



# Inflammatory Bowel Diseases GI Pathophysiology

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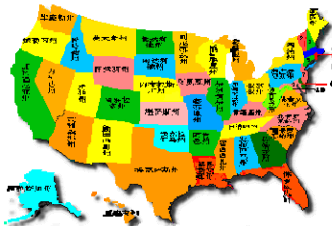
# Epidemiology of IBD: Crohn's Disease and Ulcerative Colitis

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- 1 Million cases of IBD in the U.S.
- Approximately 10,000 new cases dx annually
- Peak onset: 15 to 25 years of age
- Second “peak” incidence: 50 to 65 years of age
- Approximately equal between males and females
- Incidence increased in industrialized nations from 1970 to 1990

# IBD Epidemiology

- Family History: Greatest risk factor
  - 15-20% of patients have a (+) family history
  - Risk to offspring of affected patients: ~9%
  - Risk to siblings of affected patients: ~9%
  - Risk to parents of affected patient: 3.5%
  - Concordance in Identical twins: CD (58%), UC (4%)
  
- Jewish > Non-Jewish populations:
  - Crohn's 3-8x more likely, Ulcerative colitis 2-4x more likely
  
- Caucasian > African American



Europe >> South America/Asia/Africa??



# Case Presentation

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- CC: Bloody diarrhea
- HPI:
  - 22 yo ashkenazi jewish female
  - 6 weeks ongoing symptoms, 6 bm's day (occ at night), +Urgency
  - 5 lbs unintentional weight loss
  - No travel, no sick exposures
- FHx
  - Mother with “stomach” problems
- PMHx/PSHx:
  - None
- Meds:
  - Seasonale (BCP's) x 3yrs
- Physical Exam:
  - Thin F, anxious, soft abdomen, mild LLQ tenderness to palpation, no external hemorrhoids



# Differential Diagnosis

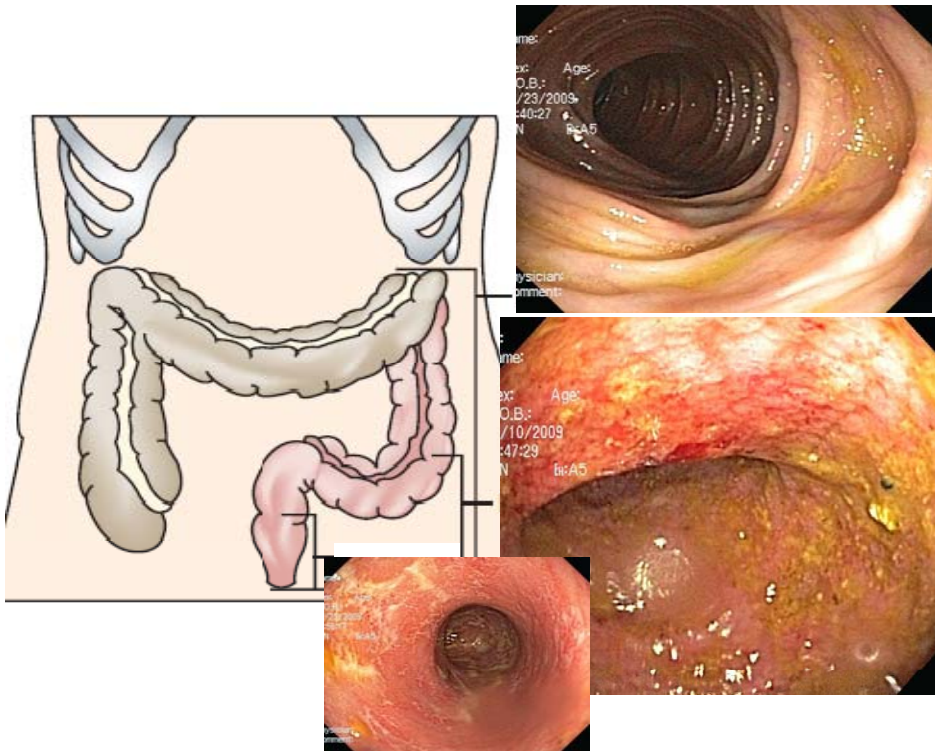
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- ❑ **Infection** (viral, bacterial, fungal, parasitic)
- ❑ Toxicity (drugs)
- ❑ Allergy
- ❑ Ischemia
- ❑ Radiation
- ❑ Graft-vs-host disease
- ❑ Malignancy
- ❑ **Idiopathic**

# Investigation:

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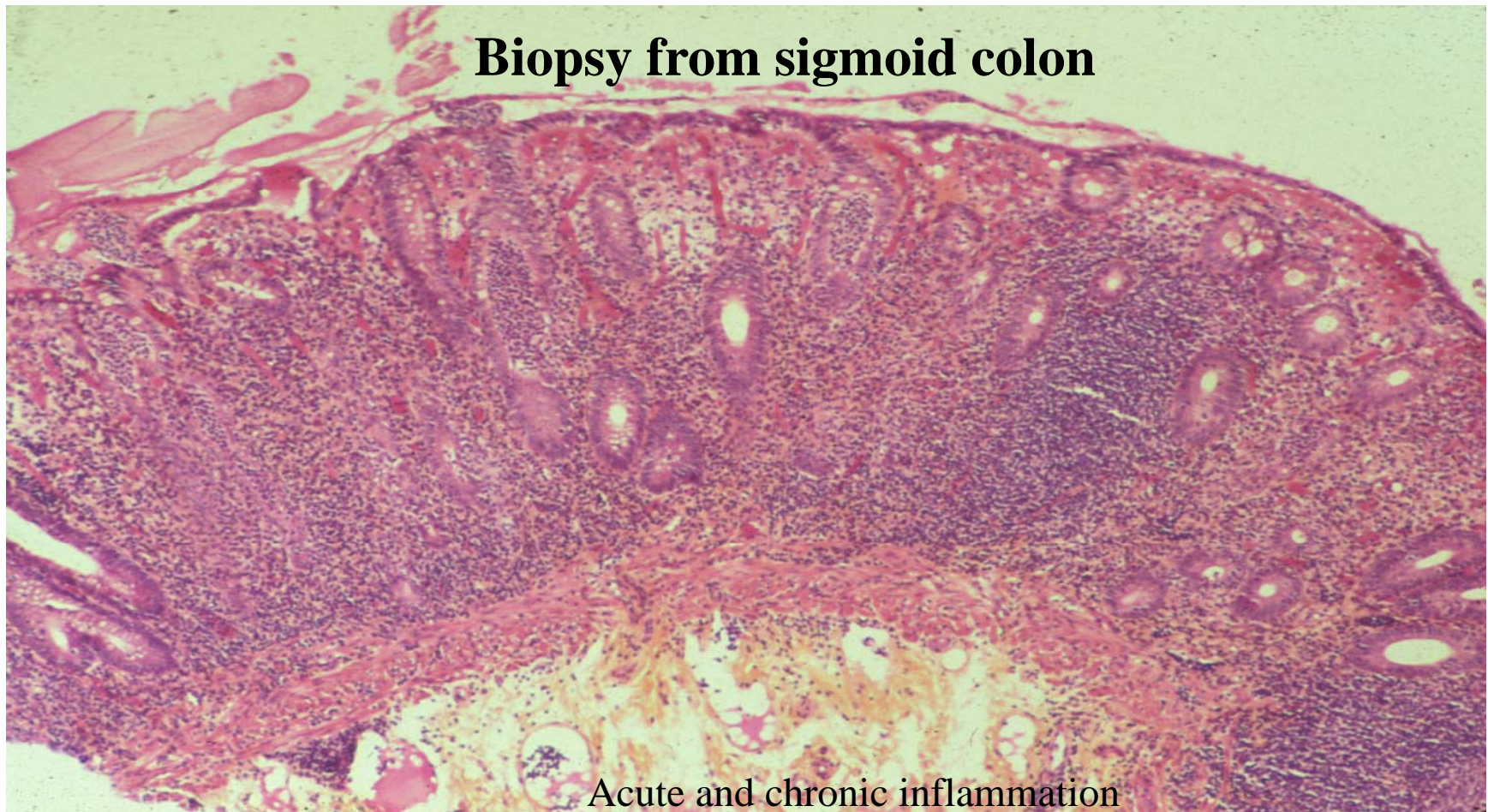
- ❑ Labs: Hgb 10.5 g/dl (nl 12-15)
- ❑ Colonoscopy with biopsy



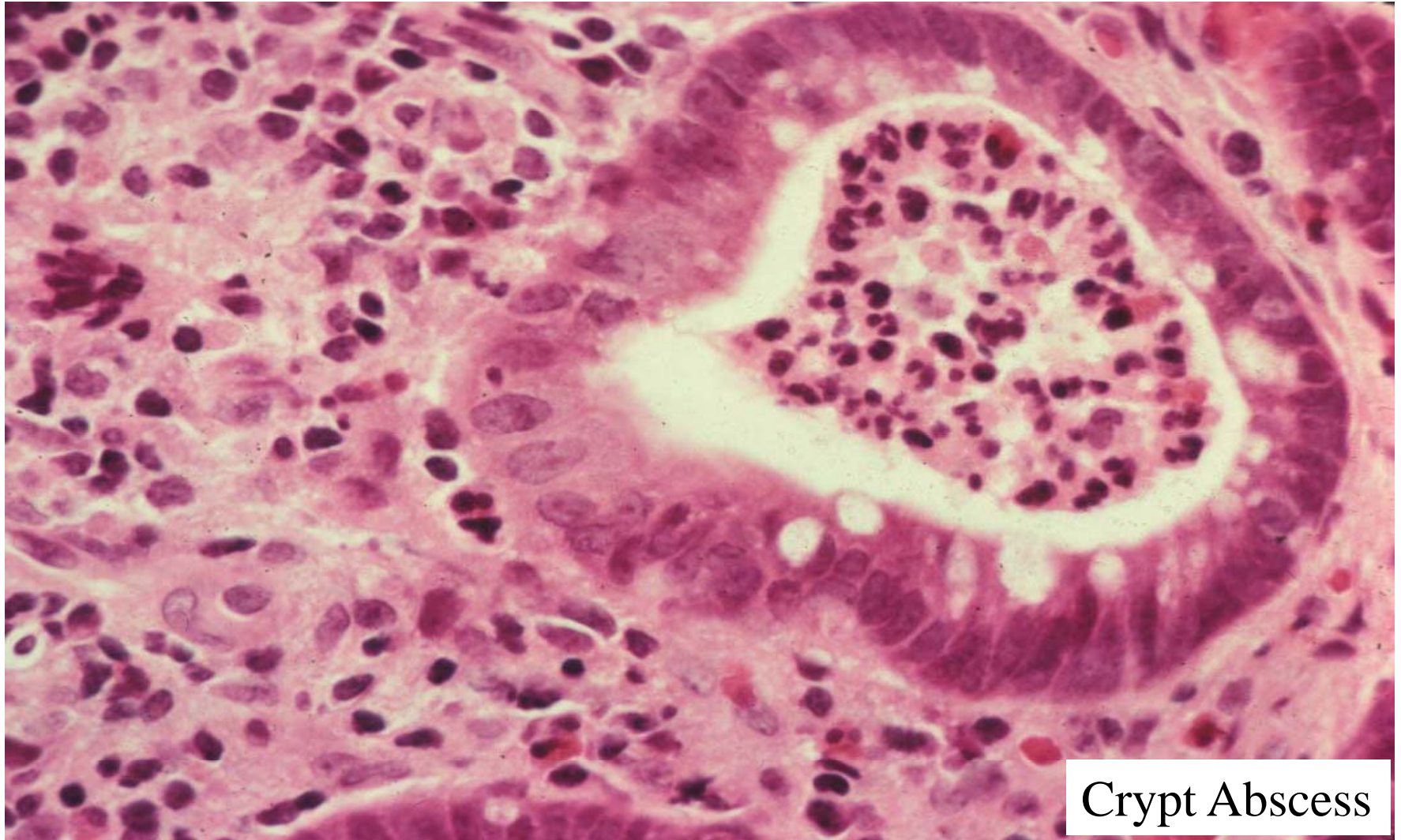
# Ulcerative Colitis

## Microscopic Pathology

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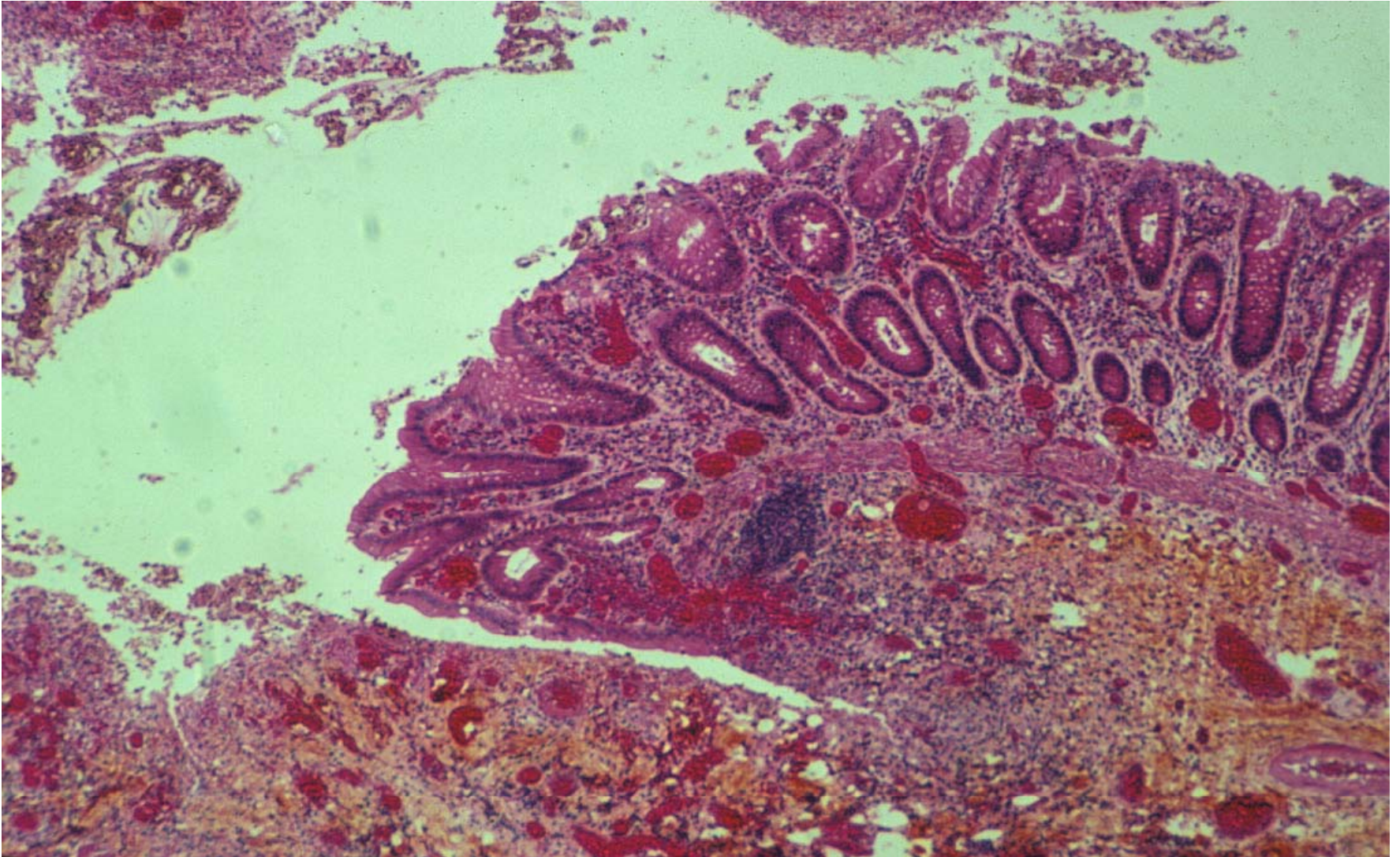


## Biopsy from sigmoid colon





## Biopsy from sigmoid colon



Flat ulcer with overhanging mucosa

Biopsy from transverse colon



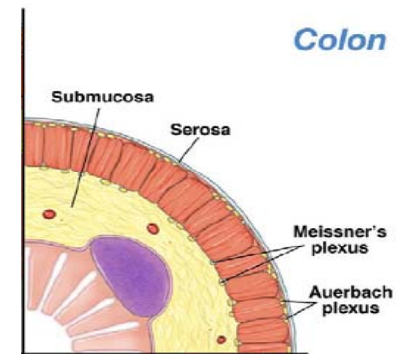
Chronic inactive phase

# Ulcerative Colitis

## Microscopic Pathology

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- Diffuse mucosal inflammation (plasma cells, lymphocytes, eosinophils, neutrophils)
- Cryptitis
- Crypt abscesses
- Ulcers
- Crypt irregularity and atrophy
- Metaplasia: Paneth cell



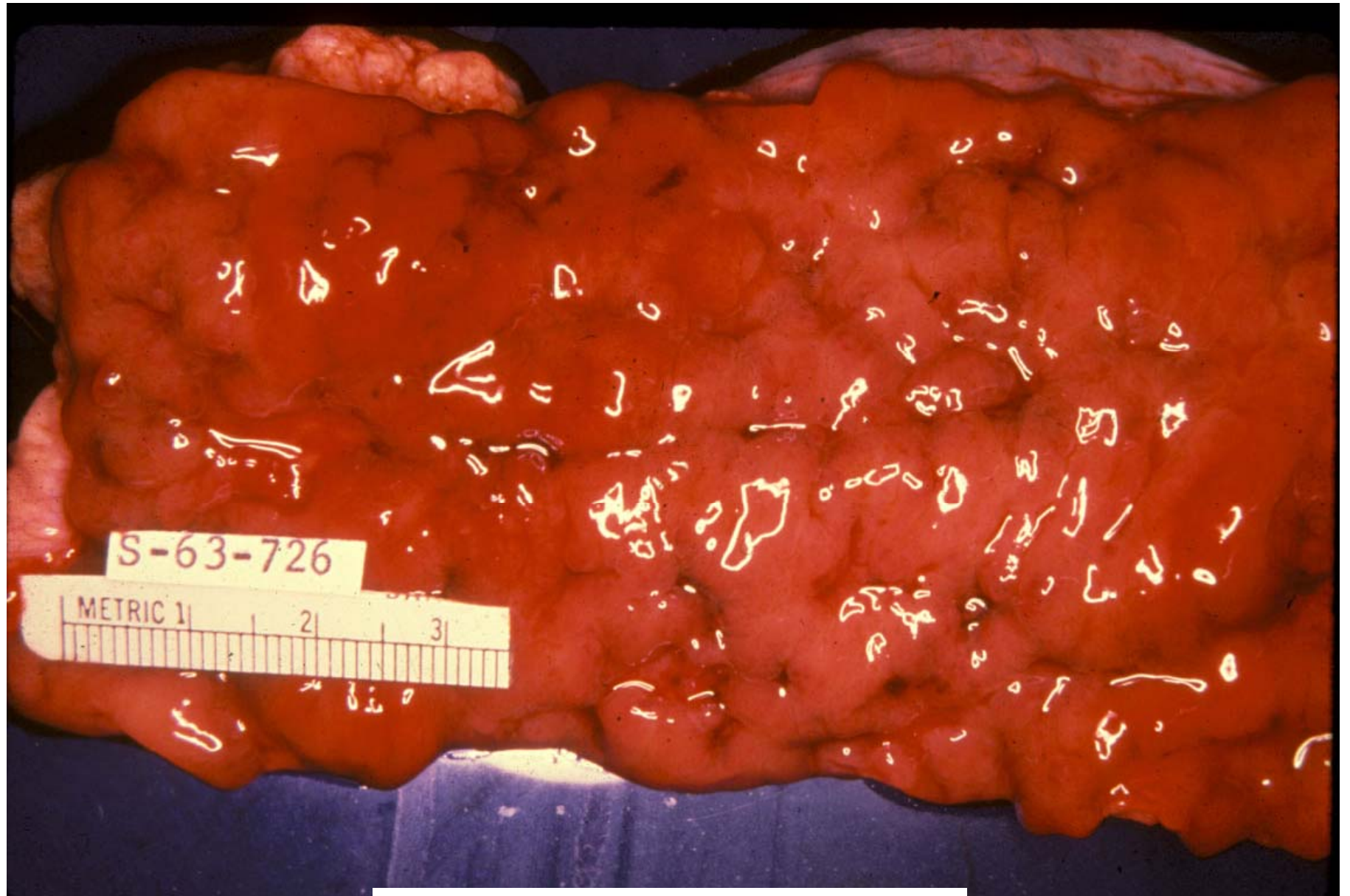


# Ulcerative Colitis

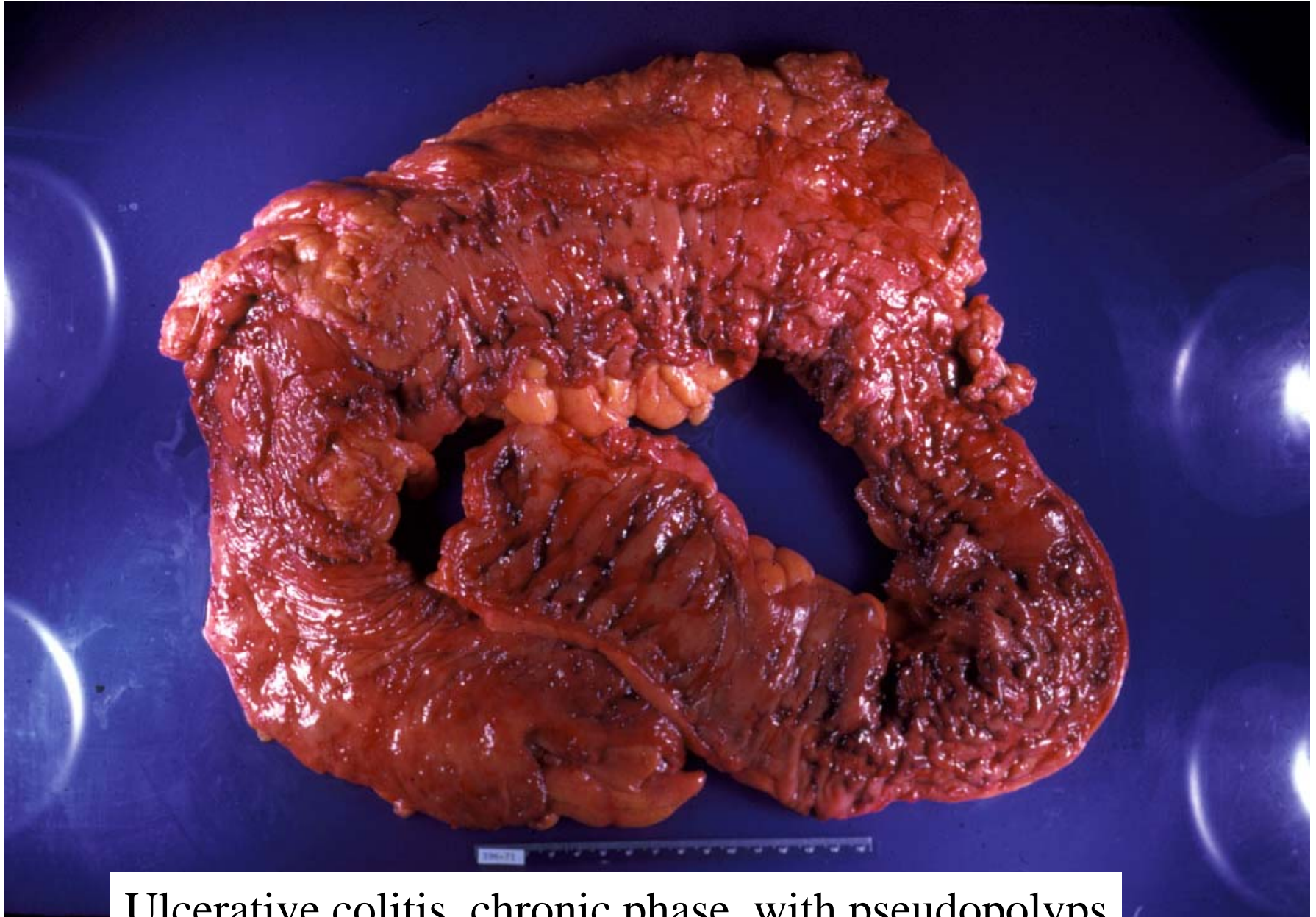
## Macroscopic Pathology

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- Diffuse colitis, usually most marked distally
- Red friable mucosa
- Broad-based ulcers
- Pseudopolyps
  
- Shortened colon
- Backwash ileitis



Ulcerative colitis, acute phase



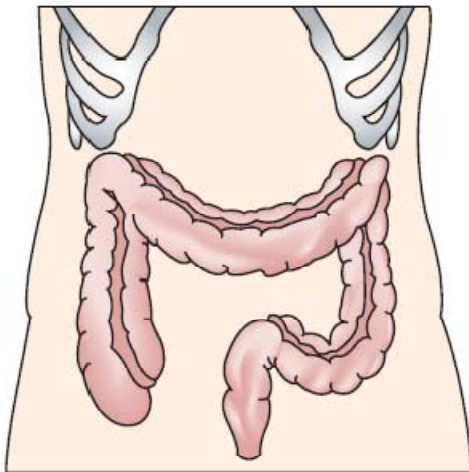
Ulcerative colitis, chronic phase, with pseudopolyps



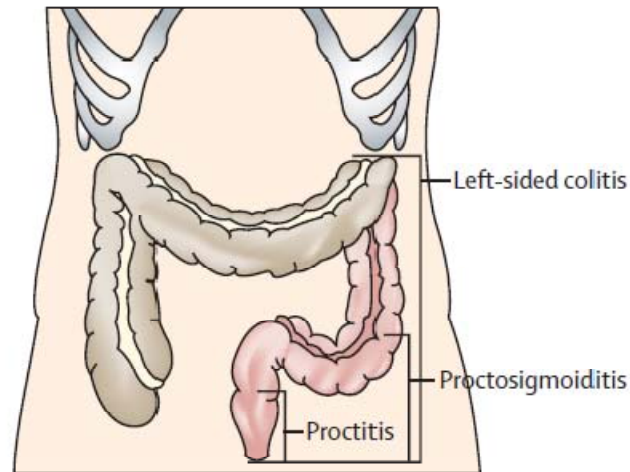
Pseudopolyps in UC

# Terminology: Distribution

Pancolitis/right-sided colitis



Left-sided colitis/proctitis

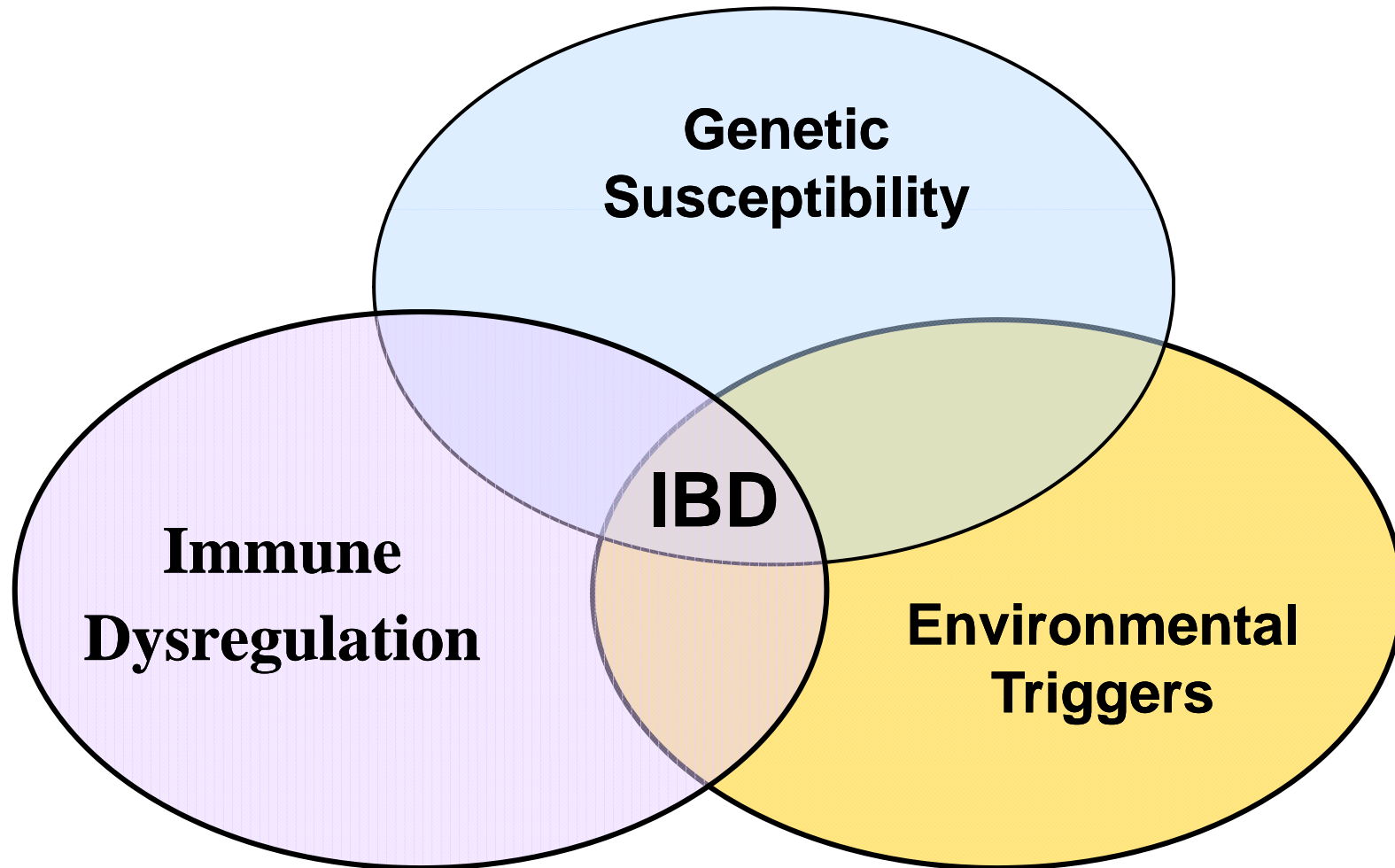


- Ulcerative proctitis / proctosigmoiditis (60 - 80%)
- Left-sided colitis (30 - 40%)
- Extensive colitis / pancolitis (10 - 20%)

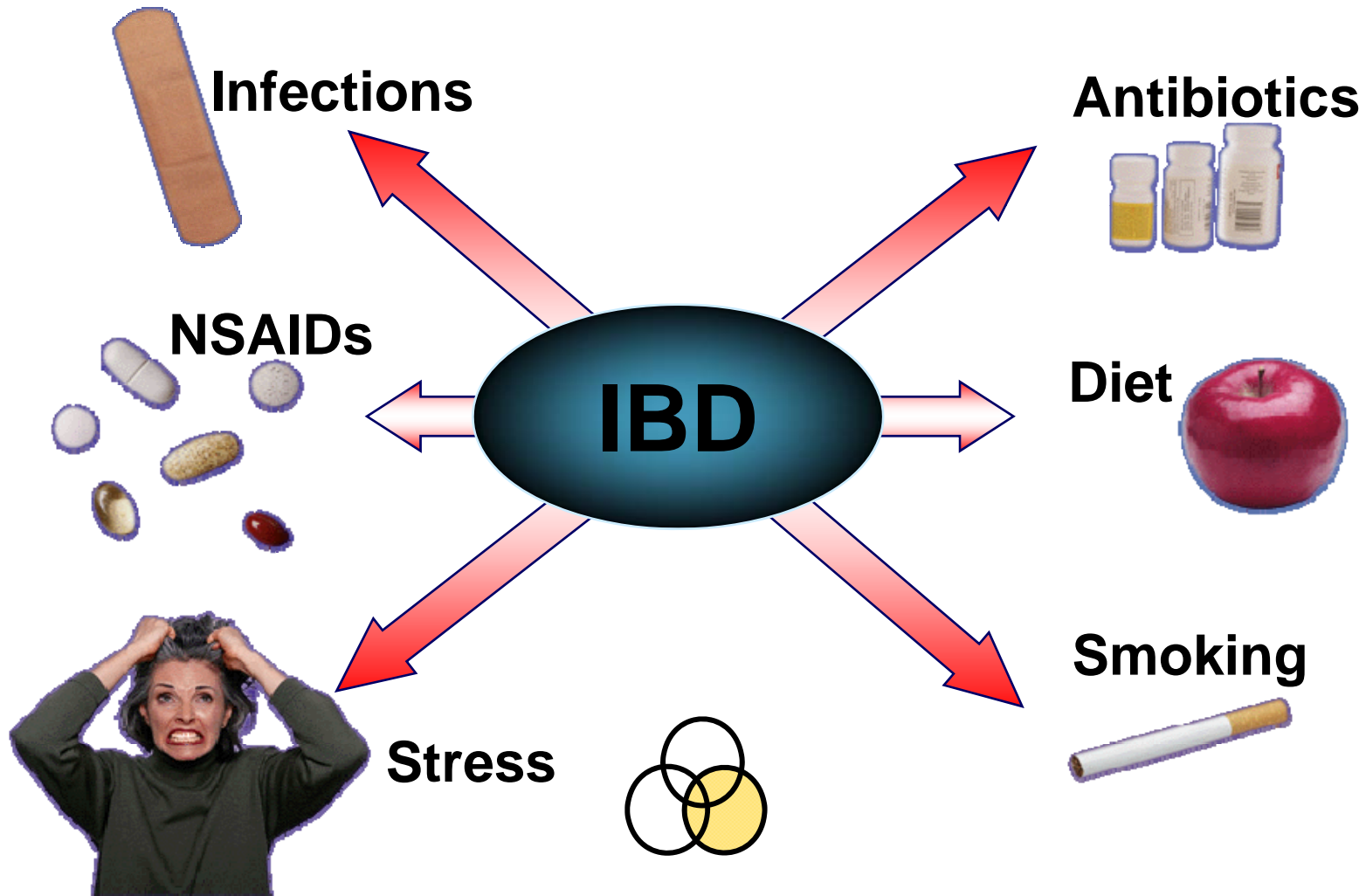


# IBD – Interaction of Genetic Susceptibility, Immune Dysregulation, and Environmental Triggers

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# Pathogenesis: Environmental Triggers

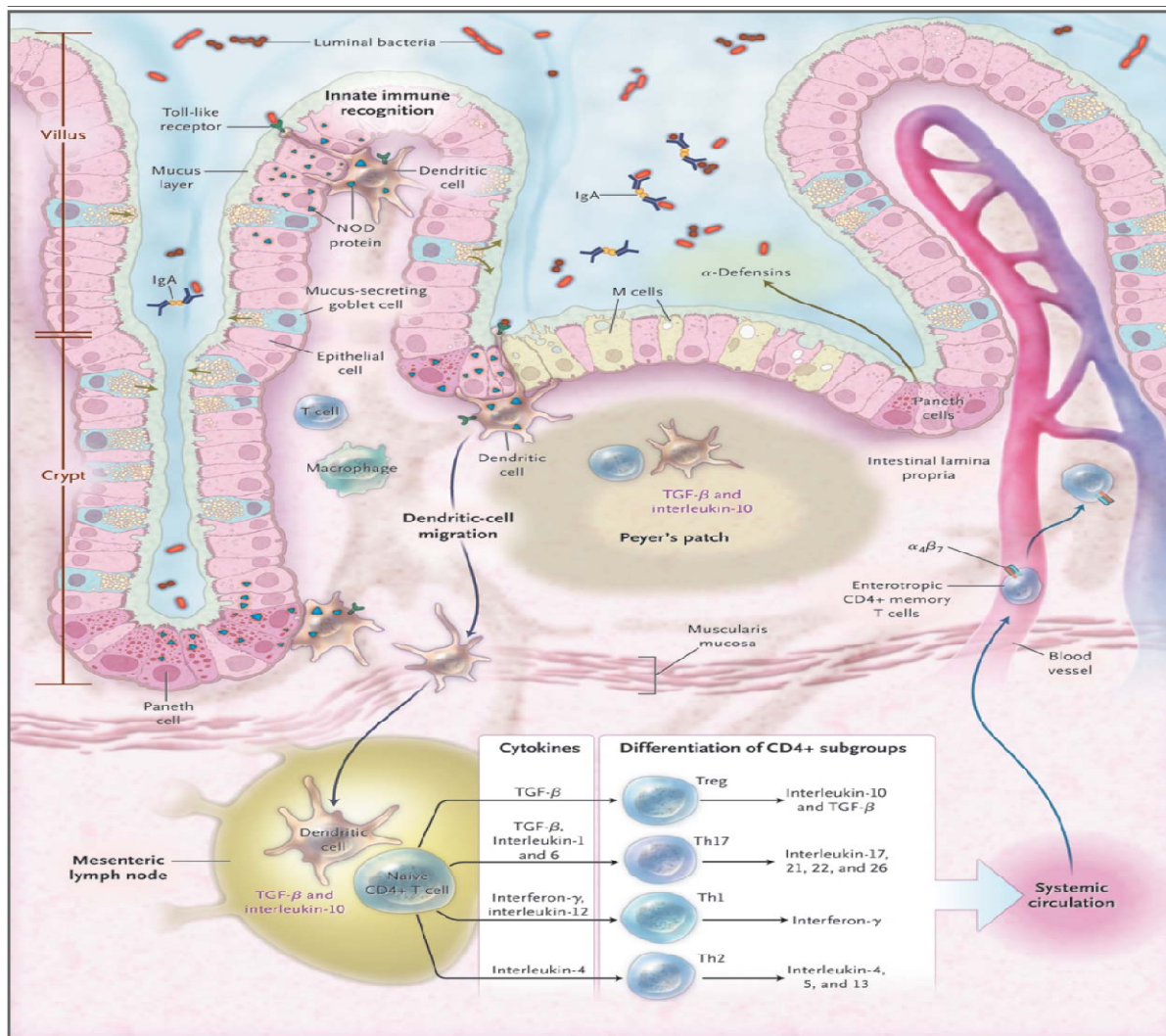


# Genetic Associations with CD and UC

**Table 1. Genetic Associations with Crohn's Disease and Ulcerative Colitis.\***

Gene	Genomic Region	No. of Genes in Region†	Associated with Crohn's Disease	Associated with Ulcerative Colitis	Function
<b>Innate immune responses</b>					
<i>NOD2</i> (nucleotide-binding oligomerization domain 2)	16q12	1	Yes	No	Senses bacterial peptidoglycan to activate cell signaling
<i>ATG16L1</i> (autophagy-related, 16-like)	2q37	1	Yes	No	Component of autophagy complex
<i>IRGM</i> (immunity-related GTPase M)	5q33	3	Yes	Equivocal	Role in autophagy; required for interferon- $\gamma$ -mediated clearance of intracellular pathogens
<b>Interleukin-23–Th17 pathway</b>					
<i>IL23R</i> (interleukin-23 receptor)	1p31	1	Yes	Yes‡	Unique component of heterodimeric interleukin-23 receptor
<i>IL12B</i> (interleukin-12B, p40 subunit)	5q33	1	Yes	Yes‡	Component of interleukin-23 cytokine; common to interleukin-12
<i>STAT3</i> (signal transducer and activator of transcription 3)	17q21	4	Yes	Yes‡	Major STAT downstream of various cytokines, including interleukin-6, 10, 17, 21, 22, and 23
<i>CCR6</i> (chemokine [C-C motif] receptor 6)	6q27	3	Yes	No	Cell-membrane protein mediating migration and recruitment of inflammatory cells
<b>Other genes in association regions</b>					
<i>PTGER4</i> (prostaglandin E receptor 4)	5p13	0	Yes	No	One of the receptors for the inflammatory mediator PGE2
<i>ZNF365</i> (zinc finger protein 365)	10q21	1	Yes	No	Reported role in mitosis
<i>SLC22A4</i> (solute-carrier family 22, organic-cation transporter)	5q31	7	Yes	Equivocal	Plasma membrane polyspecific organic cation transporter
<i>PTPN2</i> (T-cell protein tyrosine phosphatase)	18p11	1	Yes	No	Multiple interactions with STAT proteins; also associated with type 1 diabetes
Major histocompatibility complex (MHC)	6p21	—	Yes‡	Yes	Distinct MHC class II associations between ulcerative colitis and Crohn's disease
<i>NKX2-3</i> (NK2–transcription-factor–related, locus 3)	10q24	1	Yes	Yes‡	Homeodomain-containing transcription factor affecting lymphoid and spleen development
<i>MST1L</i> (macrophage stimulating 1)	3p21	33	Yes	Yes‡	Involved in macrophage chemotaxis and activation following proinflammatory signals
<i>PLA2G2E</i> (secretory phospholipase A <sub>2</sub> )	1p36	0‡	No	Yes	Releases arachidonic acid from membrane phospholipids
<i>IL10</i> (interleukin-10)	1q32	1¶	Equivocal	Yes	Immunosuppressive cytokine with a central role in regulating intestinal inflammation
<i>IFNG</i> (interferon- $\gamma$ )	12q15	2‡	No	Yes	Critical cytokine in innate and adaptive immunity against intracellular pathogens

# The intestinal immune system



## Targeted Therapies:

### Clinically Active

a4B7 – Natalizumab

Macrophage (dendritic)/Monocytes/Th Cells– Anti-TNF

### Clinical Investigation

Th 17 – Anti IL12/23

Mucus layer – Phosphatidylcholine replacement

### Poor Clinical Results:

Th1 - IL 10 Therapy

Th1 - Anti- Interferon gamma (fontalizumab)



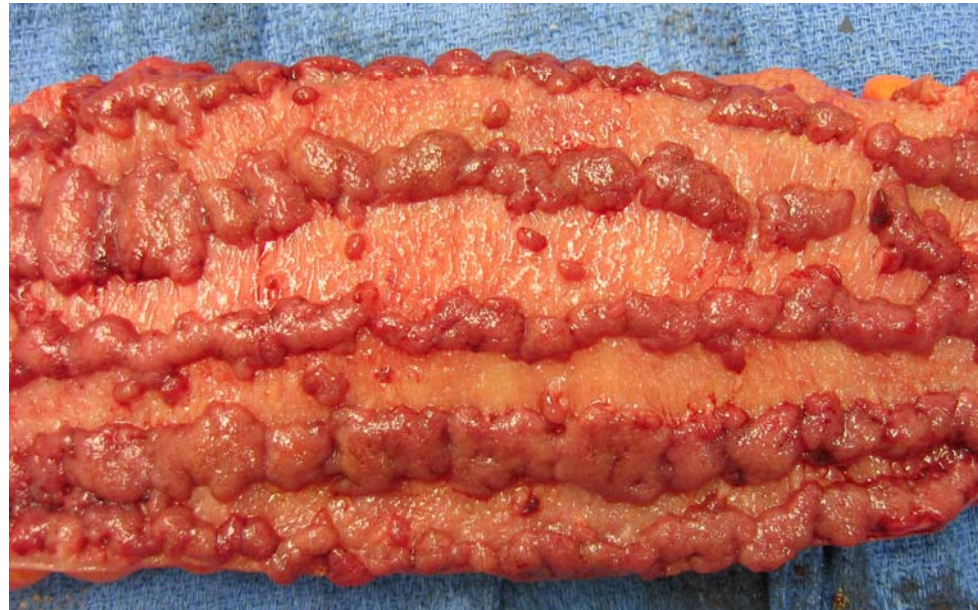
# Ulcerative Colitis

## Complications

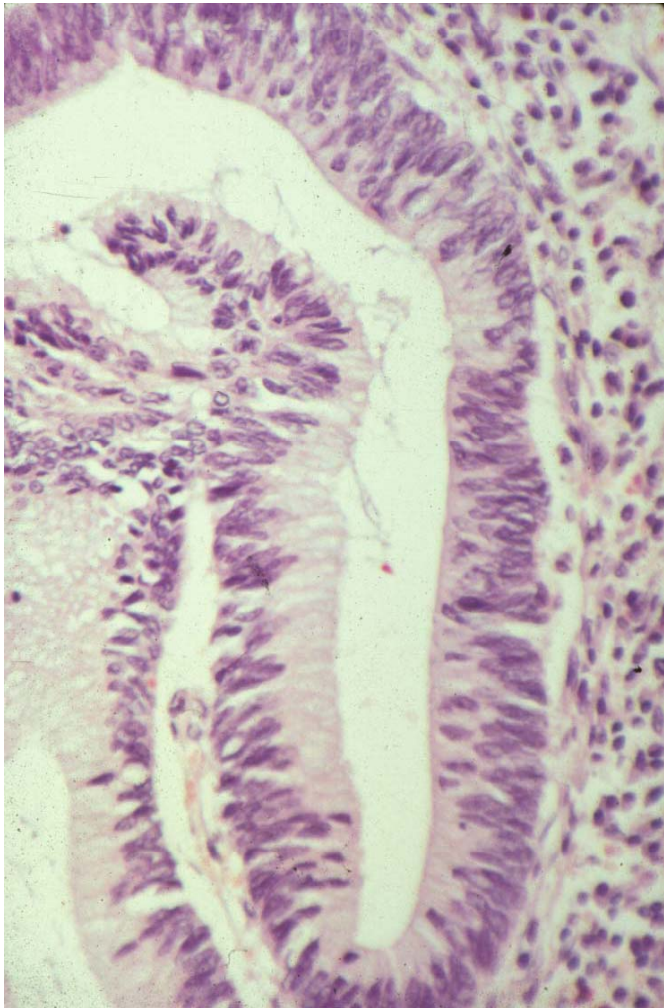
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- Toxic megacolon
- Dysplasia
- Carcinoma:
  - 2% after 20 years of left-sided colitis
  - 10% after 20 years of pancolitis
  - 15 - 20% after 30 years of pancolitis

# Toxic Megacolon



## Dysplasia, low grade, in UC



# Dysplasia: Management

Provisional Schema of Patient Management  
Related to Classification of Dysplasia

Biopsy Classification	Implications for Patient Management
Negative Normal mucosa Inactive (quiescent) colitis Active colitis	Continue regular follow-up
Indefinite Probably negative	
Unknown Probably positive	Institute short-interval follow-up
Positive Low-grade dysplasia	Institute short-interval follow-up <i>or</i> Consider colectomy, especially with gross lesion, after dysplasia is confirmed
High-grade dysplasia	Consider colectomy after dysplasia is confirmed





# Case 2: HPI

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21 yo M

- RLQ pain x 6mo
- Inc freq of bm's – 6-8x/day; no hematochezia
- 8 lbs unintentional weight loss
- Avoids eating because it makes his symptoms worse
- PMHx: None                      PShx: Appendectomy, 6mo ago
- Fhx: None
- Shx: Tobacco: ½ ppd, college student (5<sup>th</sup> year senior)

# Case 2: Physical Exam

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- ❑ HEENT: Aphthous ulcer
- ❑ Abominal Exam: RLQ fullness, + ttp, no guarding/rebound
- ❑ Buttock: Perianal fistual, nondraining

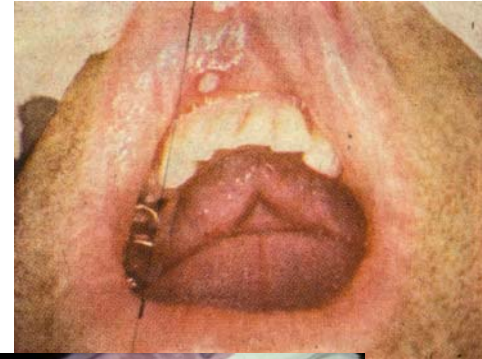
Labs:

CBC: mild anemia (Hbg 11.5)

ESR: 75 mm/hr

Imaging:

Abominal Xray: Unremarkable



# Case 2: Additional Investigations

- Colonoscopy: WNL; unable to intubate terminal ileum
- Capsule Endoscopy:



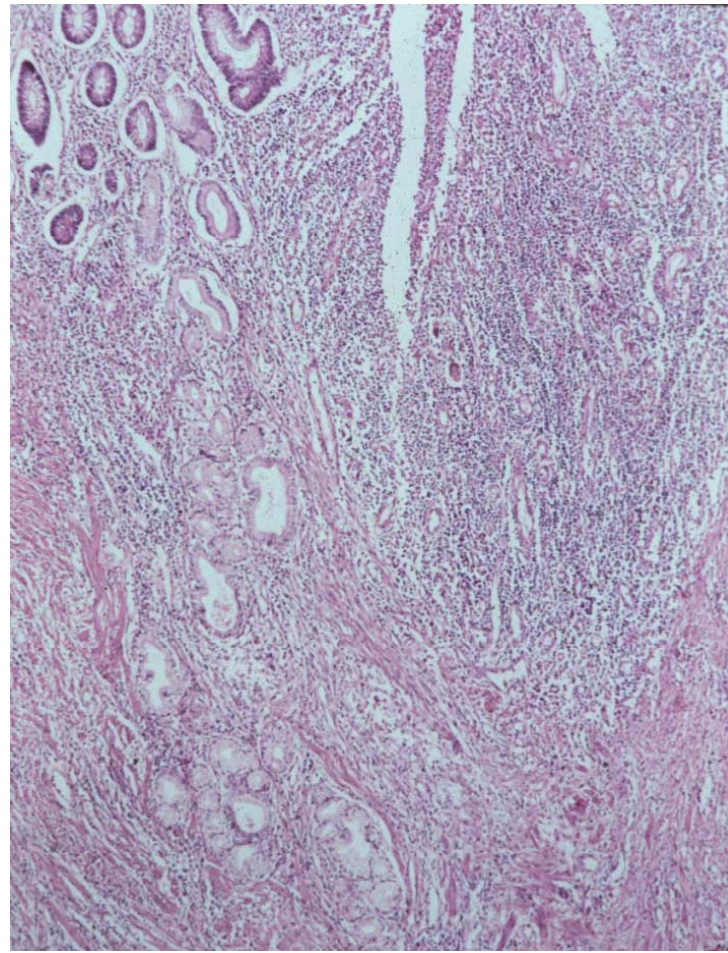
- Small Bowel Follow Through:
  - Ileal Stricture
- Double Balloon Enteroscopy
  - Obtained Ileal biopsy



## Case 2: Biopsy Results

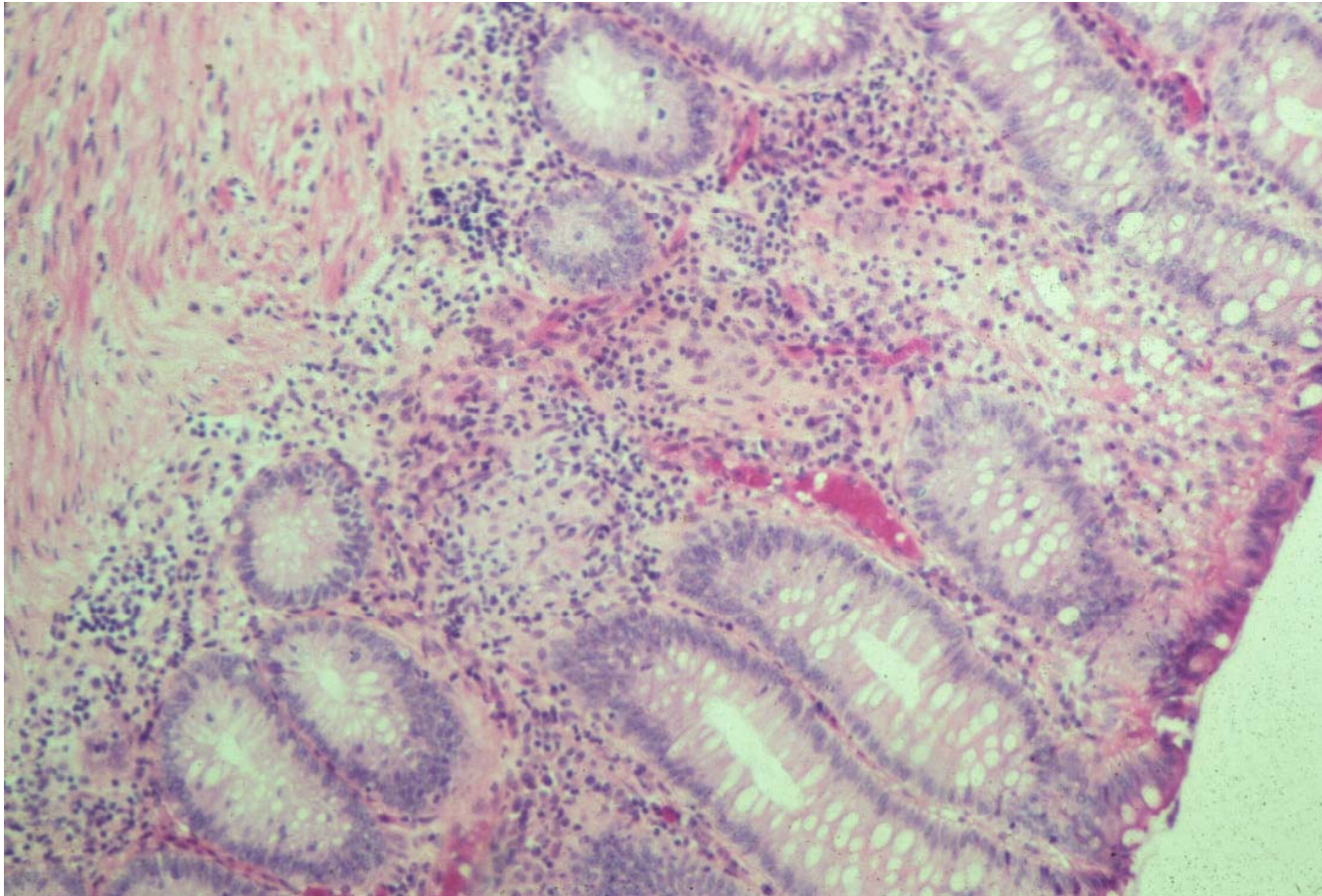
Fissure and pyloric gland metaplasia in Crohn's disease

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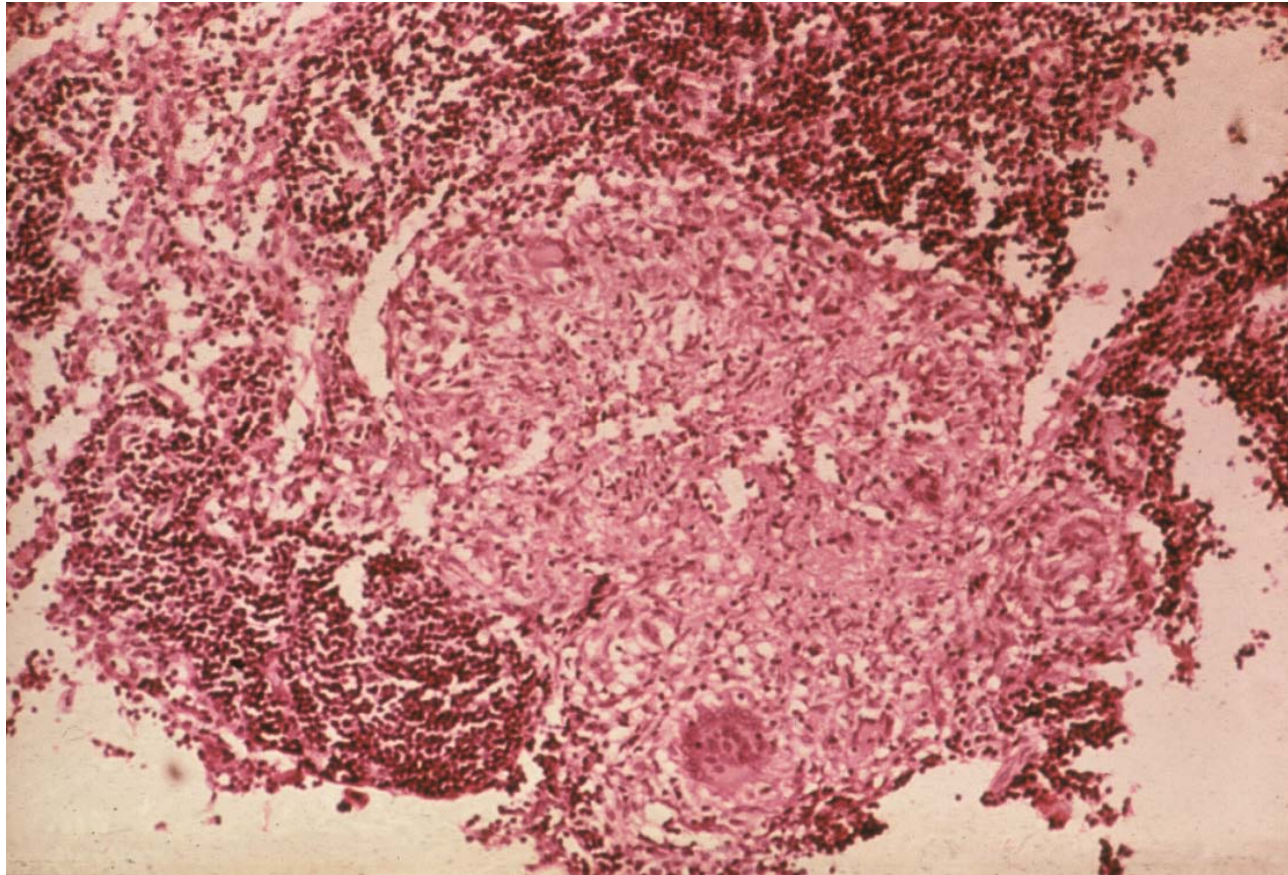
## Microgranuloma in Crohn's colitis

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## Nonnecrotizing granuloma in lymph node

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# Crohn's Disease

## Microscopic Pathology

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- Necrosis of individual epithelial cells
- Cryptitis and crypt abscesses
- **Aphthoid ulcers**
- **Fissures**
- **Patchy** chronic inflammation, **transmural**
- **Granulomas**
- Crypt irregularity
- Metaplasia: Paneth cell, **pyloric**



# Crohn's Disease

## Complications

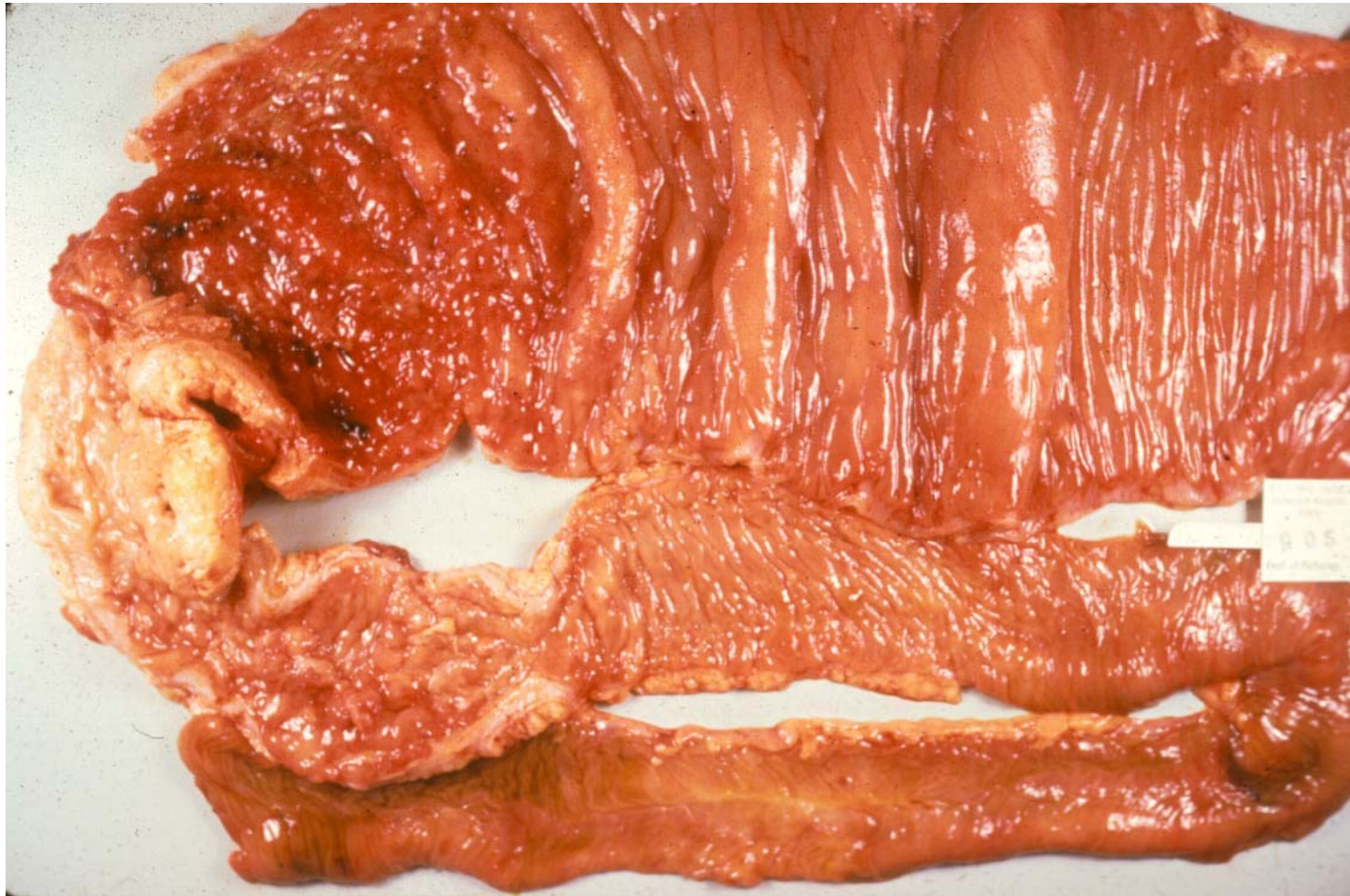
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- Stricture
- Fistulae
- Dysplasia
- Colon Cancer (4 - 20x)



## Stricture in Crohn's disease

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# Crohn's Disease

## Classification

- Terminal ileitis (40%)
- Ileocolitis (30%)
- Colitis (30%)
- Upper GI Crohn's disease (2 - 20%)

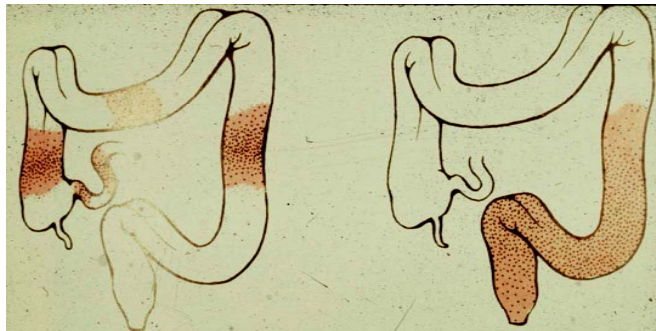
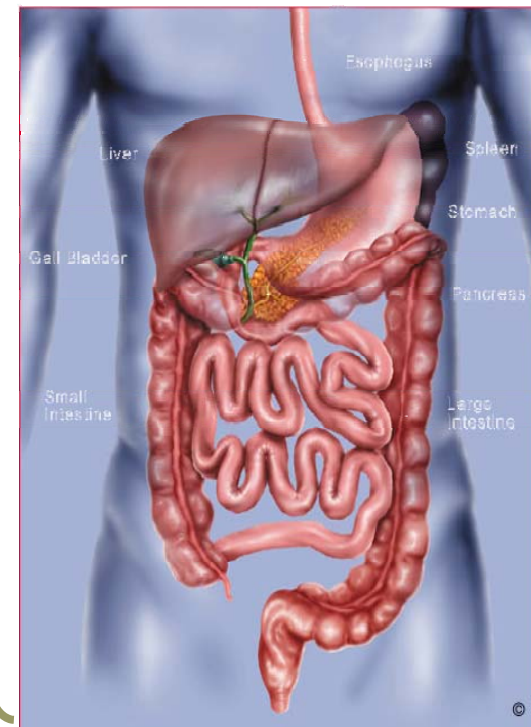


Figure 18-50. Crohn's disease (*left*) and ulcerative colitis (*right*). While Crohn's disease typically involves the small and large intestine in a segmental manner with intervening "skip" areas, ulcerative colitis is generally a disease of contiguity that starts in the rectum and progresses in a retrograde fashion to involve varying

Crohn's  
Disease

The Human Digestive System





# Crohn's Disease

## Macroscopic Pathology

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- Segmental
- Skip areas
- Stiff thickened bowel wall
- Linear ulcers
- Cobblestone mucosa
- Creeping fat
- Rectal sparing

## Crohn's disease of ileum

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## Crohn's disease of colon

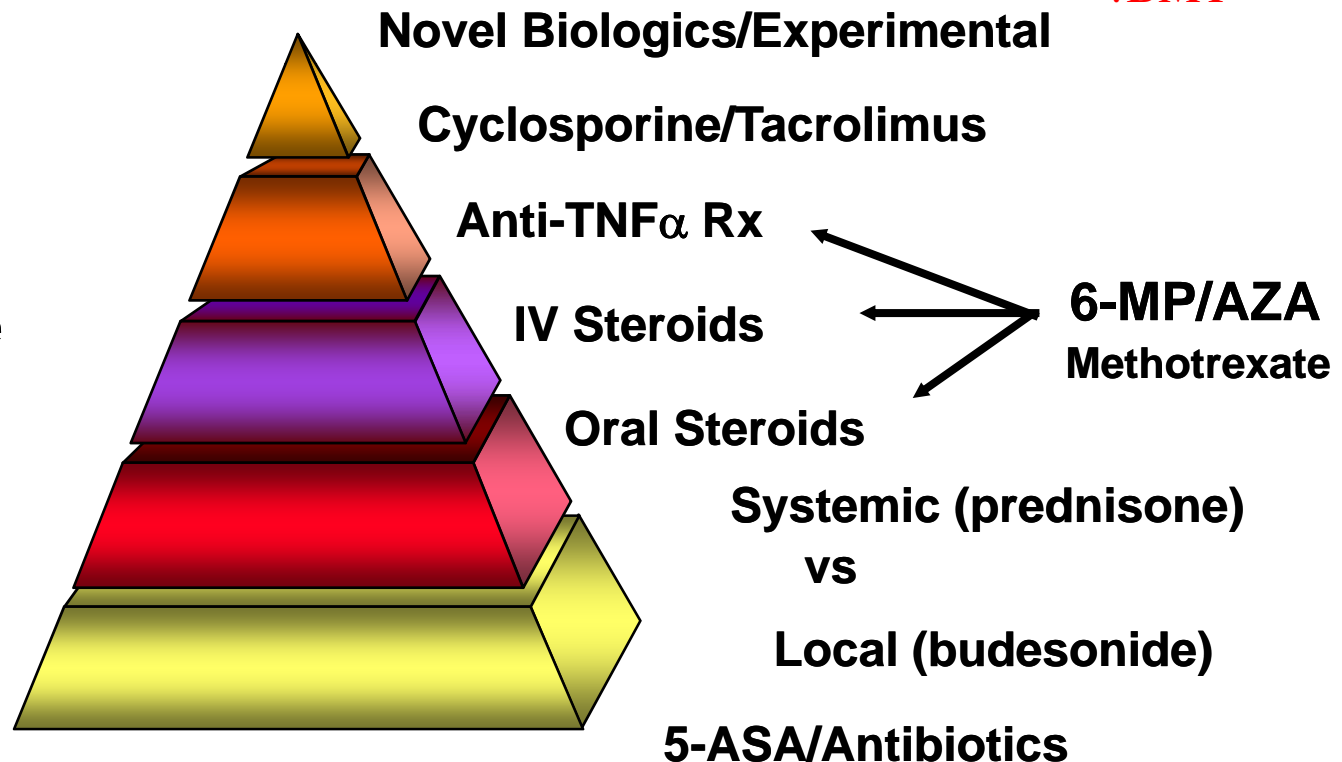


# The Therapeutic Pyramid for IBD

“Activity”

Severe  
↑  
Moderate  
↑  
Mild

“Level of Therapy”





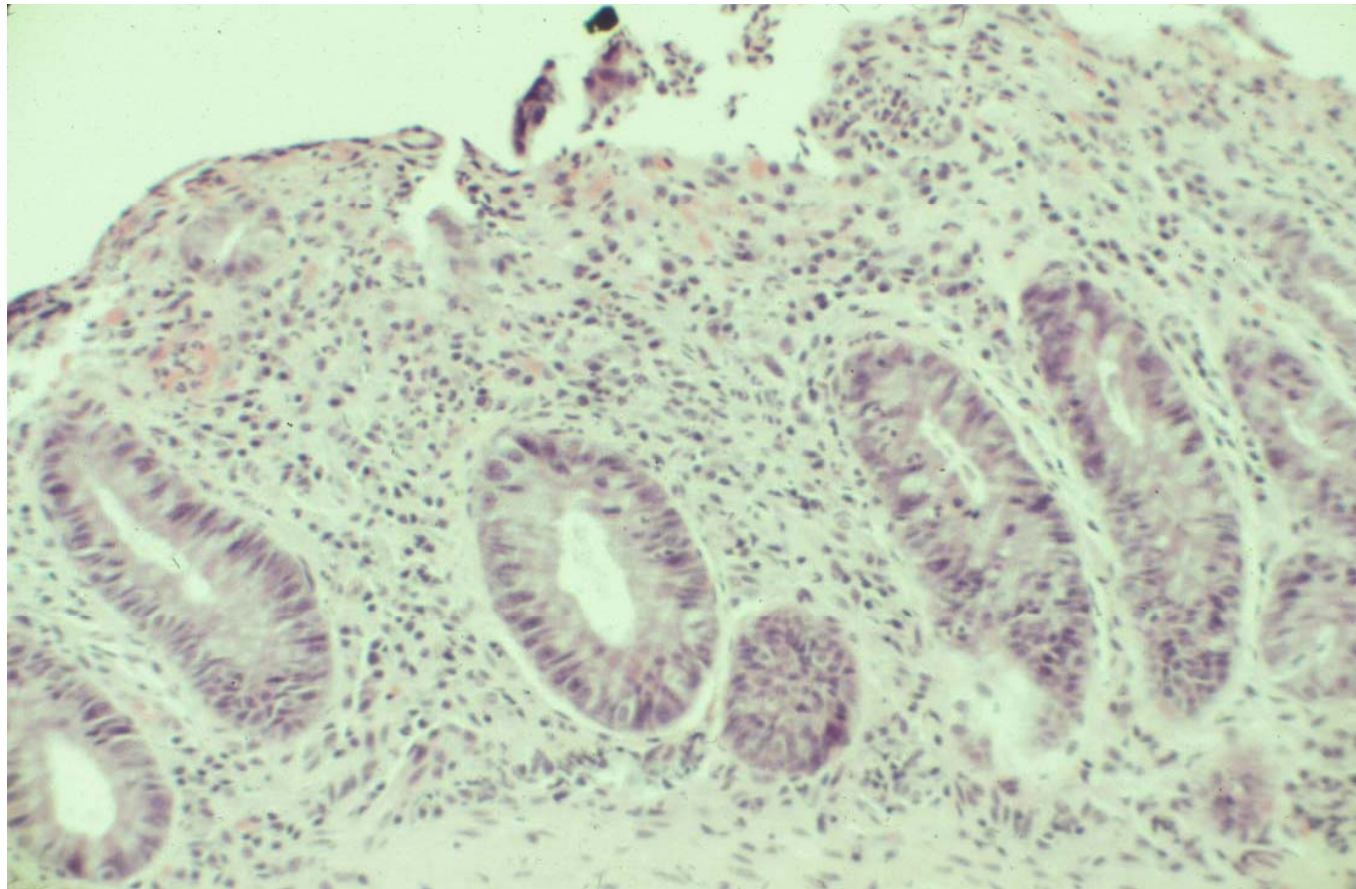
# IBD: Differential Diagnosis

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- Infectious colitis
- Ischemic colitis
- Microscopic colitis
- Irritable bowel syndrome (IBS)

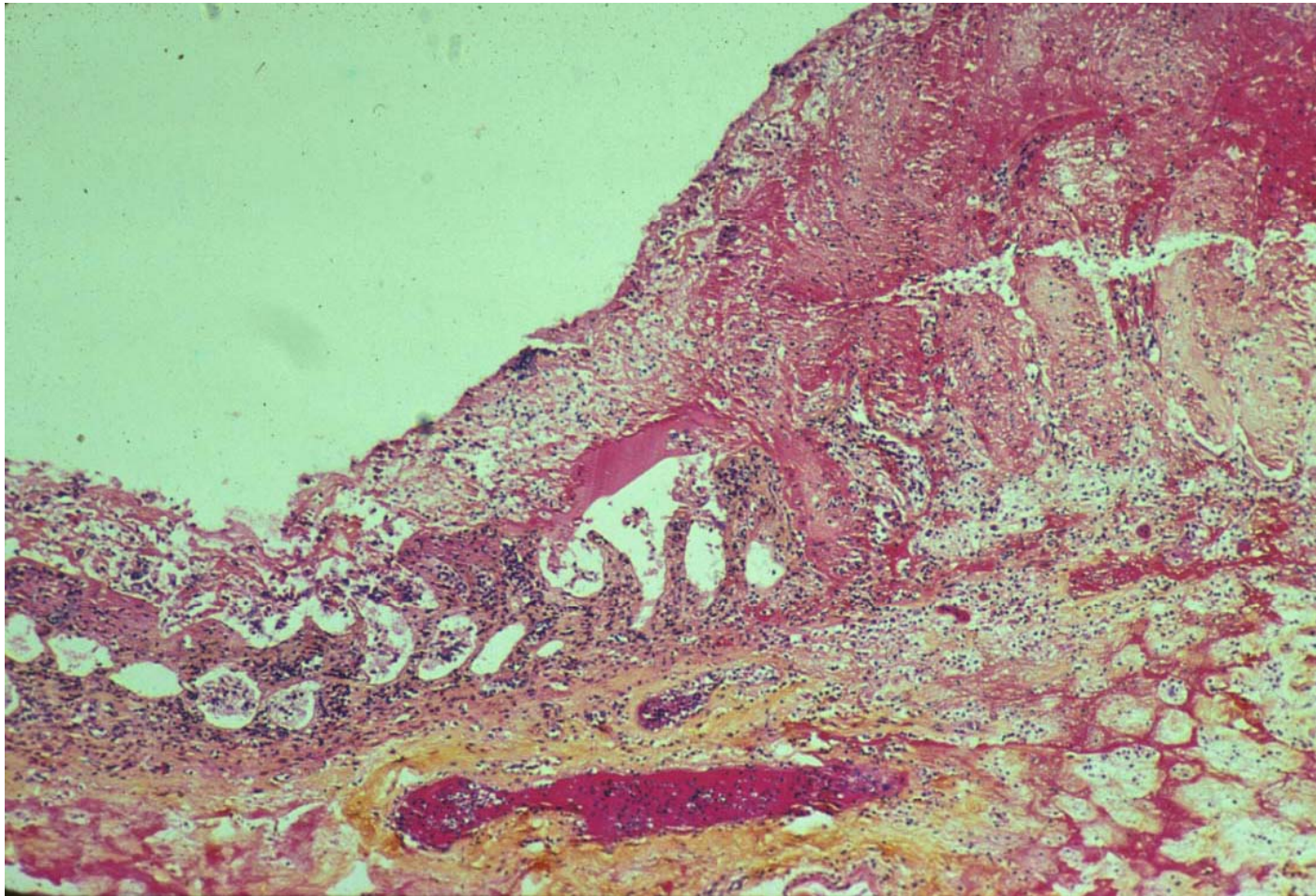
## Infectious colitis (acute self-limited colitis)

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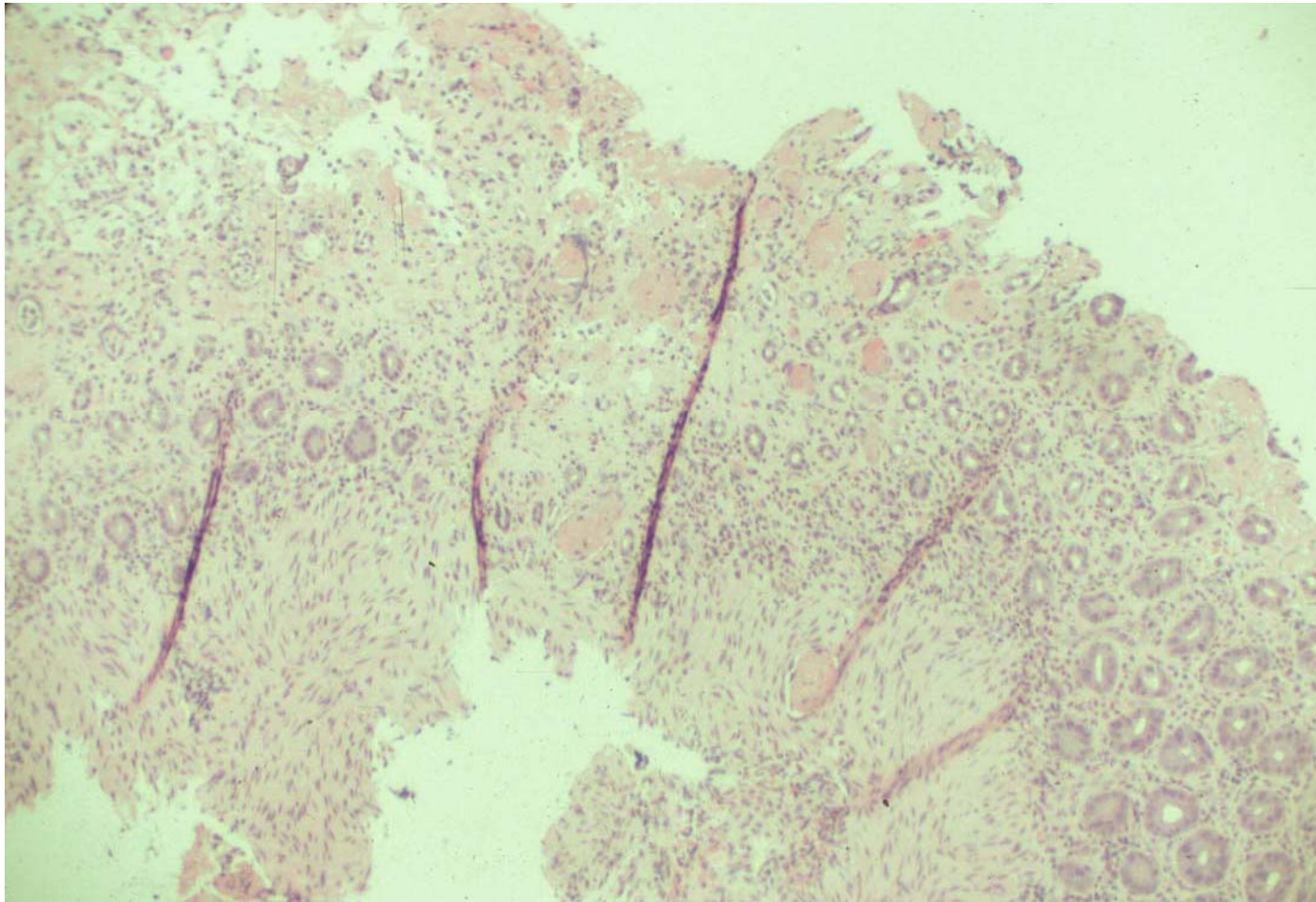
## Pseudomembranous colitis



## Pseudomembranous colitis



# Ischemic colitis



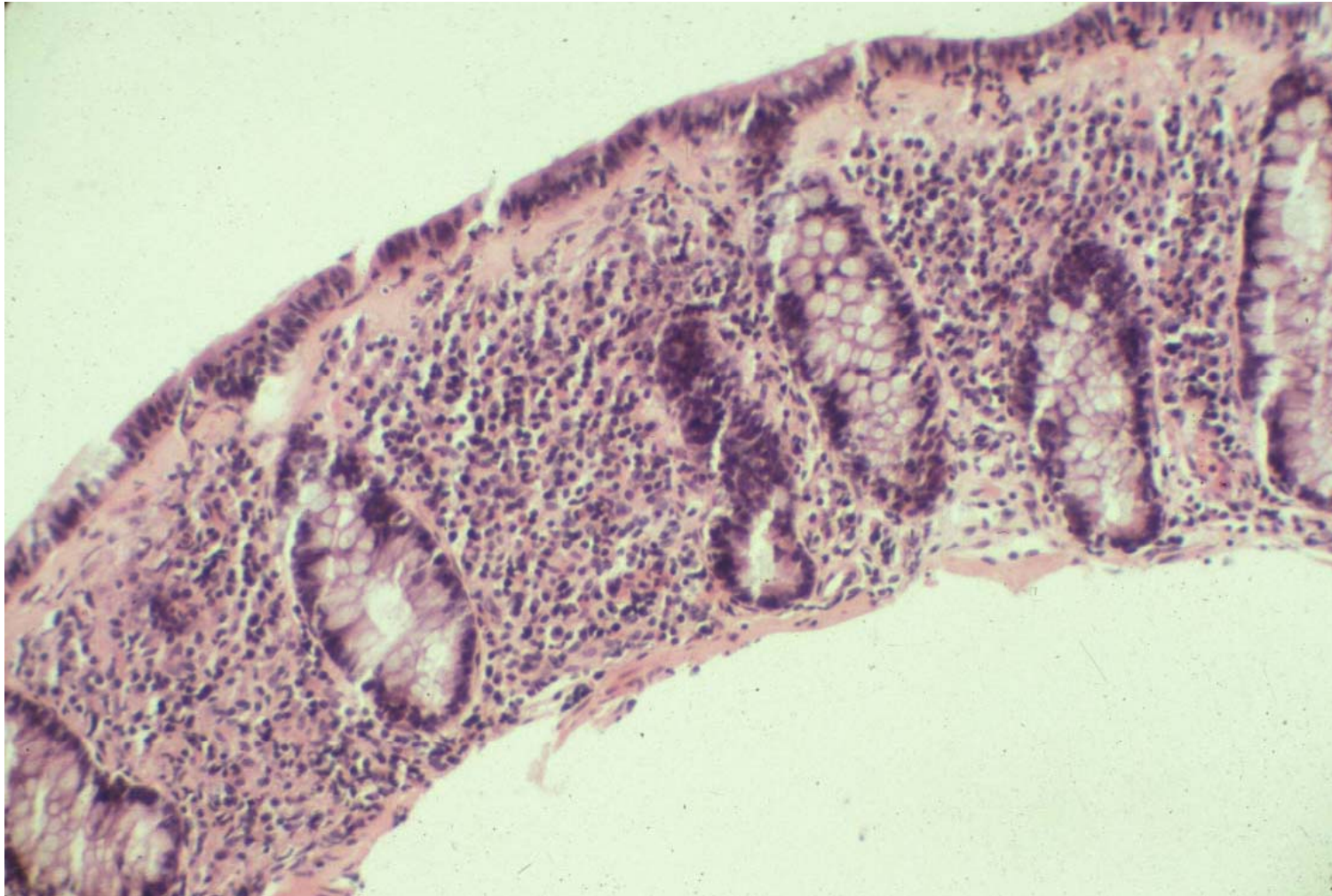


# Microscopic Colitis

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- **Lymphocytic colitis:** lymphocytic infiltration of surface and crypt epithelium, increased inflammatory cells in the lamina propria
- **Collagenous colitis:** same as above plus increased subepithelial collagen
- **Clinical:** watery diarrhea, endoscopically normal colon, middle aged adults
- **Cause:** unknown, association with celiac disease, multiple drugs, family hx of intestinal diseases

## Collagenous colitis



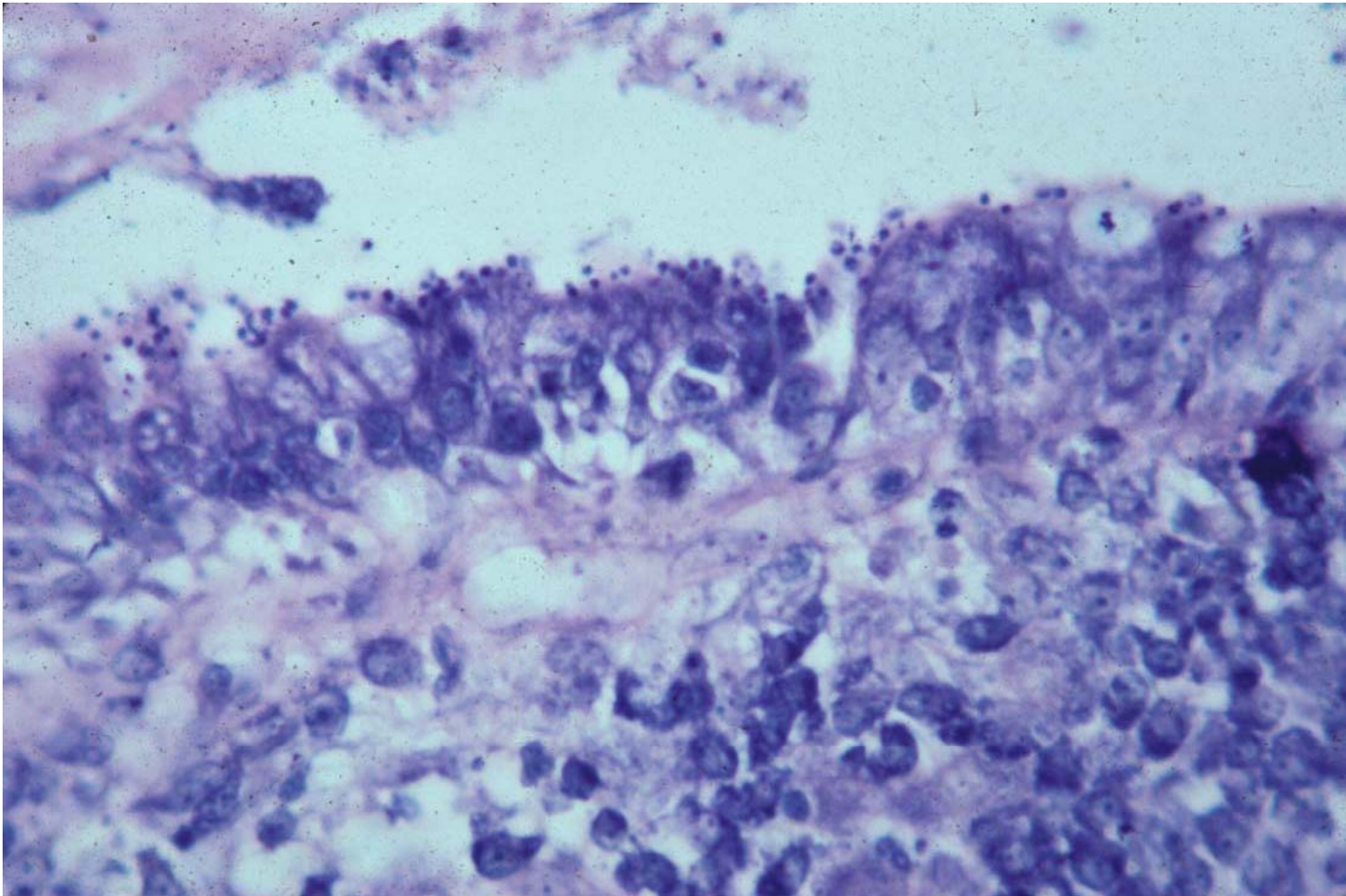


# Diarrhea in AIDS

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- Cryptosporidiosis
- Microsporidiosis
- Isosporiasis
- Cyclosporiasis
- CMV colitis
- MAC enterocolitis
- HIV enteropathy

# Cryptosporidiosis



## CMV and cryptosporidial colitis

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