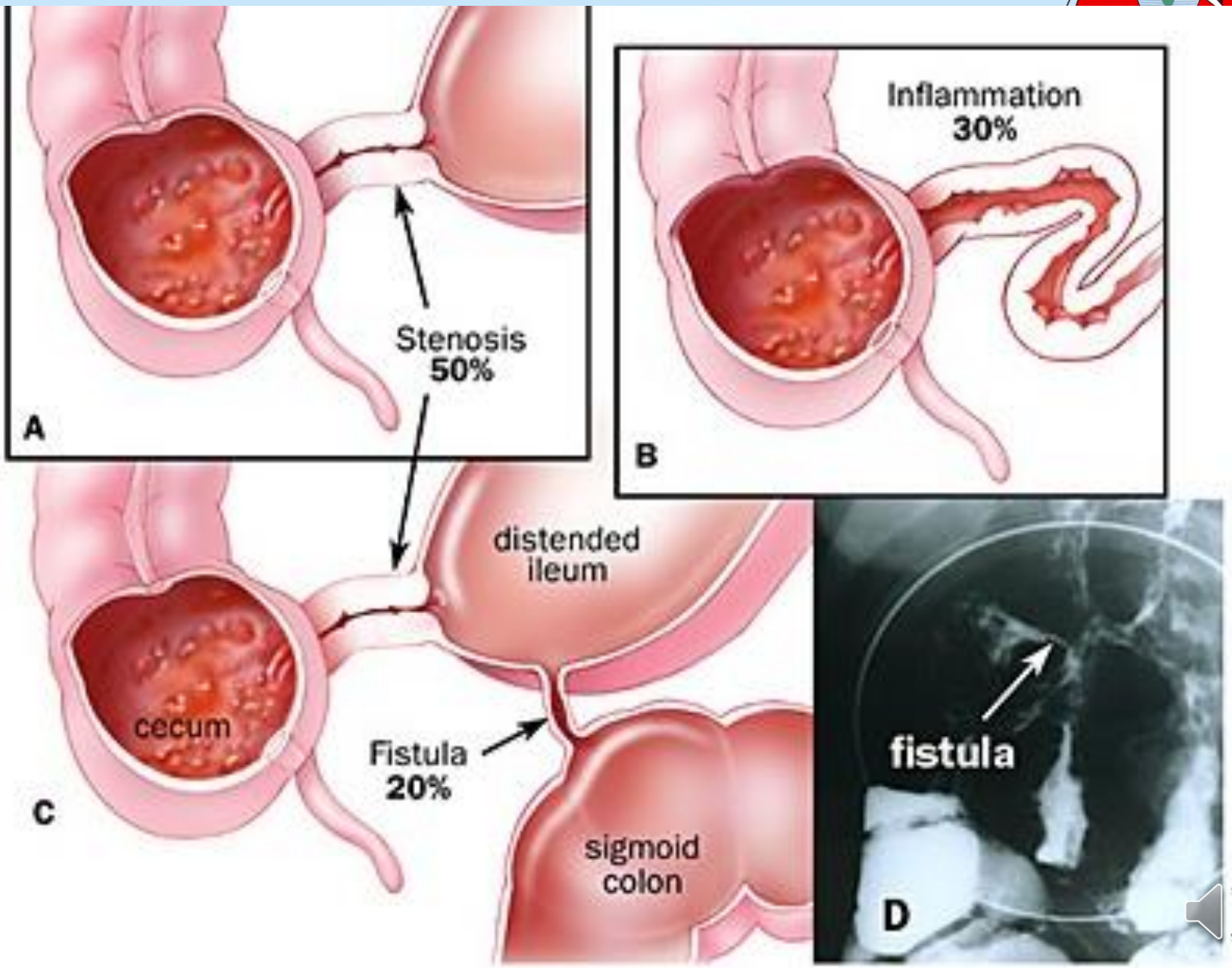
...the pseudopolyps are not coated with barium and appear dark on the barium enema.

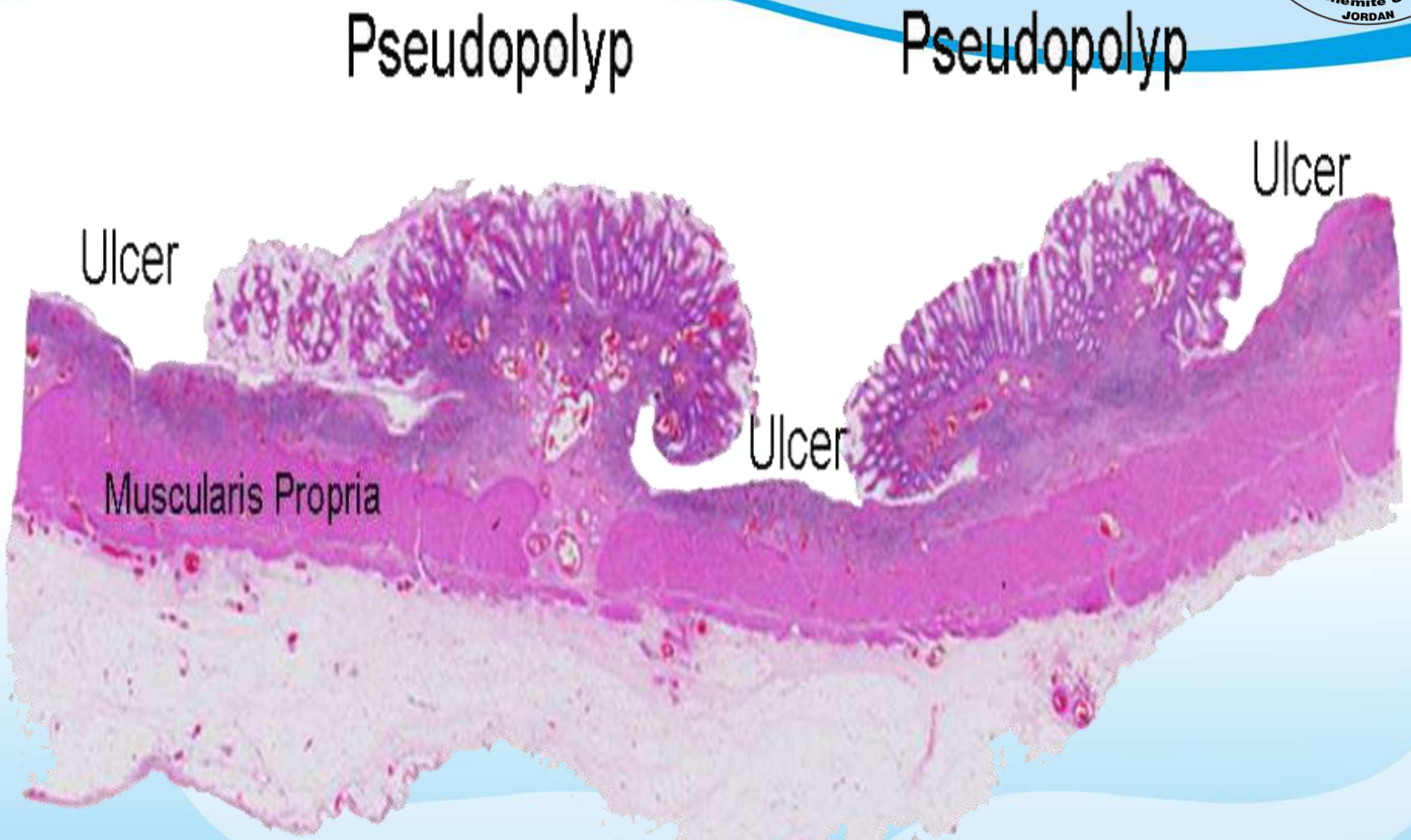




Fissuring ulcers in Crohn’s disease :

Crohn's Disease has 3 distinct disease courses :




Pseudopolyp
Pseudopolyp
Ulcer
Ulcer
Ulcer
Muscularis Propria

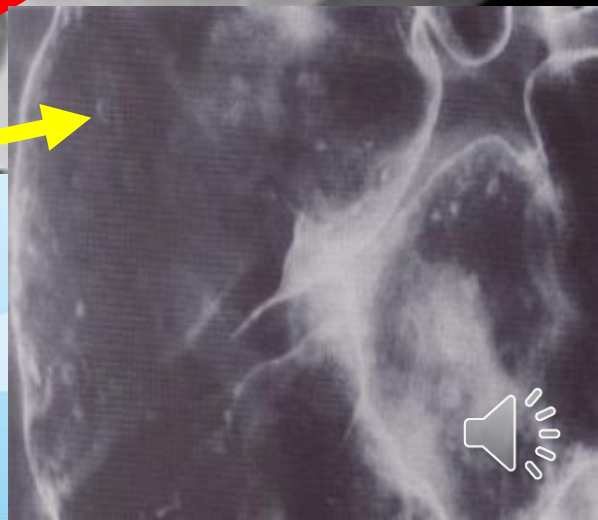
Microscopic features

- Crypts atrophy & irregularity
- Superficial erosion
- Diffuse mixed inflammation
- Basal lymphoplasmacytosis

Ulcerative Colitis Summary of Histology :

- Inflammation limited to mucosa and submucosa
- Involvement of the colonic mucosa is symmetrical

…which is another way of saying circumferential and is equally involved all round…



(as opposed to Crohn's which may involve the bowel eccentrically…which means only a part of the circumference.)

Summary :

Histology

Ulcerative Colitis

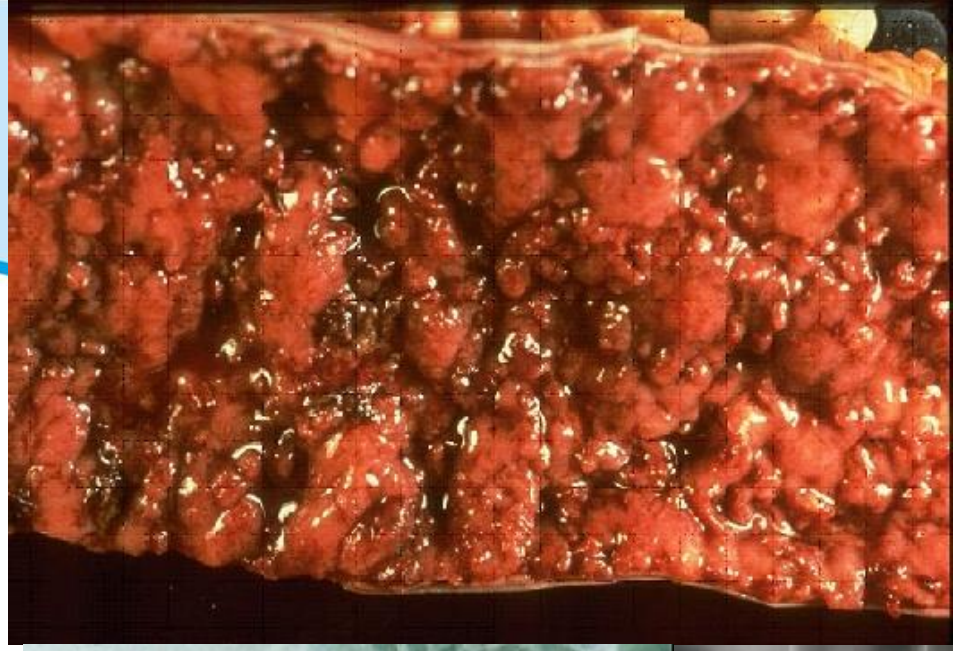
- Inflammation limited to mucosa and submucosa
- Submucosa often compressed
- Crypt abscesses common
- Goblet cells diminished
- Paneth cell metaplasia common
- Epithelioid granulomas absent in submucosa and deeper tissue levels

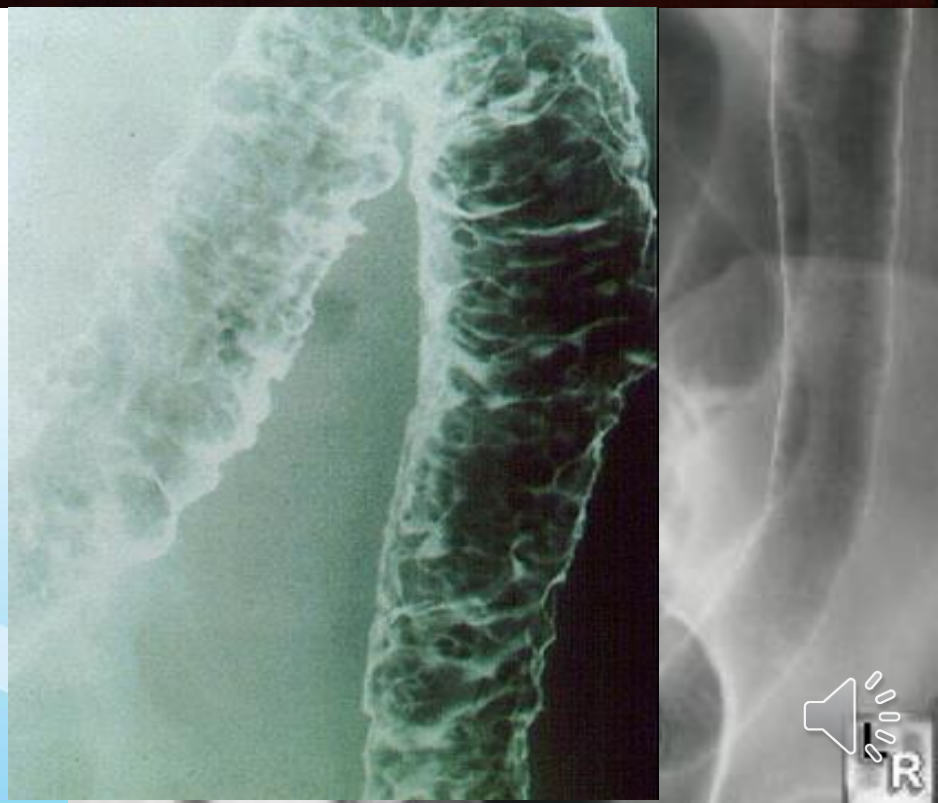
Crohn's Disease

- Transmural inflammation with lymphoid aggregates
- Submucosa expanded by inflammation and fibrosis
- Crypt abscesses less common
- Goblet cells often normal
- Paneth cell metaplasia rare
- Granulomas are frequent (40-60%)

Ulcerative Colitis:

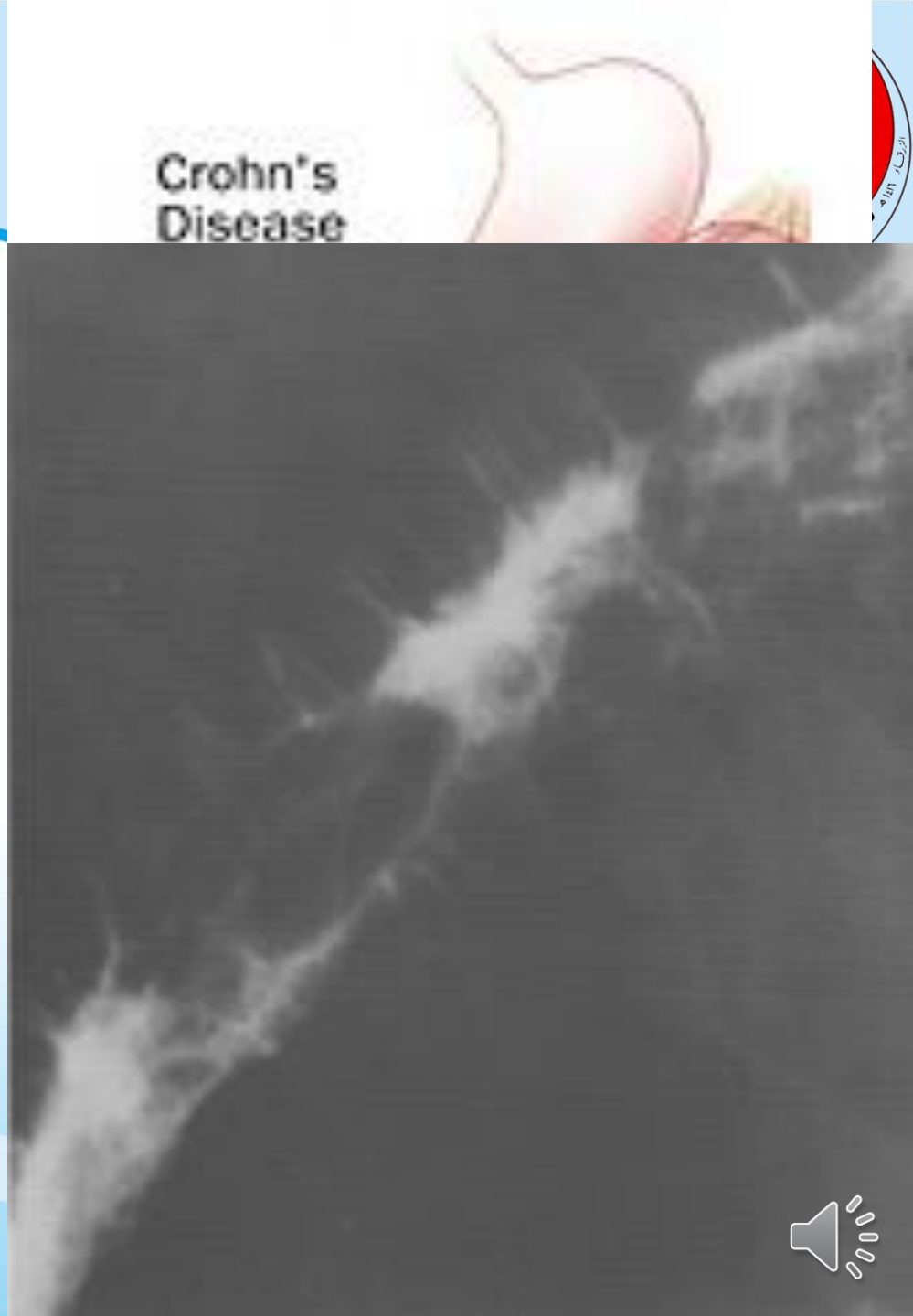
- Rectum usually involved
- Ileum not directly involved
- Diffuse (confluent) left sided or pancolitis
- Intestinal wall normal calibre without fibrosis
- Granular friable mucosa
- Pseudopolyps are common
- Discrete ulcers are uncommon
- Ulcers when present are small and superficial

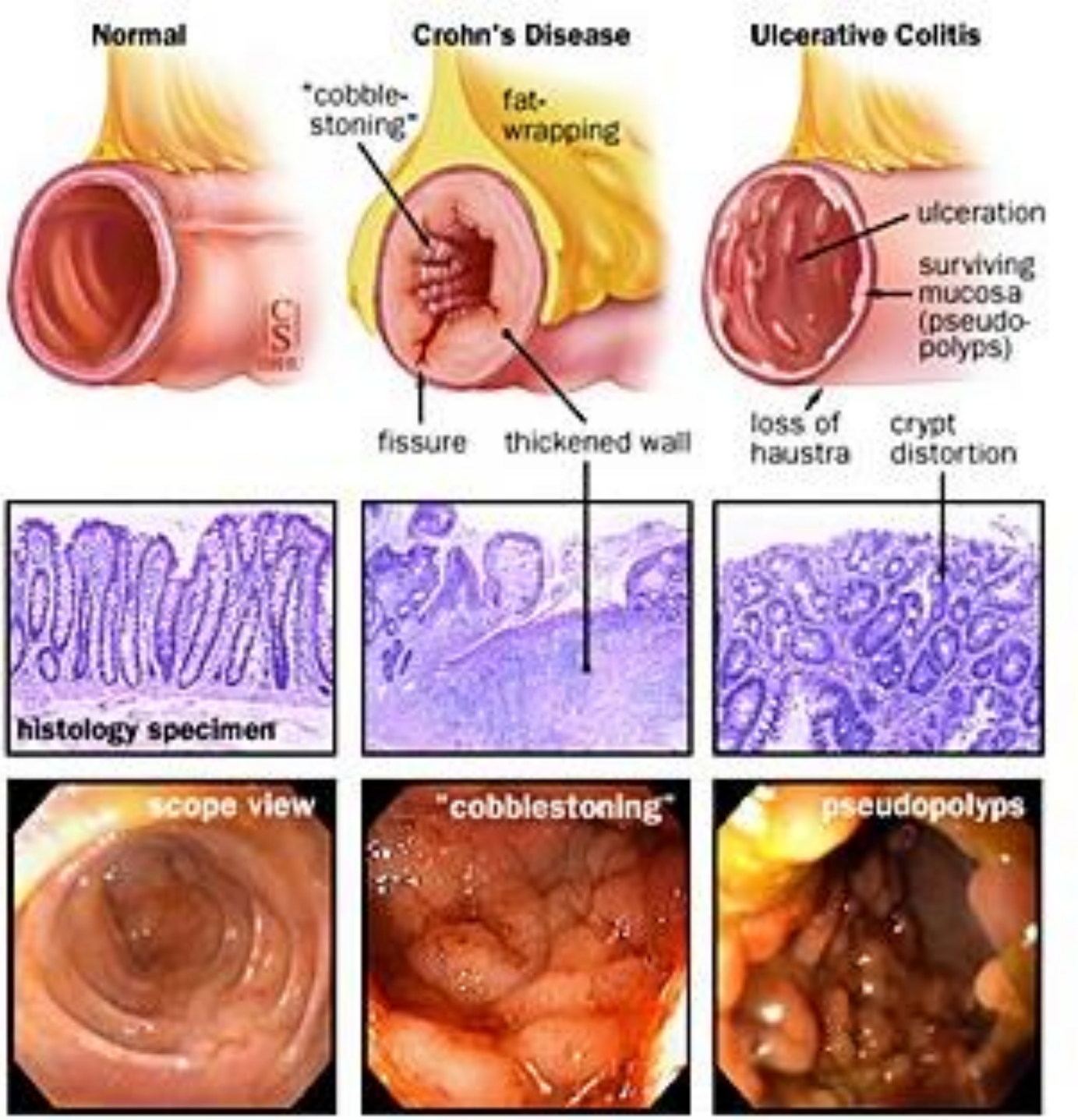




Crohn's Disease

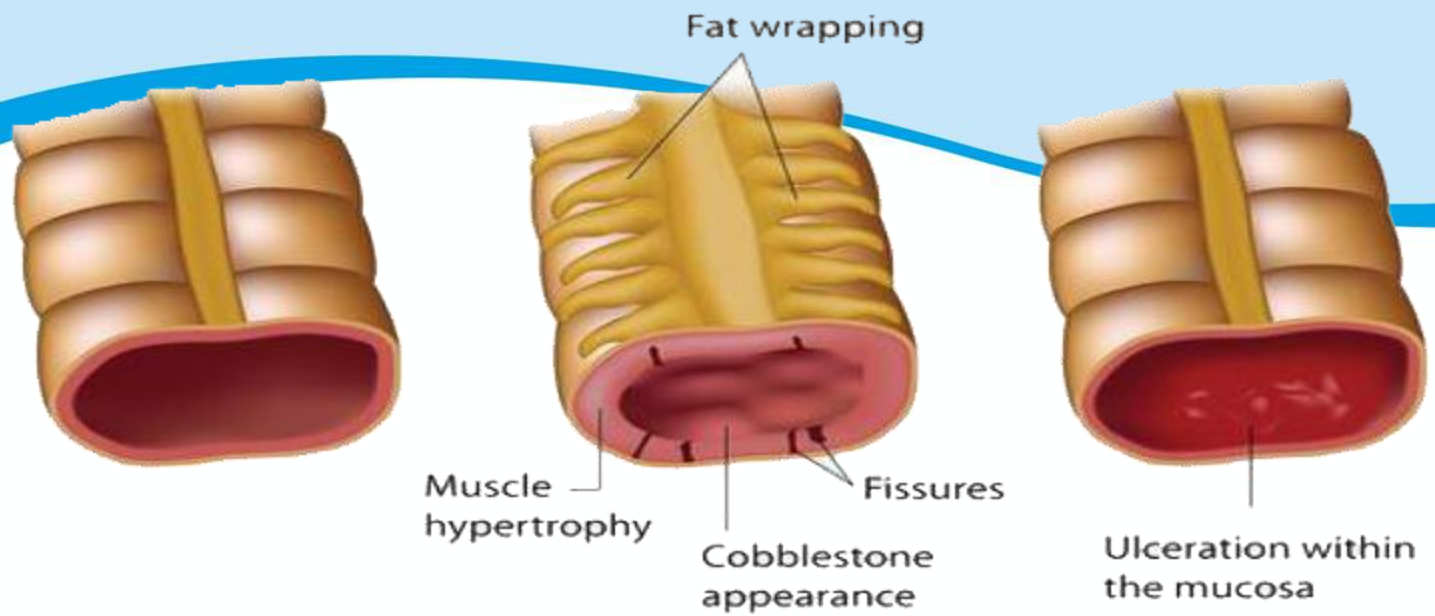
- Rectum typically spared
- Ileal disease is common
- Segmental Disease (skip lesions)
- Intestinal wall thickened with fibrosis
- Cobblestoning
- Pseudopolyps are less common
- Ulcers are prominent – aphthoid, deep linear and fissuring ulcers and mucosal bridges.




Normal
Crohn's Disease
Ulcerative Colitis
"cobble-stoning"
fat-wrapping
ulceration
surviving mucosa (pseudo-polyps)
fissure
thickened wall
loss of haustra
crypt distortion
histology specimen
scope view
"cobblestoning"
pseudopolyps

Other forms of IBD

- Collagenous colitis
- Lymphocytic colitis
- Behcet’s syndrome
- Intermediate colitis


Healthy
Crohn's disease
Ulcerative colitis
Fat wrapping
Muscle hypertrophy
Fissures
Cobblestone appearance
Ulceration within the mucosa


Healthy Colon
Ulcerative Colitis
Crohn's Disease

Epidemiology

- Ulcerative colitis is slightly more common in males
- Crohn’s disease is more frequent in women.
- Prevalence (number of existing cases per 100,000 population)
  - Crohn's disease 26 to 199 cases
  - Ulcerative colitis 37 to 246 cases

	Ulcerative colitis	Crohn's
Incidence / 1 lac.	2.2-14.3	3.1-14.6
Age of onset	15-30, 60-80	
Ethnicity	Jewish	
Male: Female	1:1	1.1-1.8 : 1
Smoking	May prevent	Causative
Oral contraceptives	No risk	1.4 odds ratio
Appedicectomy	Protective	Not
Monozygotic	6%	58%
Dizygotic	0%	4%

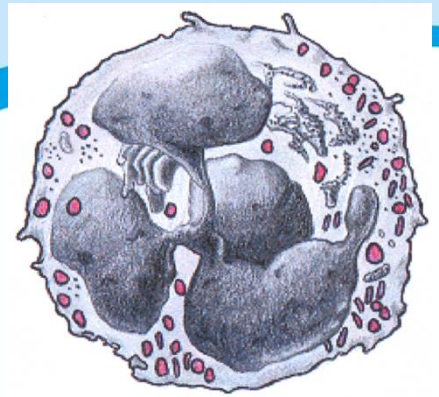
Etiology

- Environmental factors
  - Diet
  - Smoking
- oral contraceptives
- Infectious agents
  - Viruses (Measles)
  - Bacteria (Mycobacteria)
- Genetics
- Psychological factors
  - Stress
  - Emotional or physical trauma

Pathophysiology

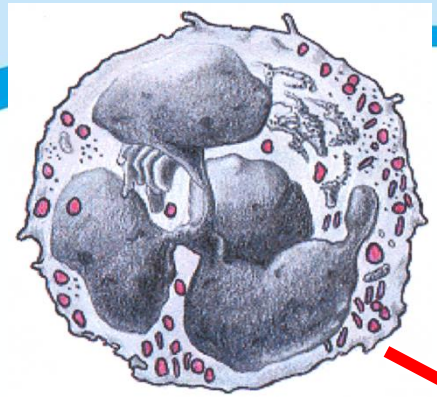
- ALTERED MUCOSAL IMMUNE RESPONSE
- Dietary and bacterial antigens penetrate into the intestinal wall and activates the immune system.
- This causes increased production of pro-inflammatory mediators which will lead to inflammation of the mucosal layer.

Inflammatory Bowel Disease

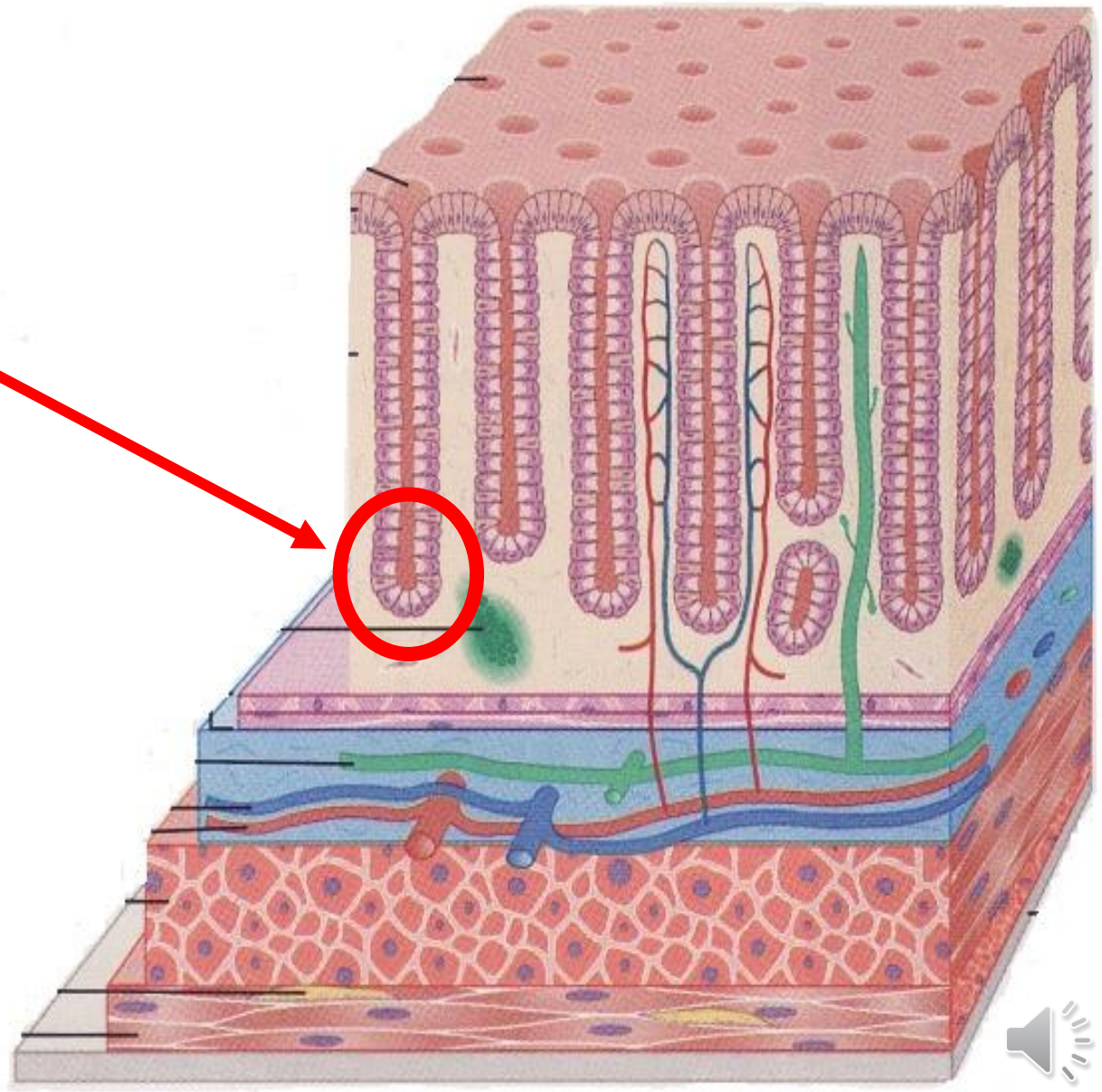


The initial neutrophil target is apparently not the epithelial cell itself…

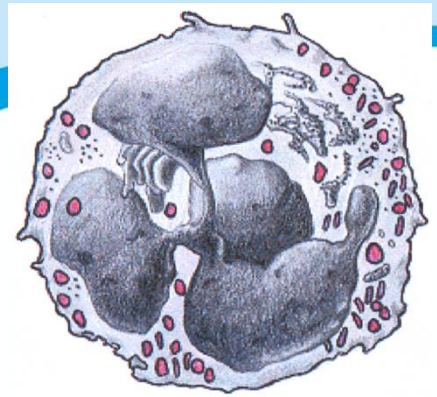
Inflammatory Bowel Disease



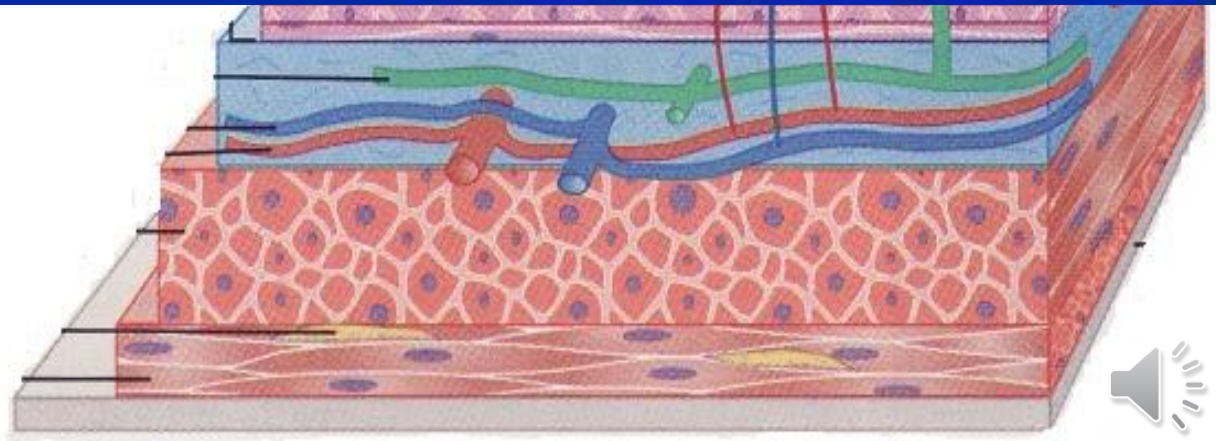
…it is instead going to attack the crypt…



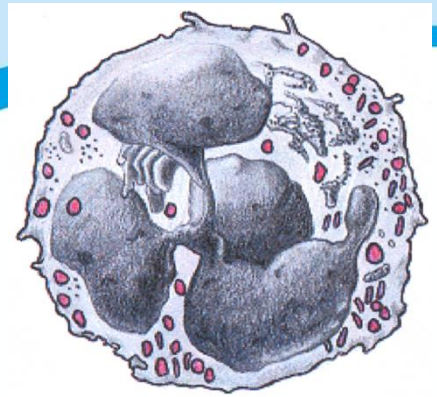
Inflammatory Bowel Disease

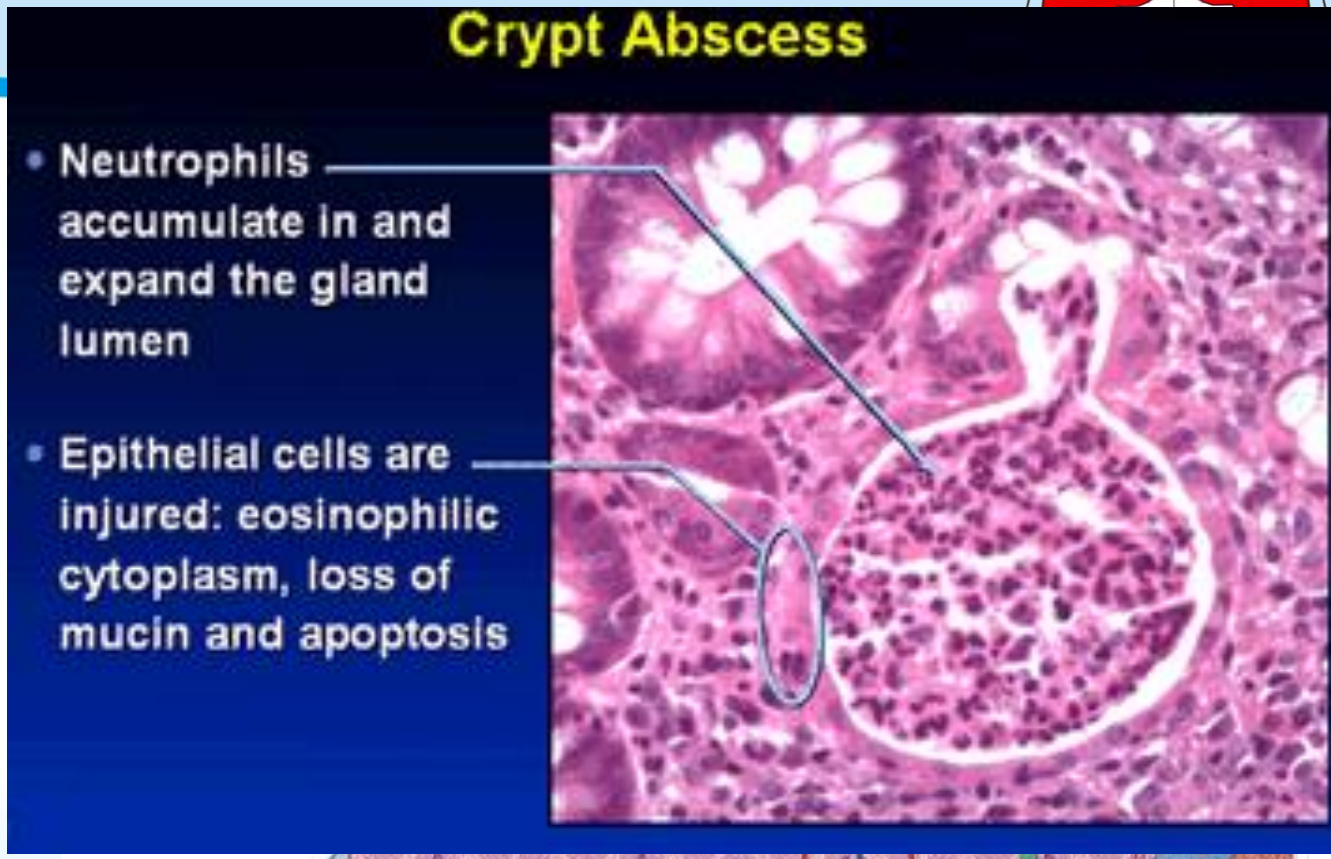


This is called cryptitis and heralds active mucosal disease

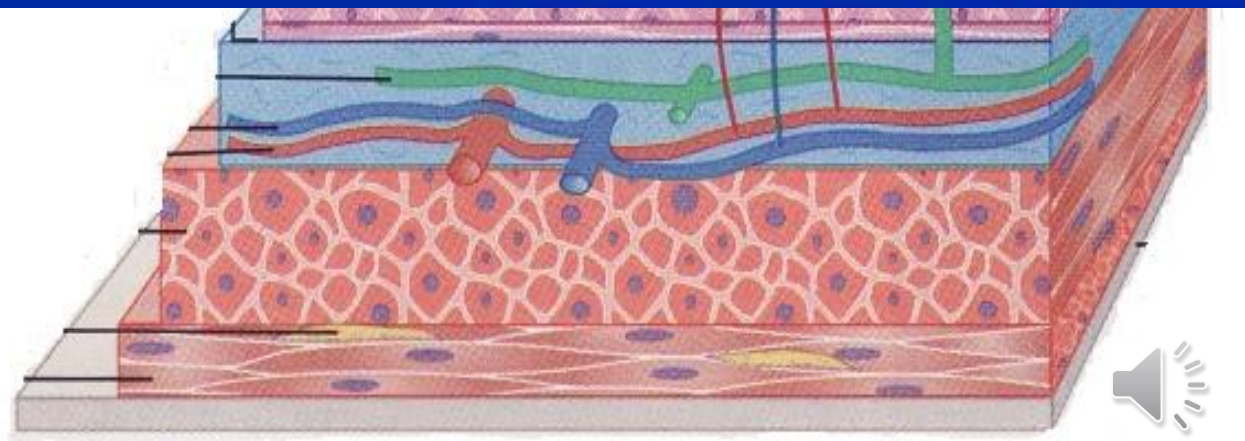


Inflammatory Bowel Disease

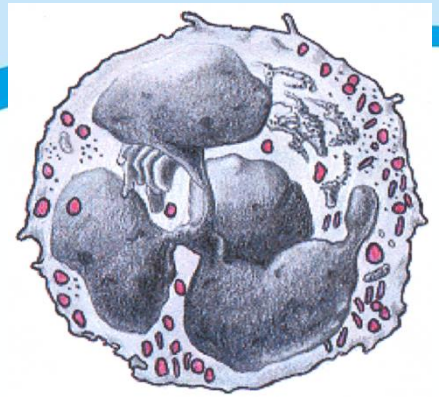




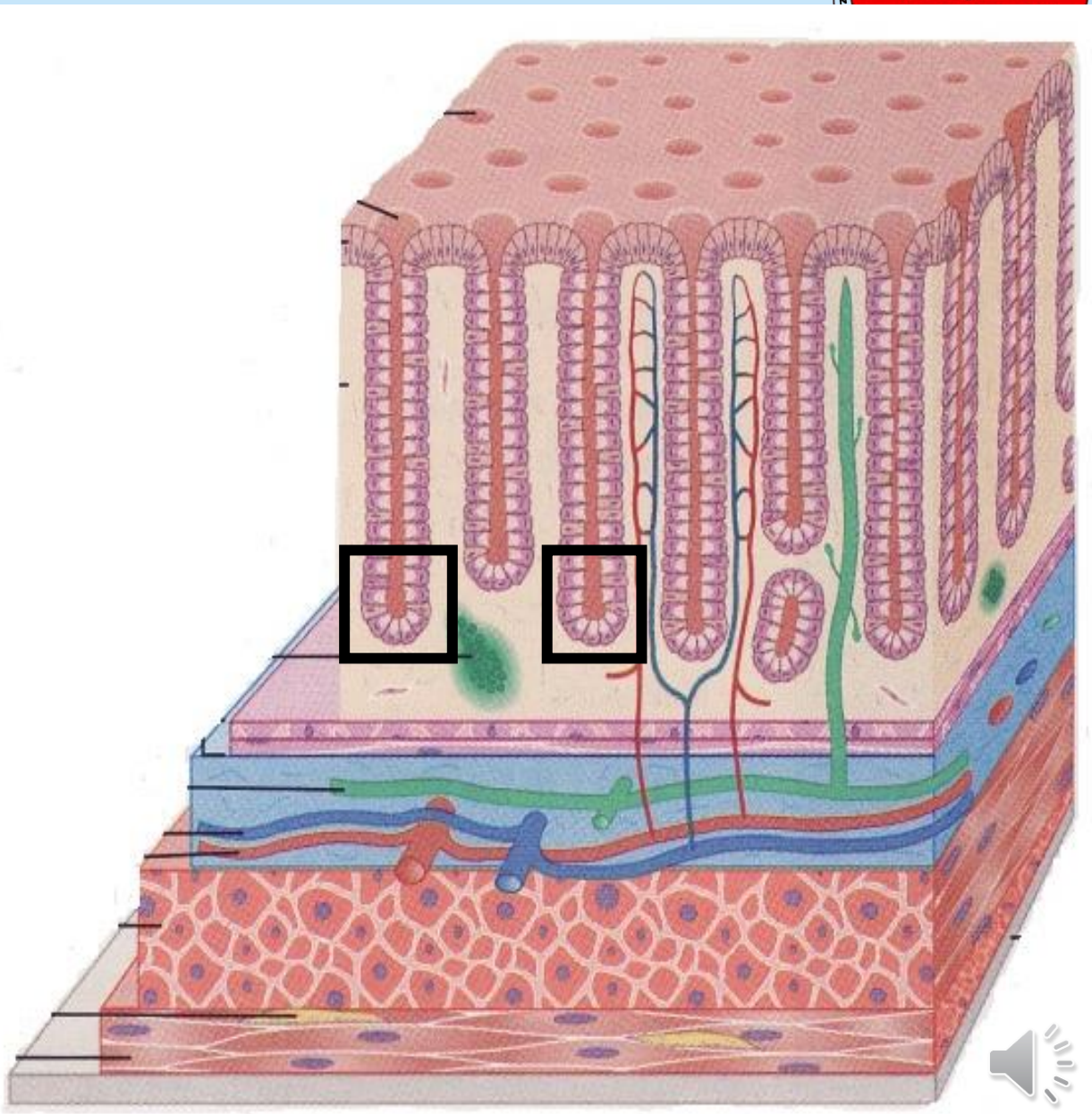
The neutrophils then accumulate in the crypt lumen forming a crypt abscess



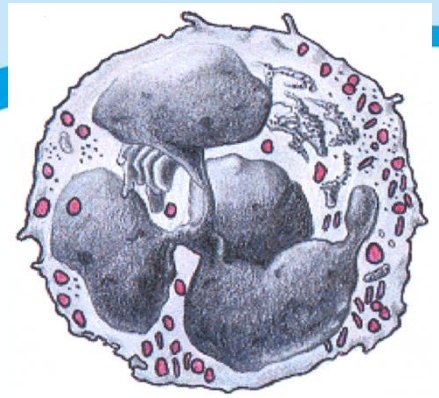
Inflammatory Bowel Disease



In IBD, especially UC, the base of the crypt is more affected…

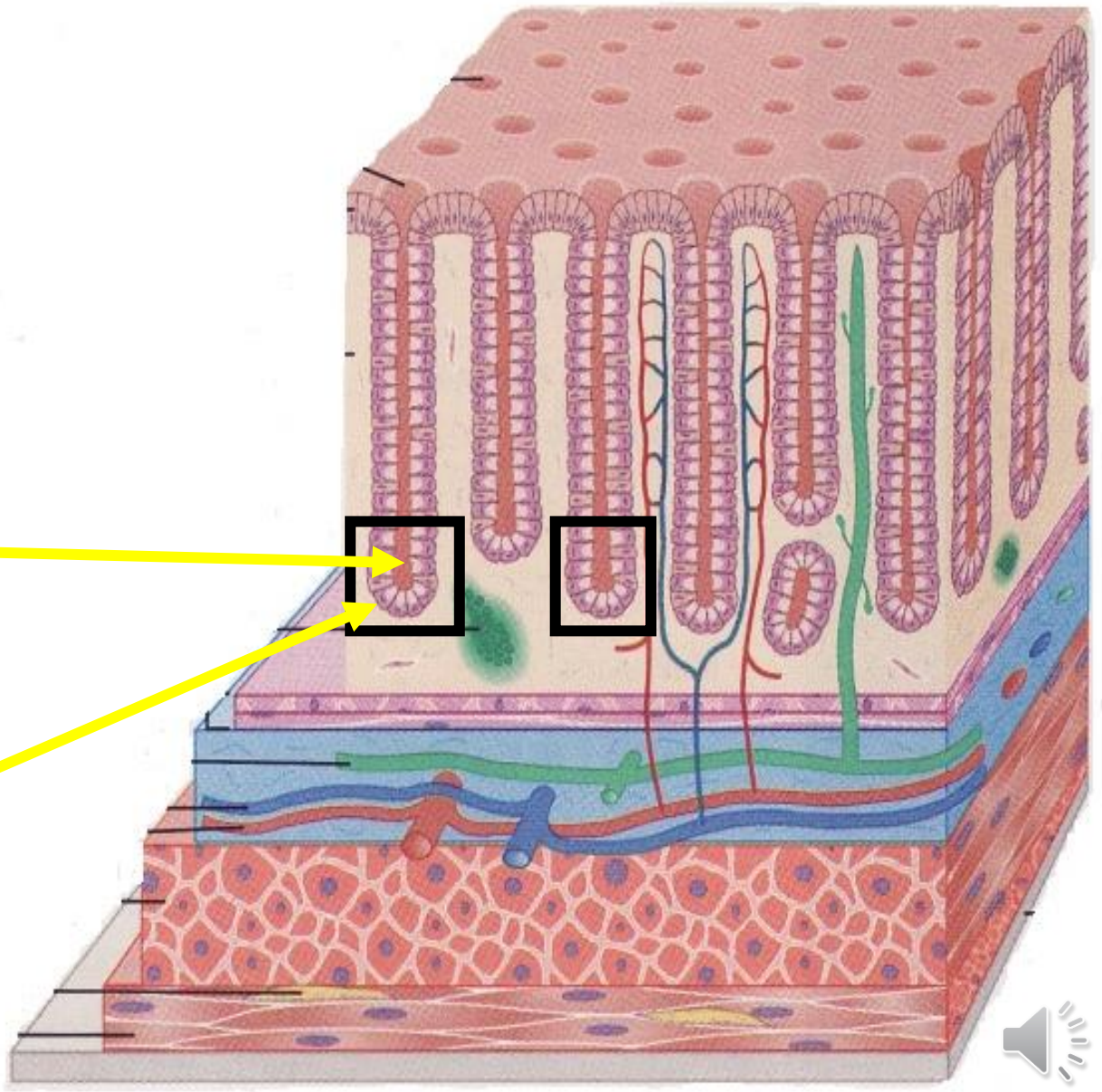


Inflammatory Bowel Disease

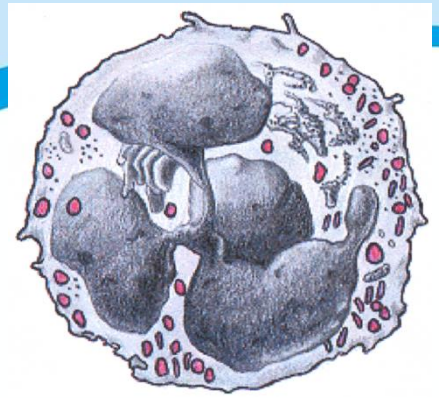


…with expansion of the lumen

and epithelial injury…

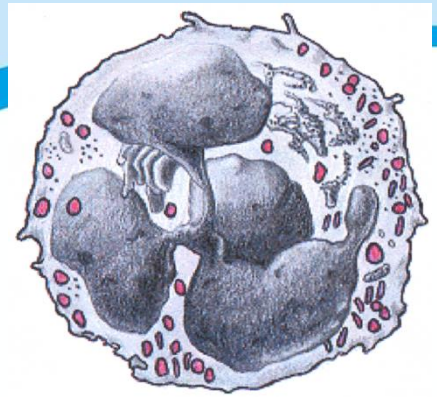


Inflammatory Bowel Disease

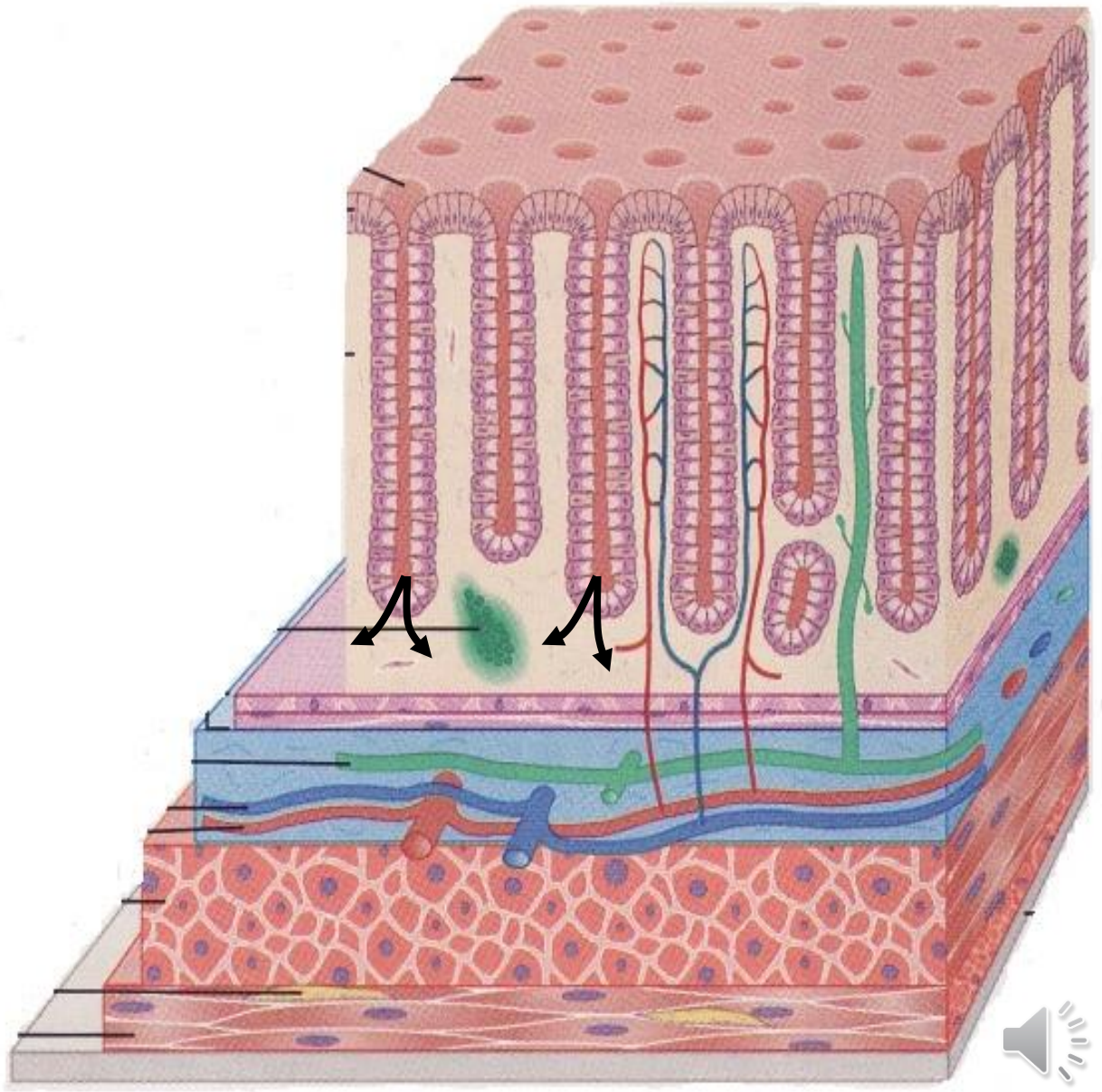


…and finally breach of the base of the crypt…

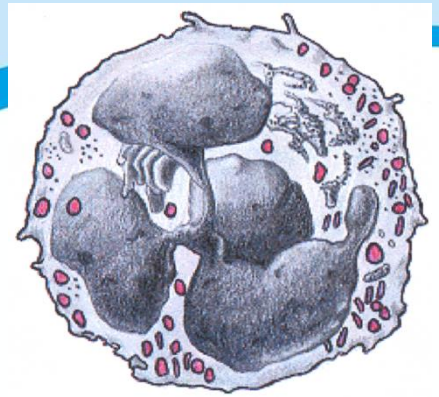
Inflammatory Bowel Disease



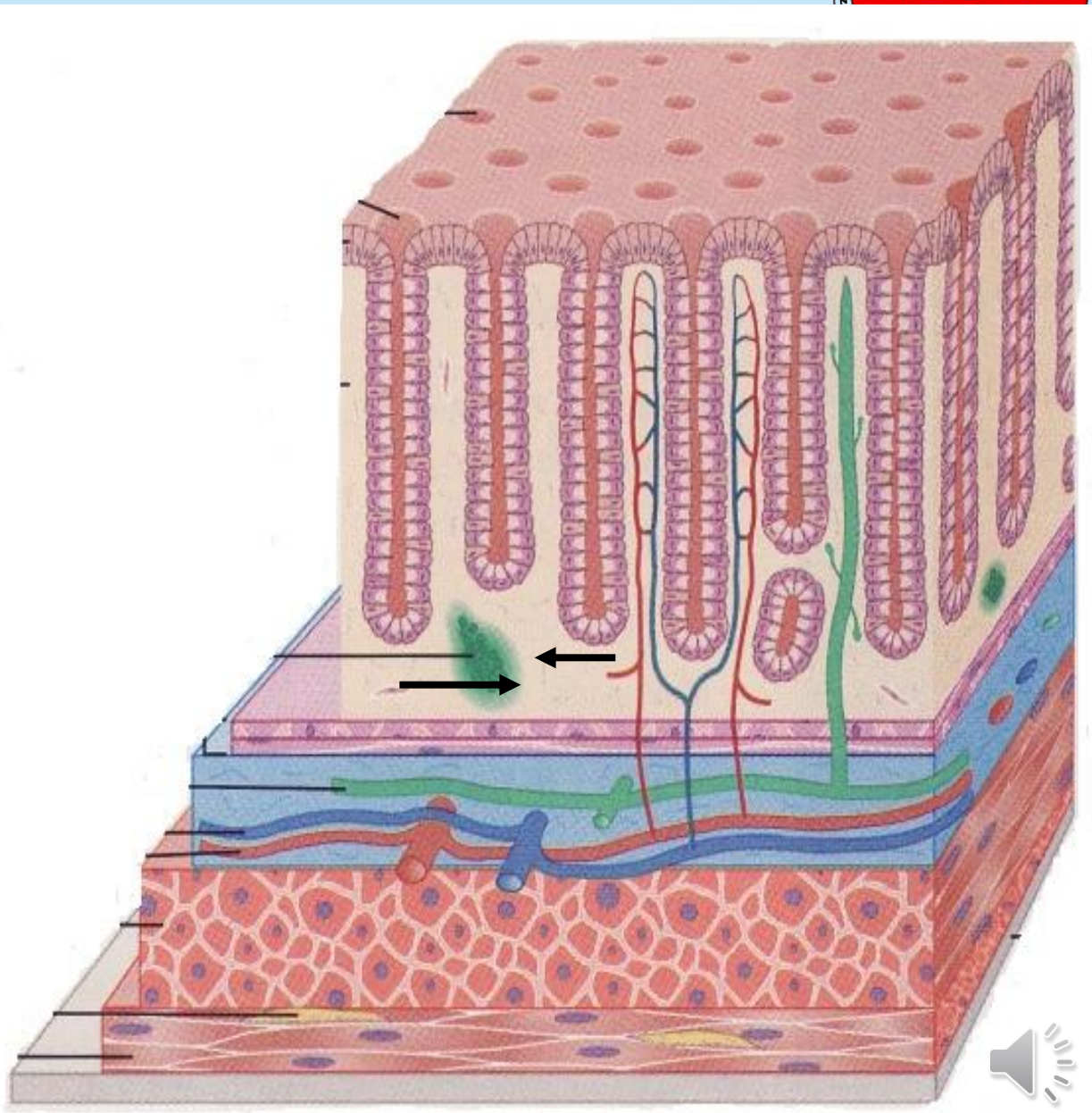
and extension of an inflammatory exudative process into the deep lamina propria…



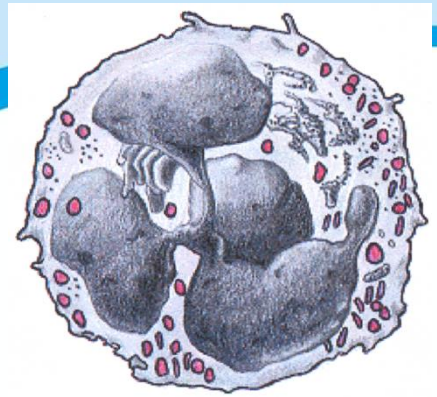
Inflammatory Bowel Disease



..the lateral spread of this inflammatory exudate …

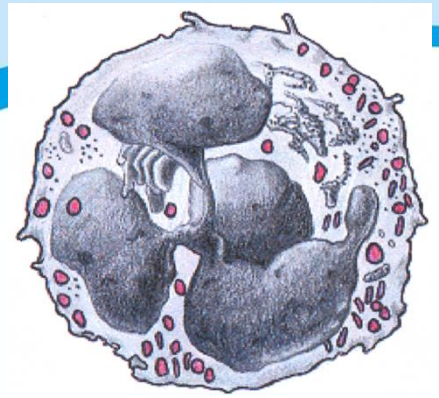


Inflammatory Bowel Disease

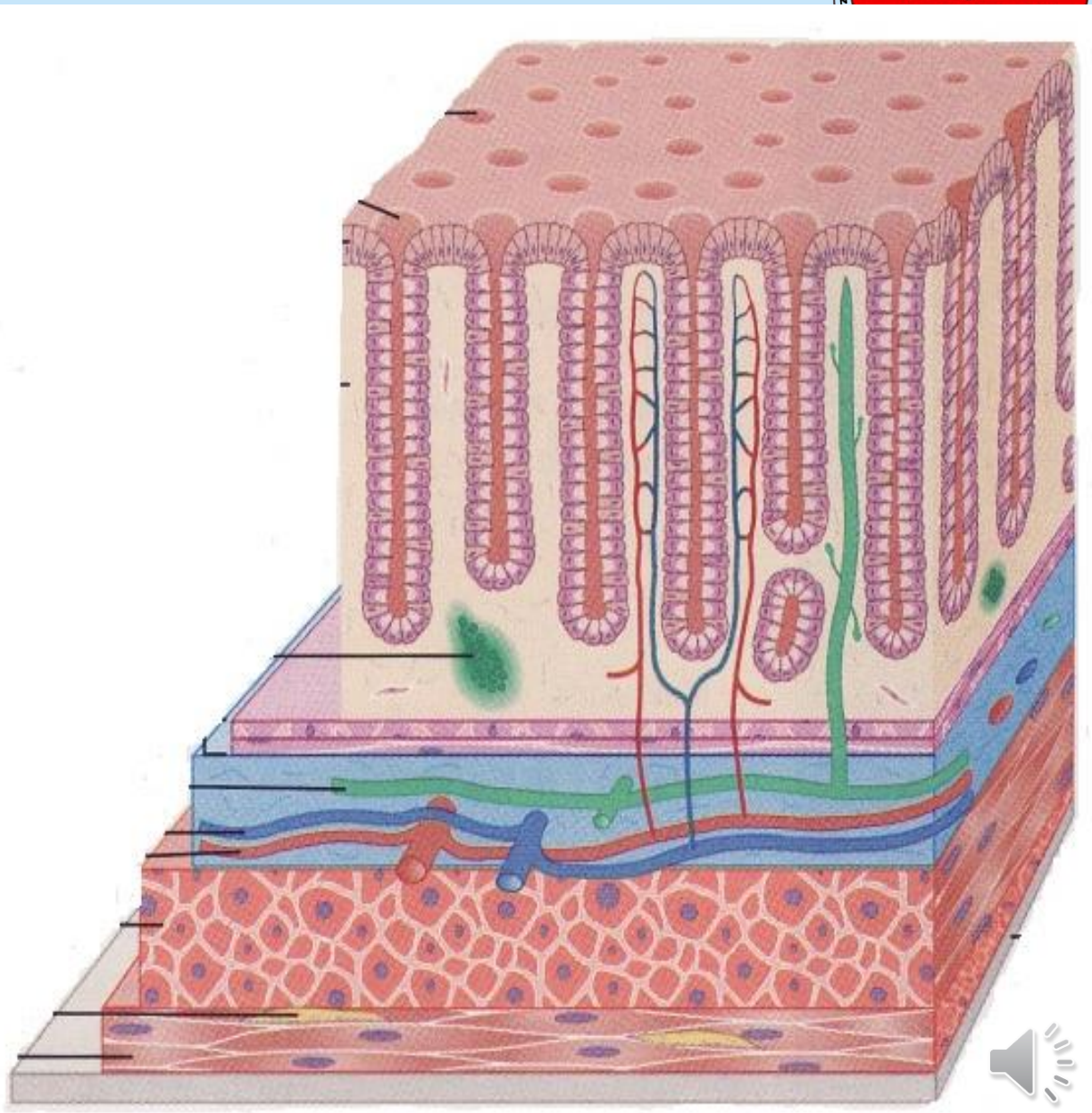


..and spread into the adjacent lamina propria …

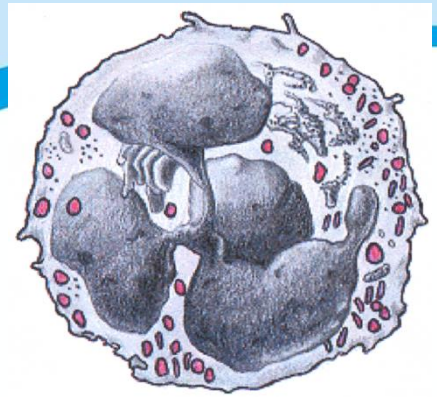
Inflammatory Bowel Disease



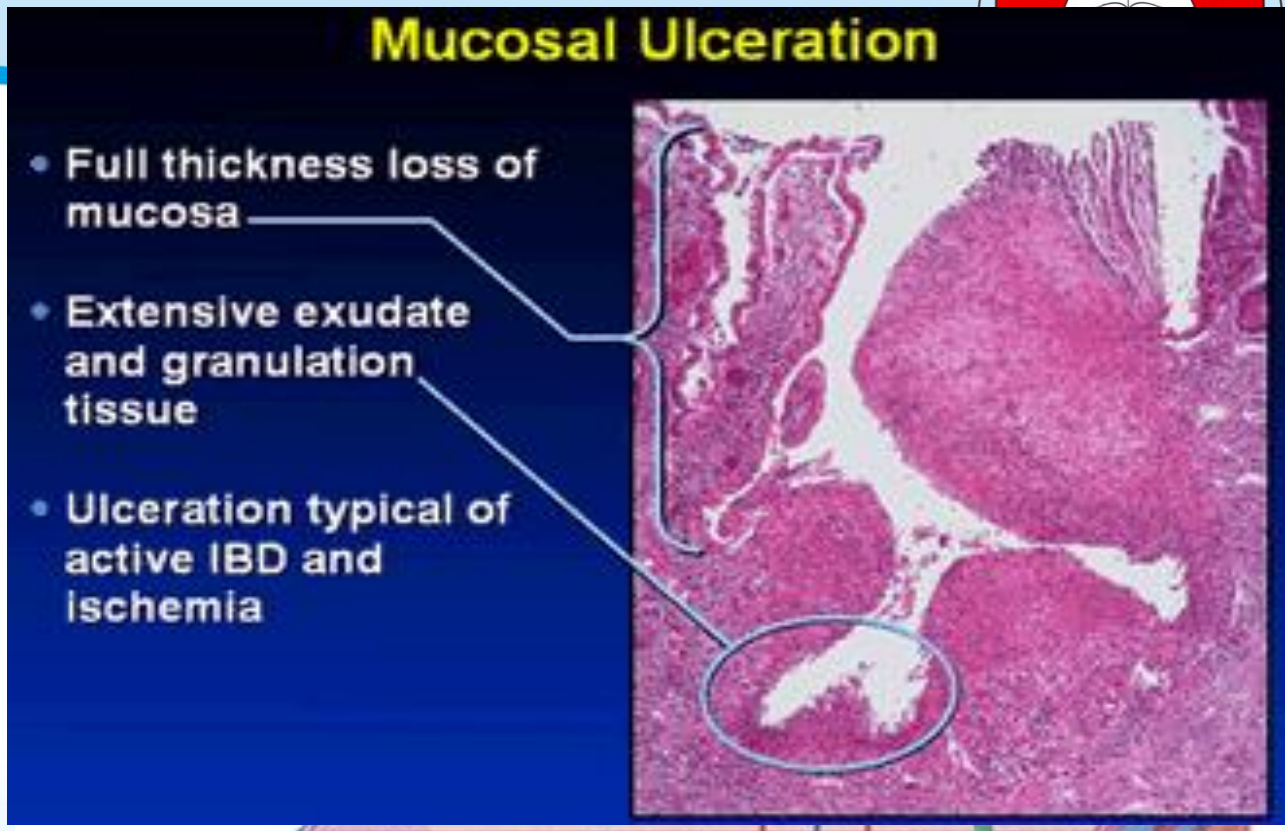
..with full thickness loss of the mucosa (epithelium and lamina propria)...

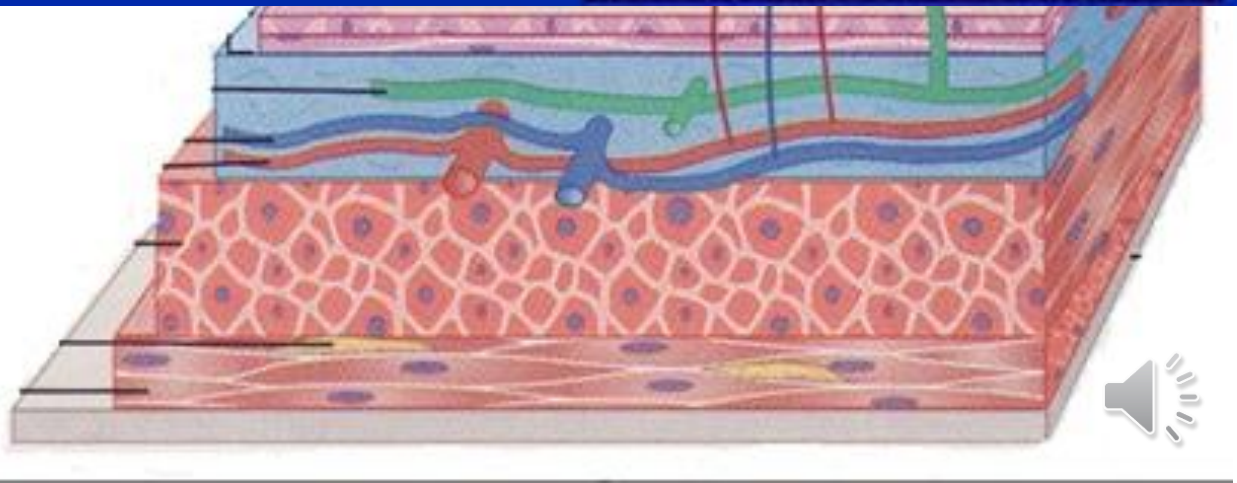


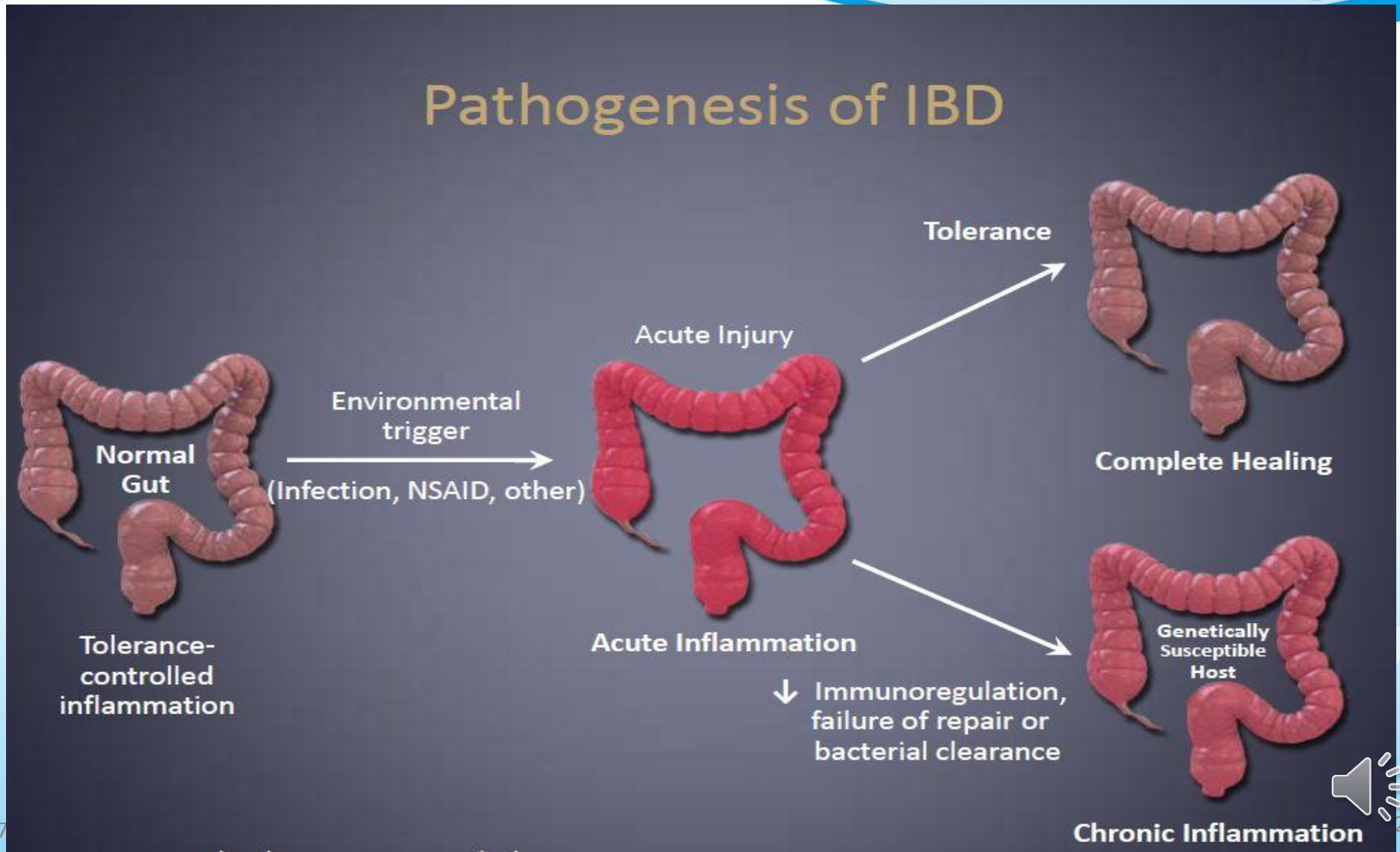
Inflammatory Bowel Disease



…this is called mucosal ulceration…






Pathogenesis of IBD
Tolerance
Acute Injury
Environmental trigger
(Infection, NSAID, other)
Normal Gut
Complete Healing
Tolerance-controlled inflammation
Acute Inflammation
Immunoregulation, failure of repair or bacterial clearance
Genetically Susceptible Host
Chronic Inflammation

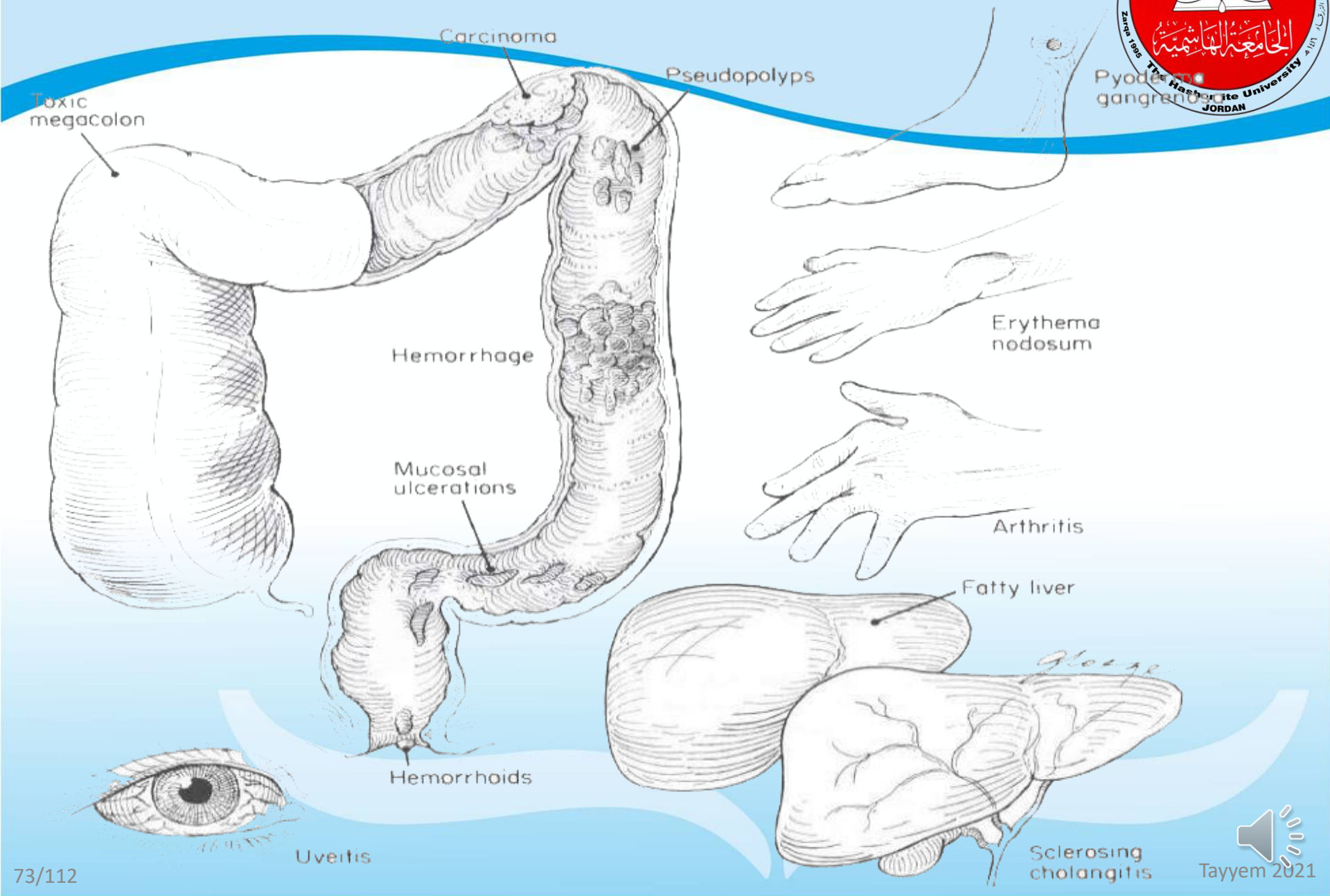
Clinical Manifestations

- Diarrhoea
- Abdominal pain, cramping & bloating due to bowel obstruction
- Hematochezia : Blood in stool
- Low fever
- Decreased appetite
- Weight loss and anorexia
- Fatigue
- Arthritis

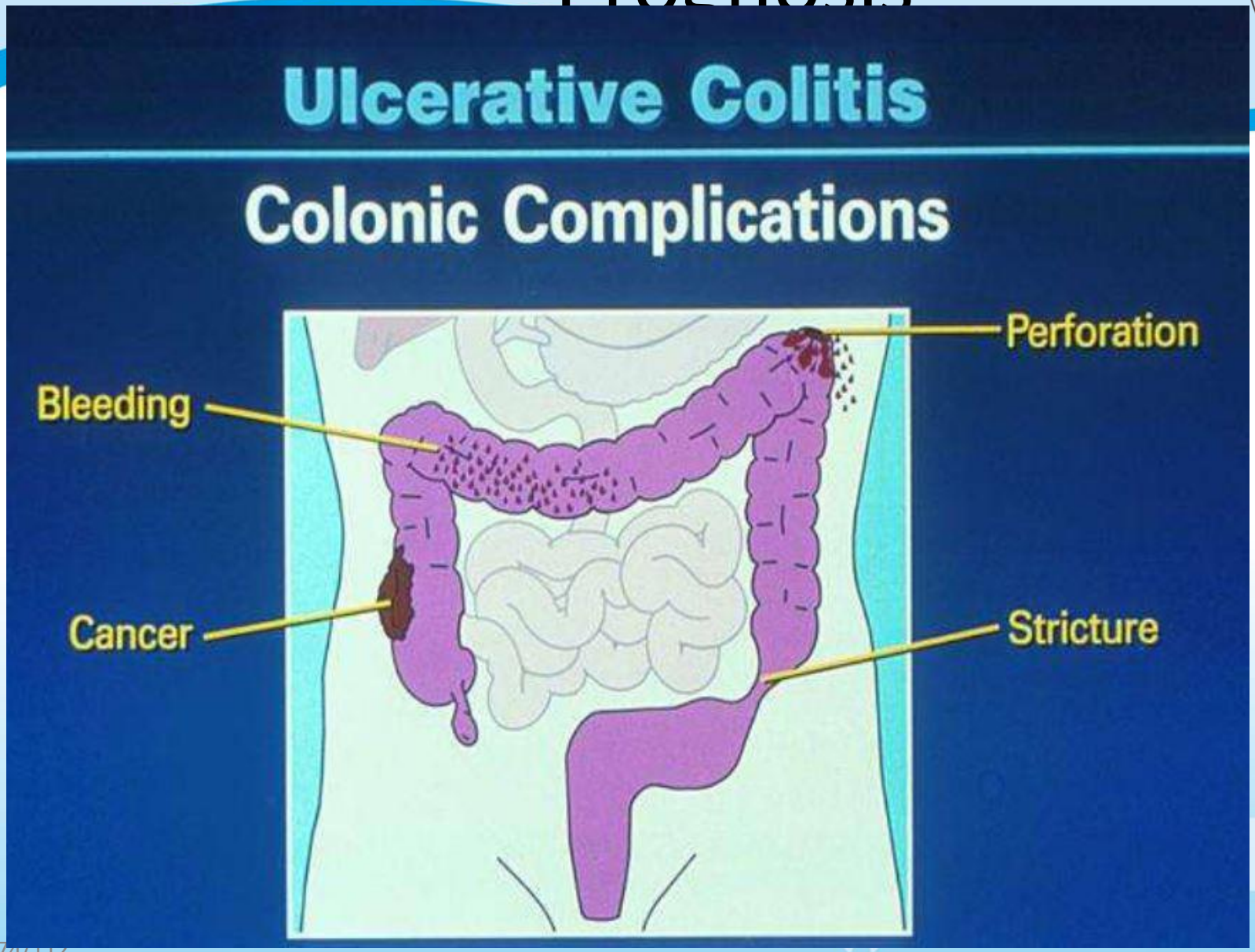
Clinical Severity of UC

	Mild	Moderate	Severe	Fulminant
Bowel movement	<4	Intermediate	>6	>10
Blood in stool	Intermittent		Frequent	Continuous
Temperature	Normal		>37.5°	>37.5°
Pulse	Normal		>90 bpm	>90 bpm
Hemoglobin	Normal		<75% normal rate	Transfusion required
ESR	<30 mm/hour		>30 mm/hour	>30 mm/hour
Clinical signs			Abdominal tenderness	Abdominal distension and tenderness

Extra intestinal manifestations



Prognosis


Ulcerative Colitis
Colonic Complications
Perforation
Bleeding
Cancer
Stricture

Diagnosis

- Physical Examination
- Endoscopy
- Biopsy
- Radiology
- Blood Test

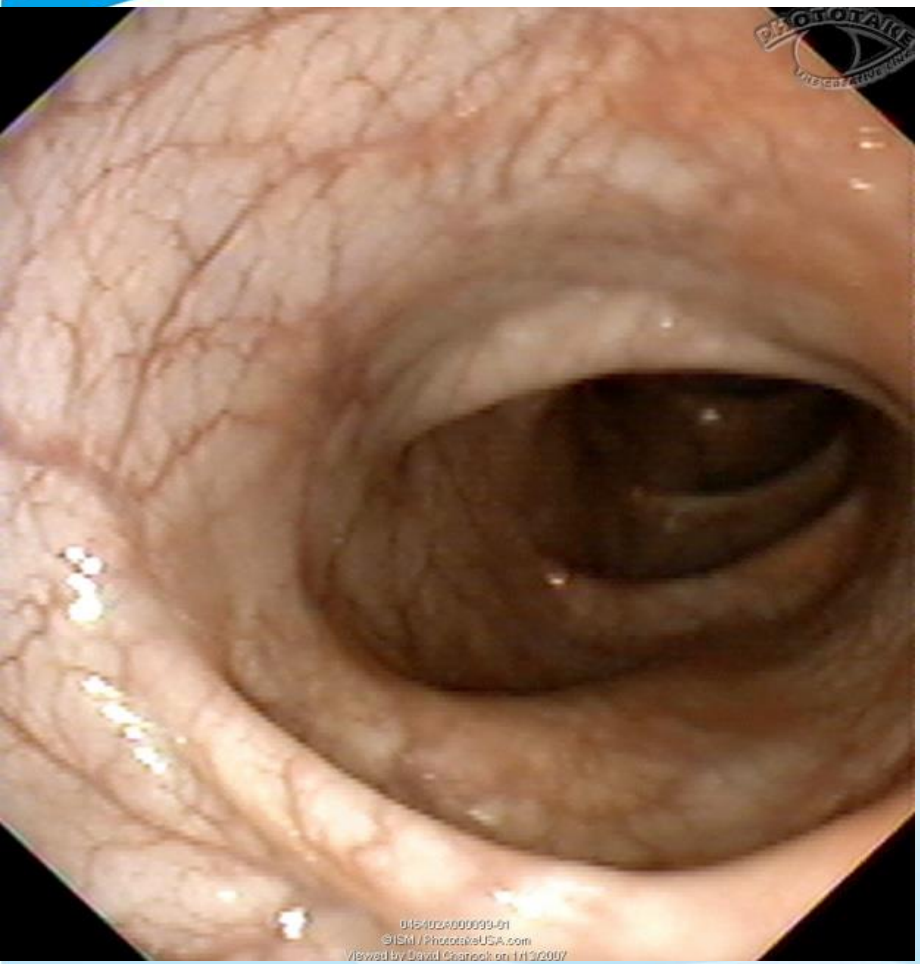
Physical Examination

- The main features to look for are:
  - oral aphtosis
  - abdominal tenderness and masses
  - anal tags, fissure and fistulae
  - nutritional deficiency.
  - An important feature in children is growth retardation.

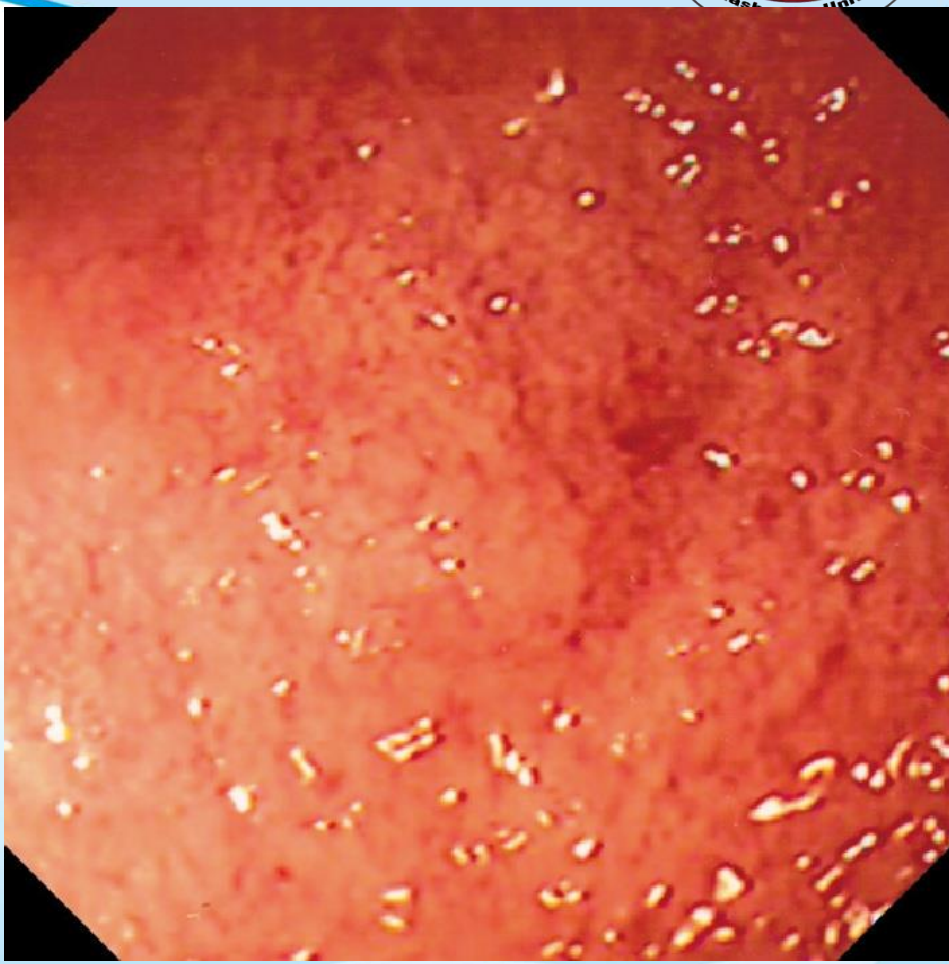
Colonoscopy

- determine the pattern and severity of colonic and terminal ileum inflammation and allows biopsies to be obtained.
- Endoscopic features are
  - aphtous ulcers
  - deeper ulceration
  - postinflammatory polyps (which indicate previous severe inflammation), but always accompanied by intervening normal mucosa, which is an important differential feature between CD and UC .

What the pathologist doesn't get to see though and what the endoscopist does, is erythema of the bowel wall :

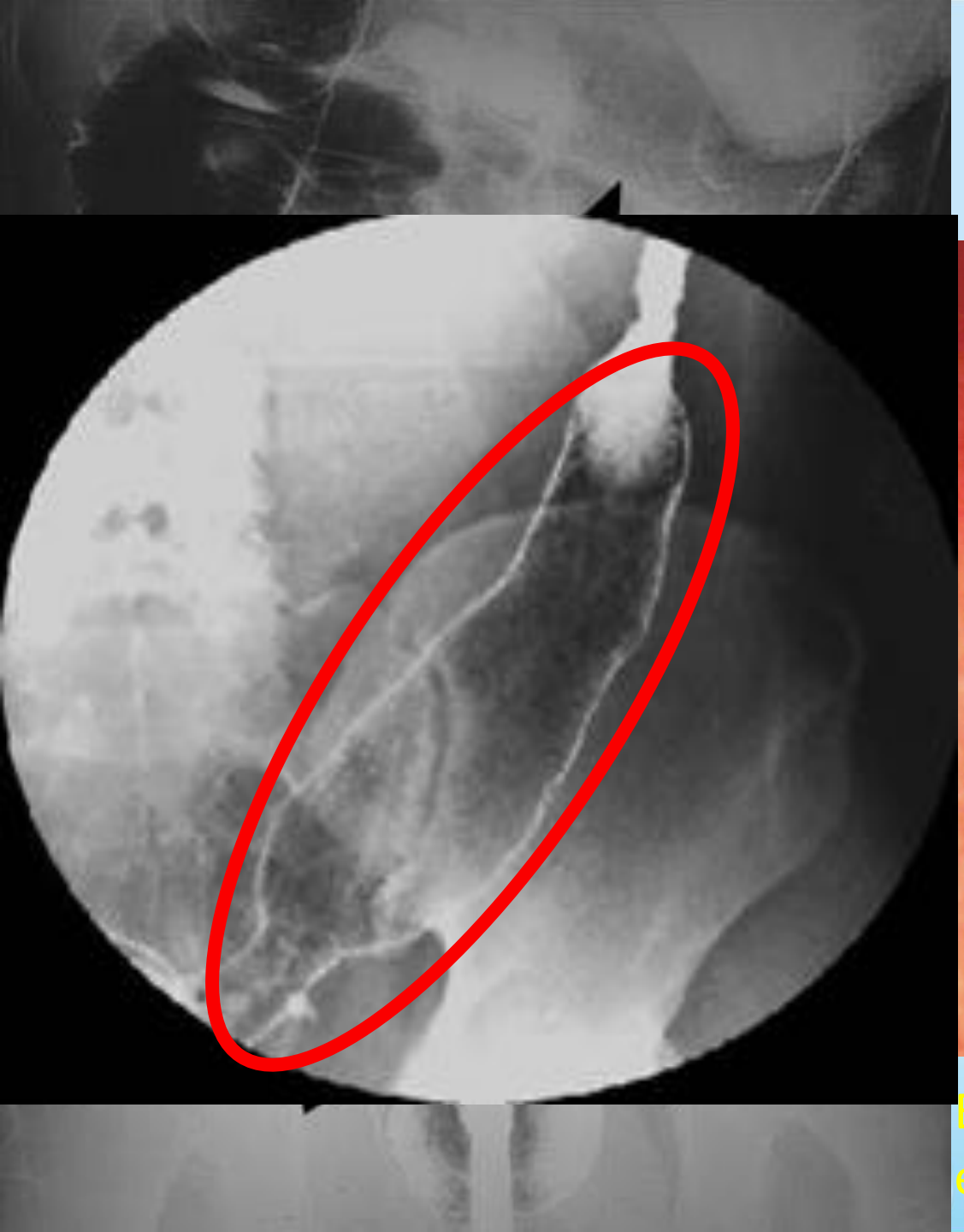


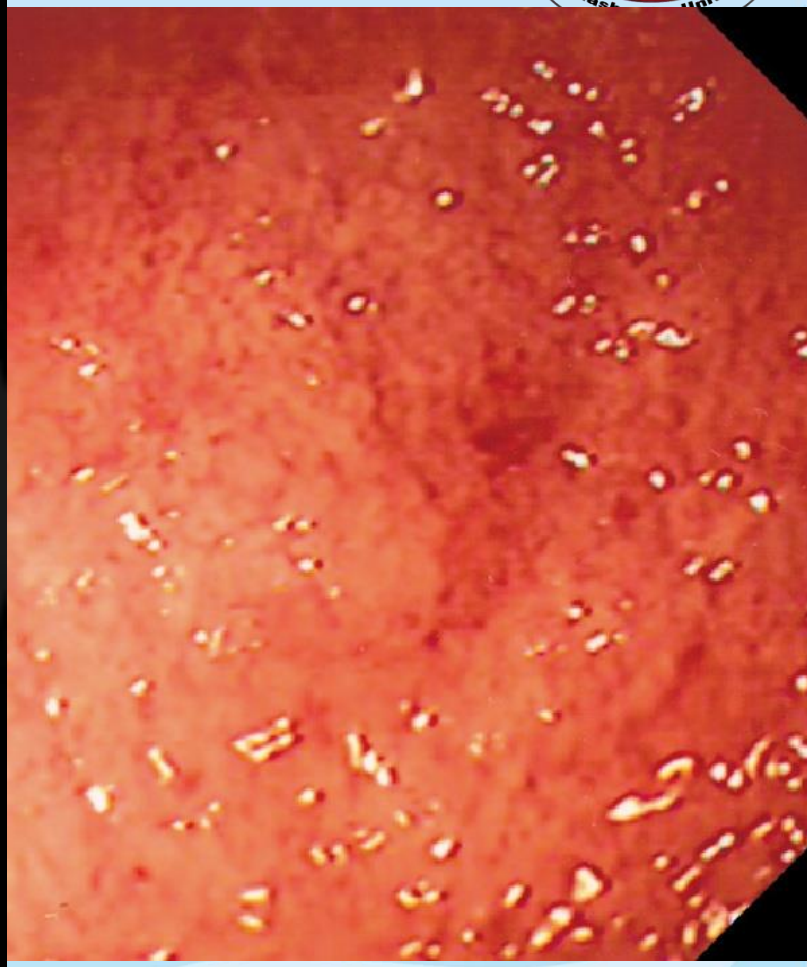
Normal Colon



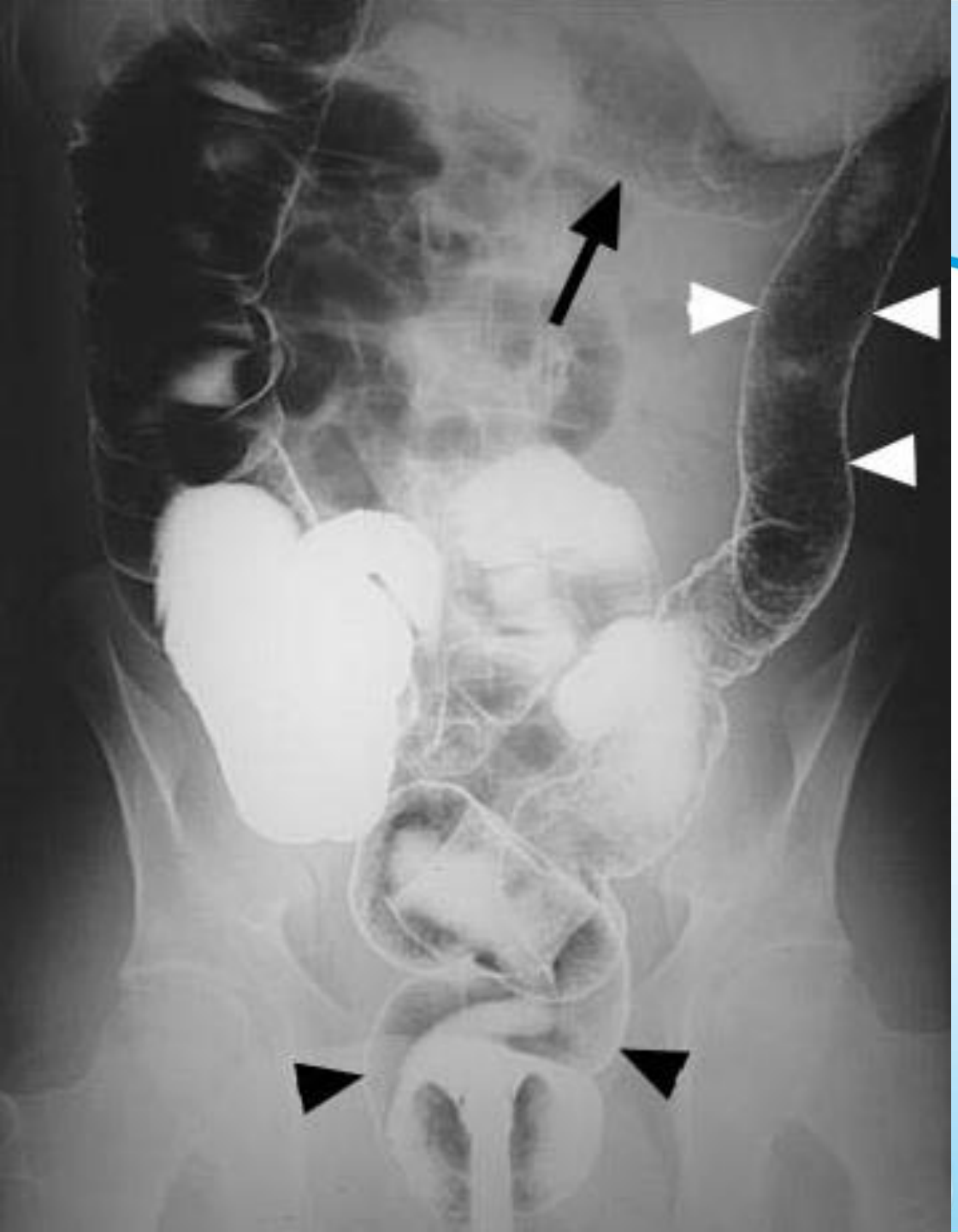
Early Ulcerative Colitis – erythema and granularity

A barium enema demonstrates this as a granular pattern



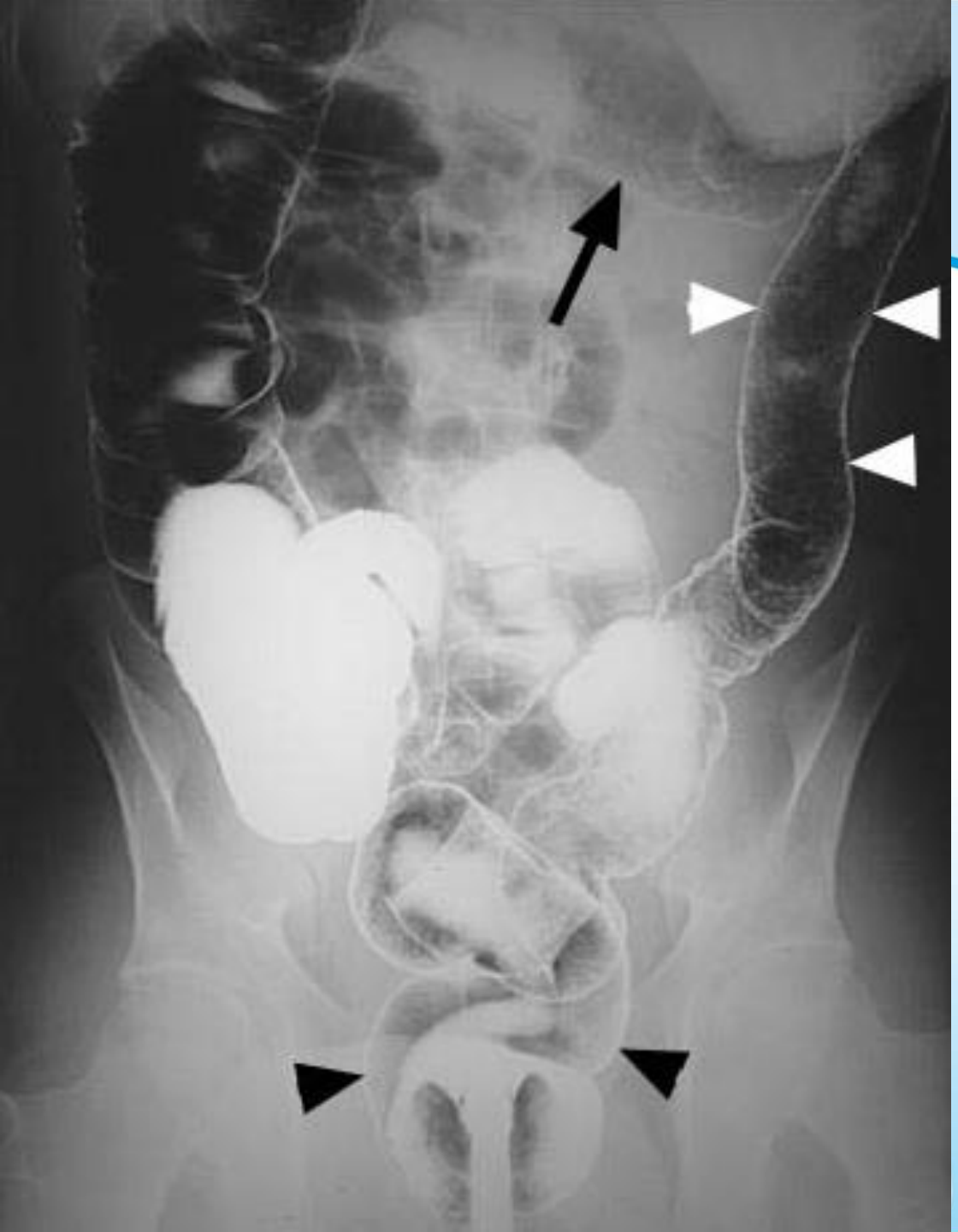


Early Ulcerative Colitis – erythema and granularity



Granularity is a manifestation of diffuse erythema with erosions

In tangential view the mucosal line is intact, but may be a little thickened.



Granularity is typical of ulcerative colitis…

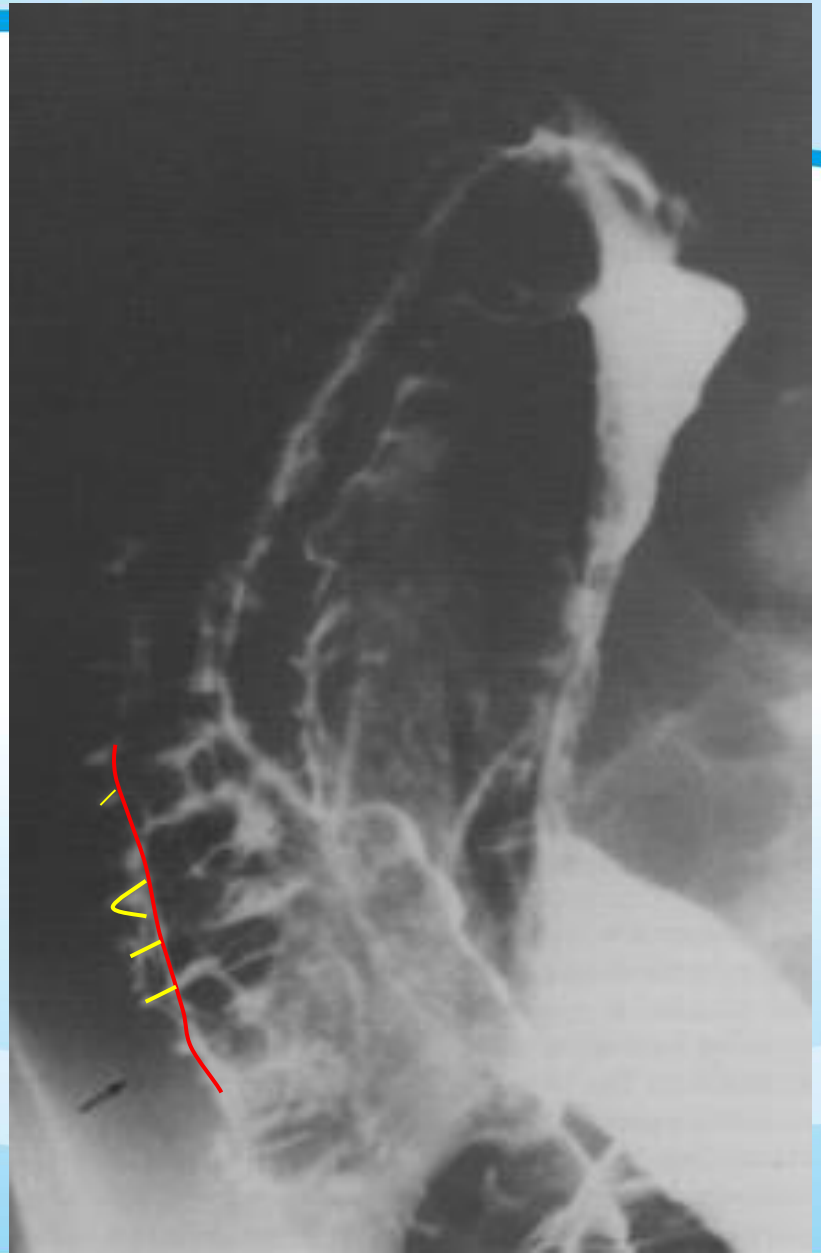
but is sometimes seen in early Crohn's disease…

and any infective colitis may present with granularity and the change is not specific.

Any projection outwards from the mucosal line indicates ulceration (the exception to this being aphtous ulceration).

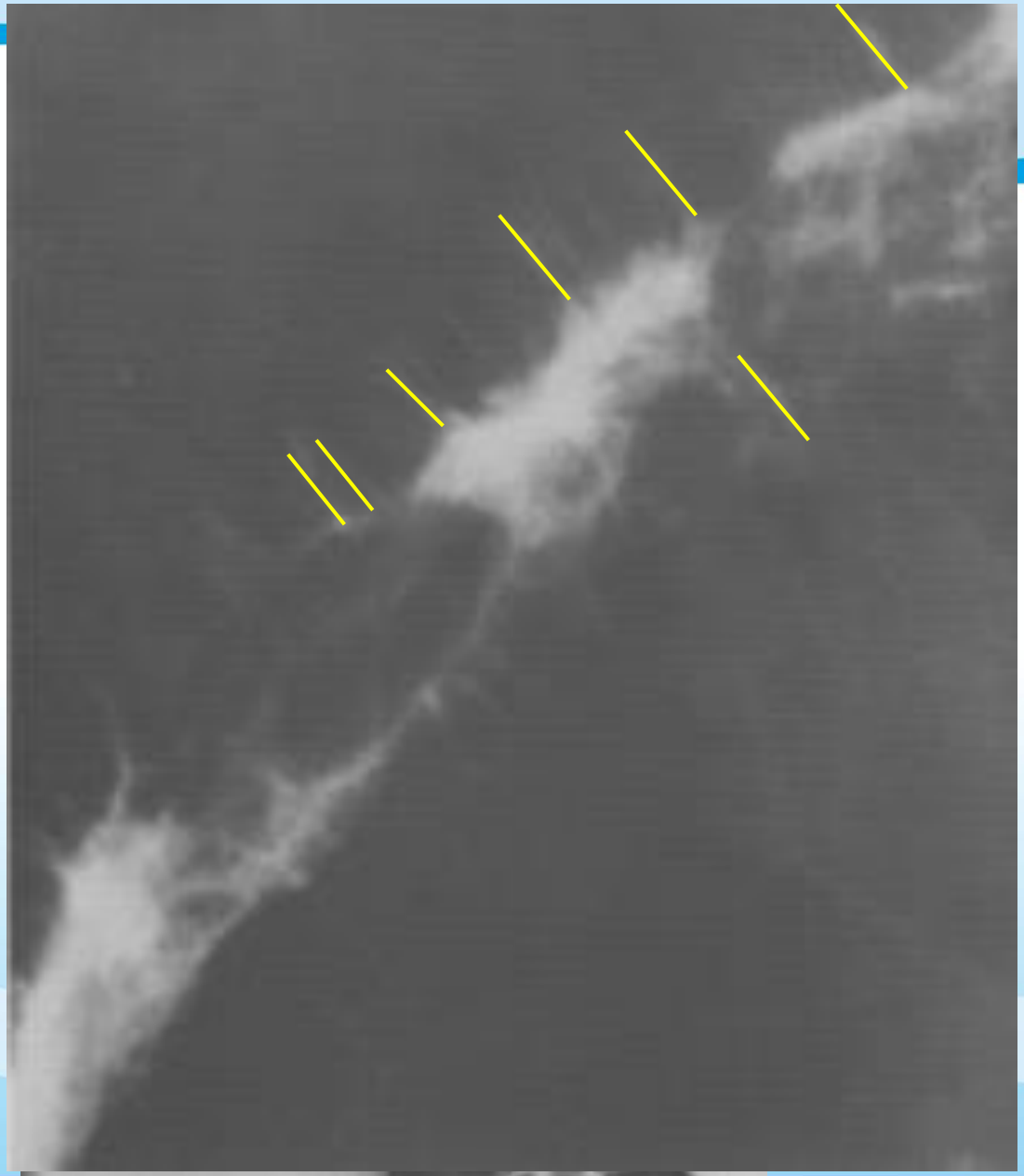
Mucosal Line

Mucosal Ulcers



Any projection outwards from the mucosal line indicates ulceration (the exception to this being aphtous ulceration).

Deep fissuring ulcers in Crohn's disease



Any projection outwards from the mucosal line indicates ulceration (the exception to this being aphtous ulceration).

Ulcers in an acute attack of Ulcerative colitis

Biopsy

- to find the nature of the inflammation
  - (ulcerative colitis versus CD)
  - collagenous colitis
  - infection.

Barium enema

- Barium inserted into rectum
- Fluoroscopy used to image bowel
- Rarely used due to colonoscopy
- Useful for identifying colonic strictures or colonic fistulae

Barium enema / UC

- Fine mucosal granularity
- Superficial ulcers seen
- Collar button ulcers
- Pipe stem appearanceloss of haustrations
- Narrow & short colon and ribbon contour colon

Barium enema / CD

- String sign

Barium Small bowel follow- through

- Barium sulfate suspension drink
- Fluoroscopic images of bowel taken over time
- Useful for looking for inflammation and narrowing of small bowel

CT enterography

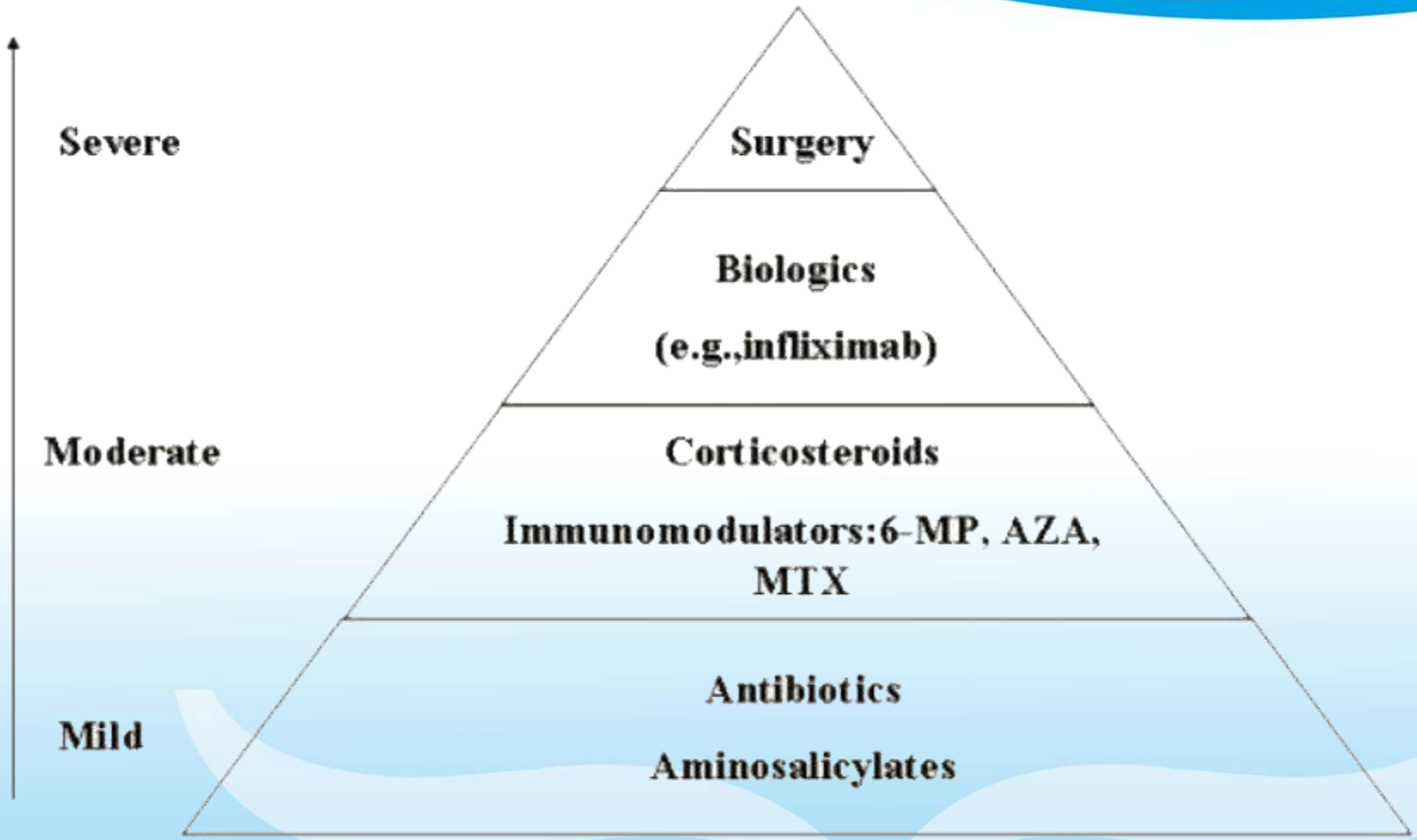
- Mural hyperenhancement
- Stratification
- Perienteric inflammatory changes

Blood Test

- Anemia may be present due to
  - blood loss (iron deficiency)
  - chronic inflammation
  - B12 malabsorption (macrocytic).
- Hypoalbuminemia suggests severe disease with denutrition.
- Fecal Calponectin levels correlate with histological inflammation, predict relapses &detect pouchitis
- markers of inflammation
  - C-reactive protein a
  - platelet count.
- Autoantibodies
  - Anti-saccharomyces cerevisiae antibodies (ASCA) are positive in 50-60% of CD
  - anti-neutrophil polynuclear antibodies (ANCA) are positive in 50-60% of UC patients.

	Crohn's disease	Ulcerative colitis
Terminal ileum involvement	Commonly	Seldom
Colon involvement	Usually	Always
Rectum involvement	Seldom	Usually
Involvement around the anus	Common	Seldom
Bile duct involvement	No increase in rate of primary sclerosing cholangitis	Higher rate
Distribution of Disease	Patchy areas of inflammation (Skip lesions)	Continuous area of inflammation
Endoscopy	Deep geographic and serpiginous (snake-like) ulcers	Continuous ulcer
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Fistulae	Common	Seldom
Stenosis	Common	Seldom
Autoimmune disease	Widely regarded as an autoimmune disease	No consensus
Cytokine response	Associated with T_h17	Vaguely associated with T_h2
Granulomas on biopsy	May have non-necrotizing non-peri-intestinal crypt granulomas	Non-peri-intestinal crypt granulomas not seen
Surgical cure	Often returns following removal of affected part	Usually cured by removal of colon
Smoking	Higher risk for smokers	Lower risk for smokers

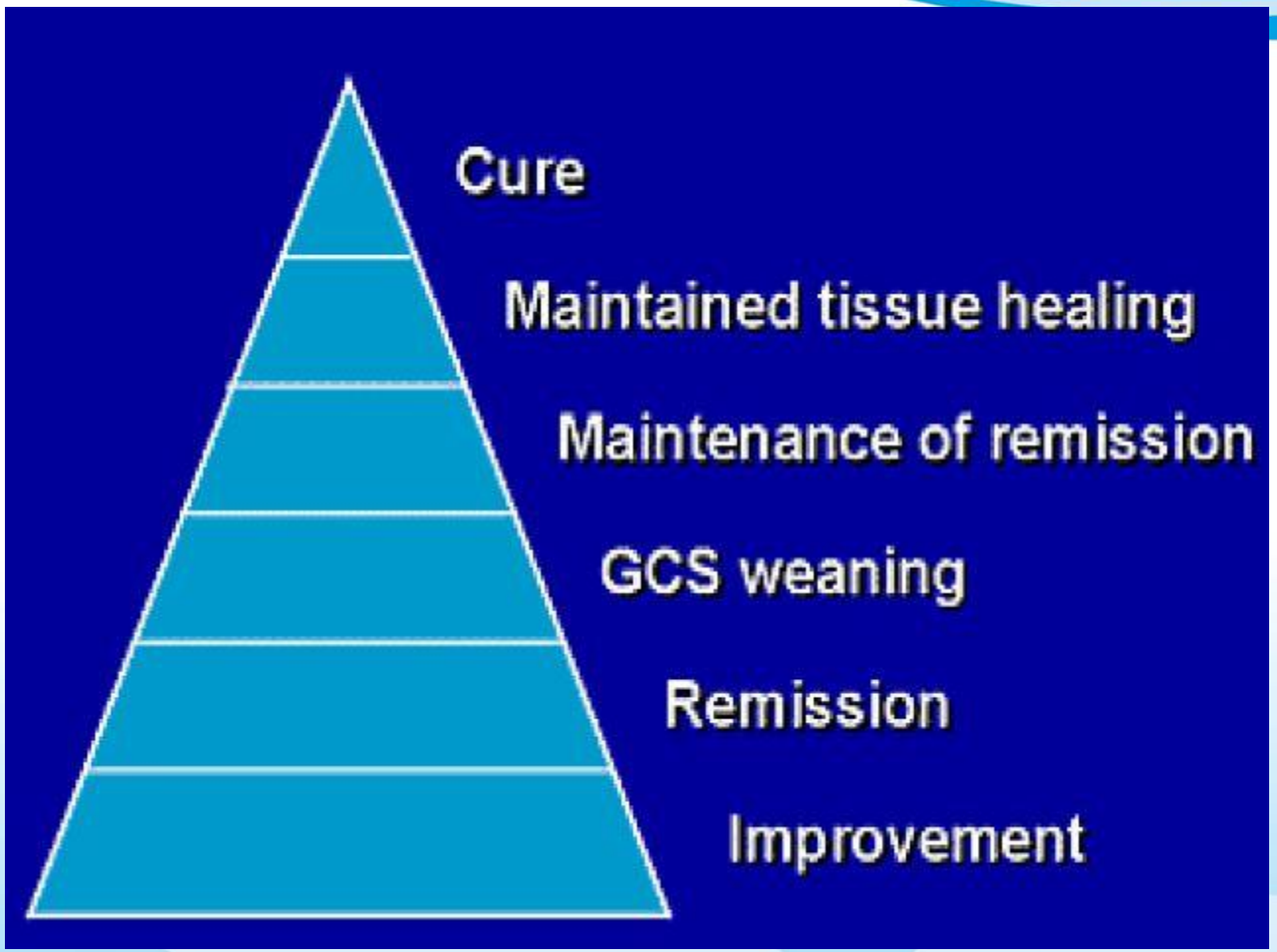
Lines of Treatment



Principles of treatment

- Maintain or improve quality of life.
- Terminate the acute attack and induce clinical remission.
- Prevent symptoms during chronic symptomatic periods.
- Prevent or reduce complication.
- Use the most cost-effective drug treatment.
- Avoid surgery if possible.
- Replacement of vitamin A, D, K if necessary in case of malabsorption.

Goals of treatment



Non-Pharmacological Treatment

- smoking cessation
- reduce alcohol consumption
- avoid the use of NSAIDs
- avoid spicy and fried/oily food
- take fiber rich diet as tolerated
- incorporate more omega-3 fatty acids in the diet. These fats may have an anti-inflammatory effect. They are found in fish.

Pharmacological Treatment

- Aminosalicylates
- Corticosteroids
- Immunosuppressive agents
- TNF – Tumor Necrosis Factor Inhibitor
- Antimicrobials

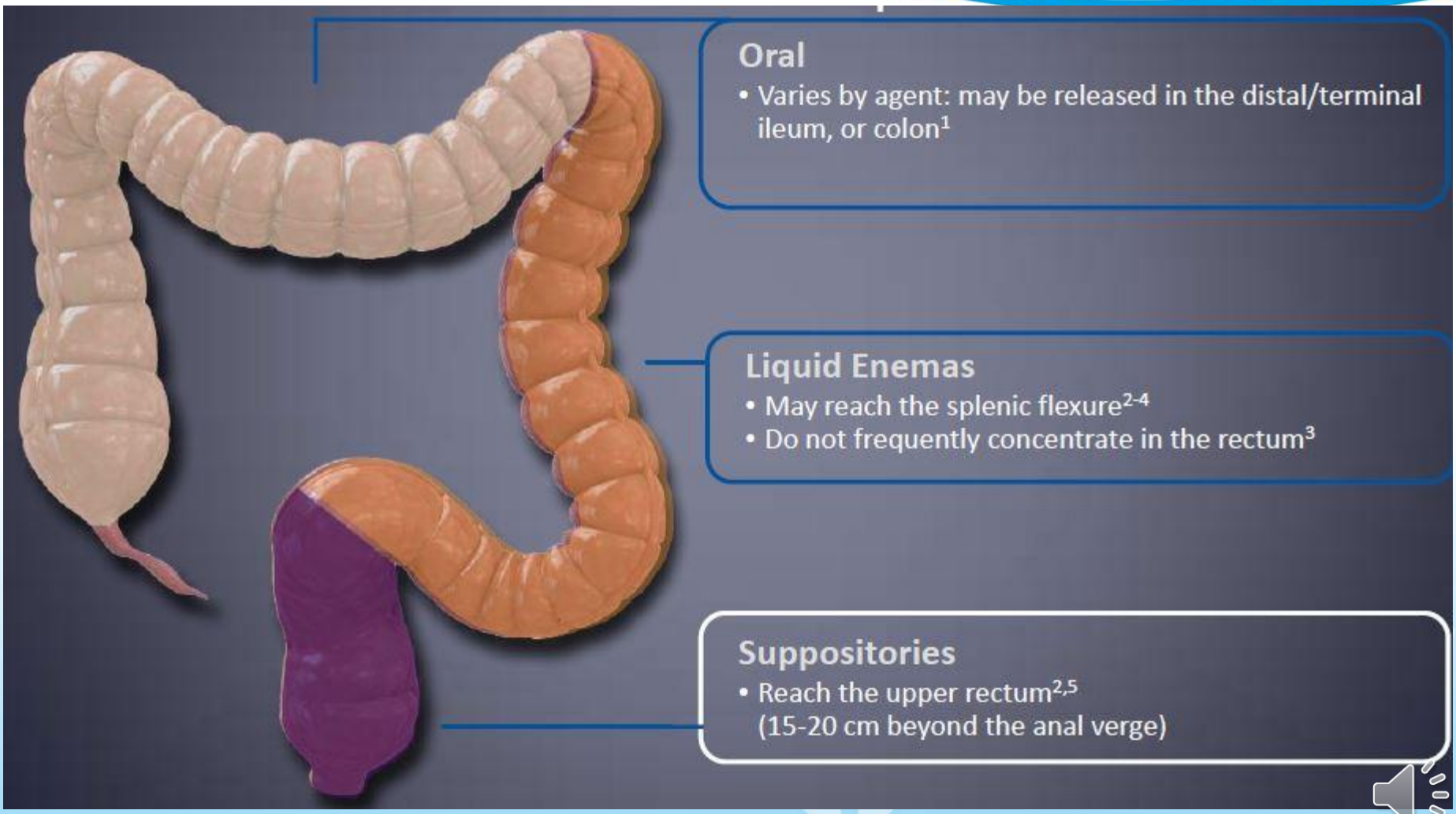
Aminosalicylates / 5-ASA

- These agents have anti-inflammatory effects.
- They are used to induce and maintain remission in mild – moderate disease.
- The side effects are
  - hemolytic anemia
  - pruritic dermatitis, hypersensitivity
  - headache,
  - GI: Nausea, epigastric pain, diarrhoea, pancreatitis

Cont

- Sulfasalazine
  - 5-aminosalicylic acid and sulfapyridine as carrier substance
- Mesalamine
  - Mesalazine (5-ASA), e.g. Asacol, Pentasa (sustained-release preparation (coated with ethylcellulose) that delivers 5-ASA to the distal ileum and colon)
- Balsalazide (prodrug of 5-ASA)
- Olsalazine (5-ASA dimer cleaves in colon)

Topical Action of 5-ASA



Corticosteroids

- Corticosteroids (I mg/kg/day) are effective in decreasing disease activity and inducing remission in most patients.
- However, due to undesirable side effects, long-term use of corticosteroids is not recommended.
- indicated for the treatment of moderate to severe colitis whose symptoms cannot be controlled by aminosalicylates.
- 50% of patients experience adverse effects
  - cosmetic effects
  - suppression of linear growth in children
  - osteopenia.
- Egs.
  - Prednisolone
  - Budenoside

Immunosupressive Agents

- Indication:
  - impossible to taper corticosteroids
  - frequent relapses occur, immunomodulating therapy should be considered.
- E.g:
  - Azathioprine
  - 6-mercaptopurine
  - Cyclosporine
  - tacrolimus
- Due to delayed onset of action, these agents are not used to treat acute colitis.

TNF Inhibitors

- Thalidomide, originally used for its sedative and antiemetic properties, has recently been shown to inhibit TNF-α production by monocytes and other cells.
- Infliximab is a chimeric mouse-human monoclonal antibody to TNF. It binds free and membrane-bound TNF and thus prevents the cytokine from binding to its cell surface receptor
- Golimumab is a human anti-TNF-α monoclonal antibody that blocks the inflammatory activity of TNF-α.
- Adalimumab is a recombinant human anti-TNF-alpha IgG1 monoclonal antibody that blocks the inflammatory activity of TNF-α.

Infliximab

- Infliximab binds to TNF trimers with high affinity, preventing cytokine from binding to its receptors
- It also binds to membrane-bound TNF- a and neutralizes its activity & also reduces serum TNF levels.
- **Use**
  - Fistulizing CD
  - Severe active CD
  - Refractory/intolerant of steroids or immunosuppression
- **Side effects**
  - Infusion reactions, Sepsis, Reactivation of Tb, Increased risk of Tb

Antimicrobial Agents

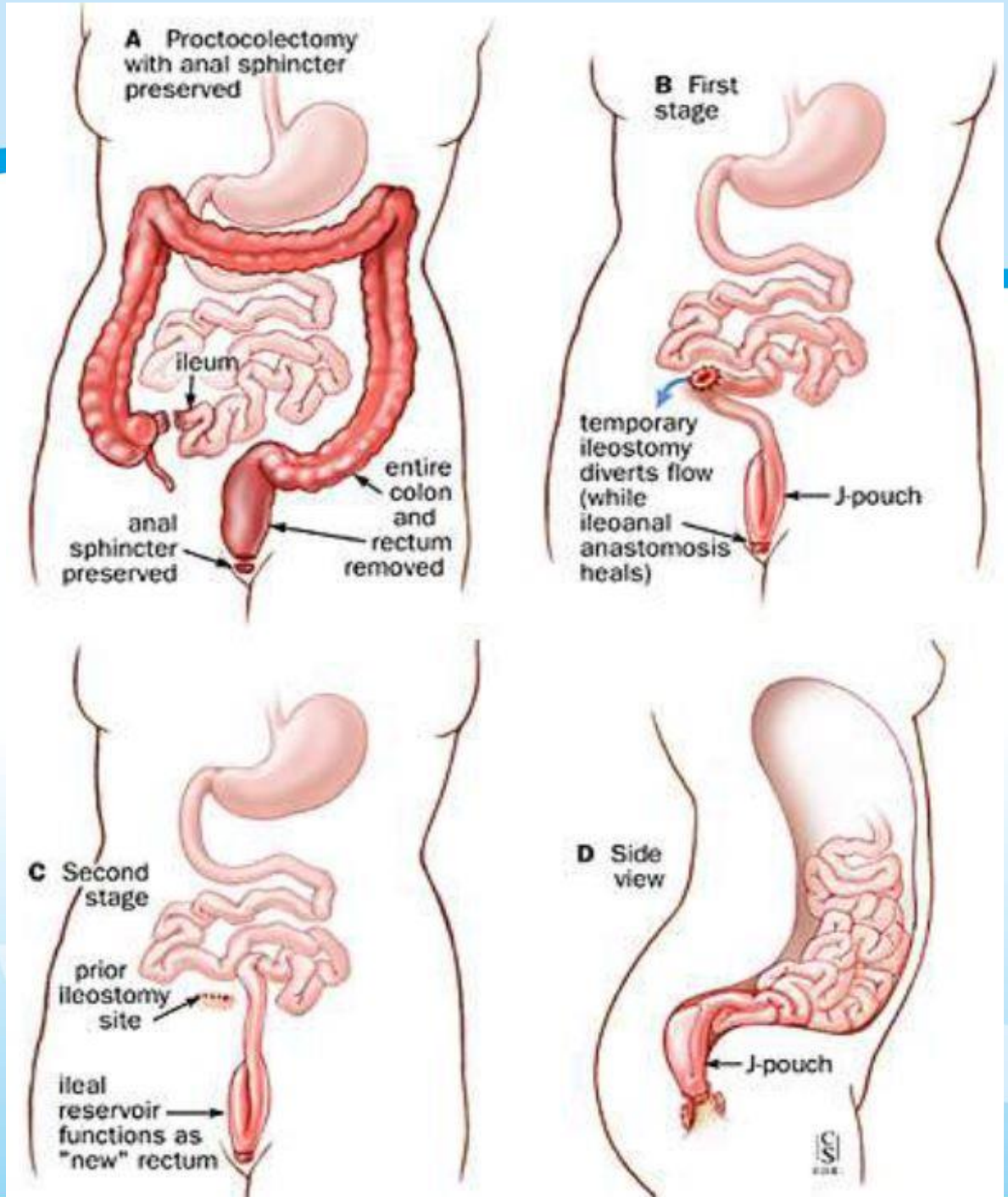
- Metronidazole and ciprofloxacin are useful in the treatment of mild to moderate disease, particularly in patients with perianal disease and infectious complications.
- Sensory neuropathy, which may be seen with long-term metronidazole use, usually resolves completely or improves after discontinuation of the drug.
- Rifaximin

Other medications

- Anti- diarrheals - Loperamide (Imodium)
- Laxatives - senna, bisacodyl
- Pain relievers. acetaminophen (Tylenol).
- Iron supplements
- Nutrition

Surgery for Ulcerative Colitis

- Proctocolectomy (removing the colon and rectum) with ileostomy
- Restorative proctocolectomy, also known as ileoanal pouch anal anastomosis (IPAA)

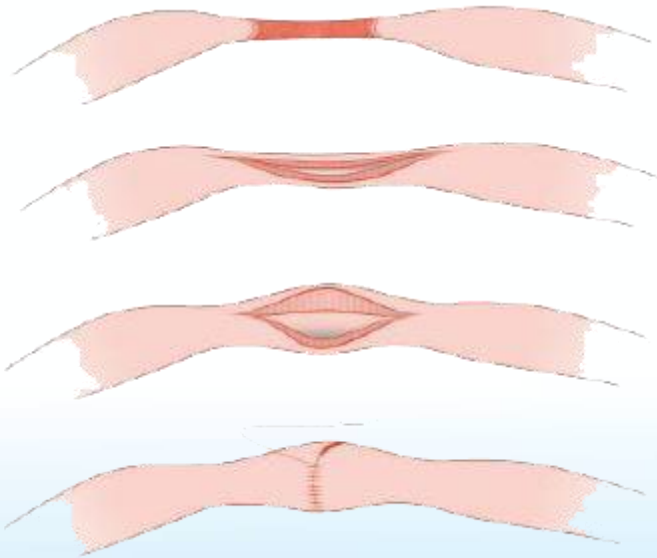

A Proctocolectomy with anal sphincter preserved
ileum
entire colon and rectum removed
anal sphincter preserved
B First stage
temporary ileostomy diverts flow (while ileoanal anastomosis heals)
J-pouch
C Second stage
prior ileostomy site
ileal reservoir functions as "new" rectum
D Side view
J-pouch

Indication / UC

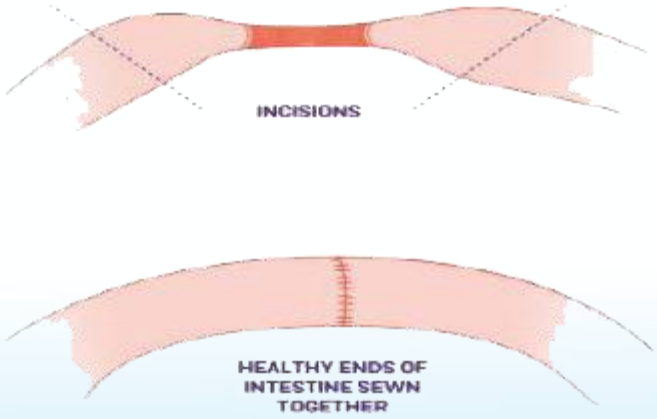
- Fulminating disease
- Chronic disease with anemia, frequent stools, urgency & tenesmus
- Steriod dependant disease
- Risk of neoplastic change
- Extraintestinal manifestations
- Severe hemorrhage or stenosis

Surgery for Crohn's Disease

- Strictureplasty



Resection & anastomosis



Surgery for Crohn's Disease

- Surgery for abscesses and fistulas
- Colectomy
- proctocolectomy