The Role of Mucosal Biopsy in the Evaluation of IBD Patients

Suspected

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Overview

- Distinction between acute and chronic colitis
- Features of ulcerative colitis and Crohn disease
- The differential diagnosis of chronic colitis

Patterns of Colonic Injury

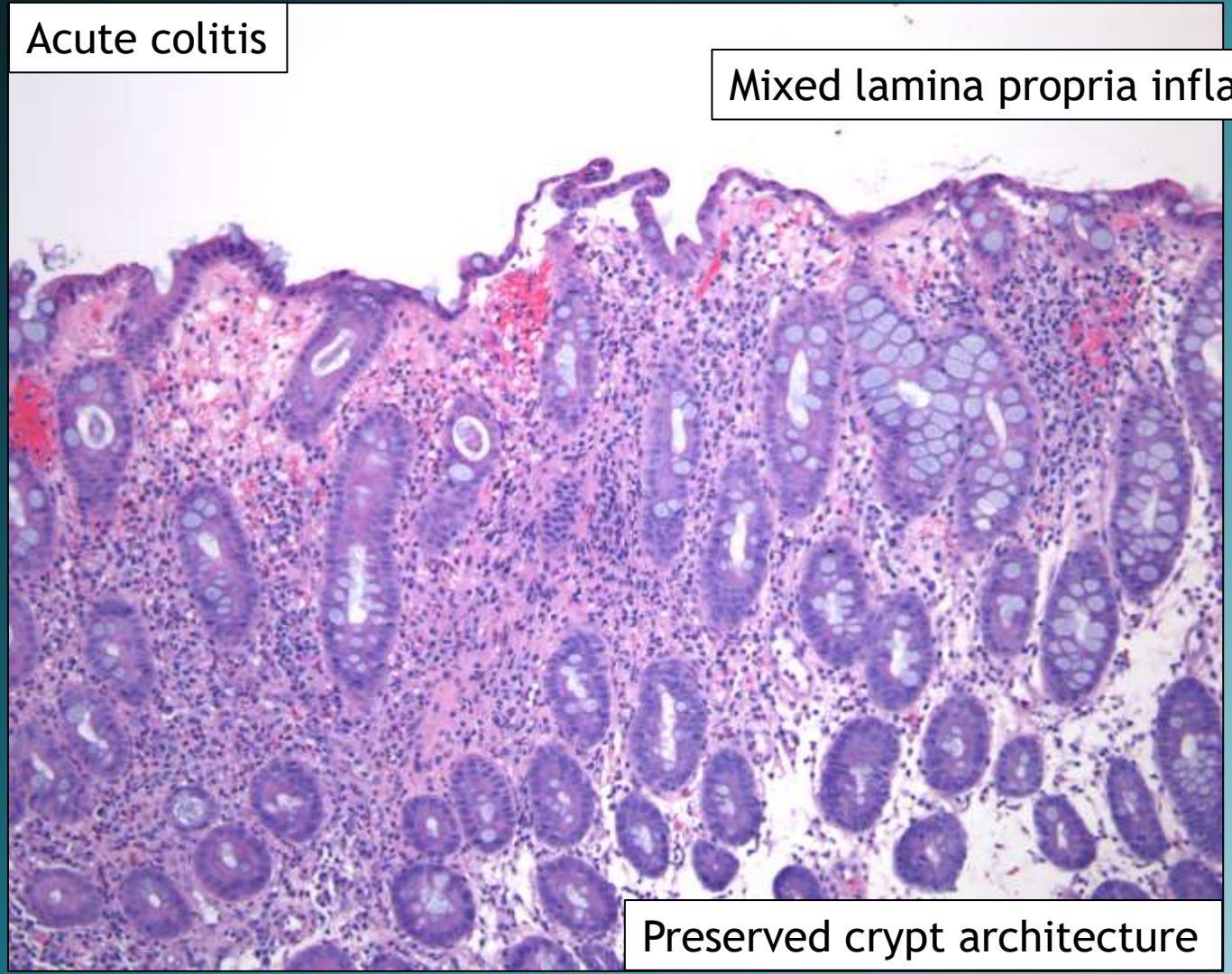
- Colitis
  - Inflammation and epithelial injury
  - Acute colitis
    - Neutrophilic inflammation
  - Chronic colitis
    - Plasma cell-rich inflammation with or without neutrophils
- Colopathy
  - Epithelial injury in the absence of inflammation
    - Ischemia
    - Radiation

Colitis
Patterns of Injury

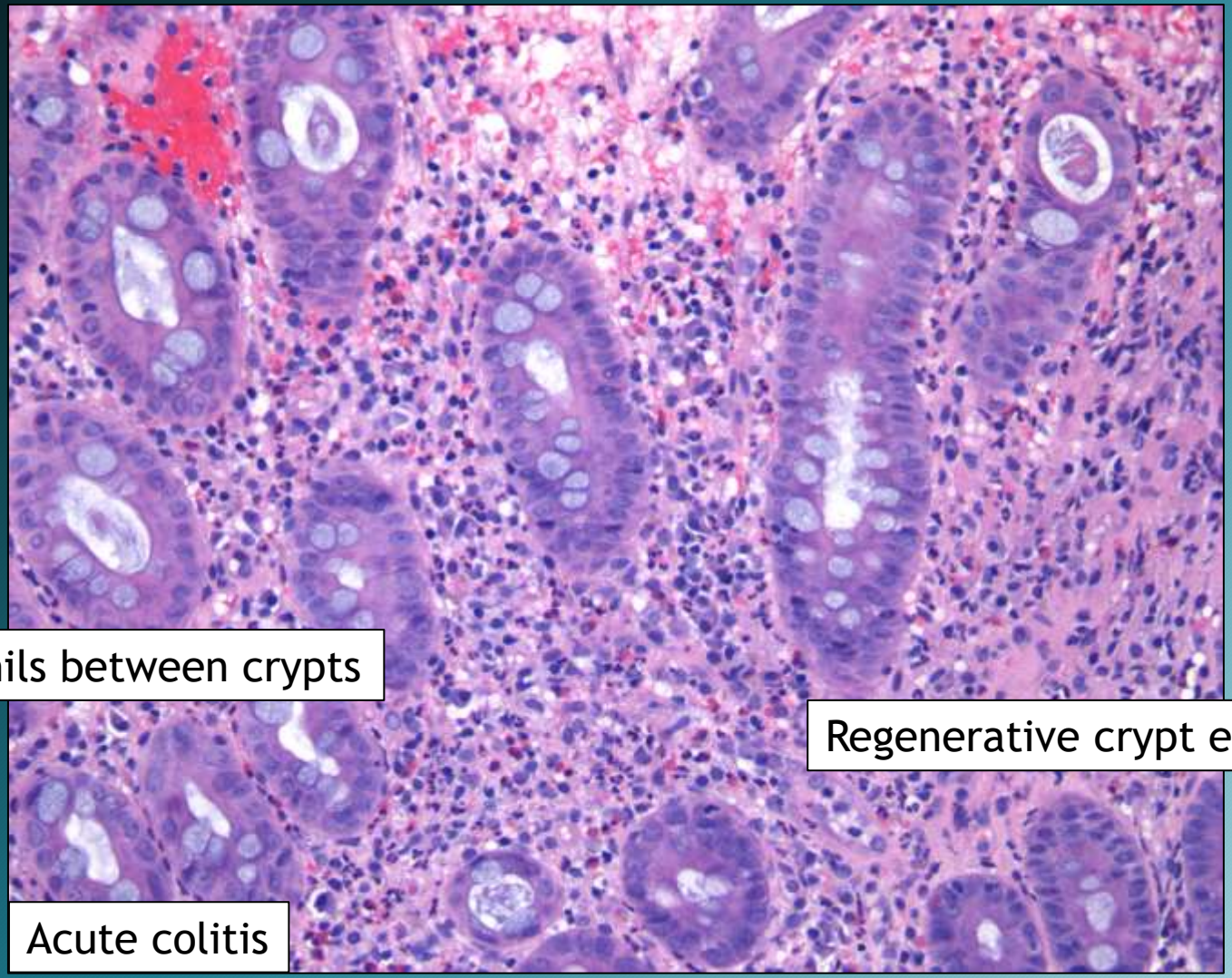
- Acute Colitis
  - Pattern typically seen in drug injury and infections
  - Neutrophilic infiltration of crypt epithelium
  - No metaplasia or architectural changes
- Chronic Colitis
  - Plasma cell-rich inflammation
  - Metaplasia, atrophy architectural changes
  - Neutrophils may be present (chronic active colitis)

Acute colitis

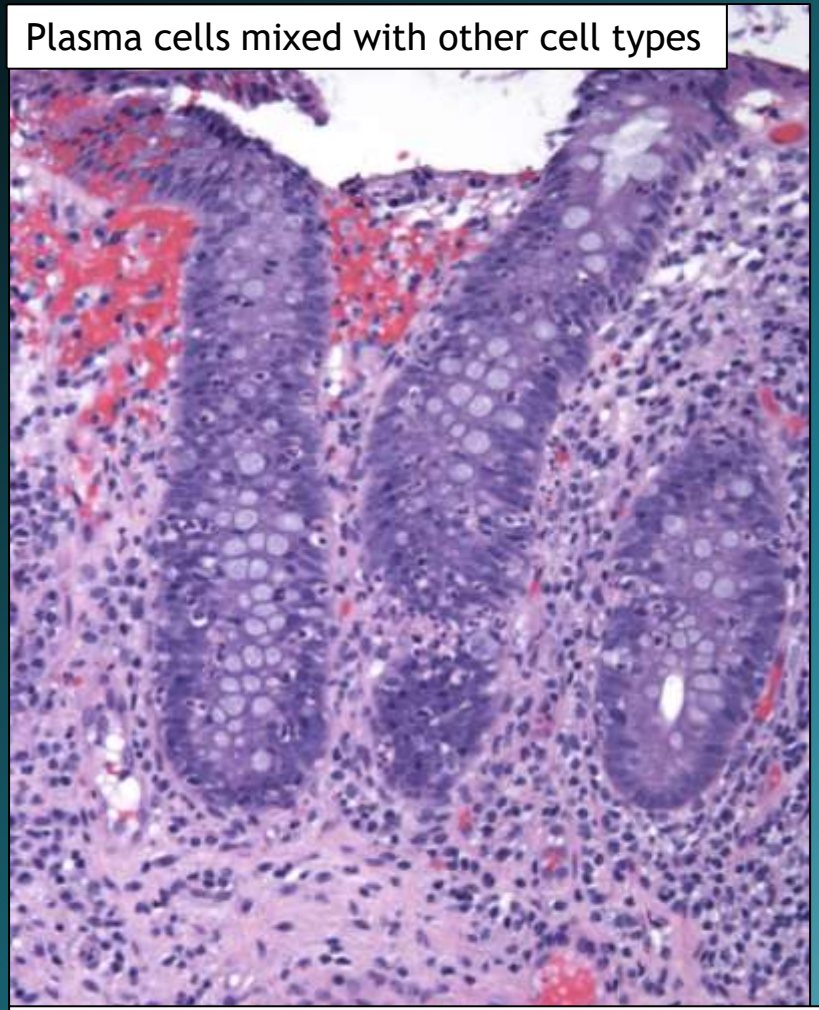
Mixed lamina propria inflammation



Preserved crypt architecture


Neutrophils between crypts
Regenerative crypt epithelium
Acute colitis

Plasma cells mixed with other cell types



Crypts lost, but not distorted

Acute colitis can contain plasma cells 1-2 weeks after symptom onset

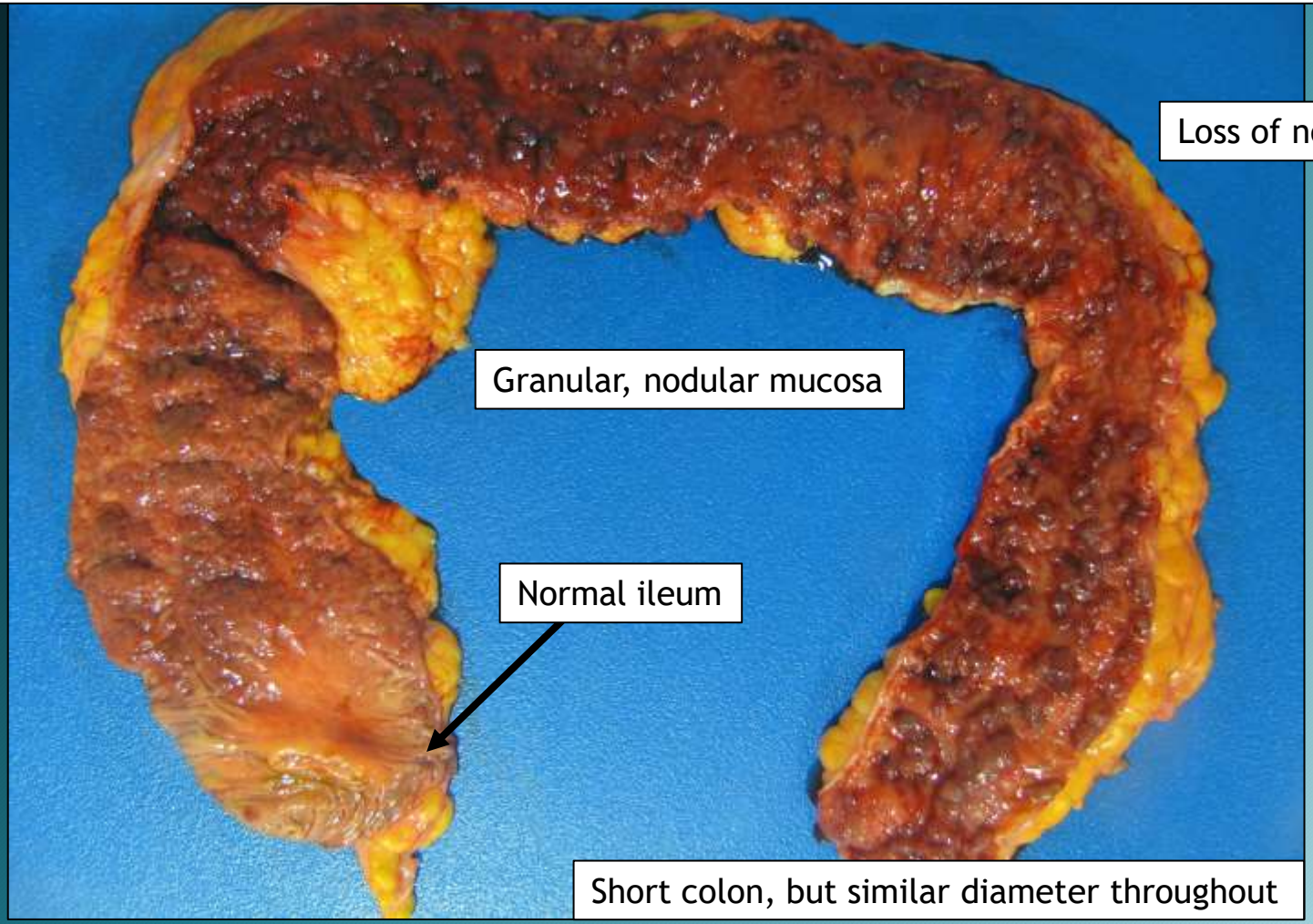
Colitis
Patterns of Injury

- Active Colitis
  - Neutrophilic infiltration of crypt epithelium
  - No metaplasia or architectural changes
  - Pattern typically seen in drug injury and infections
- Chronic Colitis
  - Plasma cell-rich inflammation
  - Metaplasia, atrophy architectural changes
  - Neutrophils may be present (chronic active colitis)

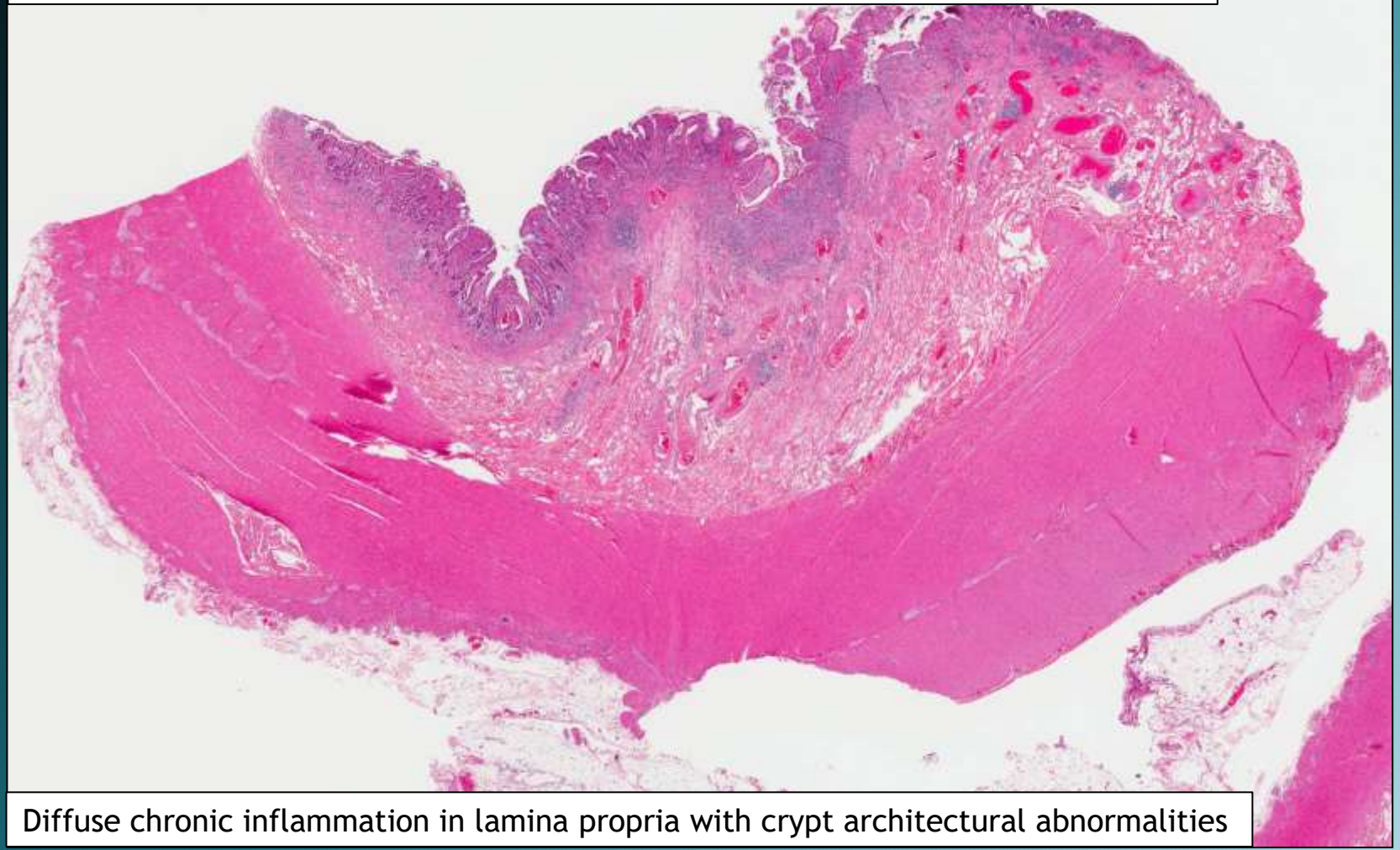
Chronic Colitis

- Destructive
  - Idiopathic inflammatory bowel disease
- Non-destructive
  - “Microscopic colitis”
- Other causes
  - Diverticular disease-associated colitis
  - Diversion-related colitis
  - Medications
  - Some infections

Classic ulcerative colitis is diffuse and continuous, extending from rectum in retrograde fashion

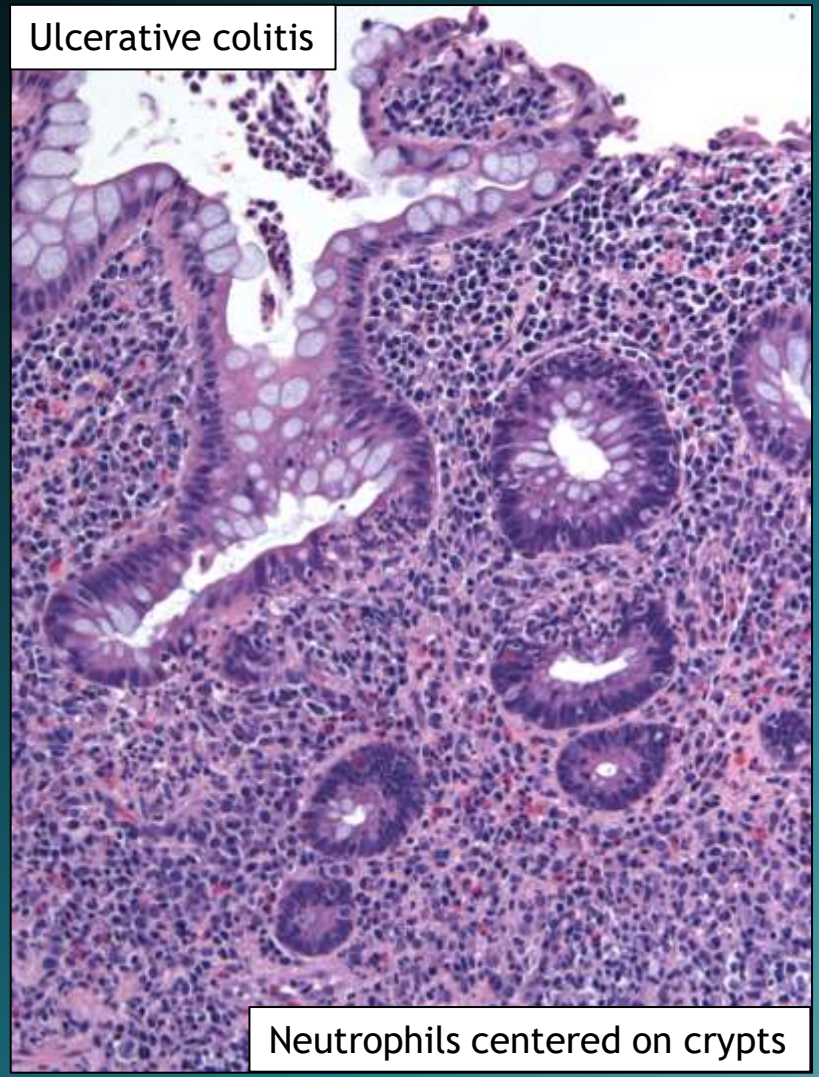


Classic ulcerative colitis is superficial, involving mucosa and superficial submucosa

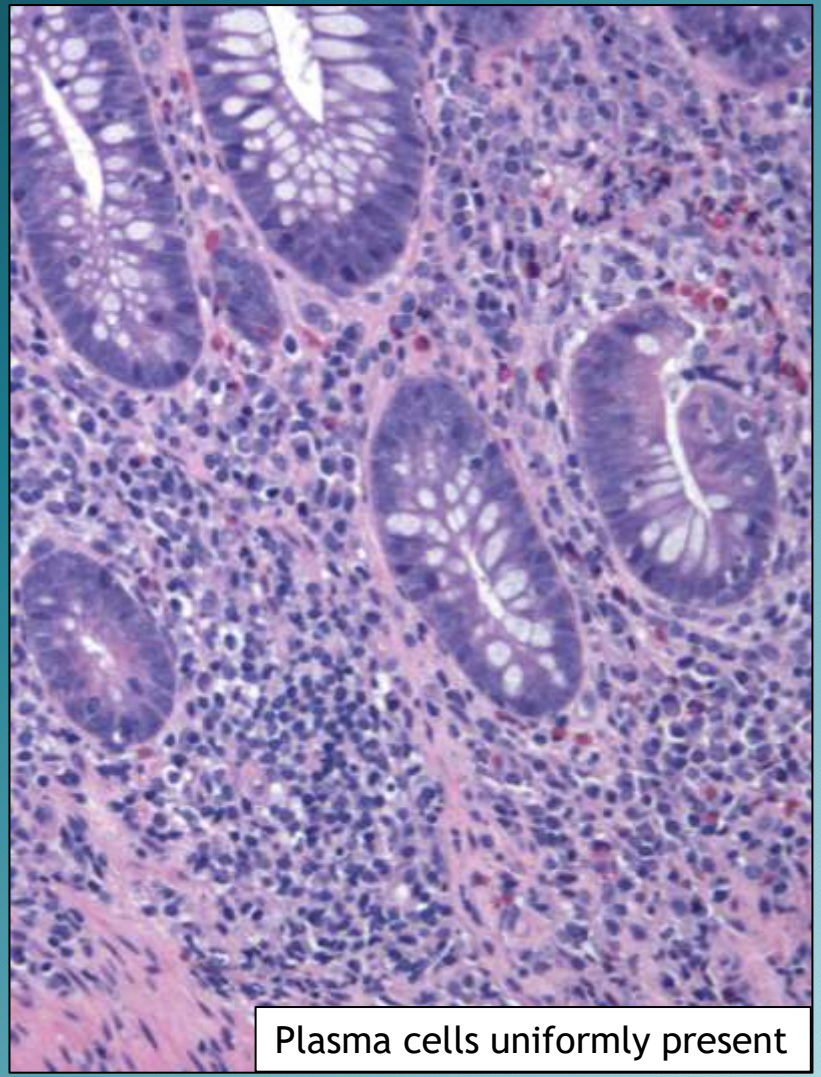


Diffuse chronic inflammation in lamina propria with crypt architectural abnormalities

Ulcerative colitis

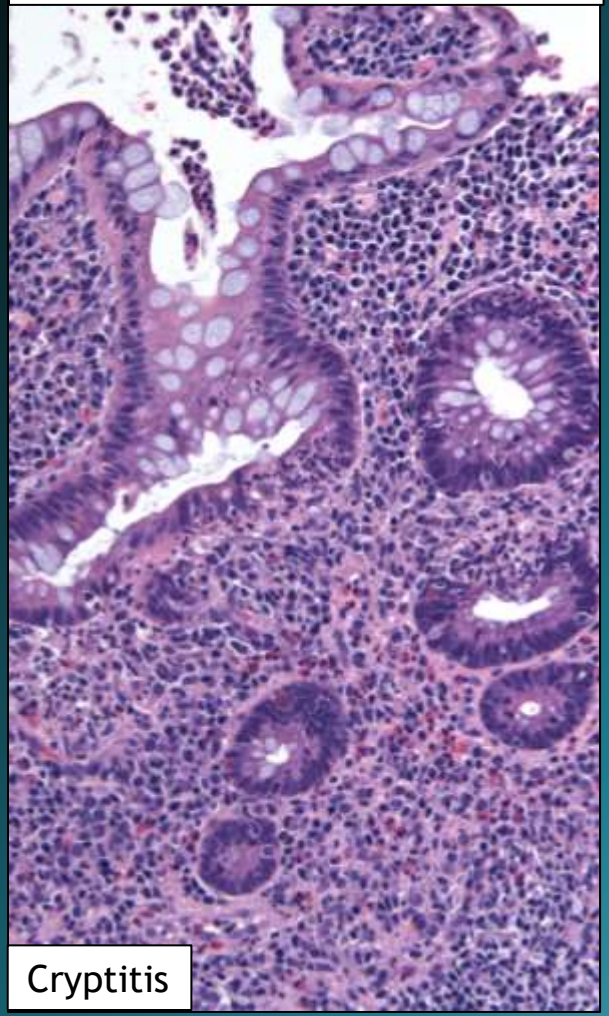


Neutrophils centered on crypts

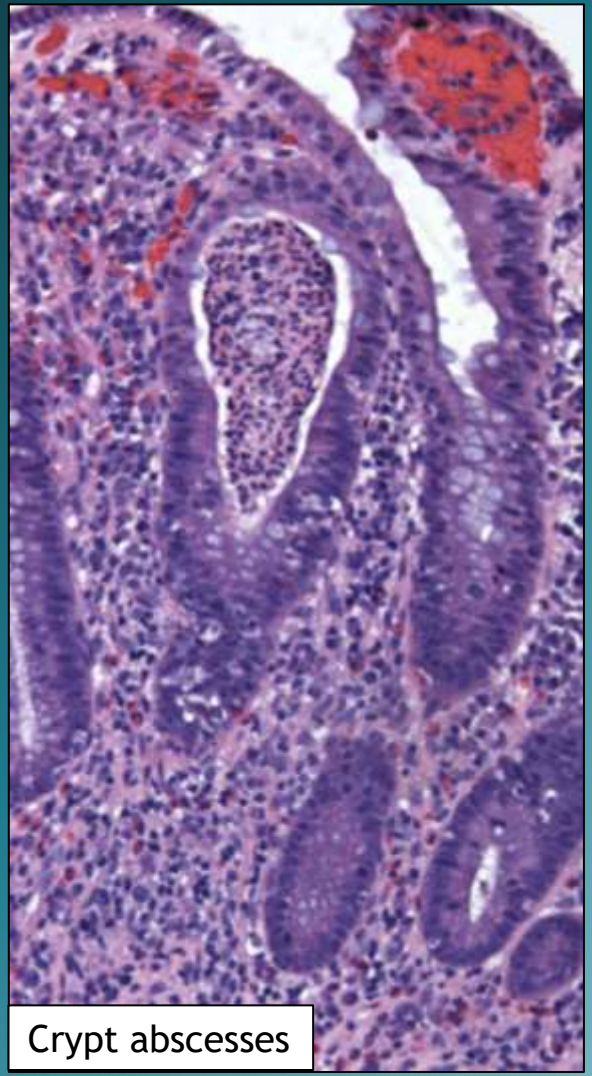


Plasma cells uniformly present

Ulcerative colitis disease activity



Cryptitis

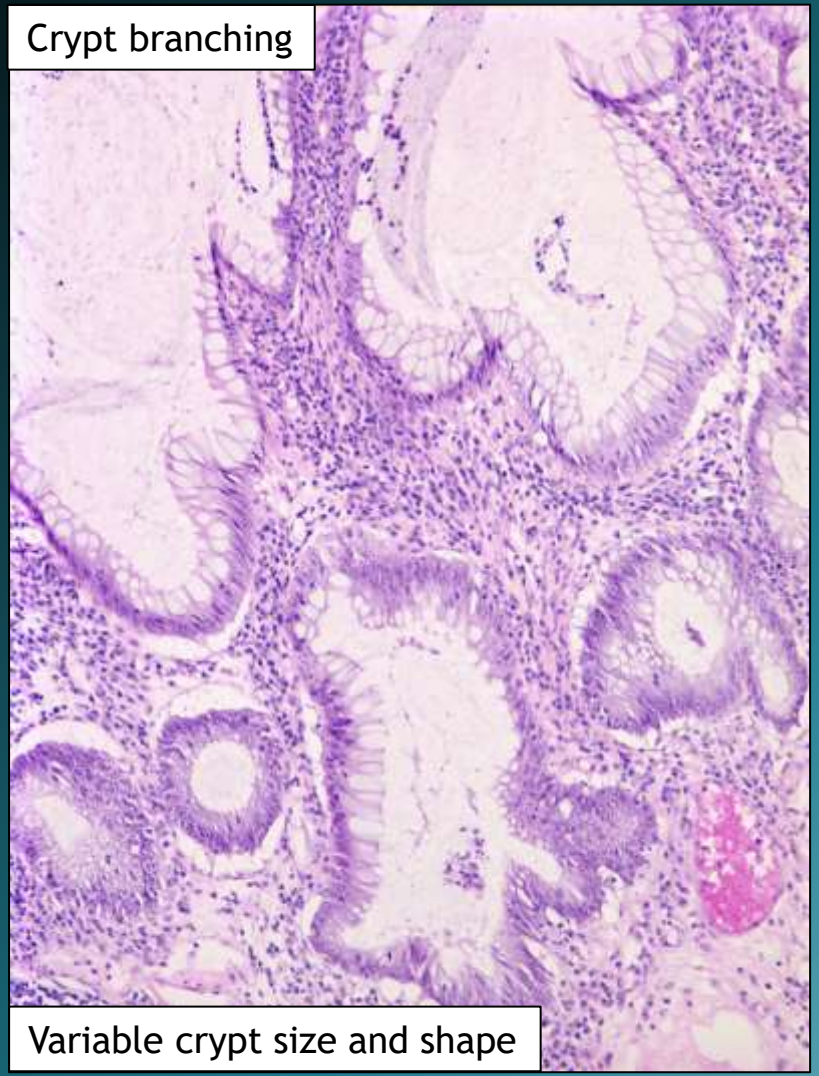


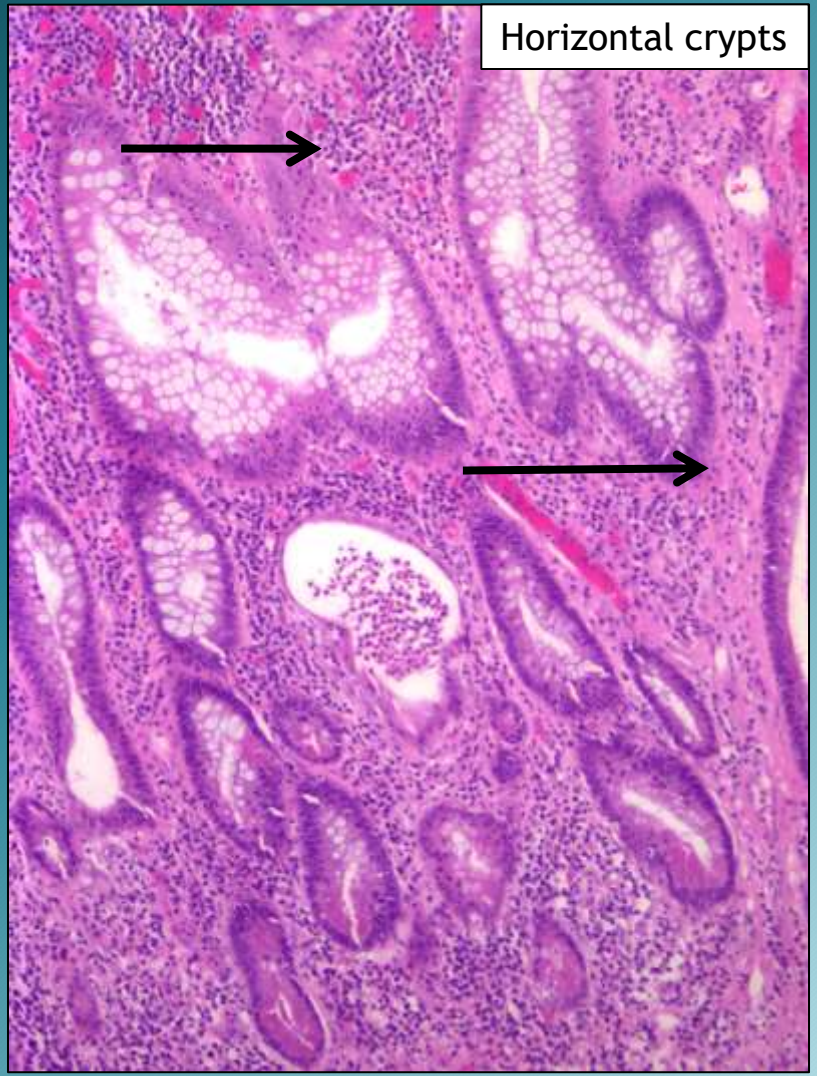
Crypt abscesses

Crypt destruction

Classic Ulcerative Colitis

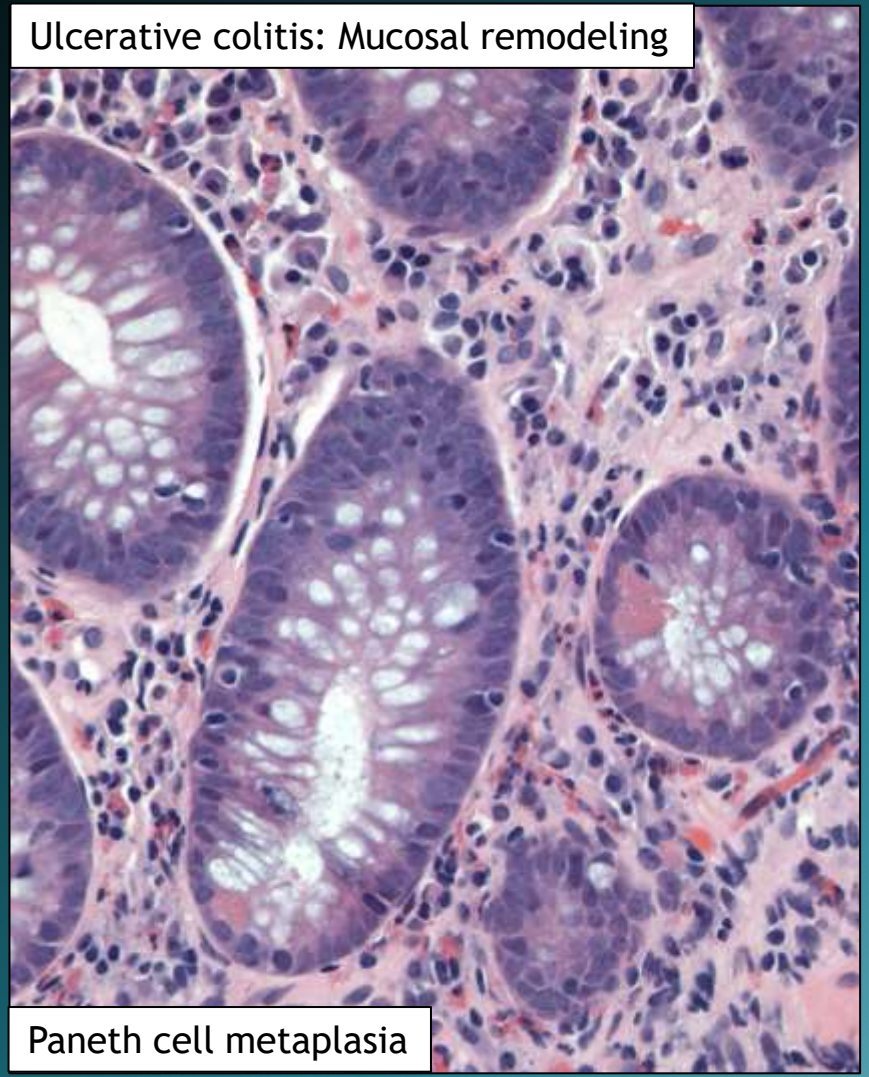
- Repetitive cycles of crypt destruction, ulcers, and repair lead to mucosal remodeling
- Crypt architecture
  - Variable size, shape, and orientation
- Loss of crypts
- Villiform surface contour


Crypt branching
Variable crypt size and shape

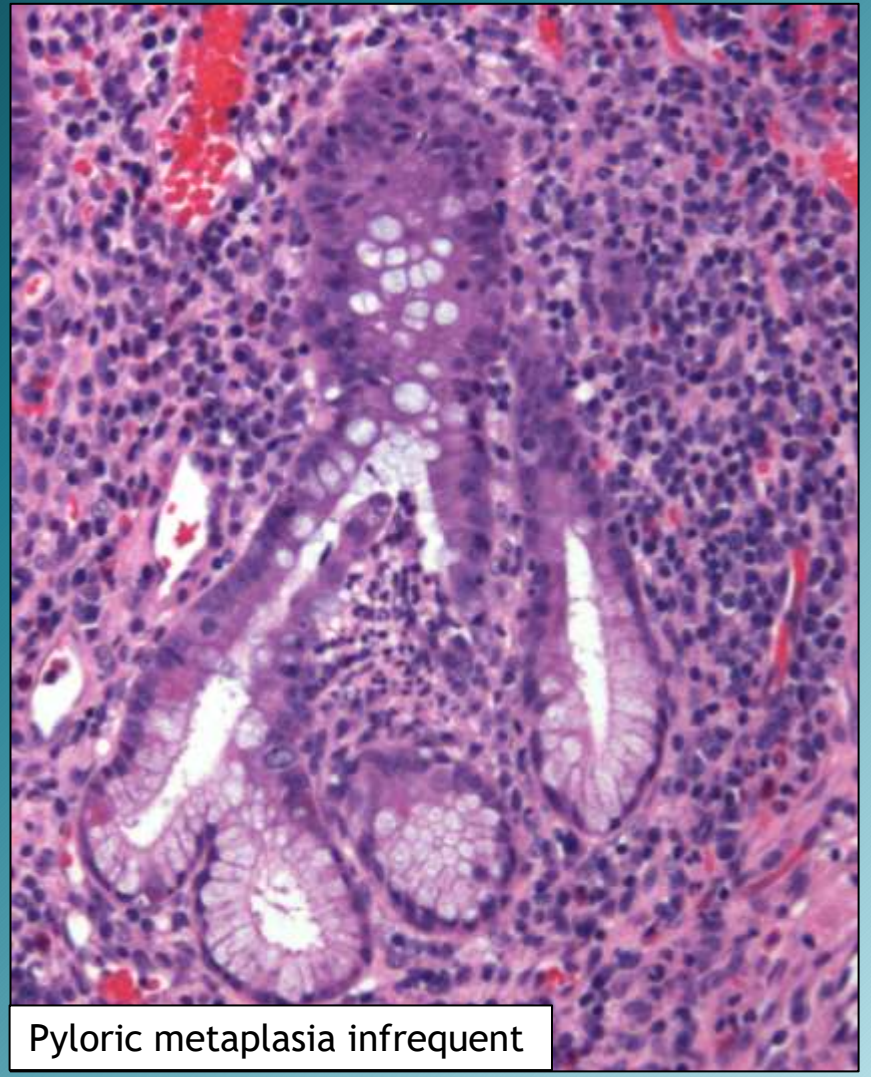

Horizontal crypts

Mucosal remodeling: Marked crypt hyperplasia

Ulcerative colitis: Mucosal remodeling



Paneth cell metaplasia



Pyloric metaplasia infrequent

What about grading disease activity and assessing mucosal healing?

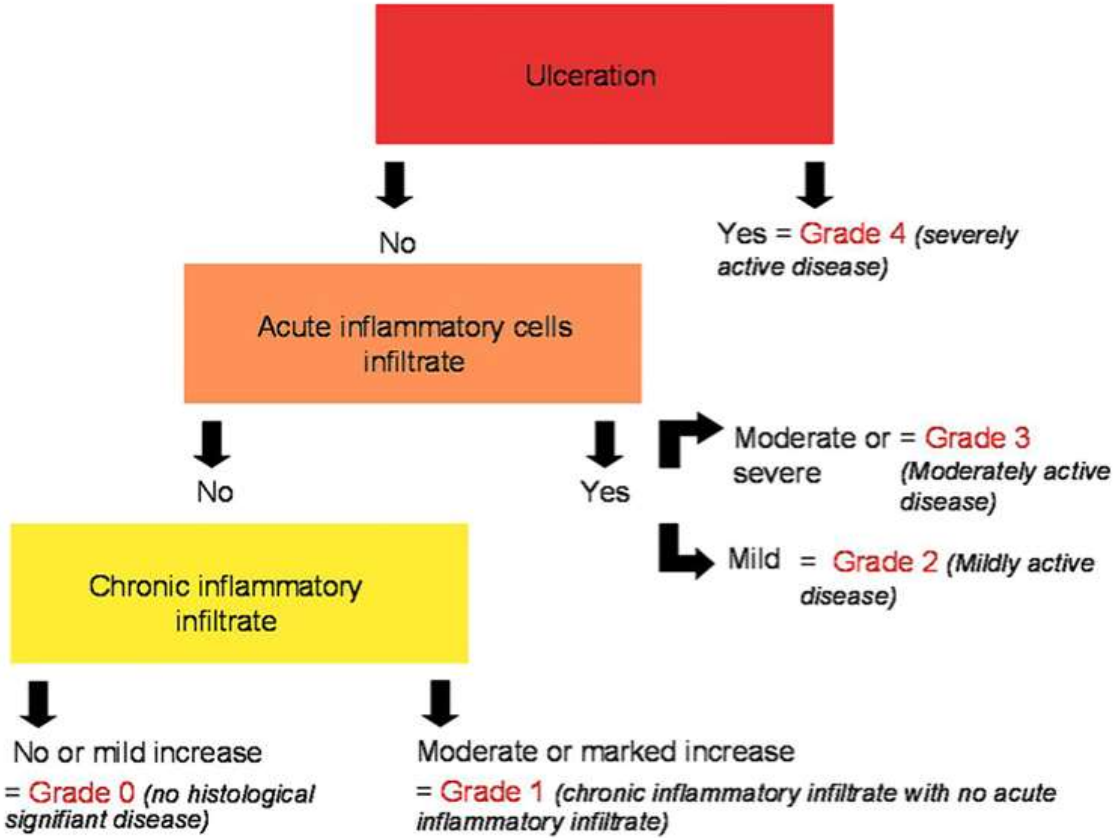
- Disease activity is generally measured in terms of neutrophilic infiltrates in epithelium, not chronic changes
- Grading schemes incorporate features of chronic colitis that are not markers of activity into grade
- Schemes are overly cumbersome with poor reproducibility
  - The more parameters measured, the more variable the results

Geboes, et al. Gut 2000; 47: 404-409

Table 1 Different grades used for evaluation of disease severity in ulcerative colitis

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable—local excess of neutrophils in part of crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Figure 2 Algorithm of the Nancy histological index composed of three histological items resulting in a five-grade classification of histological disease activity for UC.



Bressenot, *et al*. *Gut* 2017; 66(1): 43-49.

Grading Disease Activity

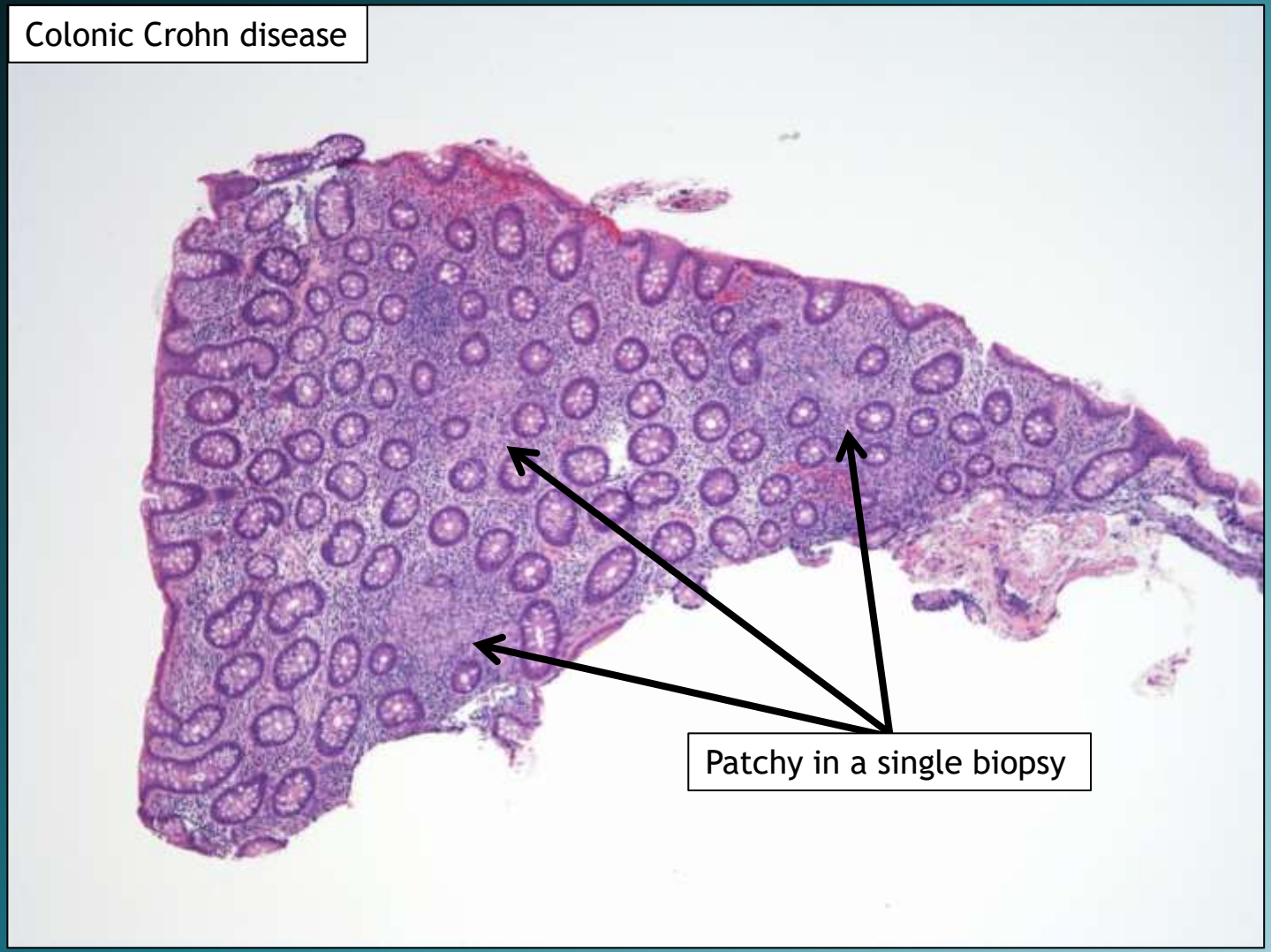
- Correlation with endoscopy
  - The more extensive the pathologic changes, the more likely they correlate with endoscopic findings
    - Mild activity doesn't correlate all that well
    - Severe activity correlates very well with endoscopy
- Clinical value of histologic grade
  - Most clinicians treat clinical, not histologic activity
  - Some data suggest that severity of histologic activity is associated with higher risk of neoplasia (which makes sense)

Rosenberg, *et al*. Clin Gastroenterol Hepatol 2013; 11(8): 991-996.
Rubin, *et al*. J Clin Gastroenterol 2013;11: 1601-1608.

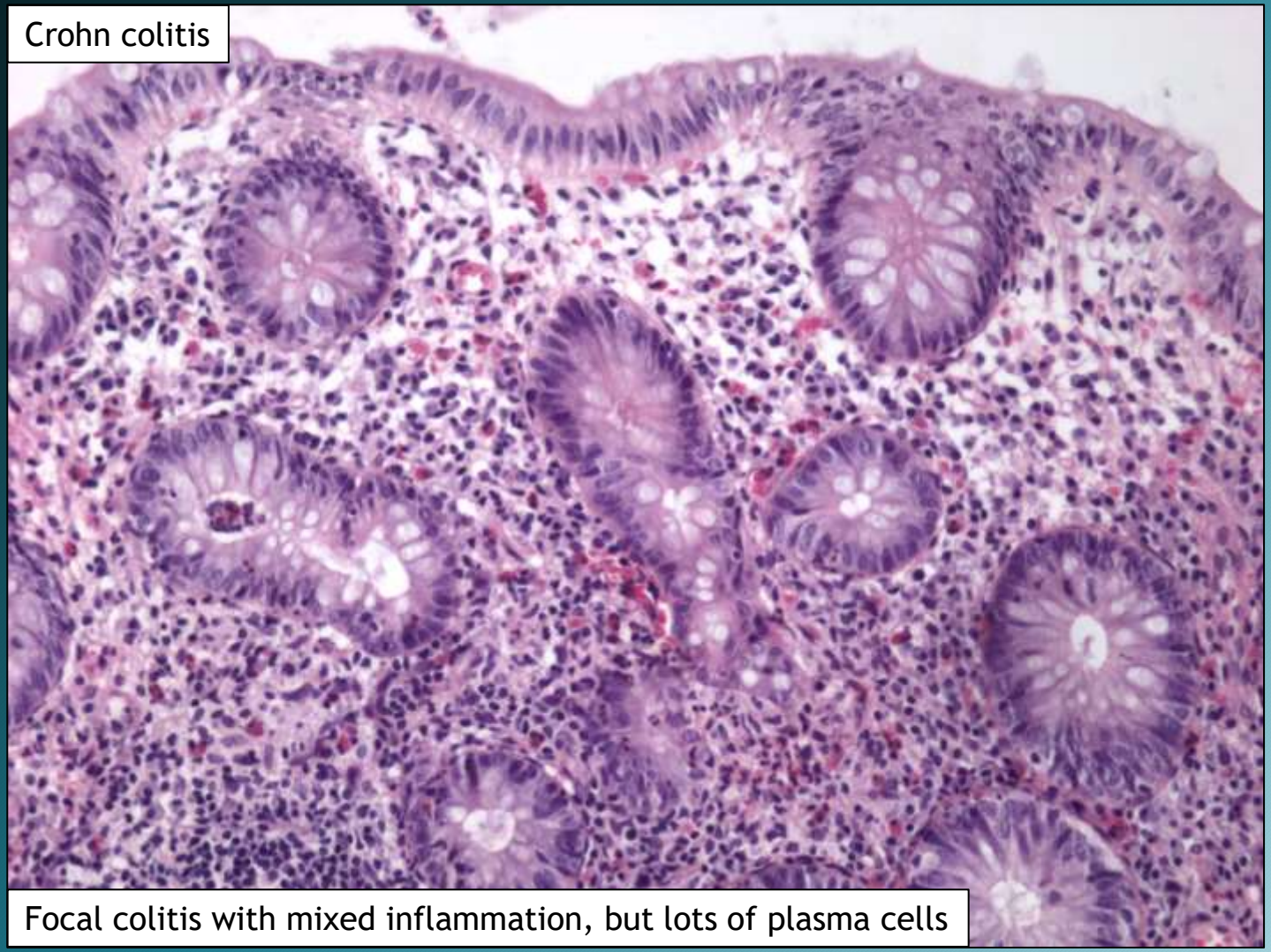
Colonic Crohn Disease in Biopsies

- Some cases show diffuse colitis similar to ulcerative colitis
- Tends to be more patchy than ulcerative colitis
- Focal intense inflammation
- Complete sparing of tissue fragments in samples from same area
- Patchy inflammation within a single fragment

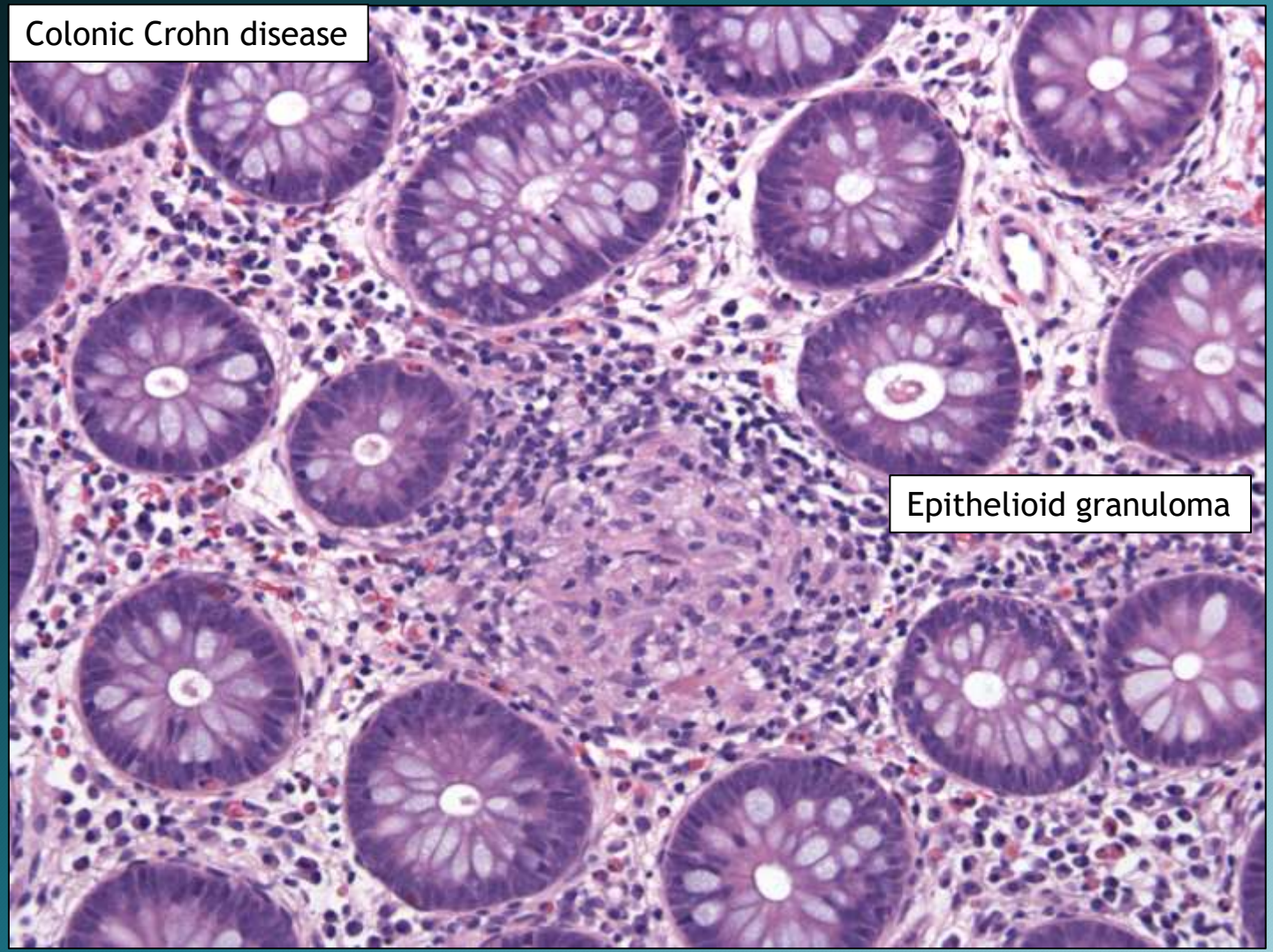
Colonic Crohn disease



Crohn colitis



Focal colitis with mixed inflammation, but lots of plasma cells


Colonic Crohn disease
Epithelioid granuloma

Crohn Disease in Colonic Biopsy Samples

- Crohn disease is typically patchy with wide variation in severity of injury
- Plenty of ulcerative colitis cases show patchy disease (especially if treated, or early in disease)
- In absence of granulomata or ileal disease, almost impossible to definitively diagnose Crohn colitis based on biopsy alone

Classic Features of Ulcerative Colitis and Crohn Disease

Ulcerative Colitis	Crohn Disease
Colon only	Any part of GI tract
Diffuse, continuous disease	Segmental disease
Rectal involvement	Variable rectal involvement
Disease worse distally	Variable disease severity
No fissures or fistulae	Fissures and fistulae
Disease in mucosa/submucosa	Transmural lymphoid aggregates
No ileal involvement, except distal 1-2 cm (backwash)	Ileal involvement in 80%, upper GI tract involvement also common
	Epithelioid granulomata
	Perianal disease

Evolving Views of Ulcerative Colitis

- Historical views of disease
  - Based on resection specimens, barium studies, rigid sigmoidoscopy
- Modern era
  - Colonoscopic access to proximal colon
  - Disease shows greater variability than previously appreciated
    - Changes with time and treatment
  - Blurring distinction between ulcerative colitis and Crohn disease

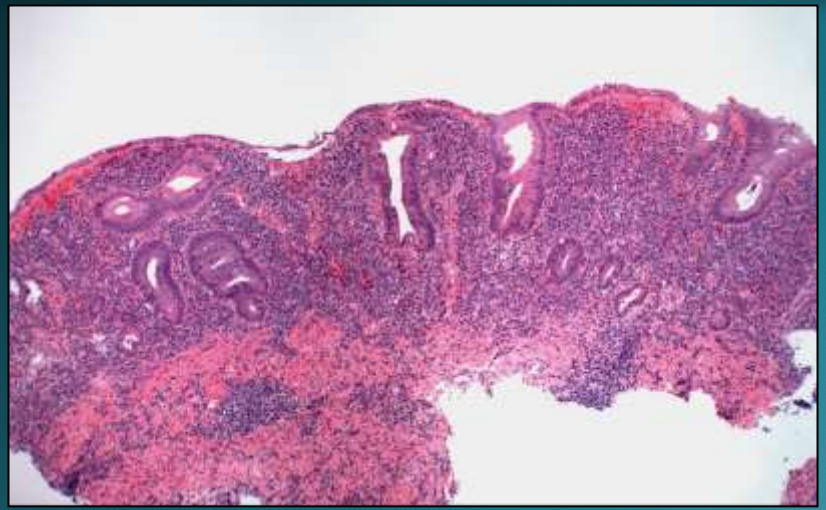
- Discontinuous ulcerative colitis
  - Left-sided colitis with sparing of intervening colon and inflammation of right colon
  - Cecal patch
  - Peri-appendiceal inflammation

Unusual Features of Ulcerative Colitis
Rectal Sparing in Early-Onset Disease

- Initial presentation of pediatric patients
  - 30-42% have some degree of rectal sparing
    - 6% have histologically normal rectal mucosa
  - Only 32% show diffuse disease
- Early ulcerative colitis in adults
  - 53% have diffuse disease
  - 31% show milder rectal inflammation compared to abdominal colon

Washington, *et al*. Am J Surg Pathol 2002; 26:1441; Glickman, *et al*. Am J Surg Pathol 2004; 28:190. Robert, *et al*. Am J Clin Pathol 2004; 122: 94-9.

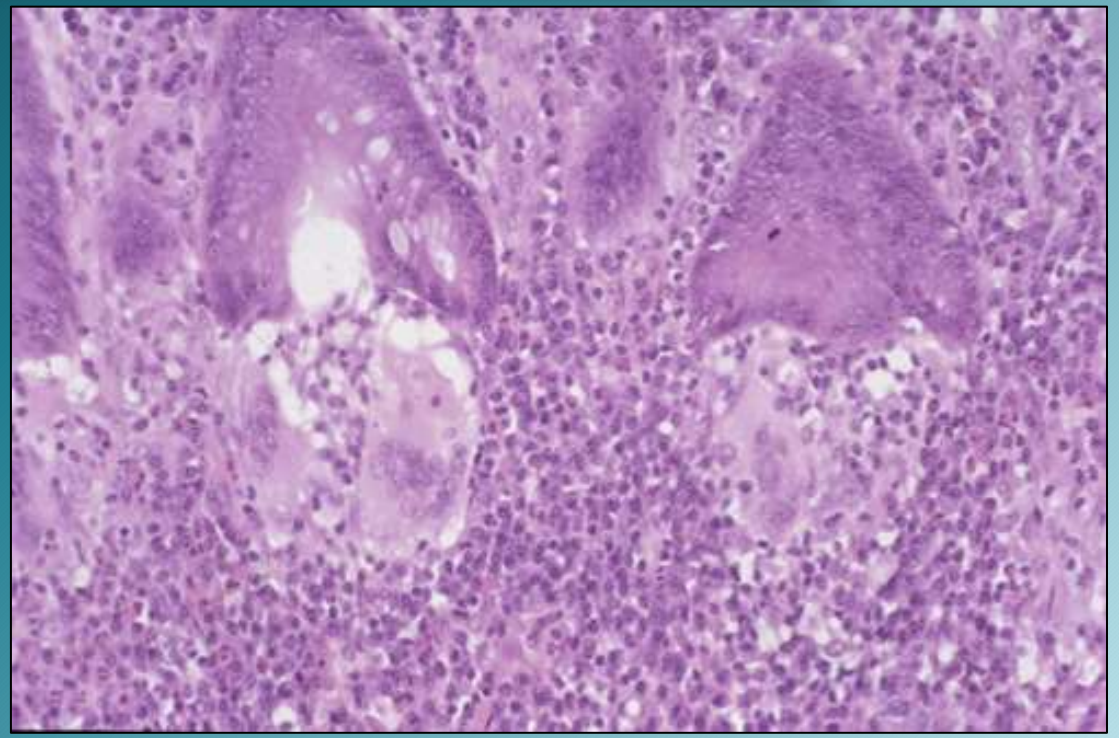
Ulcerative Colitis
Mucosal Healing with Therapy

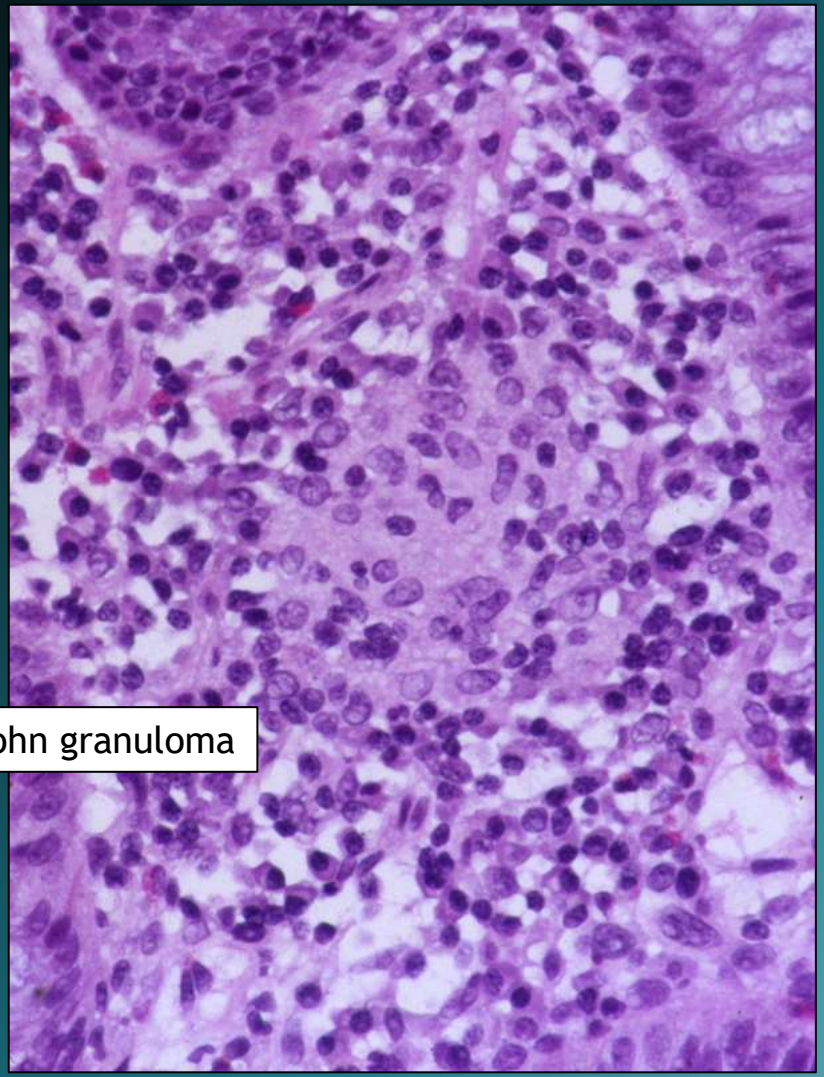


- Neutrophilic inflammation (activity) subsides, then chronic inflammation regresses
- Mucosal remodeling
  - Architecture can revert to normal over time
  - Corollary: The longer the quiescent period, the more “normal” the mucosa becomes

Granulomatous Inflammation of Ulcerative Colitis

- 20% of ulcerative colitis cases
- Usually related to crypt rupture
- Other etiologies
  - Barium
  - Particulate matter
  - Infections
  - Drugs

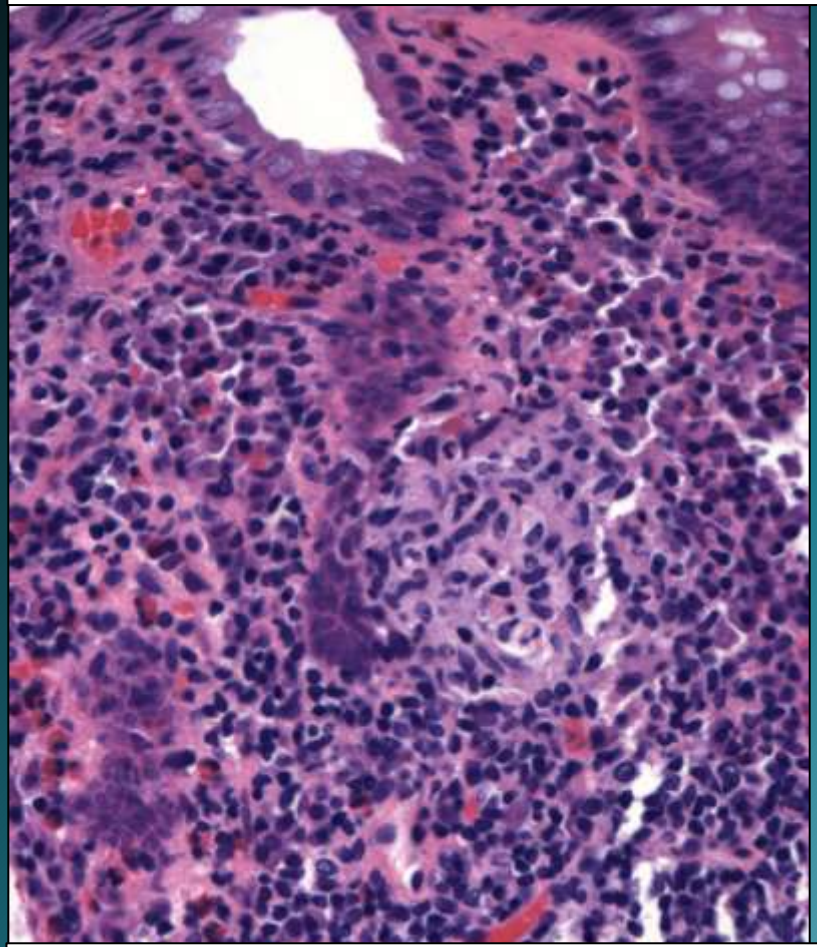


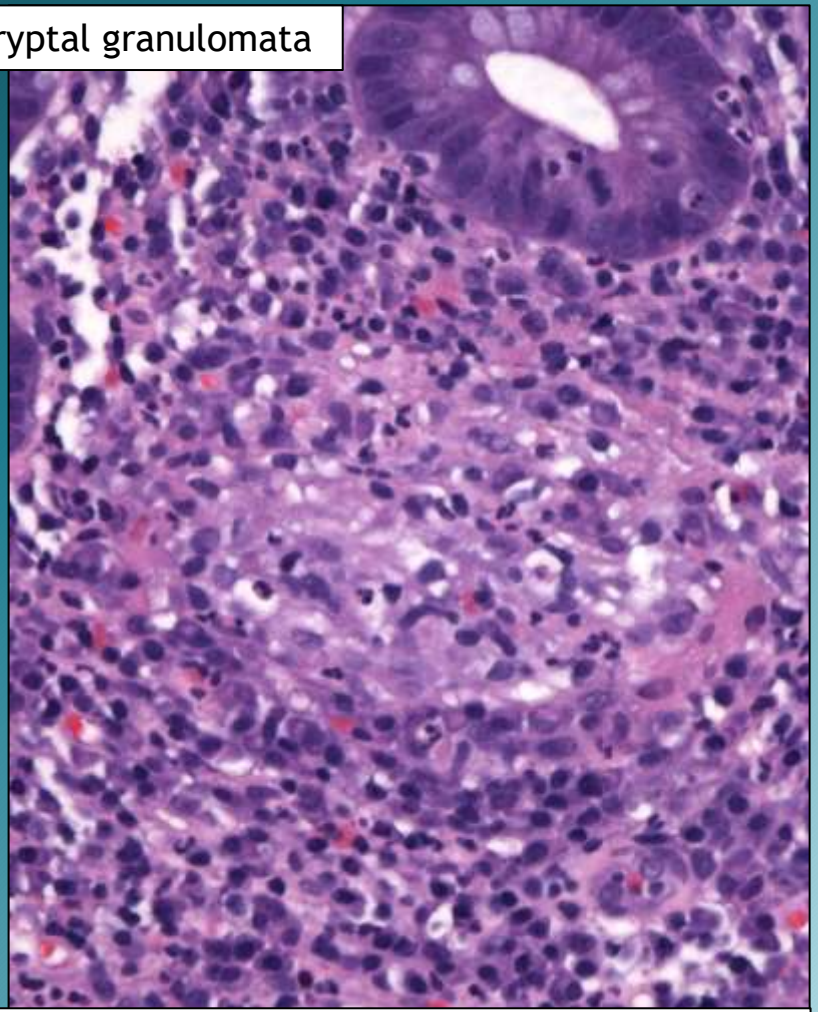


Crohn granuloma

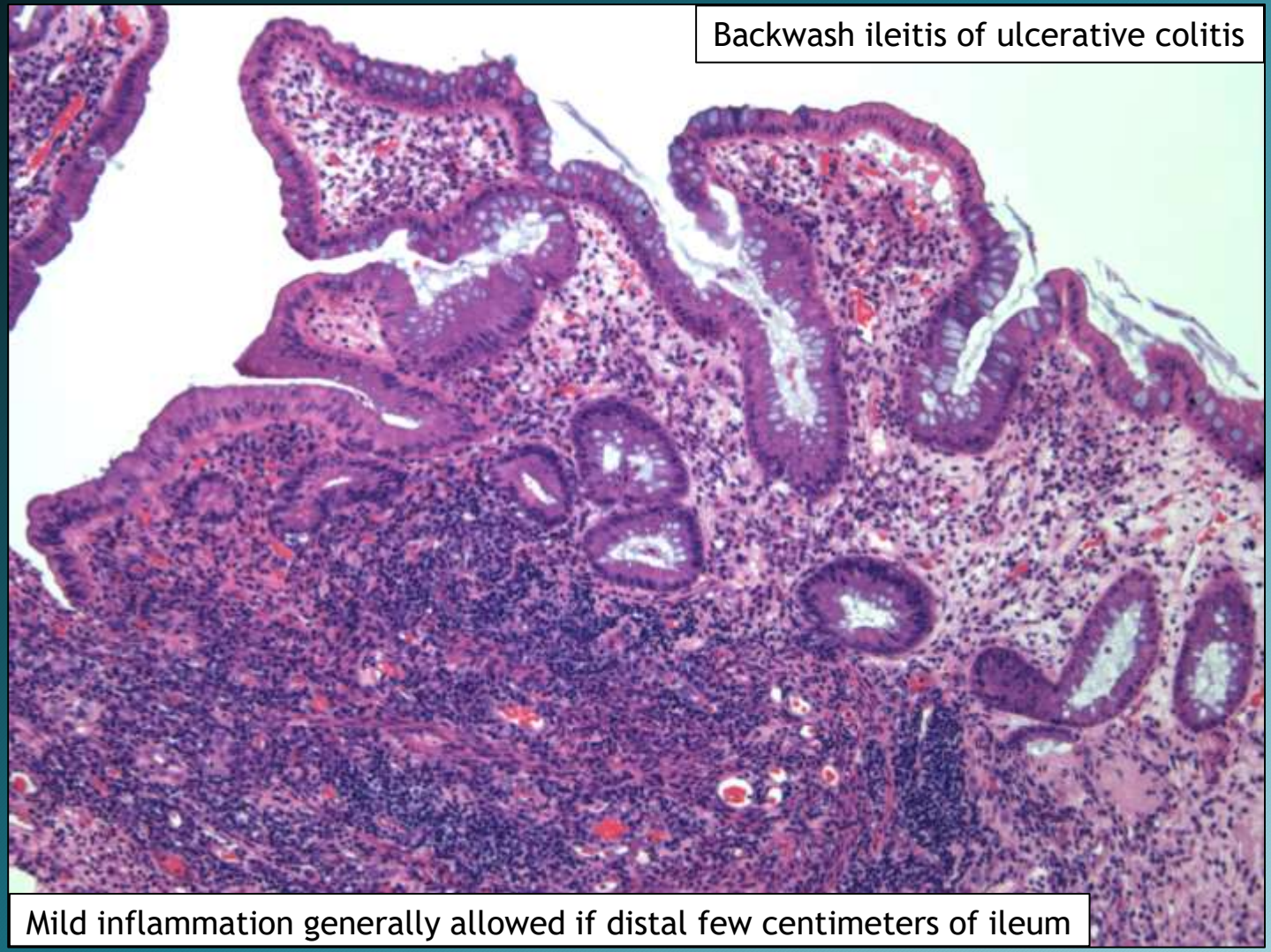
Mucin granuloma of ulcerative colitis

Be careful diagnosing Crohn disease based on pericryptal granulomata

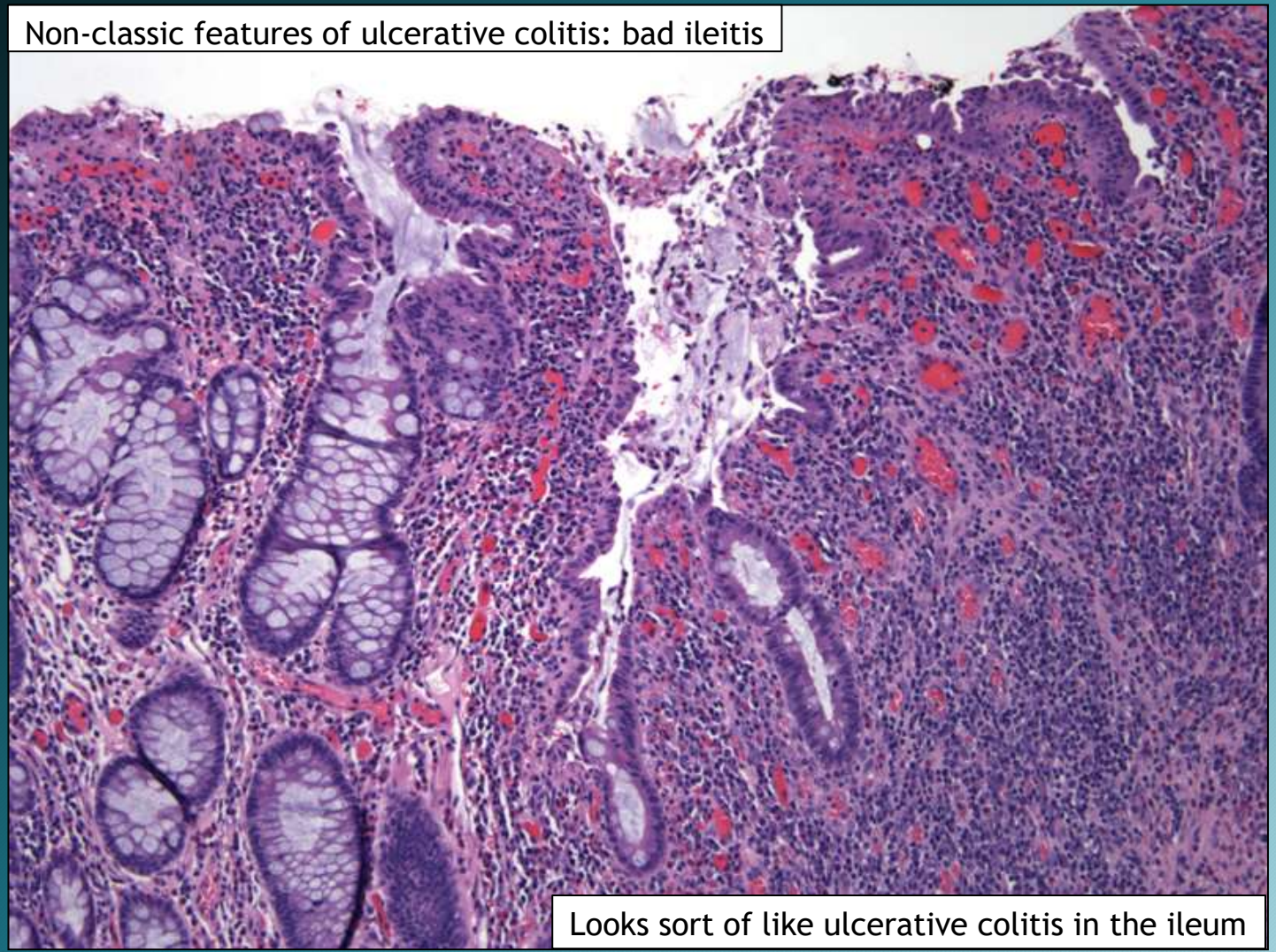




Granulomata containing mixed inflammatory cells are a clue to ruptured crypts, not Crohn disease


Backwash ileitis of ulcerative colitis
Mild inflammation generally allowed if distal few centimeters of ileum

Non-classic features of ulcerative colitis: bad ileitis



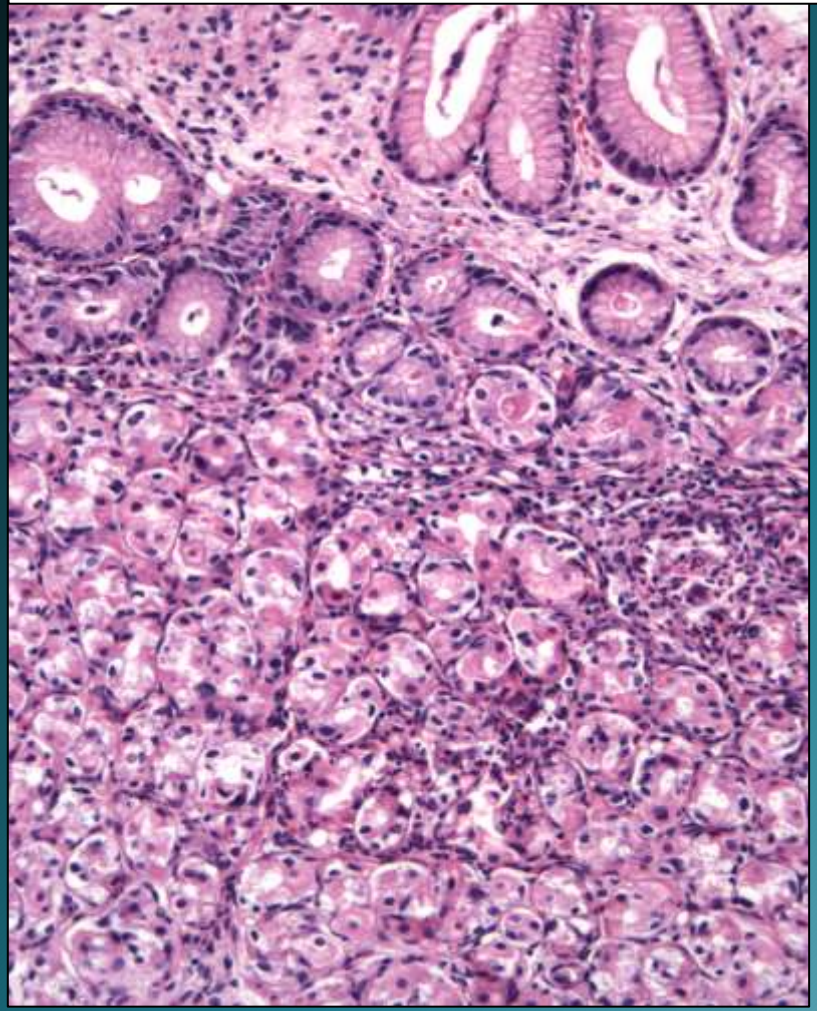
Looks sort of like ulcerative colitis in the ileum

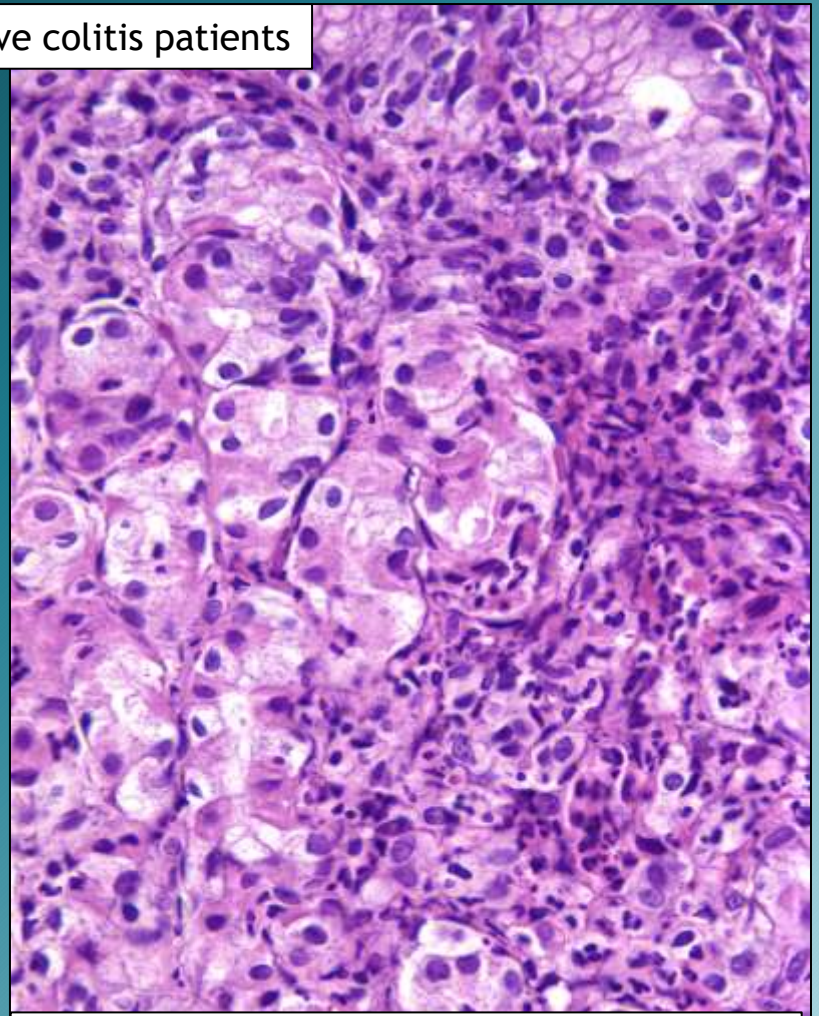
Non-Classic Features of Ulcerative Colitis
"Backwash Ileitis" Probably Isn't Backwash

- May not have severe pancolitis (no reflux of luminal inflammation)
- Possible etiologies
  - Bowel preparation or medications, especially NSAIDs
  - Stasis secondary to decreased colonic motility
  - Bacterial overgrowth
  - Infection
  - Ischemia
  - Involvement of ileum by ulcerative colitis
- Not associated with IPAA complications

Patil, *et al.* Am J Gastroenterol 2017; 112(8): 1211-1214.

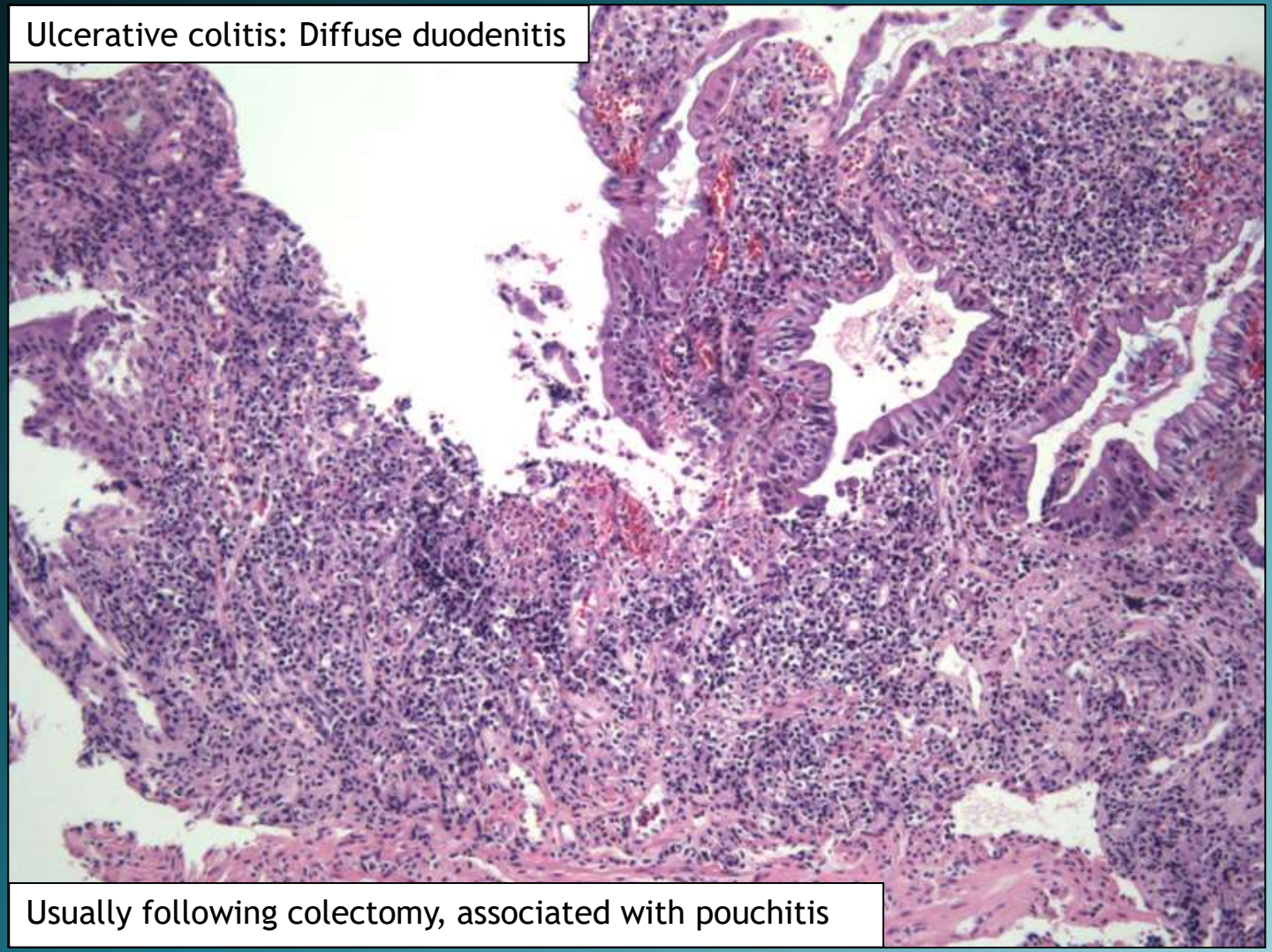
Chronic, focally active gastritis in 30% of ulcerative colitis patients





Lin, *et al*. Am J Surg Pathol 2010; 34(11): 1672-1677

Ulcerative colitis: Diffuse duodenitis



Usually following colectomy, associated with pouchitis

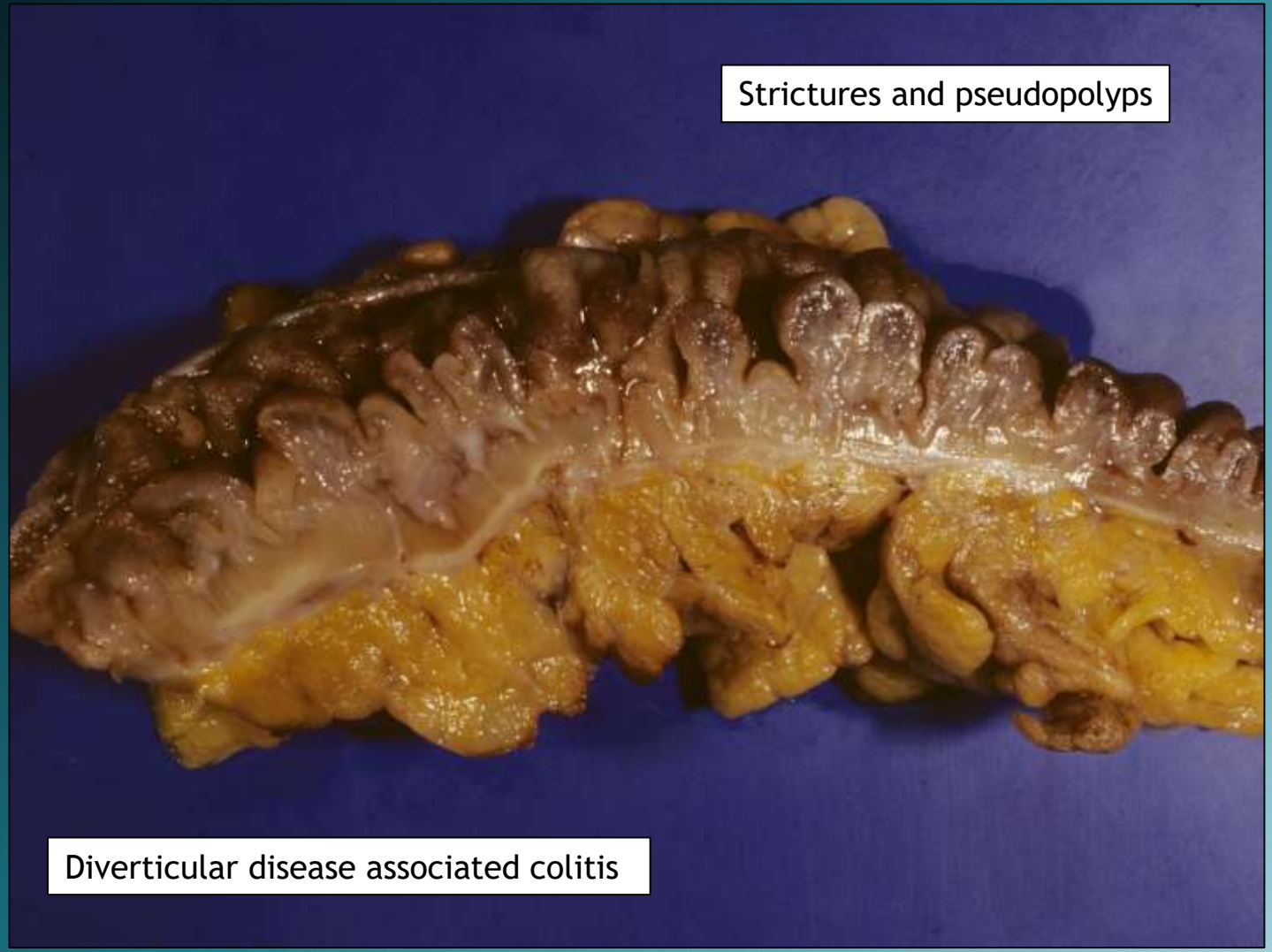
Non-Classic Features of Ulcerative Colitis

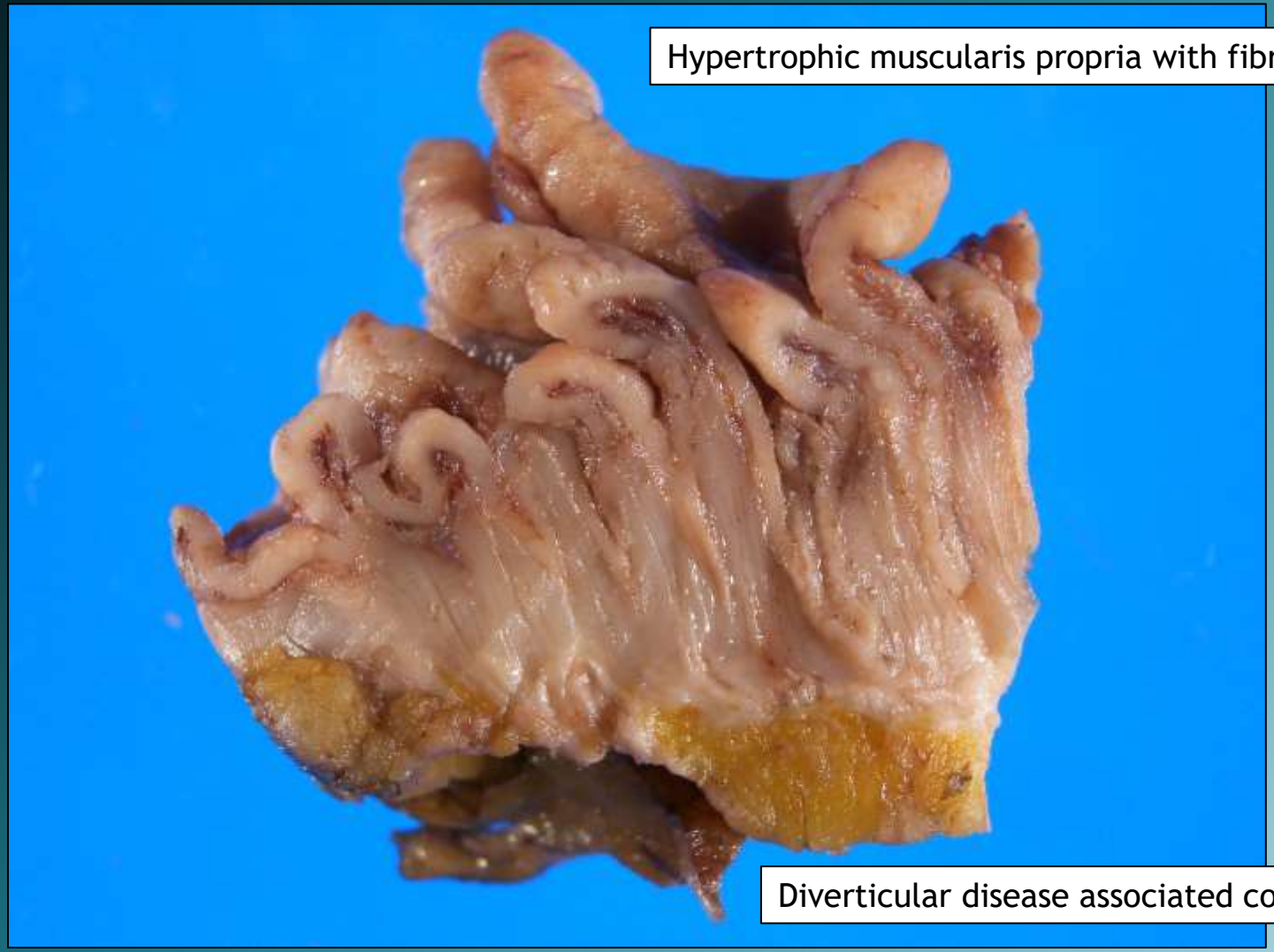
- Ulcerative colitis can show rectal sparing, especially in early phases or with therapy
- Ulcerative colitis may show mural inflammation, especially in fulminant colitis
- Ulcerative colitis can show granulomatous inflammation related to ruptured crypts
- Ulcerative colitis is usually confined to colon, but limited ileal involvement with ulcers can be present
- Ulcerative colitis can involve upper GI tract

Other Causes of Chronic Colitis

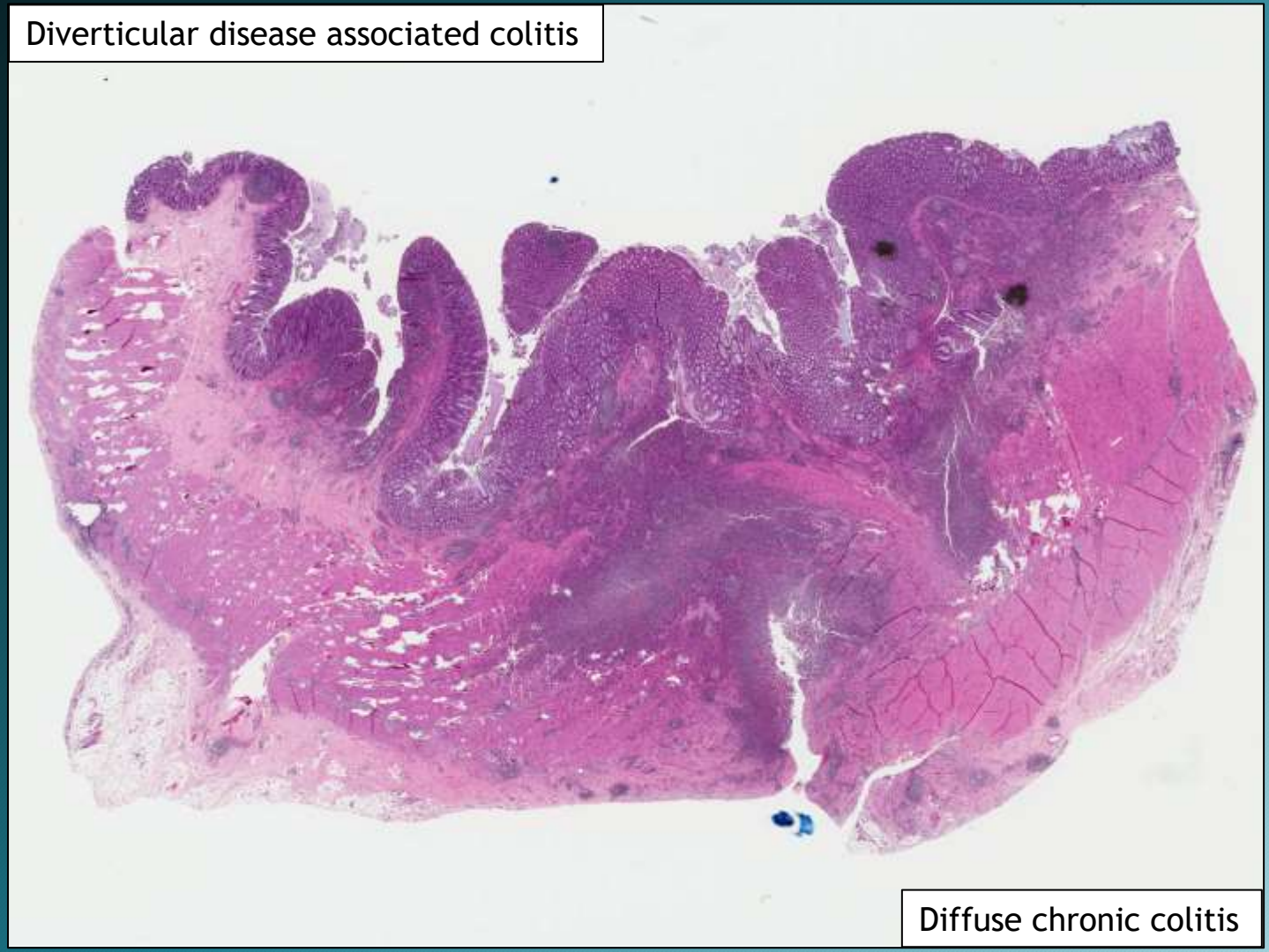
Diverticular Disease-Associated Colitis

- Obstructive symptoms and hematochezia
- Extra-intestinal manifestations (arthropathies, pyoderma gangrenosum)
- Colitis in area affected by diverticulitis
  - Ulcers, friability, strictures
  - Rectal sparing

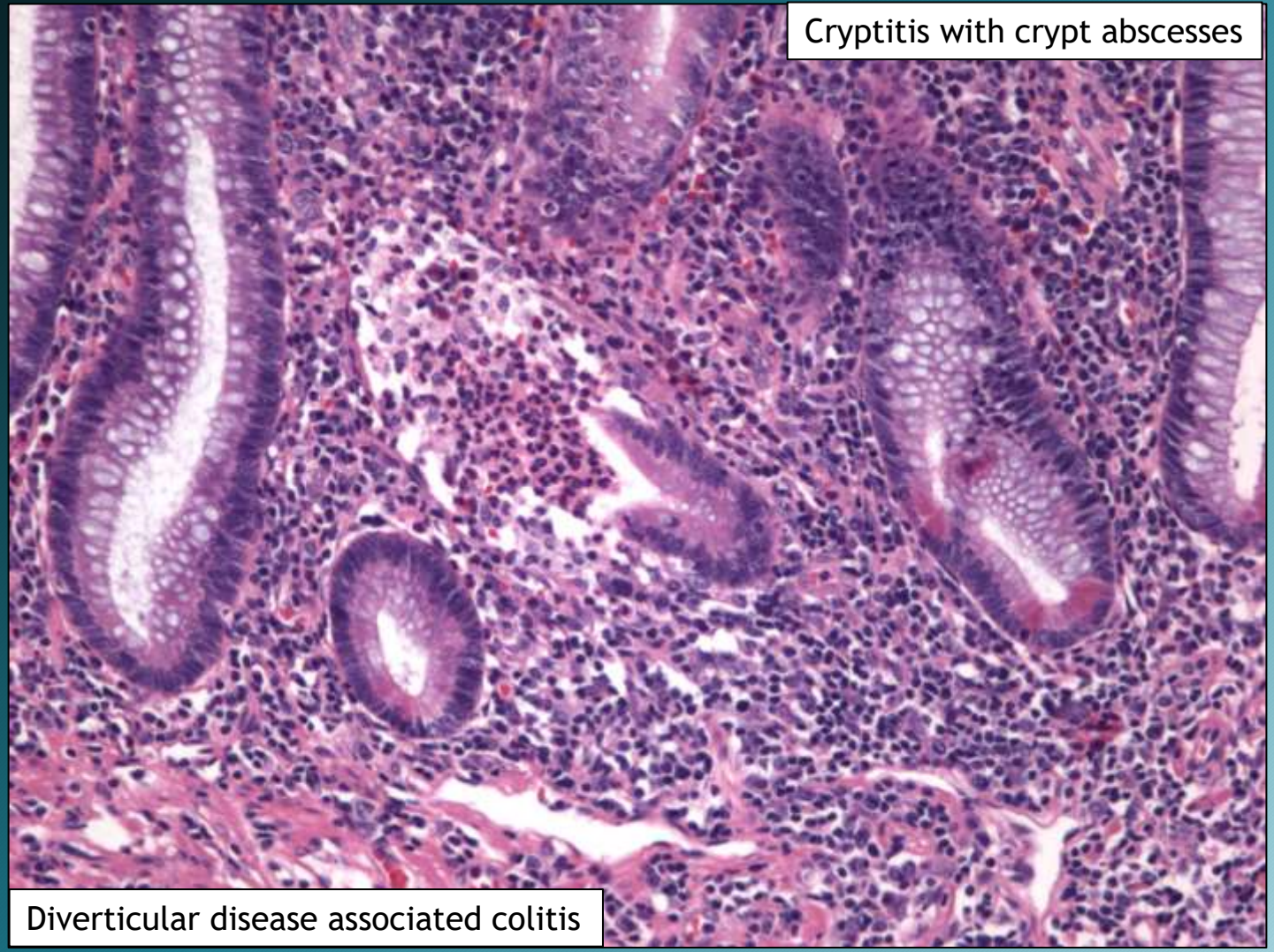

Strictures and pseudopolyps
Diverticular disease associated colitis


Hypertrophic muscularis propria with fibrosis
Diverticular disease associated colitis

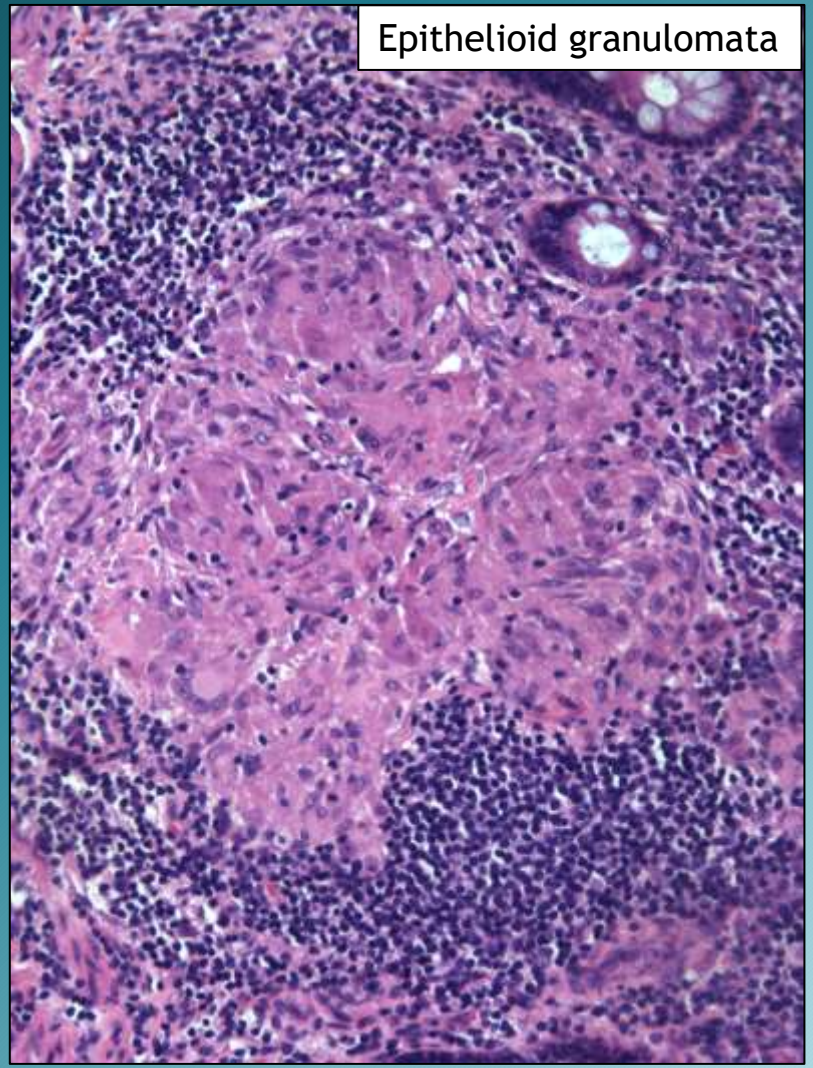
Diverticular disease associated colitis



Diffuse chronic colitis


Cryptitis with crypt abscesses
Diverticular disease associated colitis

Diverticular disease associated colitis



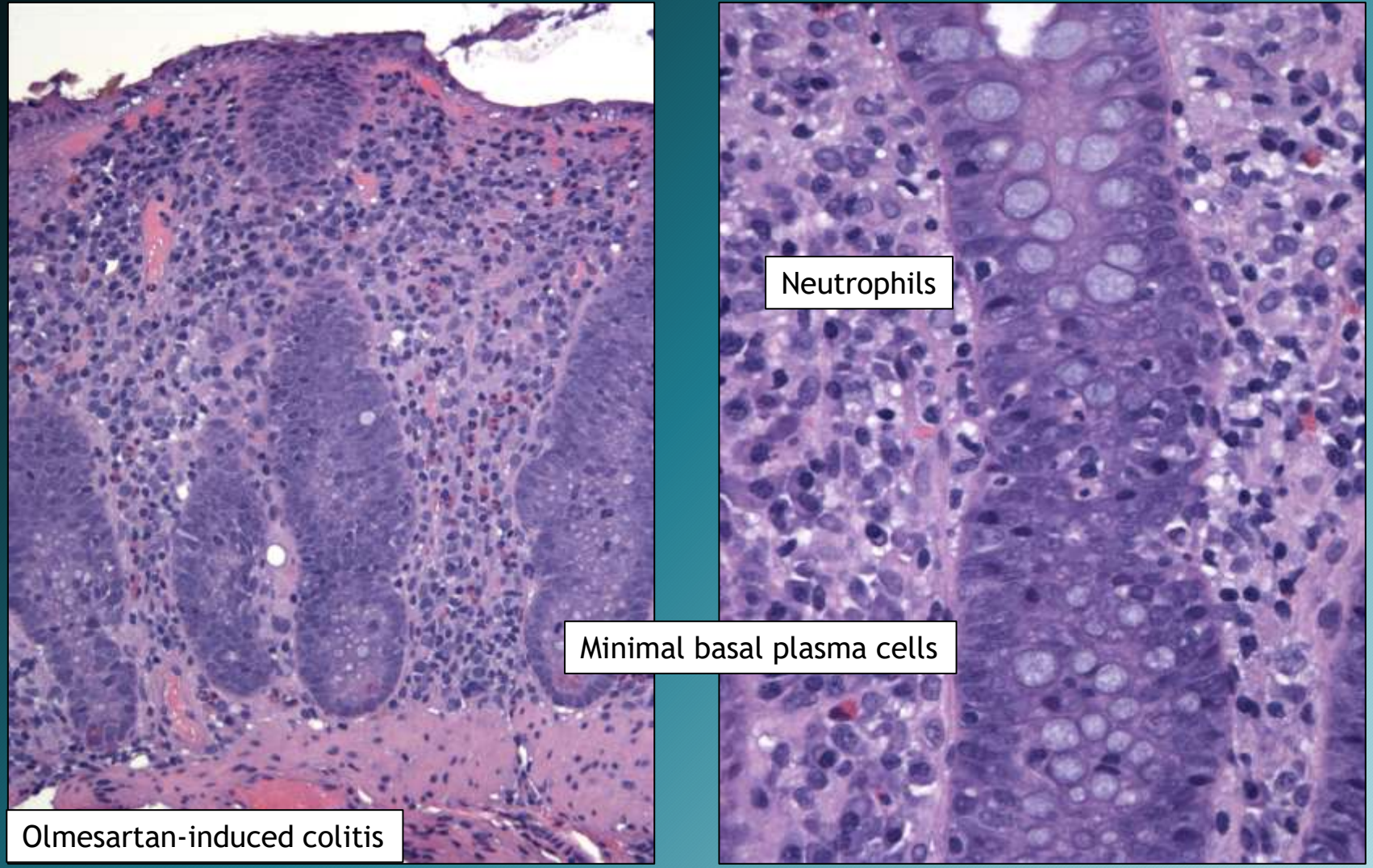
Epithelioid granulomata

Medications that Mimic Idiopathic Inflammatory Bowel Disease

- Olmesartan (causes sprue-like lesions as well)
- Ipilimumab
  - Monoclonal antibody to CTLA-4 (regulates cytotoxic T-cells)
  - Treatment of melanoma
- Emerging evidence regarding other immune checkpoint inhibitors (pembrolizumab and related compounds)

Olmesartan-induced injury

60-year-old man with severe diarrhea; rule out IBD (colonoscopy showed mildly congested colonic mucosa)


Neutrophils
Minimal basal plasma cells
Olmesartan-induced colitis

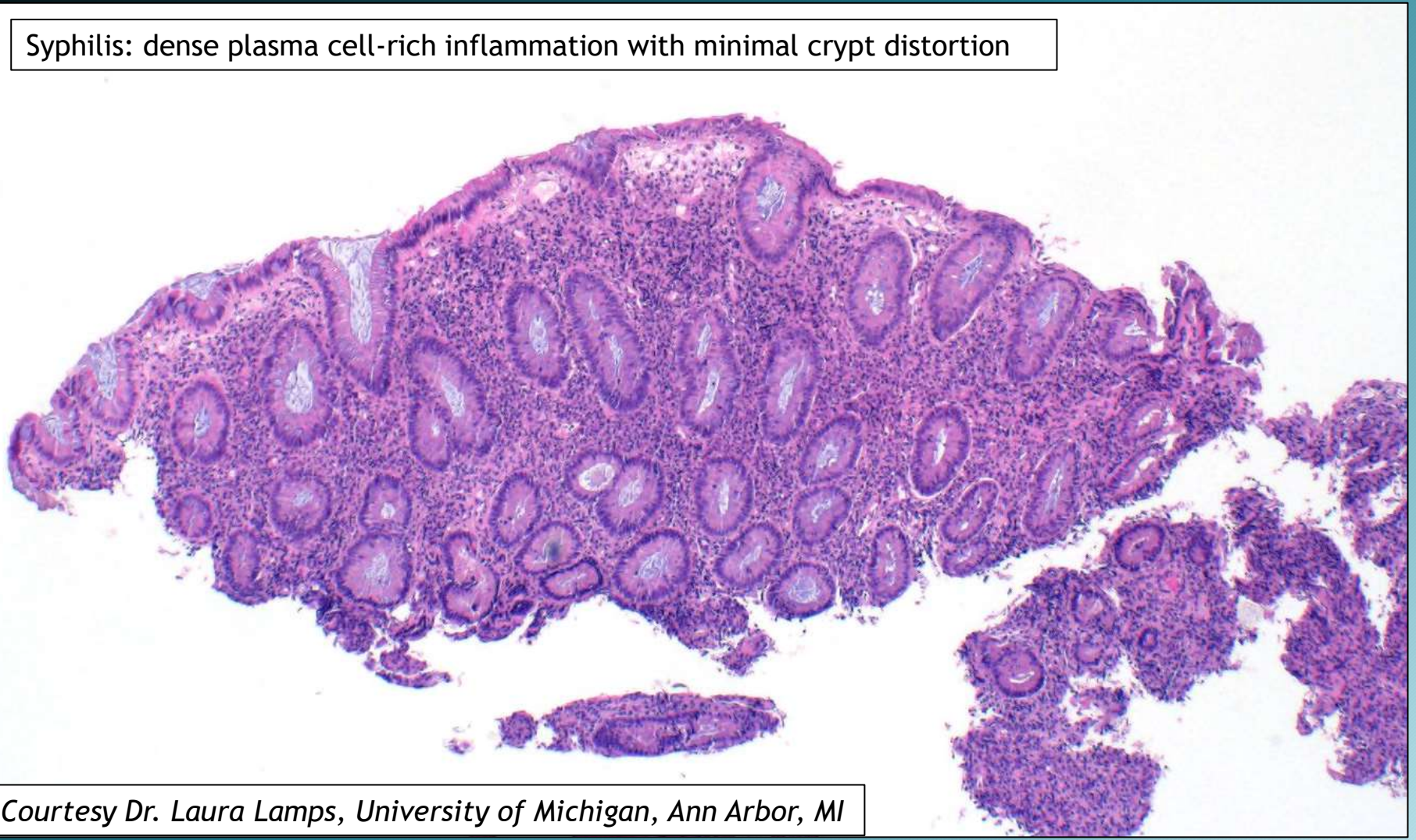
Mimics of Inflammatory Bowel Disease
Medication-Induced Colitis

- Apoptotic crypt debris, neutrophils, and patchy intraepithelial lymphocytosis
- Plasma cell-rich inflammation
  - Spares deep regions
  - Accompanied by minimal crypt distortion
- Think about it in older patients before making a new diagnosis of IBD

Infectious Proctitis
Syphilis and Lymphogranuloma Venereum

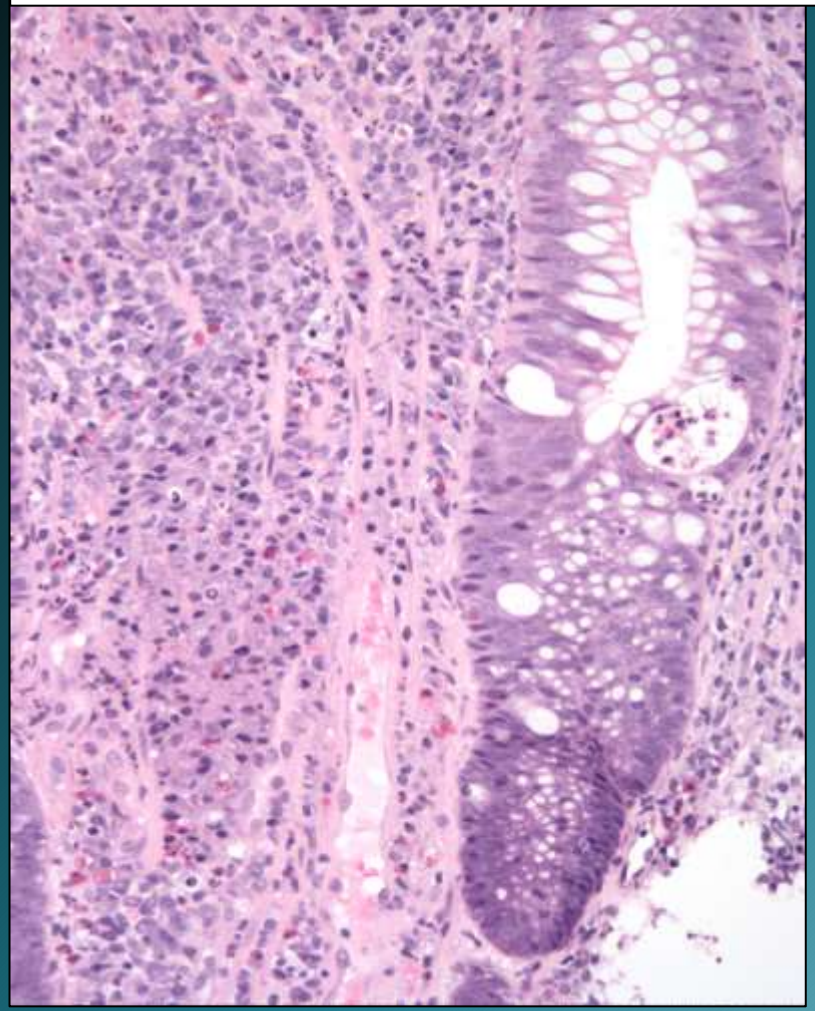
- Increasing incidence of both infections in the United States and Europe
  - Rates more than doubled in 10 years
- Men affected more than women (>90% of reported cases) in the United States
- Often occurs in patients co-infected with HIV (20-70%)
- These infections are histologically indistinguishable (need to mention both in the differential diagnosis)

Syphilis: dense plasma cell-rich inflammation with minimal crypt distortion

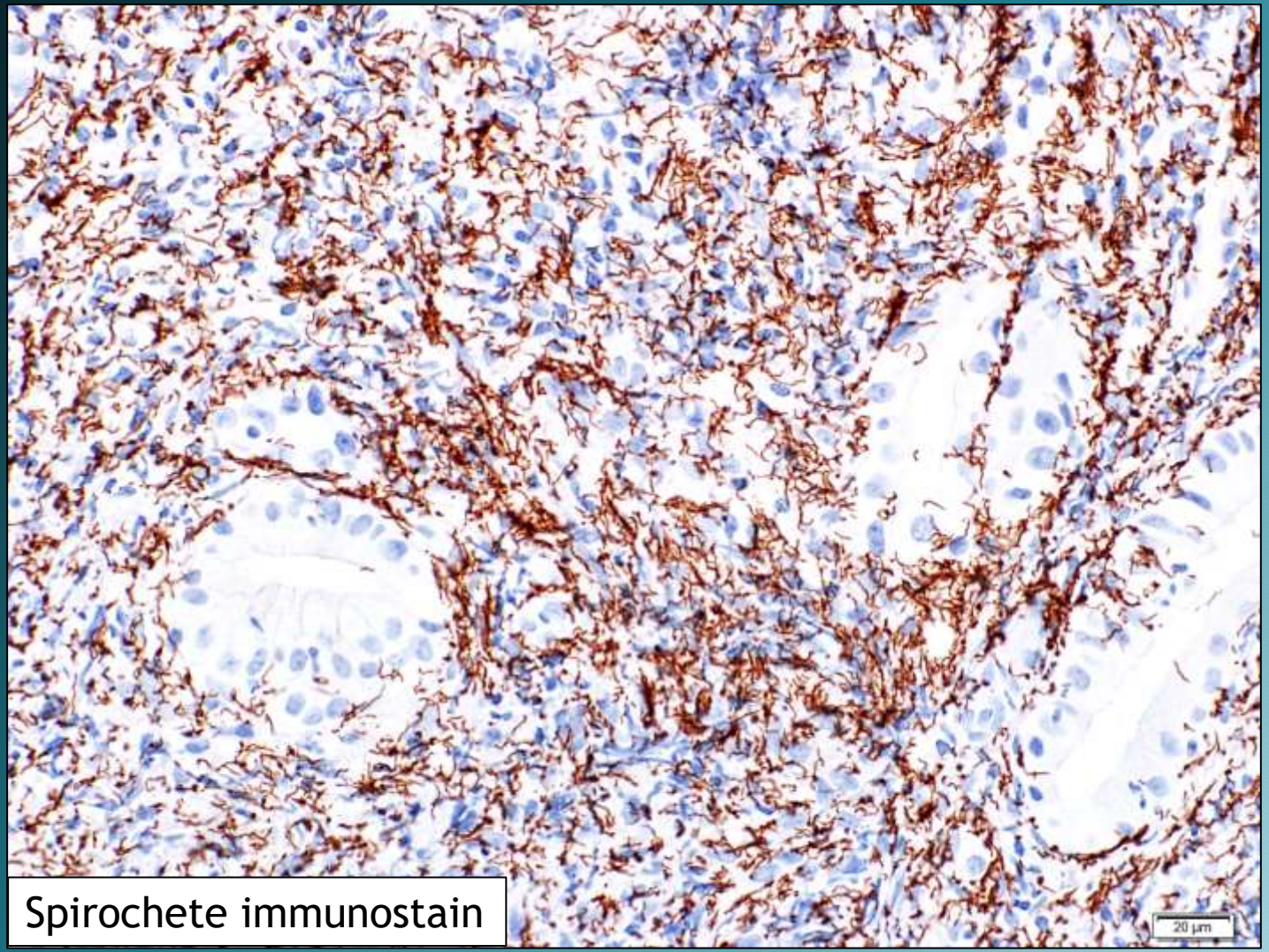


Courtesy Dr. Laura Lamps, University of Michigan, Ann Arbor, MI

Syphilis: plasma cell-rich inflammation with disproportionately less crypt injury

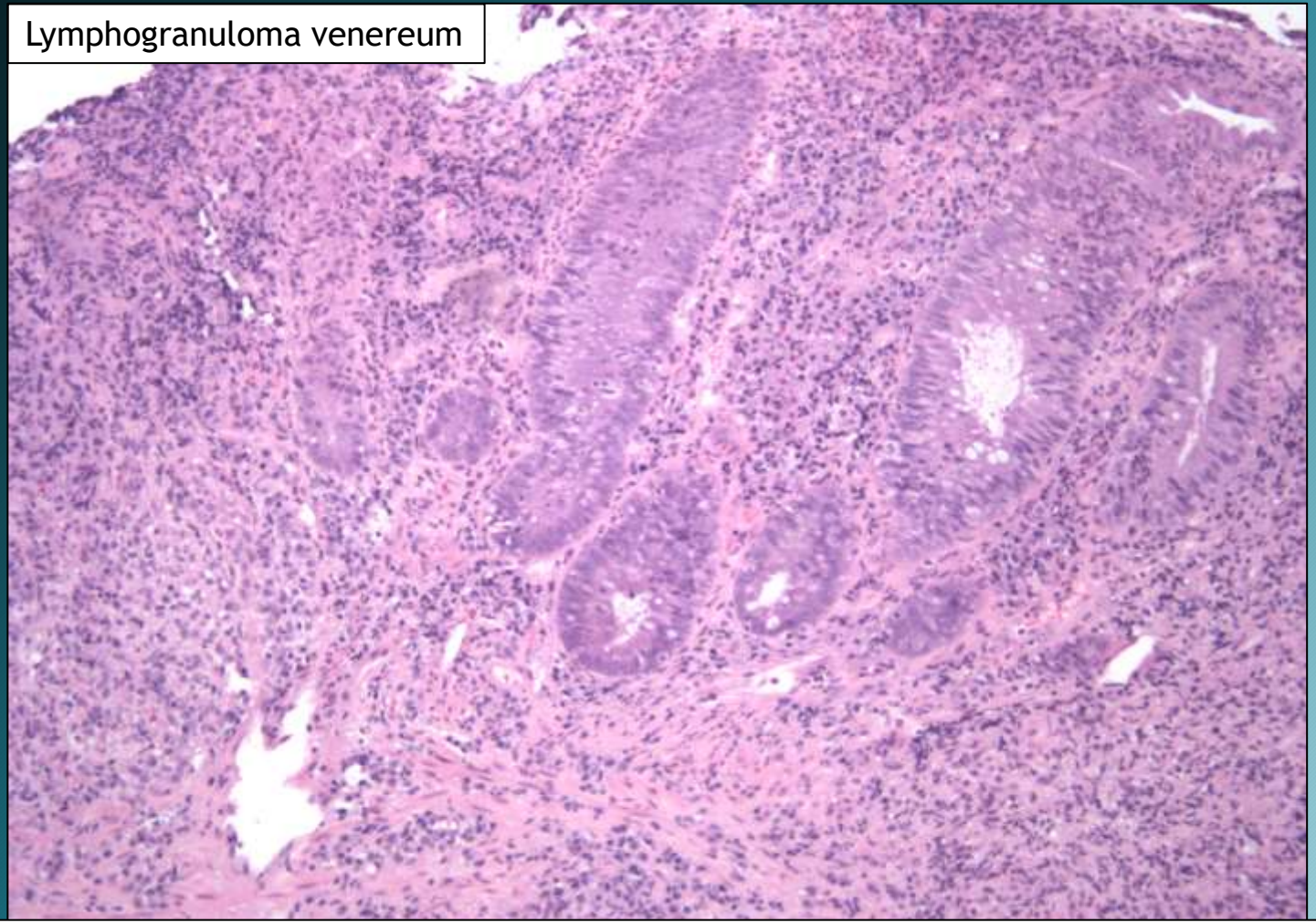


Loose macrophage aggregates



Spirochete immunostain

Lymphogranuloma venereum



Plasma cell-rich inflammation with preserved crypt architecture and minimal crypt destruction

Inflammatory Bowel Disease
Take Home Points

- Features of chronic colitis change with time and treatment, and may revert to normal
- Ulcerative colitis can show many “Crohn-like” features in biopsies
- Inflammatory bowel disease is idiopathic; always exclude other possibilities, especially when the story doesn’t fit