

Biopsy Evaluation of Non-Neoplastic Diseases of the Large Bowel: an algorithmic approach

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Medical (lung, GI, liver, kidney, skin) pathology has different challenges from tumor pathology.

- Nonspecific by definition
 - Infinite variety of insults cause finite variety of tissue reactions
 - Cirrhosis
 - Interstitial fibrosis
 - Lichenoid dermatitis
 - Villous blunting

Biopsy Diagnosis of Colitis

Clinically Relevant Diagnosis vs. Description

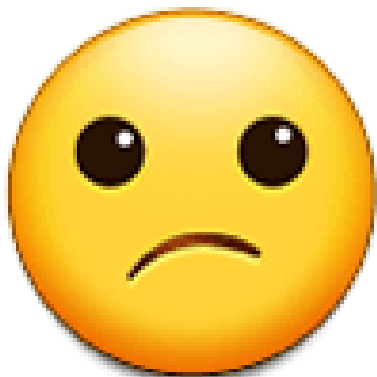
- **68%** of biopsy specimens obtained for non-neoplastic colonic disease showed an abnormal inflammatory process
- **59%** were originally given only descriptive diagnoses; reclassified upon review
- **BUT, 75%** of these could actually be classified into specific types of colitis based on morphology + available clinical data

Biopsy Diagnosis of Colitis

Clinically Relevant Diagnosis vs. Description

Description

Acute inflammation
Chronic nonspecific
inflammation
Unspecified colitis,
acute/subacute, etiology
undetermined



Clinically Relevant Diagnosis

Active colitis, suggestive of
acute infectious-type colitis
Chronic, active colitis,
consistent with.....
Histologic changes consistent
with ischemia



General Evaluation of Intestinal Mucosal Biopsies:

the question-oriented approach

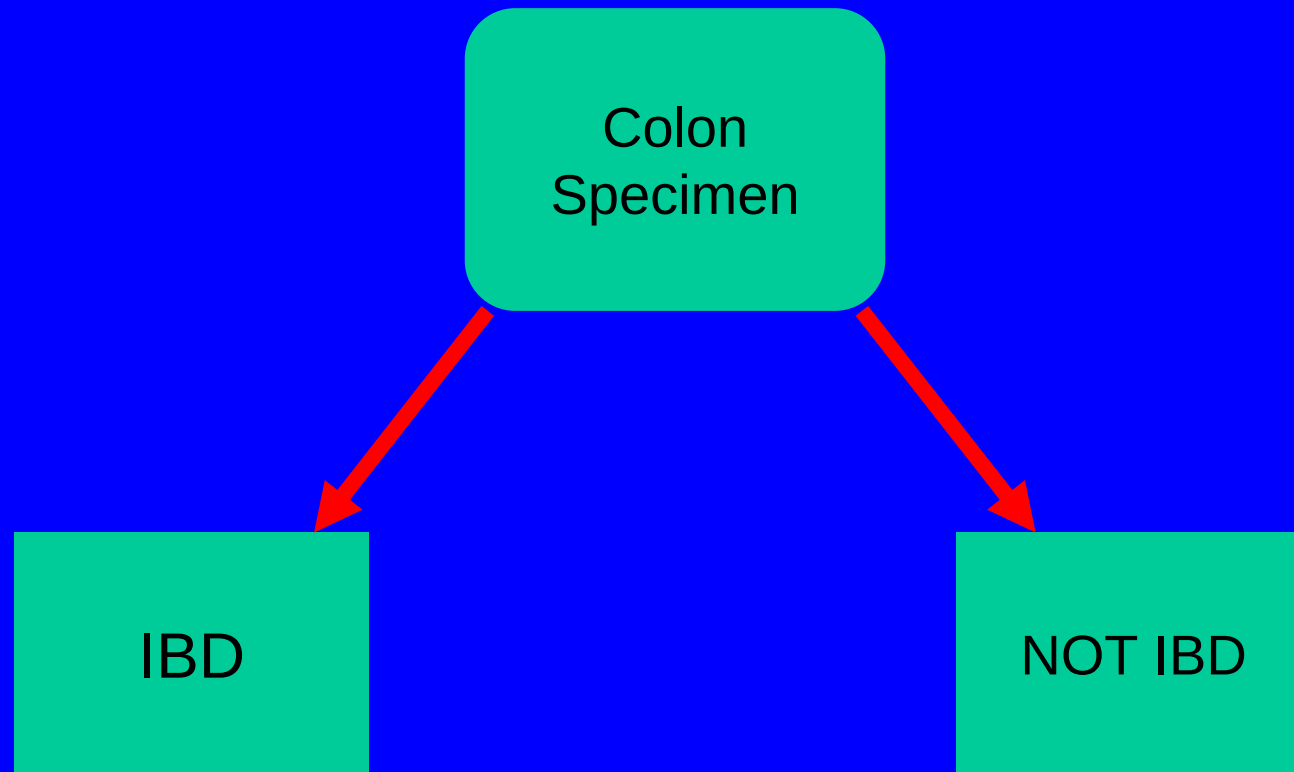
(made easier by the advent of widely accessible EMRs)

- Why was the biopsy done?
- What are the nature and duration of the patient's symptoms?
- From EXACTLY where was the biopsy taken?
- What were the endoscopic findings?

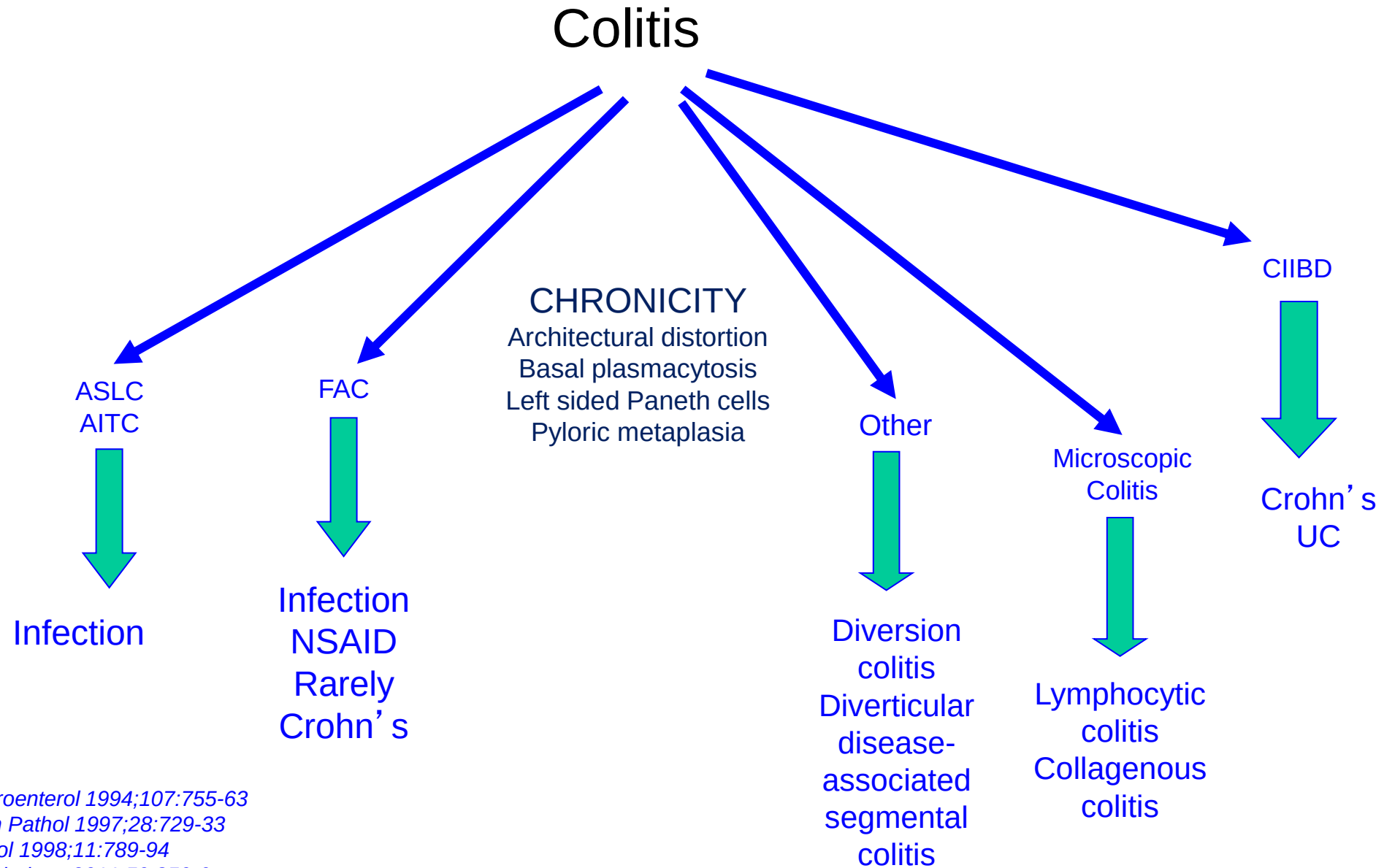
Fear not the normal biopsy!

“One of the most common complaints that endoscopists have...is that pathologists label all cases ‘mild chronic inflammation.’ The intestinal tract...is constantly bombarded with antigenic stimulation, and thus always contains mild chronic inflammation. The real question is, ‘is enough inflammation seen to explain the patient’ s symptoms?’ ”

- Riddell, Lewin, and Weinstein, Pathologist-Gastroenterologist Interaction: the changing role of the pathologist. Am J Clin Path 103: S9-S12, 1995.

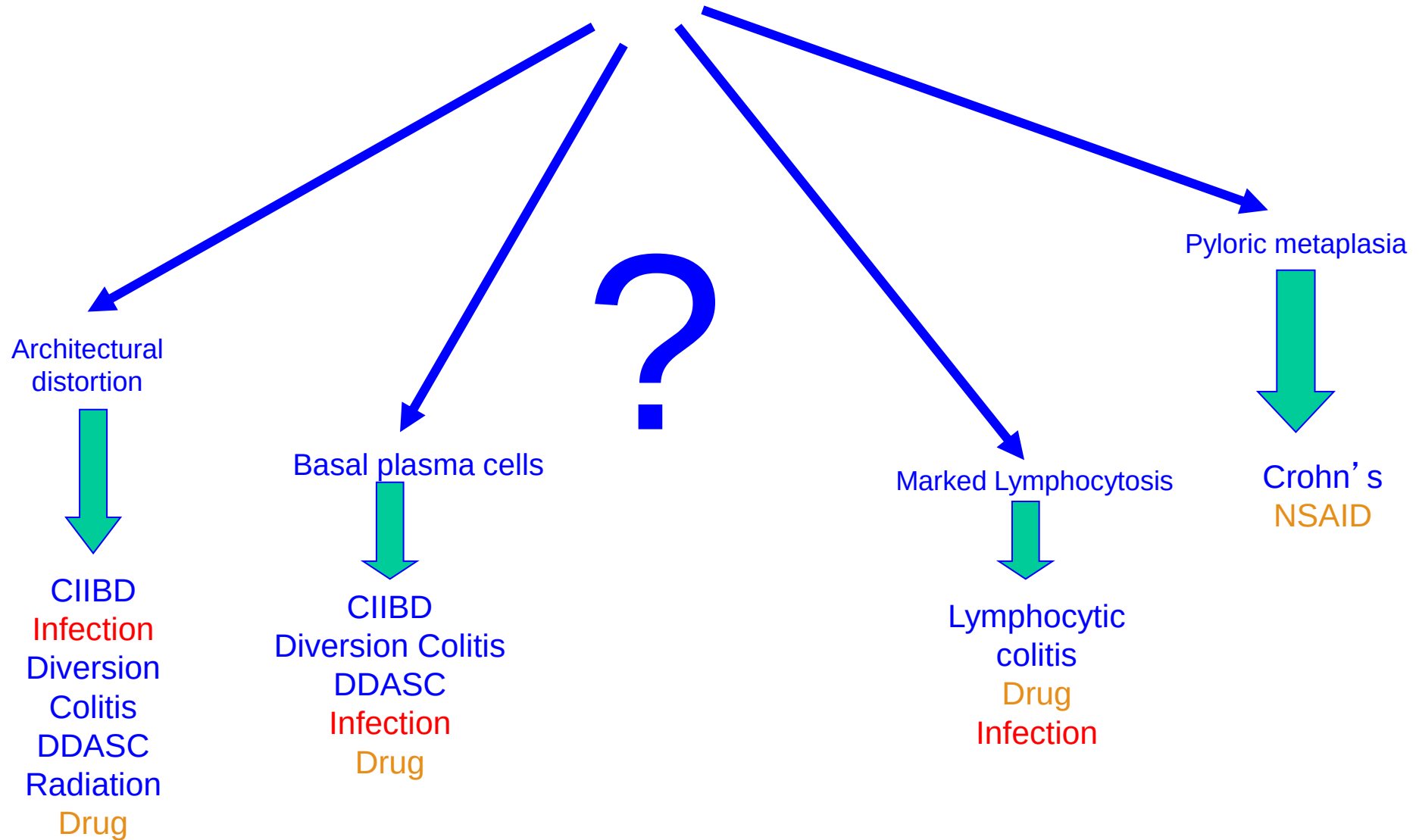


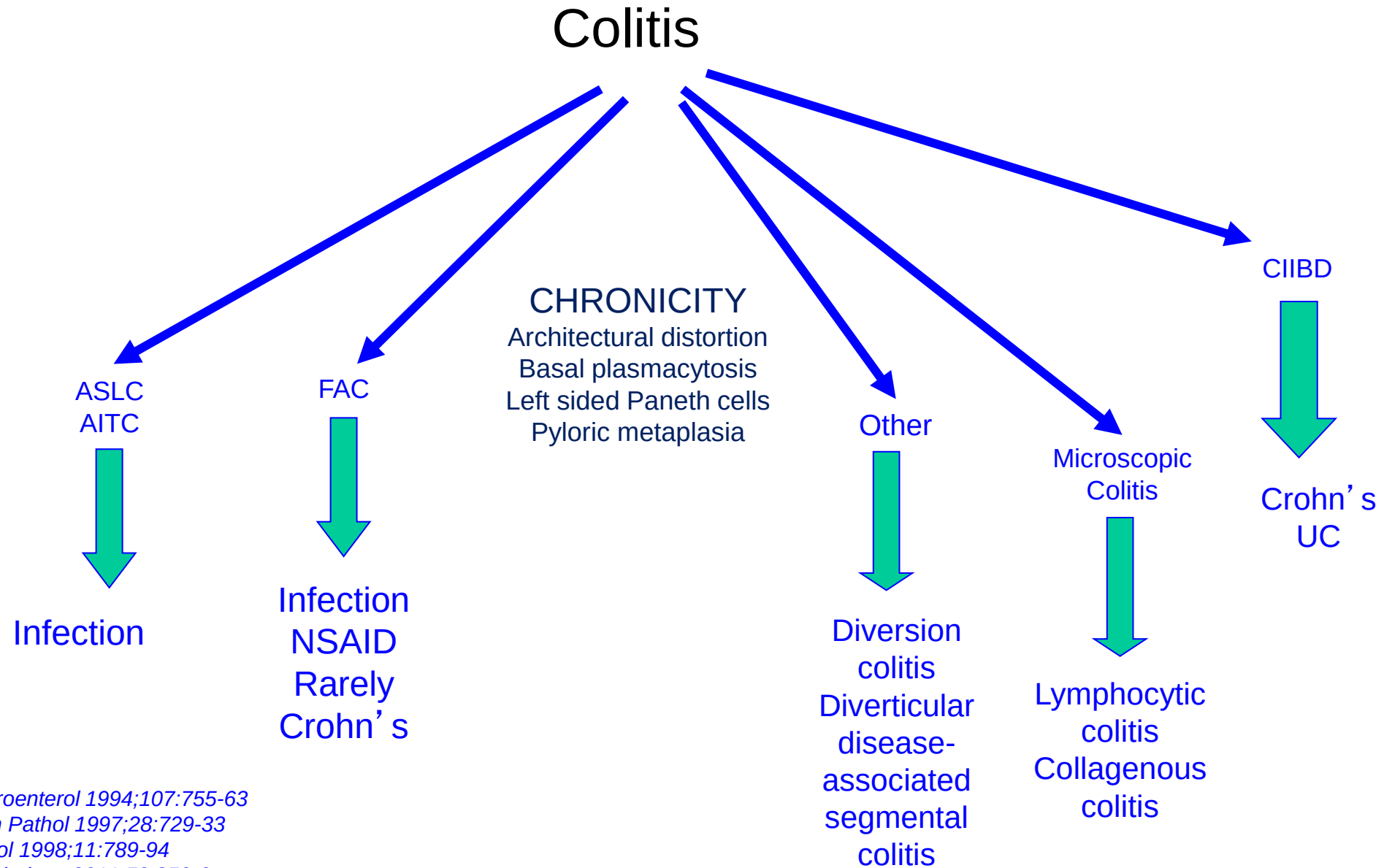
The good old days



Surawicz et al. Gastroenterol 1994;107:755-63
Greenson et al. Hum Pathol 1997;28:729-33
Volk et al. Mod Pathol 1998;11:789-94
Shetty et al. Histopathology 2011;59:850-6

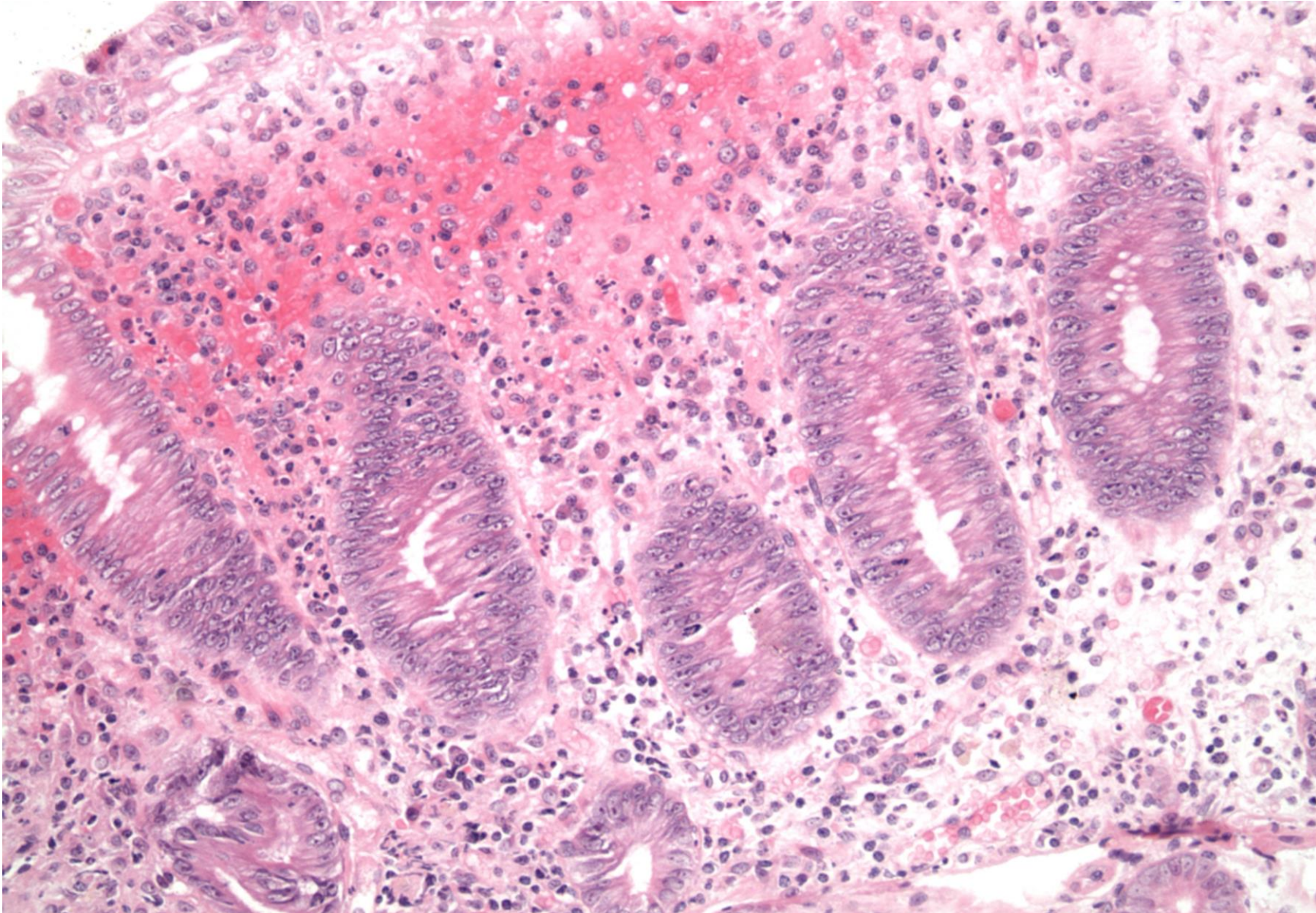
Colitis



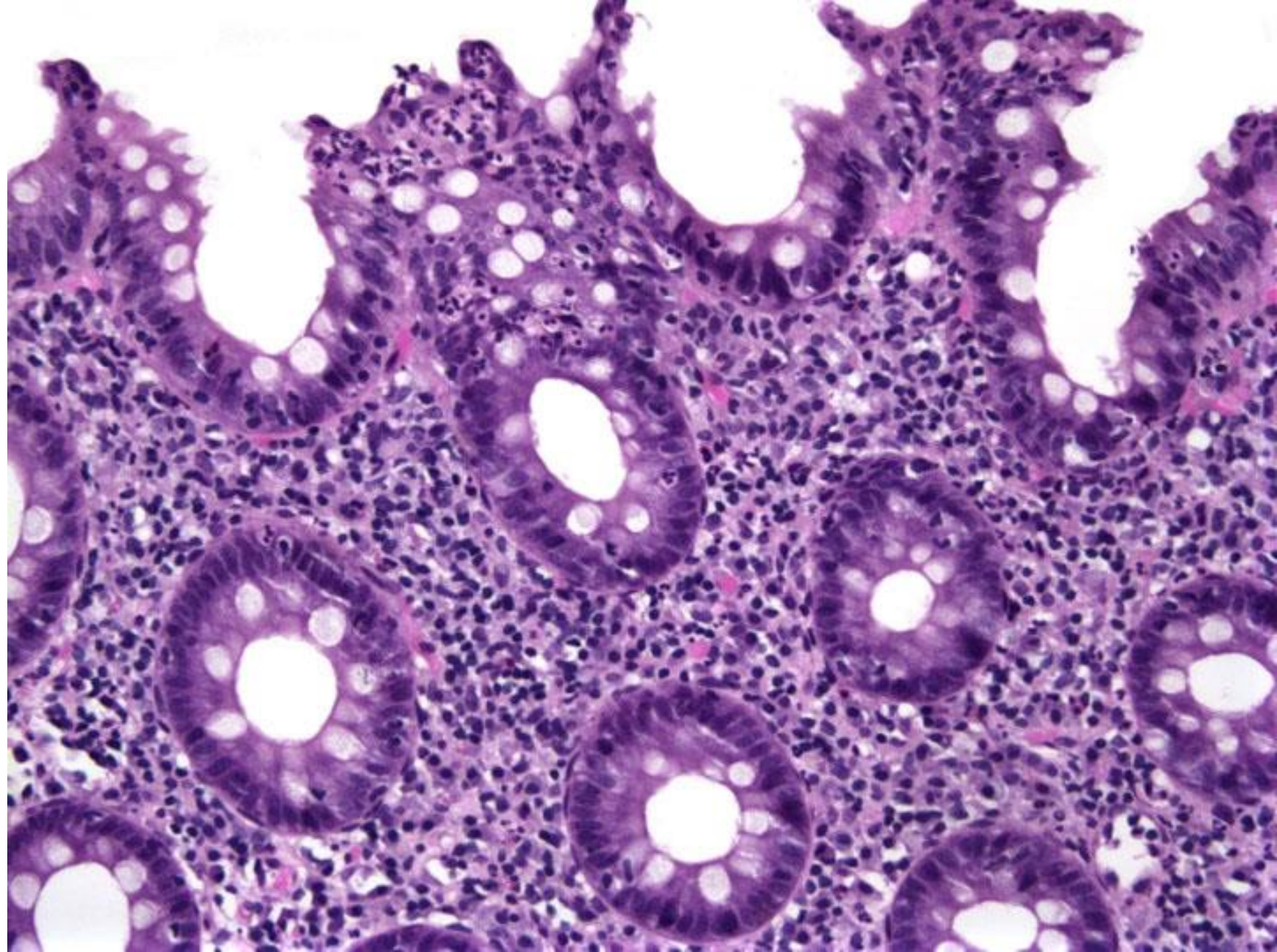


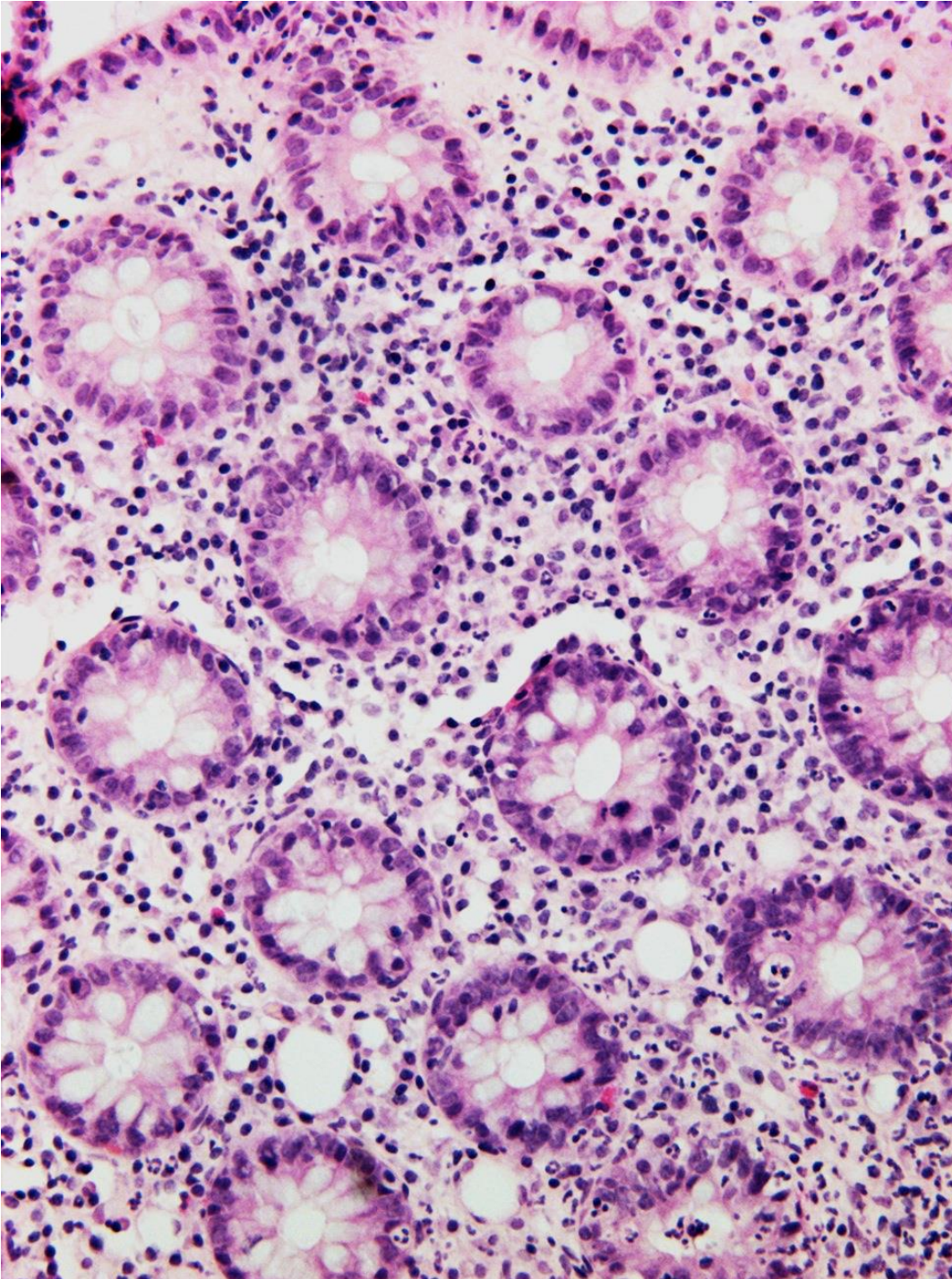
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Volk et al. Mod Pathol 1998;11:789-94
Shetty et al. Histopathology 2011;59:850-6

Acute infectious-type colitis



30 year old man with sudden onset of bloody diarrhea-right colon bxs





Focal Active Colitis

Often has:

Lamina propria neutrophils

Focal cryptitis

Surface injury

Should not have:

Architectural distortion

Basal plasmacytosis

Paneth cell metaplasia (left)

Implications of FAC

- Infection
- NSAID
- Nothing
- Occasionally Crohn's (less than 10% in adults; around 30% in kids)

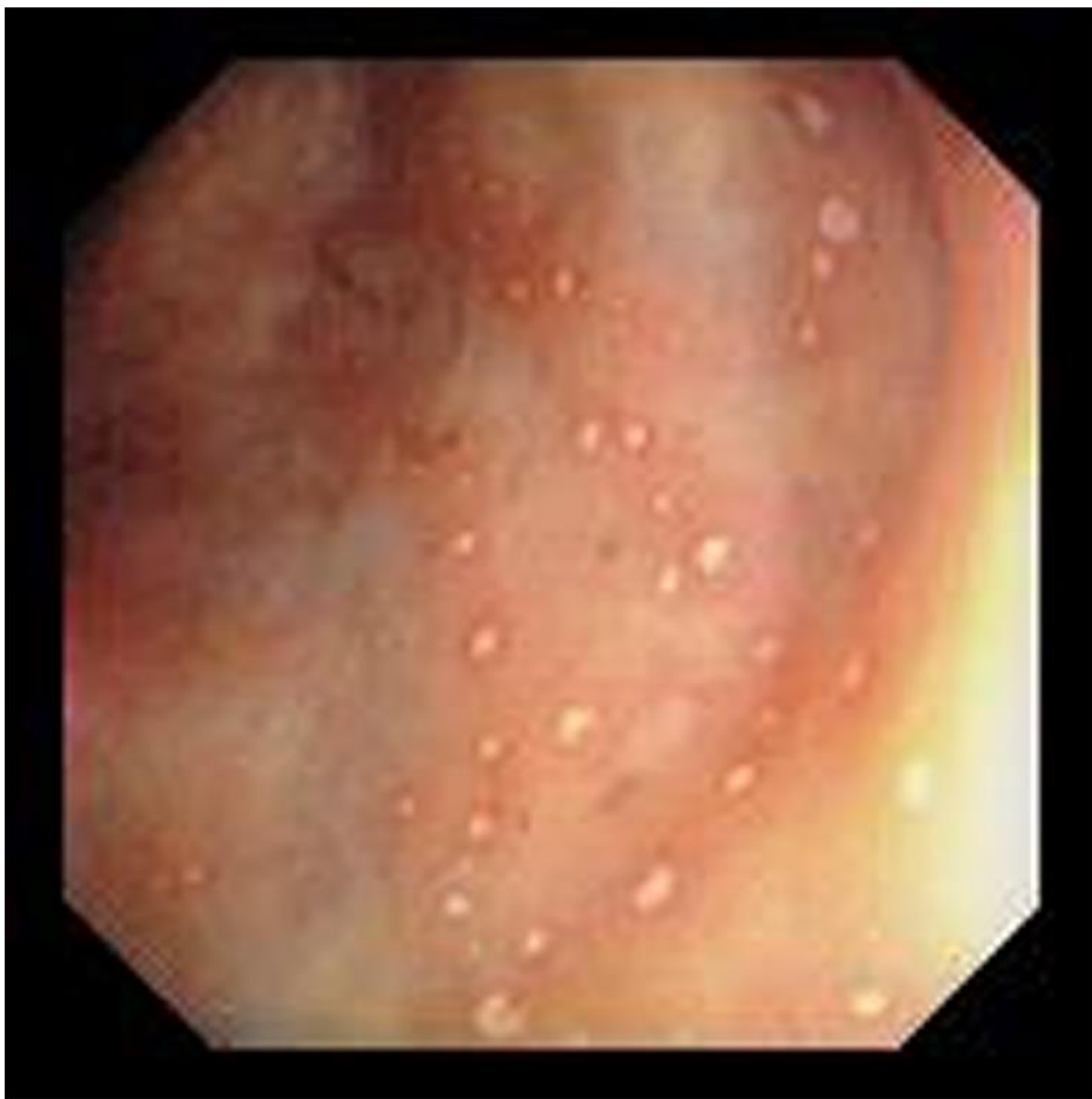
1. Greenson et al. The clinical significance of focal active colitis. Hum Pathol 28:729-33, 1997.

2. Xin et al. The clinical significance of focal active colitis in pediatric patients. Am J Surg Pathol 27:1134-8, 2003.

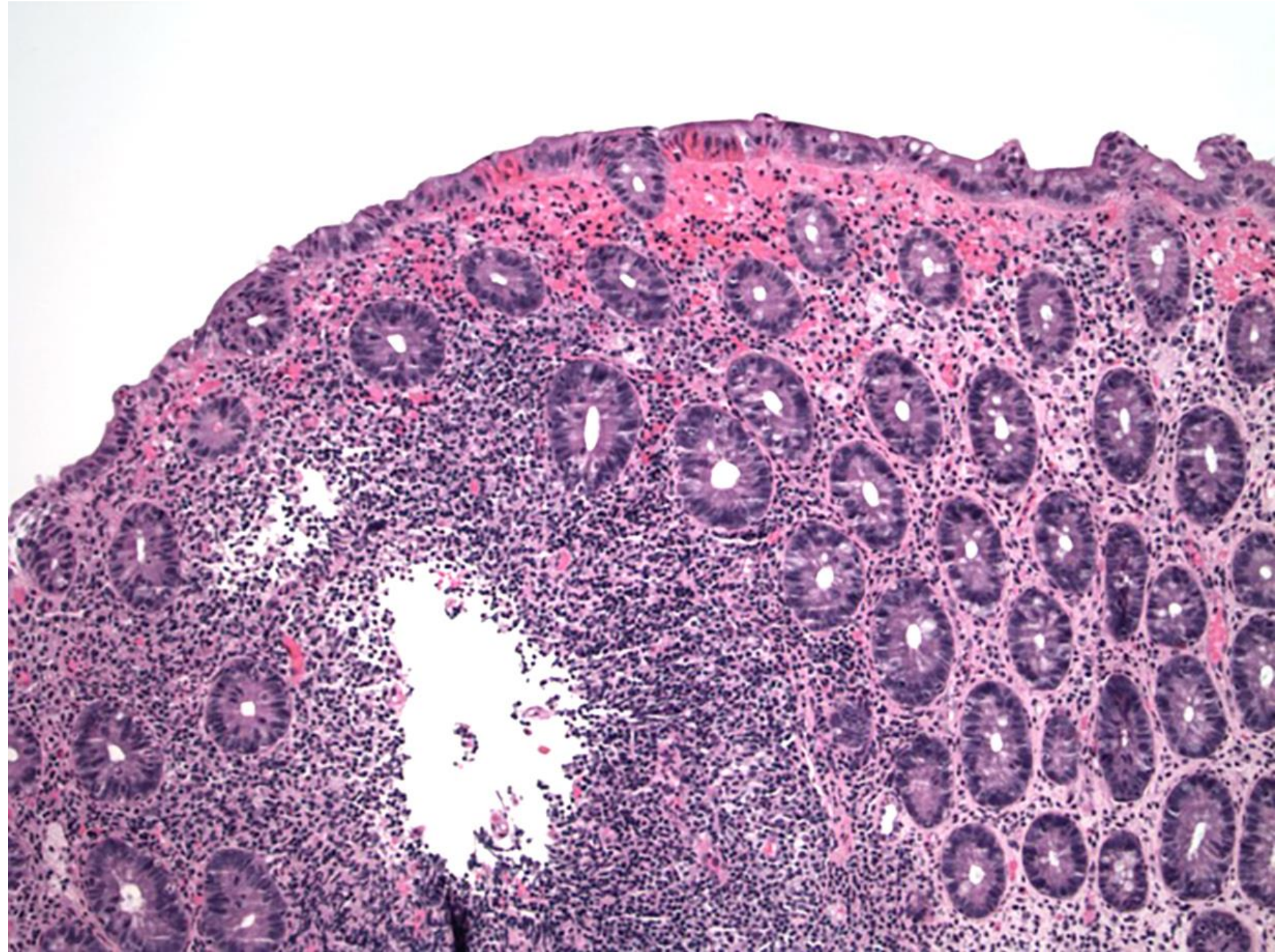
3. Volk et al. The clinical significance of a biopsy-based diagnosis of focal active colitis: a clinicopathologic study of 31 cases. Mod Pathol 11:789-94, 1998.

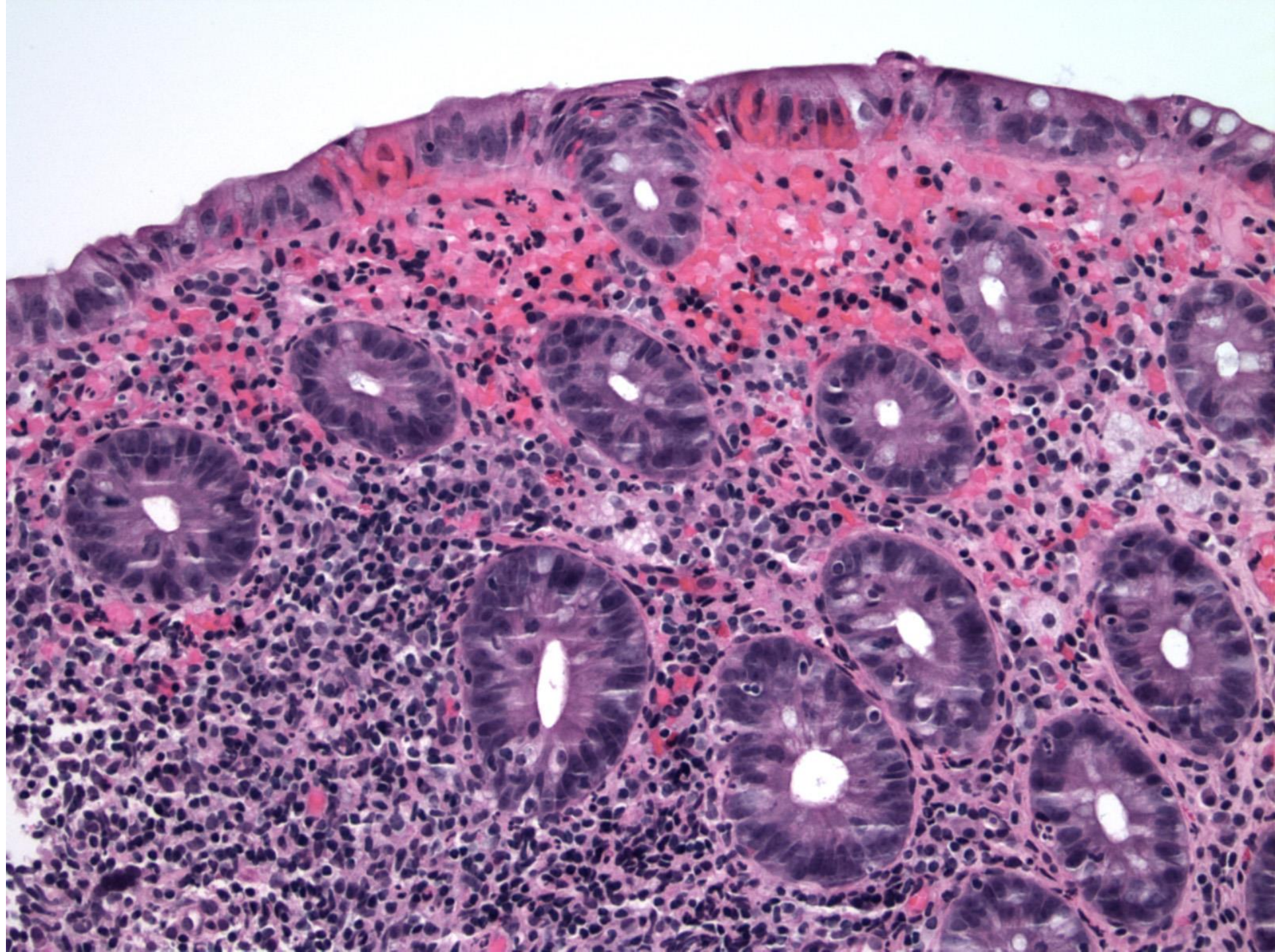
Remember the bowel prep artifacts!

- Aphthous ulcers
- Cryptitis
- Superficial hemorrhage
- Apoptotic debris at surface

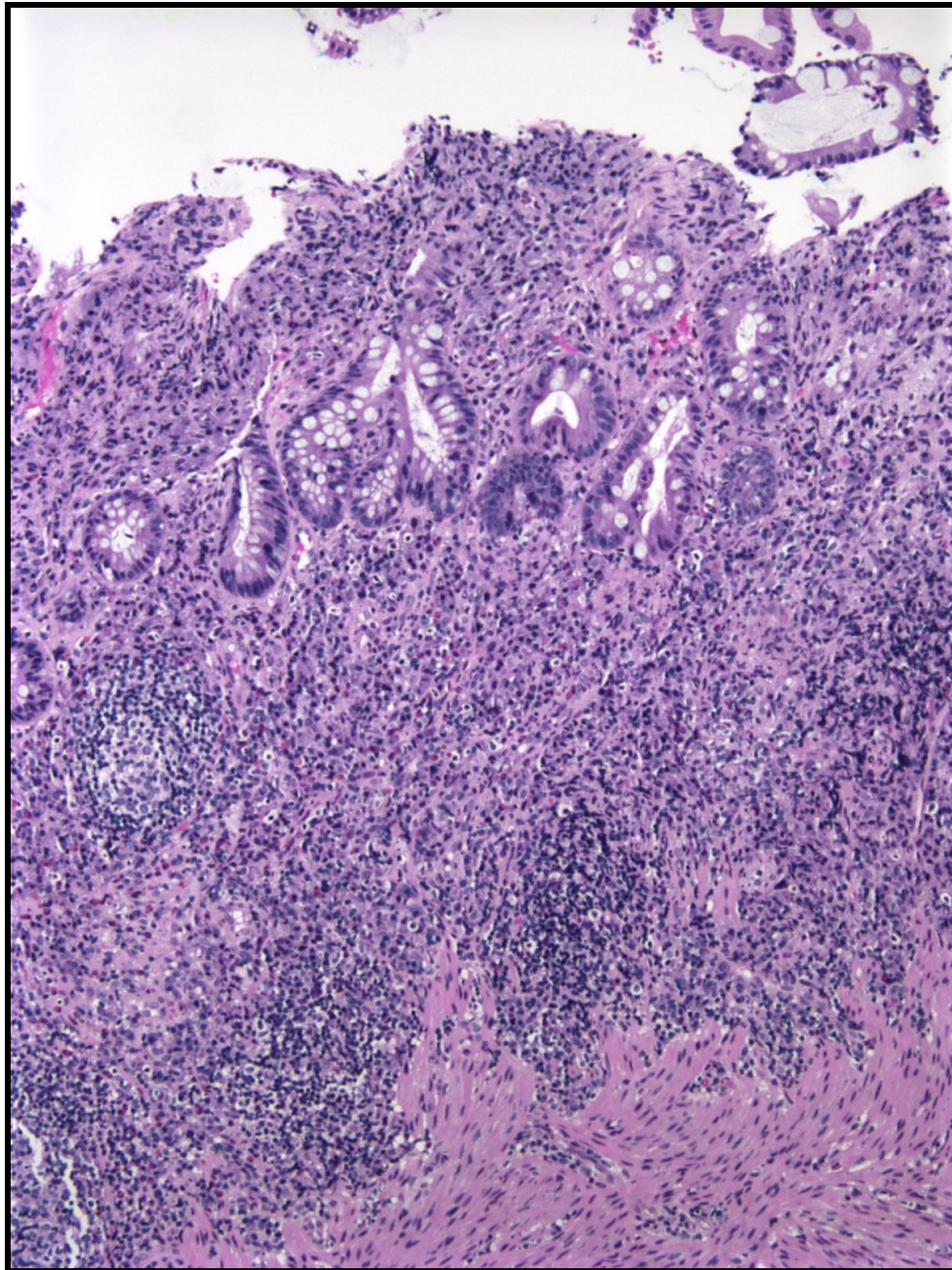


Courtesy Dr. Joel Greenson



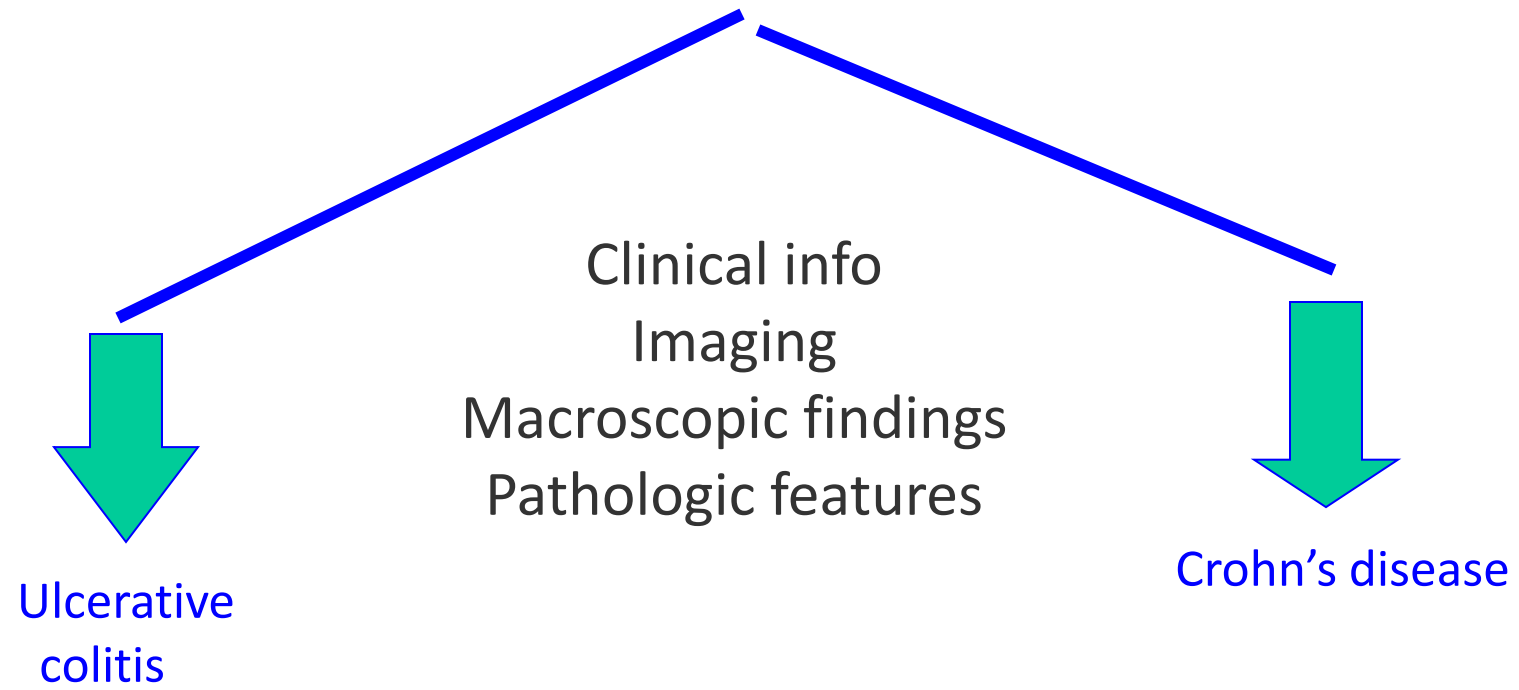






43 year old male, 3 month
history of diarrhea, crampy
abdominal pain; left colon and
rectosigmoid bxs

Chronic idiopathic inflammatory bowel disease: UC vs. Crohn's



Classic Features of Untreated Ulcerative Colitis and Crohn's Disease

Ulcerative colitis

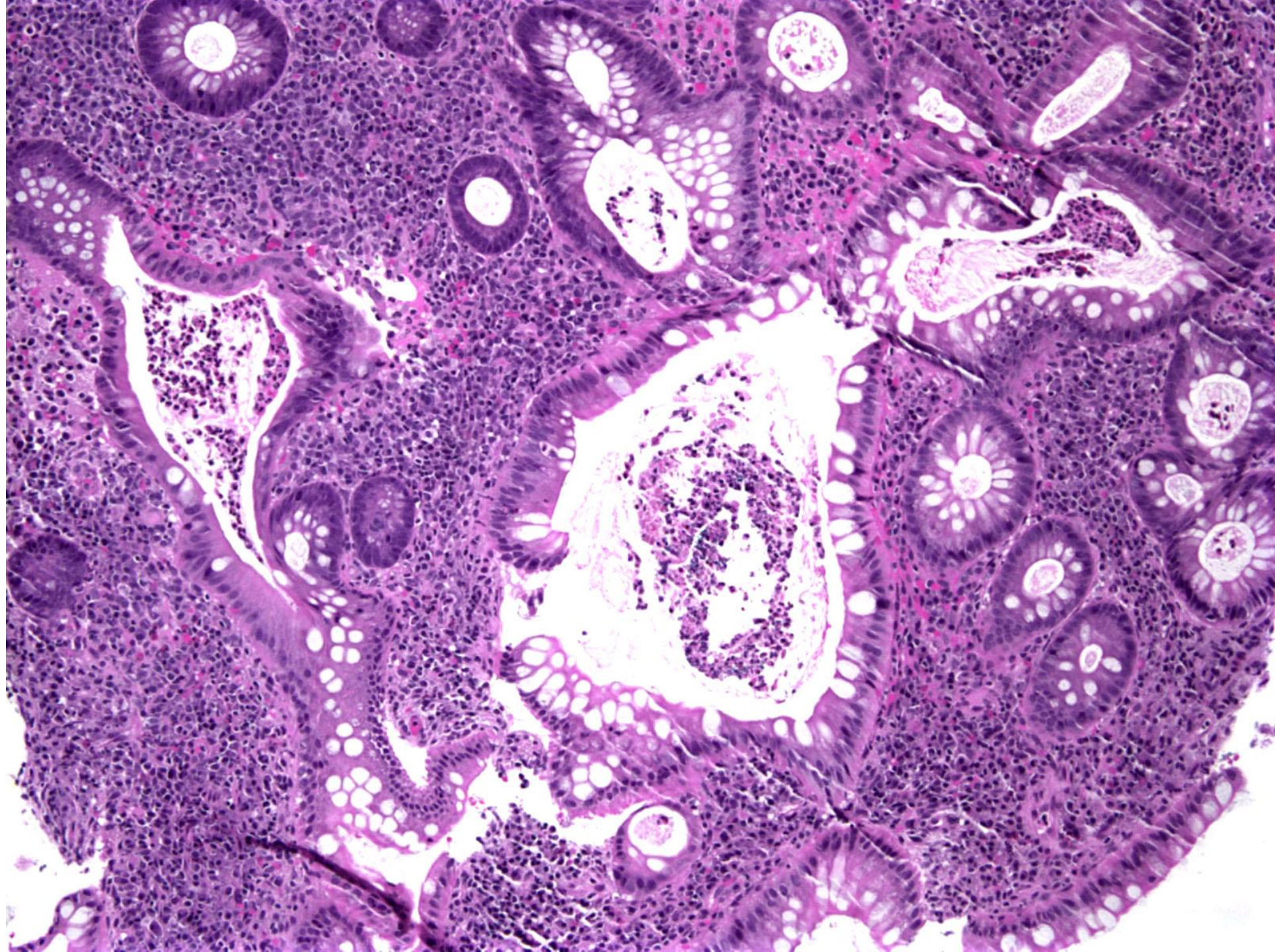
Diffuse continuous disease
Rectal involvement
Disease worse distally
Usually limited to mucosa
Ileum spared (except backwash)
If granulomas, associated with ruptured crypts

Crohn's disease

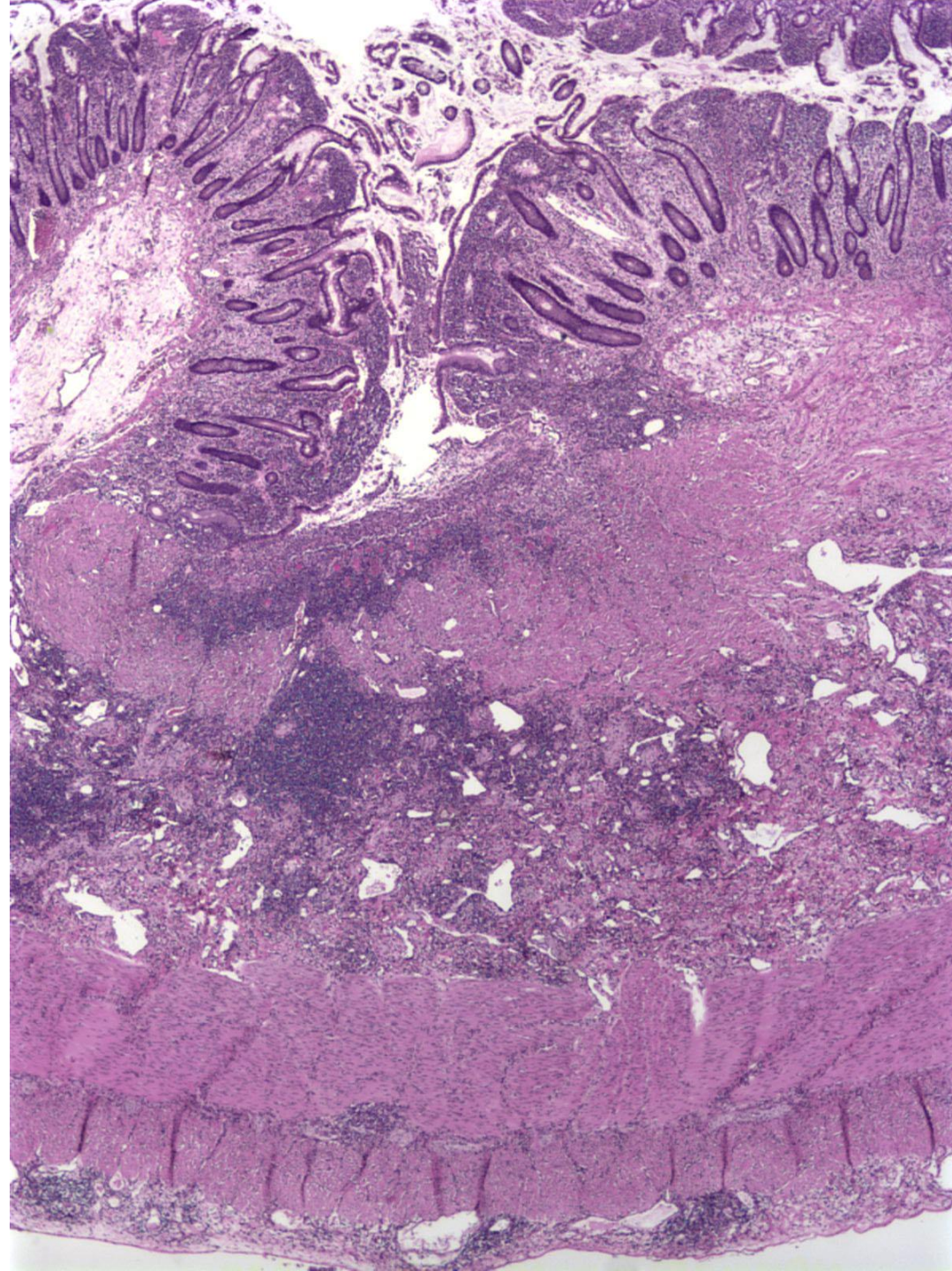
Segmental disease +/- upper tract involvement
Variable severity
Transmural lymphoid aggregates, other mural changes
Granulomas
Pyloric metaplasia
Perianal disease

Ulcerative colitis

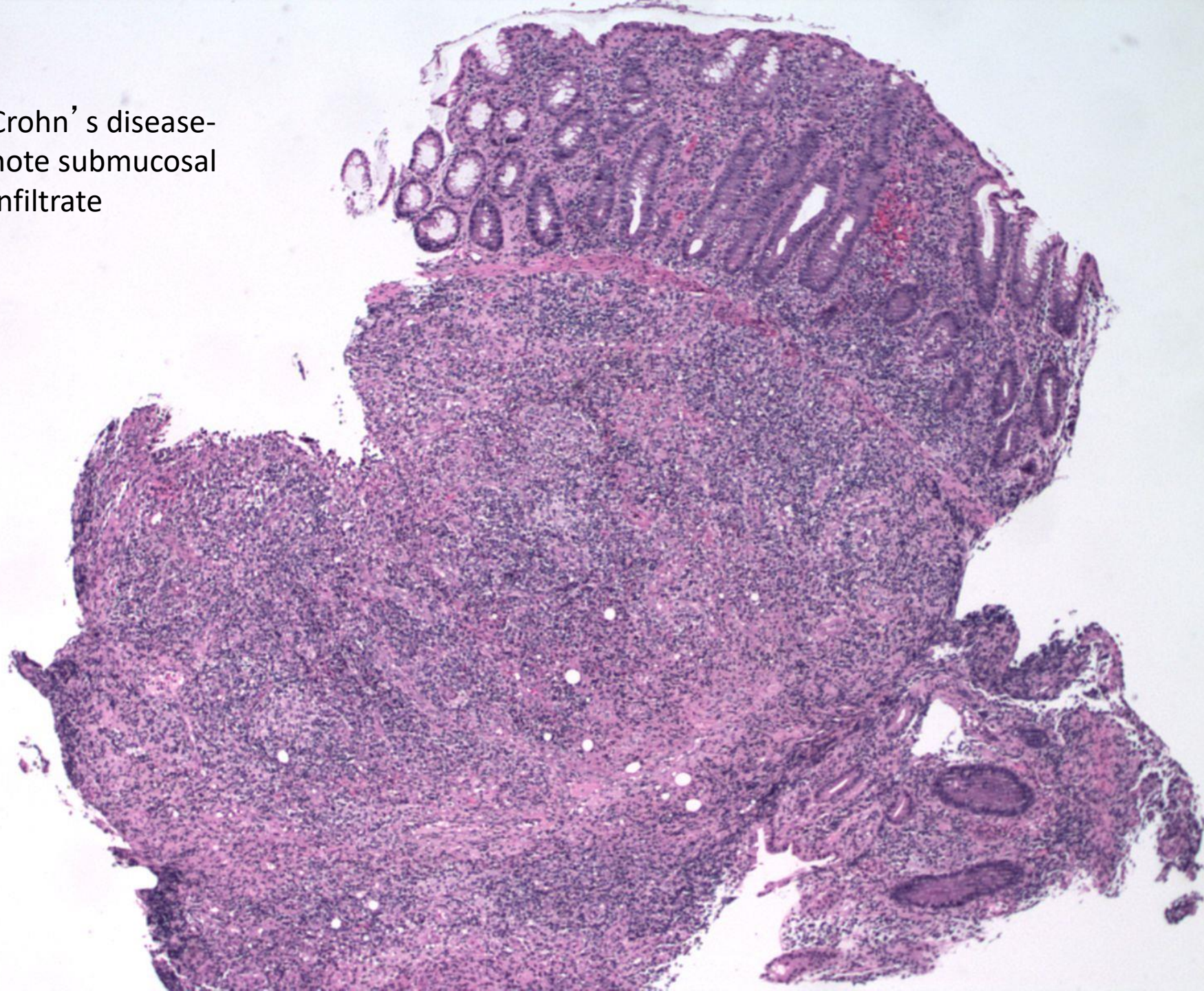


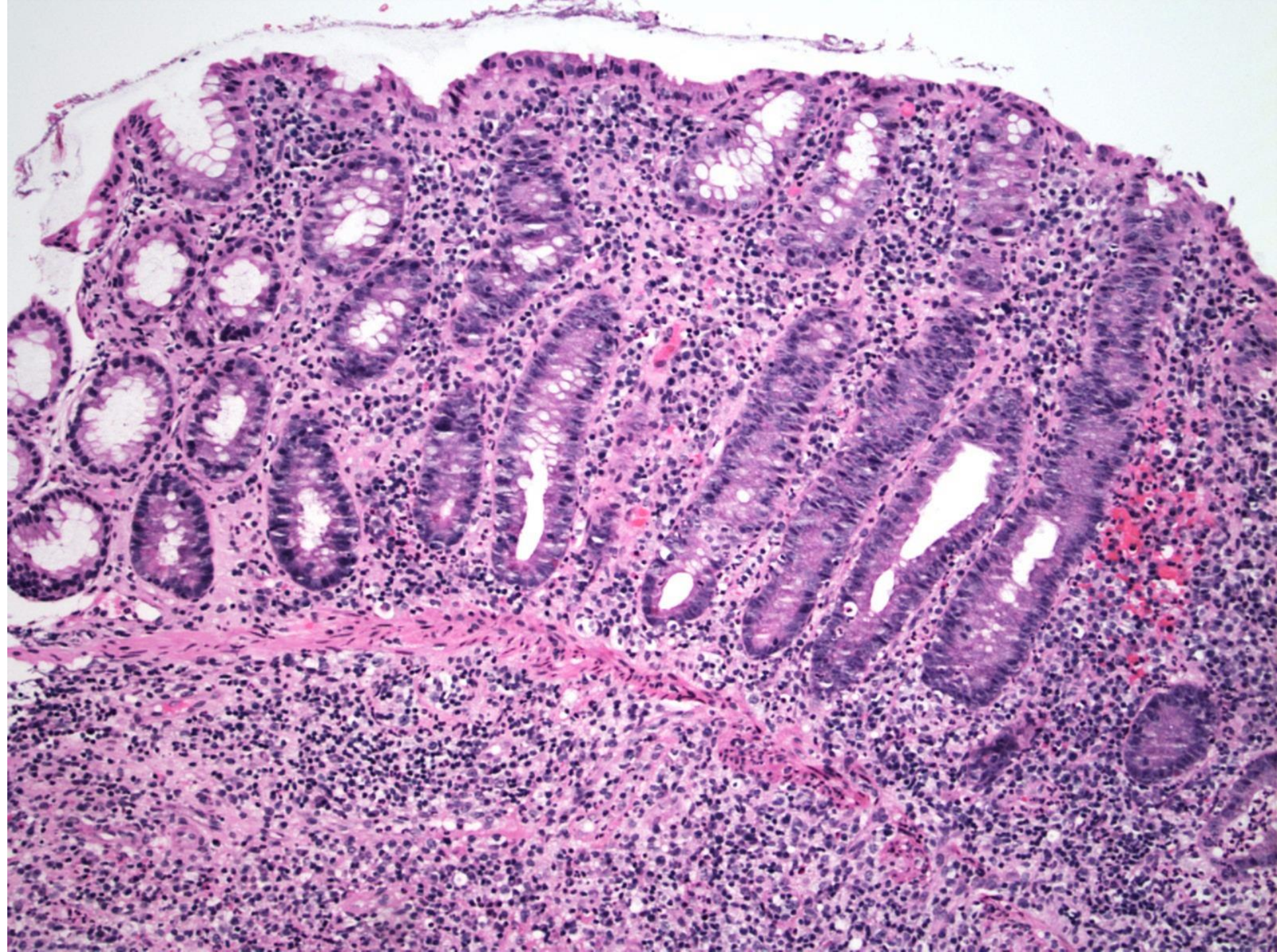


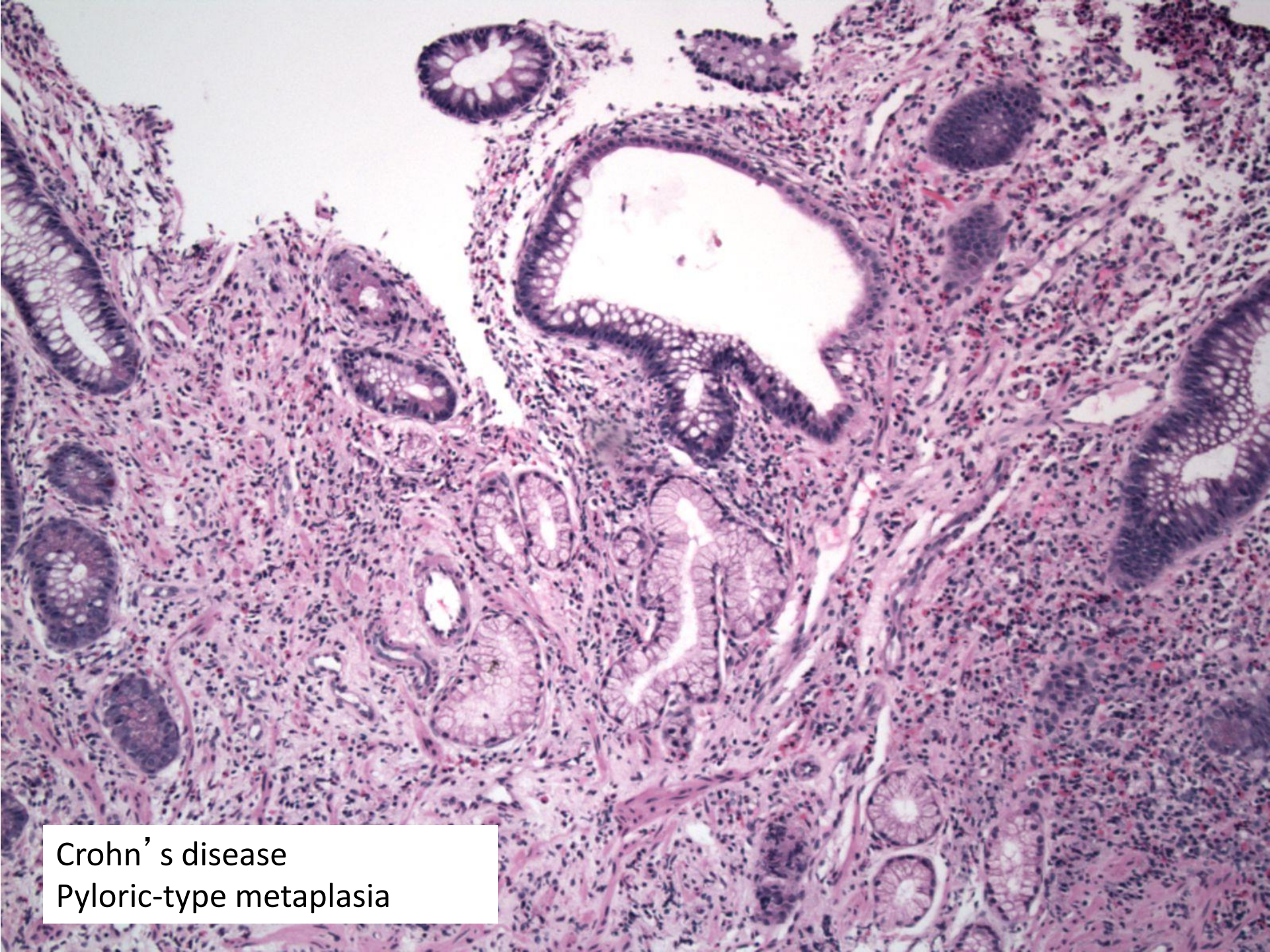
Crohn's disease



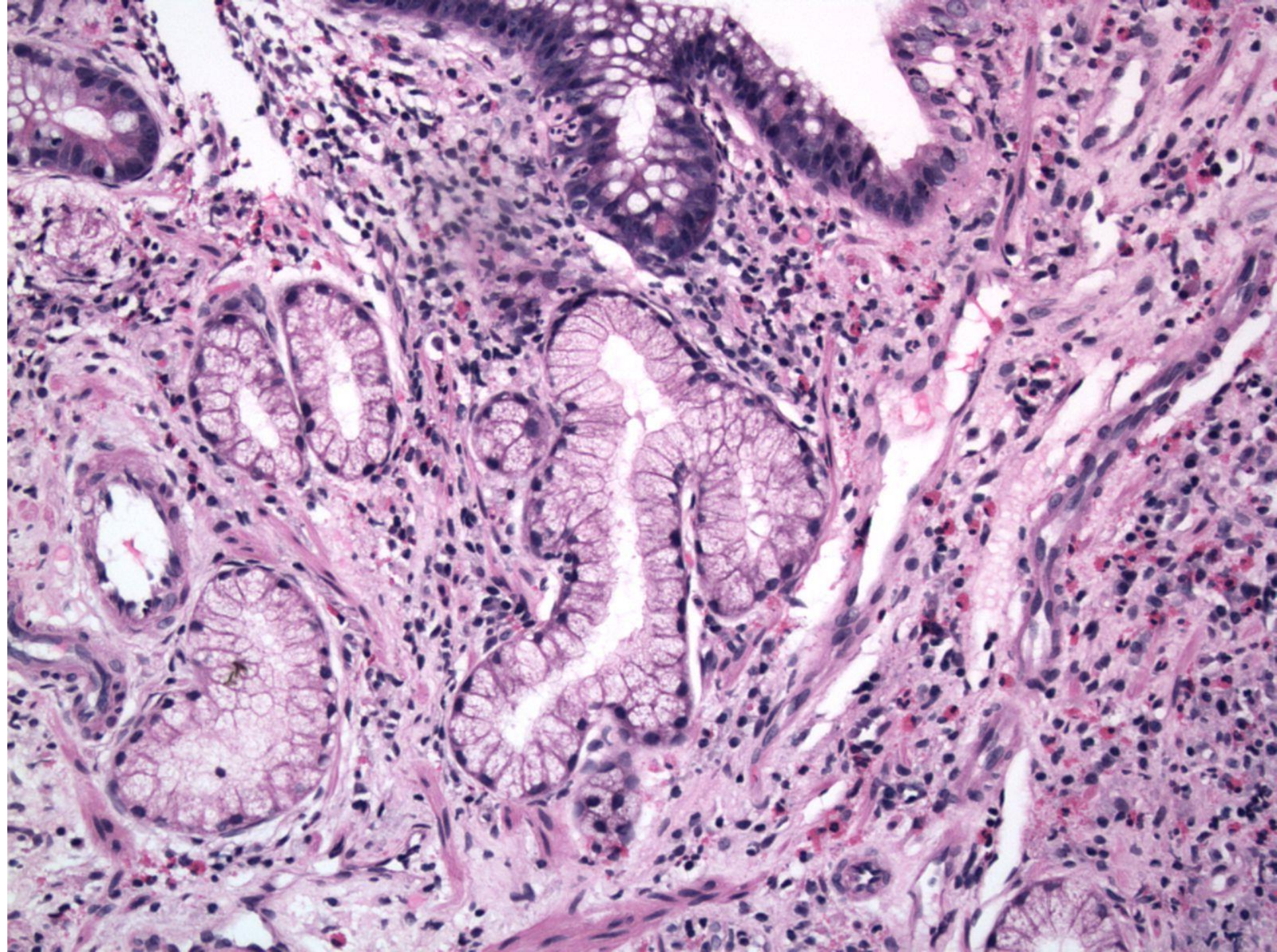
Crohn's disease-
note submucosal
infiltrate



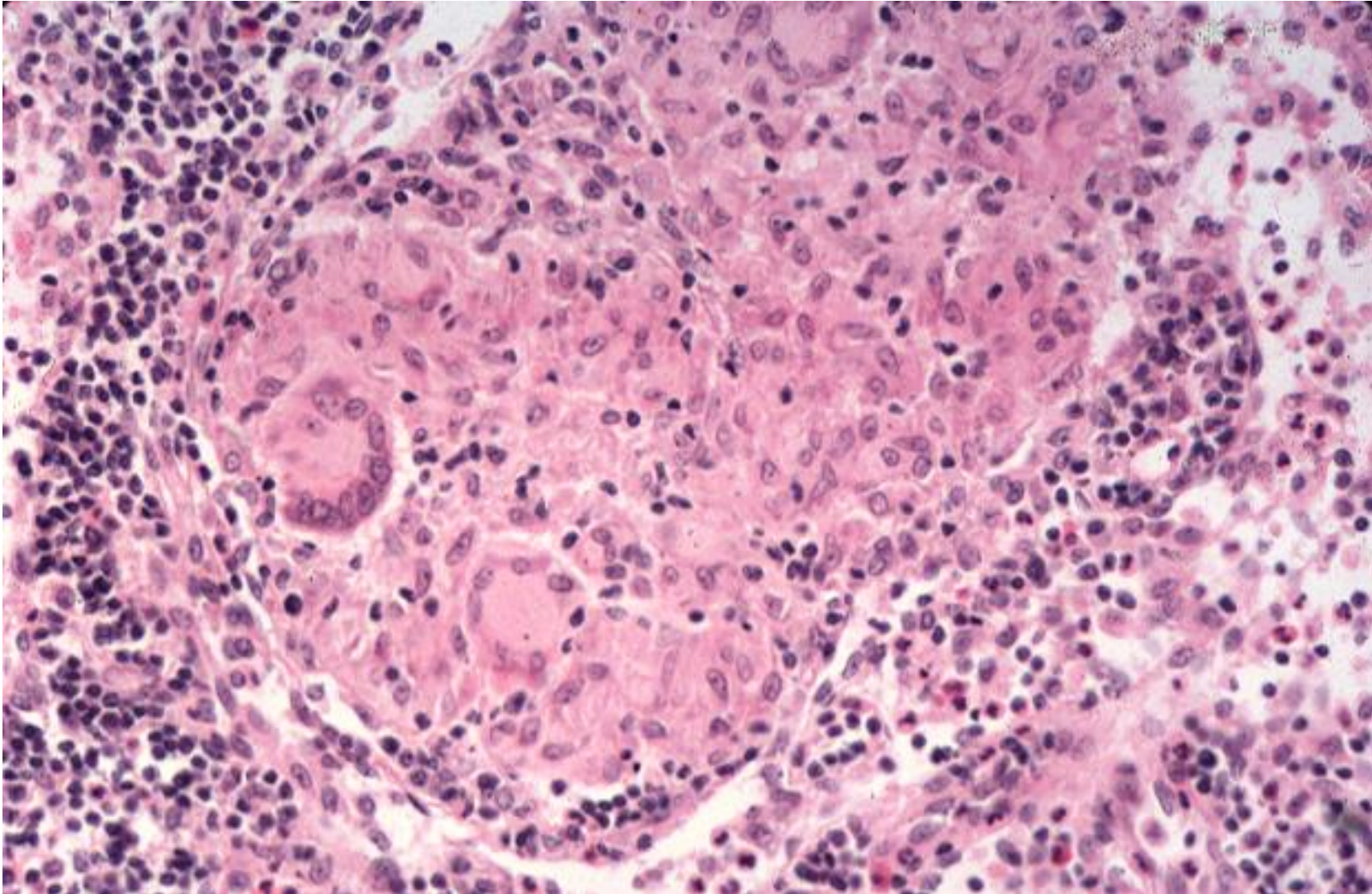




Crohn's disease
Pyloric-type metaplasia



Only if you've been living right...



Important Clinical/Endoscopic Information

Insufficient clinical/radiographic info is most common cause of error in the Crohn's vs. UC scenario

Clinical

Family hx, PSC, symptoms/signs,
prior surgery, perianal disease

Radiologic

Segmental vs diffuse, SB involvement,
strictures, fistulas, wall thickness

Endoscopic

Type/appearance of ulcers, distribution
of disease, appearance of ileum

Pathologic

Prior biopsies (and resections), ideally pre-treatment

Ulcerative Colitis Variants

(things we used to call Crohn's Disease)

- Patchy Distribution
 - Left sided UC with peri-appendiceal disease (the cecal patch)
 - After therapy there is often uneven healing
- Rectal Sparing
 - Steroid enemas
 - Burnout in long-standing disease
 - Rare cases can present with a normal rectum
- Upper tract involvement



Courtesy Dr. Joel Greenson

Ulcerative Colitis

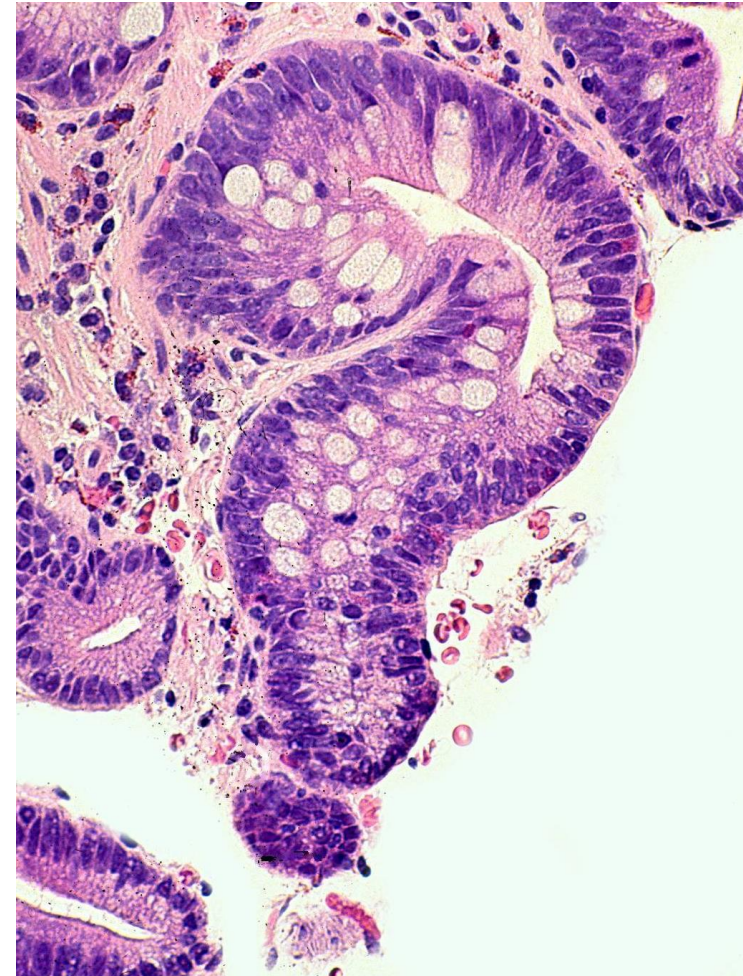
Extra-Colonic Disease?

- Gastritis
 - Focally enhanced gastritis (FEG) thought to be typical of Crohn's.
 - 2 recent studies found 12% and 50% of UC patients had FEG compared to 43% and 35% of CD patients.
- Duodenitis
 - Over the last 5 years many case reports have found diffuse duodenitis in patients with resection proven UC
 - Several of these patients also had gastritis
 - Pts tolerated endorectal pull-through procedures

Crohn's Disease

Can you diagnose it in biopsies?

- Small bowel ulcers/erosions
 - NSAIDs, Ischemia
- Pyloric gland metaplasia
 - NSAIDs
- Patchy or focal distribution
 - UC, especially after treatment
- Granulomas
 - Not due to mucin, TB, Yersinia



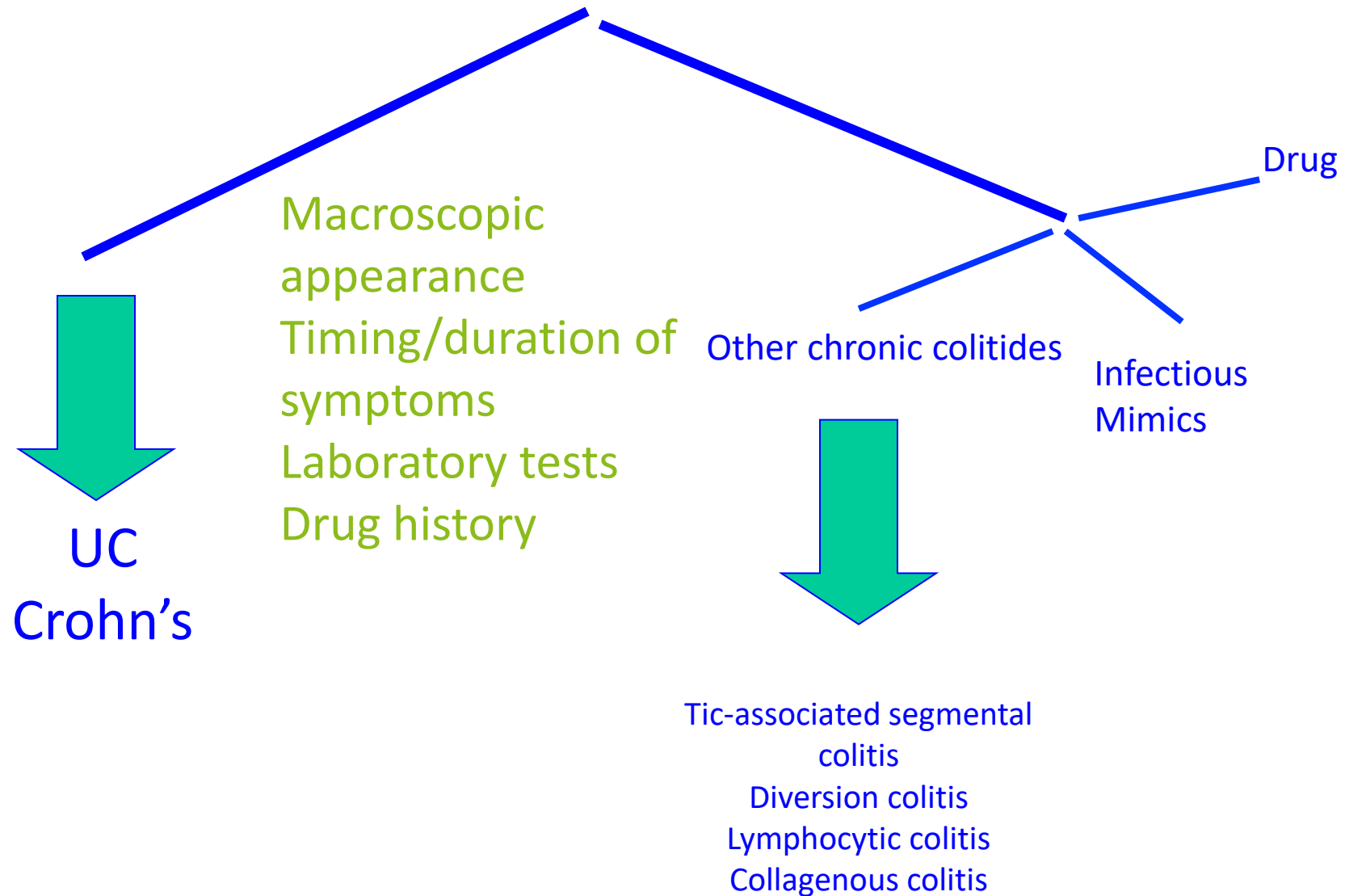
UC vs. Crohn's on biopsy: how far can you go?

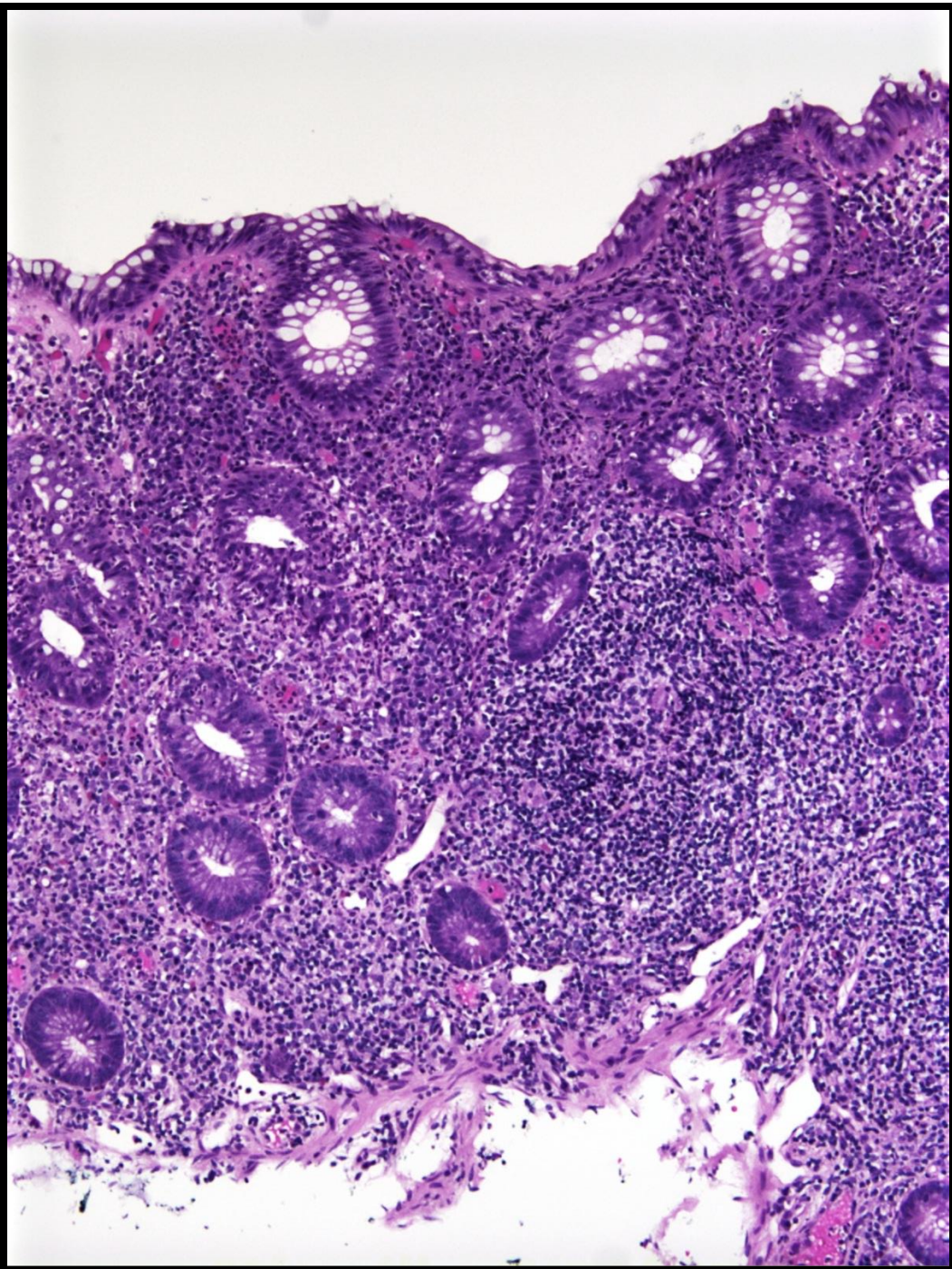
- Depending on quality of other information, may get to UC or CD
- If not, if you can get to CIIBD, then the drugs are the same
 - Most unclear cases end up acting like UC, and do well treated that way
- Don't use indeterminate colitis as a diagnosis
 - Not a disease entity; no diagnostic criteria
 - Interim terminology
 - "CIIBD, unclassified" or a comment is preferred



This lecture has worn me out. When will be done?

Colitis with features of chronicity

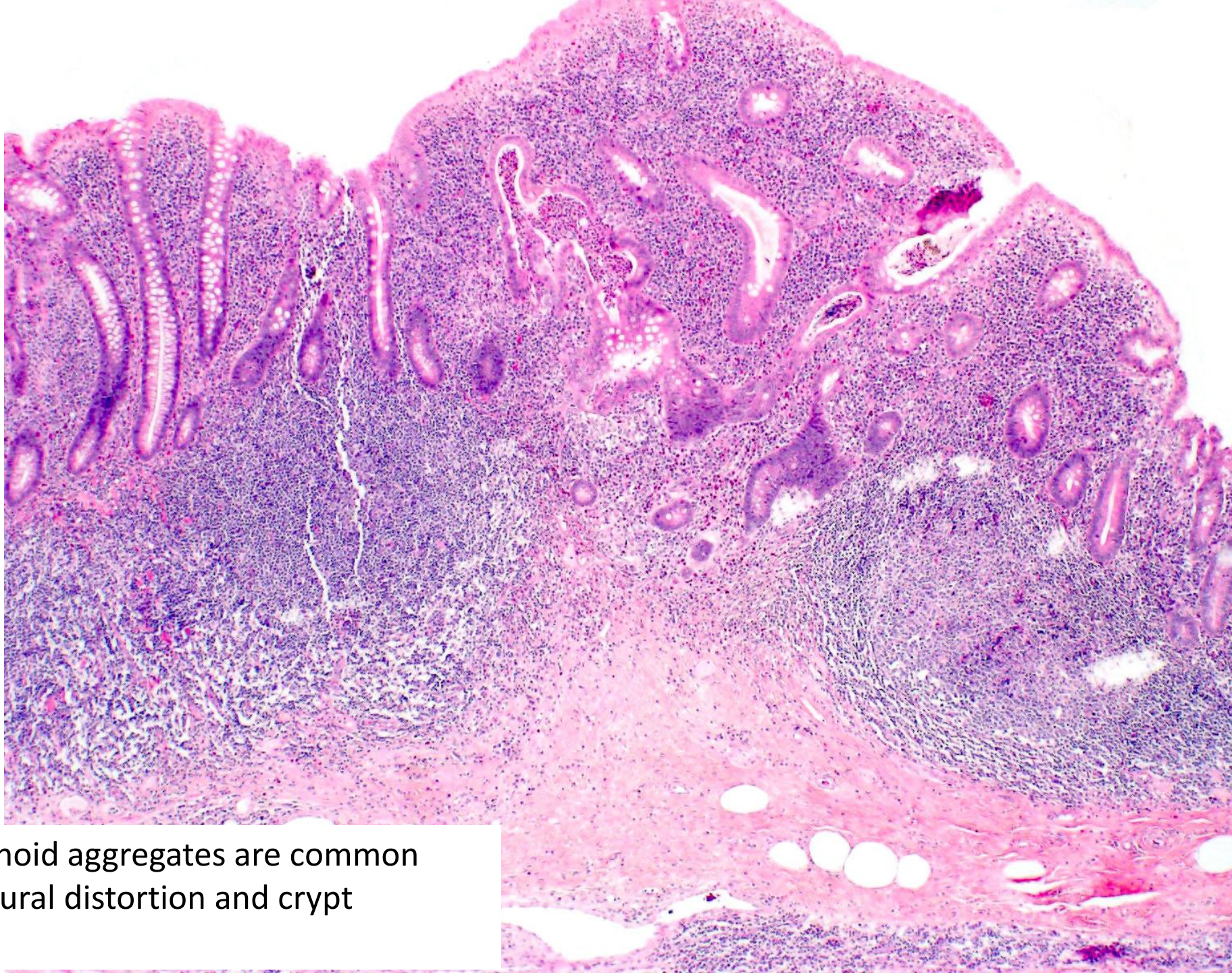




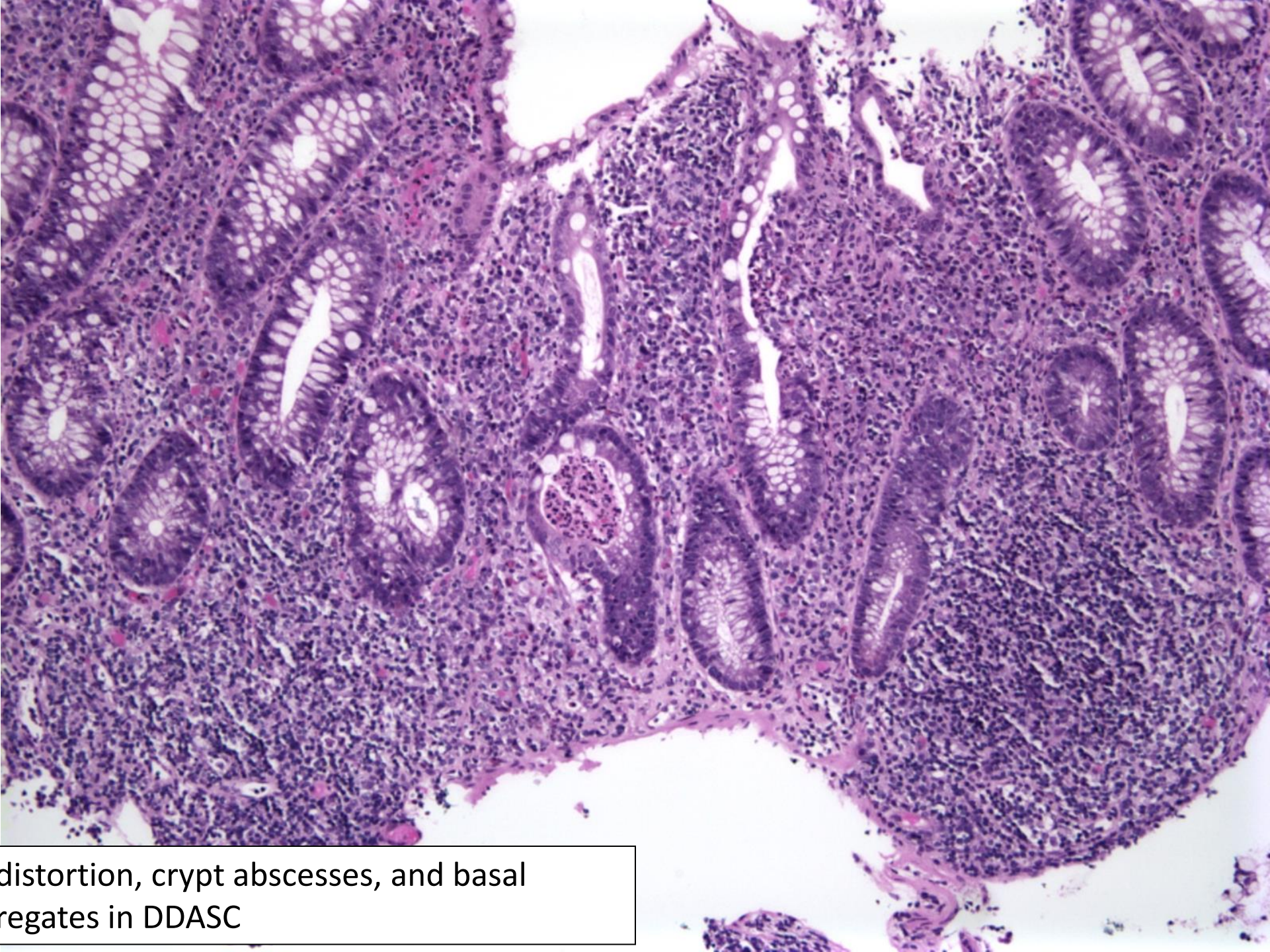
65 year old man with
diarrhea, crampy abdominal
pain; sigmoid biopsies

Diverticular-Disease Associated Segmental Colitis

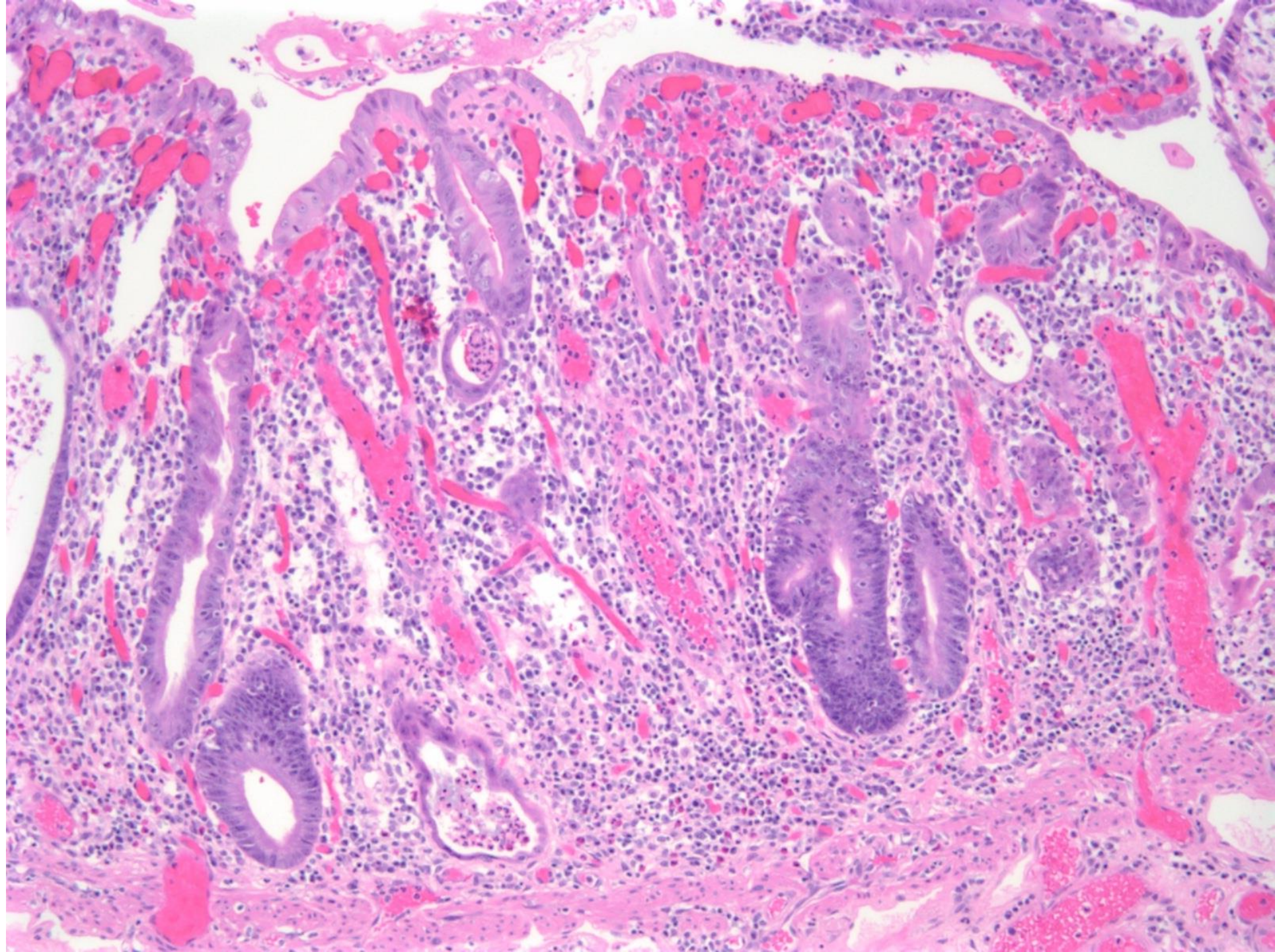
- Primarily elderly patients
- Hematochezia, mucus, cramps
- Colonoscopy:
 - Patchy or confluent hyperemia
 - Accentuated on crests of mucosal folds
 - Mucosal granularity
 - Distribution
 - Descending colon and sigmoid, in area of tics
 - Rectum is virtually always spared!



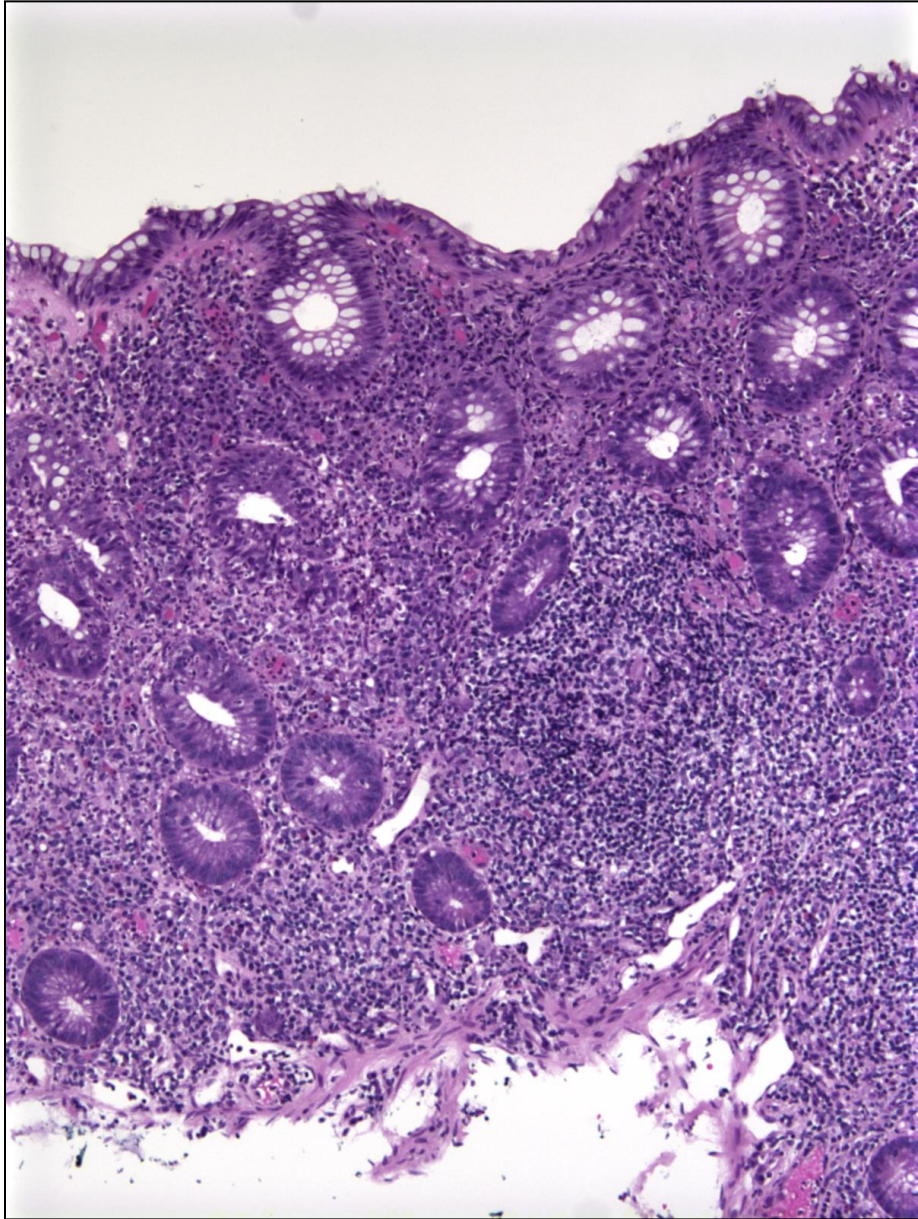
Mucosal lymphoid aggregates are common
Note architectural distortion and crypt
abscesses



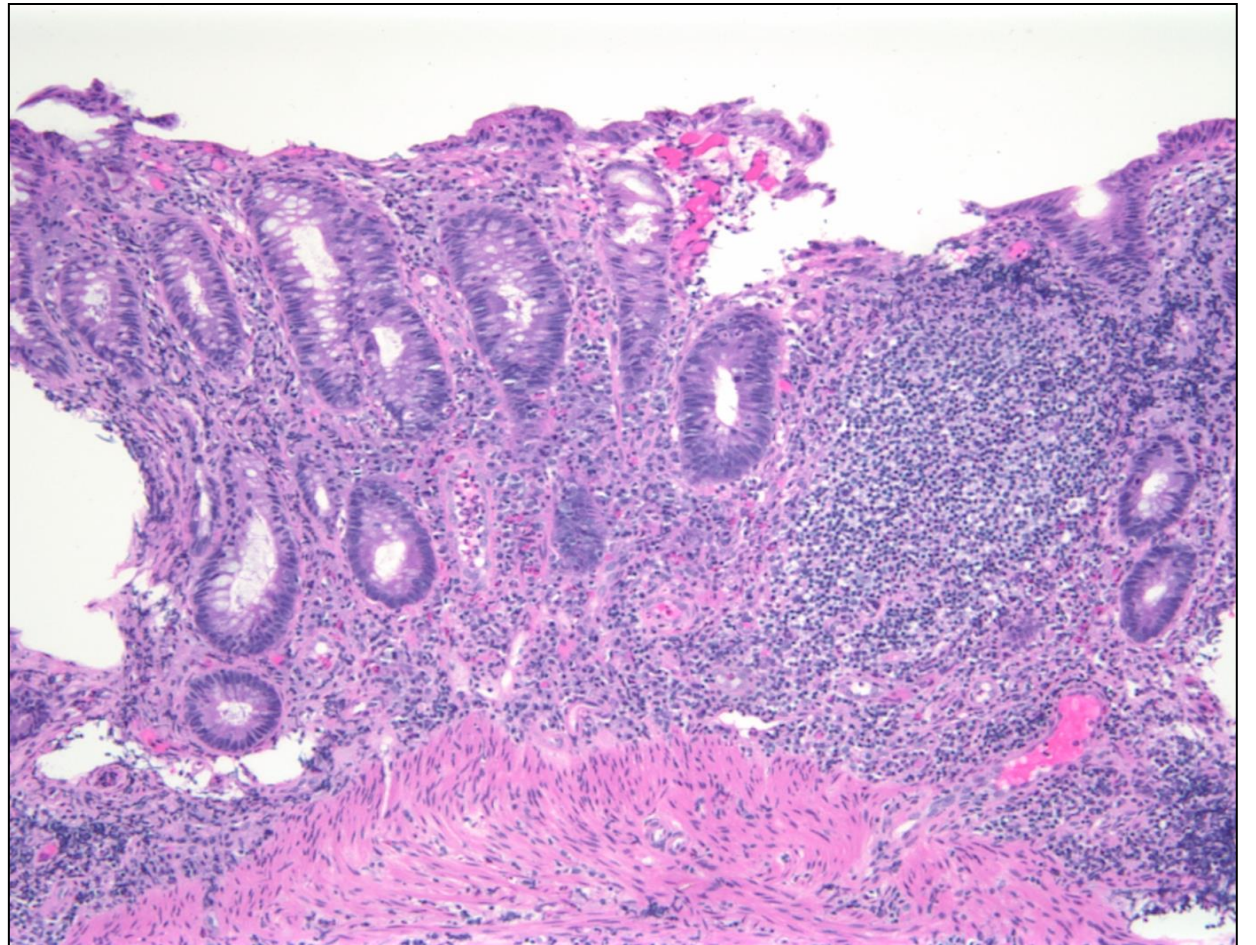
Architectural distortion, crypt abscesses, and basal lymphoid aggregates in DDASC



DDASC



Ulcerative colitis



Diverticular-Disease Associated Colitis-Differential Diagnosis

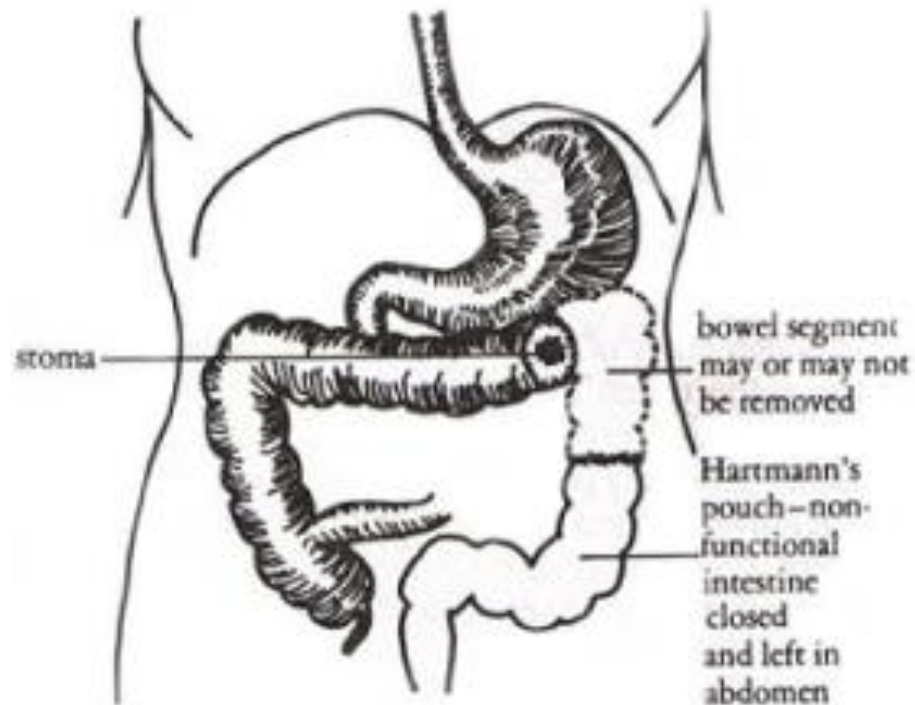
- Crohn's
 - Involvement of other segments of bowel (upper and lower)
 - Gross features
- Ulcerative colitis
 - Contiguous disease with rectal involvement
- DDASC
 - Patients have diverticula
 - Colitis limited to segment of bowel with tics
 - Rectum spared

Diversion Colitis

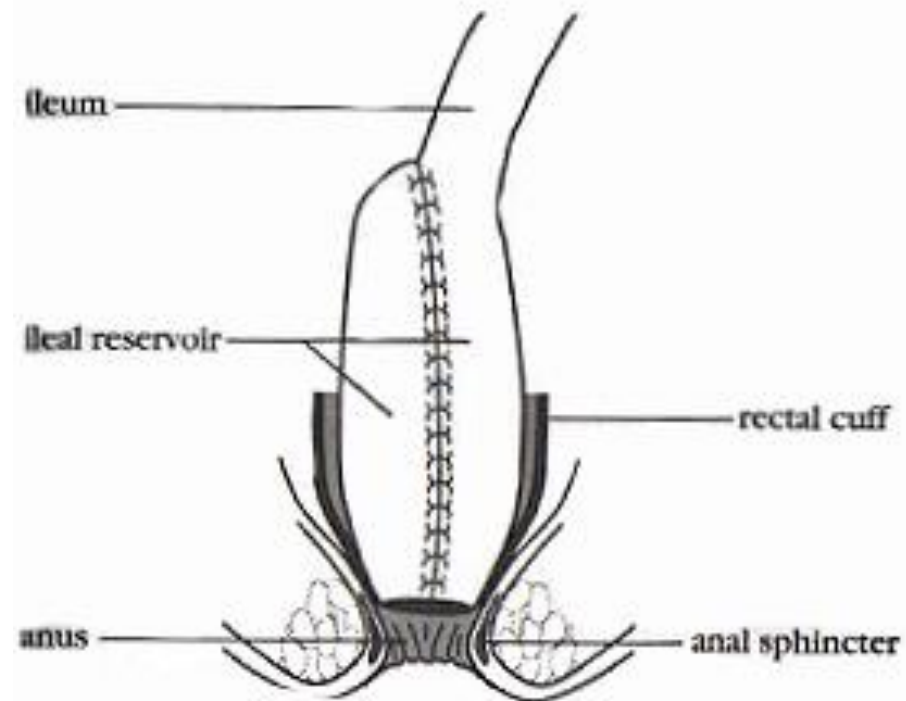
- Found in segments of bowel diverted from the fecal stream
 - Eventually occurs in almost all diversions
 - Cured by surgical reversal of diversion
- Mimics IBD
 - Need to know that it's diverted, and need to know why they were diverted
- Symptoms occur with increasing duration of diversion:
 - Bloody/mucoid discharge, abdominal pain, tenesmus

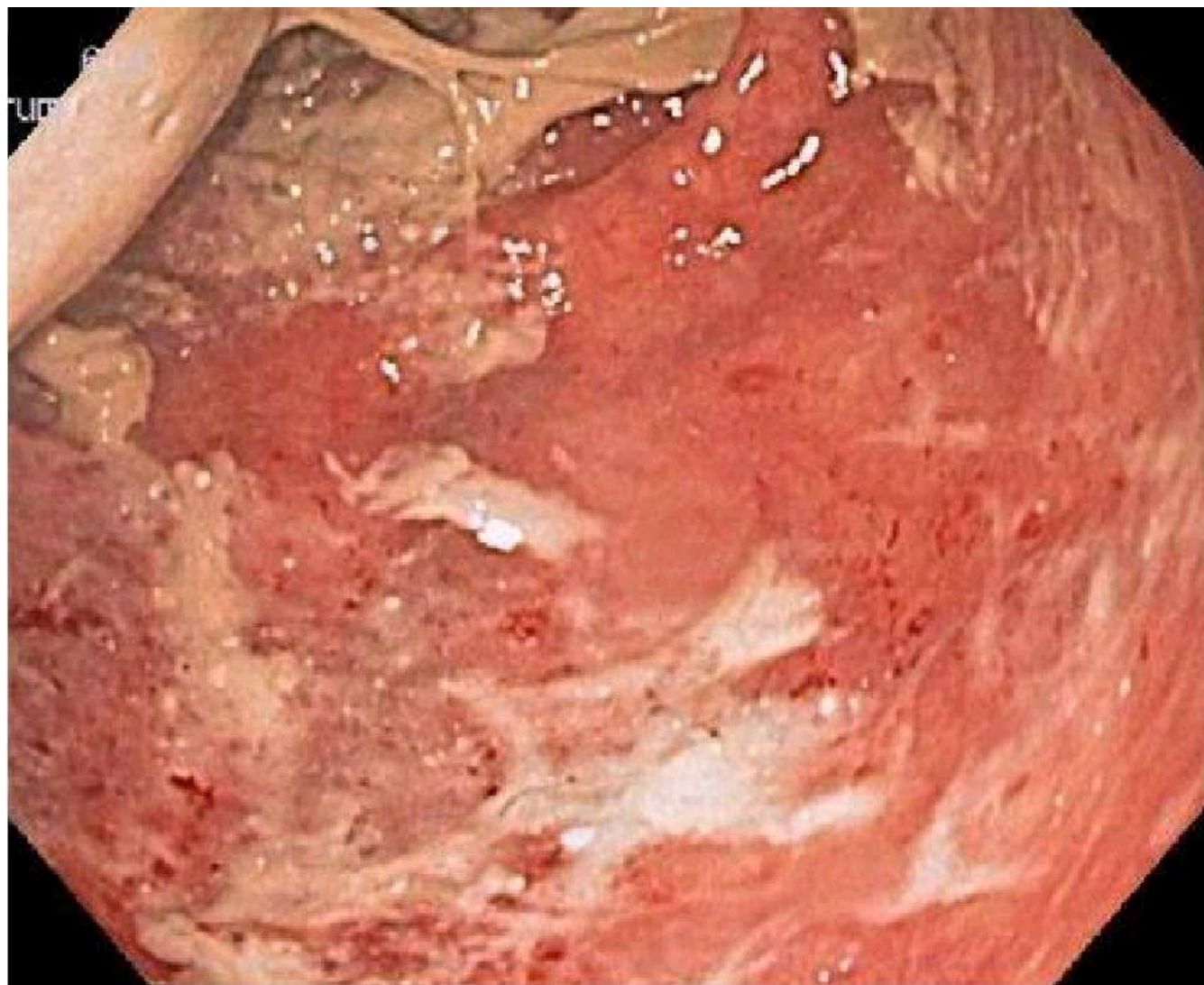
It's the Surgeon's Fault!

END OSTOMY AND HARTMANN'S POUCH — one stoma

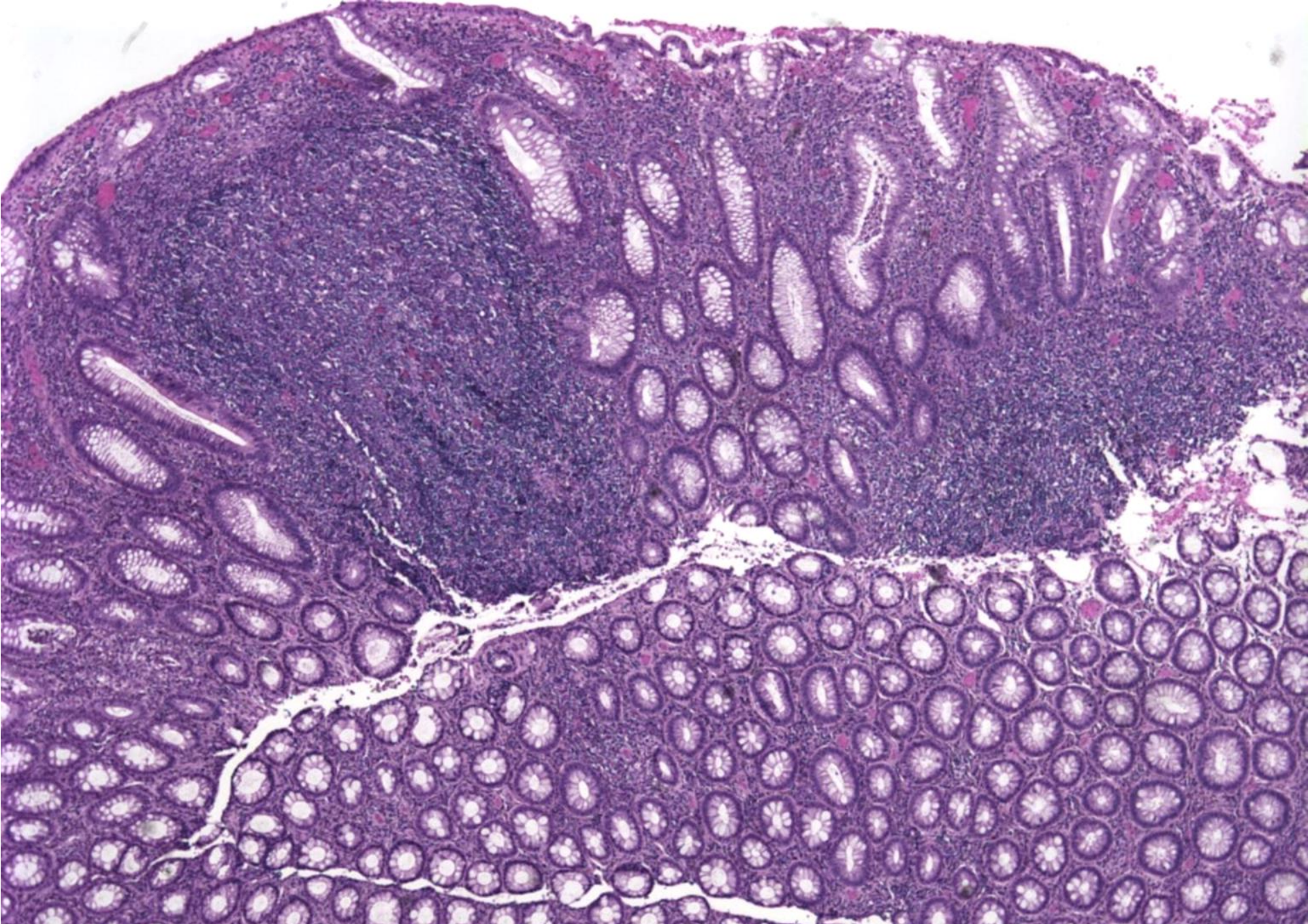


Ileoanal anastomosis with reservoir

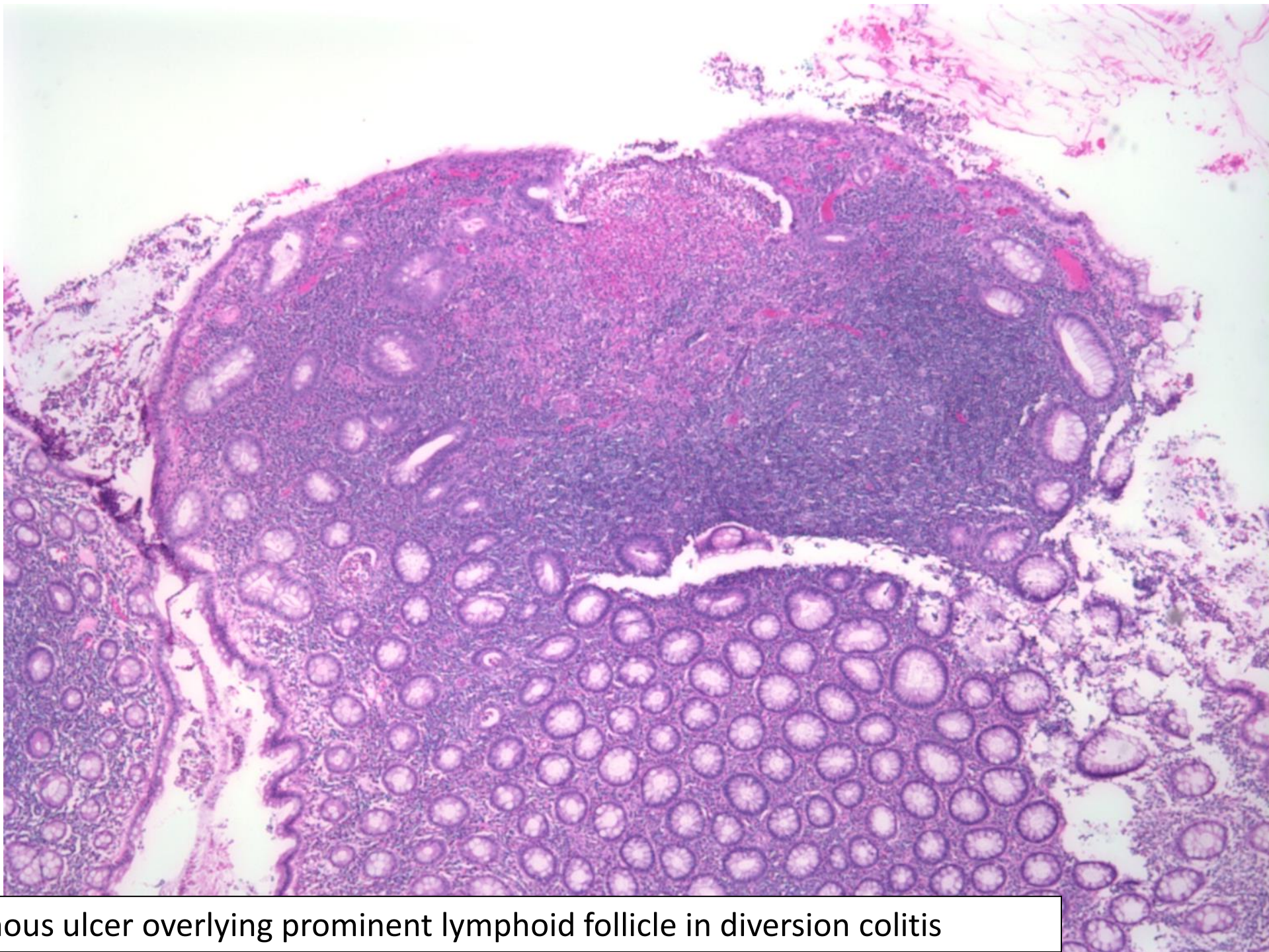




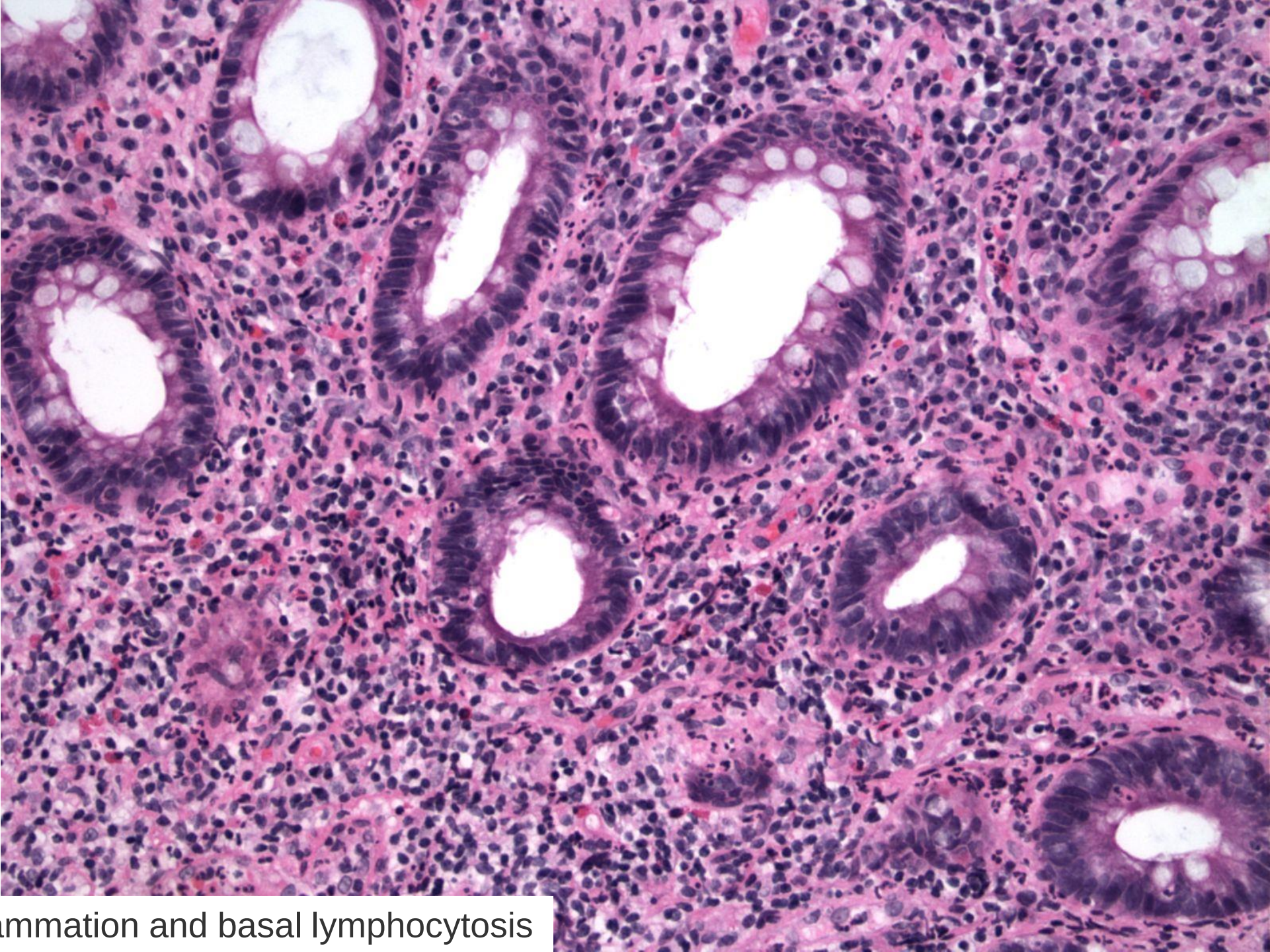
Courtesy Dr. Nathan Lee



Prominent lymphoid follicles in diversion colitis

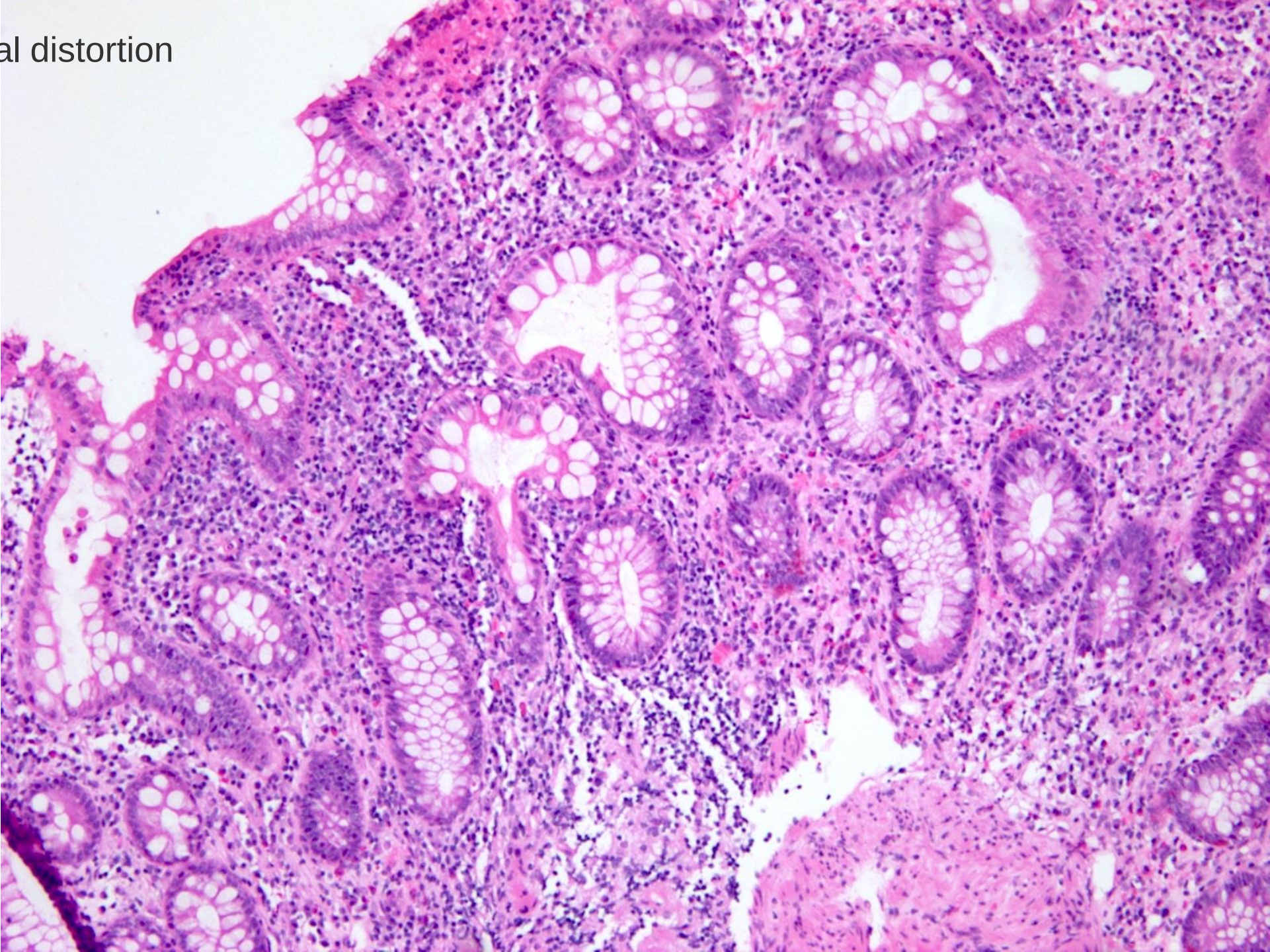


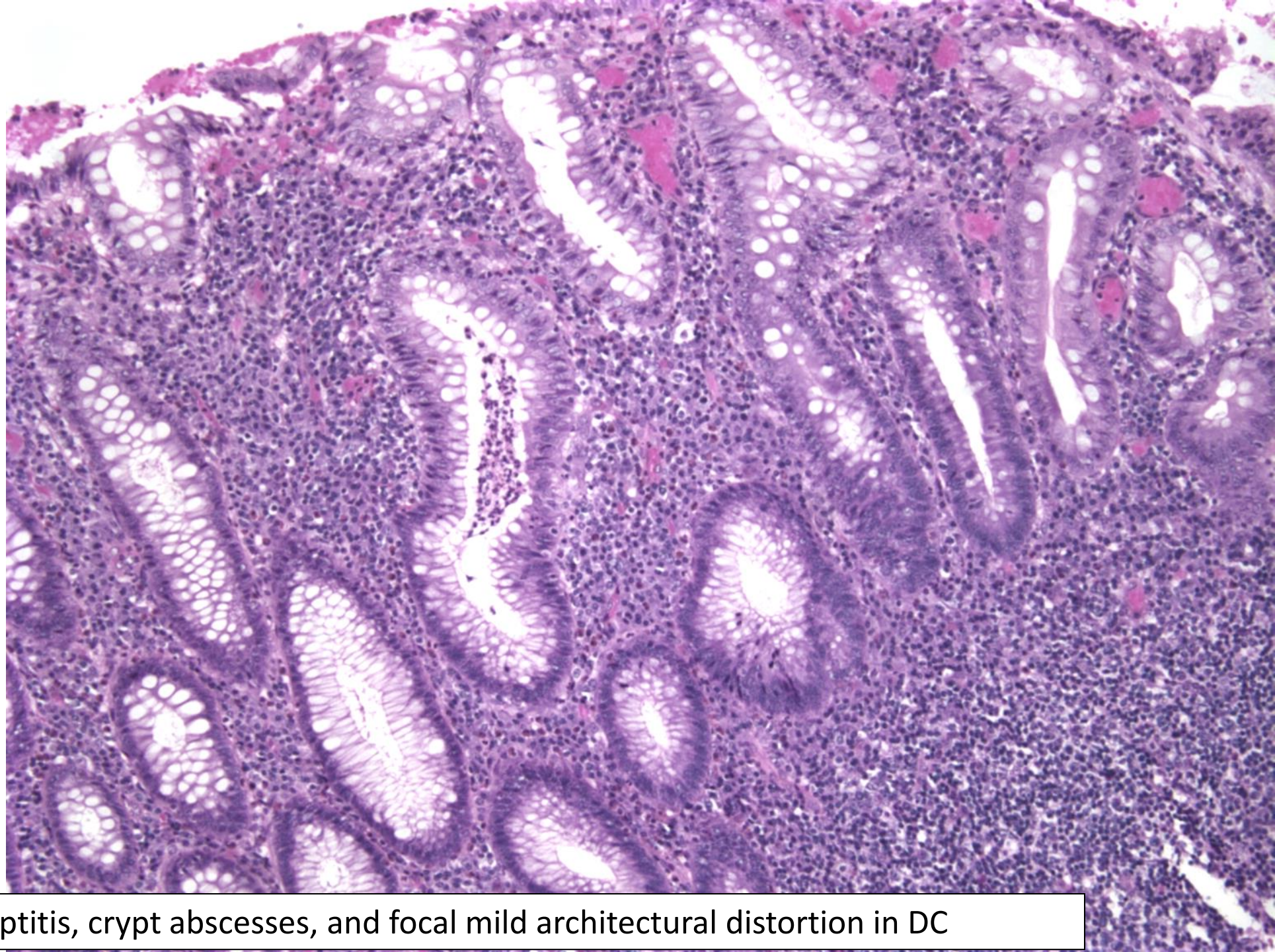
Aphthous ulcer overlying prominent lymphoid follicle in diversion colitis



Active inflammation and basal lymphocytosis

Architectural distortion





Cryptitis, crypt abscesses, and focal mild architectural distortion in DC

Diversion Colitis

Differential Diagnosis

- Distinction from chronic idiopathic IBD:
 - History of diversion!
 - Disease in remainder of bowel
 - Histology
 - Lack of significant architectural distortion
 - Milder inflammatory changes
 - May be very difficult if not impossible
 - Resolution of symptoms with surgical correction, fatty acid enemas



Drugs and Chemicals that Mimic Chronic Colitis

Immune Checkpoint Inhibitors

- Mimic CIIBD, lymphocytic colitis, or autoimmune enterocolitis

NSAIDS

- Mimic Crohn disease

Mycophenolate

- Mimics CIIBD, GVHD

Olmesartan

- Mimics microscopic colitis or autoimmune enterocolitis

Bowel prep injury

- Mimics Crohn disease

NSAID injury

Clinical

- May occur after only weeks of use
- Abdominal pain, cramps, bloody stool
- Massive bleeding, perforation

Other Risk Factors

- Older age
- Duration
- Polypharmacy

Macroscopic

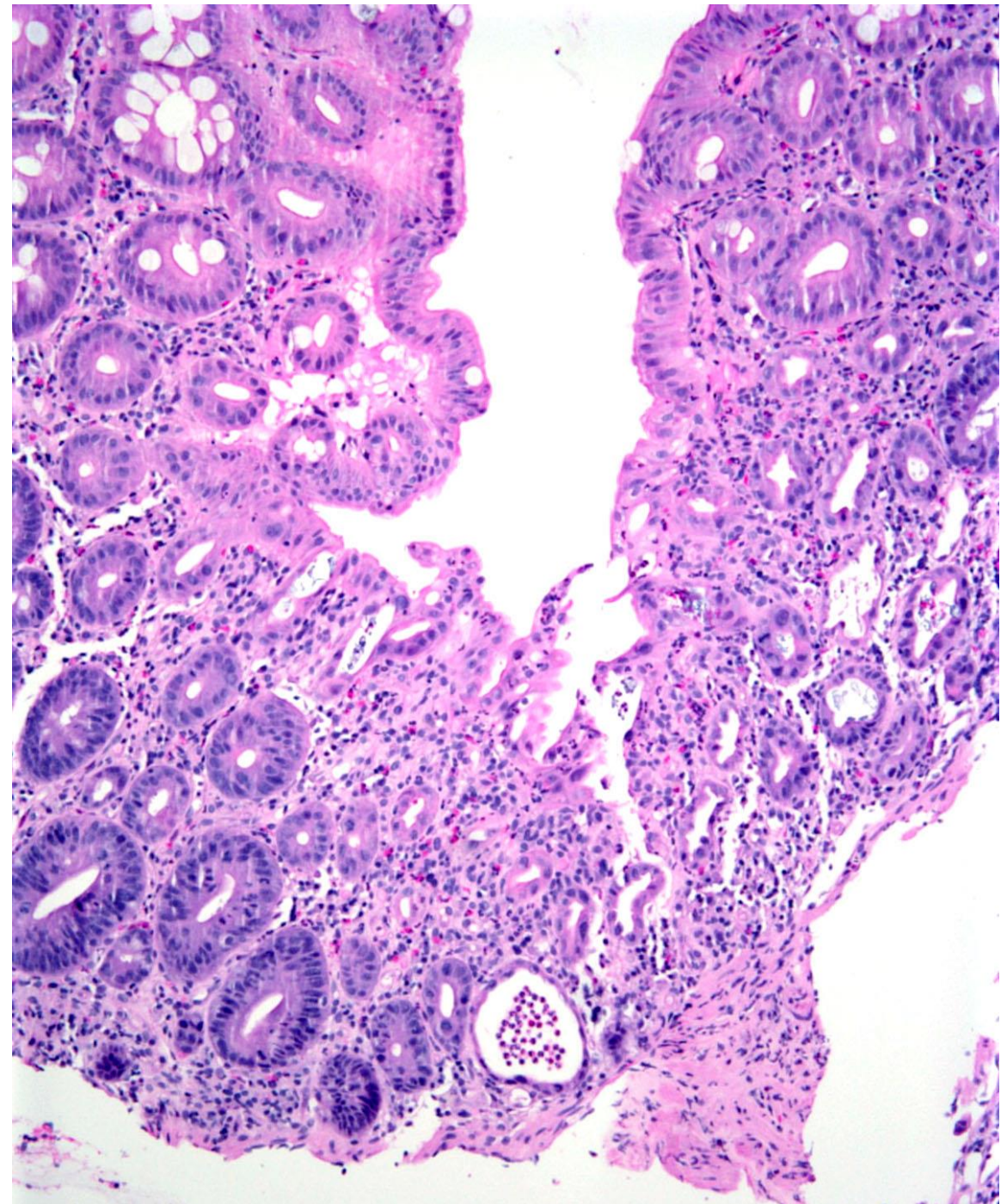
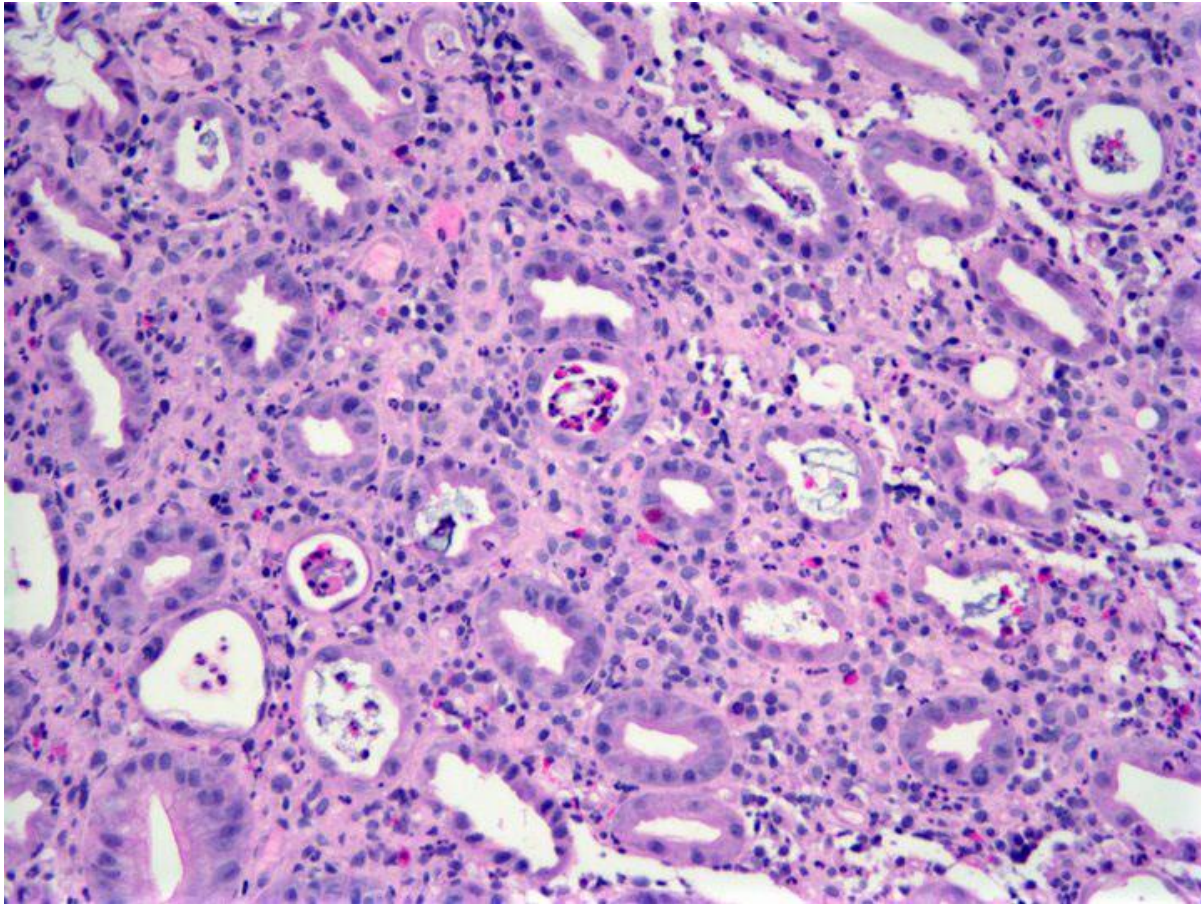
- Any part of gut but ileum most common
 - Friability
 - Ulcers
 - Diaphragm disease

Features that mimic IBD:

Patchy active colitis

Ileocecal ulcers/erosions

Focal architectural distortion



Mycophenolate mofetil (Cellcept)

Use

- Maintenance immunosuppression, usually solid organ transplants

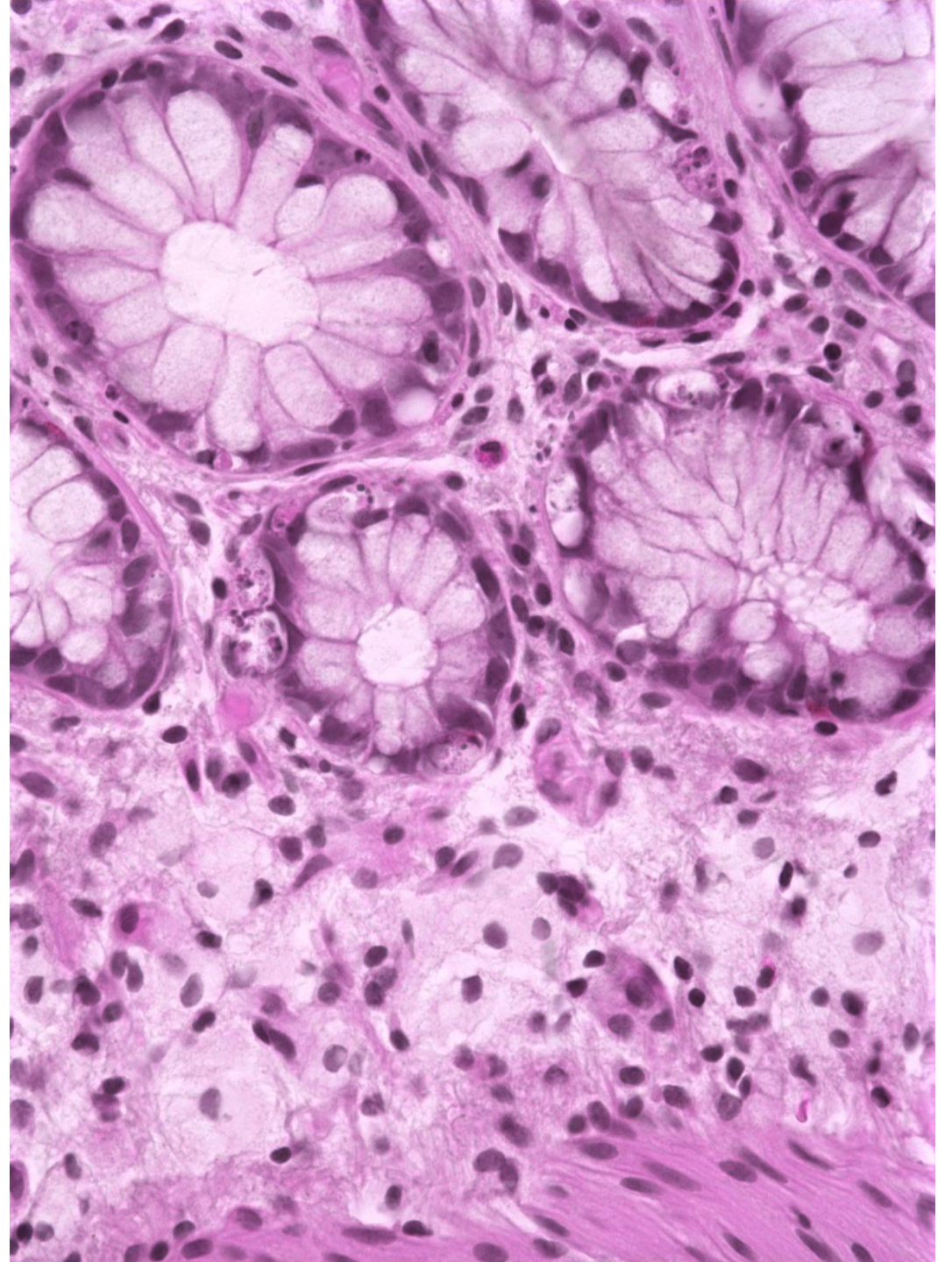
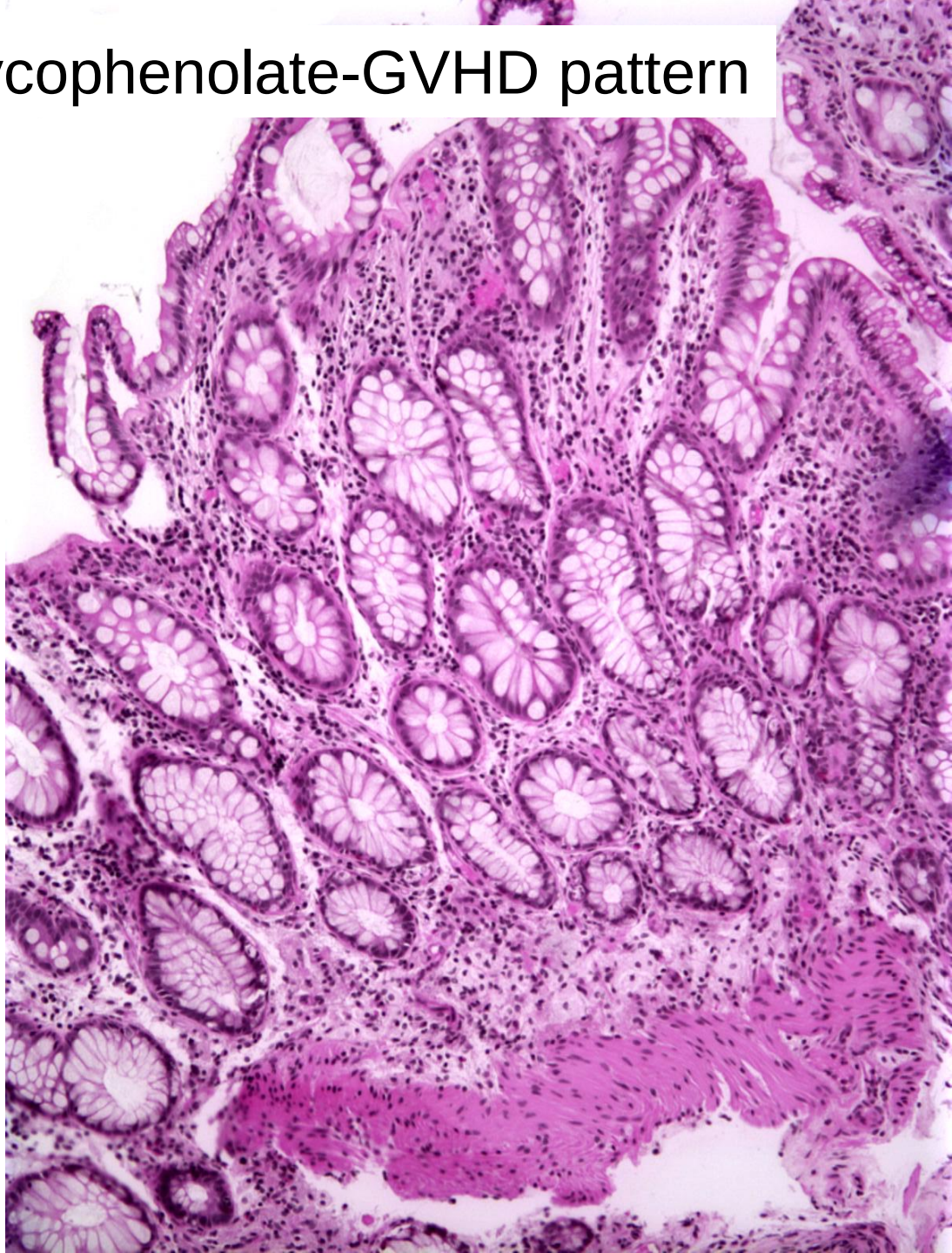
GI Toxicity

- Most common side effect
- Not dose dependent
- Worse with higher creatinine

Clinical

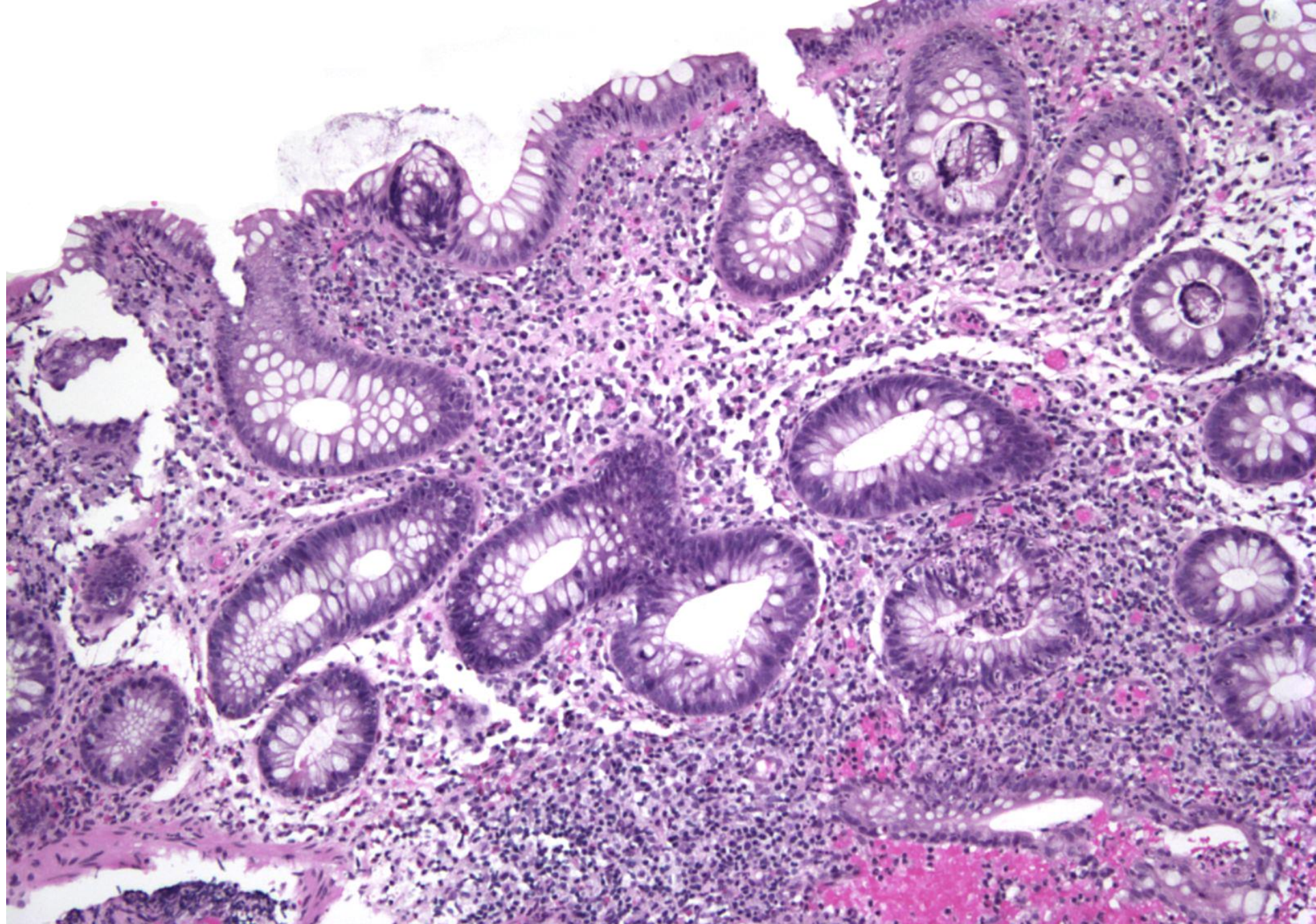
- Any part of gut
- Not dose dependent

Mycophenolate-GVHD pattern

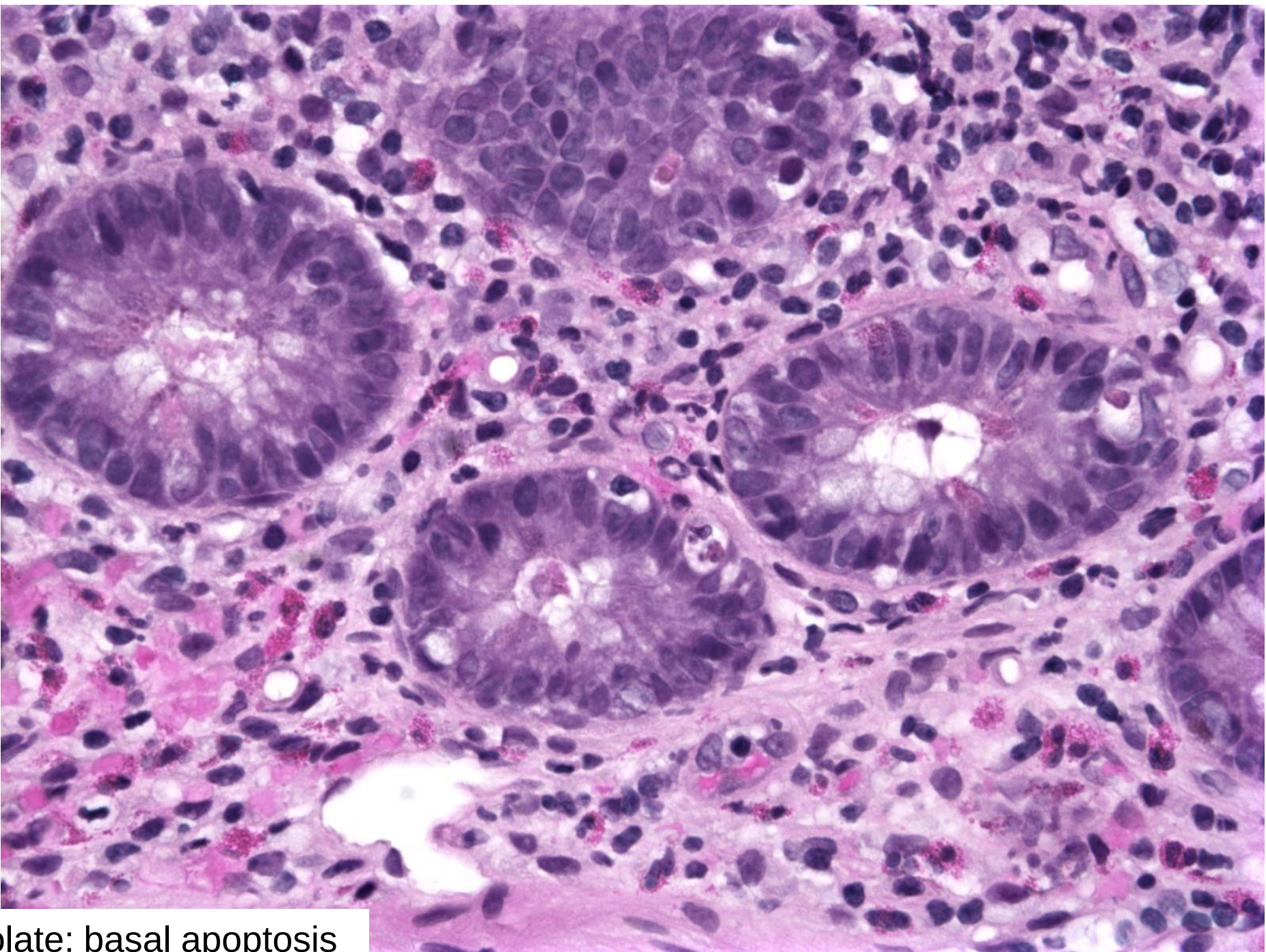




Mycophenolate-mild crypt distortion and dropout



Significant architectural distortion may be present, mimicking CIID



Mycophenolate: basal apoptosis

Immune checkpoint-inhibitors

GI Toxicity

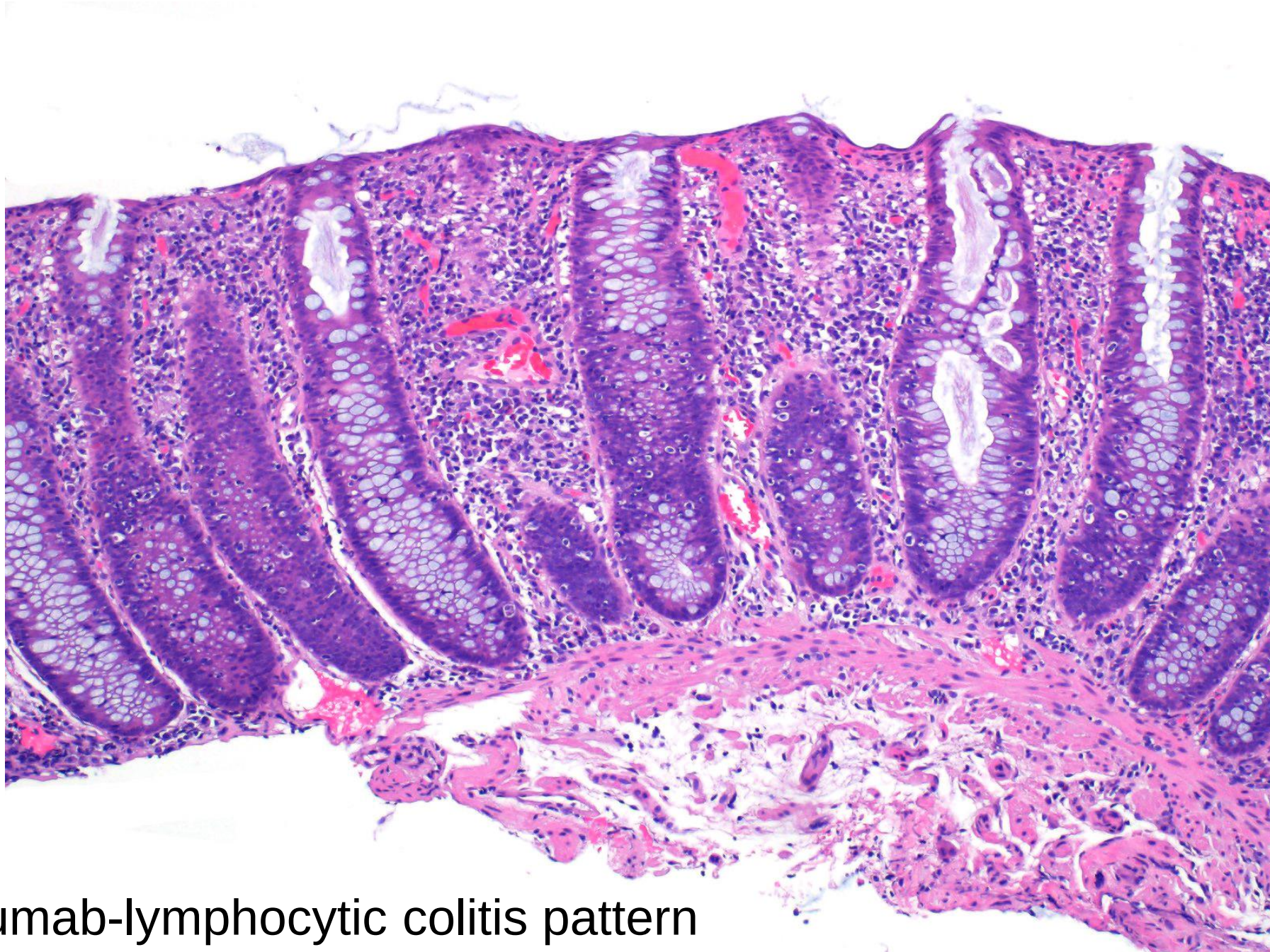
Clinical	Agent	Treatment
• Most common reported adverse side effect (~1/3 patients) • Typically involves colon, sometimes small bowel and stomach • May take 5-10 weeks to develop • Colonoscopy usually abnormal but not always	• CTLA-4 inhibitors (ipilimumab) more likely to cause GI problems than PD-1/PD-L1 inhibitors • Combination of the two increases risk	• Steroids are first line therapy • Infliximab if steroid-resistant or very severe • Superimposed infection common with steroid therapy

Table 1 Food and Drug Administration-approved immune checkpoint inhibitors

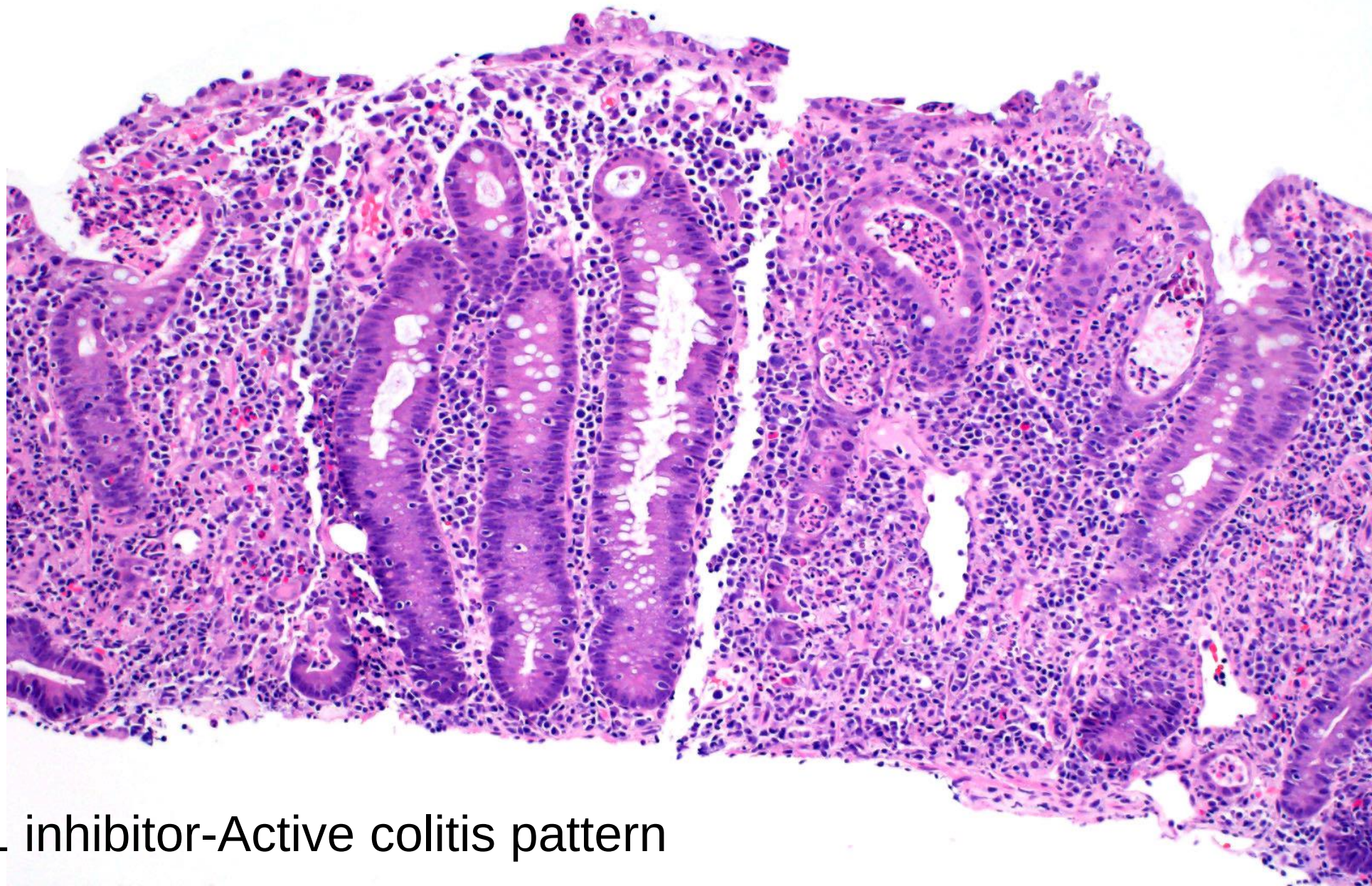
Drug	Trade name	Target	Indications
Ipilimumab	Yervoy (2011)	Cytotoxic T-lymphocyte antigen 4	Melanoma
Nivolumab	Opdivo (2014)	Programmed cell death-1	Melanoma Non-small-cell lung carcinoma Renal cell carcinoma Hepatocellular carcinoma Classic Hodgkin's lymphoma Squamous cell carcinoma of head and neck Urothelial carcinoma Colorectal cancer with microsatellite instability or mismatch-repair deficiency
Pembrolizumab	Keytruda (2014)	Programmed cell death-1	Melanoma Non-small-cell lung carcinoma Classic Hodgkin's lymphoma Squamous cell carcinoma of head and neck Urothelial carcinoma Gastric cancer Solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	Tecentriq (2016)	Programmed cell death ligand-1	Non-small-cell lung carcinoma Urothelial carcinoma
Avelumab	Bavencio (2017)	Programmed cell death ligand-1	Merkel cell carcinoma Urothelial carcinoma
Durvalumab	Imfinzi (2017)	Programmed cell death ligand-1	Urothelial carcinoma

Table 2 Summary of key histological features of various immunotherapeutic agents

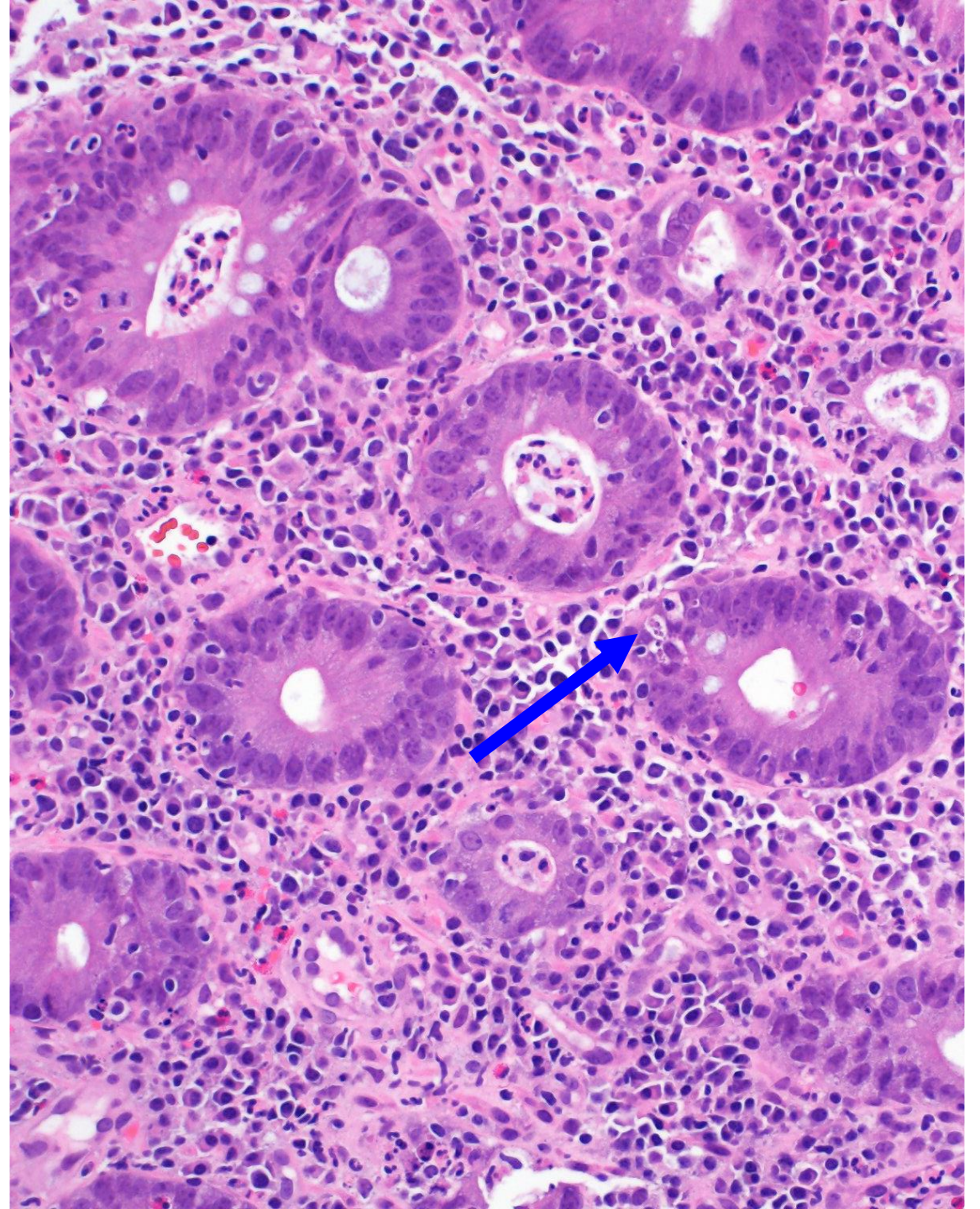
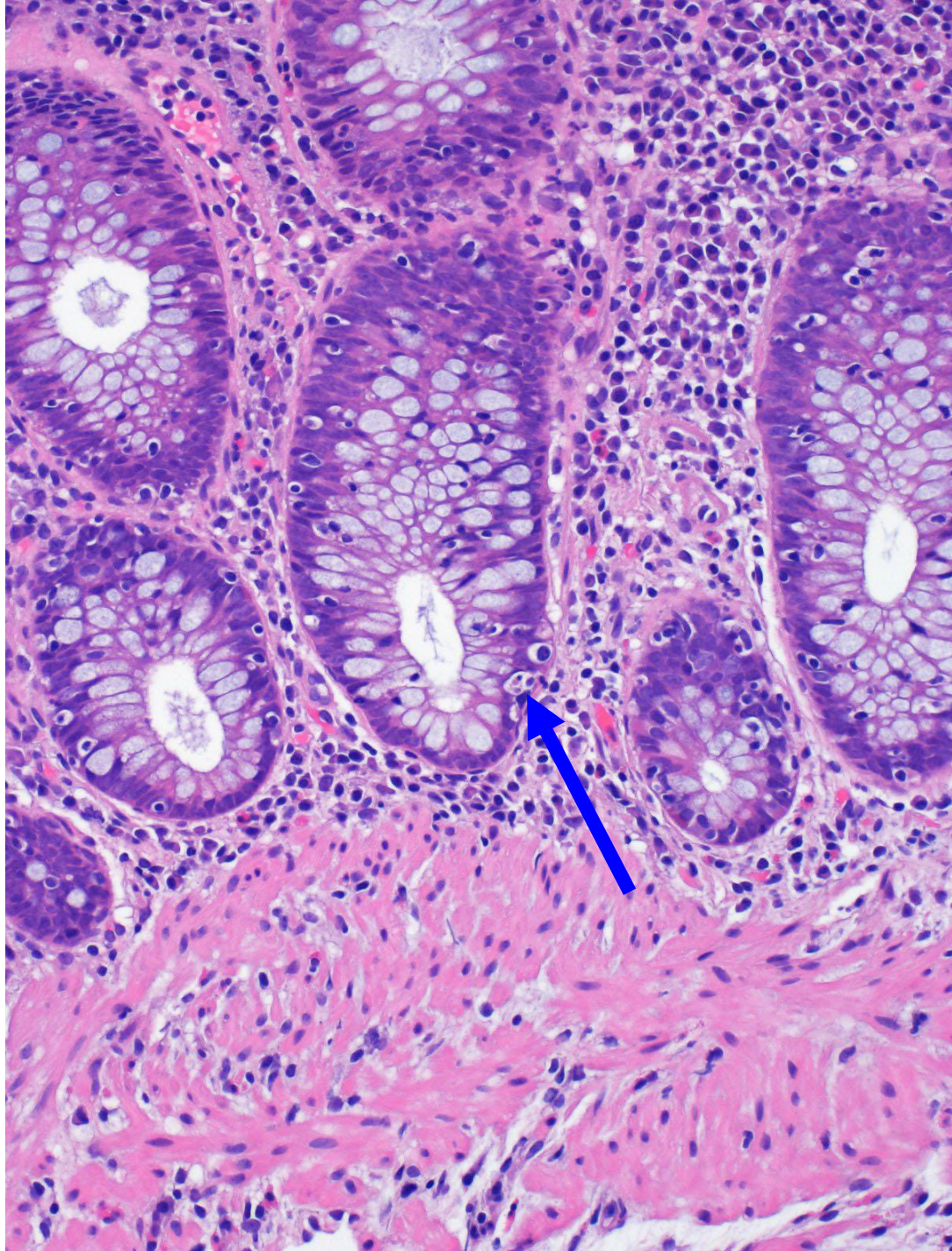
CTLA4 inhibitors (ipilimumab)	<i>Autoimmune-like</i> enterocolopathy: – Lymphoplasmocytic expansion of lamina propria – Increased apoptosis and intraepithelial lymphocytes – Cryptitis and crypt elongation – Lack of basal plasmocytosis
PD1 inhibitors (pembrolizumab and nivolumab)	– <i>Active colitis pattern</i> with increased apoptosis – <i>Lymphocytic colitis pattern</i> – Features of chronicity in recurrent cases – Ruptured granuloma
PI3K δ isoform inhibitor (idelalisib)	“ <i>Triad</i> ” of: – Intraepithelial lymphocytosis – Epithelial cell apoptosis – Neutrophilic cryptitis



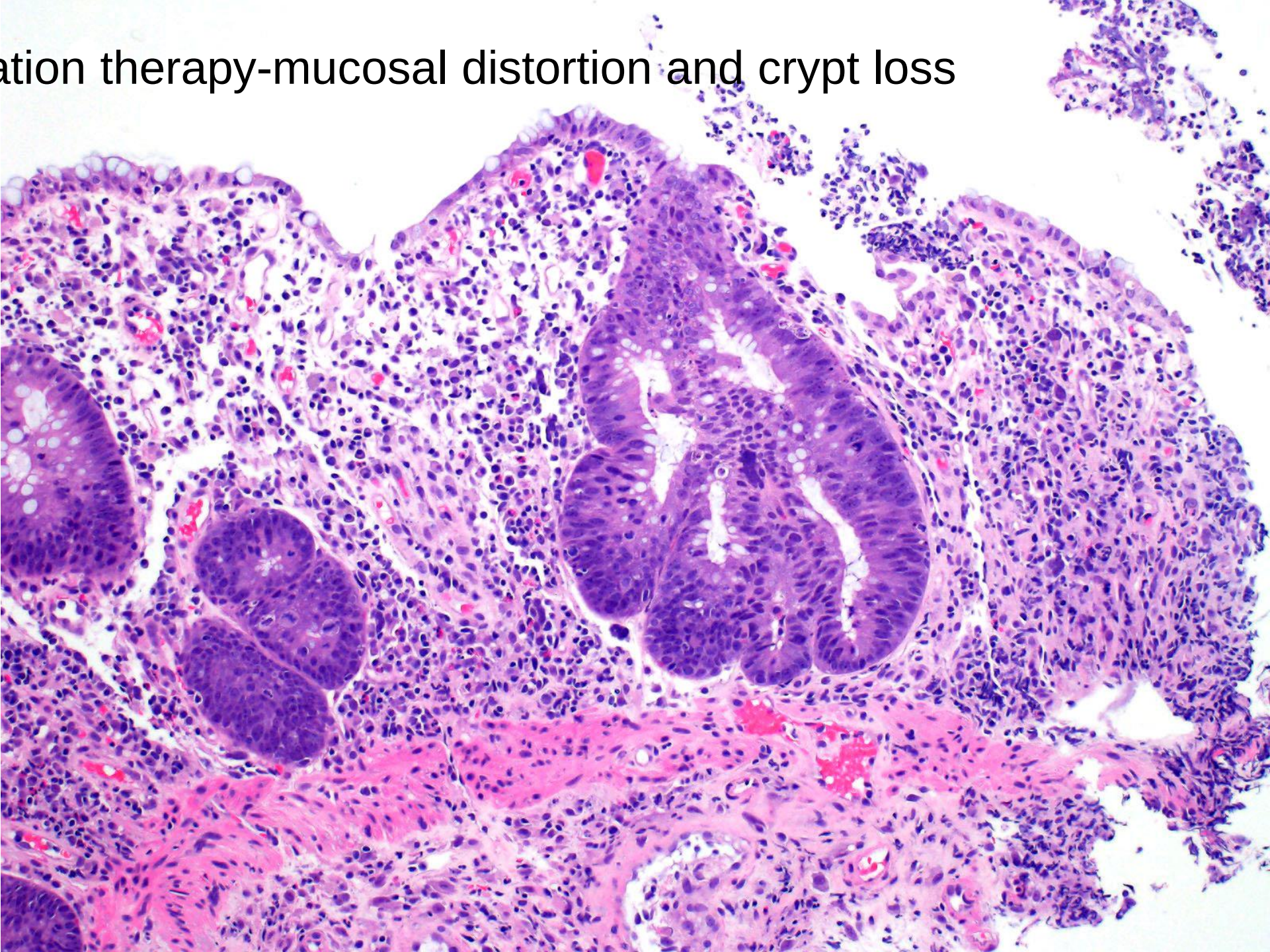
Pembrolizumab-lymphocytic colitis pattern



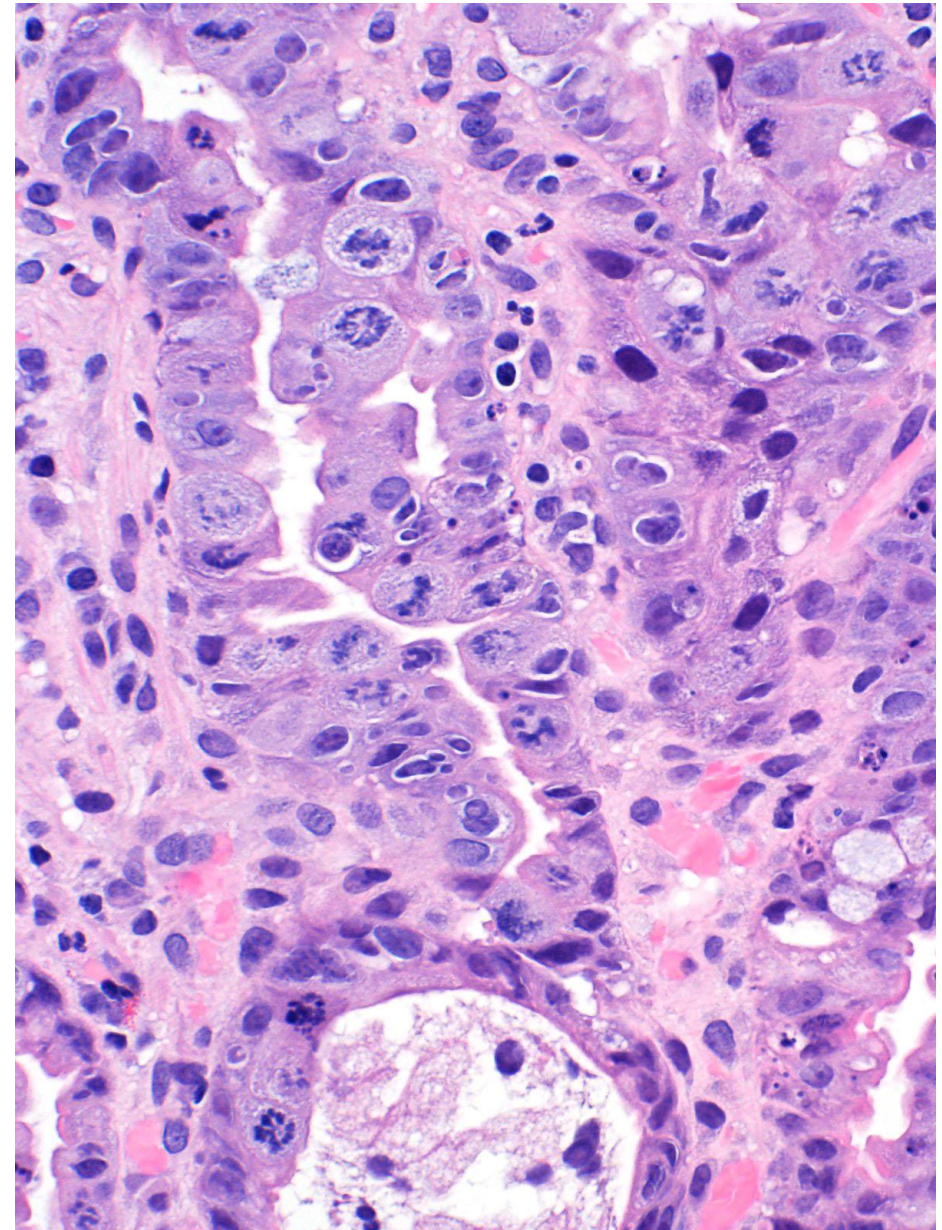
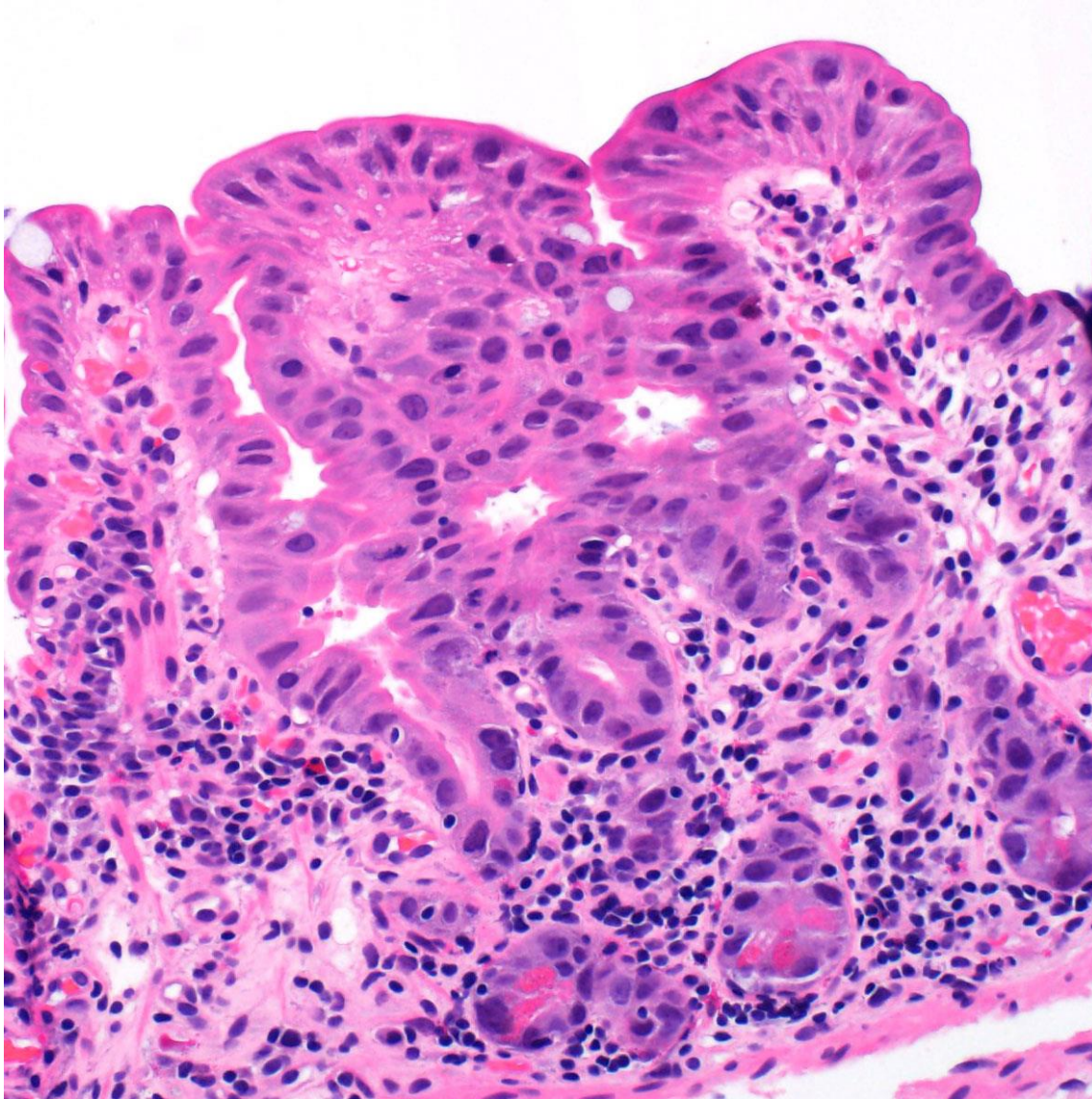
PDL1 inhibitor-Active colitis pattern



Combination therapy-mucosal distortion and crypt loss



Warning: Chemotherapy can mimic dysplasia





What about “microscopic colitis?”

- The presence of histologic abnormalities in the context of an unremarkable colonoscopic examination (“microscopic” disease).
- Don’t use “microscopic colitis” as diagnosis
 - Collagenous colitis
 - Lymphocytic colitis
- Both patterns associated with olmesartan

What about “microscopic colitis?”

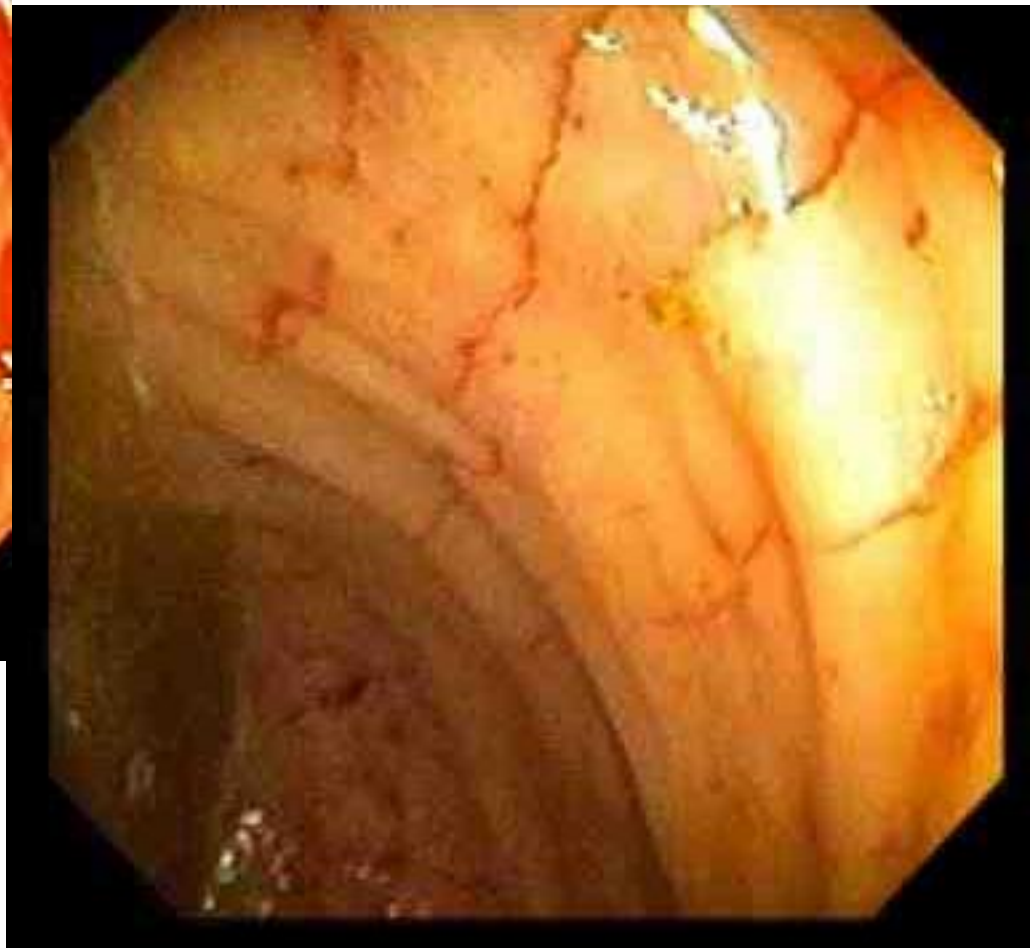
- You need:
 - History of long-term chronic watery diarrhea
 - Appropriate histology
 - Normal colonoscopy

If any of these don't fit, back off the diagnosis!!



Collagenous Colitis

- Chronic, watery diarrhea
 - Often lasts for years
- Crampy abdominal pain
- Normal colonoscopy and radiographs
- Primarily a disease of middle aged women
 - Male:female ratio 9-20:1
- Often coexistent autoimmune disorder
 - ?association with NSAIDS

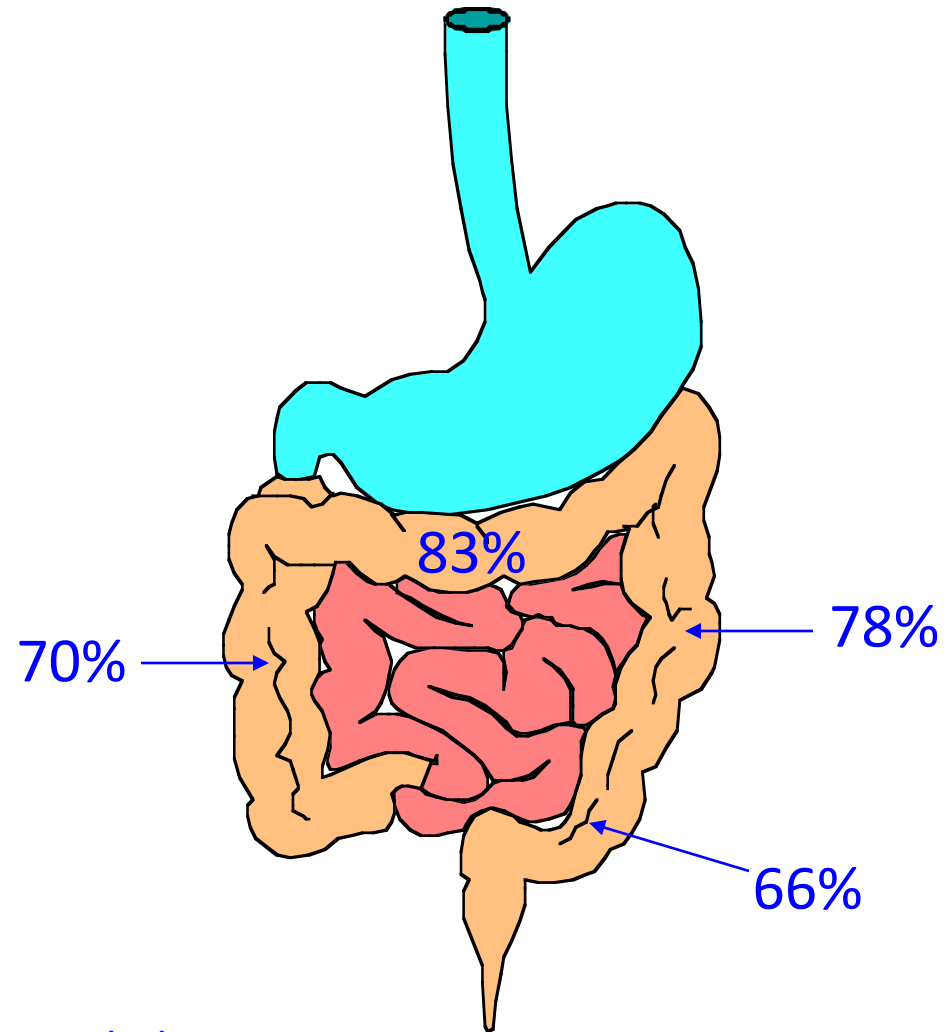


Collagenous Colitis

Histology

- Collagen
 - Thickened subepithelial collagen band
 - No numerical cutoff!
 - May abate with treatment
 - Variable, shaggy, with entrapped capillaries
- Colitis
 - Intraepithelial lymphocytosis
 - Increased mixed LP inflammatory infiltrate
 - Neutrophils should be rare
 - Surface epithelial damage

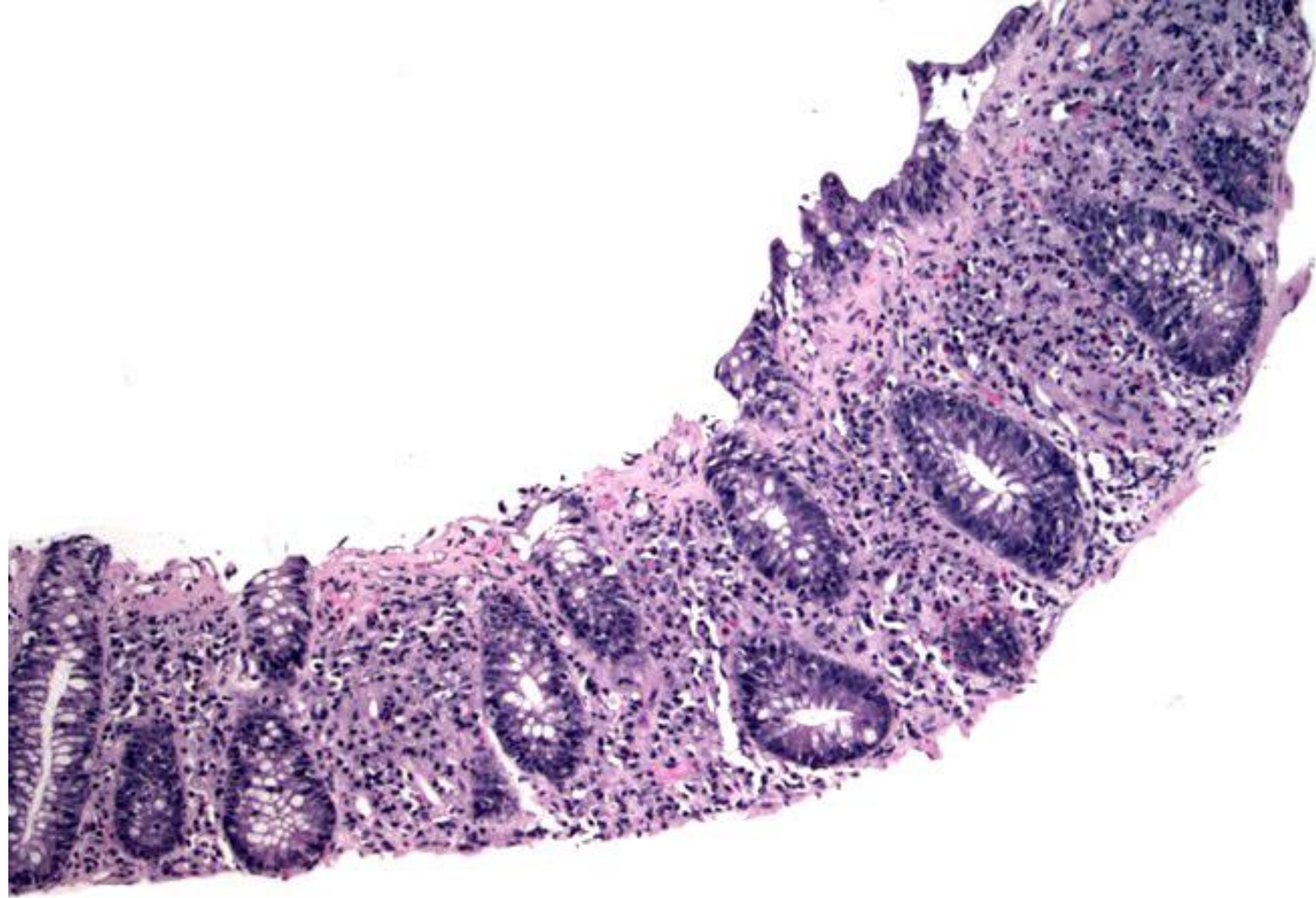
Yield of Biopsy Specimens Diagnostic of Collagenous Colitis

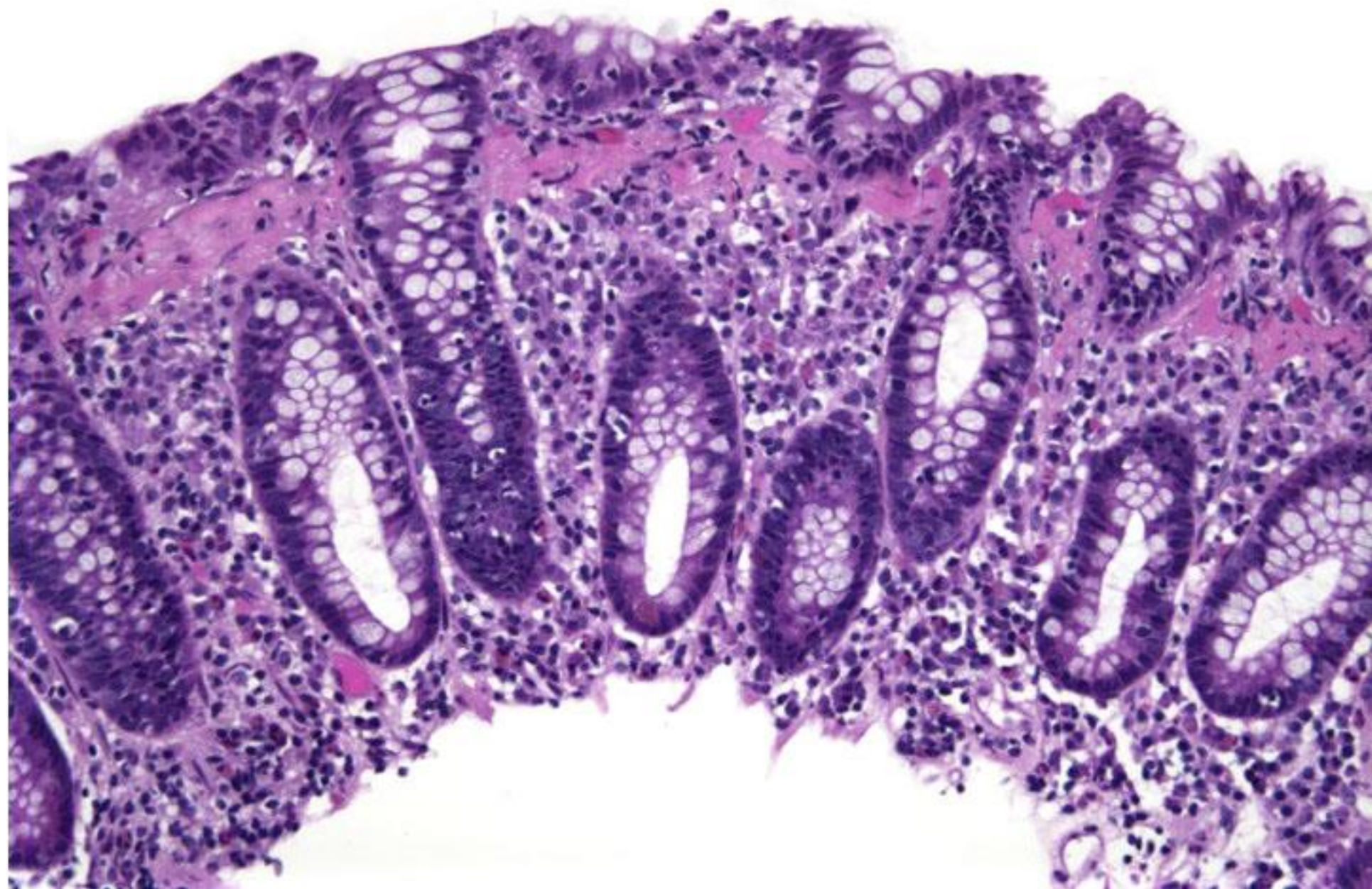


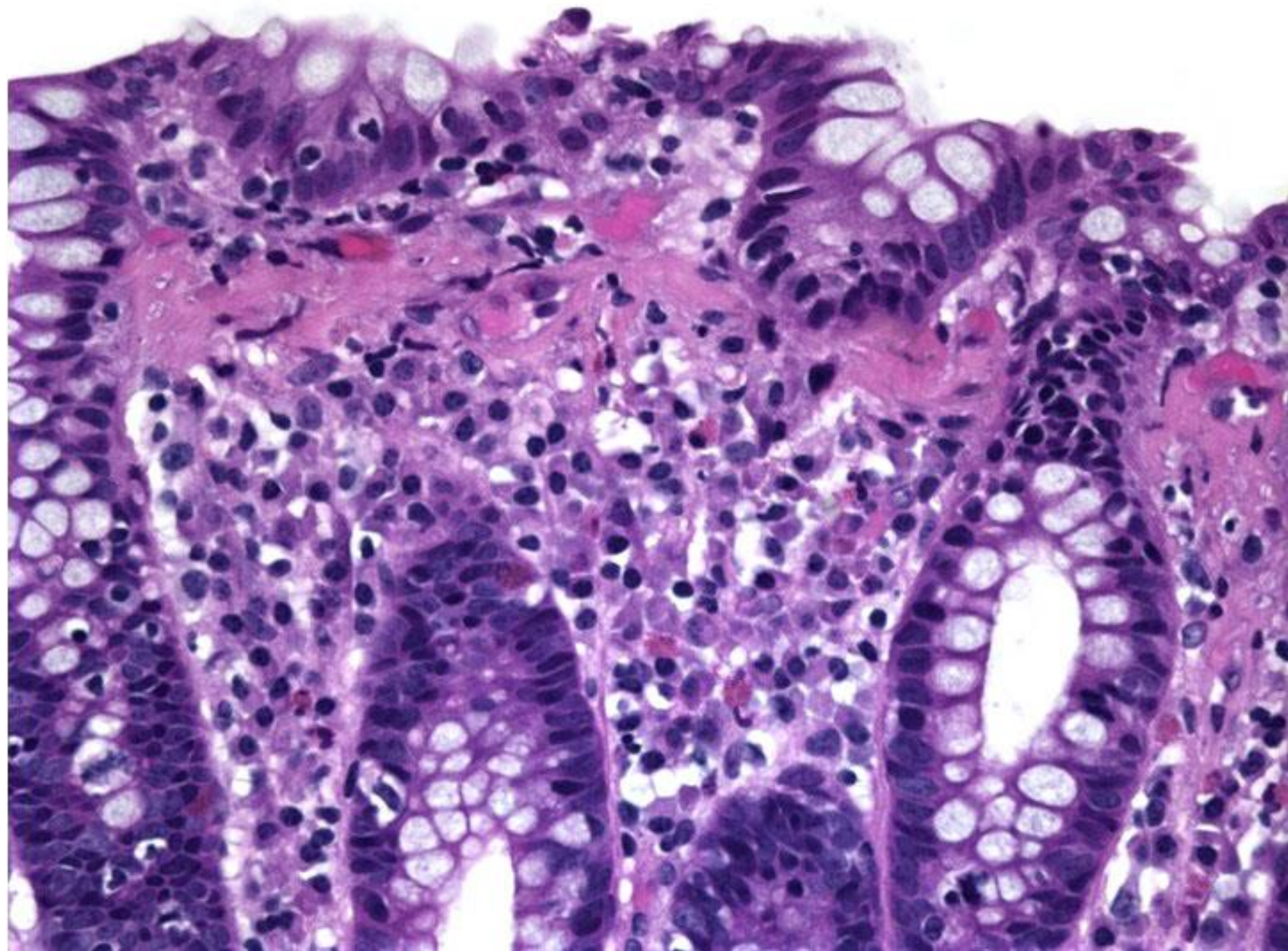
From: Offner et al, Hum Pathol 30:451-7

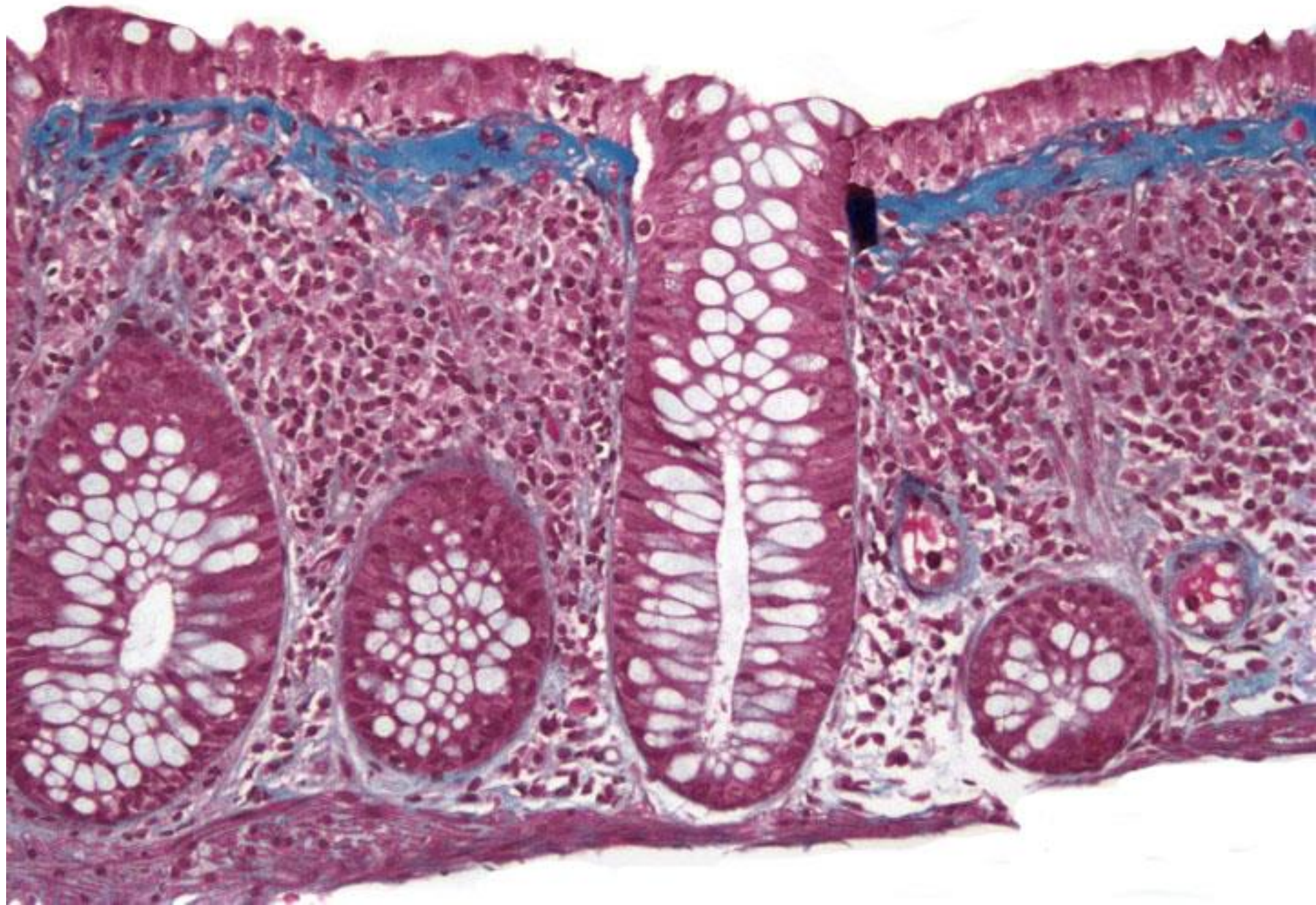


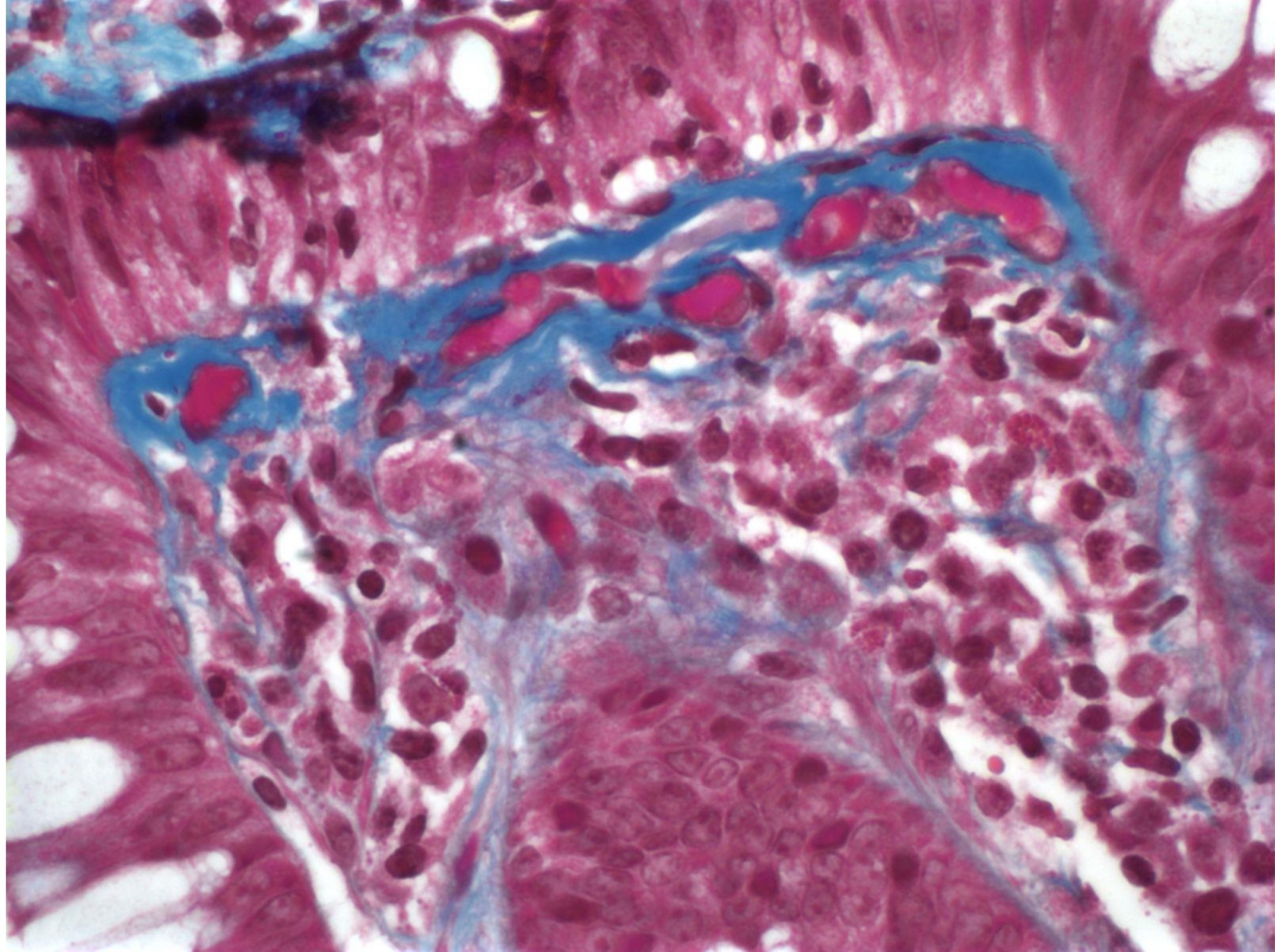
Courtesy Dr. Joel Greenson









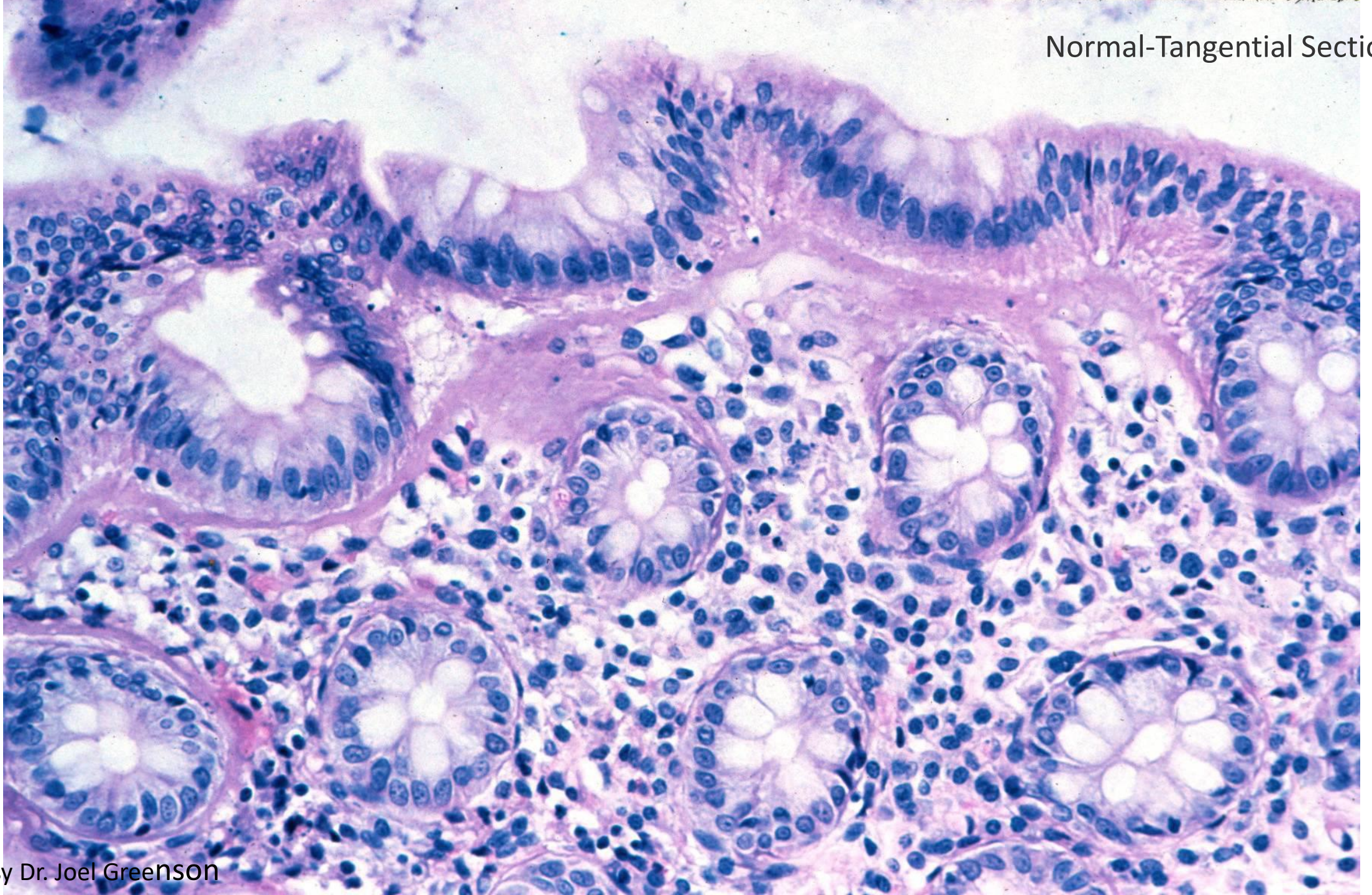


Collagenous Colitis

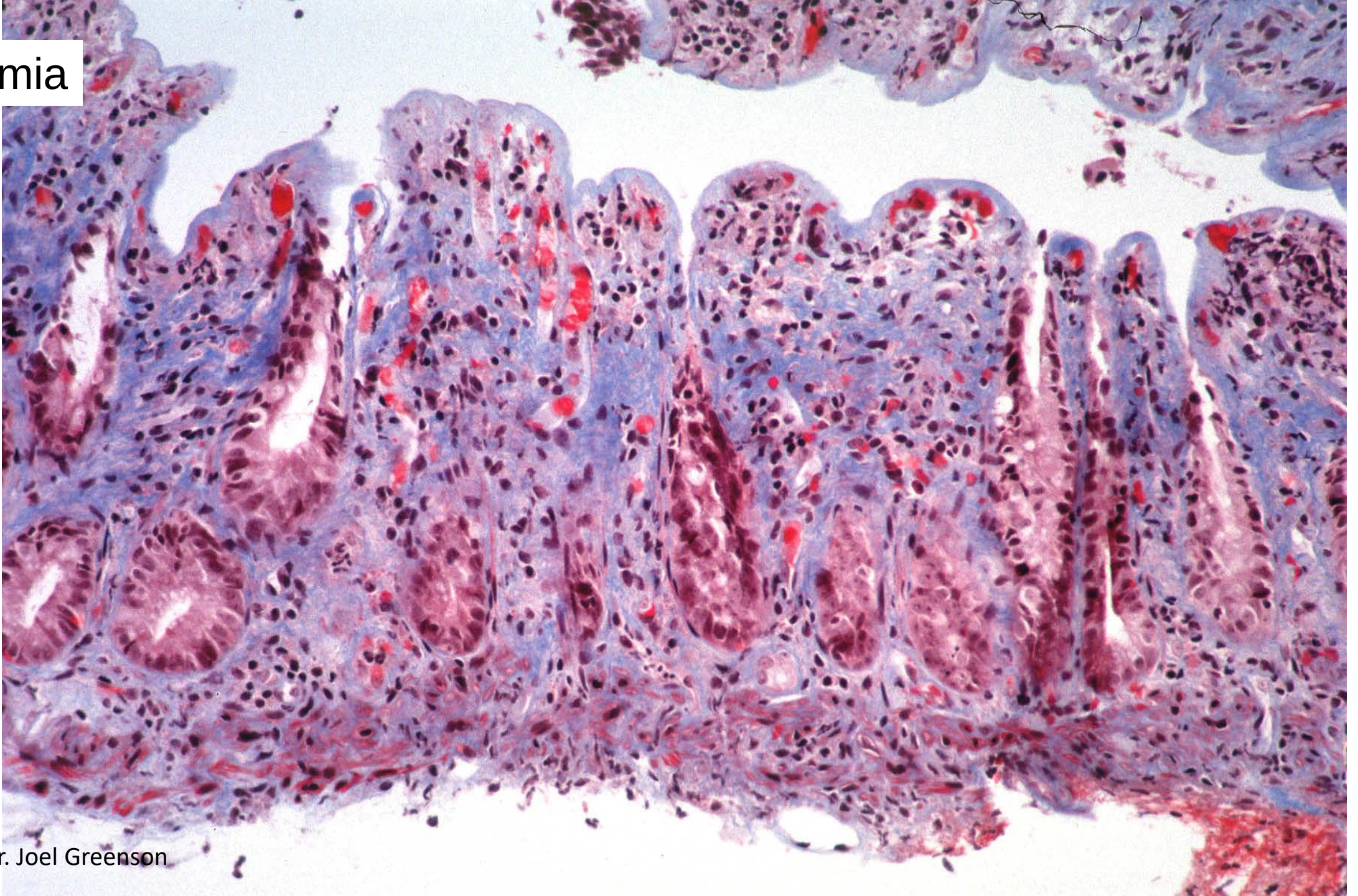
Diagnostic Pitfalls

- Failure to consider inflammatory component
- Sole reliance on numerical quantitation of collagen band
- Misinterpretation of normal structures or other types of fibrosis
 - Tangential orientation
 - Hyperplastic polyps
 - Fibrosis of ischemia, Crohn's
- Site within colon

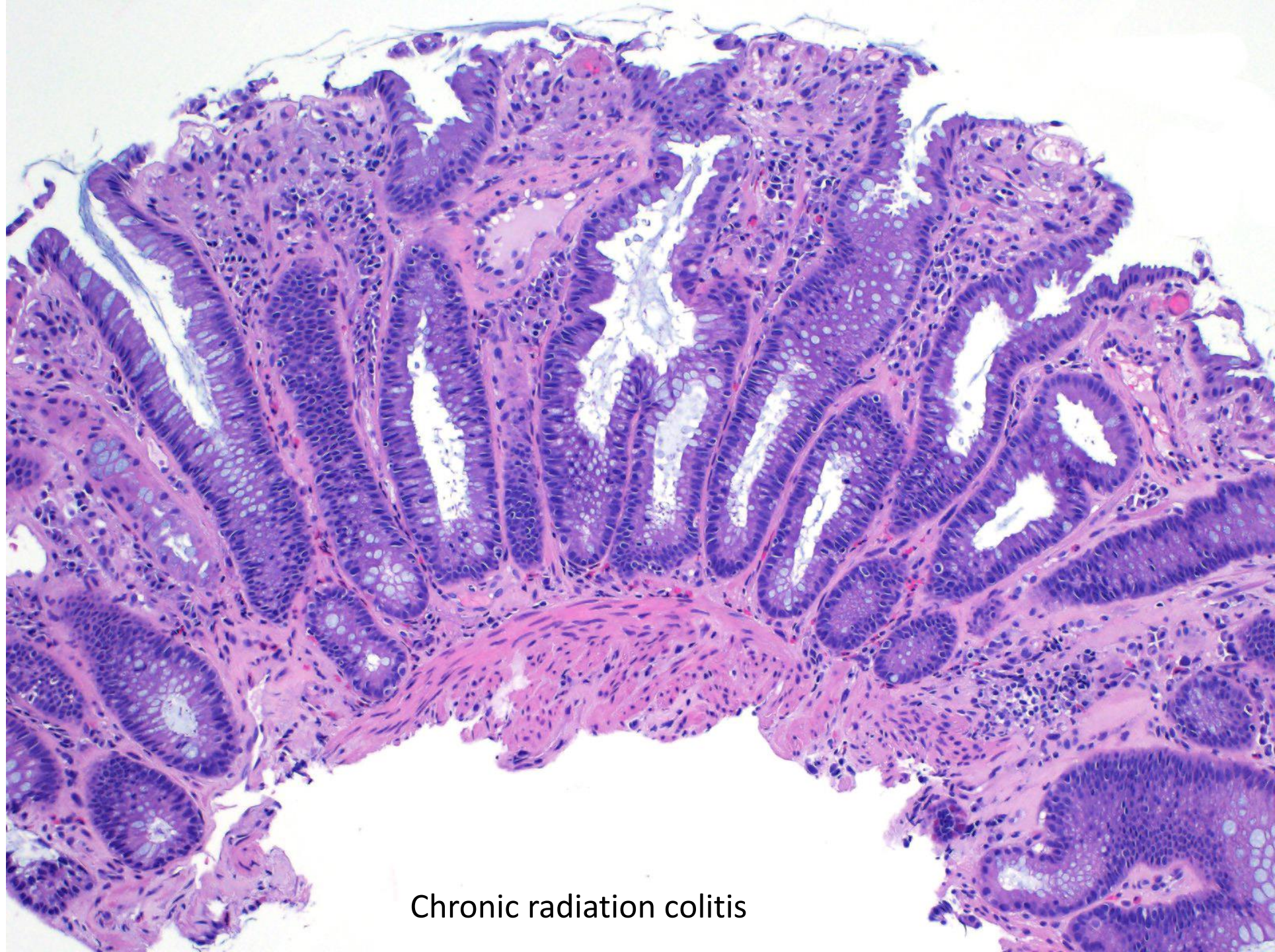
Normal-Tangential Section



Ischemia



Courtesy Dr. Joel Greenson



Chronic radiation colitis

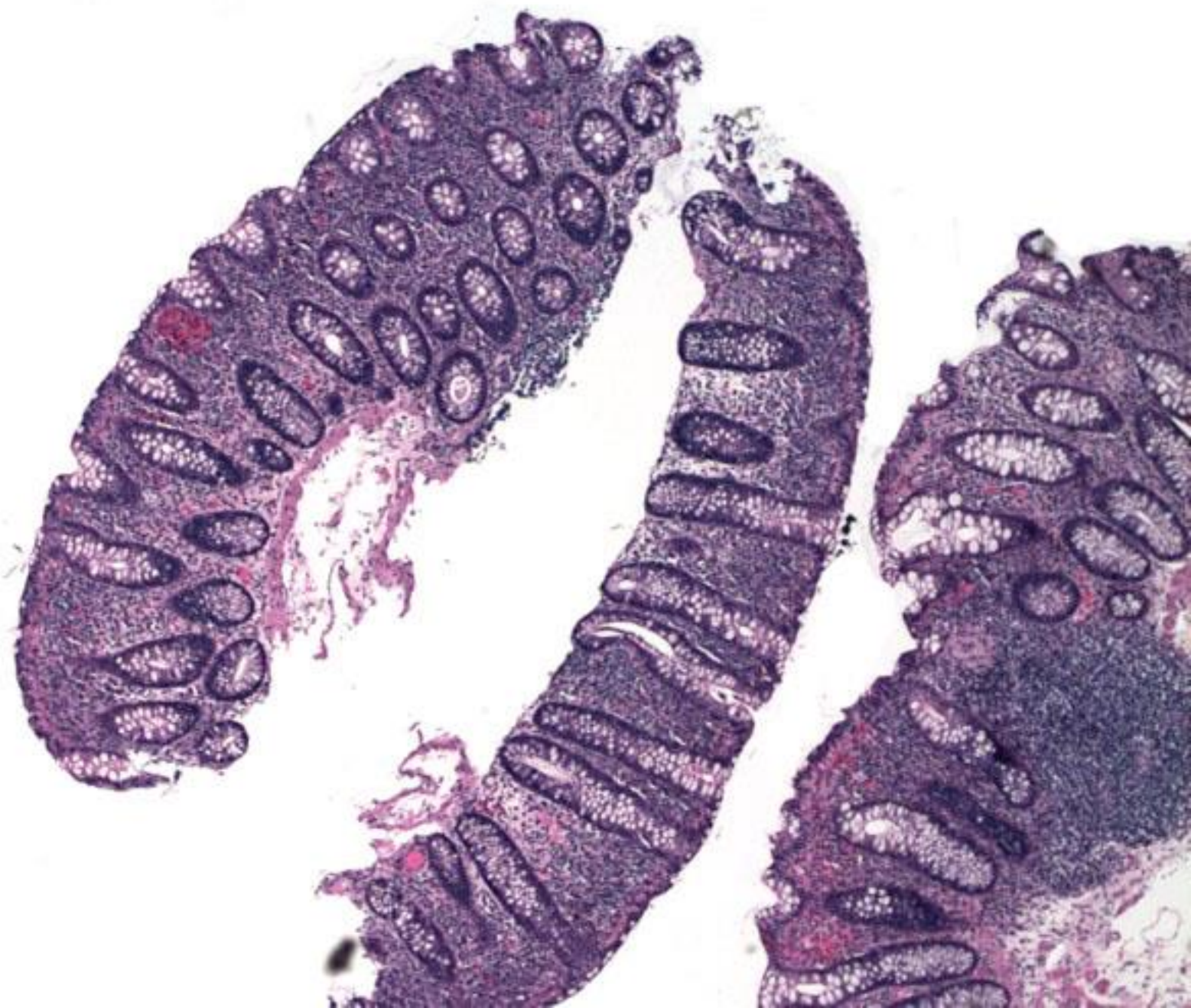
Lymphocytic Colitis

- Symptoms are similar to collagenous colitis
- Unremarkable colonoscopy
- Equal male to female distribution

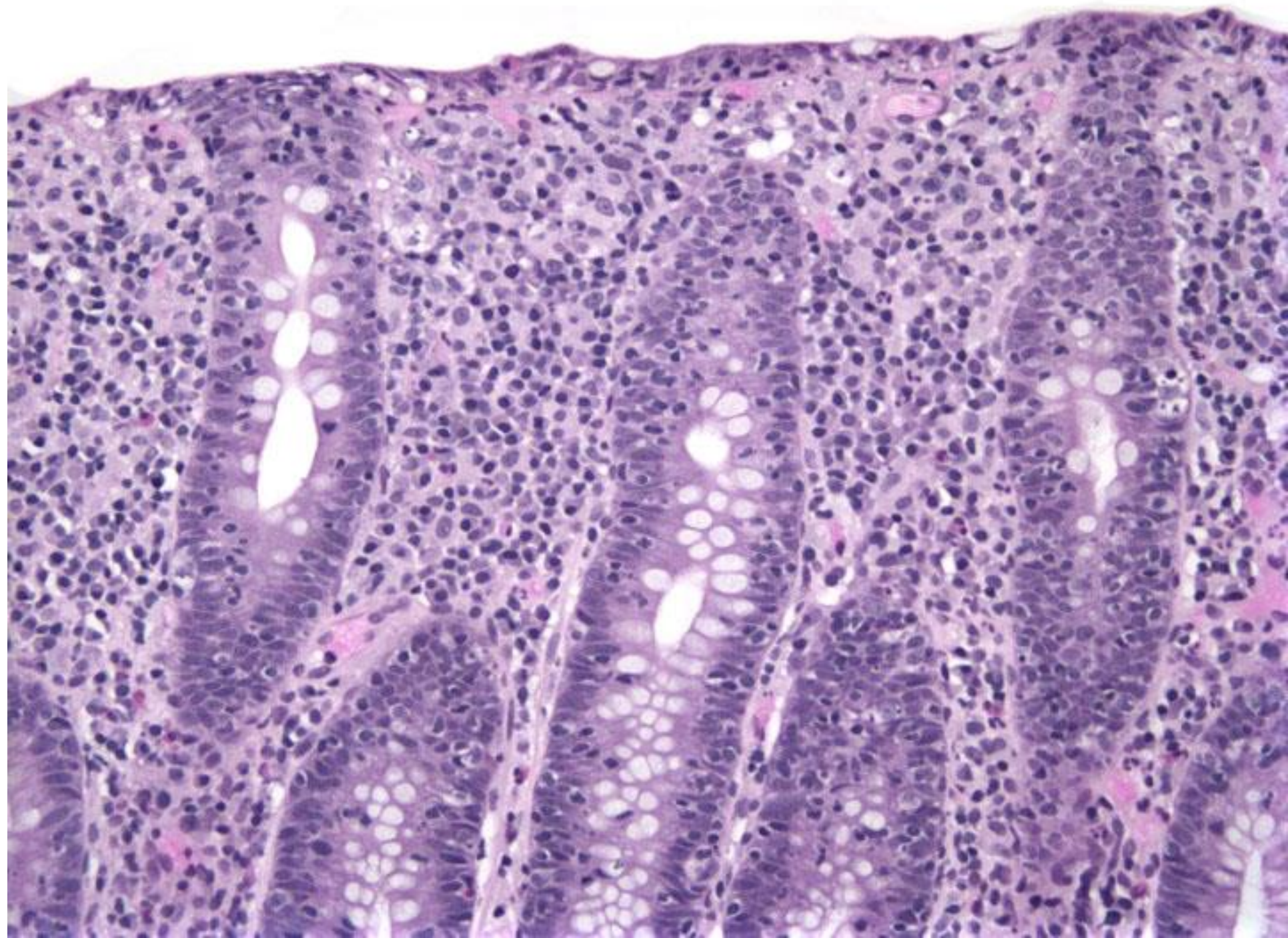
Lymphocytic Colitis

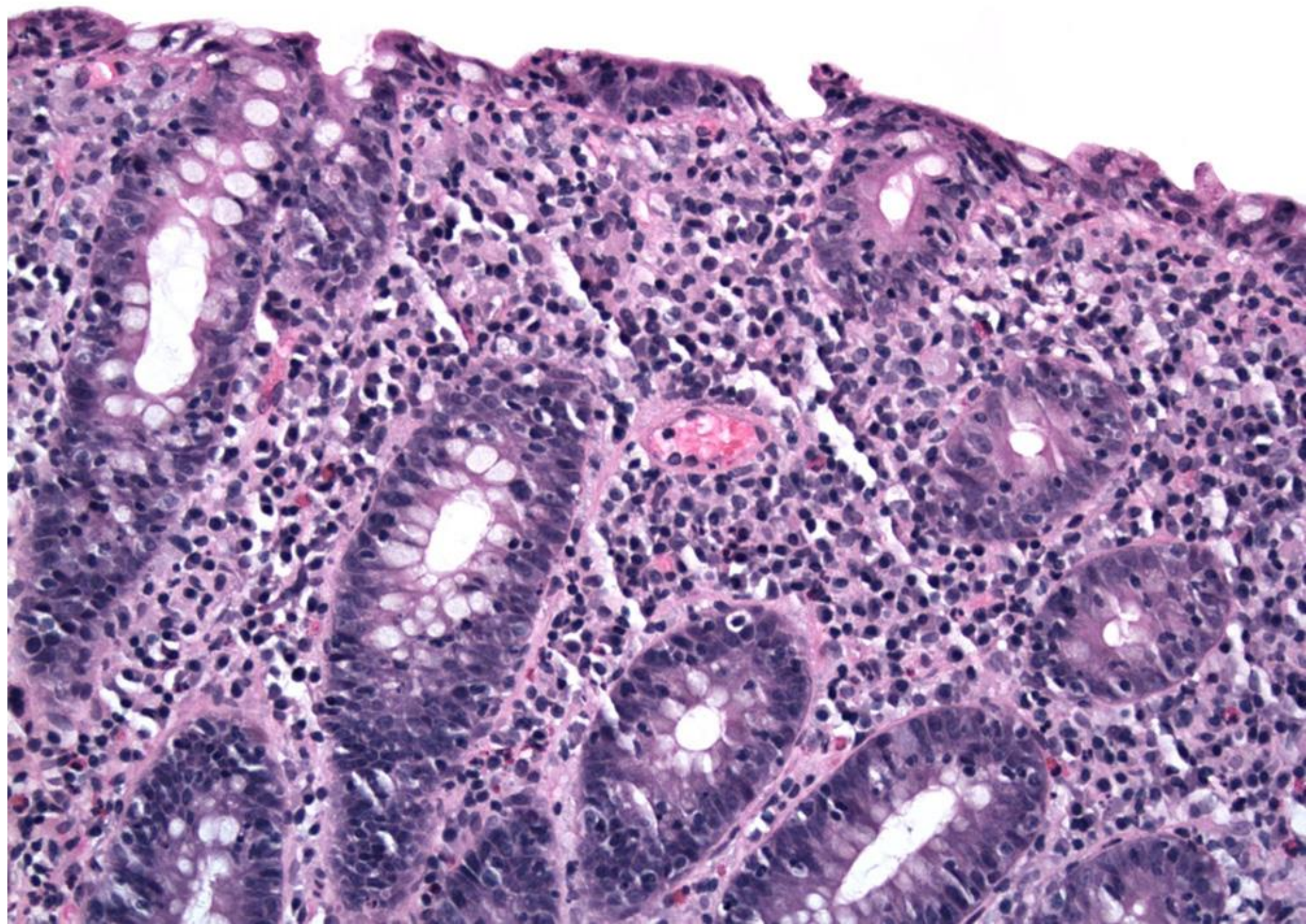
Histology

- Increased intraepithelial lymphocytosis
 - Usually greater than 10/100 enterocytes
 - Surface and crypts involved
- Surface epithelial damage
- Increased LP inflammatory component
 - Plasma cells common; neutrophils should be rare
- No abnormal subepithelial collagen band



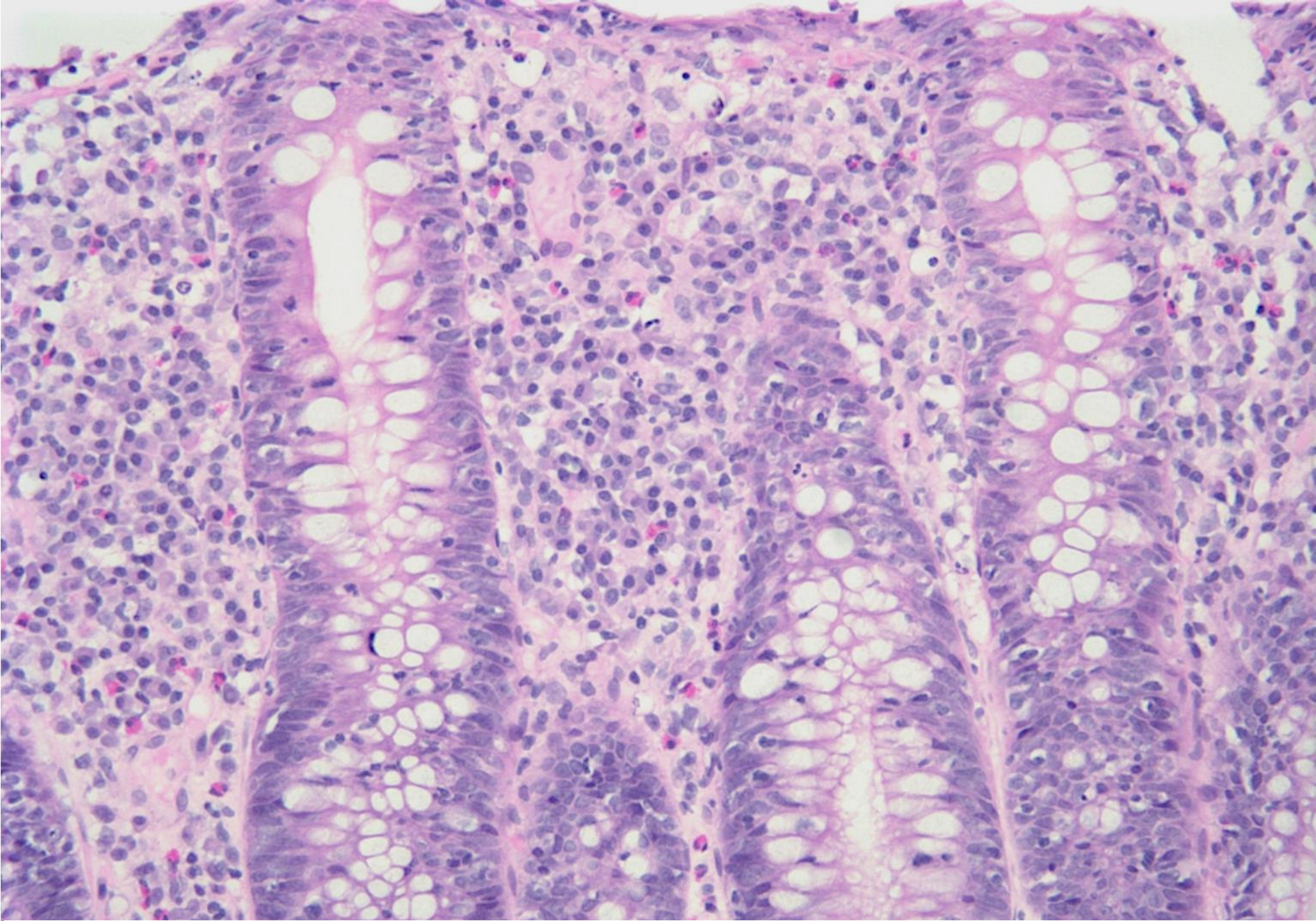






Other things that cause a lymphocytosis:

- NSAIDs, Olmesartan, checkpoint inhibitors
- Viral enterocolitis
- Crohn's
- Resolving bacterial infection
- Celiac Disease
 - 15% of LC patients have Celiac disease.
 - 5-31% of Celiac patients have LC/CC and up to 67% of refractory sprue patients have LC



Resolving Infection



Alys ponders the diagnostic nuances of inflammatory bowel disease.

Components of a useful “medical” intestinal biopsy report

- Diagnosis
 - Normal vs. inflamed
 - Chronic or not
 - How active is it
- Description
 - They like to know what we see
- Comment/implications
 - Even if there is no specific diagnosis, we need to give them a category and something to do

Report

- Colon, right, bx: Focal active colitis; sc
- Comment:
 - Description
 - There are no features of chronicity
 - These features are most commonly seen with self-limited processes such as infection, adverse drug reaction; can recommend drug history, infectious workup

Report

- Colon, left, bx: Chronic, active colitis
- Comment:
 - Description, emphasizing chronicity
 - Features compatible with _____ type of IIBD, depending on clinical/colonoscopic information
 - Dysplasia designation

Report

- Colon, left, bx: Chronic, active colitis; see comment
 - Give description
 - Note that per endoscopist colitis is present only in region of tics
 - Consistent with DDASC



newyorkermag

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Thank you!!



*"Hold on—your boarding pass says 'possum,'
but your passport says 'opossum.'"*