Small Bowel Malabsorptive Disorders:
celiac disease and other entities

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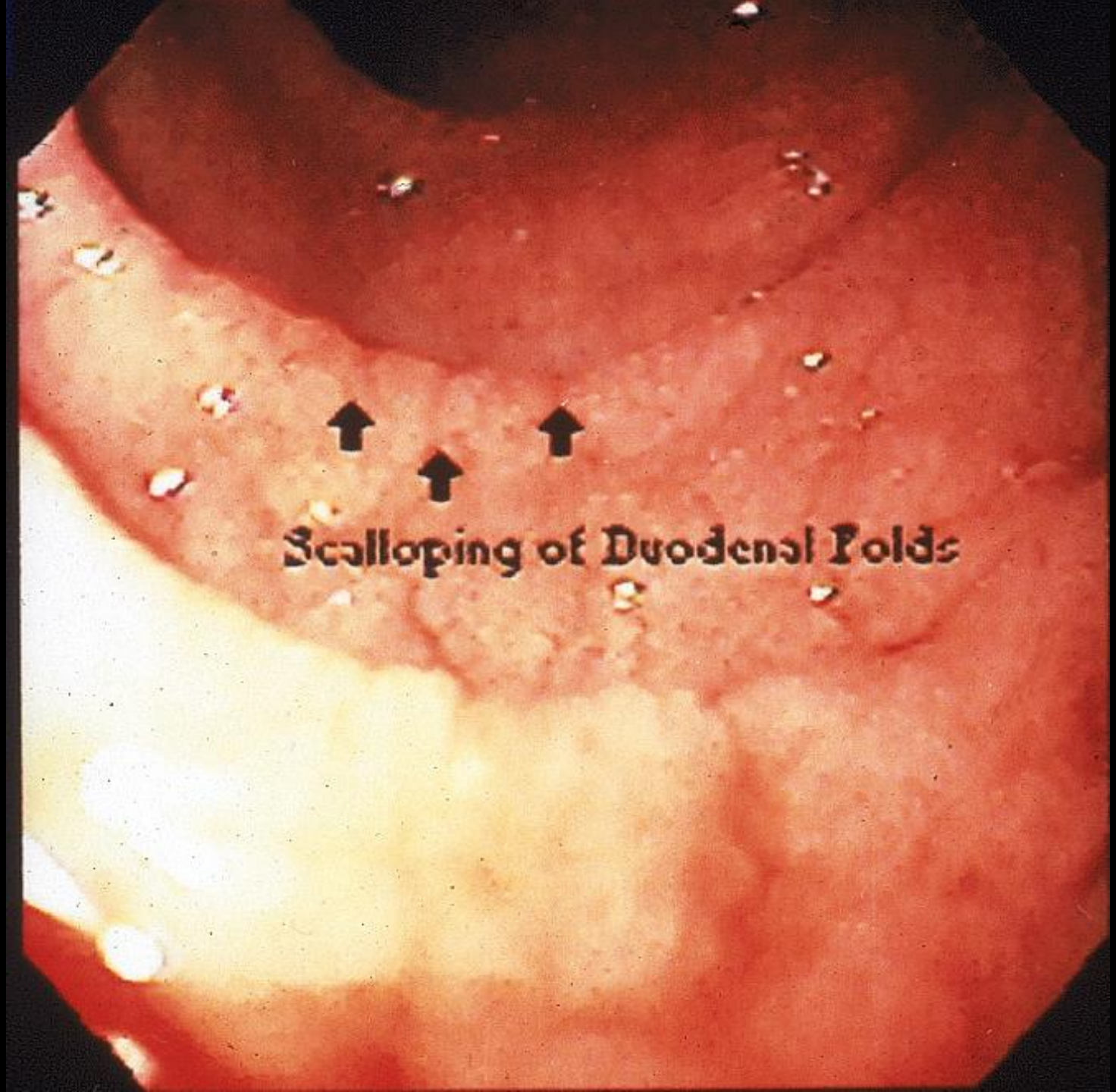
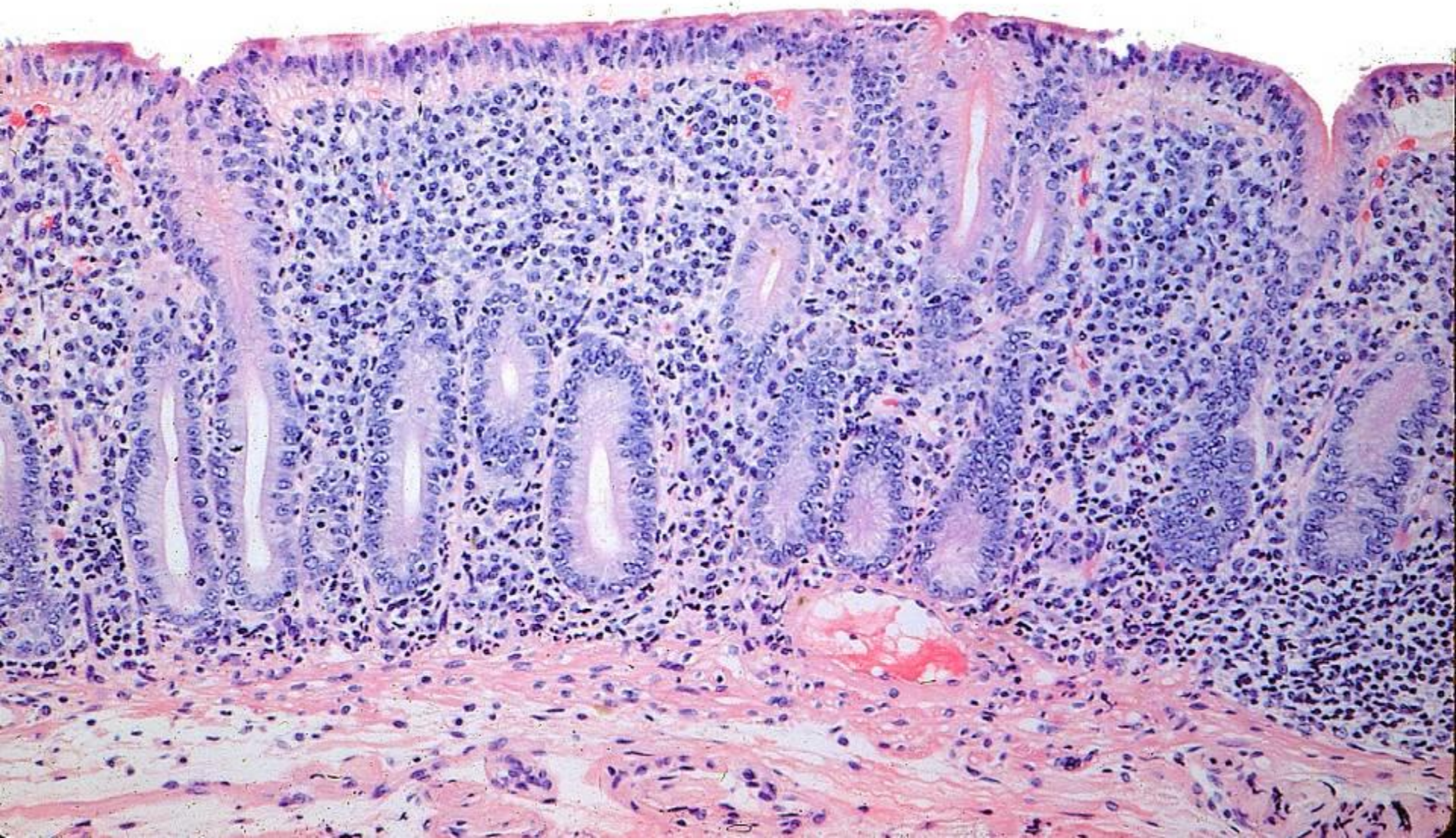
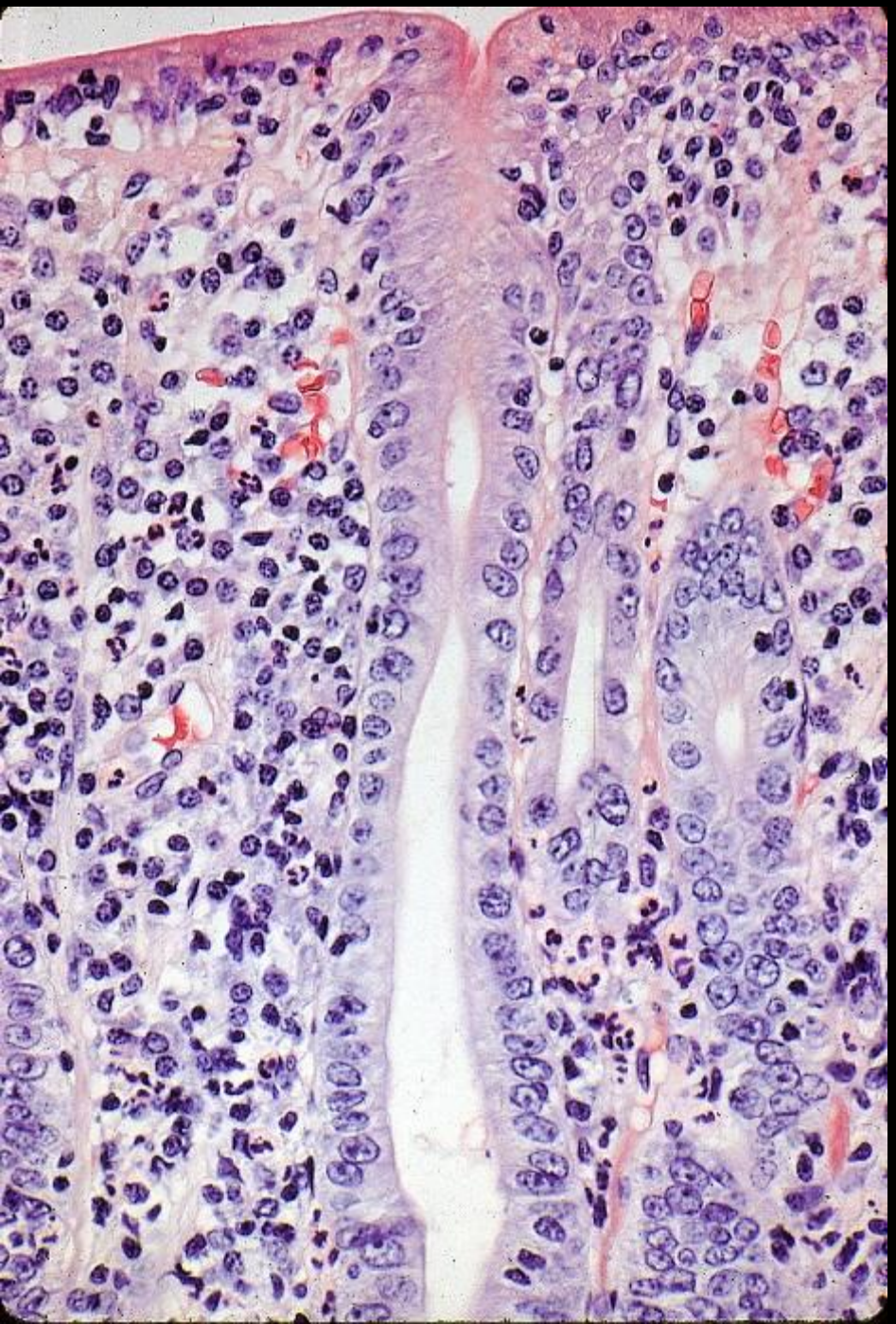
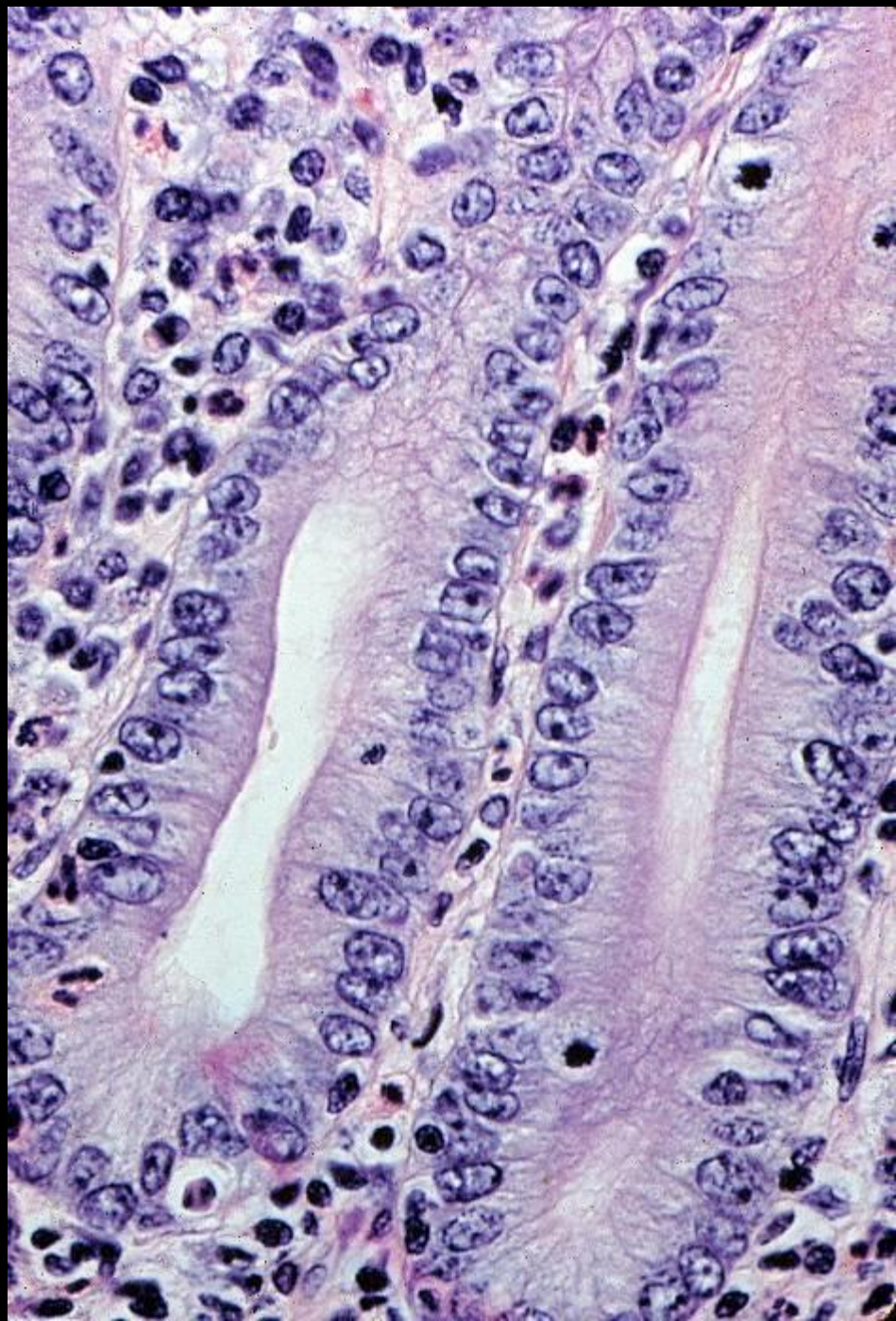

Scalloping of Duodenal Folds

Classic Old School Celiac Disease







Clinical Correlation is Mandatory

- **HLA testing:** absence of HLA DQ2 and DQ8 essentially excludes celiac disease
- **Serologic tests:**
  - Anti-tissue transglutaminase IgA (gold standard)
  - Anti-endomysium IgA antibody
  - Anti-deaminated gliadin peptide IgA
  - [Anti-gliadin IgA – no longer recommended]
- **IgA deficient individuals** (quant IgA level):
  - Anti-TTG IgG (gold standard)
  - Anti-DGP IgG

Rubio-Tapia A et al. ACG Clinical Guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013; 108:656-76.

Complete Villous Flattening with Crypt Hyperplasia

- **CELIAC DISEASE**

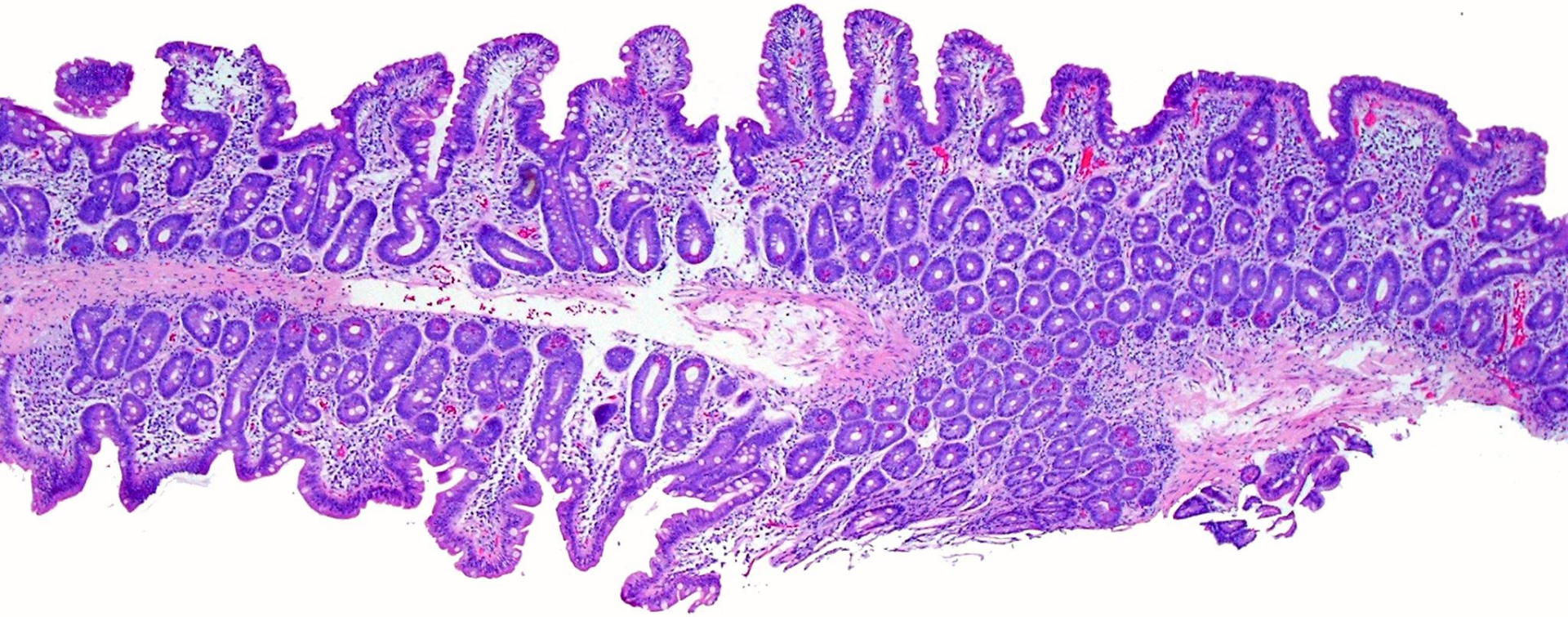
- Autoimmune enterocolitis
- Viral enteritis (rare cases)
- Tropical sprue (rare cases)
- Common variable immunodeficiency (rare cases)
- Medication (sartan) induced enteropathy

11-26029

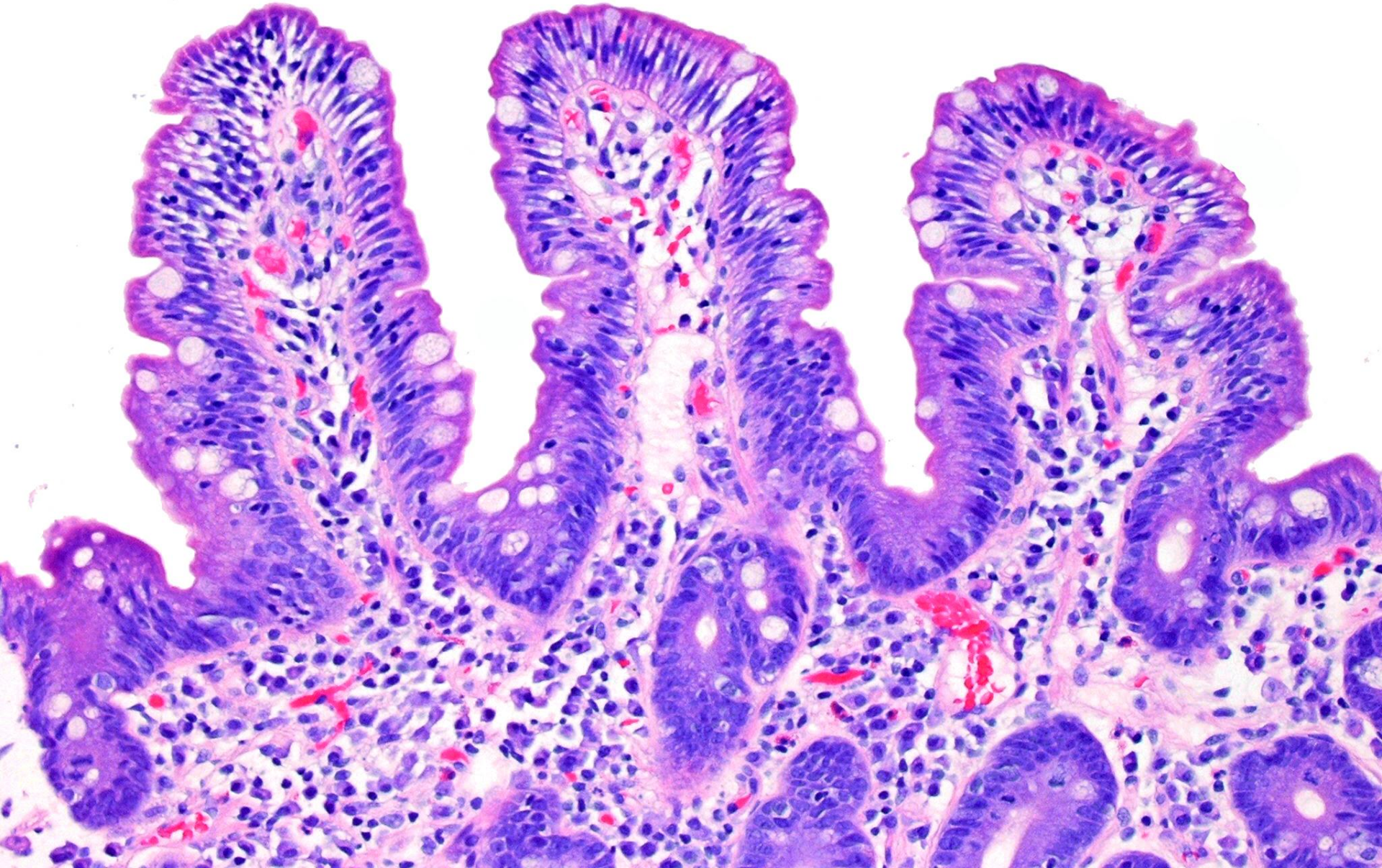
Clinical History

- 32 year old male with abdominal distress and diarrhea
- Endoscopic findings:
  - Esophagus & stomach normal
  - Flattening and decreased folds in the 2nd and 3rd parts of the duodenum
  - Scalloped folds in the 2nd part of the duodenum

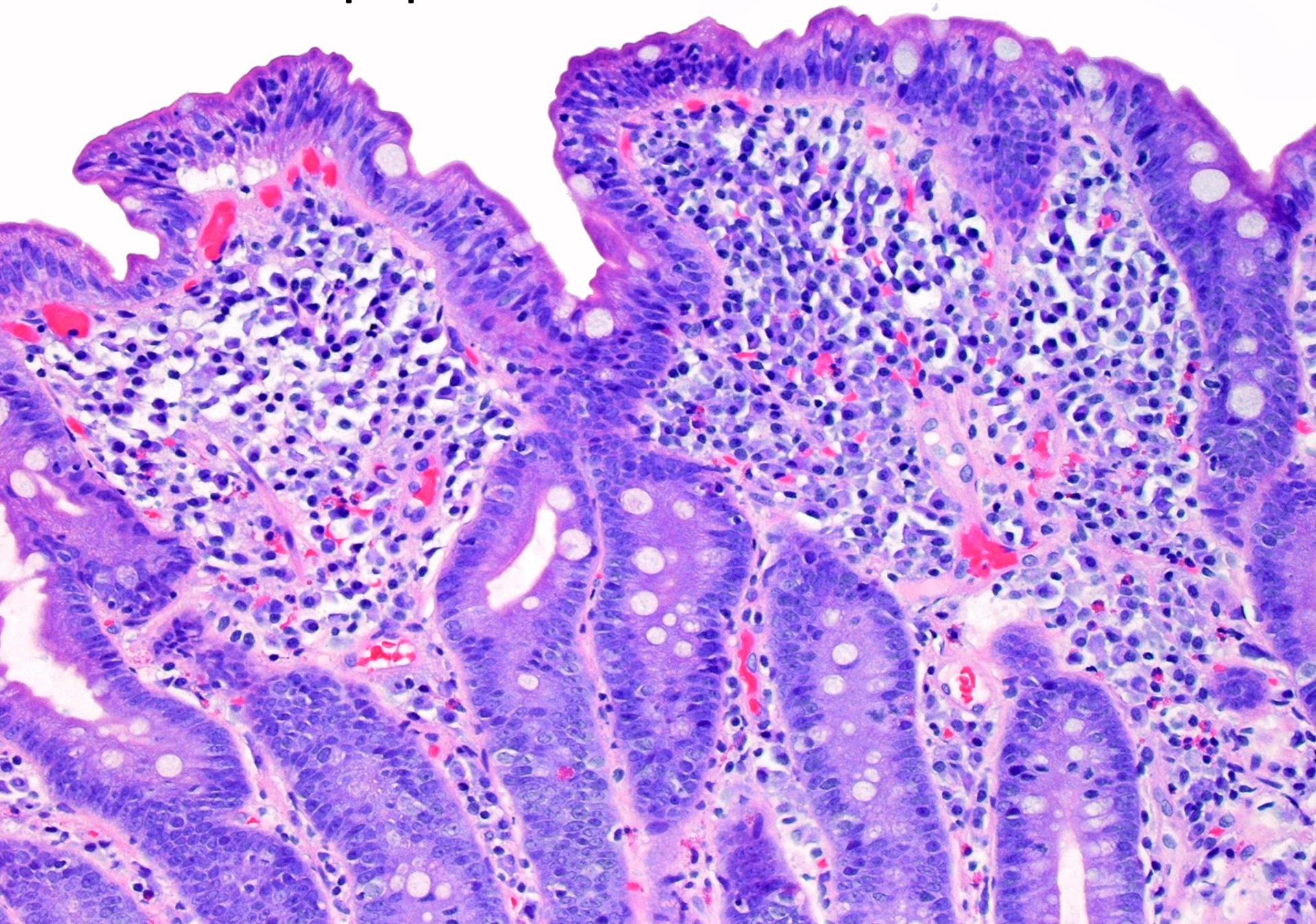
Moderate villous blunting and crypt hyperplasia



Increased intra-epithelial lymphocytes



Increased lamina propria mononuclear cells



No Knowledge of Celiac Panel Results

Upper GI endoscopic biopsies, duodenum:

- Duodenal mucosa with moderate villous blunting and increased intraepithelial lymphocytes. See comment

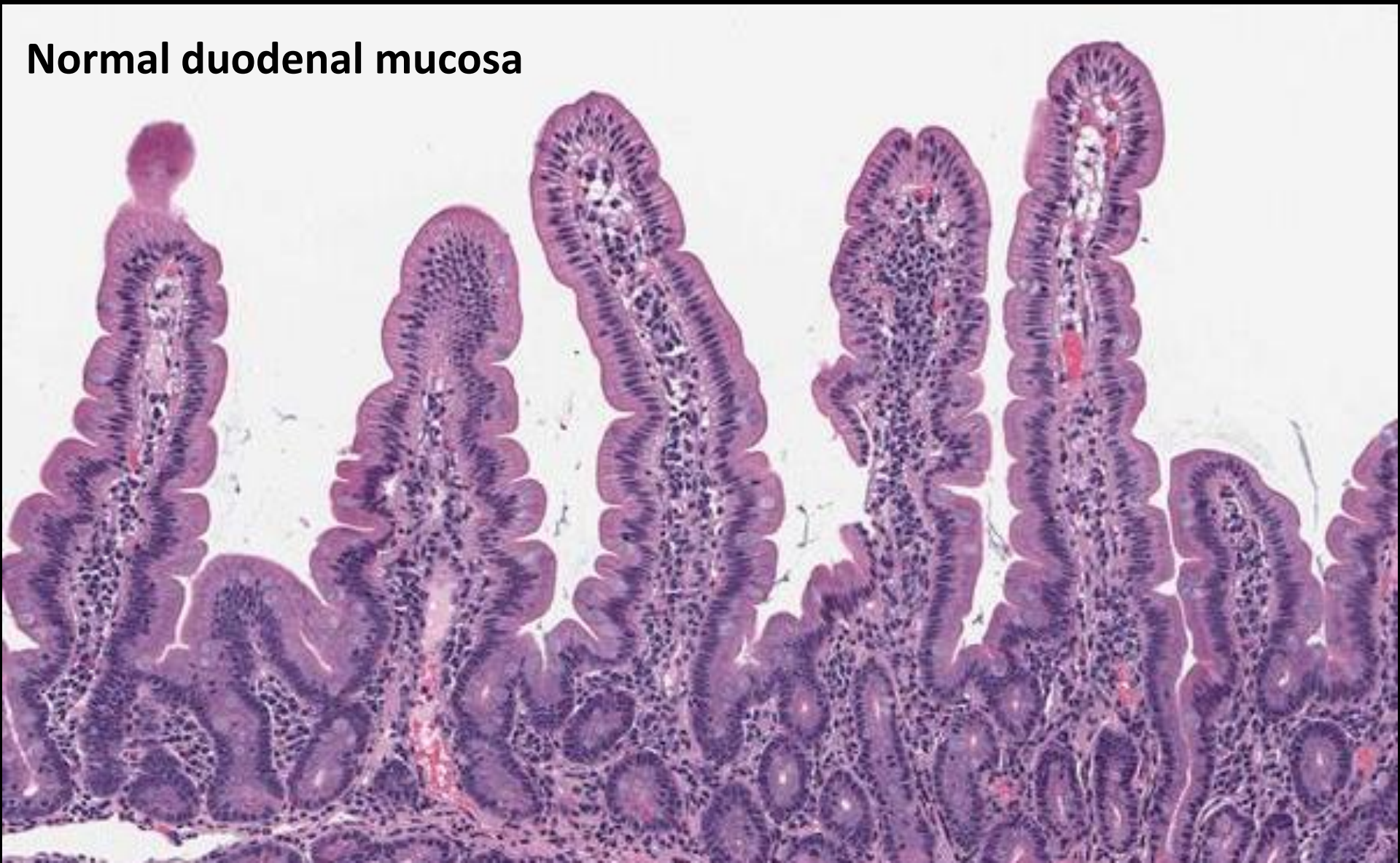
Comment: Celiac disease is a diagnostic consideration. Correlation with serologic tests results is necessary.

Pathologist is Aware Celiac Panel is Positive

Upper GI endoscopic biopsies, duodenum:

- Duodenal mucosa with moderate villous blunting and increased intraepithelial lymphocytes, consistent with celiac disease.

Provided Clinical History:
Rule out celiac disease



Whether the celiac panel is:

- not known
- negative
- positive

Upper GI endoscopic biopsies, duodenum:

- Duodenal mucosa without diagnostic abnormality.

See comment.

Comment: Sections of these large and well oriented biopsies reveal that the duodenal villi are long and slender and there is no increase in intraepithelial lymphocytes.

Malabsorptive Disorders
Morphologic Patterns

1. Complete villous blunting with crypt hyperplasia
2. Lesser degree of villous blunting with crypt hyperplasia (focal or diffuse)
3. Villous and crypt shortening (mucosal atrophy)
4. Normal mucosal architecture

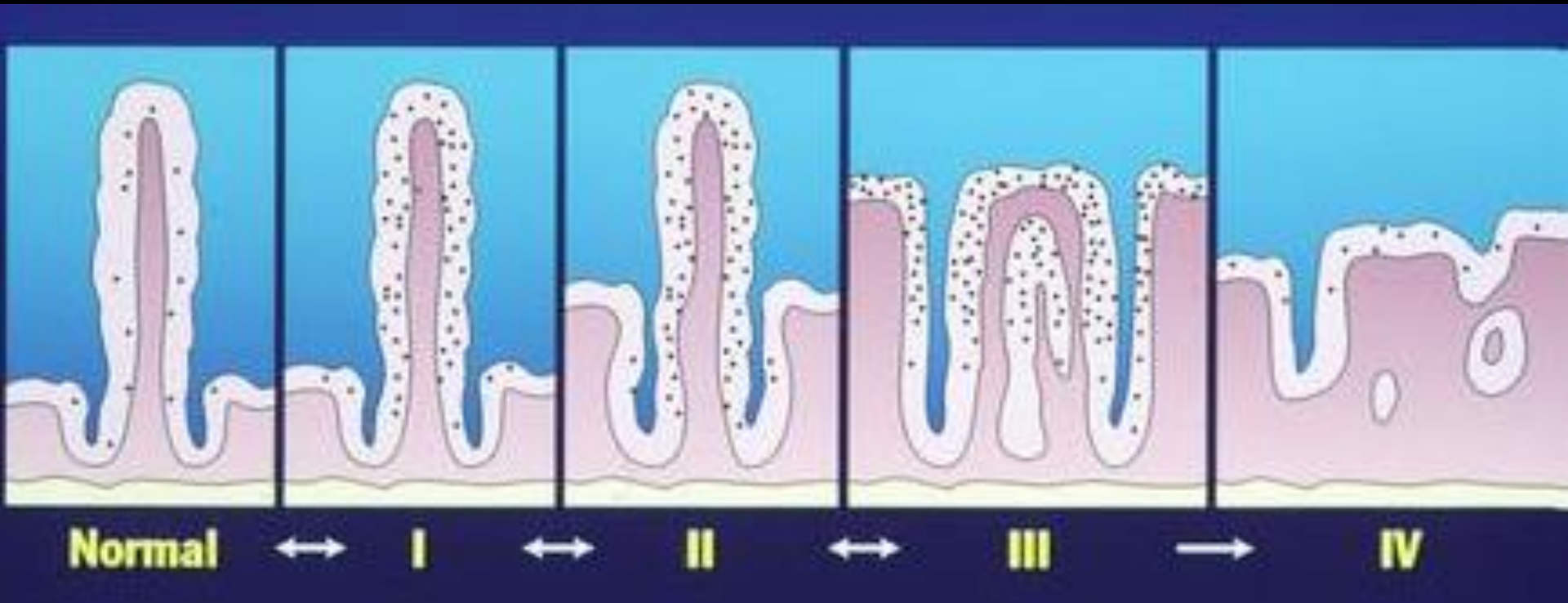
+ / - “distinctive features”

Intraepithelial lymphocytosis

Marsh Classification

Gastroenterology 1992; 102:330-54.

- **Type 0 – Normal architecture; no increase in IELs**
- **Type 1 – Normal architecture; > 40 IEL**
- **Type 2 – Crypt hyperplasia, normal villi; > 40 IELs**
- **Type 3 – Crypt hyperplasia & villous blunting; > 40 IELs**
- **Type 4 – Crypt & villous atrophy**



Modified Marsh Classification

Type 0 Normal architecture; no increase in IELs
Type 1 Normal architecture; > 25 IELs
Type 2 Crypt hyperplasia, normal villi; > 25 IELs
Type 3 Crypt hyperplasia, villous blunting; > 25 IELs
- 3a – mild villous blunting
- 3b – subtotal villous blunting
- 3c – total villous blunting

Type 4 Crypt & villous atrophy

Oberhuber G et al. Eur J Gastroenterol Hepatol 1999; 11:1185-94.

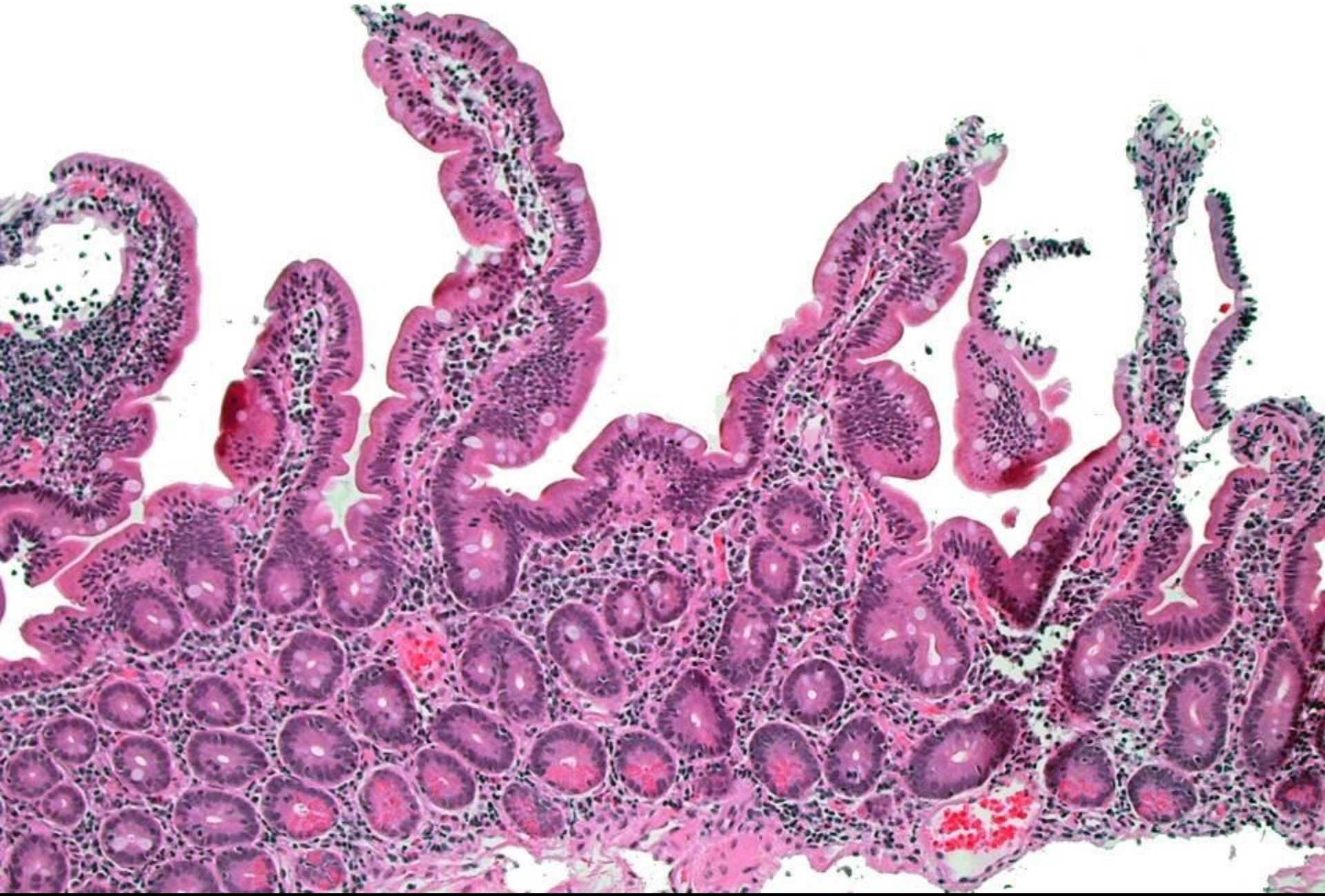
Current Treatment of Celiac Disease by Marsh/Oberhuber subtype

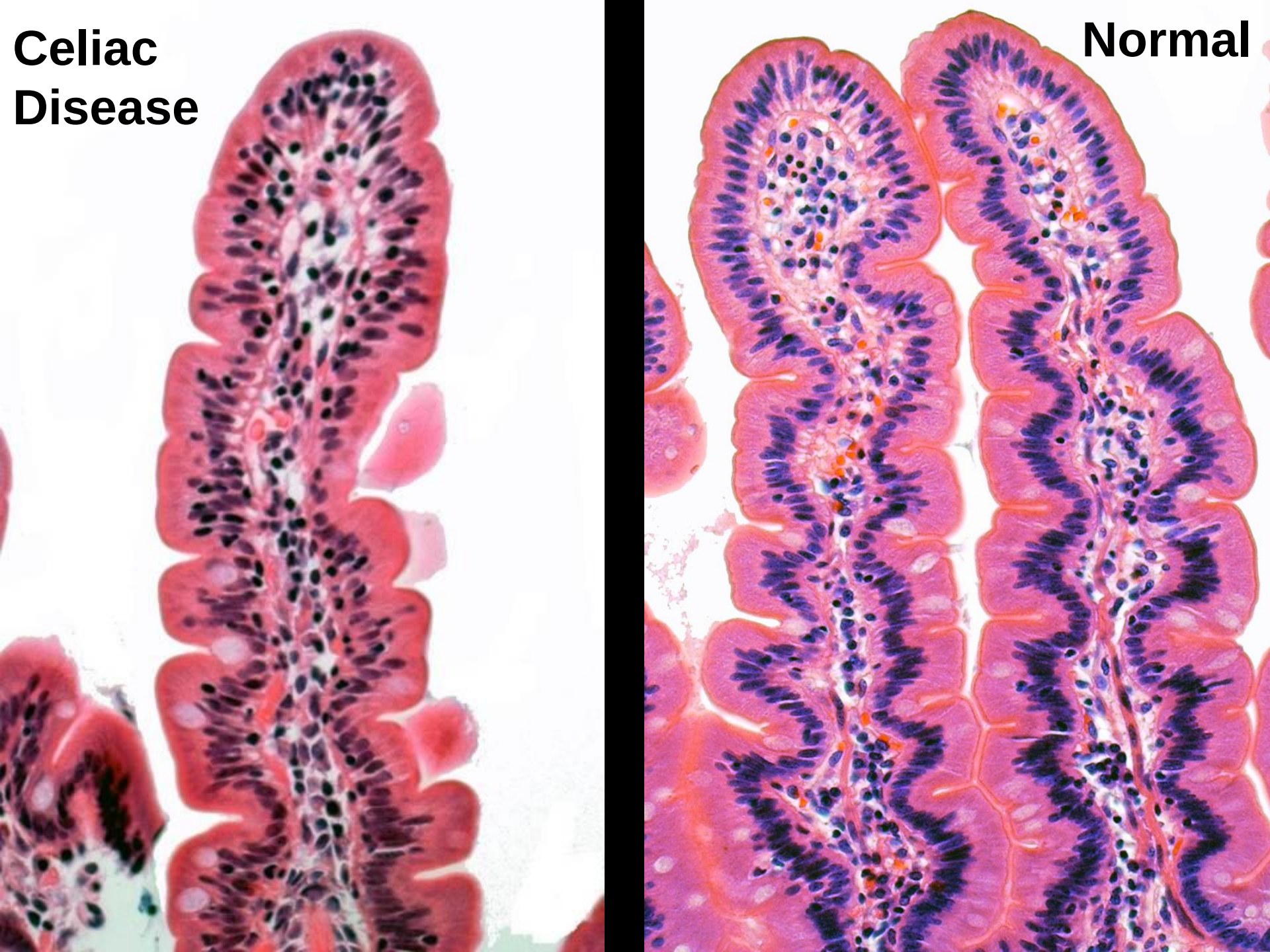
Type 0 - Gluten free diet for symptomatic patients?
Type 1 - Gluten free diet
Type 2 - Gluten free diet
Type 3
- 3a - Gluten free diet
- 3b - Gluten free diet
- 3c - Gluten free diet

Type 4 - Gluten free diet (? and immunosuppression)

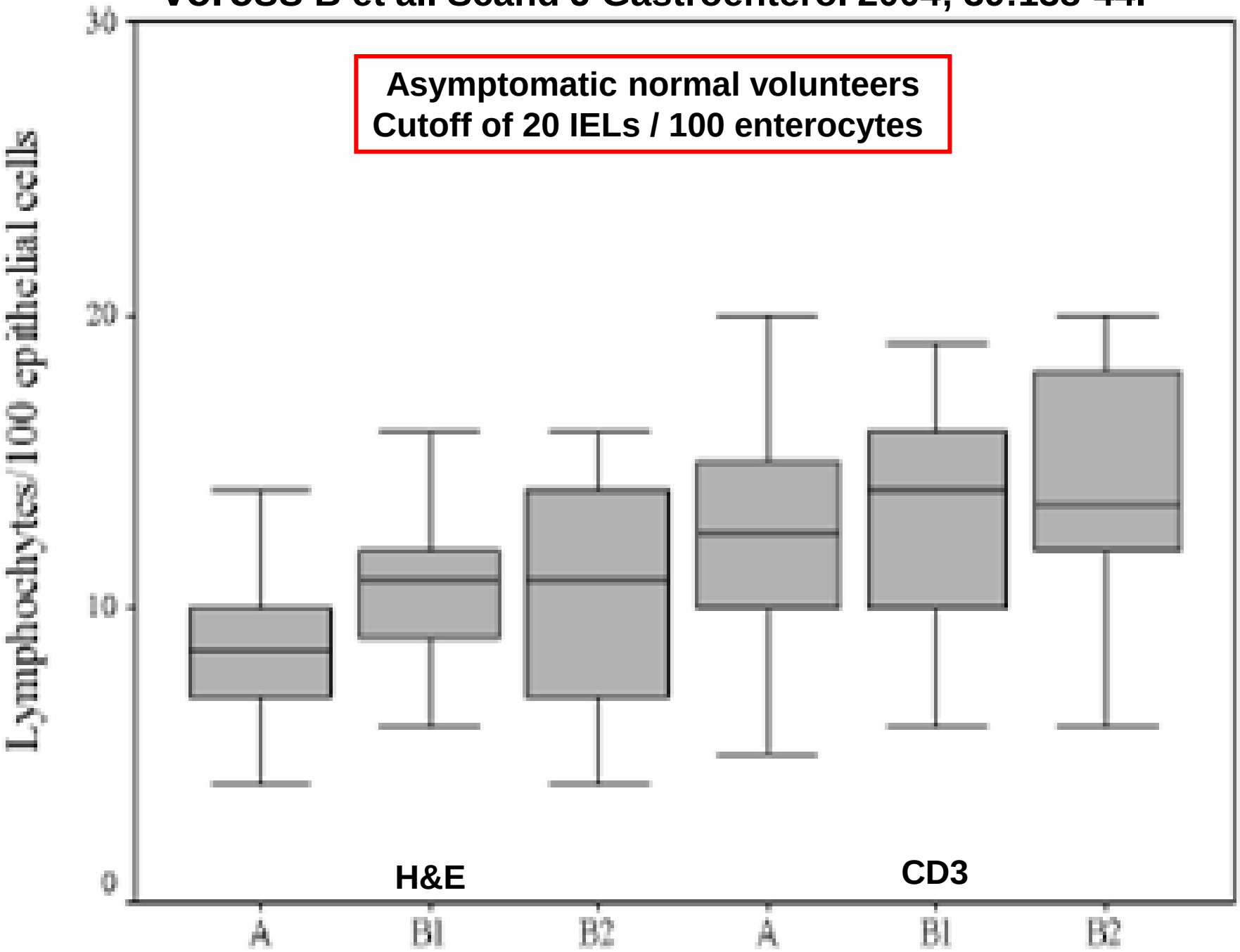
You don't have to give a MARSH score
(unless it will make your clinician love you)

Celiac Disease Type 1 (celiac serology panel positive)

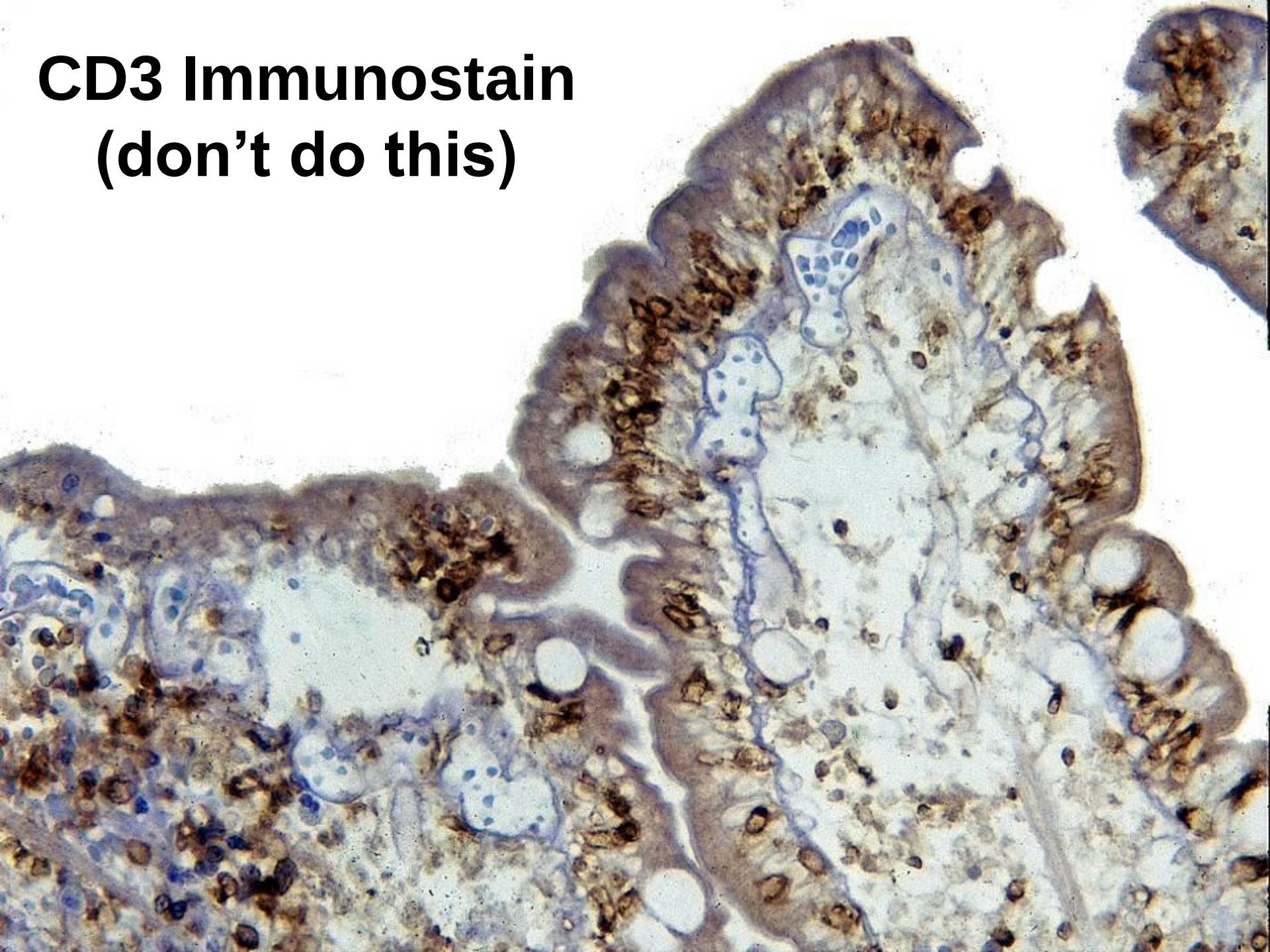



Celiac Disease
Normal

Veress B et al. Scand J Gastroenterol 2004; 39:138-44.



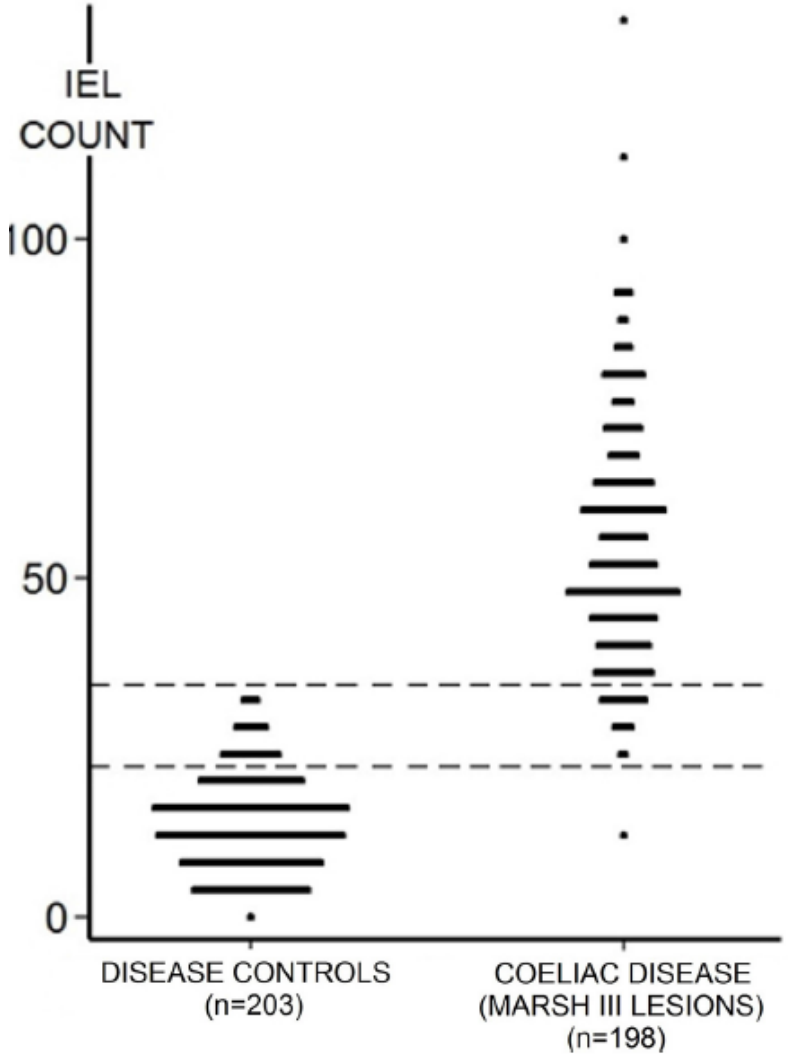
CD3 Immunostain (don’t do this)

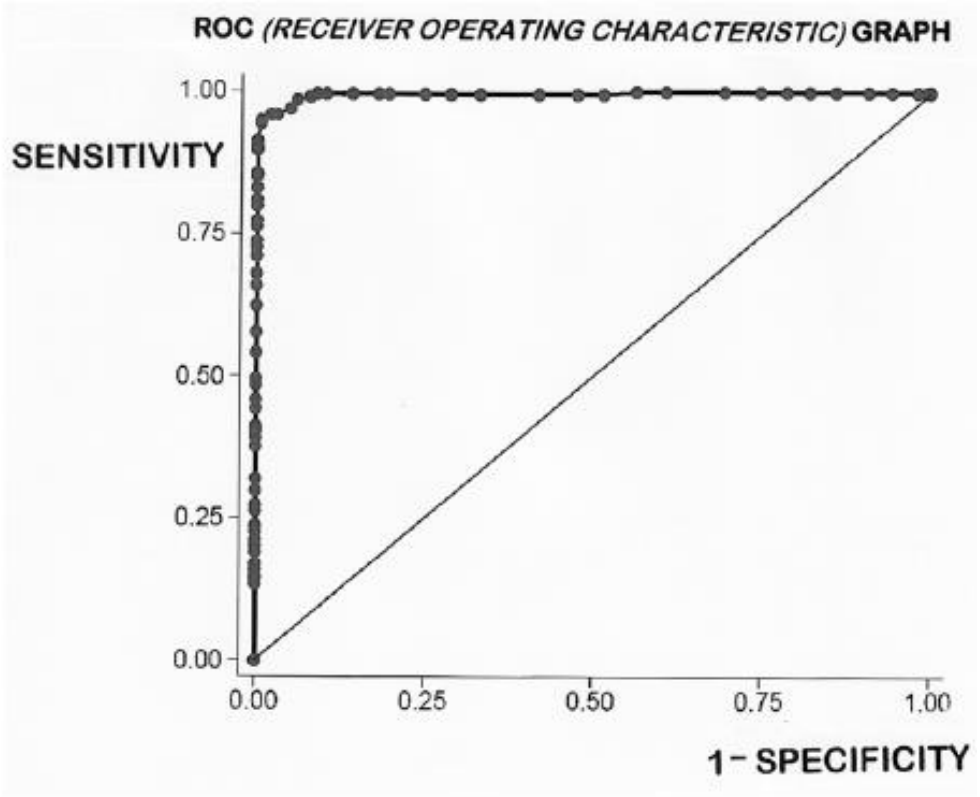


ROC-king onwards: intraepithelial lymphocyte counts, distribution & role in coeliac disease mucosal interpretation

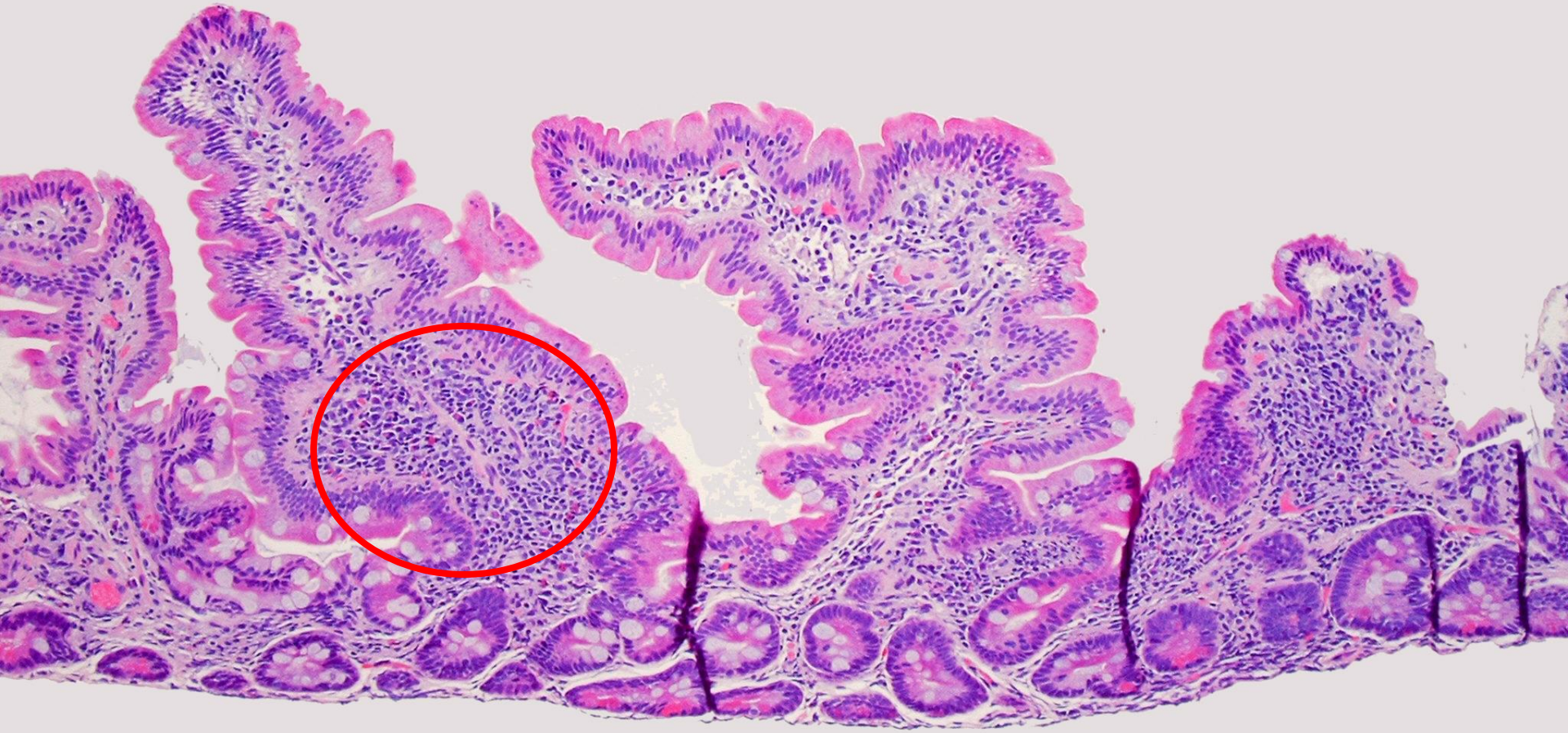
Rostami K, *et al*. *Gut* 2017;**0**:1–7. doi:10.1136/gutjnl-2017-314297

Cutoff of 25 IELs/100 enterocytes

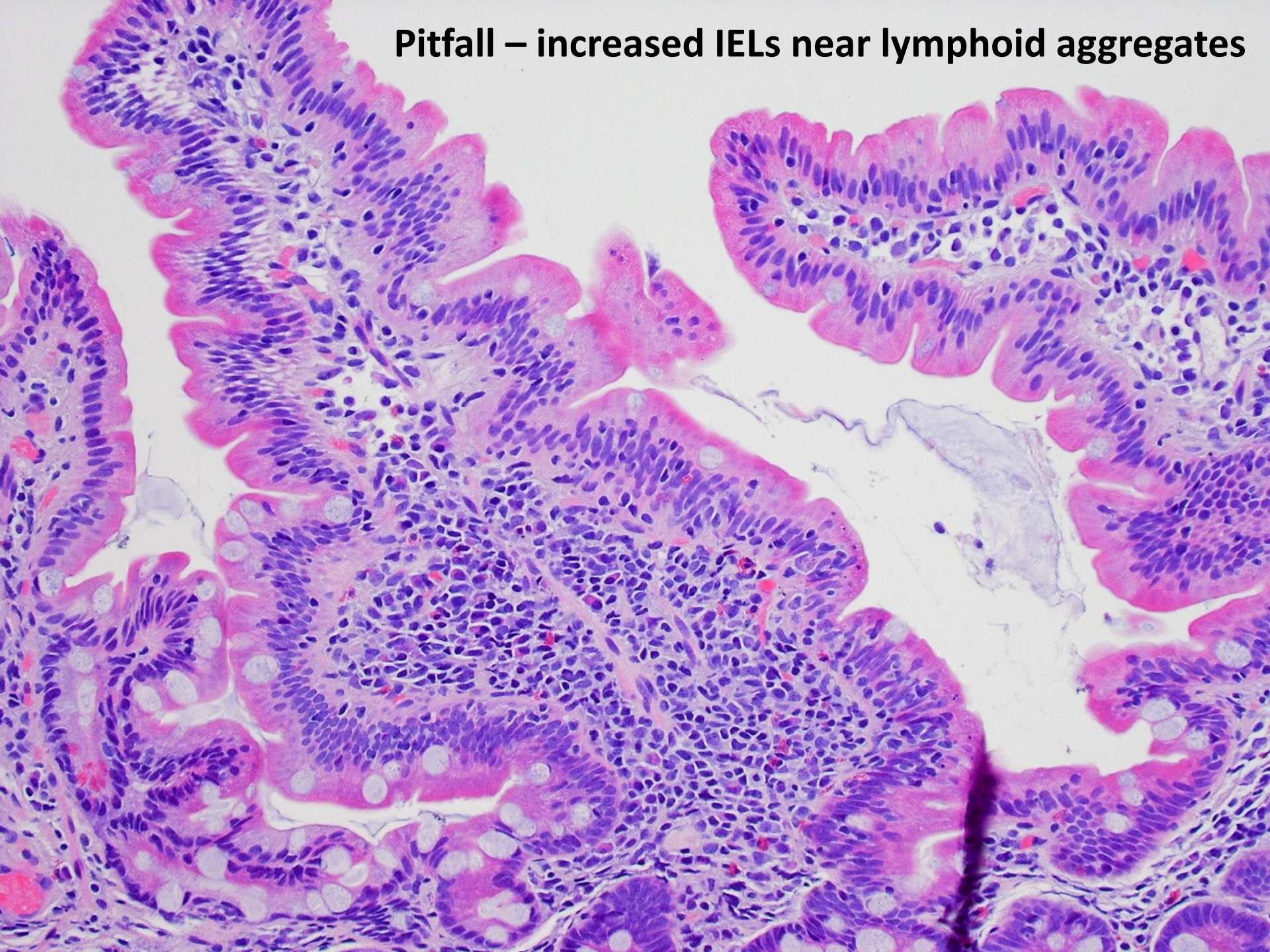




3 celiac disease pts below cutoff (false negative)
12 control patients above cutoff (false positive)



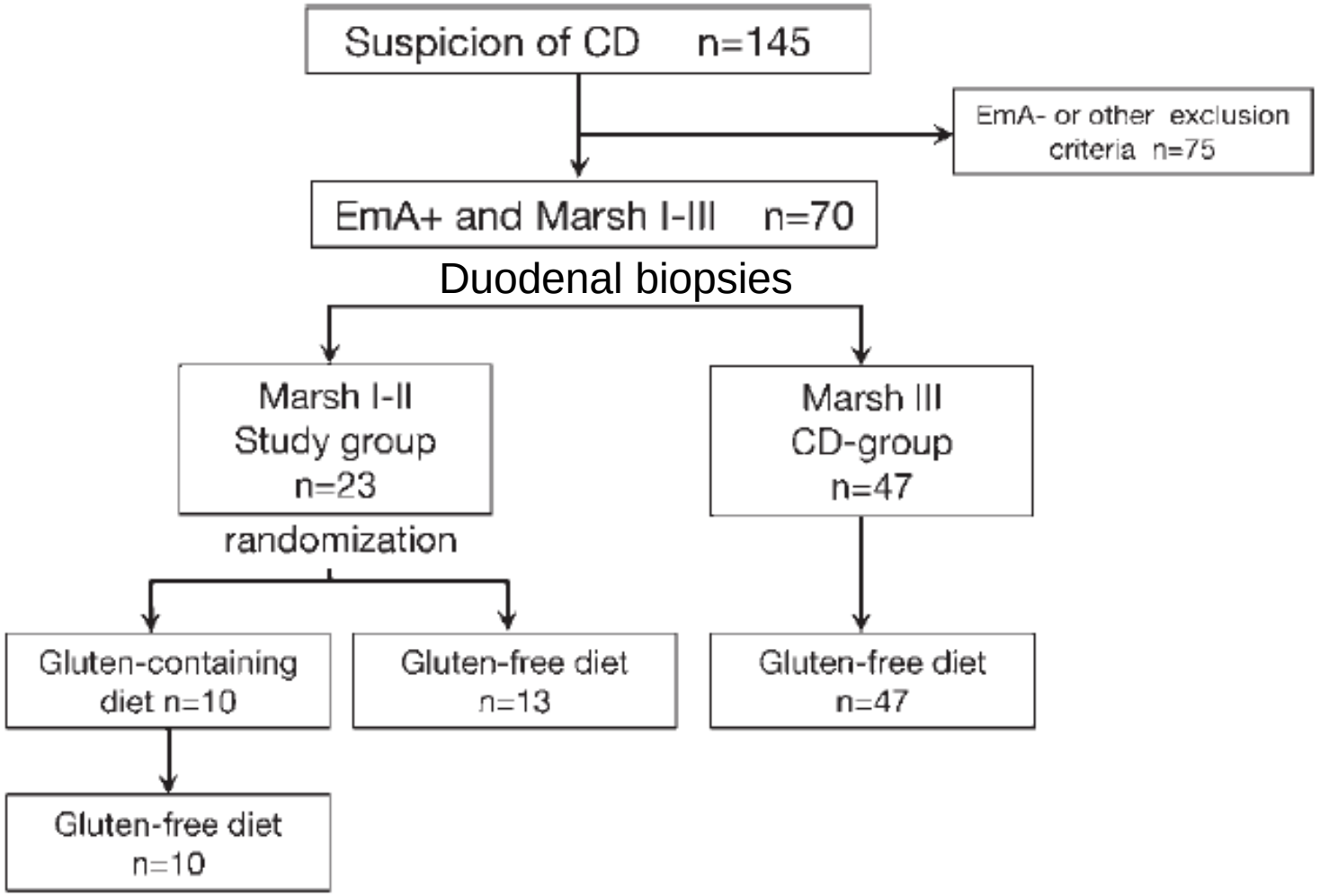
Pitfall – increased IELs near lymphoid aggregates



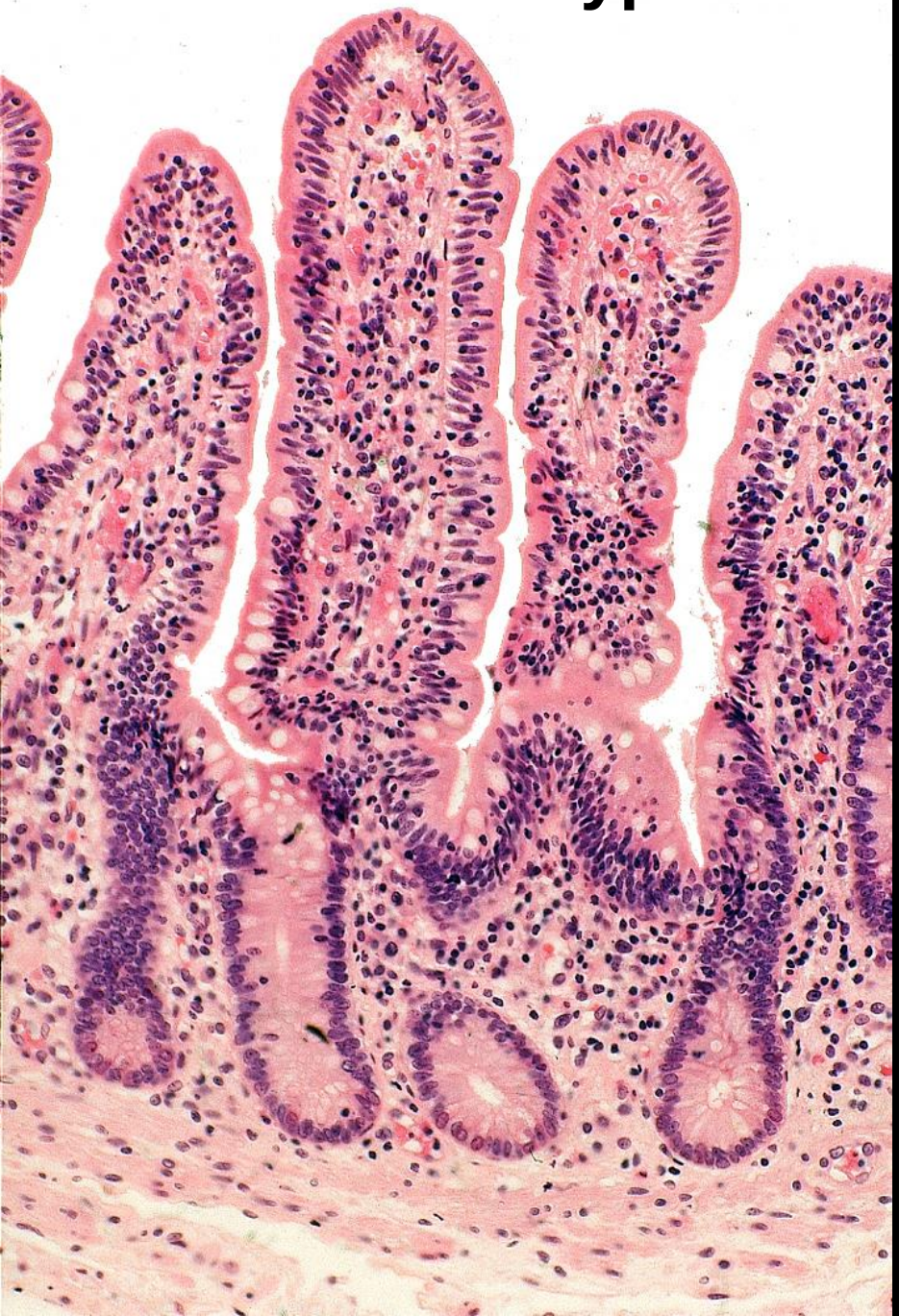
Diagnosing Mild Enteropathy Celiac Disease: A Randomized, Controlled Clinical Study

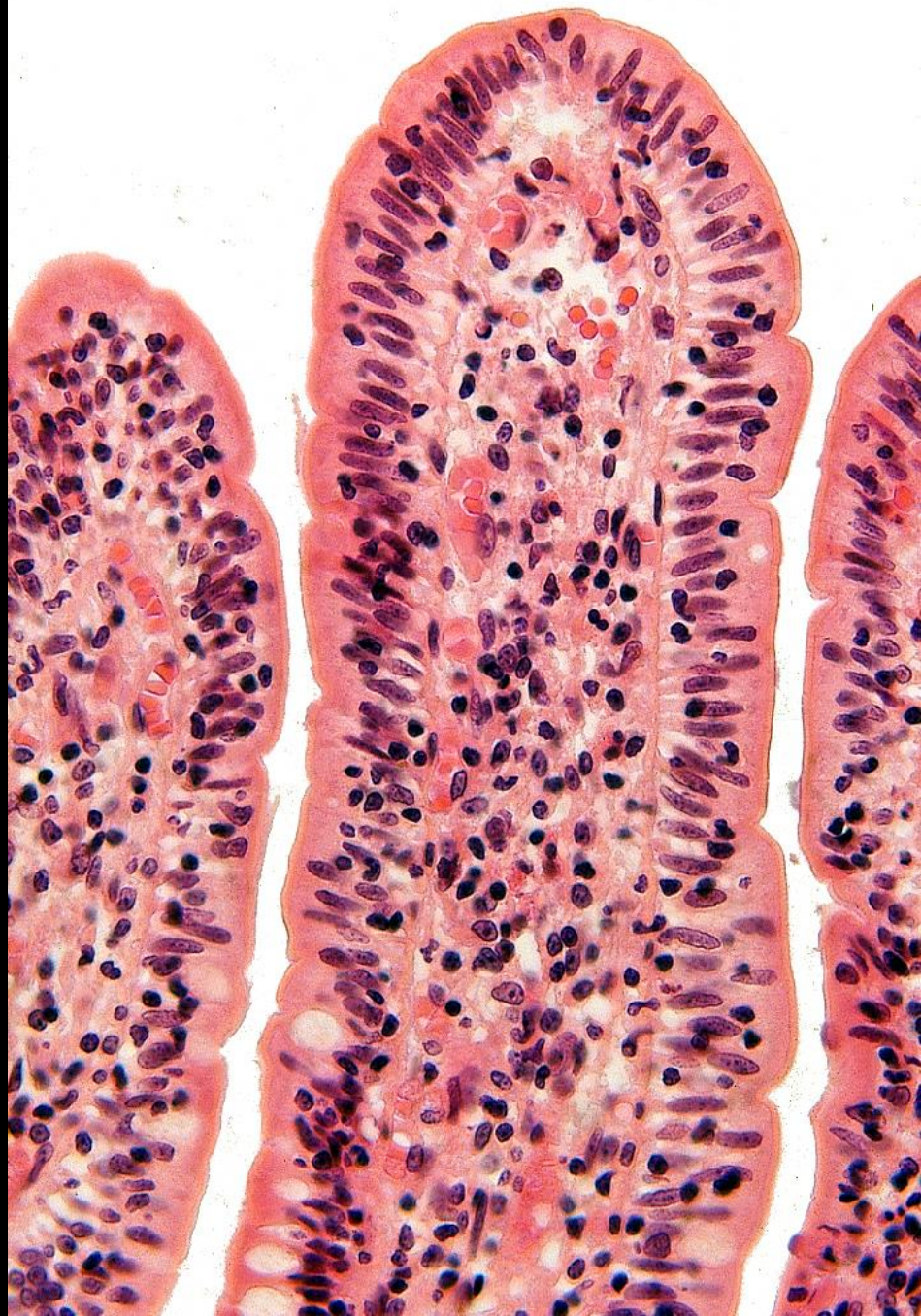
GASTROENTEROLOGY 2009;136:816–823

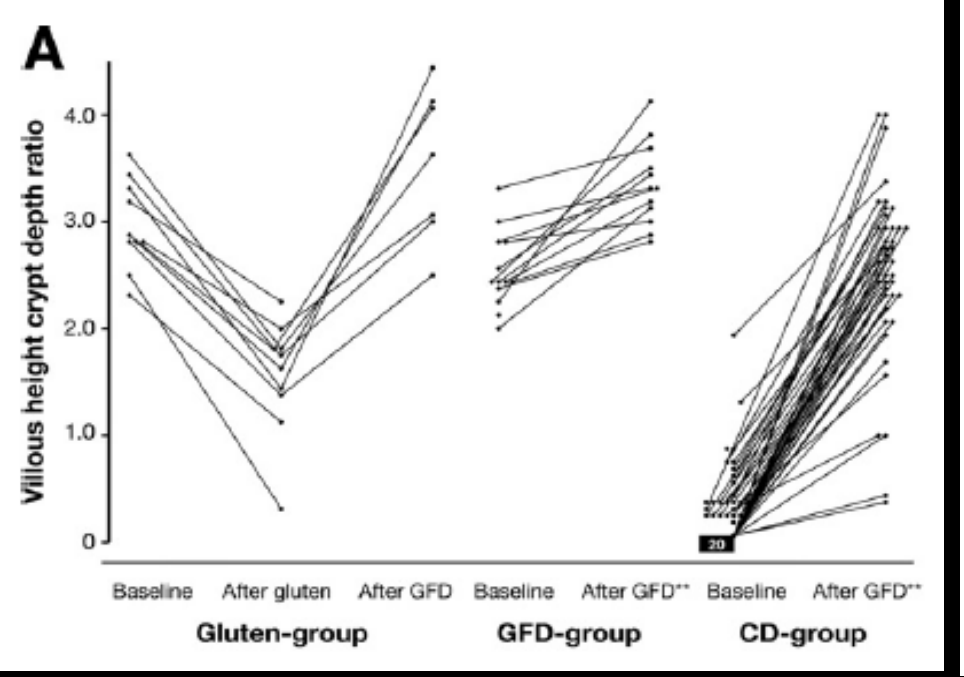
KALLE KURPPA,* PEKKA COLLIN,‡,§ MERVI VILJAMAA,* KATRI HAIMILA,‖ PÄIVI SAAVALAINEN,¶ JUKKA PARTANEN,# KAIJA LAURILA,* HEINI HUHTALA,** KAIJA PAASIKIVI,‡‡ MARKKU MÄKI,* and KATRI KAUKINEN‡,§

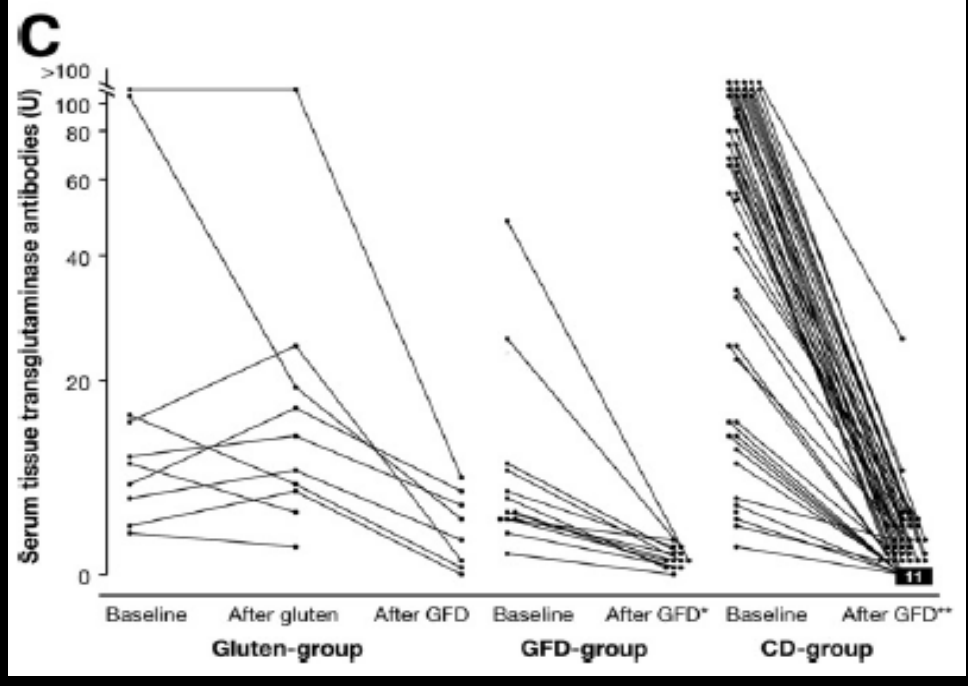


Celiac Disease Type 1









	Study group					Control groups		
	Gluten group (n = 10)			GFD group (n = 13)		CD group (n = 47)		Non-CD group (n = 34)
	Baseline	After gluten	After GFD	Baseline	After GFD	Baseline	After GFD	Baseline
CD3+ IELs, cell/mm								
Median	61[a]	62	47	62[a]	41[b]	63[a]	50[c]	32
Range	37–79	38–84	28–68	37–134	24–103	34–124	15–133	11–62
αβ + IELs, cell/mm								
Median	32[d]	38	22	44[a]	21[c]	45[a]	30[b]	24
Range	20–50	21–66	14–34	16–63	14–58	14–104	5–89	7–47
γδ + IELs, cell/mm								
Median	19.1[a]	23.0	14.0	19.1[a]	21.7[b]	19.5[a]	17.1[c]	2.1
Range	12.8–38.5	14.0–36.3	8.5–29.2	7.0–51.8	8.4–31.8	5.9–54.6	6.2–51.5	0–24.8
HLA-DR expression, n (%)								
Enhanced	8/9 (89)[d]	7/9 (78)	5/6 (83)	13/13 (100)[a]	7/12 (58)	42/42 (100)[a]	29/41 (71)	20/38 (53)
Normal	1/9 (11)	2/9 (22)	1/6 (17)	0/13 (0)	5/12 (42)	0/42 (0)	12/41 (29)	18/38 (47)

Celiac Disease without Villous Atrophy in Children: A Prospective Study

Kalle Kurppa, MD, Merja Ashorn, MD, PhD, Sari Iltanen, MD, PhD, Lotta L. E. Koskinen, PhD, Päivi Saavalainen, PhD, Outi Koskinen, MD, Markku Mäki, MD, PhD, and Katri Kaukinen, MD, PhD

(J Pediatr 2010;157:373-80).

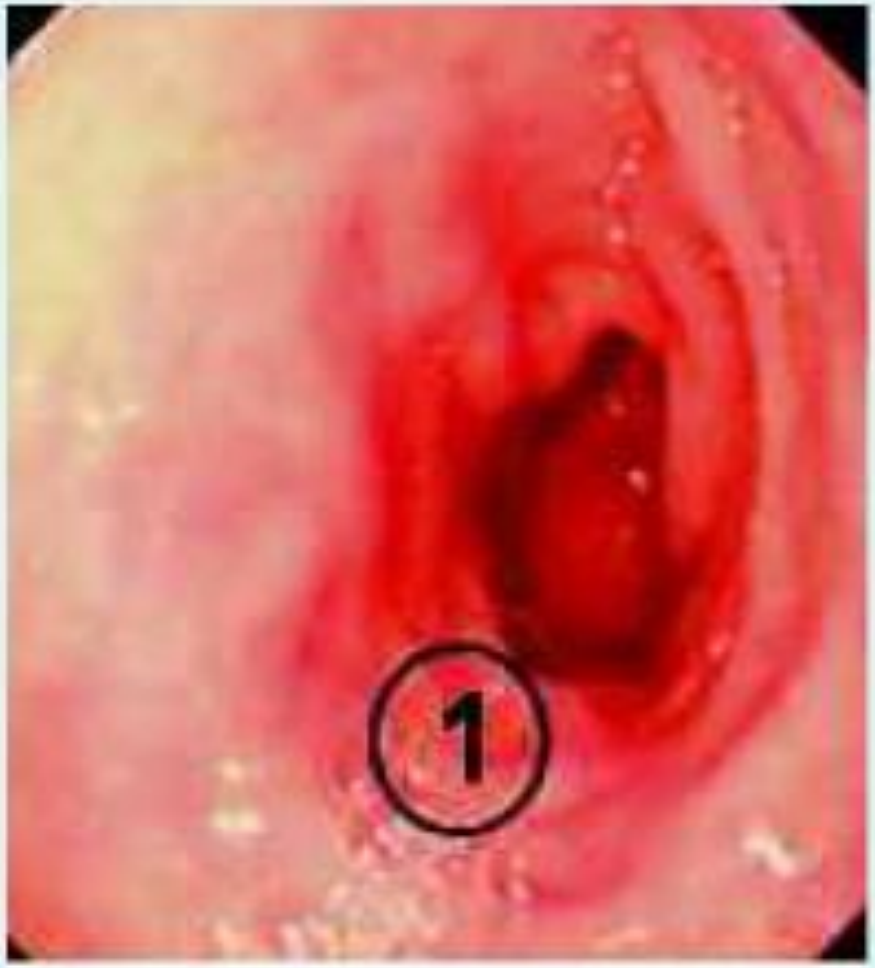
Table II. Baseline and follow-up data on the 17 children who were endomysial antibody positive with normal small-bowel mucosal villous morphology at baseline

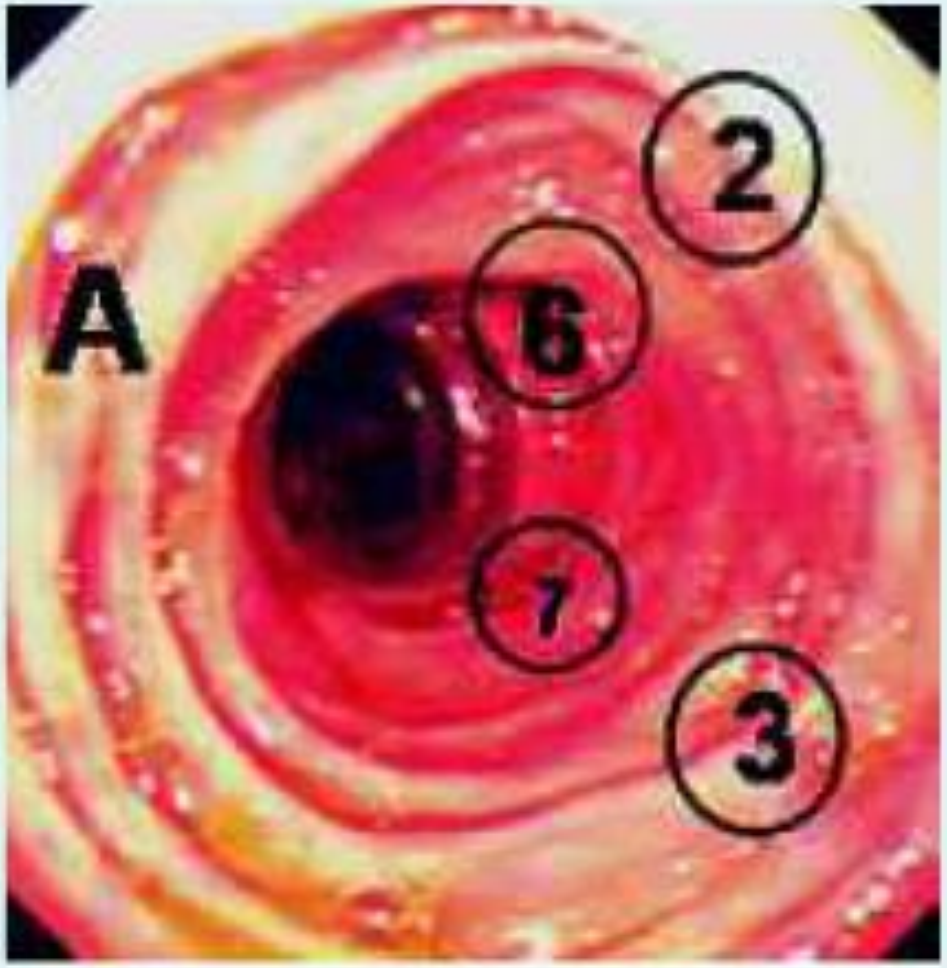
	Baseline						Follow-up				
	Sex	Age, years	Main symptom	EmA titer	TG2-ab U	Marsh grade	Intervention	Symptoms	EmA	TG2- ab U	Marsh grade
1	F	6	Abdominal pain	1:1000	33.2	1	Gluten	Remained	1:1000	40.6	3
2	M	10	Asymptomatic†	1:500	28.2	1	Gluten	None	1:500	>120.0	3
3	F	11	Abdominal pain	1:200	>120.0	1	Gluten	Remained	ND‡	ND‡	3
4	M	11	Abdominal pain	1:200	30.4	1	Gluten	Remained	1:200	112.5	3
5	F	10	Diarrhea	1:50	5.0	1	Gluten	Remained	1:500	13.9	3
6	F	17	Abdominal pain	1:5	47.0	1	Gluten	Remained	1:500	>120.0	3
7	F	6	Flatulence	1:5	9.4	1	Gluten	Remained	1:50	15.2	0
8	F	13	Abdominal pain	1:5	<5.0	0	Gluten	Remained	1:50	<5.0	3
9	F	11	Diarrhea	1:1000	52.5	1	GFD	None	1: <5	<5.0	ND*
10	M	4	Weight loss	1:200	13.6	1	GFD	Alleviated	1: <5	<5.0	ND*
11	M	5	Abdominal pain	1:100	10.3	1	GFD	None	1: <5	<5.0	ND*
12	M	13	Diarrhea	1:100	5.2	1	GFD	None	1: <5	<5.0	ND*
13	F	5	Abdominal pain	1:5	7.4	0	GFD	None	1: <5	<5.0	ND*
14	F	15	Abdominal pain	1:100	16.3	0	ND§	ND	ND	ND	ND
15	M	10	Abdominal pain	1:50	6.4	1	ND§	ND	ND	ND	ND
16	F	16	Poor growth	1:50	5.5	1	ND§	ND	ND	ND	ND
17	M	11	Weight loss	1:5	<5.0	1	ND§	ND	ND	ND	ND

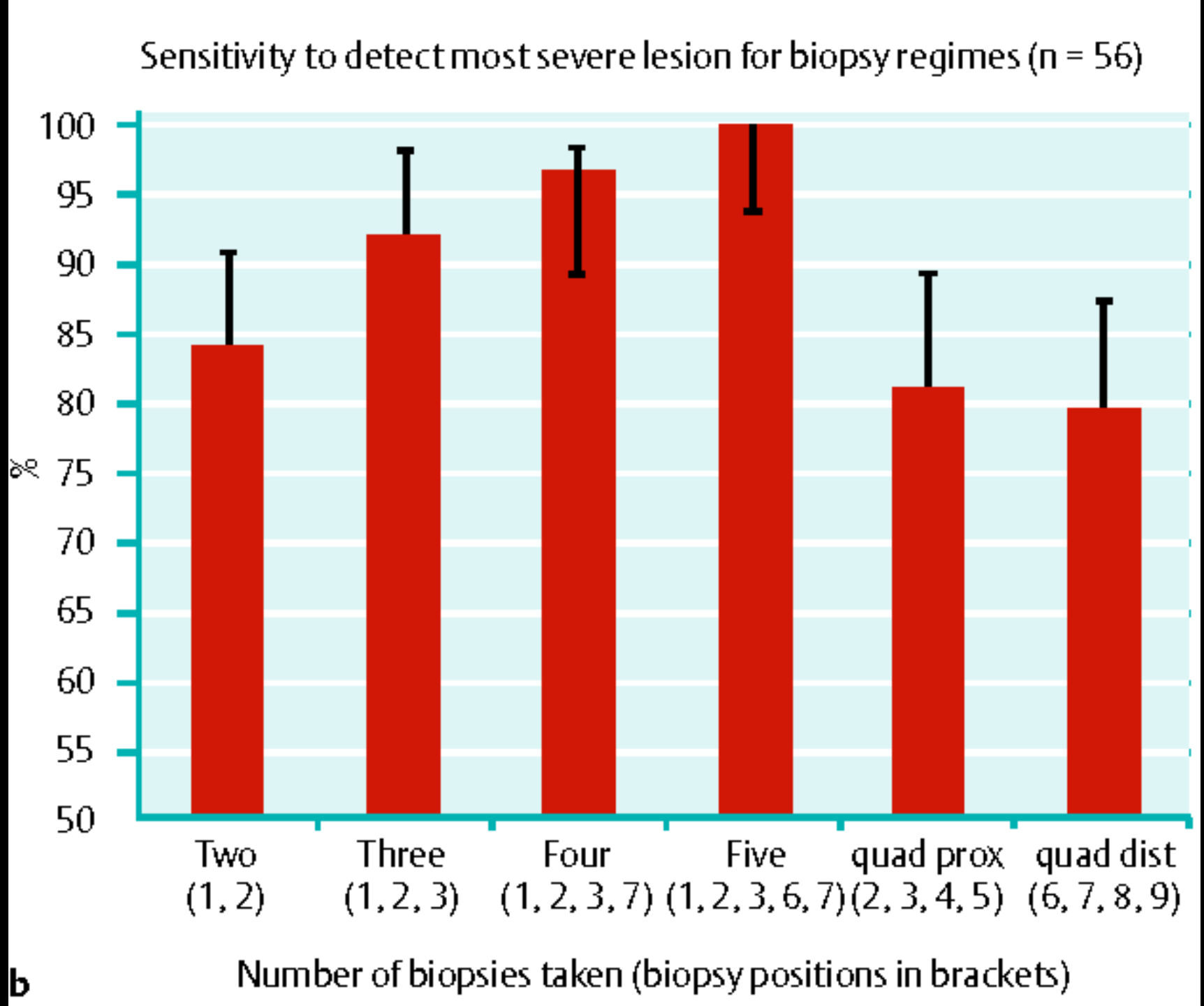
Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate?

A. D. Hopper[1], S. S. Cross[2], D. S. Sanders[1]

Endoscopy 2007; 39: 219 – 224






Sensitivity to detect most severe lesion for biopsy regimes (n = 56)
100
95
90
85
80
75
70
65
60
55
50
%
Two (1, 2)
Three (1, 2, 3)
Four (1, 2, 3, 7)
Five (1, 2, 3, 6, 7)
quad prox (2, 3, 4, 5)
quad dist (6, 7, 8, 9)
Number of biopsies taken (biopsy positions in brackets)

b

Duodenal Bulb Biopsies in Celiac Disease: A Multicenter Study

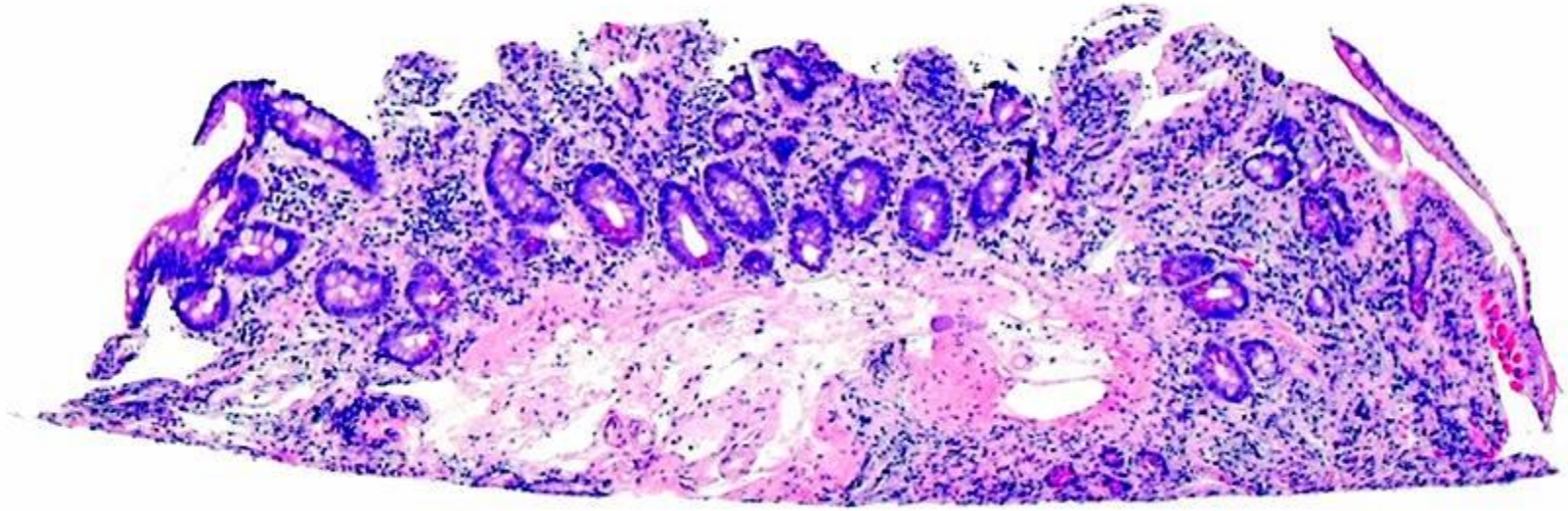
J Pediatr Gastroenterol Nutr, Vol. 47, No. 5, November 2008

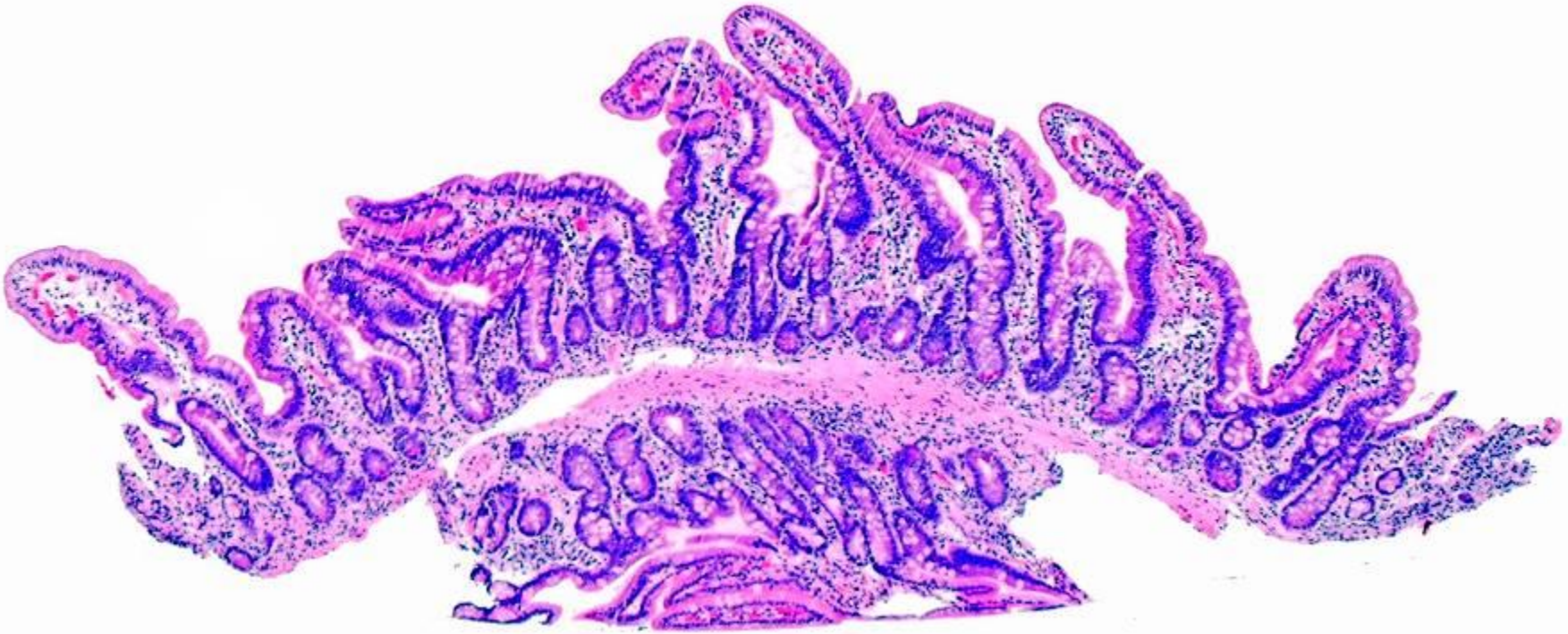
*Margherita Bonamico, *Enina Thanasi, *Paolo Mariani, *Raffaella Nenna, *Rita Pia Lara Luparia, †Cristiana Barbera, †Isabella Morra, †Pietro Lerro, ‡Graziella Guariso, §Costantino De Giacomo, ¶Serenella Scotta, ||Stefano Pontone, **Francesco Carpino, **Fabio Massimo Magliocca, and the Società Italiana di Gastroenterologica, Epatologia, e Nutrizione Pediatrica

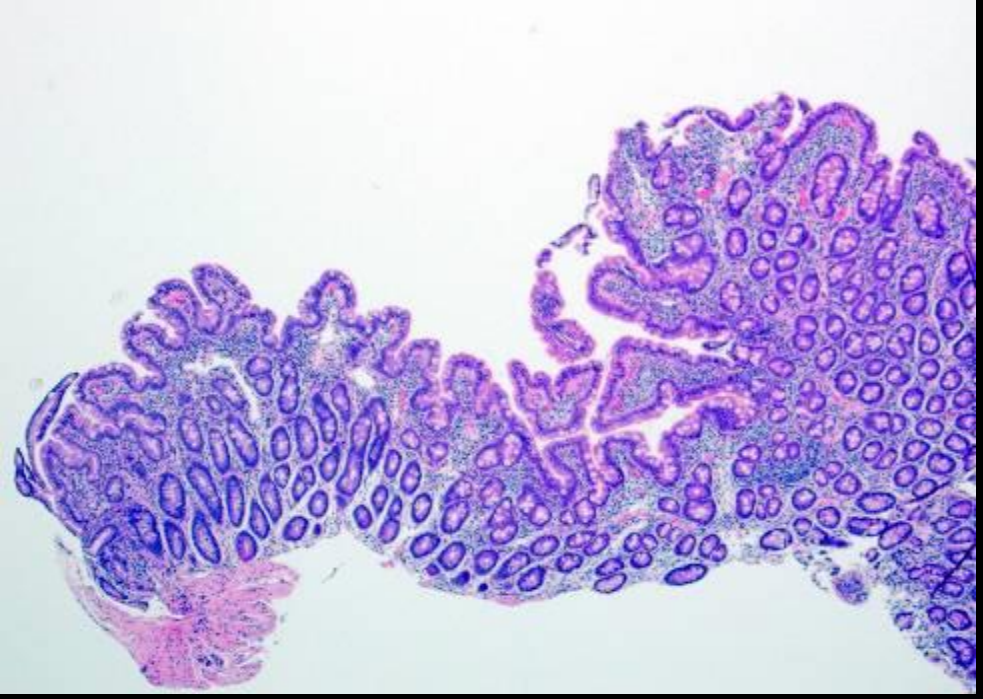
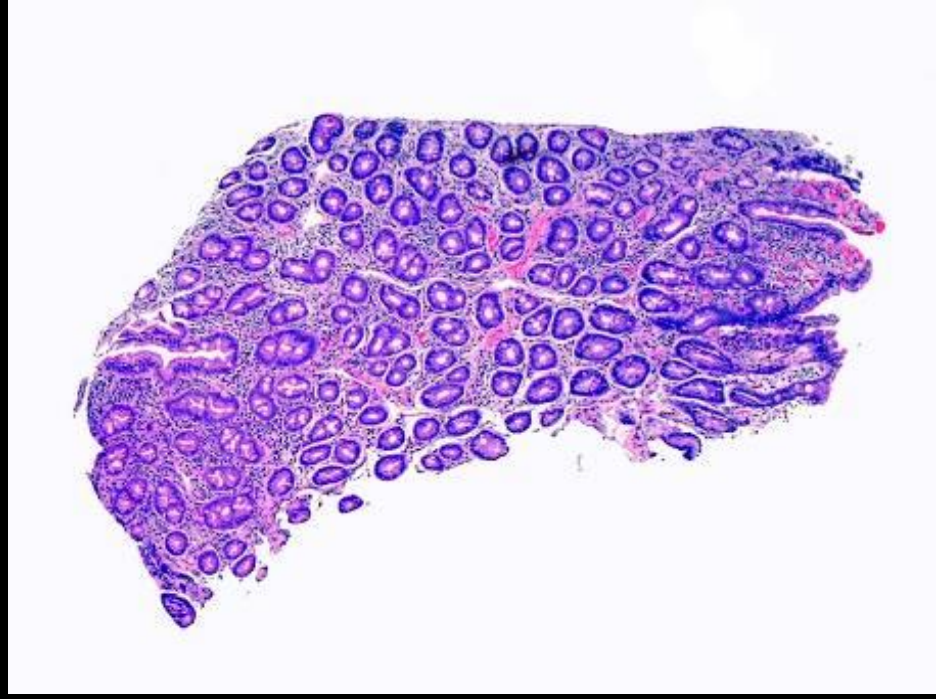
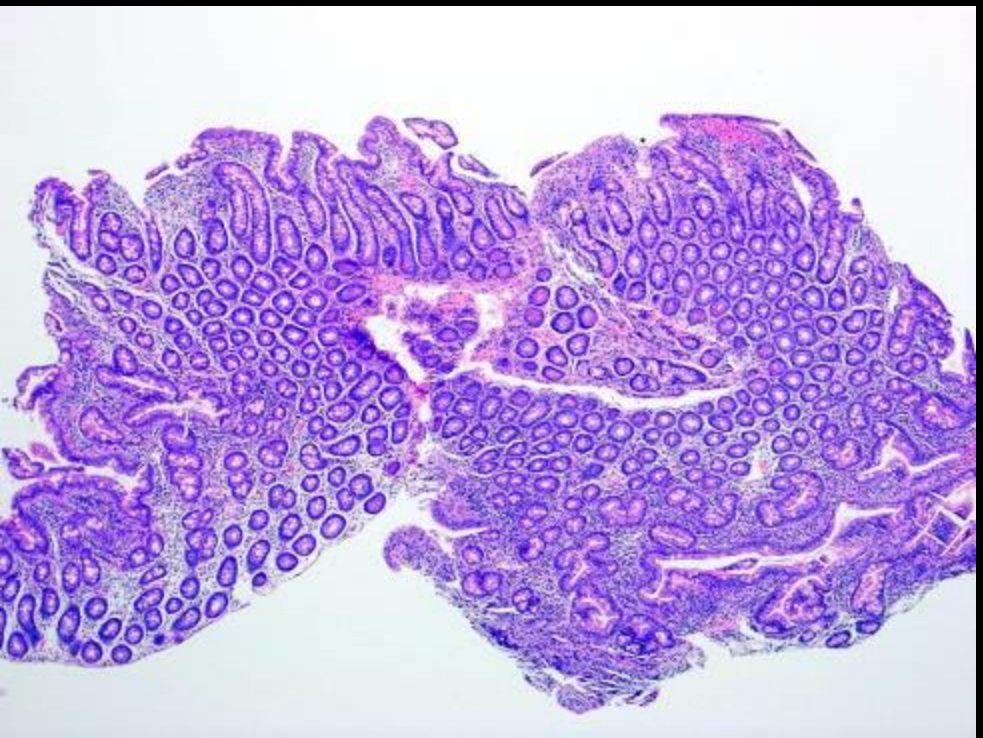
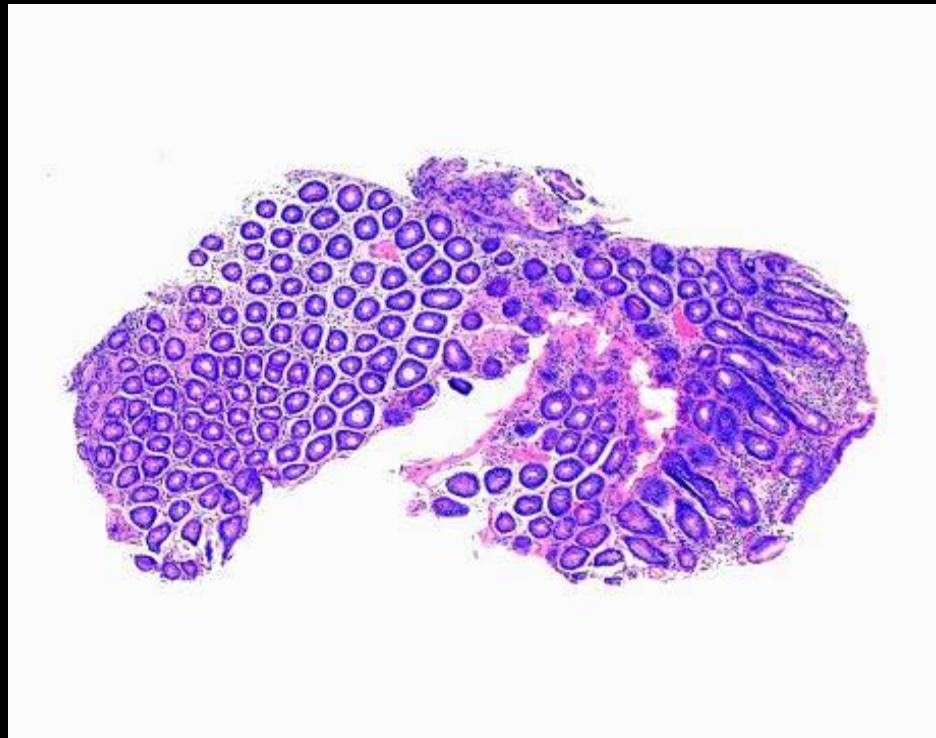
One biopsy of duodenal bulb and four of the distal duodenum

Patients (no.)	Group 1A (16)	Group 1B (20)	Group 1C (629)
Type 1 (%)	1 (6.25)	1 (5)	23 (3.67)
Type 2 (%)	1 (6.25)	0	19 (3.02)
Type 3a (%)	1 (6.25)	1 (5)	76 (12.08)
Type 3b (%)	4 (25)	5 (25)	240 (38.15)
Type 3c (%)	9 (56.25)	13 (65)	271 (43.08)

CD = celiac disease; group 1A: only bulbar lesions; group 1B: lesions patchily distributed; group 1C: diffuse lesions.



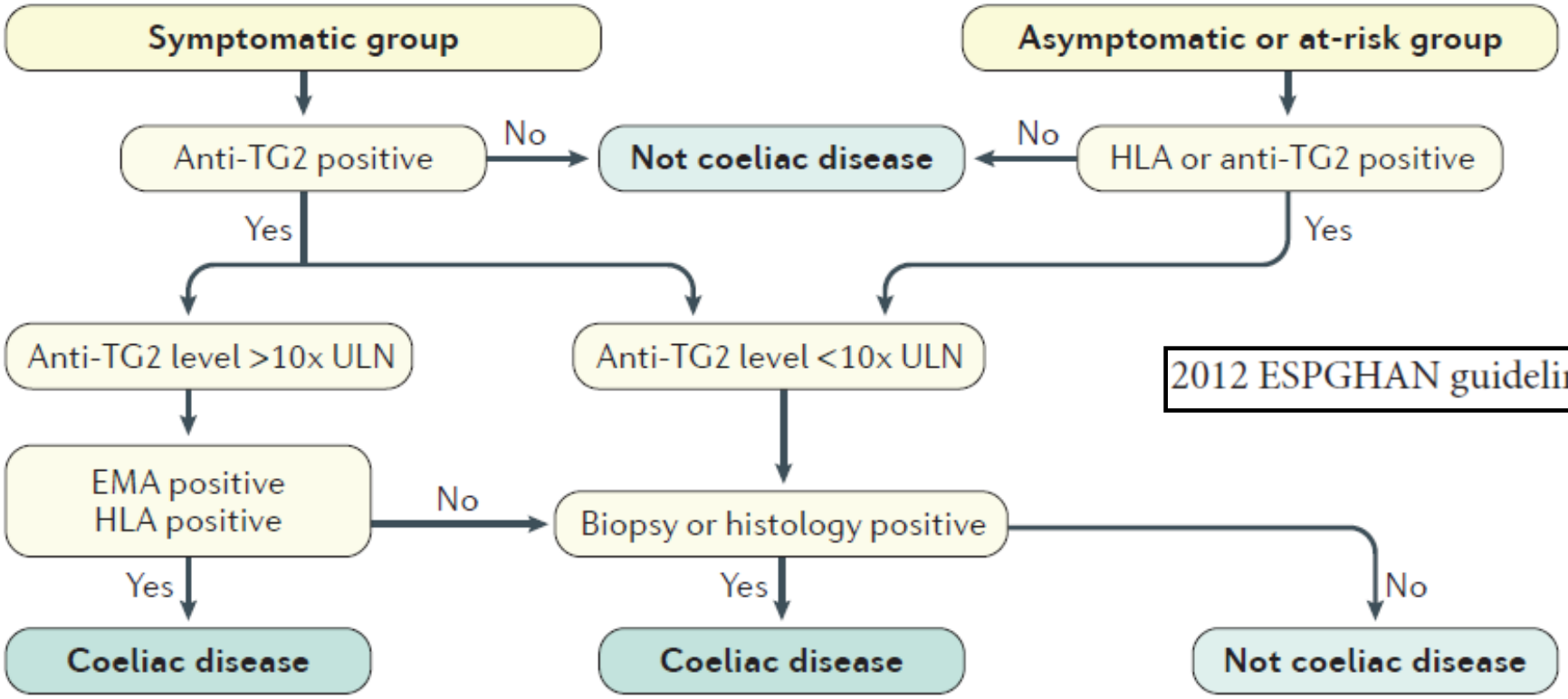


Coeliac disease: to biopsy or not?

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

Norelle R. Reilly, Steffen Husby, David S. Sanders and Peter H. R. Green



Reasons for avoiding biopsy

- General anaesthesia is often required for children and adolescents undergoing endoscopy (C)
- Cost of a no-biopsy diagnosis is generally less given the elimination of procedural and pathology costs (A, C)
- In childhood, gastrointestinal cancers are exceedingly rare and usually would be obvious on the basis of clinical evidence (C)
- Avoidance of procedural risks, such as rare anaesthesia reactions or aspiration pneumonia (A, C)
- Excellent specificity for the diagnosis of coeliac disease when serological, genetic and symptom criteria from guidelines are met (C)

A, pertains to adult populations; C, pertains to children.

Intraepithelial Lymphocytosis with Normal Villous Architecture

- Tropical sprue
- Autoimmune enterocolitis
- Viral enteritis
- Giardiasis
- Cryptosporidiosis
- Microsporidiosis
- Bacterial overgrowth
- Food allergies
- Crohn's disease
- Common variable immunodeficiency
- Systemic autoimmune diseases
- NSAIDs (and other drugs)
- H. pylori infection

Histologic Differential Diagnosis

1. Increased IELs
2. Flat mucosa w crypt hyperplasia
3. Dense lamina propria infiltrate

1. Some cases of celiac disease
2. CVID (rare cases)
3. Tropical sprue (very rare cases)
4. Viral enteritis (very rare cases)
5. Autoimmune enterocolitis
6. Drugs (very rare cases)

1. Increased IELs

1. Celiac disease (some cases)
2. Tropical sprue
3. Autoimmune enteropathy
4. Viral enteritis
5. Giardiasis
6. Cryptosporidiosis
7. Microsporidiosis
8. Bacterial overgrowth
9. Food allergies
10. Crohn's disease
11. CVID
12. Systemic autoimmune diseases
13. NSAIDs (and other drugs)
14. H. pylori infection

CLINICAL Differential Diagnosis

1. Increased IELs
2. Flat mucosa w crypt hyperplasia
3. Dense lamina propria infiltrate

AND
positive anti-tTG

1. Some cases of celiac disease
2. CVID (rare cases)
3. Tropical sprue (very rare cases)
4. Viral enteritis (very rare cases)
5. Autoimmune enterocolitis
6. Drugs (very rare cases)

1. Increased IELs

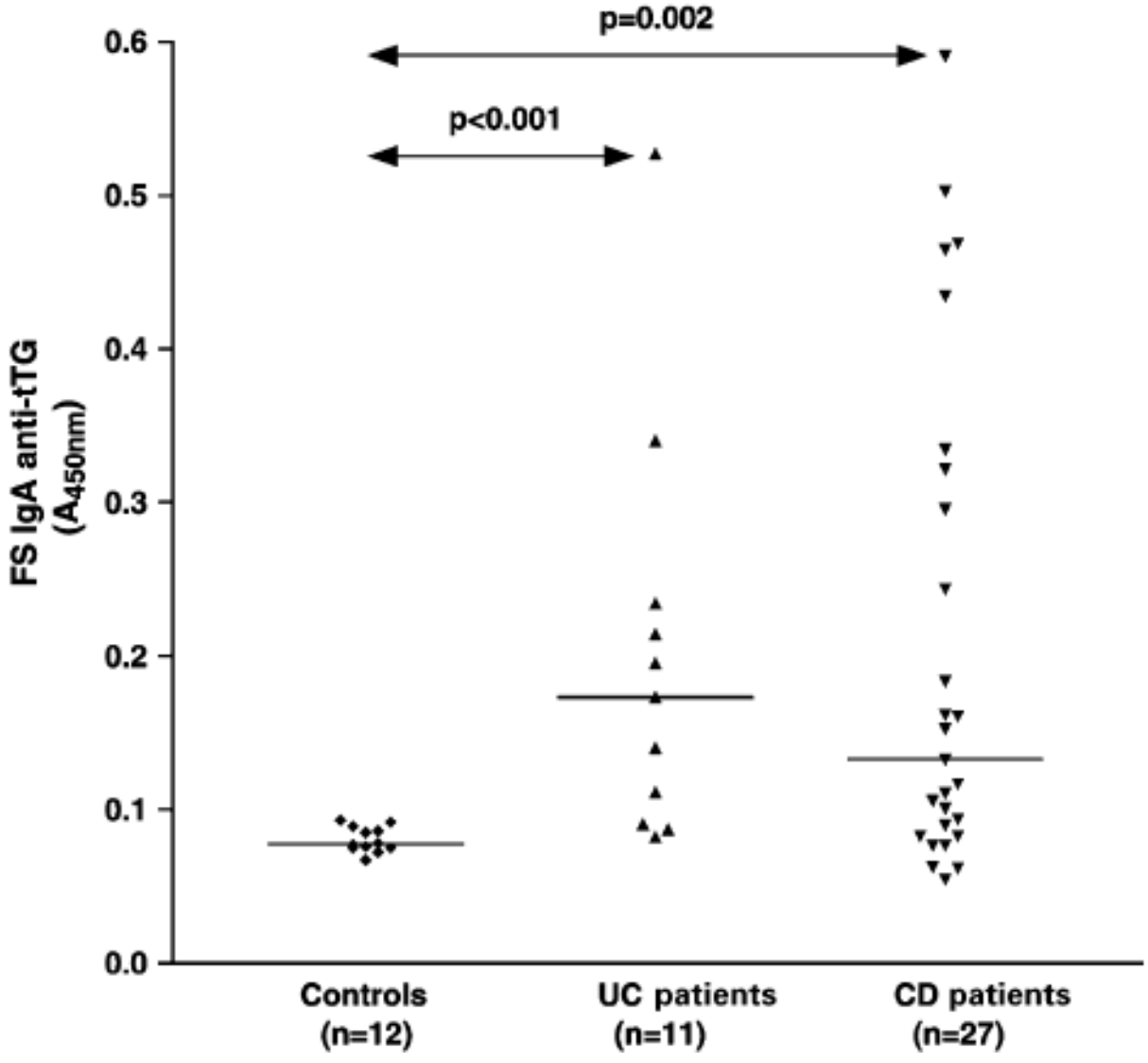
AND
positive anti-tTG

1. Celiac disease (some cases)
2. Tropical sprue
3. Autoimmune enteropathy
4. Viral enteritis
5. Giardiasis
6. Cryptosporidiosis
7. Microsporidiosis
8. Bacterial overgrowth
9. Food allergies
10. Crohn's disease
11. CVID
12. Systemic autoimmune diseases
13. NSAIDs (and other drugs)
14. H. pylori infection

Anti-tissue transglutaminase antibodies in inflammatory bowel disease: new evidence

Marco Di Tola, Luigi Sabbatella, Maria Cristina Anania, Angelo Viscido, Renzo Caprilli, Roberta Pica, Paolo Paoluzi and Antonio Picarelli*

Clin Chem Lab Med 2004;42(10):1092–1097



Anti-tissue transglutaminase antibodies in inflammatory bowel disease: new evidence

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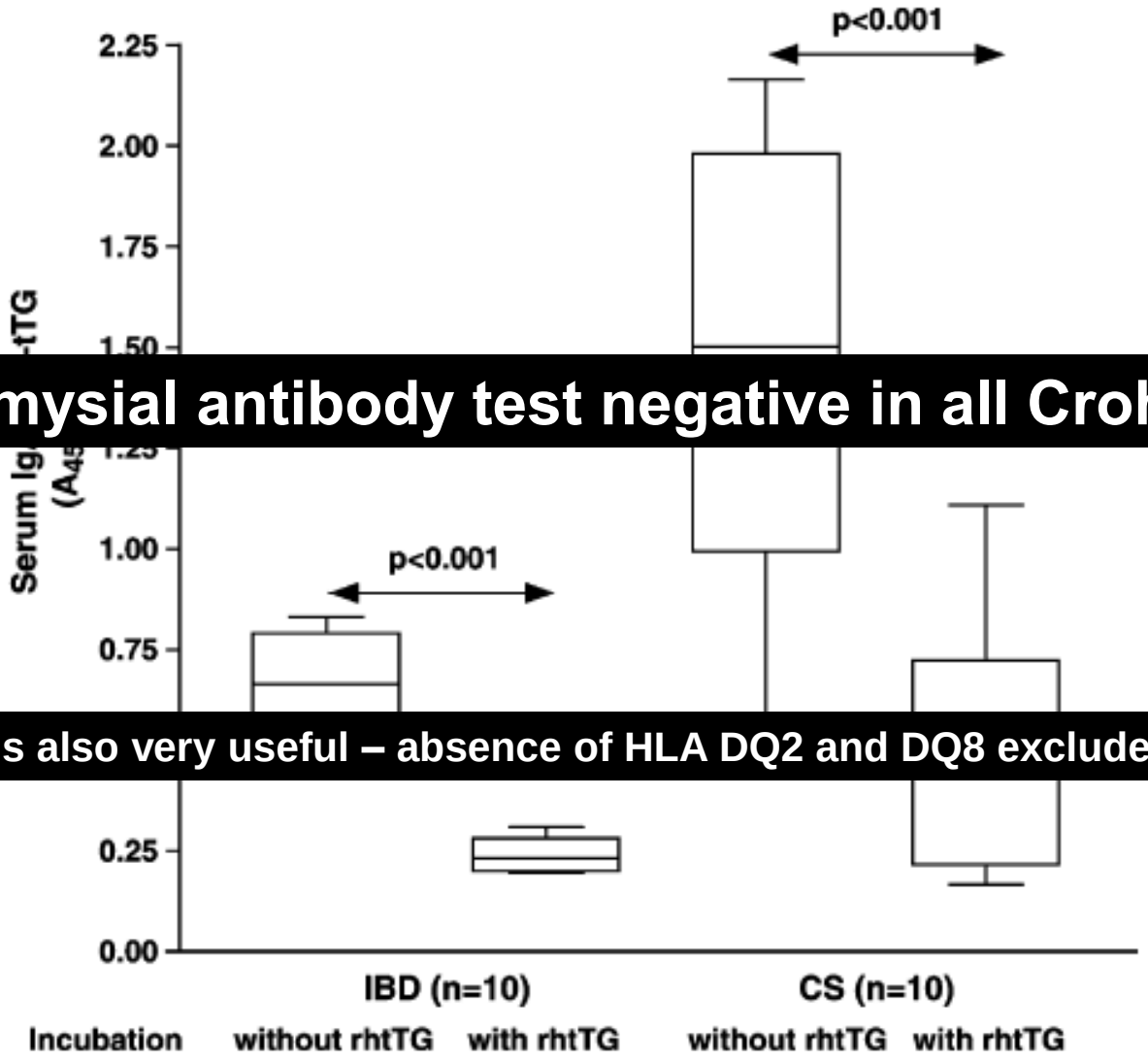
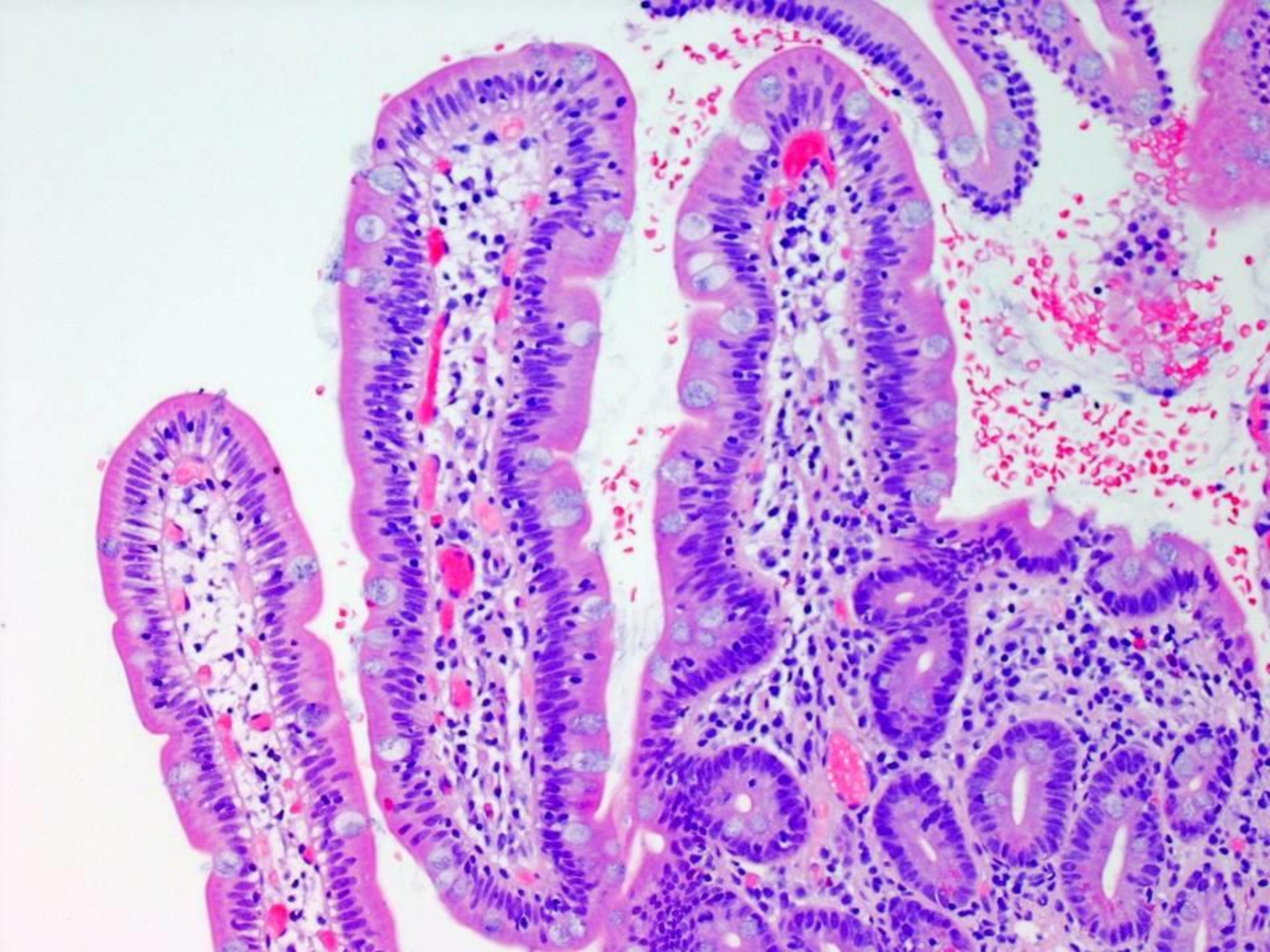


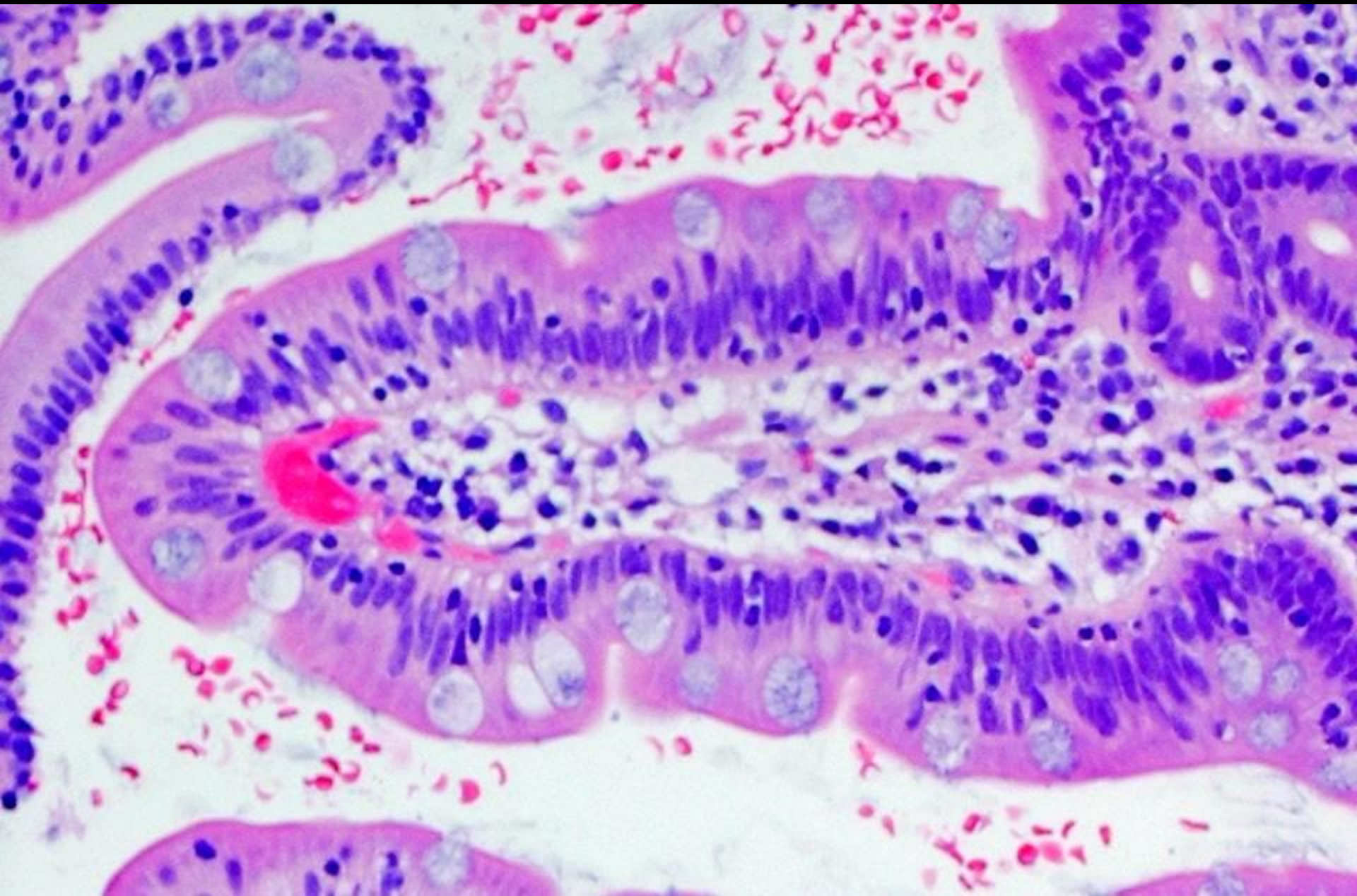
Anti-endomysial antibody test negative in all Crohn's patients

HLA testing is also very useful – absence of HLA DQ2 and DQ8 excludes celiac disease


28 year old female
with Crohn’s disease



Increased IELs in a patient with known Crohn's disease



Refractory Sprue
Clinical Features

- Redevelop diarrhea while on a GFD
- Usually elderly and with weight loss
- There should be a well established Dx of CD

Refractory Sprue

Causes

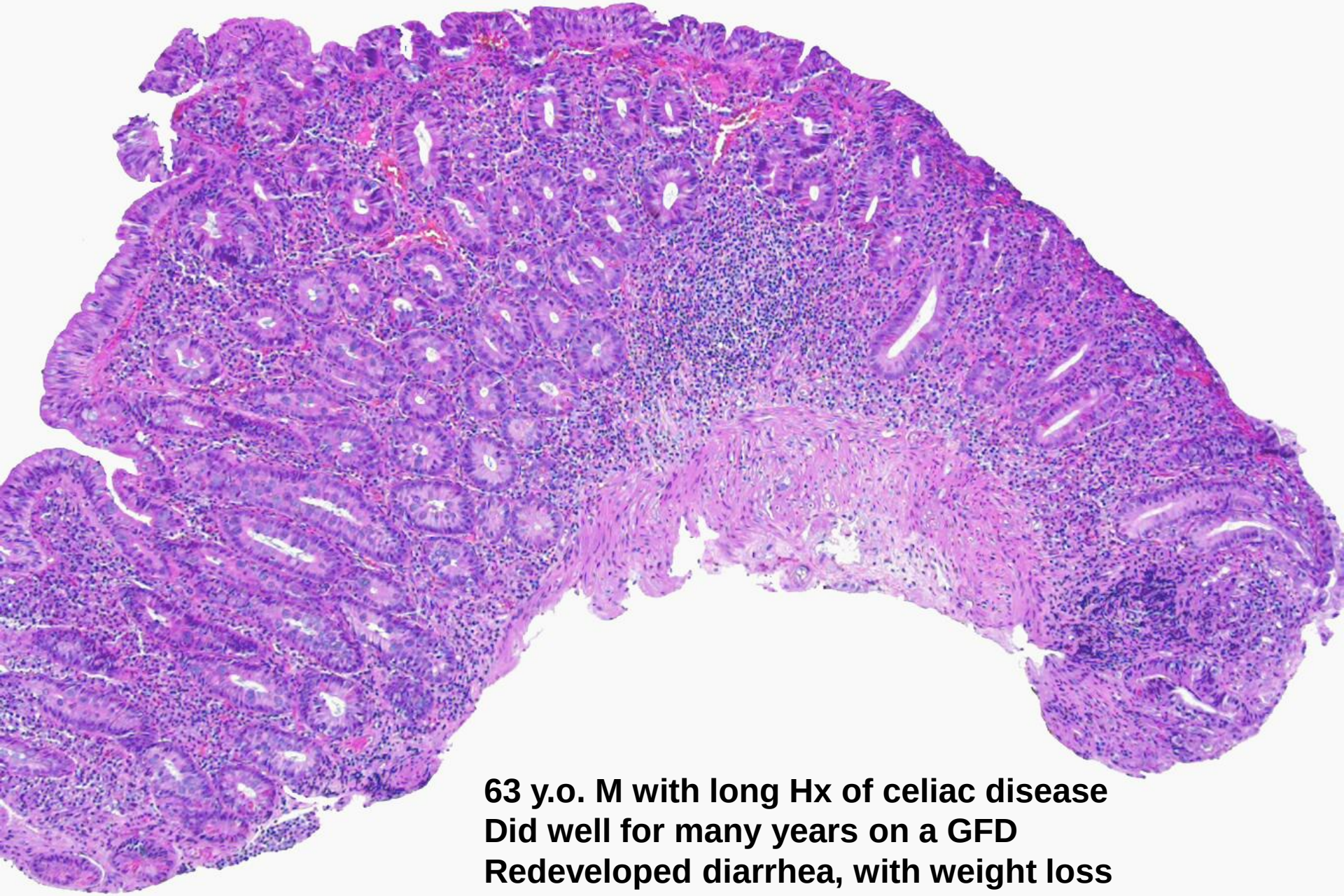
- **Inadvertent gluten ingestion**
- **Lymphocytic or collagenous colitis**
- **Ulcerative jejuno-ileitis (lymphoma)**
- **Enteropathy associated T-cell lymphoma**
- **Collagenous sprue**
- **Pancreatic insufficiency**
- **Food allergy**
- **Nutrient deficiency (zinc, folic acid)**

Refractory Sprue
Pathologic Features

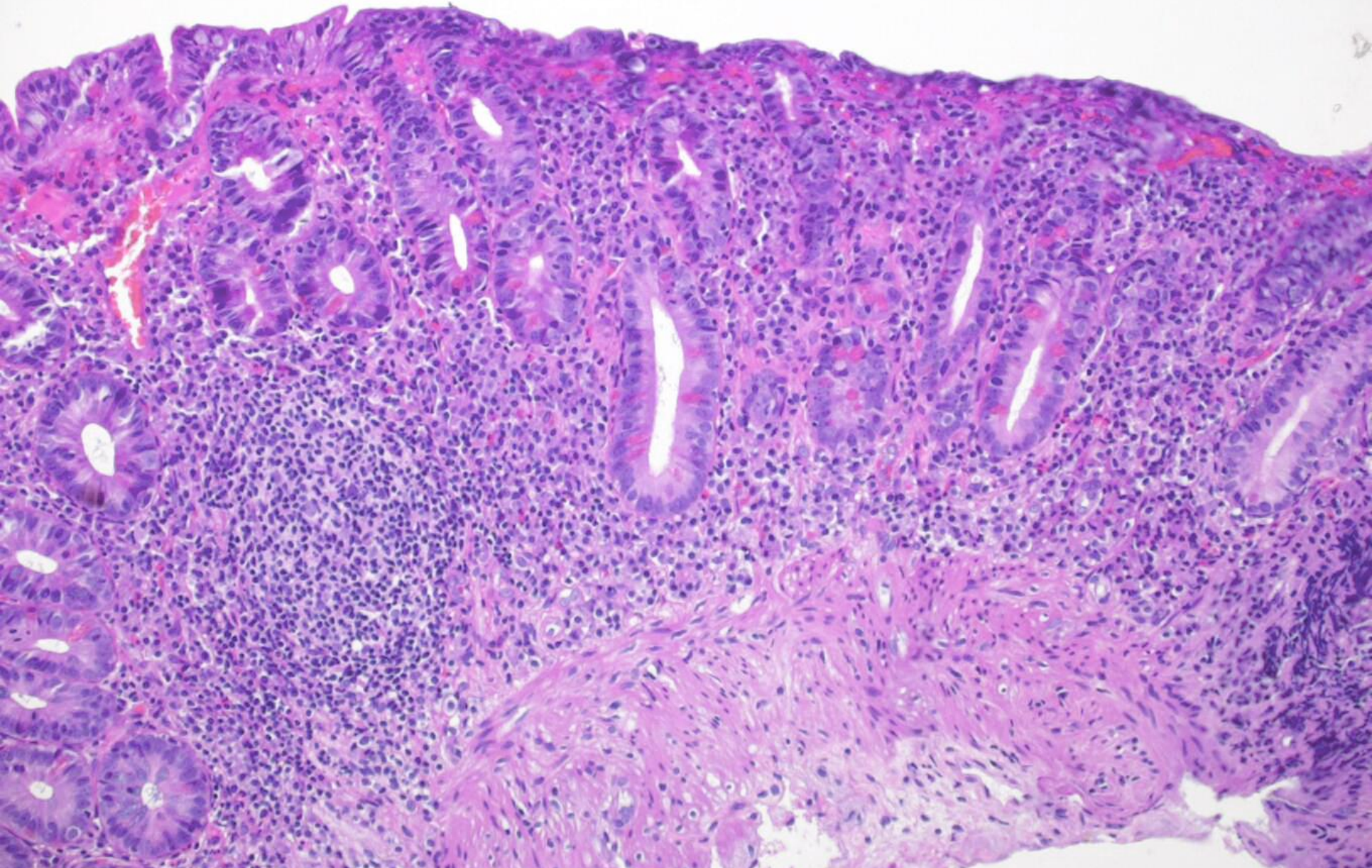
- **Persistent abnormal histology while on a GFD:**
  - **Usually there is severe villous blunting**
  - **Usually there is a marked increase in IELs**
- **Type 1:**
  - **IELs normally express CD3 with CD4 or CD8**
  - **Polyclonal by T-cell receptor gene rearrangement studies**
- **Type 2:**
  - **IELs CD3+ but CD8- and CD4- (and TCR-beta -)**
  - **Clonal T-cell receptor gene population**

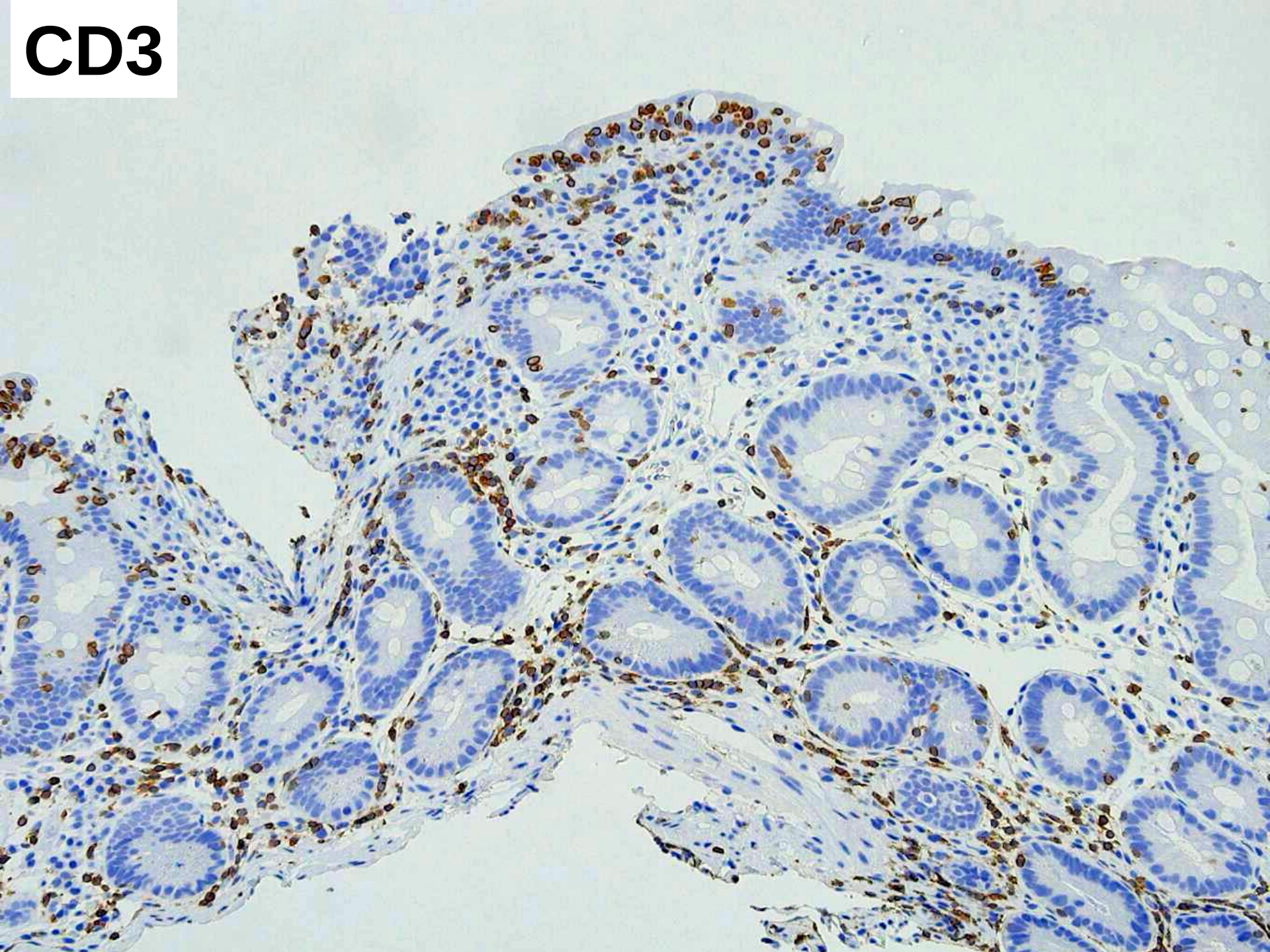
Patey-Mariaud De Serre N. et al. Histopathology 2000; 37:70-7.

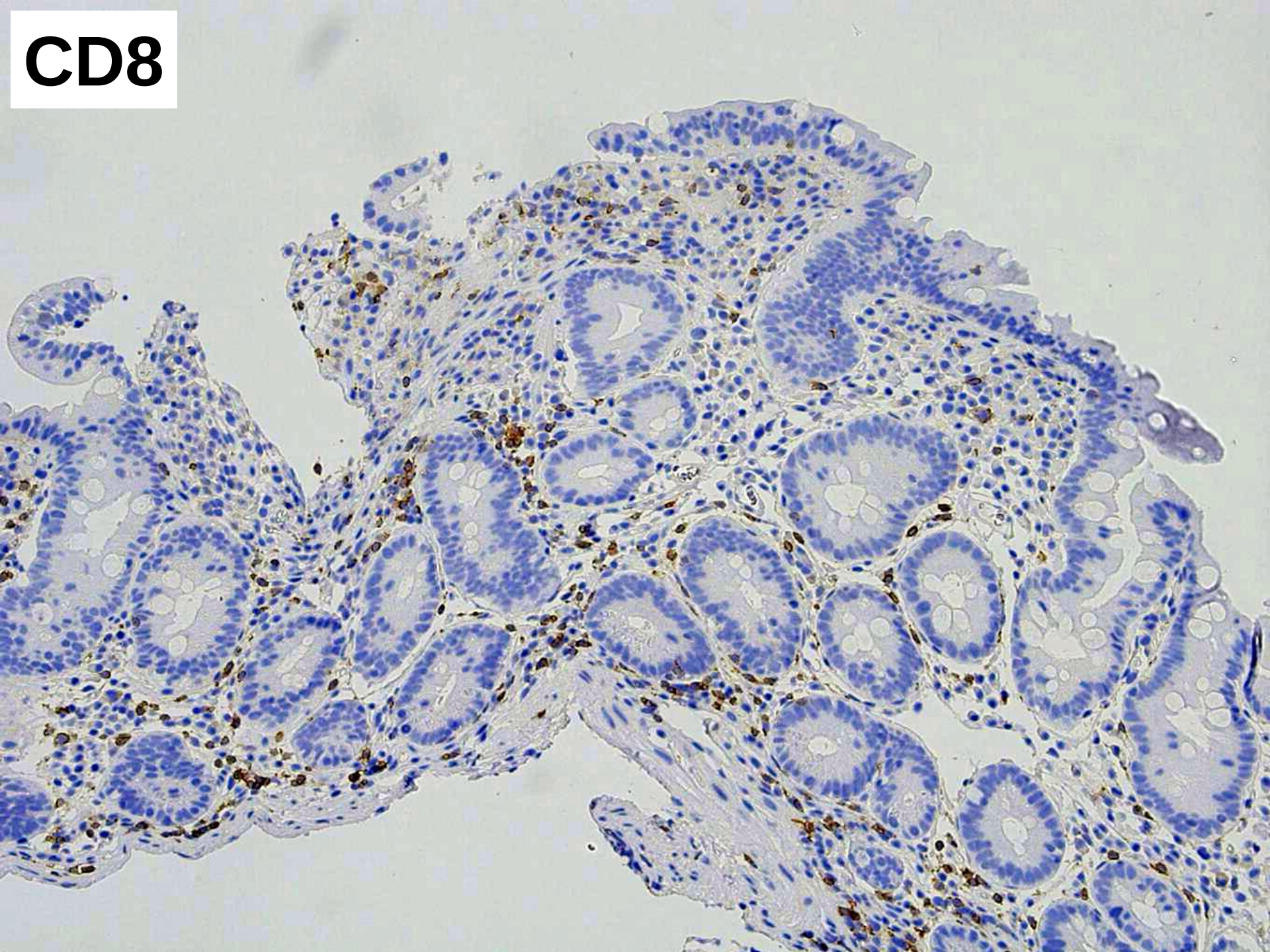
C10-8176

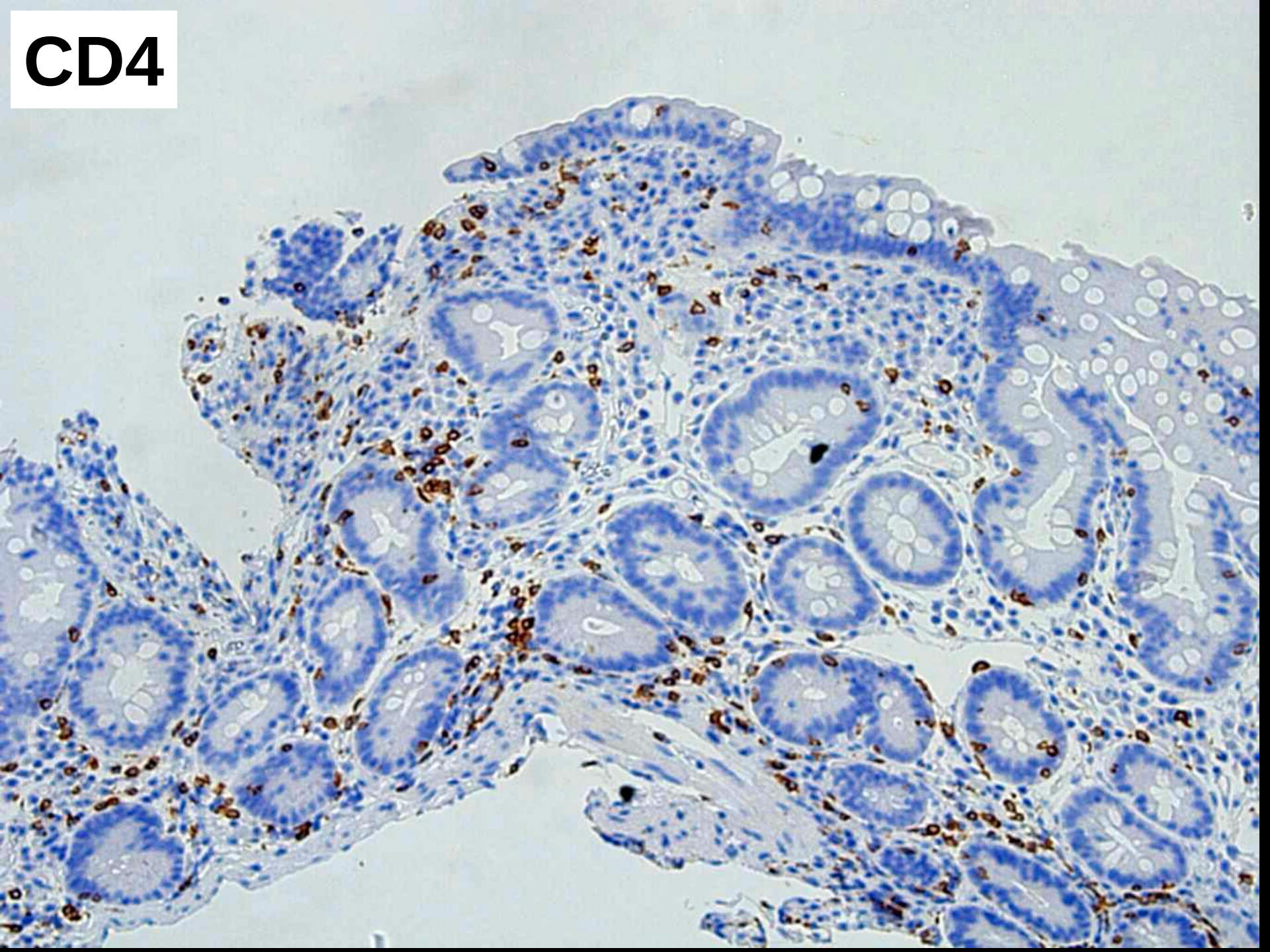


63 y.o. M with long Hx of celiac disease
Did well for many years on a GFD
Redeveloped diarrhea, with weight loss




CD3


CD8

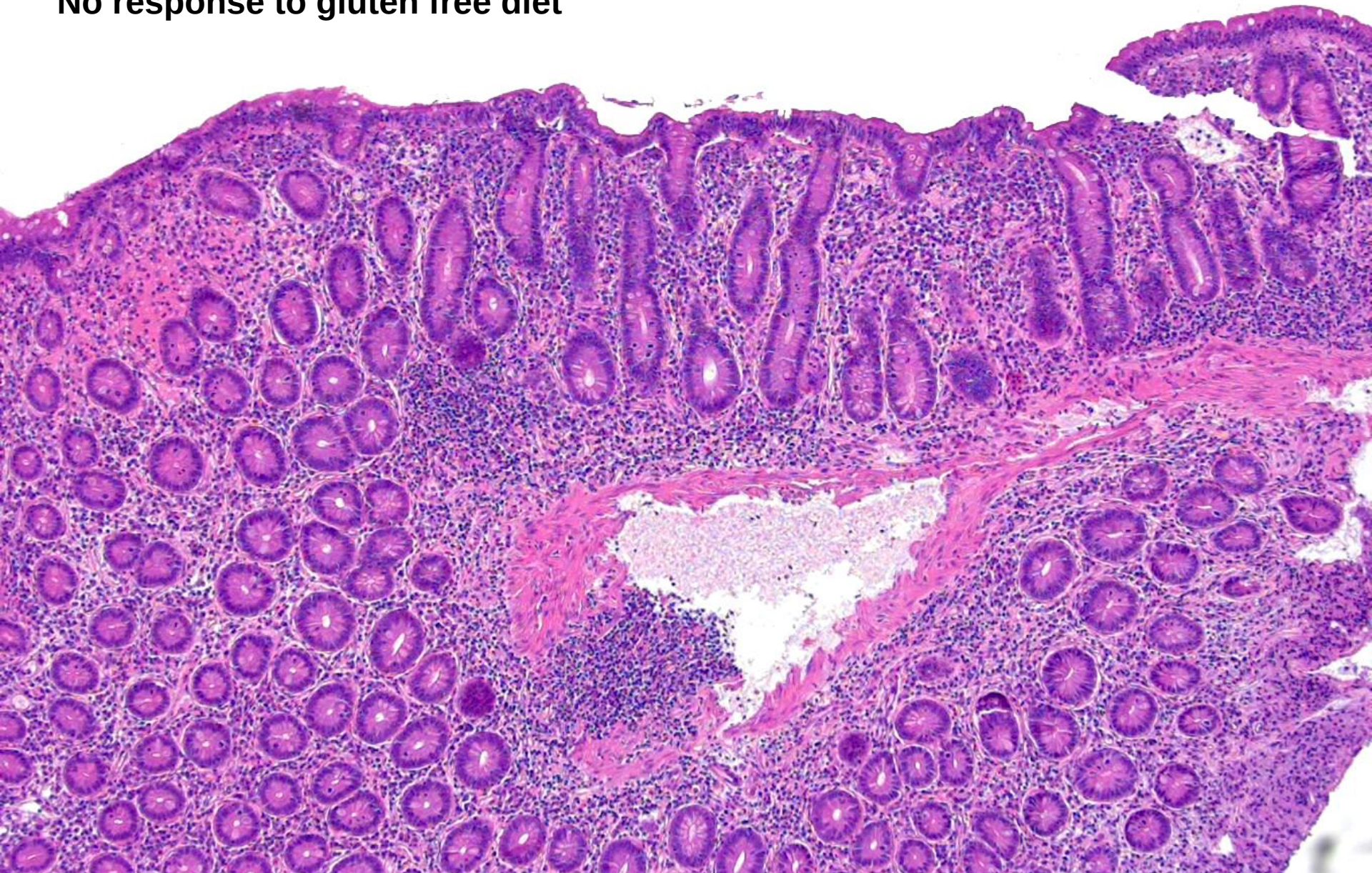

CD4

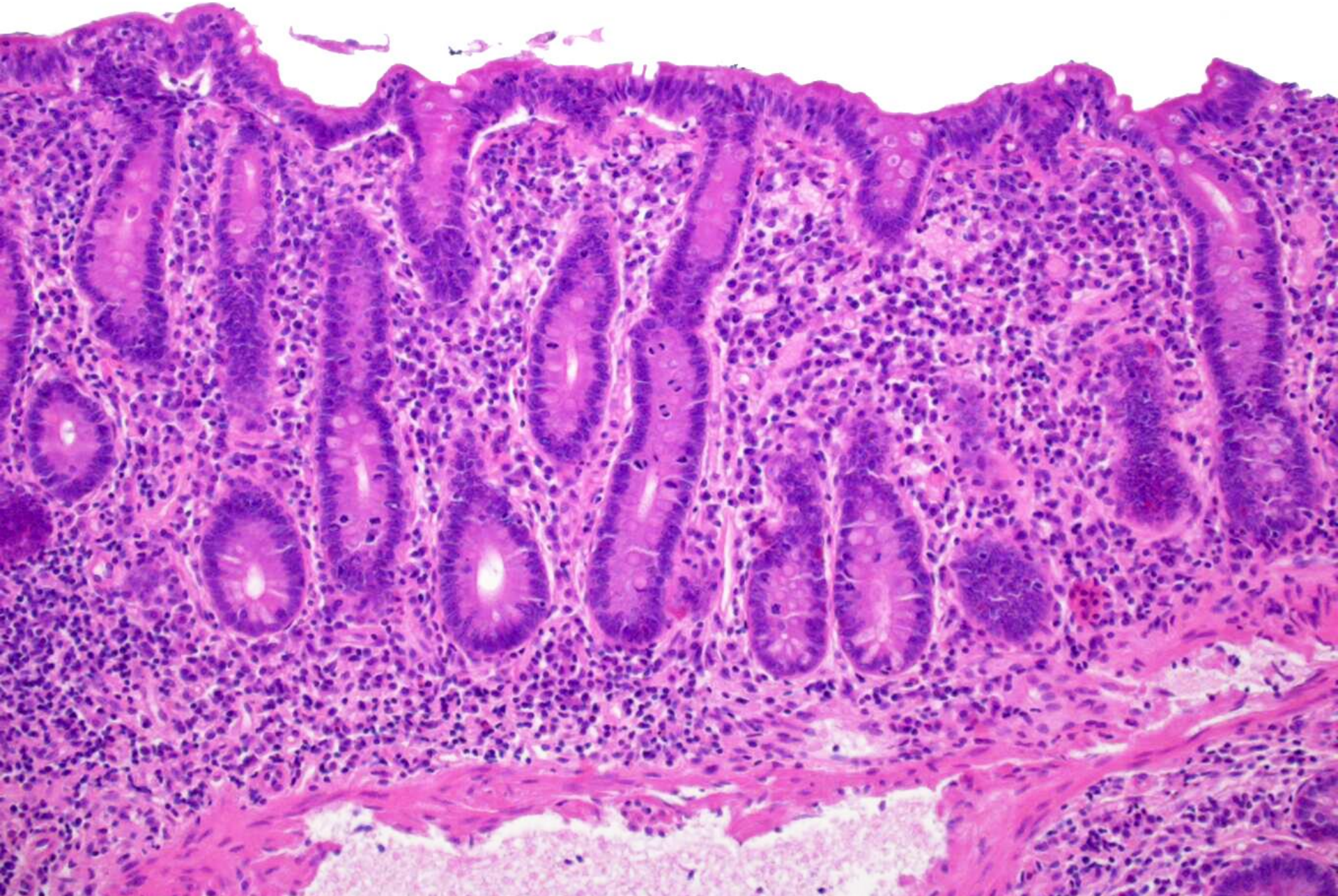
65 y.o. F with severe chronic diarrhea and 25 lb weight loss C13-4597

Negative serologic tests for celiac disease

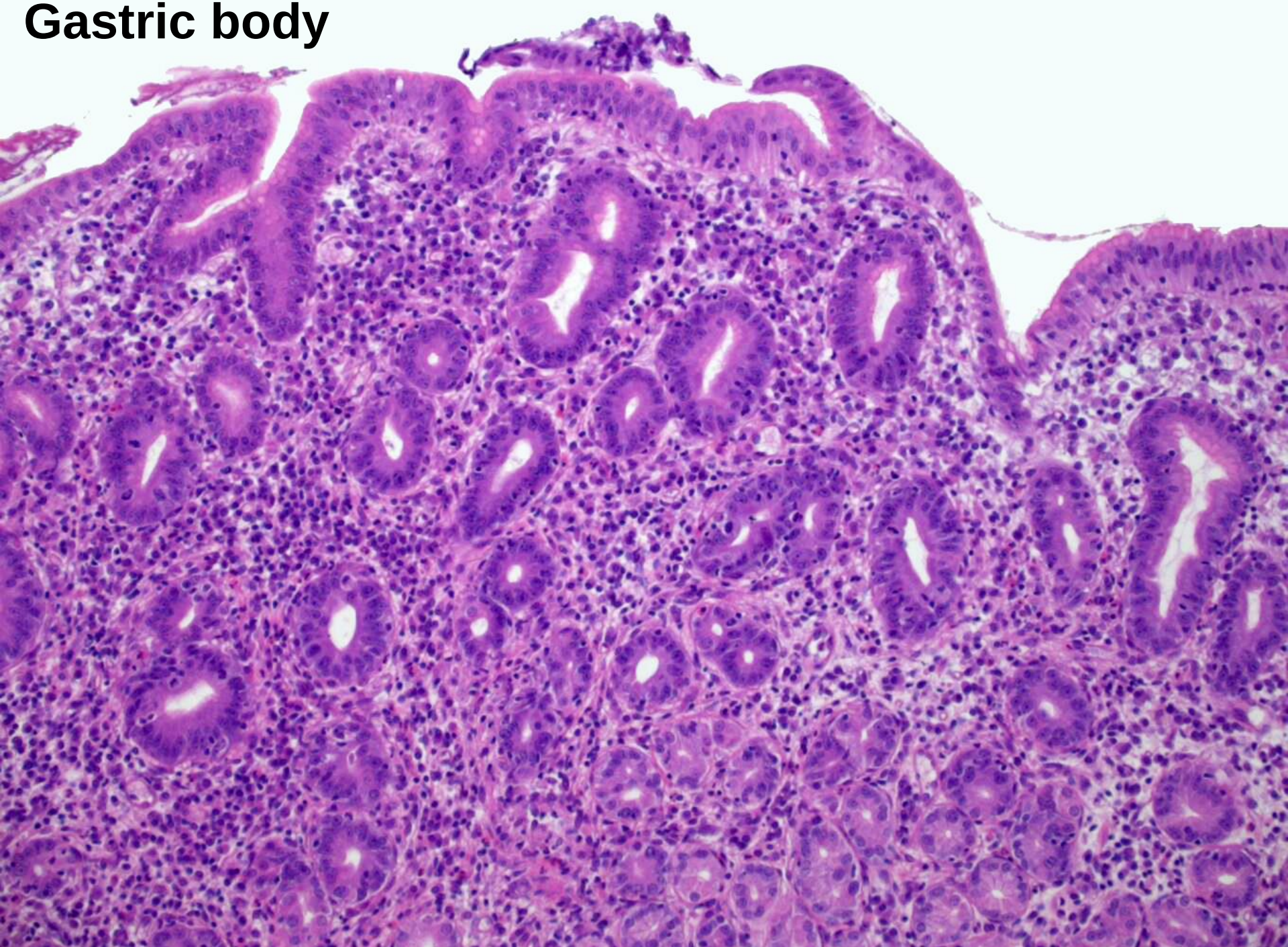
Diagnosed with “refractory celiac disease” based on duodenal biopsies

No response to gluten free diet





Gastric body



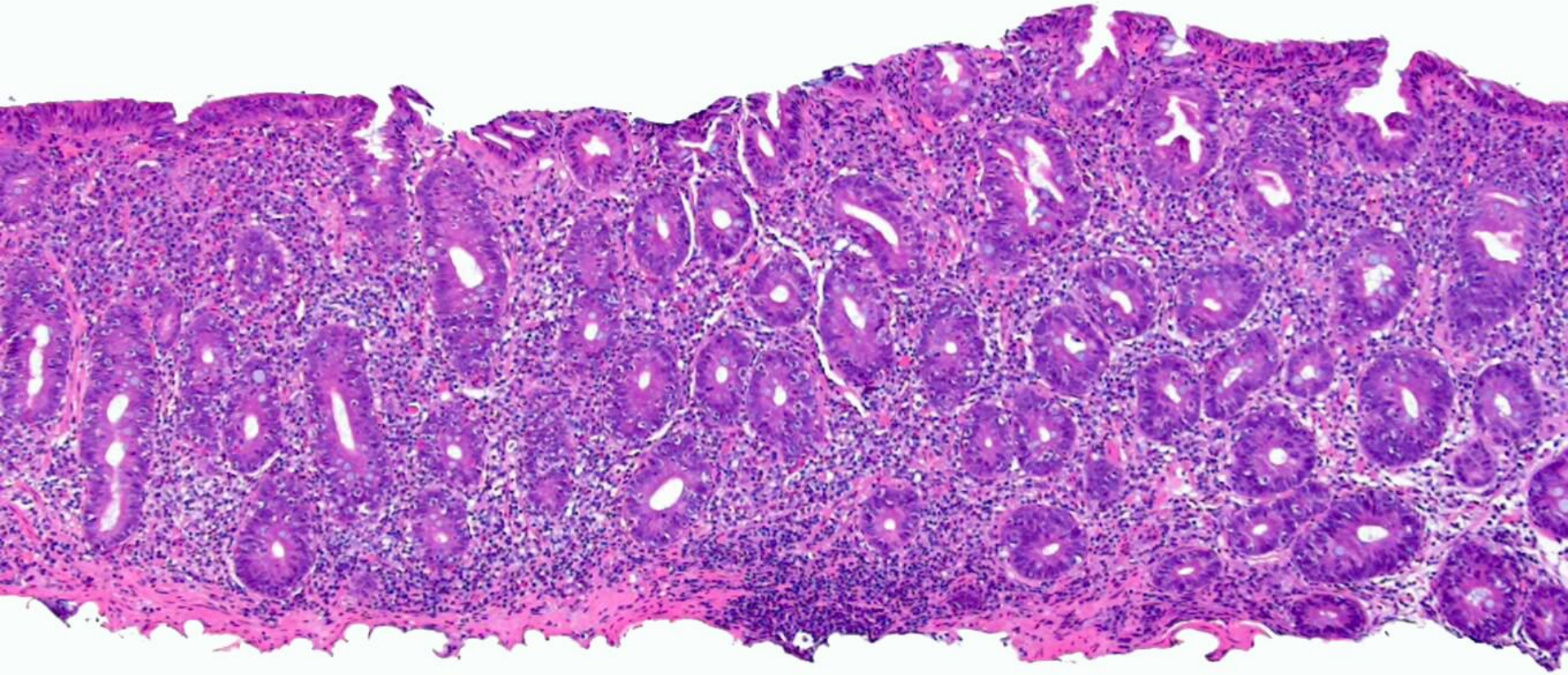
Severe Spruelike Enteropathy Associated With Olmesartan

Mayo Clin Proc. 2012;87(8):732-738

TABLE 2. Histologic Findings in 22 Patients With Spruelike Enteropathy Associated With Olmesartan[a]

	Baseline duodenal biopsy results								
Patient No.	Villous atrophy	IELs (/100 epithelial cells)[b]	Acute/active inflammation	Thickened collagen band	Aberrant cells/clone[c]	Outcome follow-up duodenal biopsy results	Time d[d]	Other GI findings[e]	
								Gastric	Colorectal
1	Total	Normal	Yes	No	No/No	Normal	404	Lymphocytic gastritis (HP negative, immunostain)	Collagenous colitis
2	Total	80-100	Yes	Yes	No/NA	Improvement, focal partial villous atrophy	54	Chronic gastritis (HP negative, immunostain)	Normal
3	Total	Normal	Yes	No	No/No	Normal	231	NA	Collagenous colitis
4	Total	40	Yes	Yes	No/No	Normal	263	Collagenous gastritis	NA
5	Total	>100	Yes	No	NA/NA	Normal	54	NA	Normal
6	Partial	60	Yes	No	NA/NA	NA	NA	NA	NA
7	Partial	>100	No	No	No/No	Normal	159	NA	Normal
8	Total	40-60	Yes	No	NA/NA	Normal	143	Lymphocytic gastritis (HP negative, immunostain)	Normal
9	Total	60-80	Yes	No	No/No	Normal	188	NA	NA
10	Partial	Normal	No	No	No/No	Normal	404	NA	NA
11	Partial	50	Yes	No	No/No	NA	NA	Mild lymphocytic gastritis (HP negative, immunostain)	NA
12	Partial	Normal	Yes	No	No/No	Normal, focal active duodenitis	116	Mild active chronic gastritis (HP negative, immunostain)	Mild active chronic colitis
13	Total	40	Yes	Yes	NA/NA	Normal	171	Active chronic gastritis (HP negative, immunostain)	NA
14	Partial	60-80	No	No	NA/NA	Normal	240	Mild active chronic gastritis (HP negative, immunostain)	NA
15	Total	Normal	No	Yes	NA/NA	Normal	181	Mild chronic gastritis (HP negative, no immunostain)	Normal
16	Total	Normal	No	Yes	No/No	Normal	607	Collagenous gastritis	Collagenous colitis
17	Total	40-60	Yes	Yes	No/No	NA	NA	Mild chronic gastritis (HP negative, no immunostain)	Focal acute colitis
18	Partial	Normal	No (marked eosinophilia)	No	NA/NA	NA	NA	NA	NA
19	Total	30	Yes	No	NA/NA	Normal	76	Severe active chronic gastritis and ulceration (HP negative, immunostain)	NA
20	Total	Normal	No	Yes	No/No	Normal	707	Lymphocytic gastritis (HP positive)	Lymphocytic colitis
21	Total	80-100	Yes	No	NA/NA	Normal	179	NA	Lymphocytic colitis
22	Total	80	Yes	No	NA/NA	Normal	184	Lymphocytic gastritis (HP negative, immunostain)	Normal

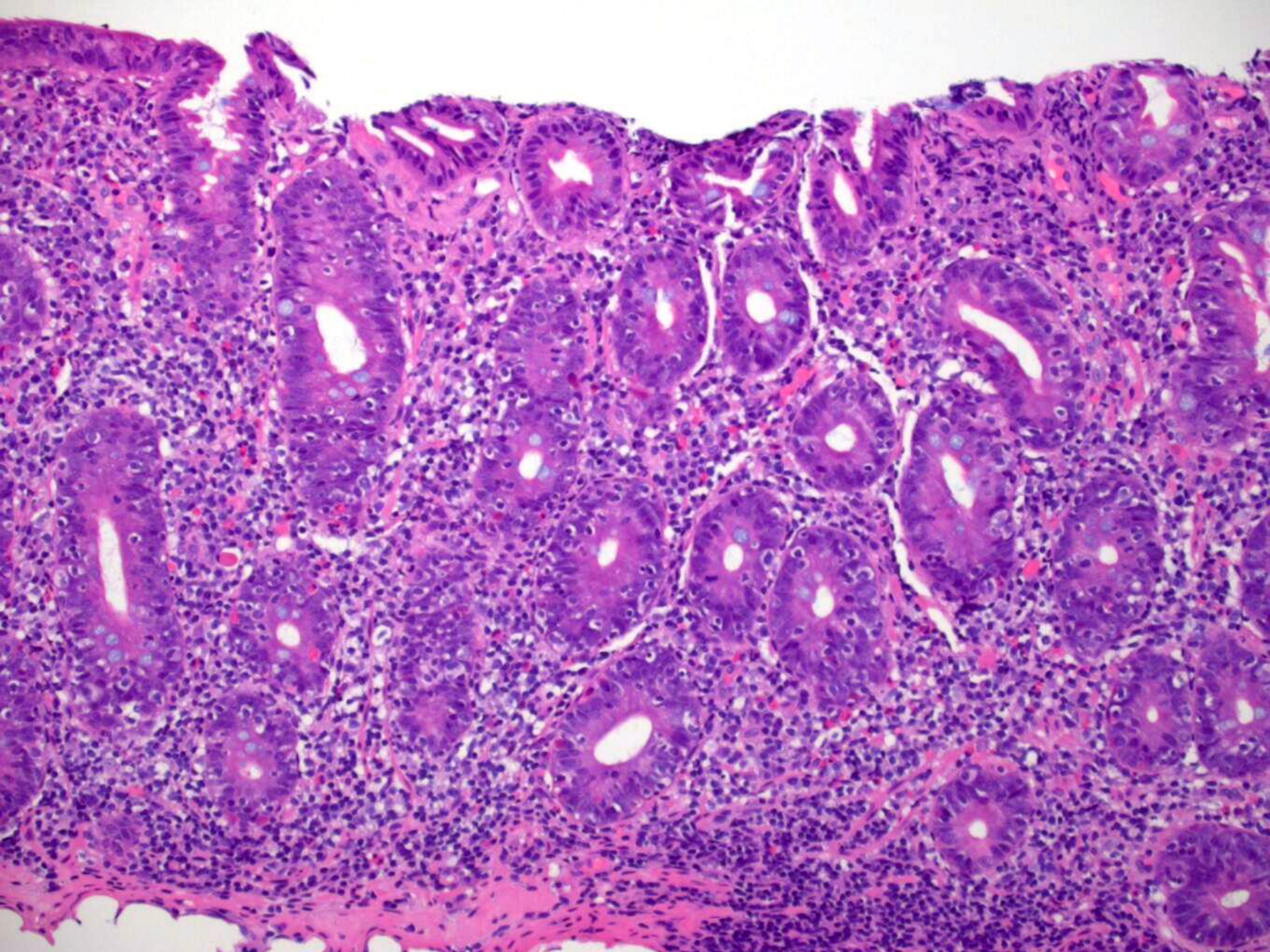
Case Courtesy of Dr James Taylor, Regional Medical Labs, Tulsa



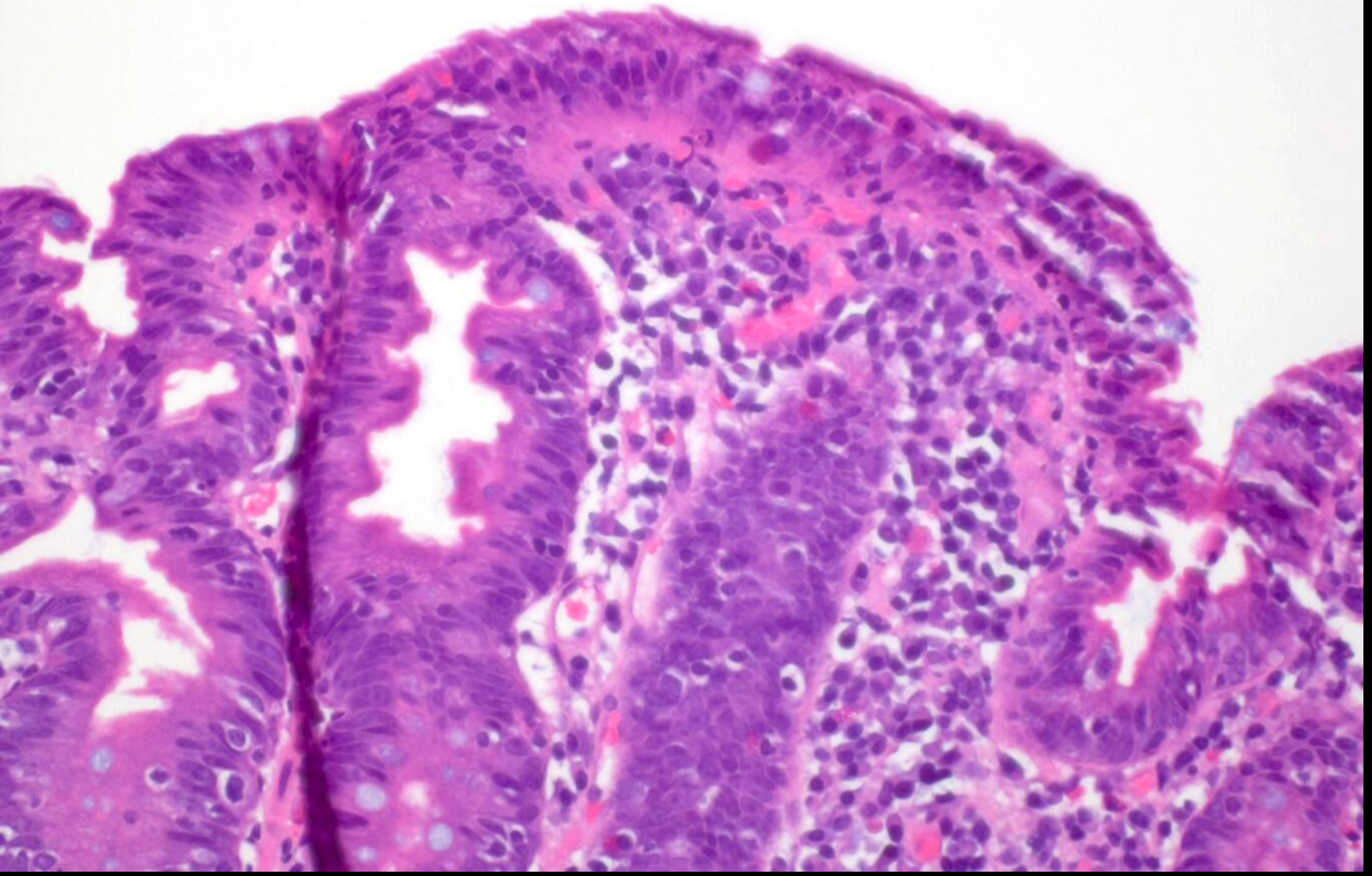
72 y.o. M with severe chronic diarrhea and weight loss
Serologic tests for celiac disease are all negative

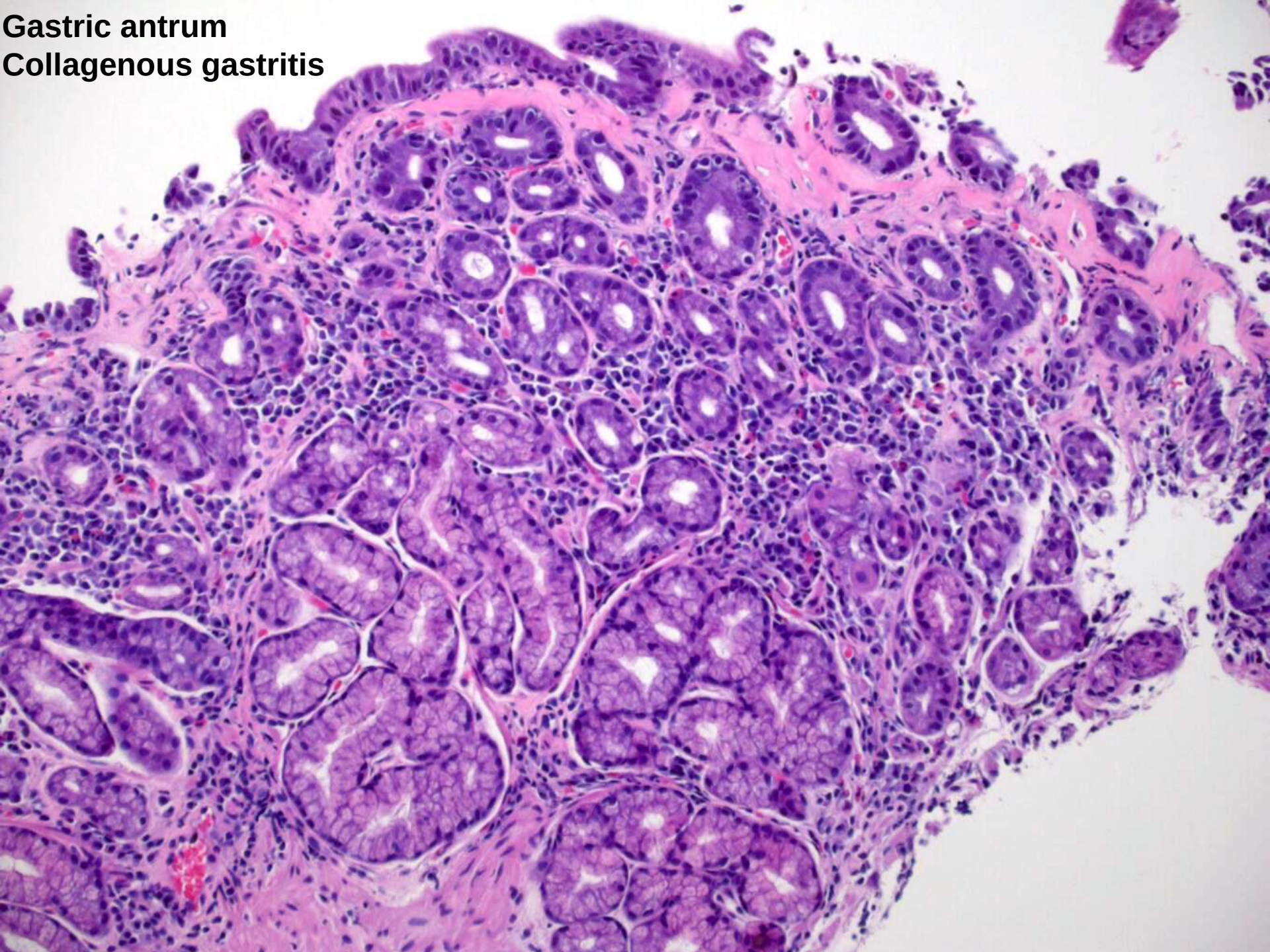
Duodenal biopsy

C11-27021



“collagenous sprue”




Gastric antrum
Collagenous gastritis

Olmesartan Induced Enteropathy

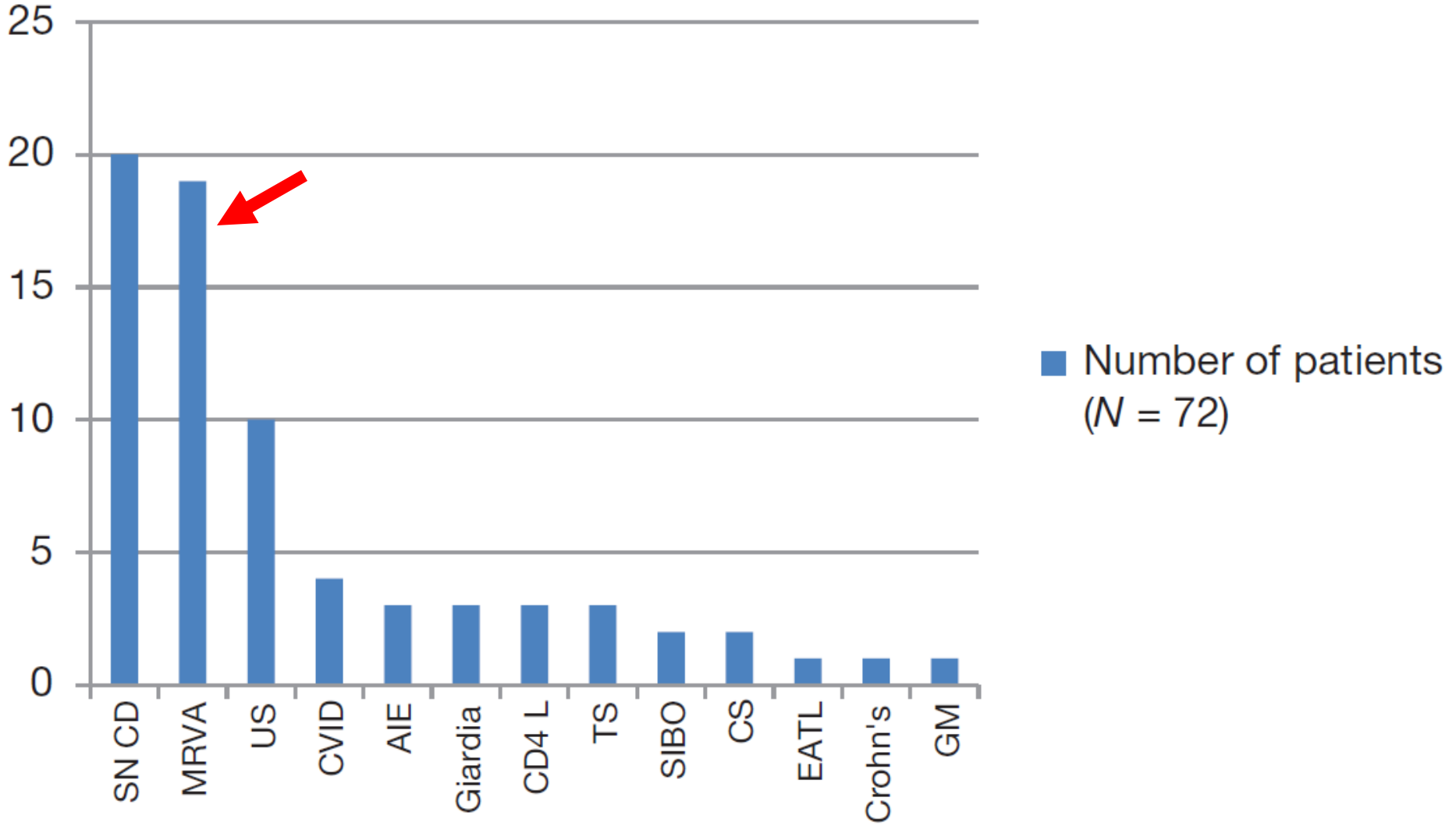
- Angiotensin II receptor antagonist
- Commonly used to treat hypertension
- Clinical presentation:
  - Diarrhea begins 2-10 years after drug is started
  - Chronic watery diarrhea and weight loss
  - Celiac-like histology (+/- collagen thickening)
  - +/- coexistent lymphocytic or collagenous gastritis
  - +/- coexistent lymphocytic or collagenous colitis
  - Negative serologic tests for celiac disease
  - Diagnosis of “refractory sprue”
  - No response to a gluten free diet
  - Responds slowly to withdrawal of medication

Scialom S et al. PLosOne 2015; 10:e0125024.

Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma

Am J Gastroenterol 2013;108:647–653

Marisa DeGaetani, MD[1,2], Christina A. Tennyson, MD[1,2], Benjamin Lebwohl, MD, MS[1,2], Suzanne K. Lewis, MD[1,2], Hussein Abu Daya, MD[1], Carolina Arguelles-Grande, MD[1], Govind Bhagat, MBBS[3] and Peter H.R. Green, MD[1,2]



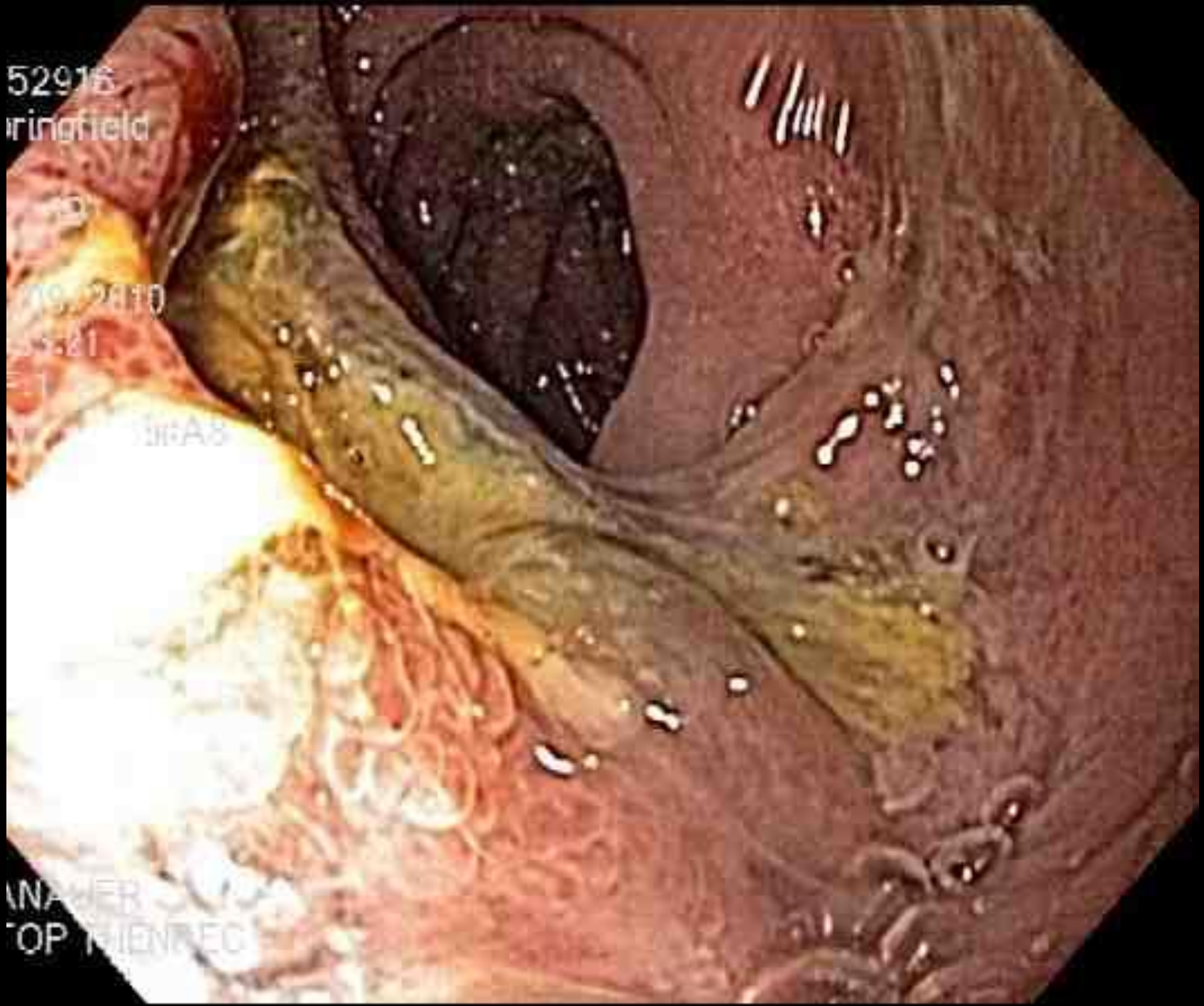
Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma

Am J Gastroenterol 2013;108:647–653

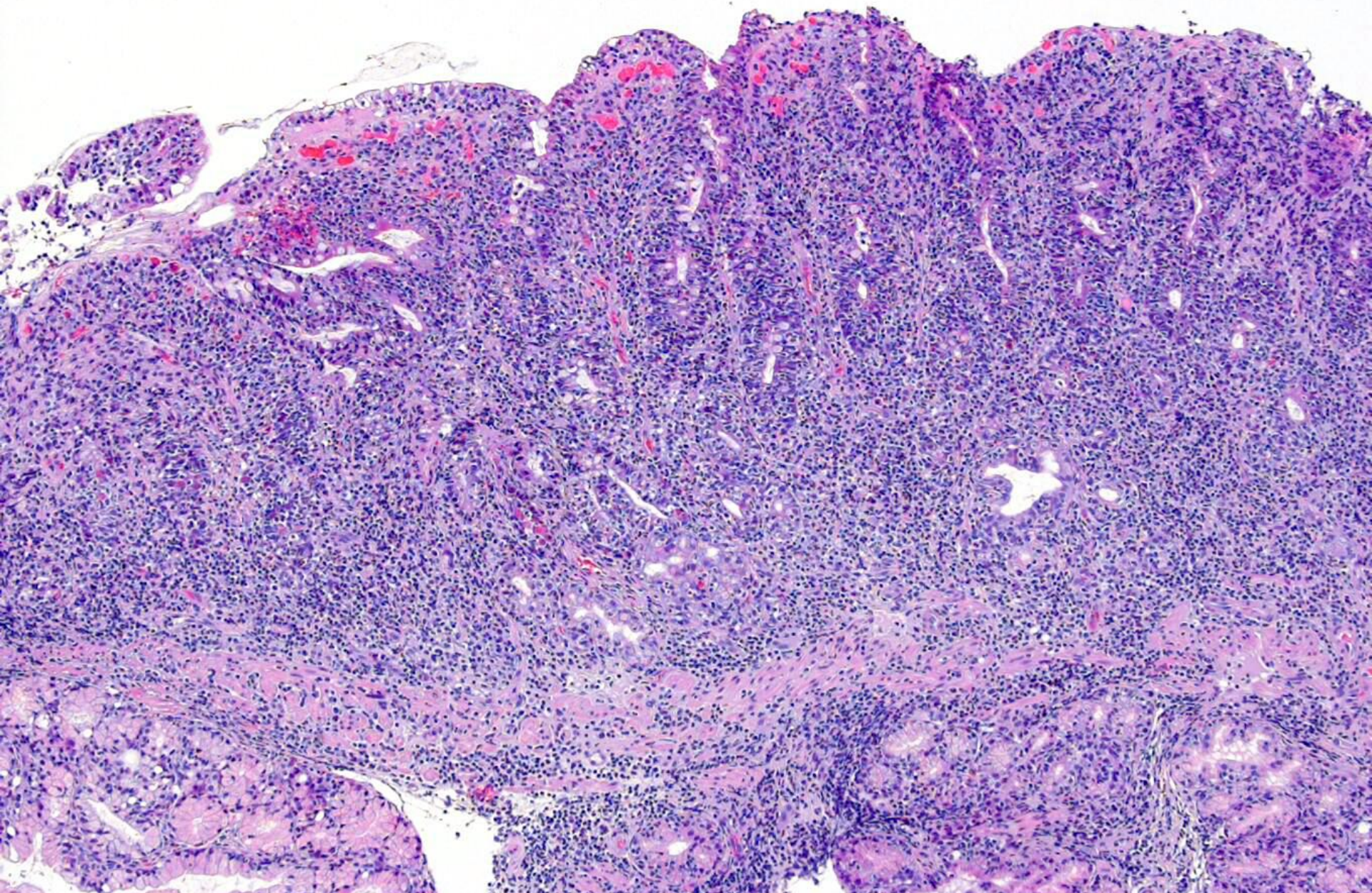
oxcarbazepine

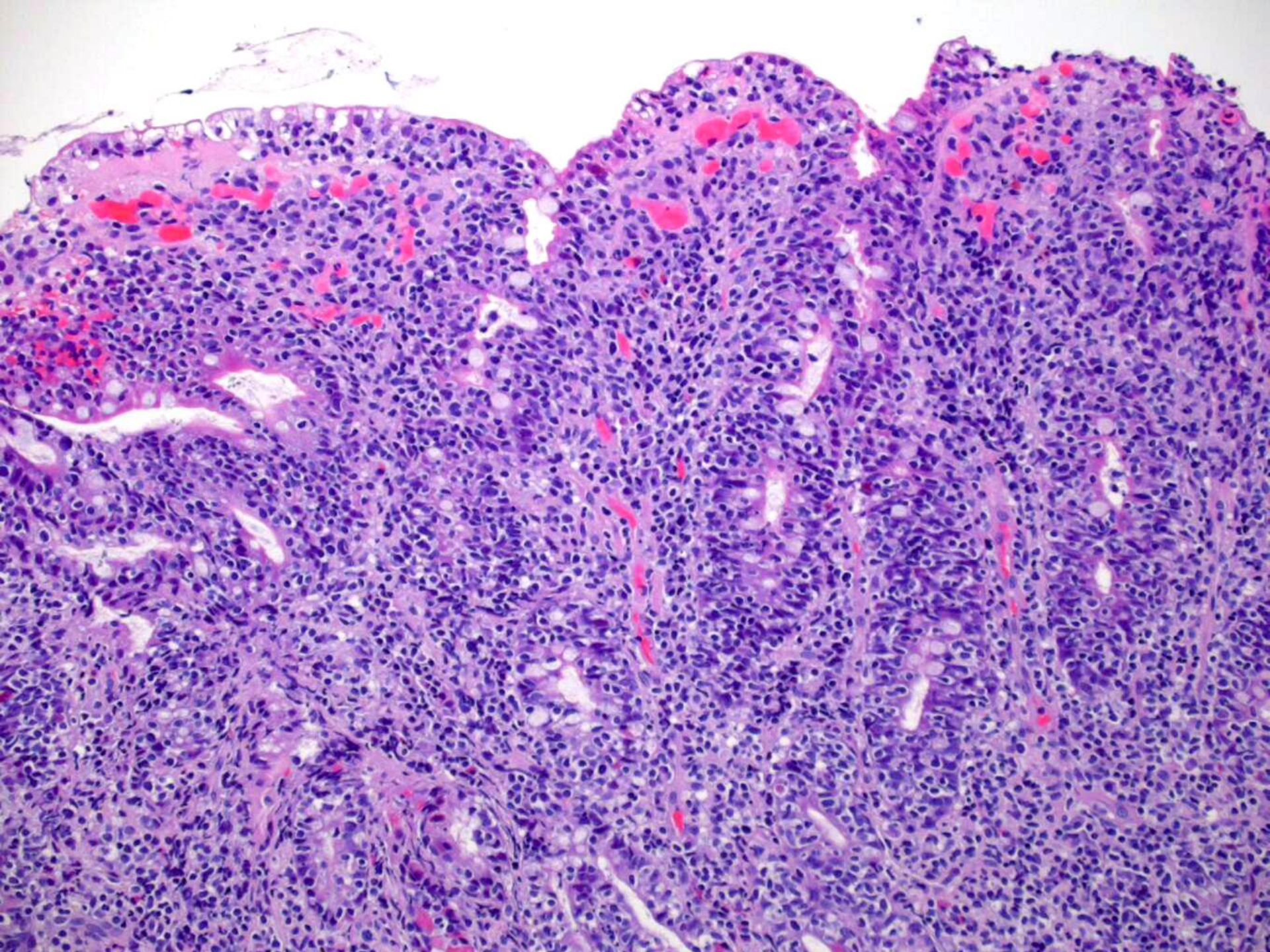
Table 3. Medication-related villous atrophy

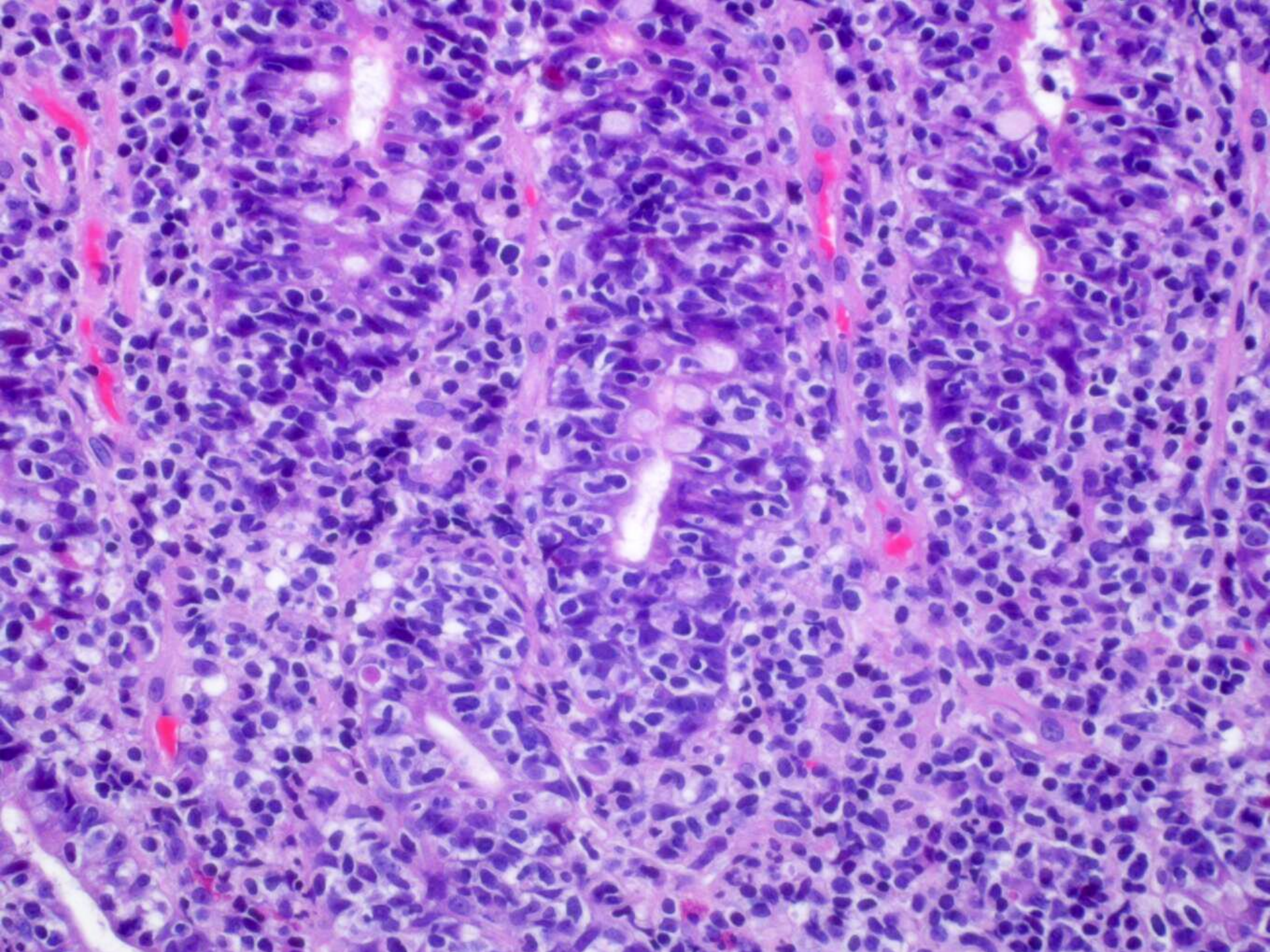
No.	Age (y)/sex	HLA DQ2/8	Culprit meds?	Degree VA initial bx	Increase subepithelial collagen	Increase IEL on bx	GFD	Clinical improv./ GFD	Abx	Clinical improv./ Abx	IS	Clinical improv./ IS	Relapse off IS?	Clinical improv. after stopping med
1	61/M	+	Olmesartan	TVA	+	+	+	–	+	?	+	+	+	+
2	73/F	+	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+
3	82/M	NT	Olmesartan	PVA	+	+	+	–	+	?	+	+	+	+
4	63/M	+	Olmesartan	STVA	+	+	+	–	–	NA	+	+	+	+
5	69/F	–	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+
6	66/M	+	Olmesartan	TVA	+	+	+	–	+	+	+	+	+	+
7	75/F	+	Olmesartan	DNS	+	+	+	–	+	+	+	+	+	?
8	63/F	+	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+
9	52/M	NT	Olmesartan	STVA	–	–	+	–	+	–	+	+	+	+
10	58/F	+	Olmesartan	PVA	+	–	+	–	–	NA	+	+	+	+
11	83/M	+	Olmesartan	DNS	–	+	+	–	+	–	+	+	+	+
12	67/F	+	Olmesartan	PVA	+	–	+	–	+	–	+	+	+	+
13	75/M	+	Olmesartan	TVA	–	–	+	+	–	NA	+	+	+	+
14	68/F	+	Olmesartan	TVA	–	+	+	–	+	–	+	+	+	+
15	62/M	+	Olmesartan	TVA	+	+	+	–	+	–	+	+	+	+
16	64/F	NT	Olmesartan	DNS	–	–	+	–	–	NA	+	+	+	+
17	74/F	+	MMF	PVA	+	–	+	–	–	NA	NA	NA[a]	NA	+
18	57/F	NT	MMF	PVA	–	–	–	NA	–	NA	NA	NA[a]	NA	+
19	67/F	NT	Methotrexate	PVA	–	–	+	+	–	NA	NA	NA[a]	NA	+



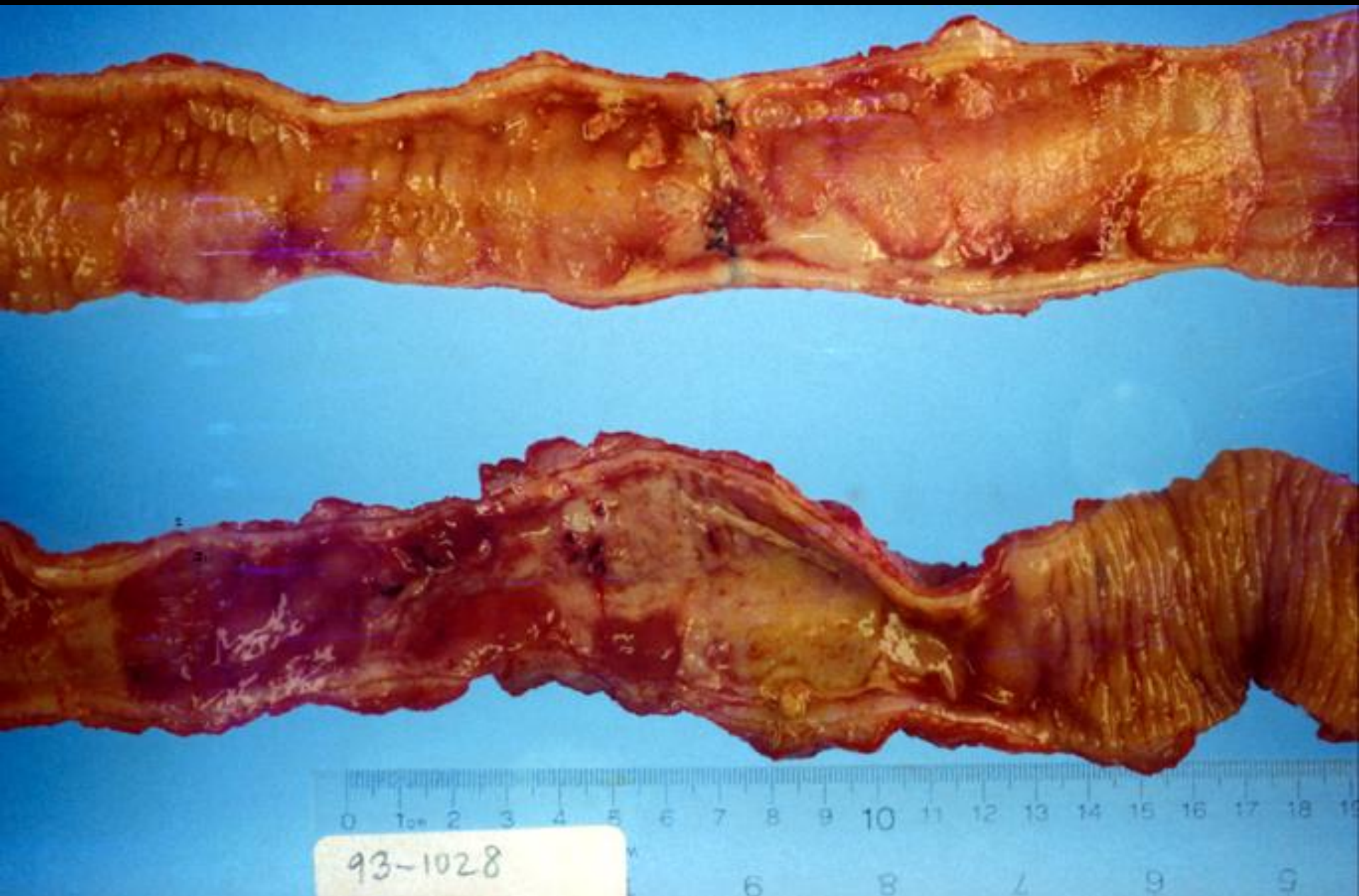
Enteropathy Associated T-cell Lymphoma (EATL)

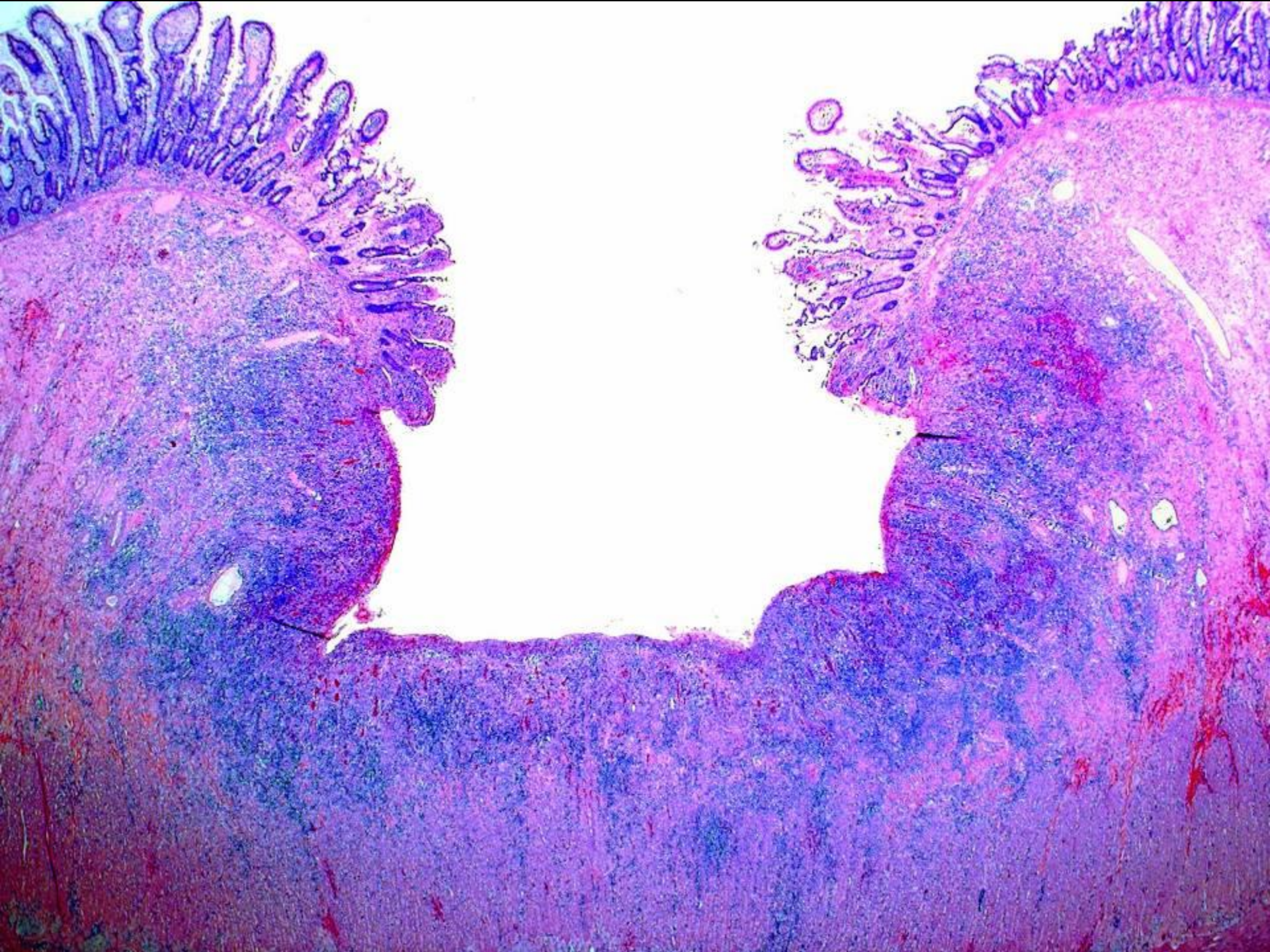


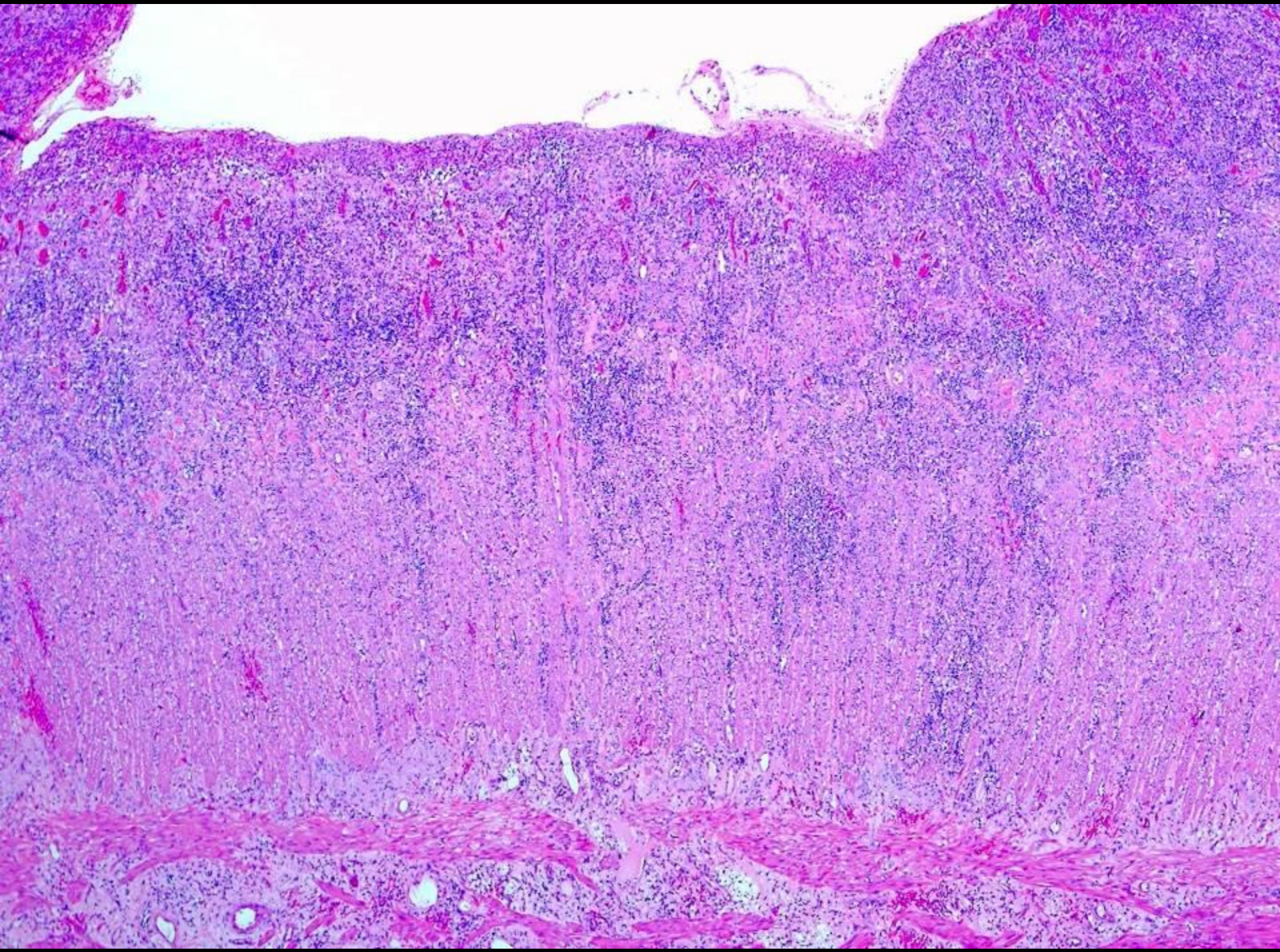


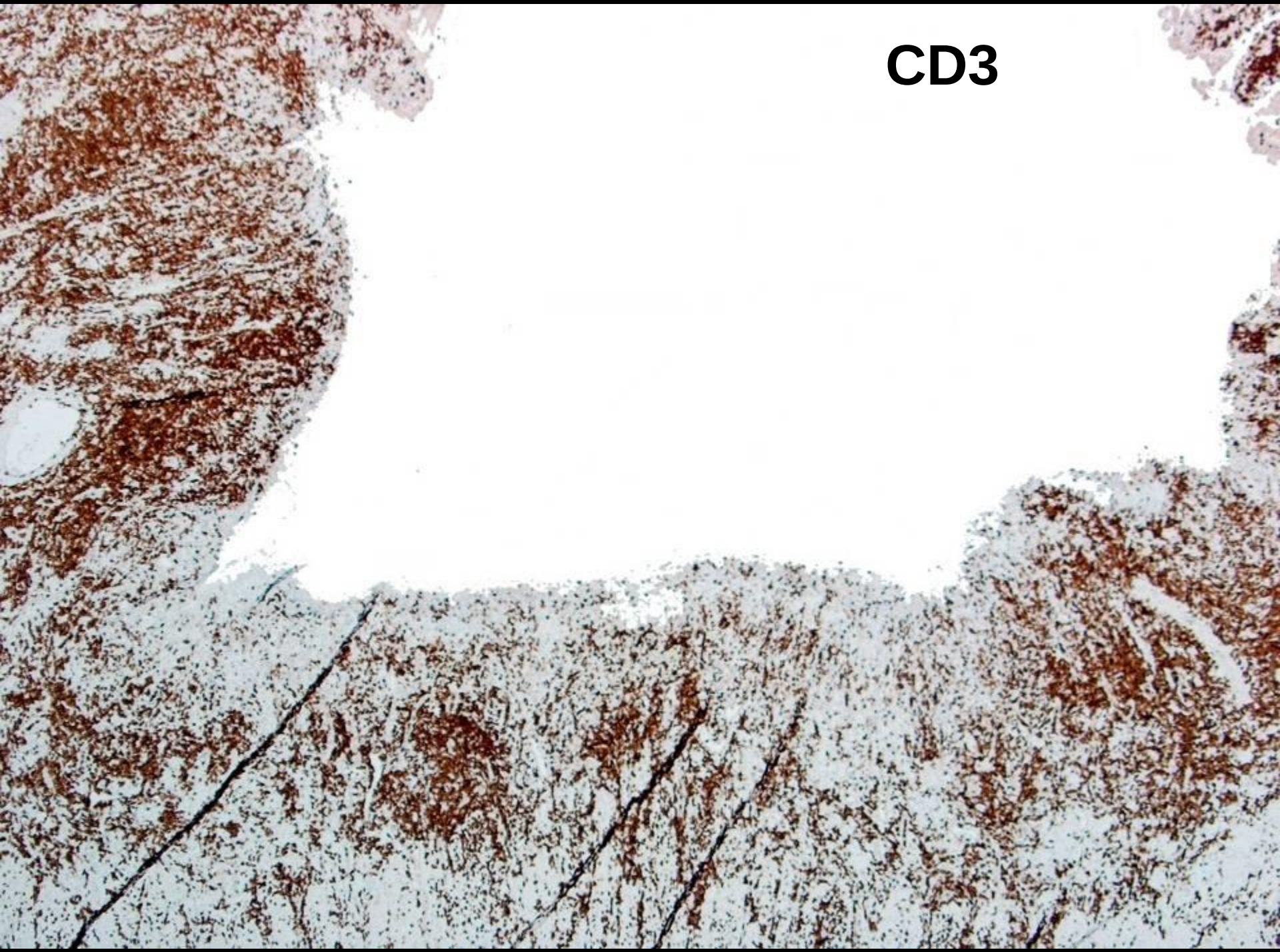


Ulcerative Jejuno-ileitis







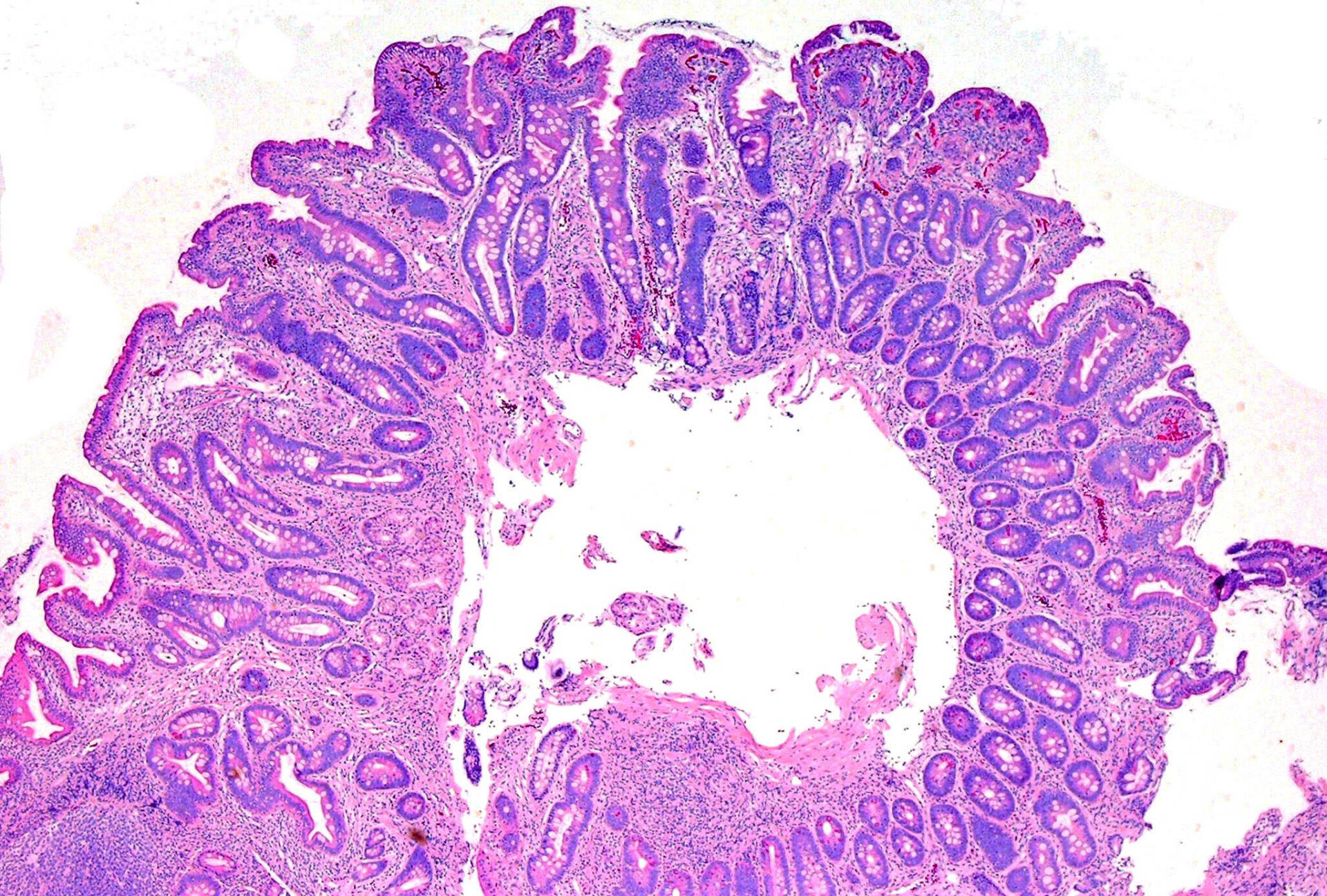

CD3

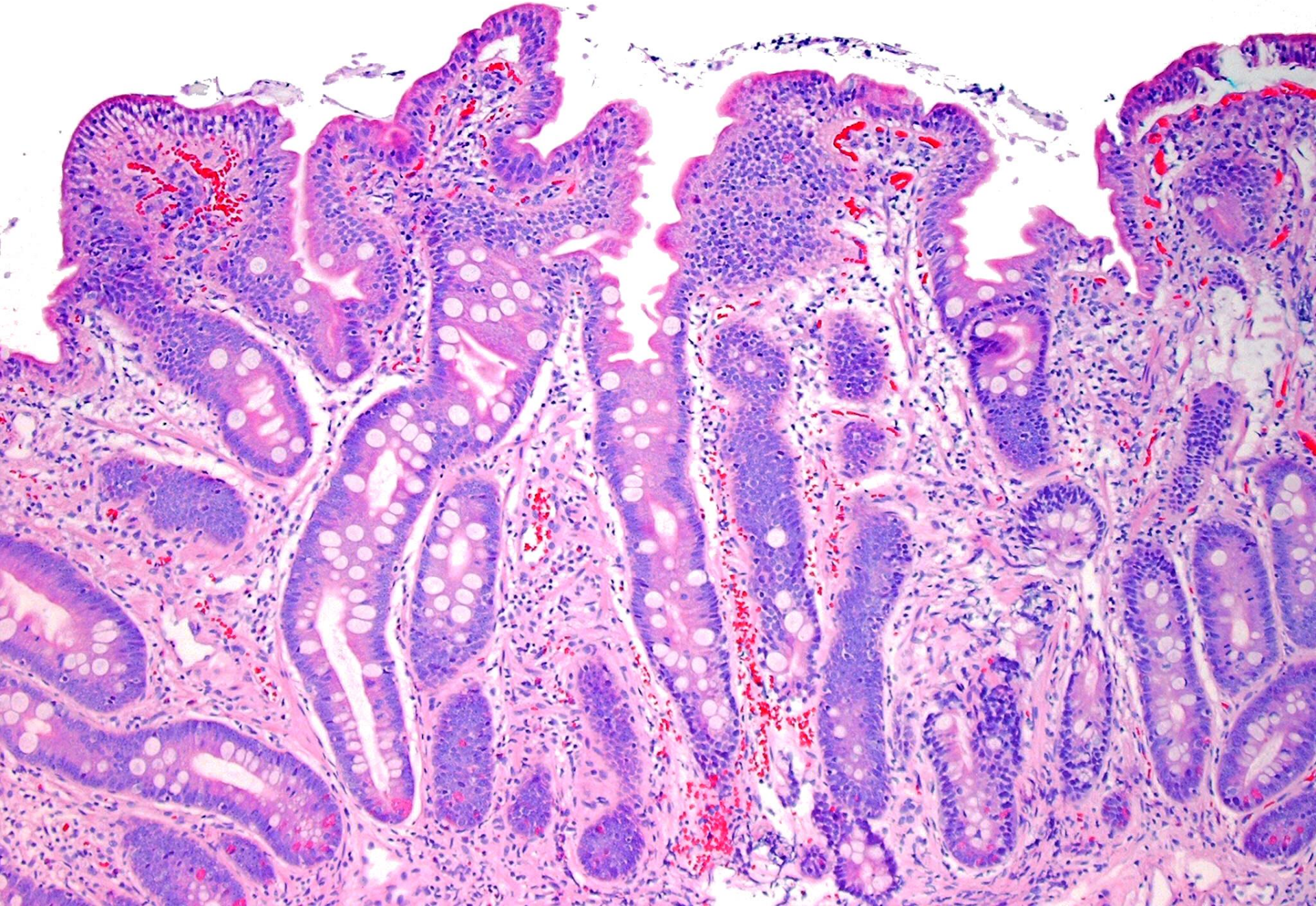
C11-25813

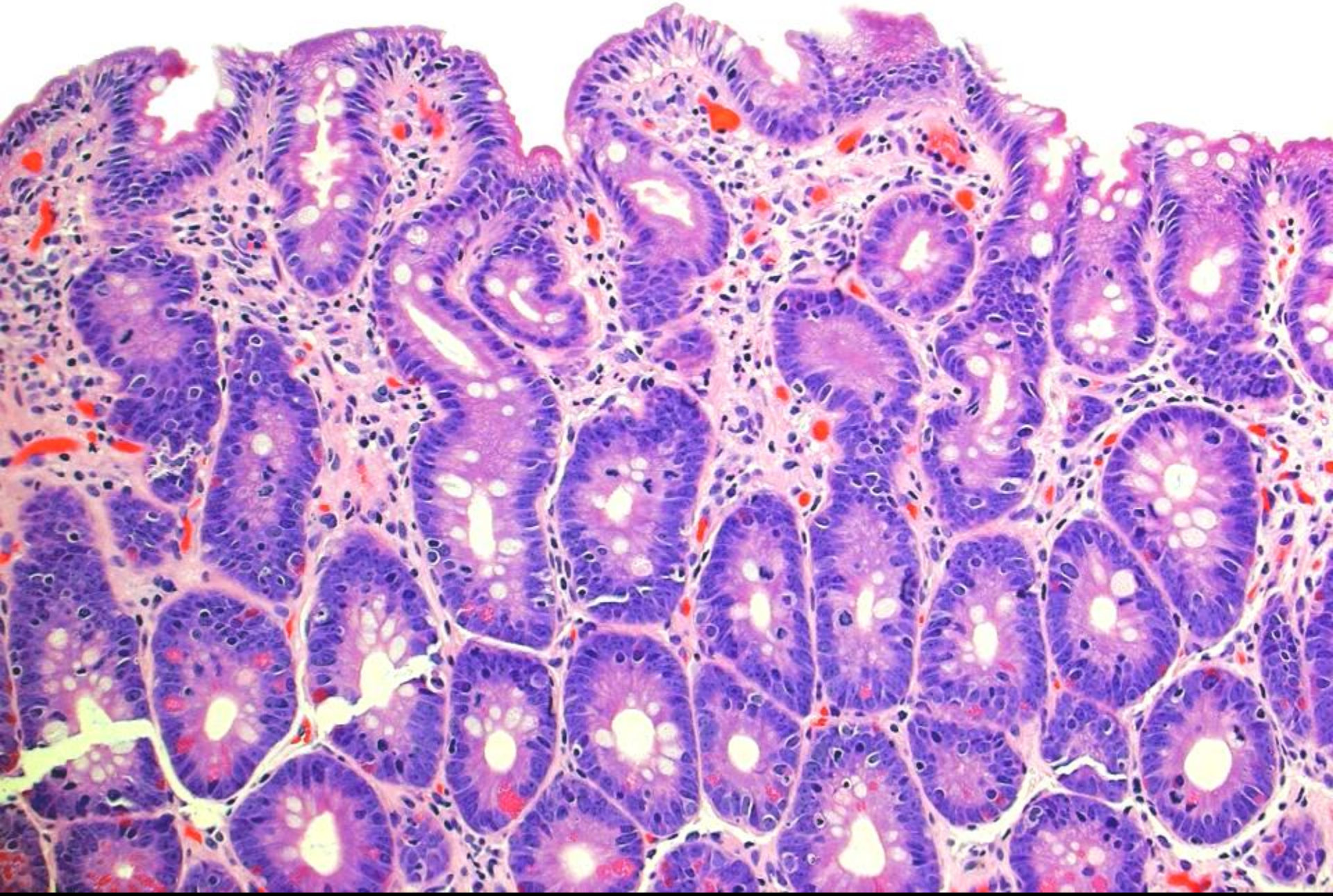
Clinical History

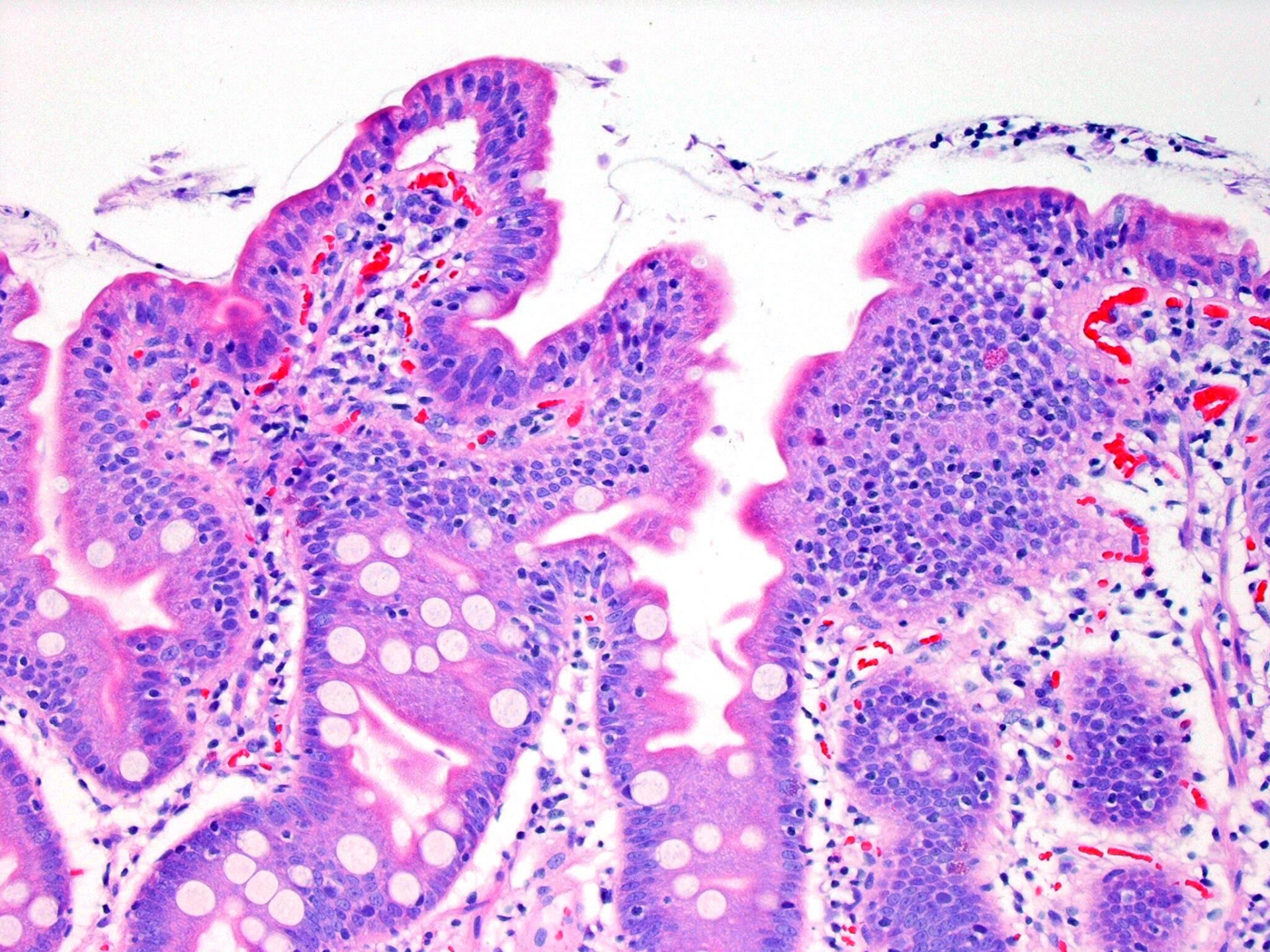
- 31 y.o. M with a long history of non-bloody diarrhea
- 25 lb weight loss over the past two years (118 lbs.)
- Diagnosed with diabetes, but no weight gain with oral hypoglycemic agents
- Upper endoscopy:
  - Scalloped duodenal folds
  - Biopsies reveal features consistent with celiac disease
- Celiac HLA and serology panel:
  - DQ2 positive
  - IgA deficient (IgA less than 5)
  - Anti-gliadin IgG positive
- Placed on GFD – continued diarrhea; no weight gain
- Repeat upper endoscopy with duodenal biopsies

First endoscopy

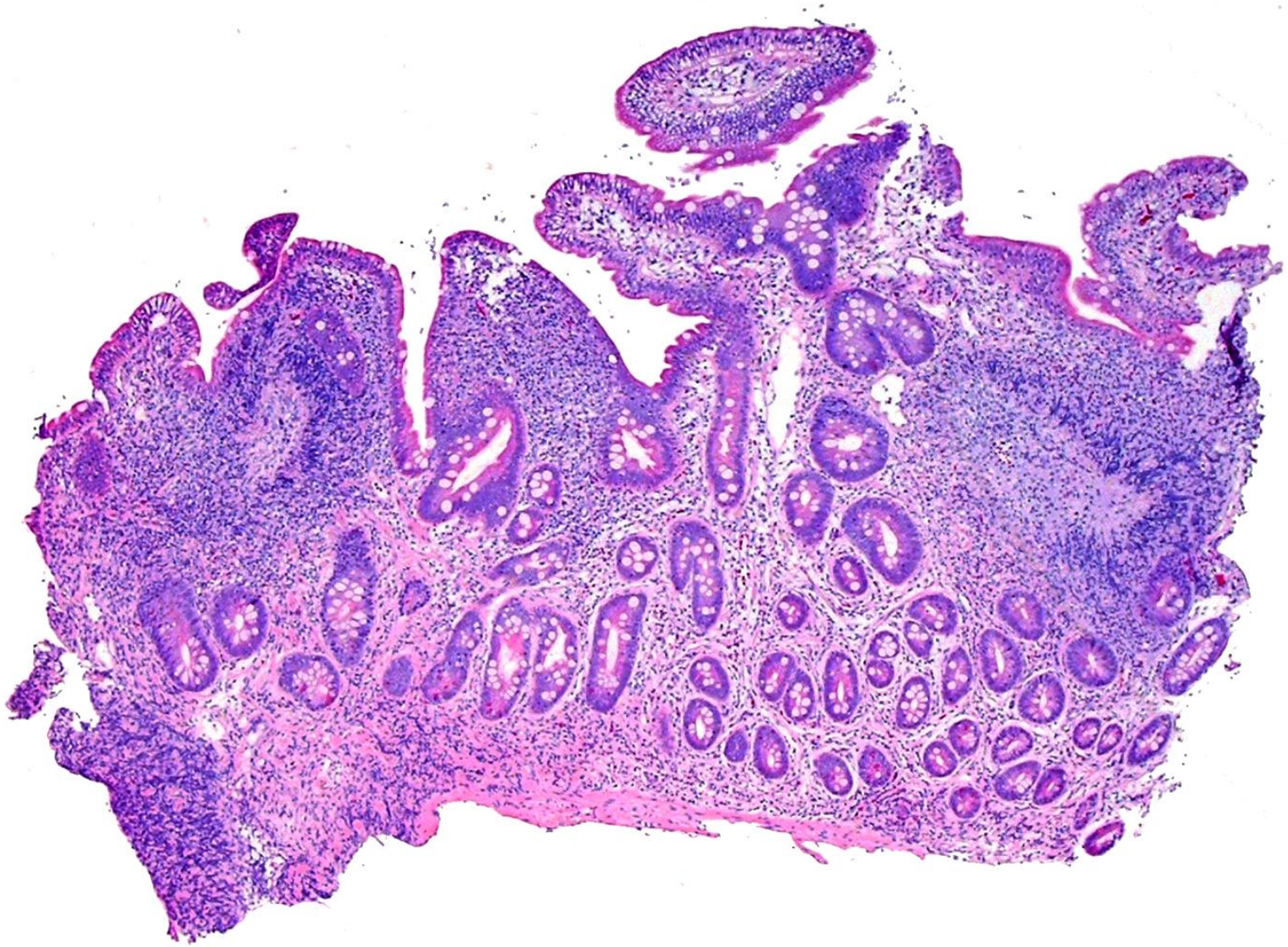


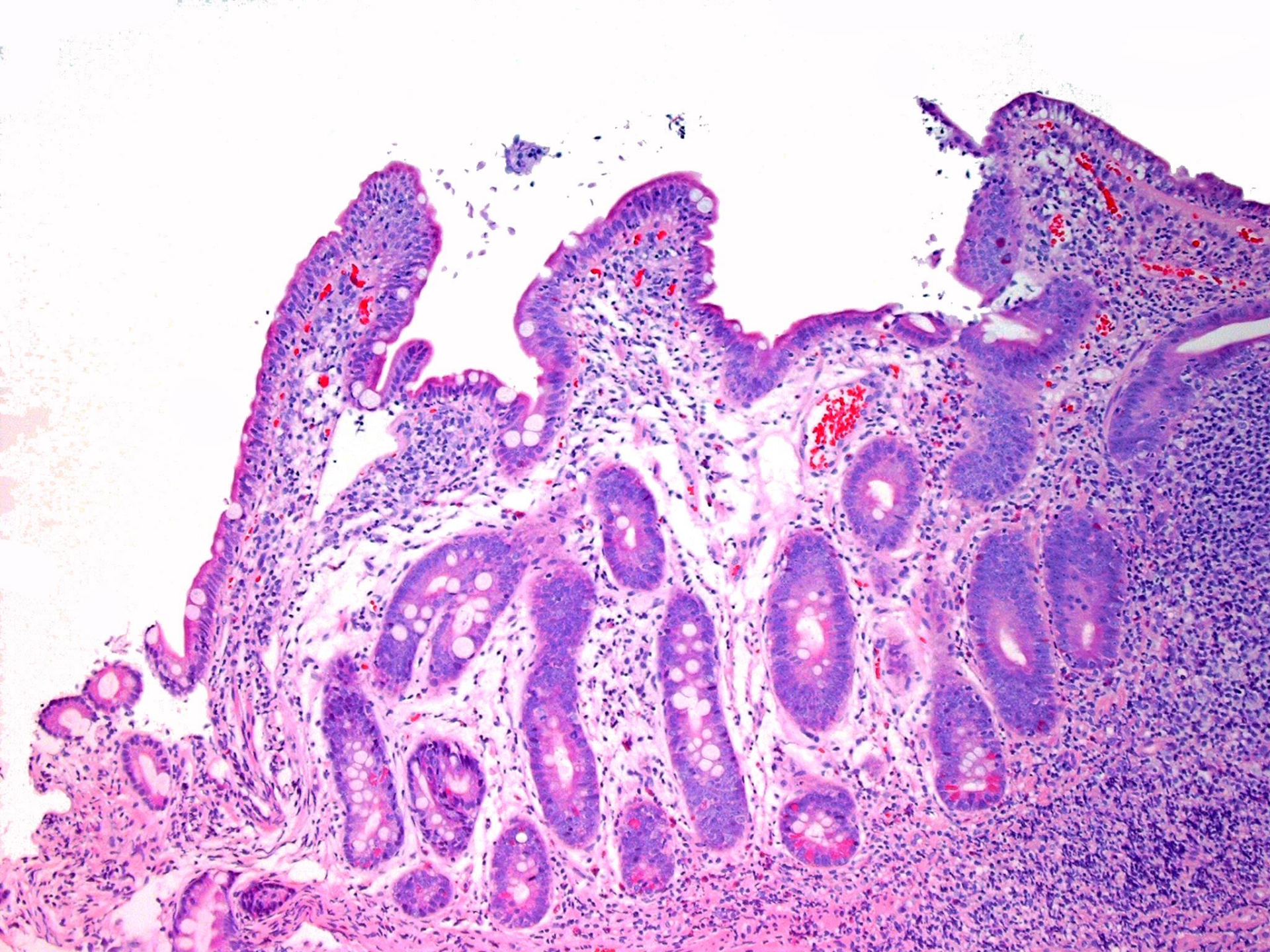


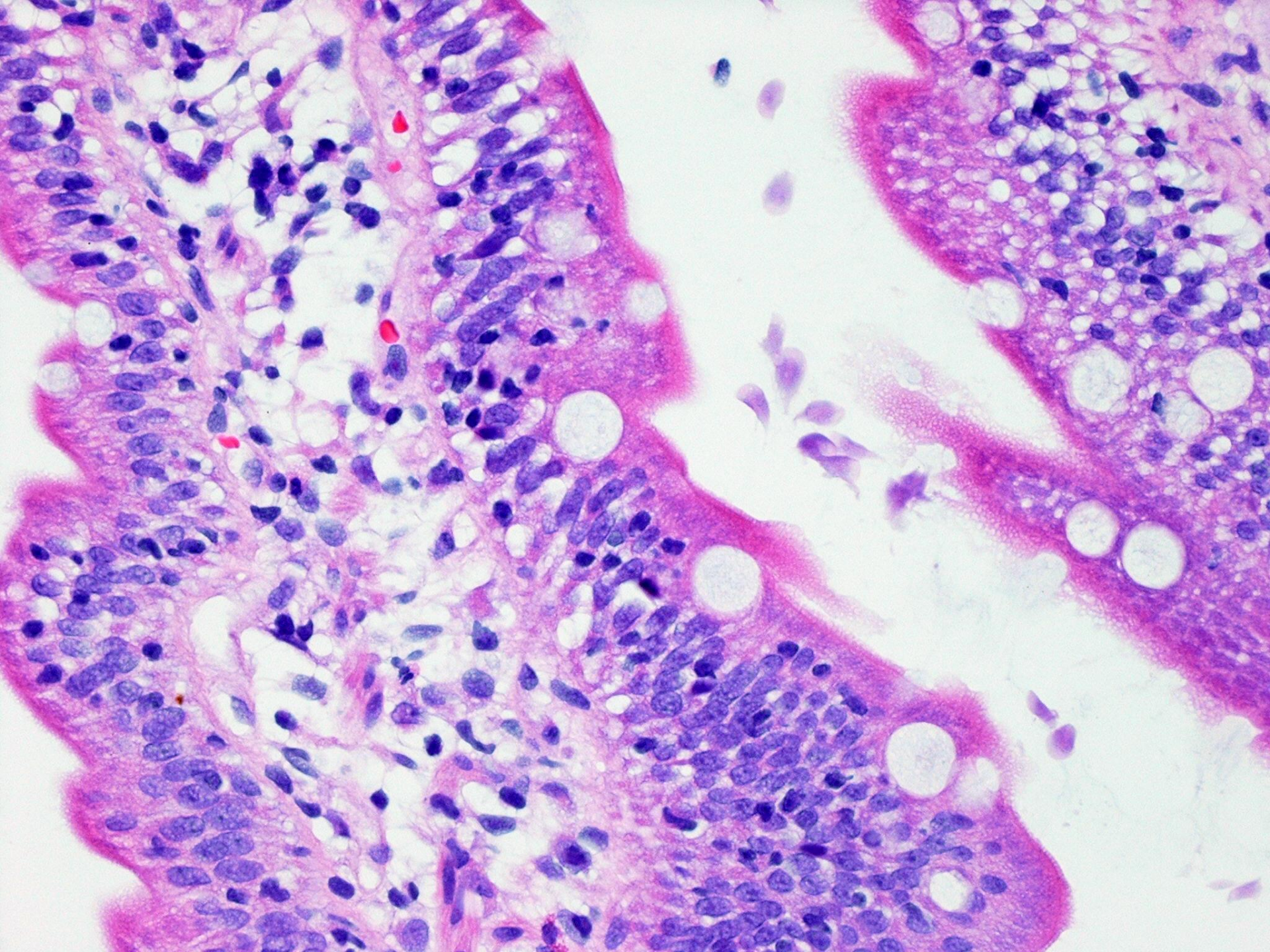


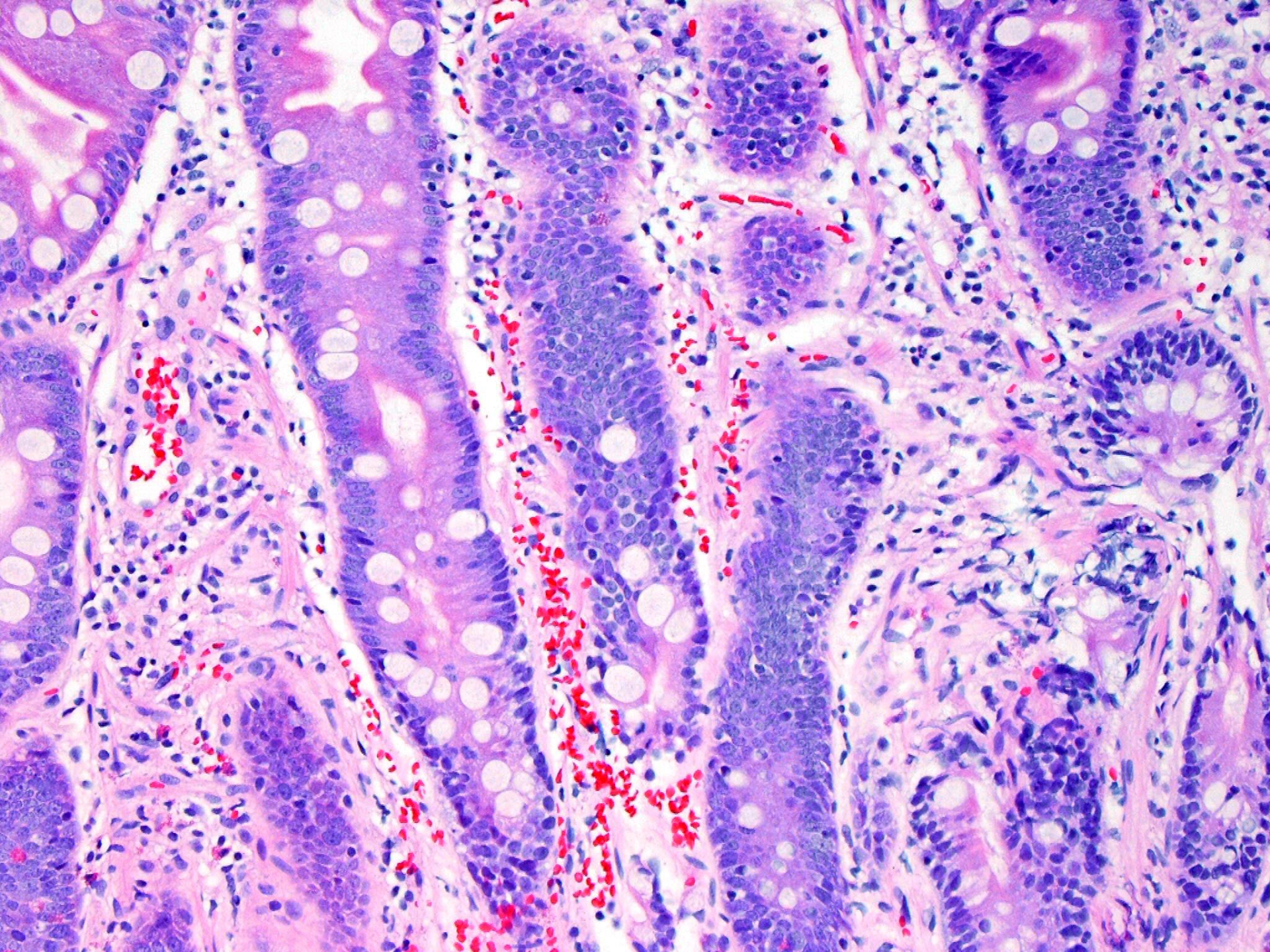


Repeat endoscopy









Additional Laboratory Evaluation

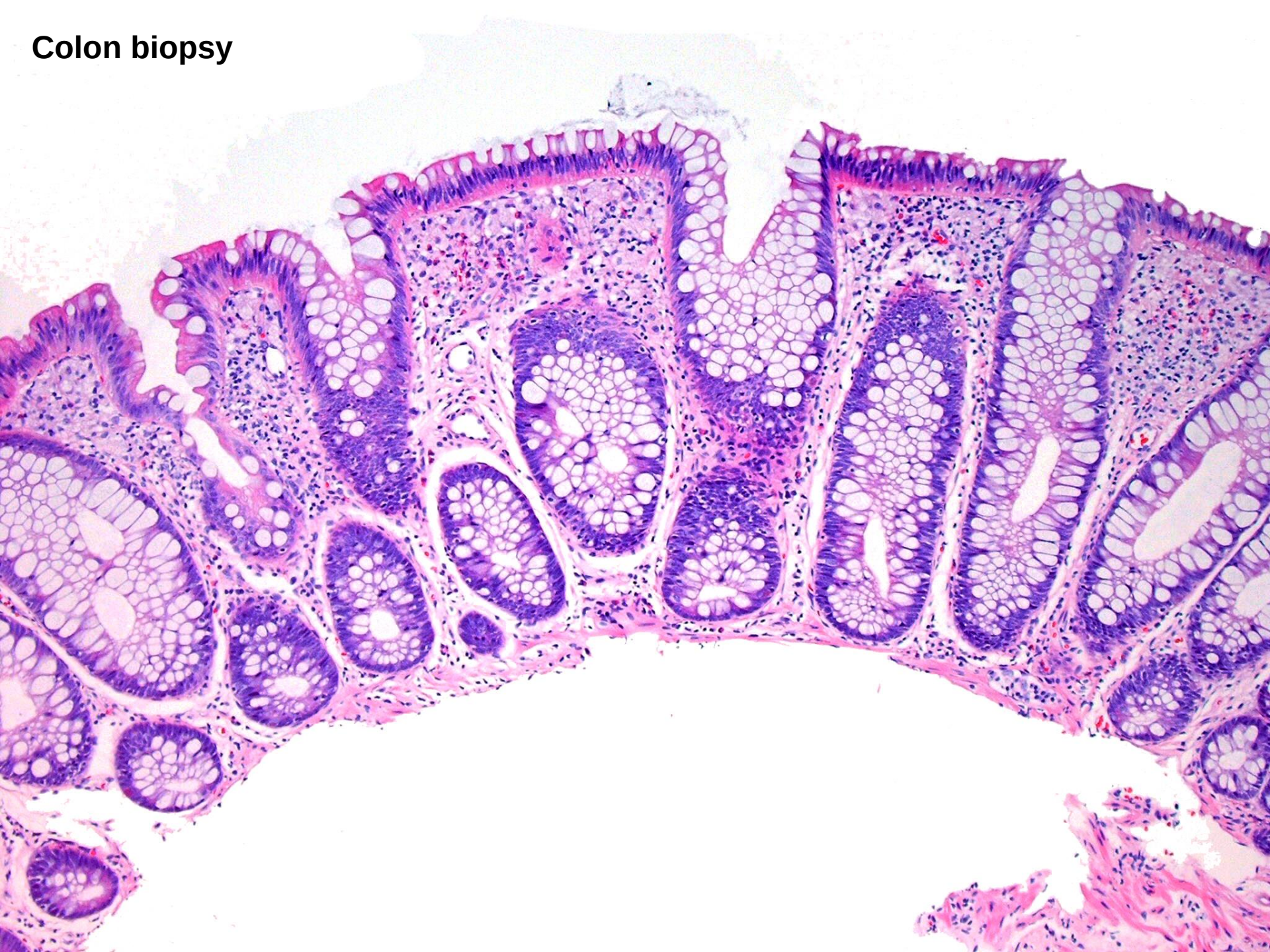
- DGP IgG negative
- Iron, vitamin D, zinc & folate deficient
- Quantitative immunoglobulin levels:
  - IgA = < 5 (110-490 mg/dL)
  - IgG = 410 (800-1700 mg/dL)
  - IgM = 6 (50-320 mg/dL)

Dx: Common variable immunodeficiency with Giardia infection

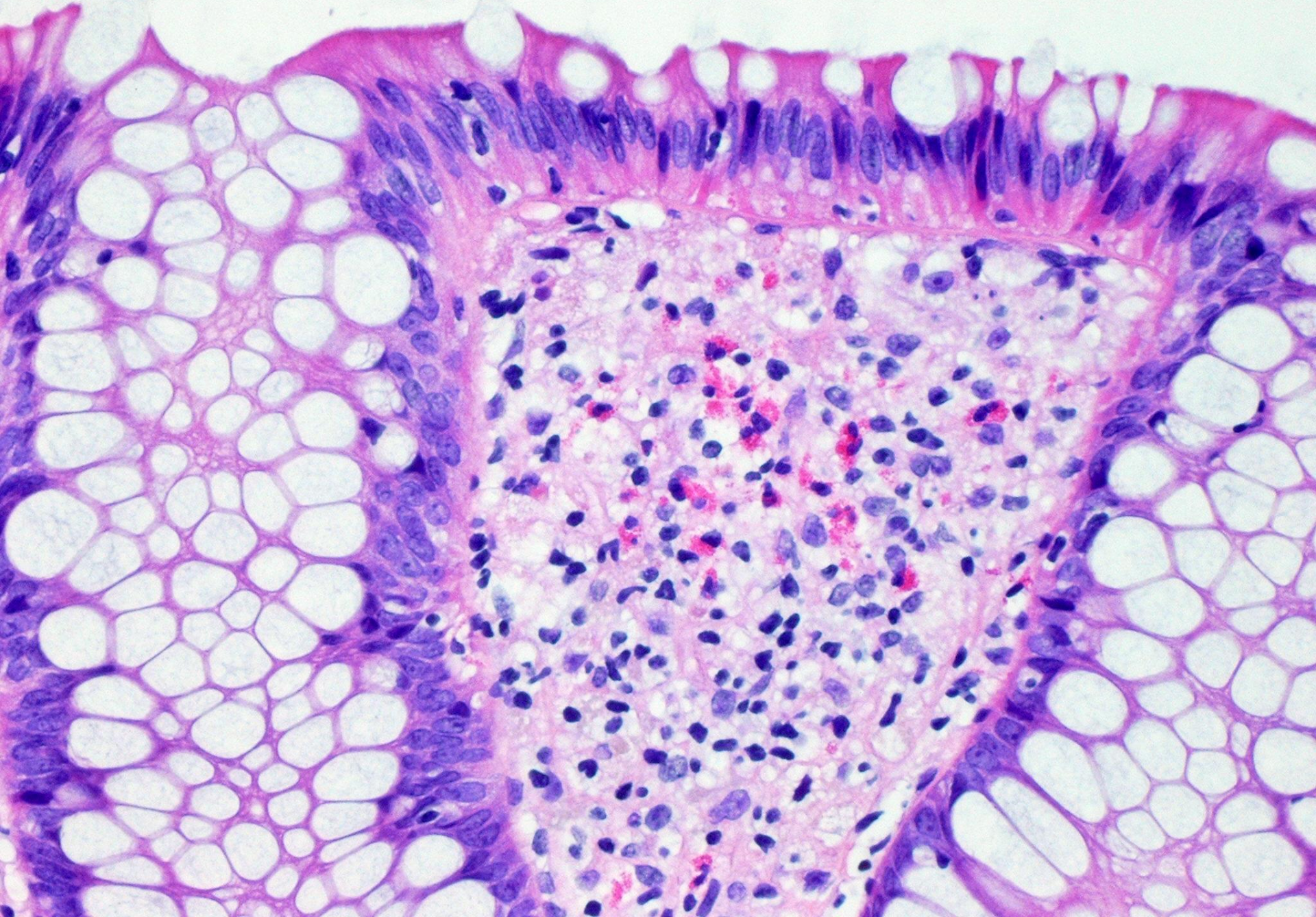
Histologic Features distinct to CVID

- Absent *or greatly decreased* plasma cells
- Crypt cell apoptosis
- Significant neutrophilic infiltrates
- Mucosal lymphoid follicles
- Giardia lamblia infection

Colon biopsy



Colon biopsy – no plasma cells!



The Enteropathy Associated With Common Variable Immunodeficiency: The Delineated Frontiers With Celiac Disease

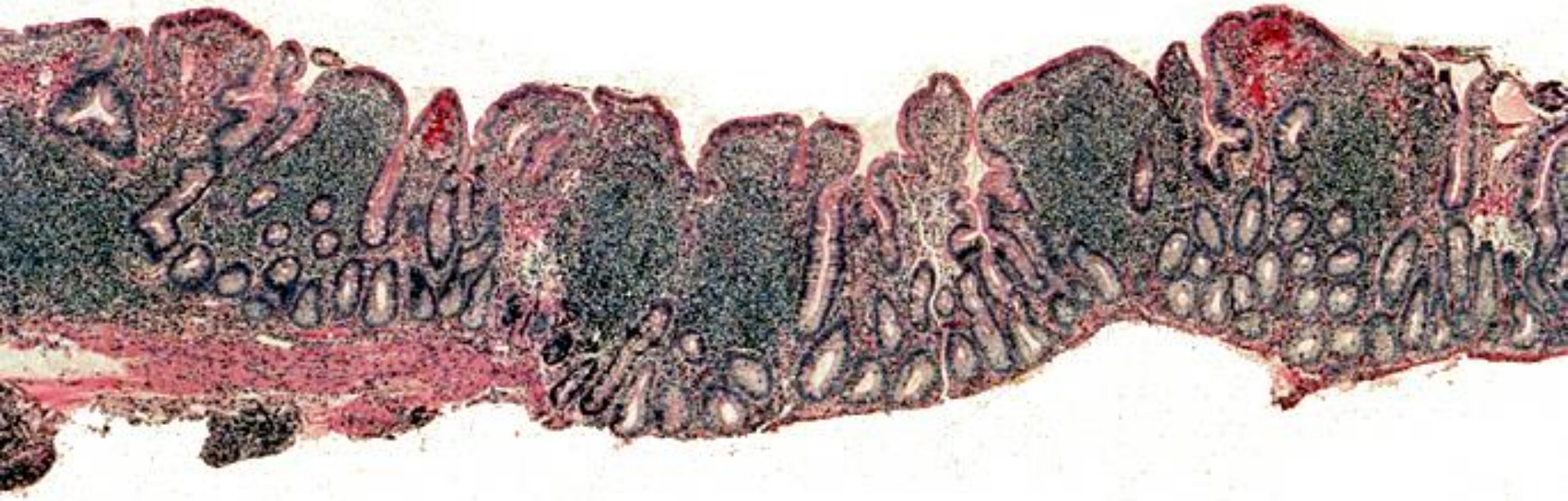
Am J Gastroenterol 2010; 105:2262–2275

Georgia Malamut, MD, PhD[1–3], Virginie Verkarre, MD, PhD[1,3,4], Felipe Suarez, MD[1,5], Jean-François Viallard, MD, PhD[6], Anne-Sophie Lascaux, MD[7], Jacques Cosnes, MD, PhD[8], Yoram Bouhnik, MD, PhD[9], Olivier Lambotte, MD, PhD[10], Dominique Béchade, MD, PhD[11], Marianne Ziol, MD, PhD[12], Anne Lavergne, MD, PhD[13], Olivier Hermine, MD, PhD[1,5], Nadine Cerf-Bensussan, MD, PhD[1,3] and Christophe Cellier, MD, PhD[1–3]

50 patients with CVID and duodenal biopsies

- **Mean age at diagnosis of CVID was 36.8 +/- 15.6 yrs**
- **Mean onset of GI symptoms was 34.5 +/- 14.3 yrs**
- **Anemia in 56% and malabsorption in 54%**
- **DQ2 or DQ8 in 77% of tested patients**
- **31 of 50 (62%) with increased duodenal IELs**
- **21 of 31 (67%) with inc. IELs had villous atrophy**
- **3 of 38 patients tested positive celiac serologic tests**
- **No response to gluten free diet in 10 treated patients**

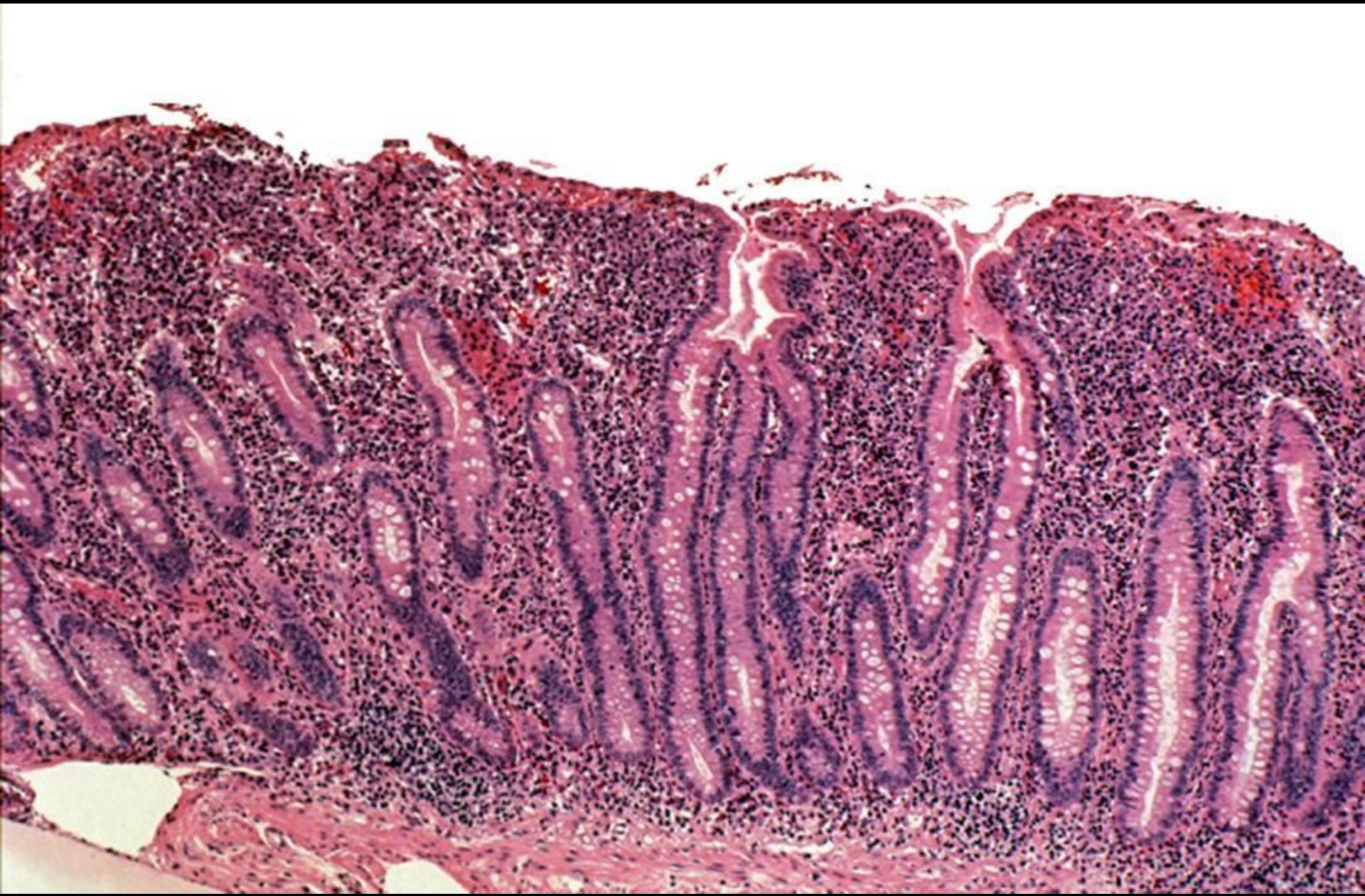
Nodular Lymphoid Hyperplasia

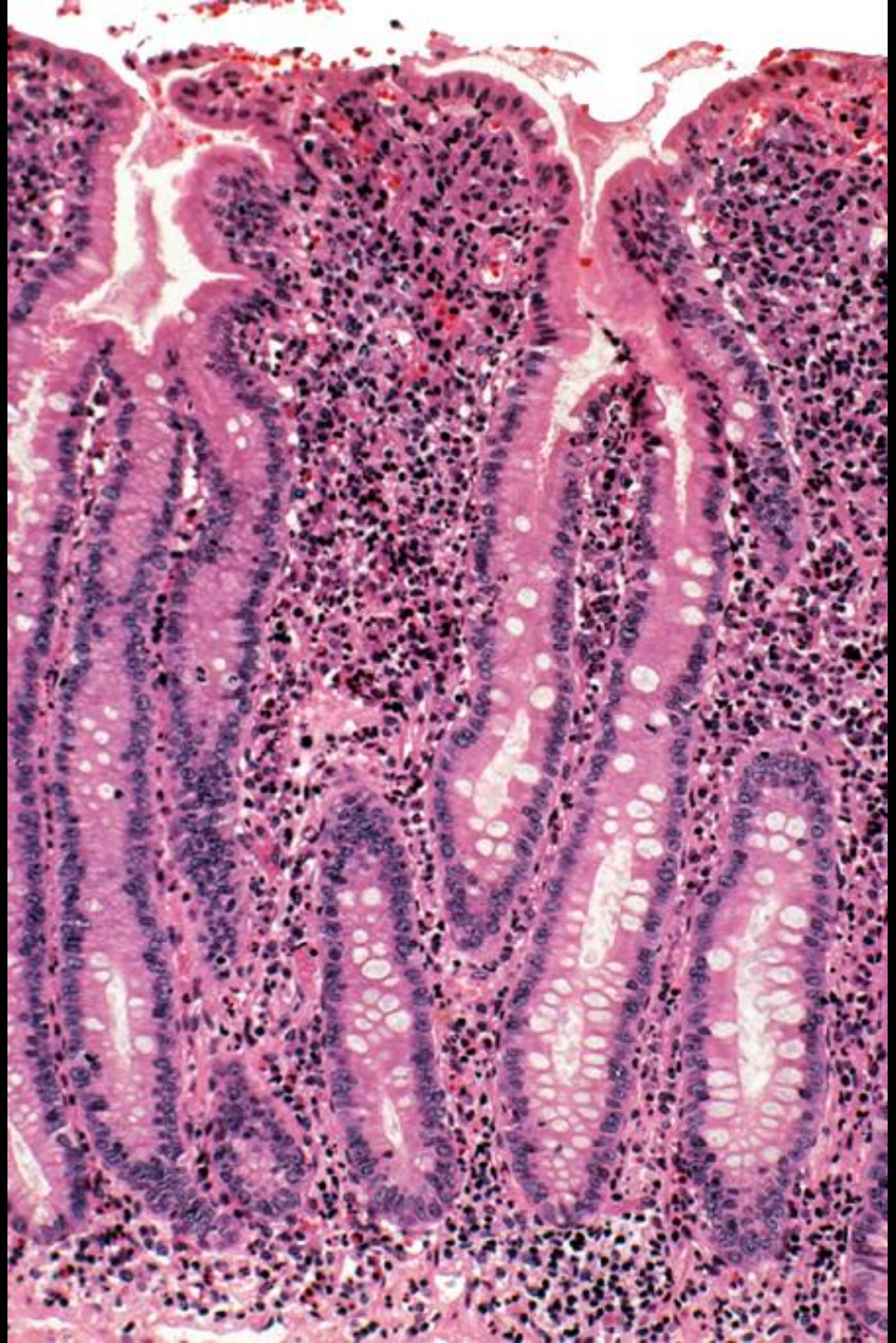


Clinical History

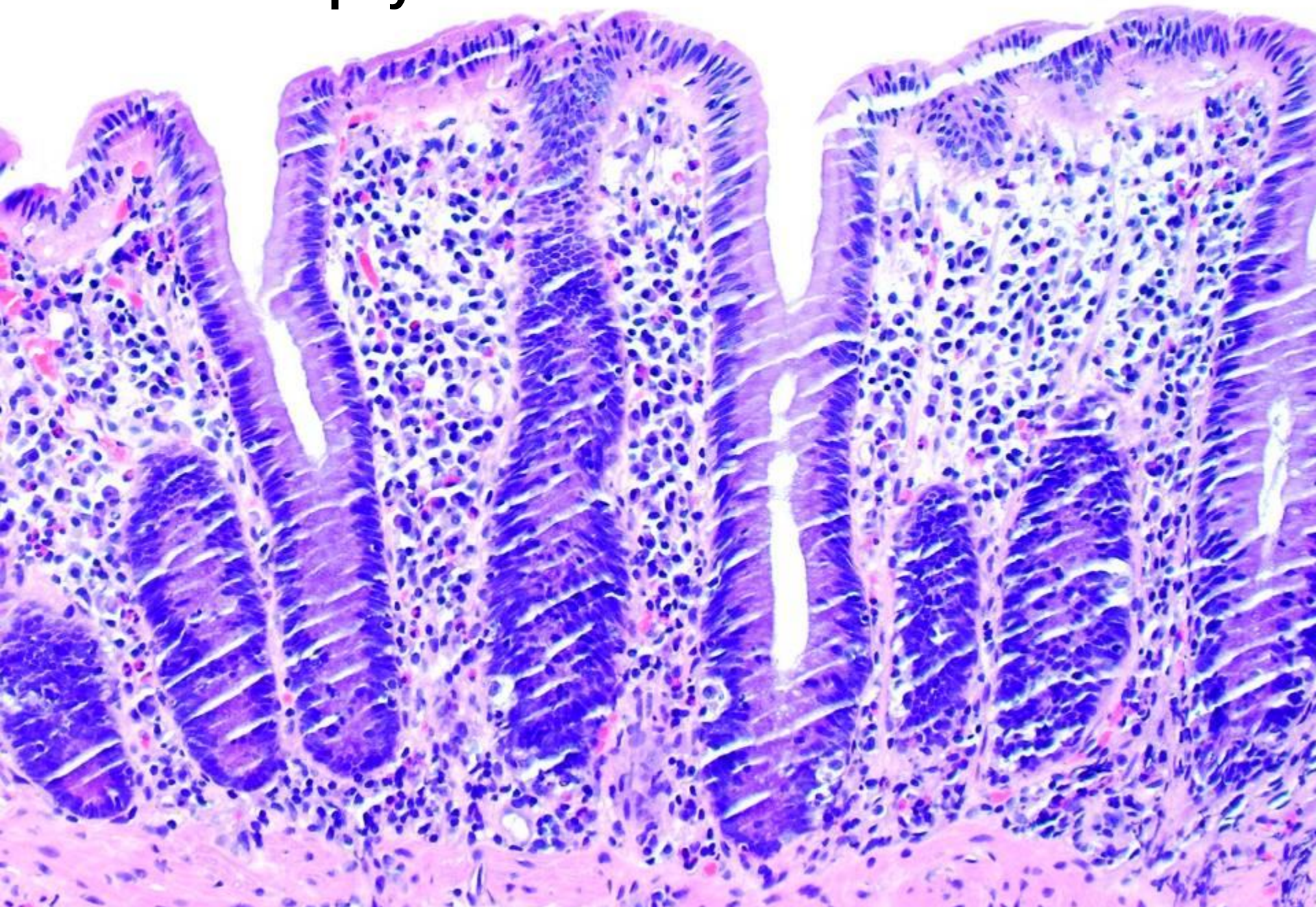
- 23-month-old M with failure to thrive and a 1 mo Hx of severe watery diarrhea.
- Diarrhea persisted despite discontinuation of oral feeding and administration of TPN.
- Serologic tests for celiac disease were all negative.
- HIV antibody test negative
- Duodenal biopsies obtained

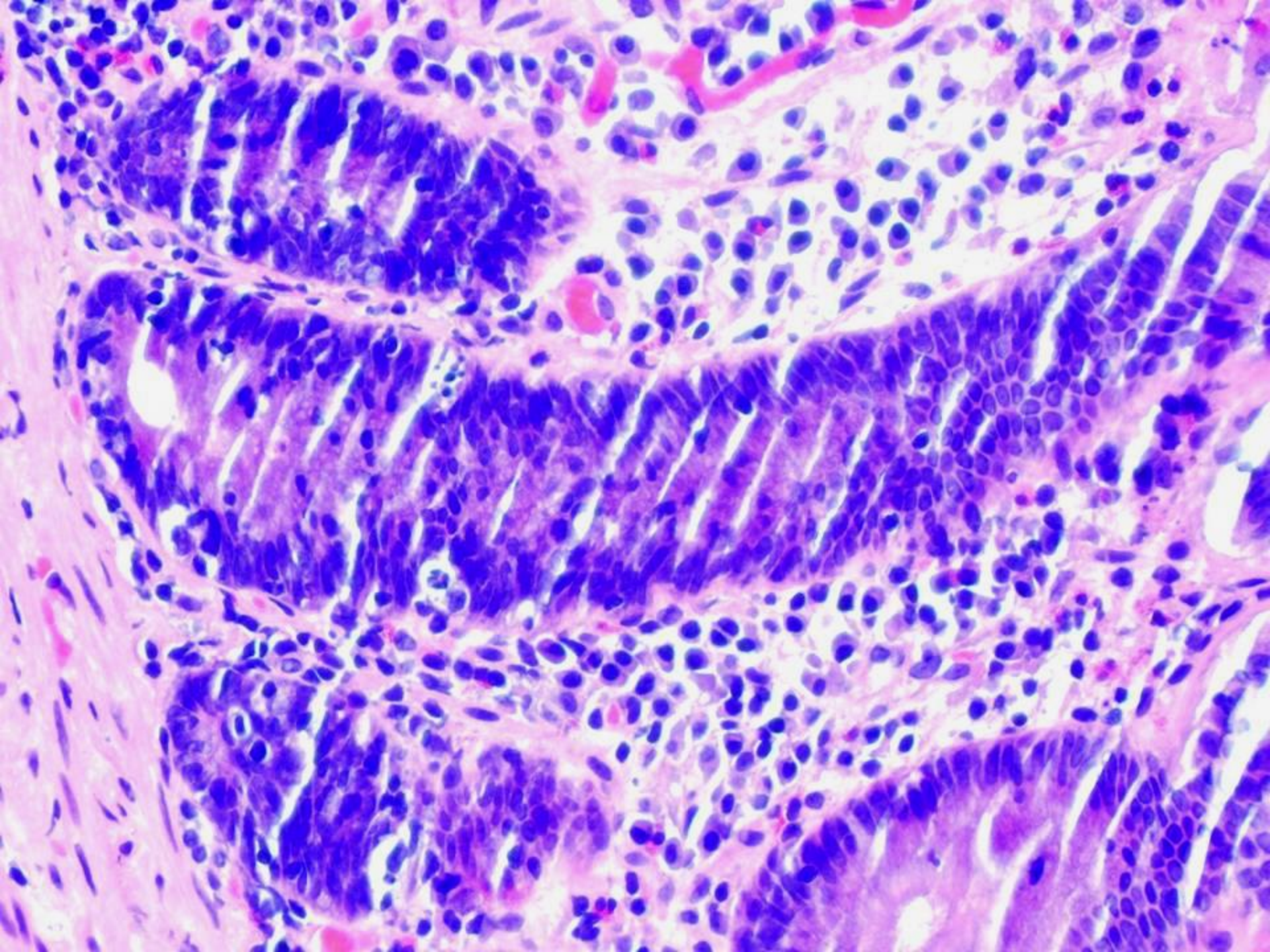
Autoimmune Enterocolitis





Colonic Biopsy





Autoimmune Enterocolitis

- Presentation in first year of life, or as adult
- Severe diarrhea, even when NPO on TPN
- Do not respond to gluten free diet
- Serologic tests for celiac disease negative
- Anti-enterocyte/goblet cell antibodies (non-specific)
- Usually affects both small and large bowel
- Duodenal morphology similar to celiac disease in some cases
- Treated with immunosuppressive drugs

Other Rare Neonatal Enteropathies

- Congenital transport protein defects:
  - Chloride-bicarbonate exchanger
  - Sodium-hydrogen exchanger
  - Ileal bile acid receptor
- Enterokinase deficiency
- Tufting enteropathy
- Microvillous inclusion disease
- IPEX syndrome

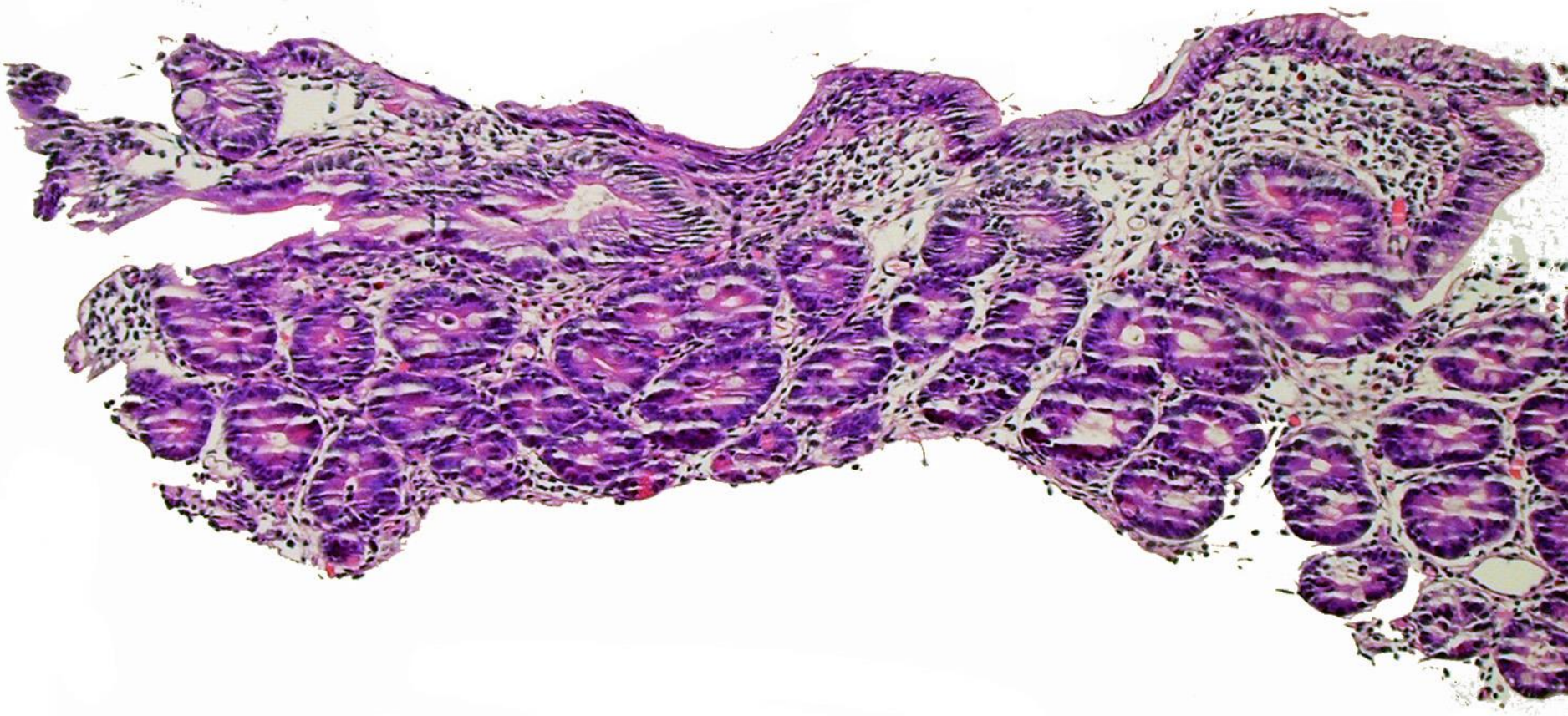
Crypt and Villous Atrophy Pattern

- Collagenous sprue
- Microvillous inclusion disease
- Drug toxicity:
  - cis-platinum
  - Vincristine
- Cow's milk protein intolerance

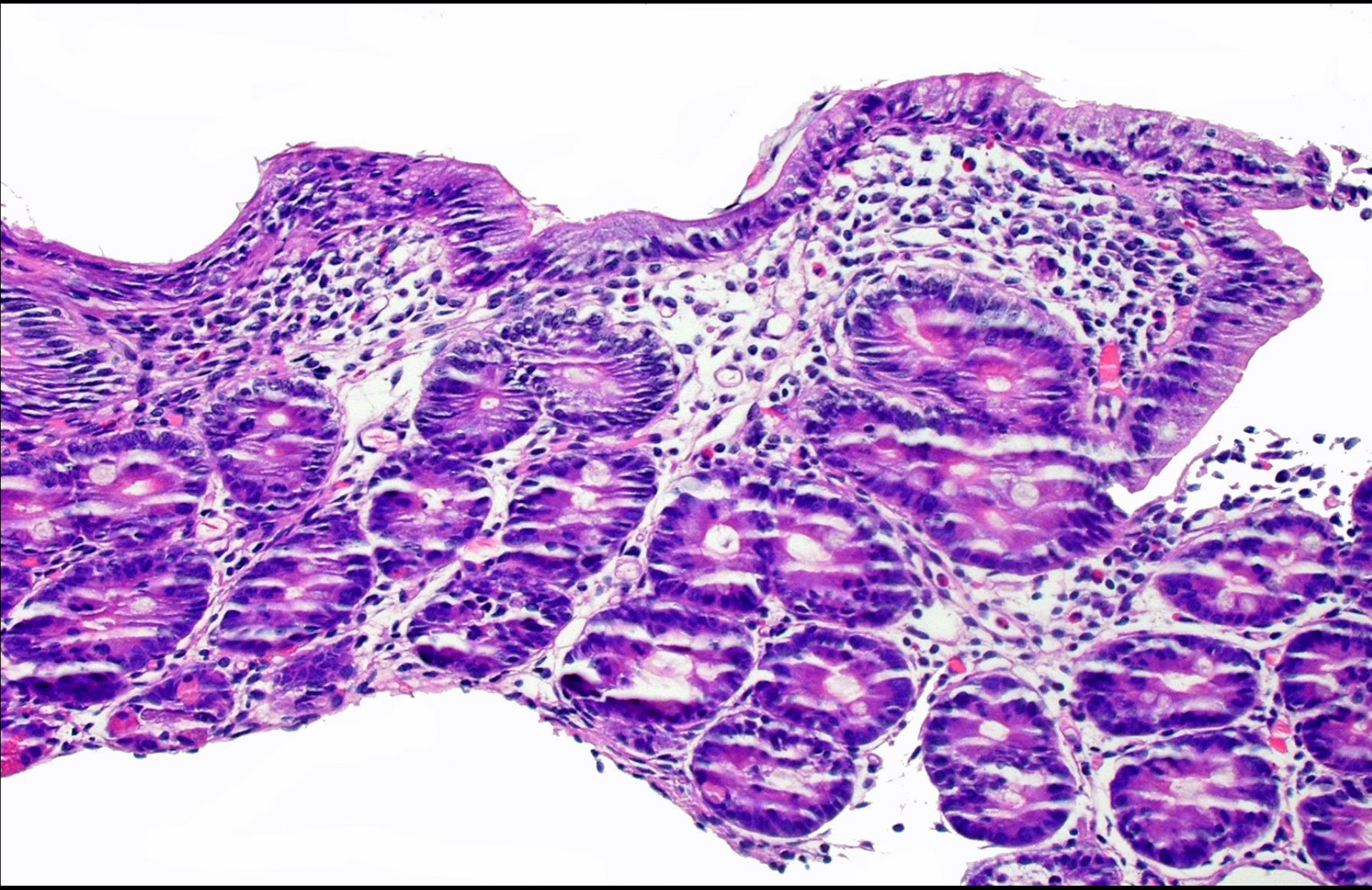
Clinical History

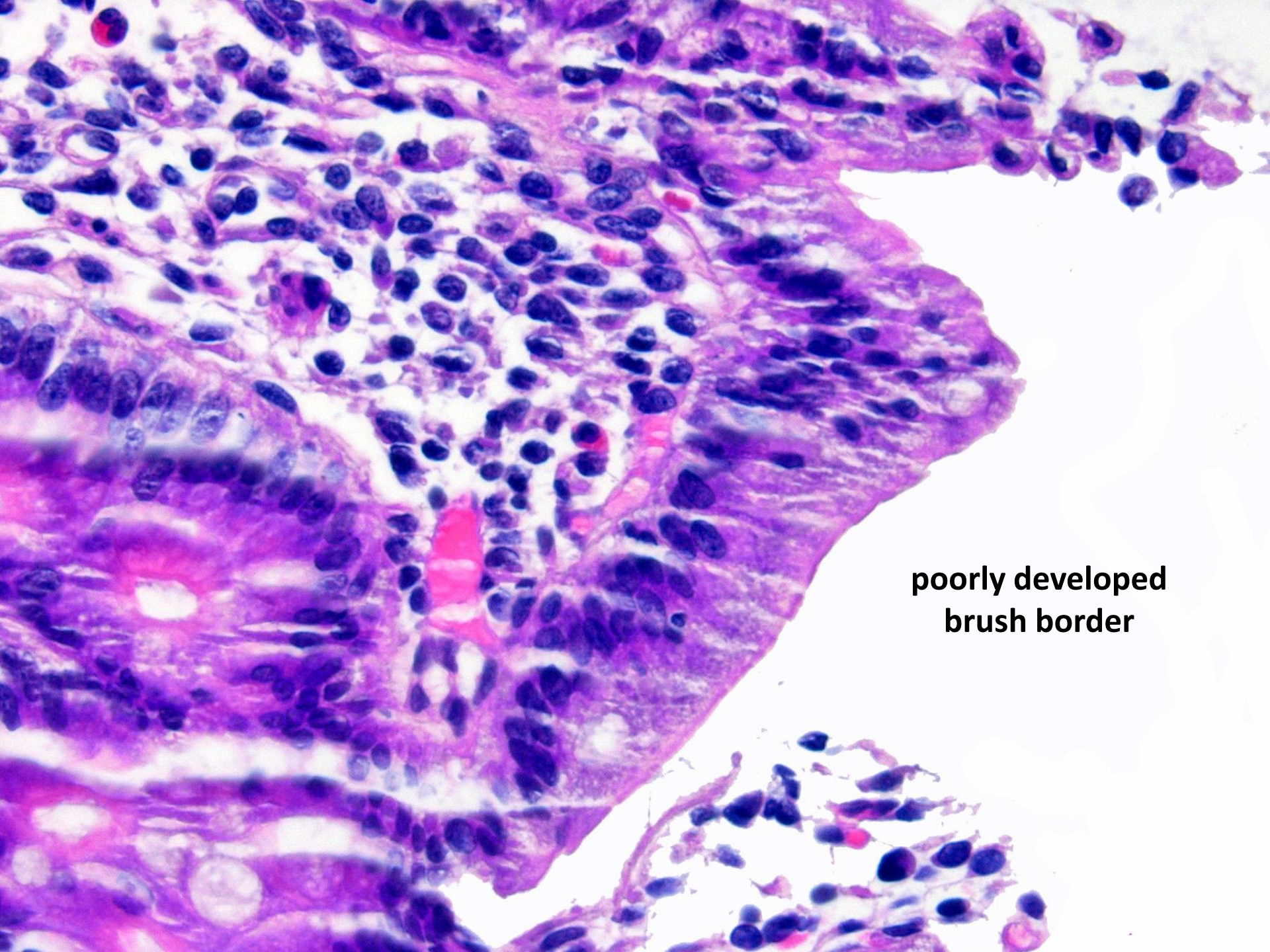
- 4-week-old F with poor weight gain and watery diarrhea and severe metabolic acidosis
- Diarrhea continued despite TPN and discontinuation of oral feedings
- Family history significant for a parental consanguineous marriage of cousins
- Older sibling died at 4 weeks of age of uncontrollable diarrhea

Microvillous Inclusion Disease

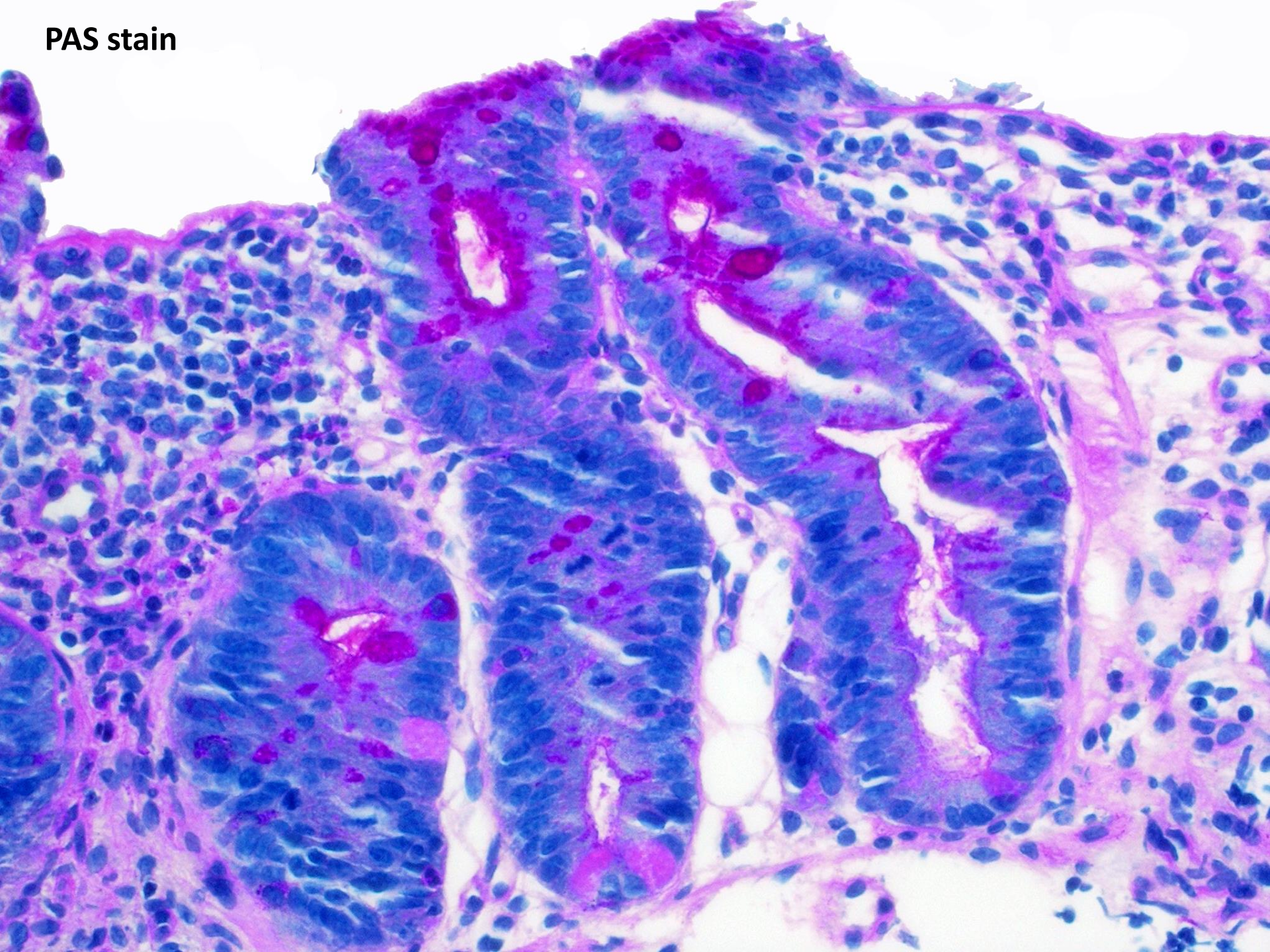


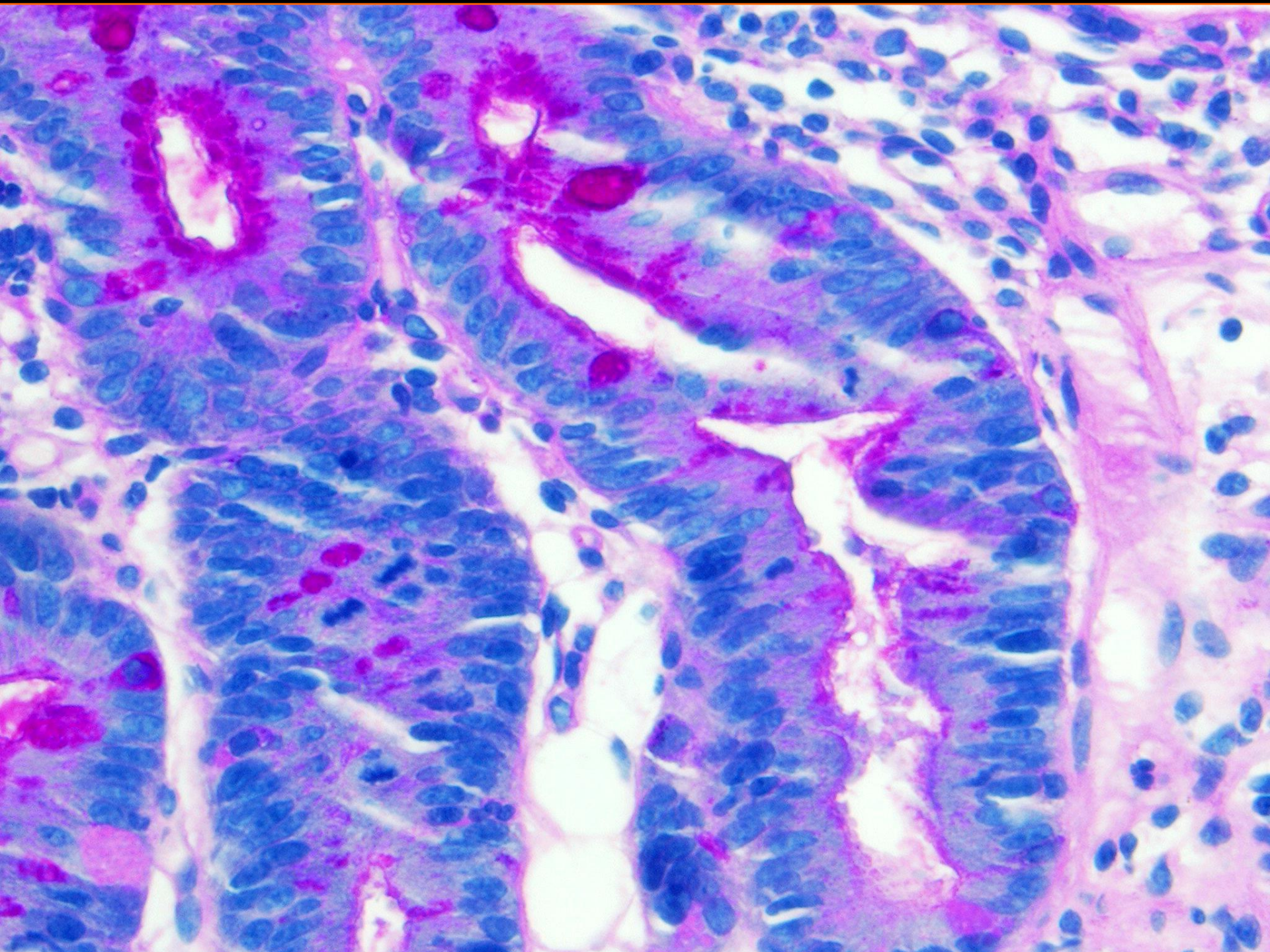
Microvillous Inclusion Disease

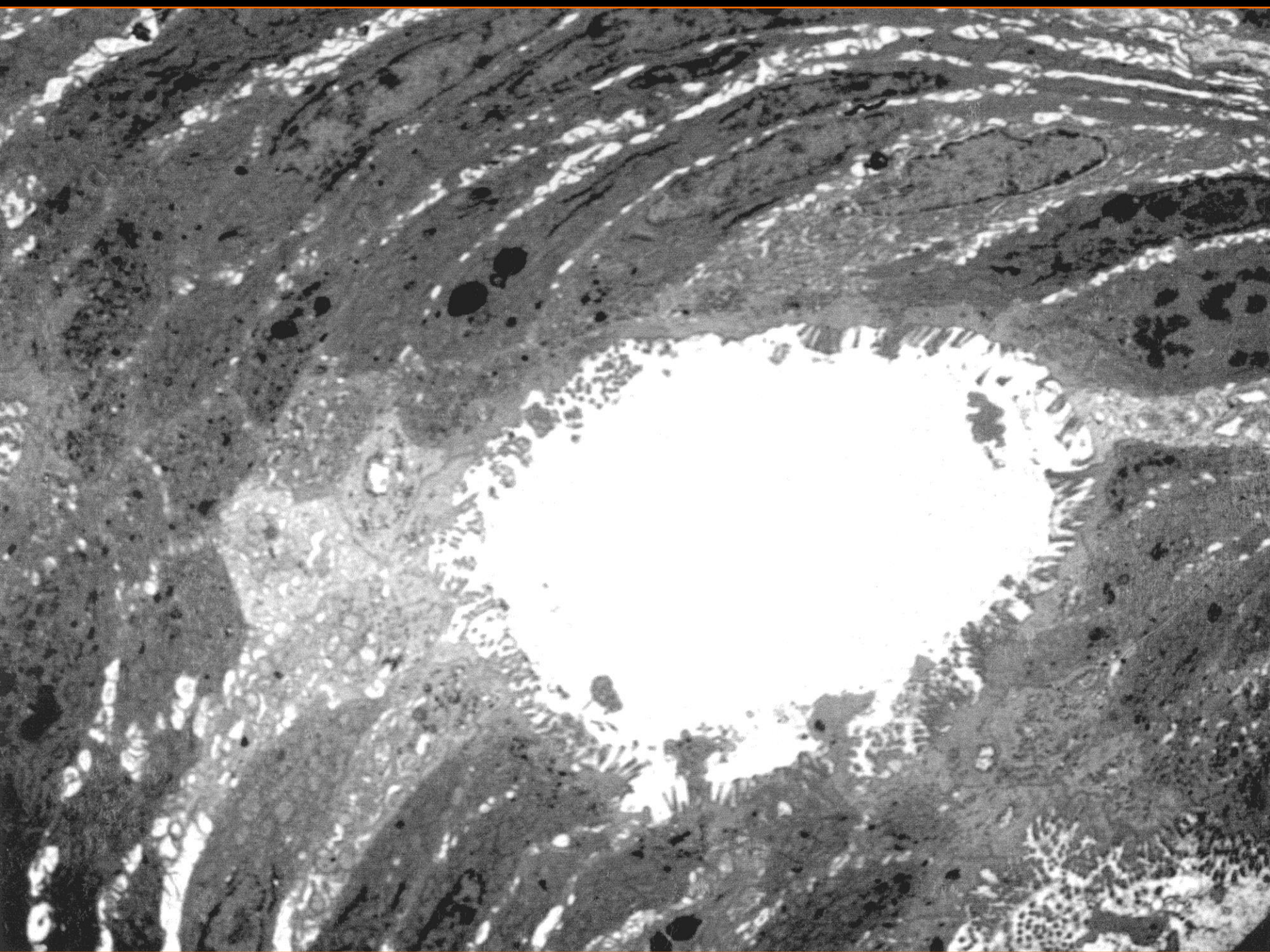


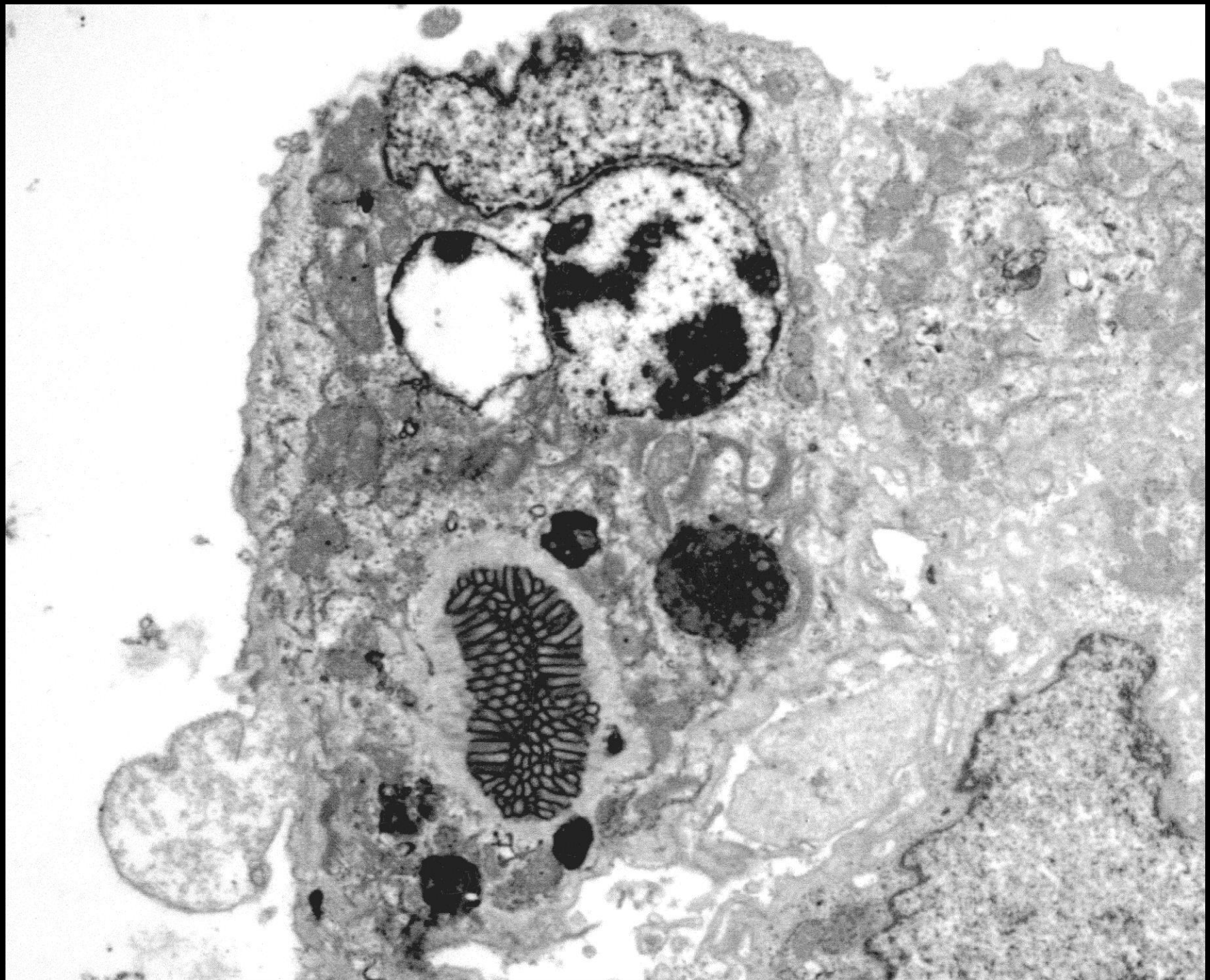

poorly developed
brush border

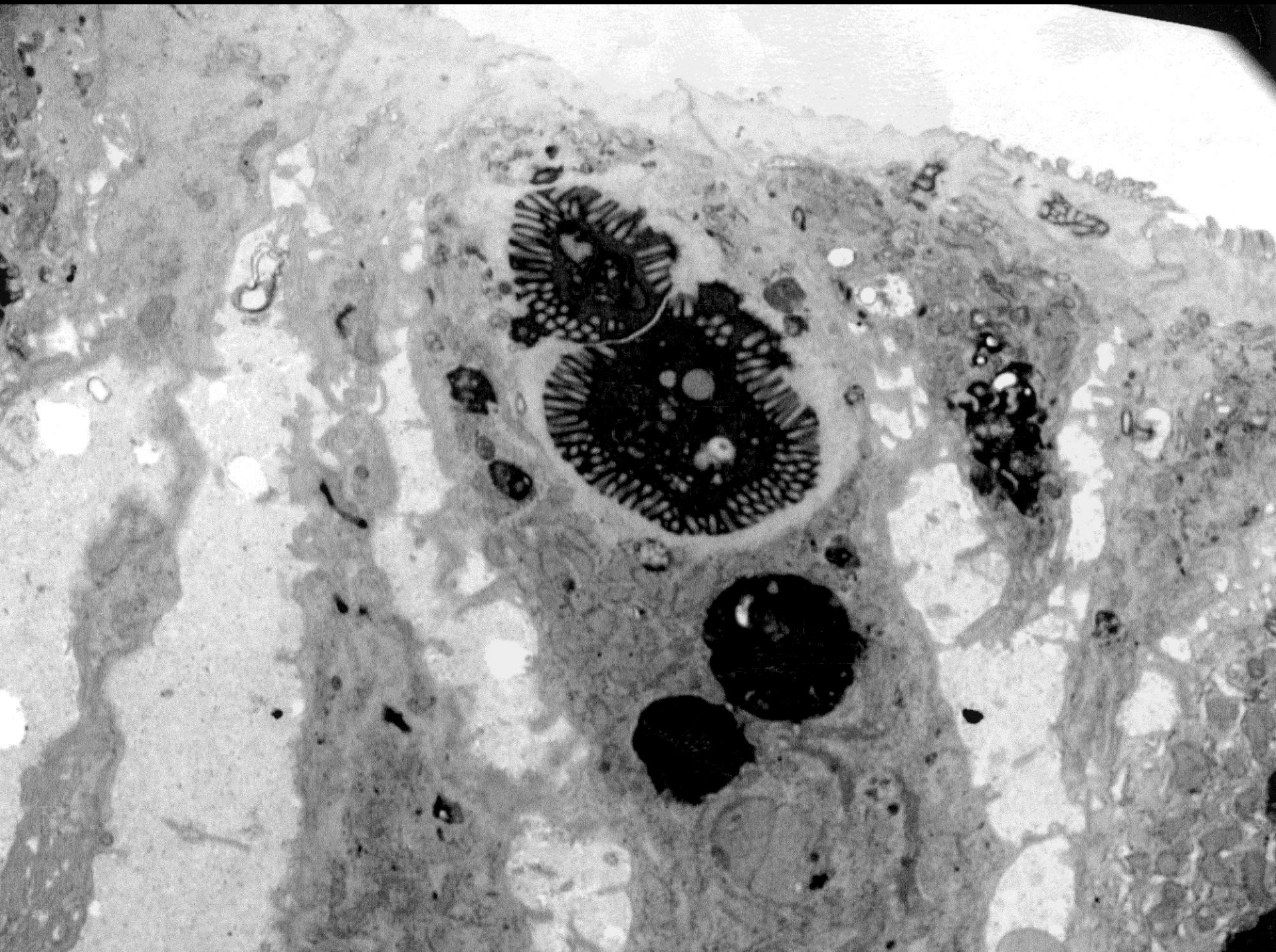
PAS stain



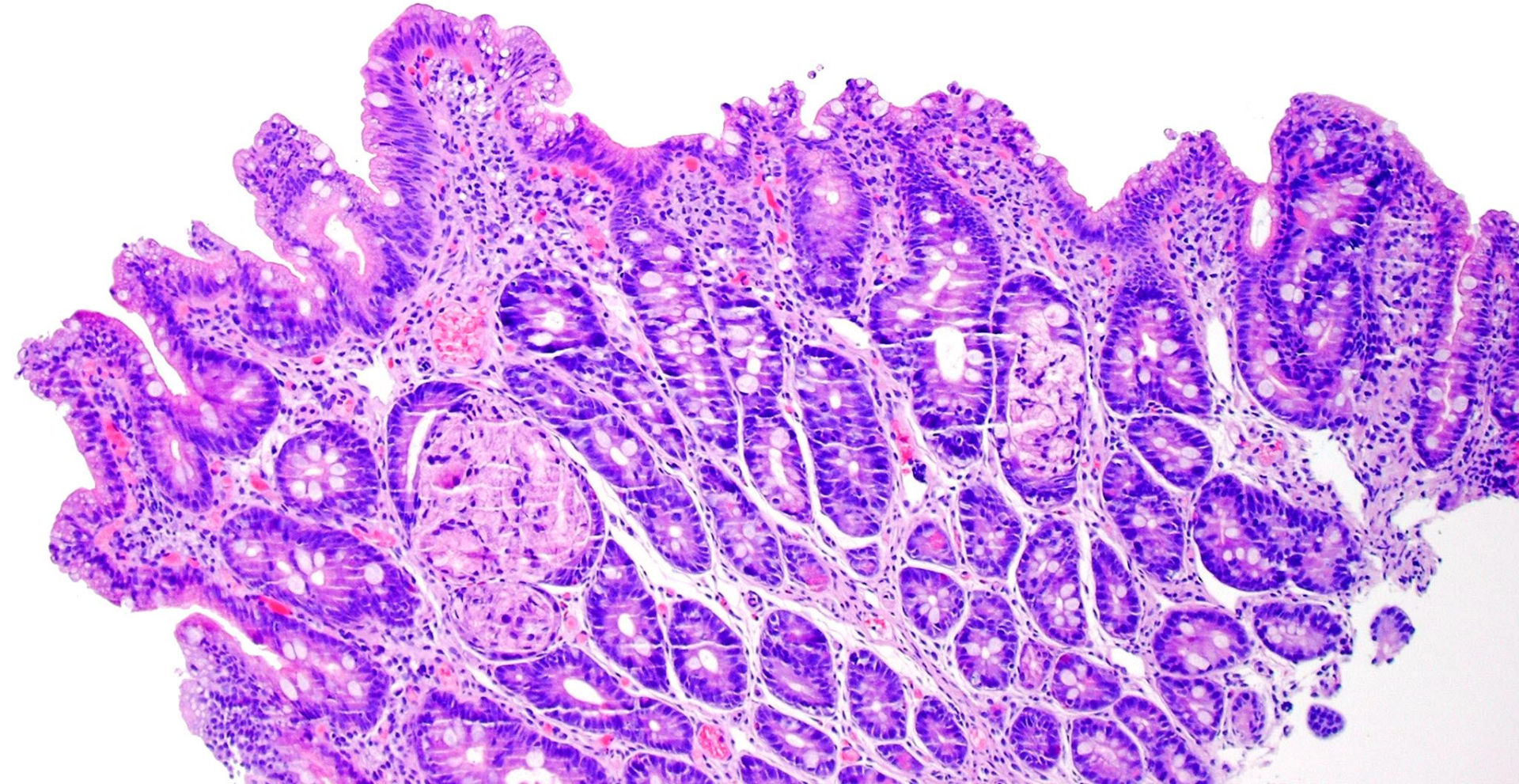




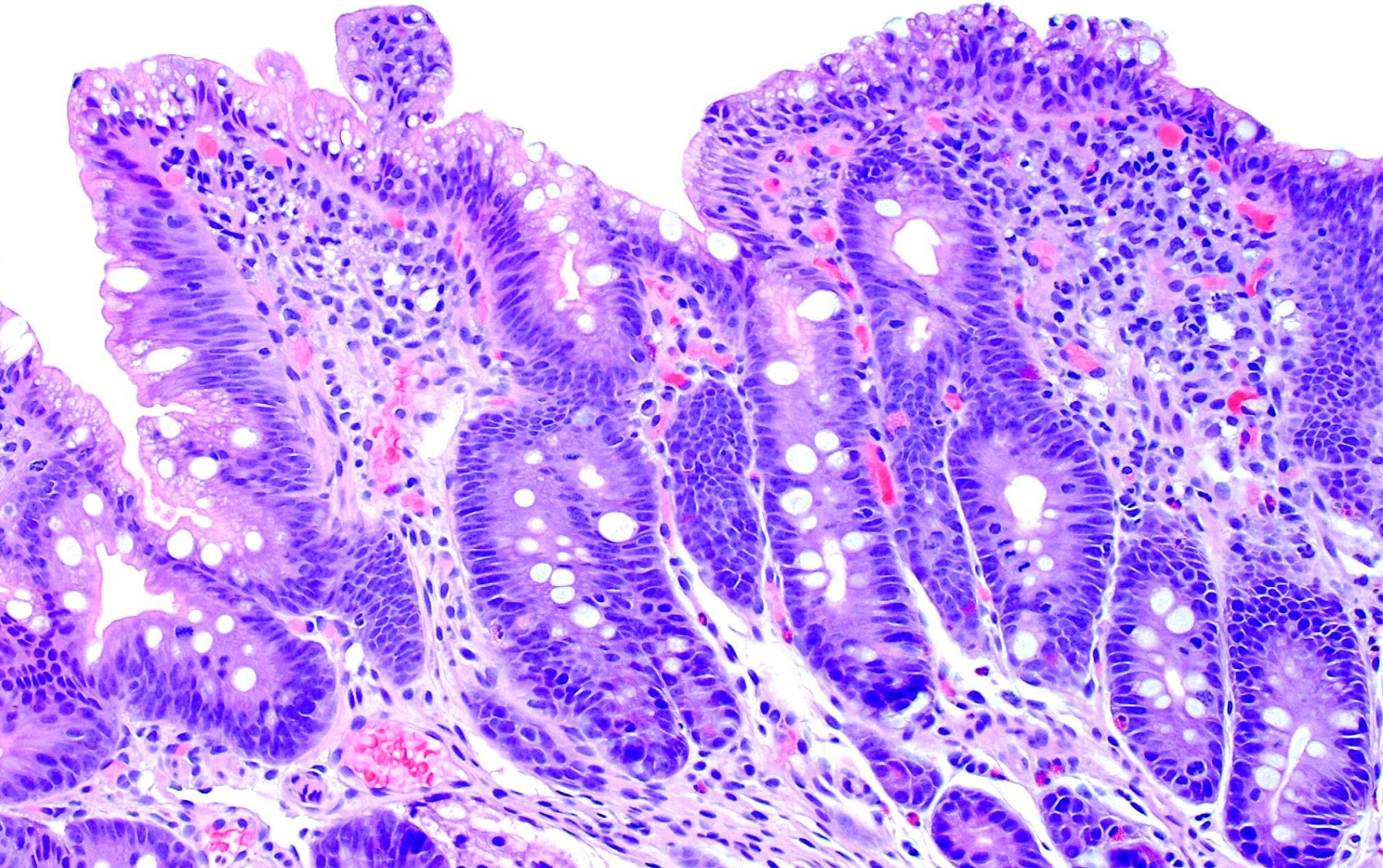




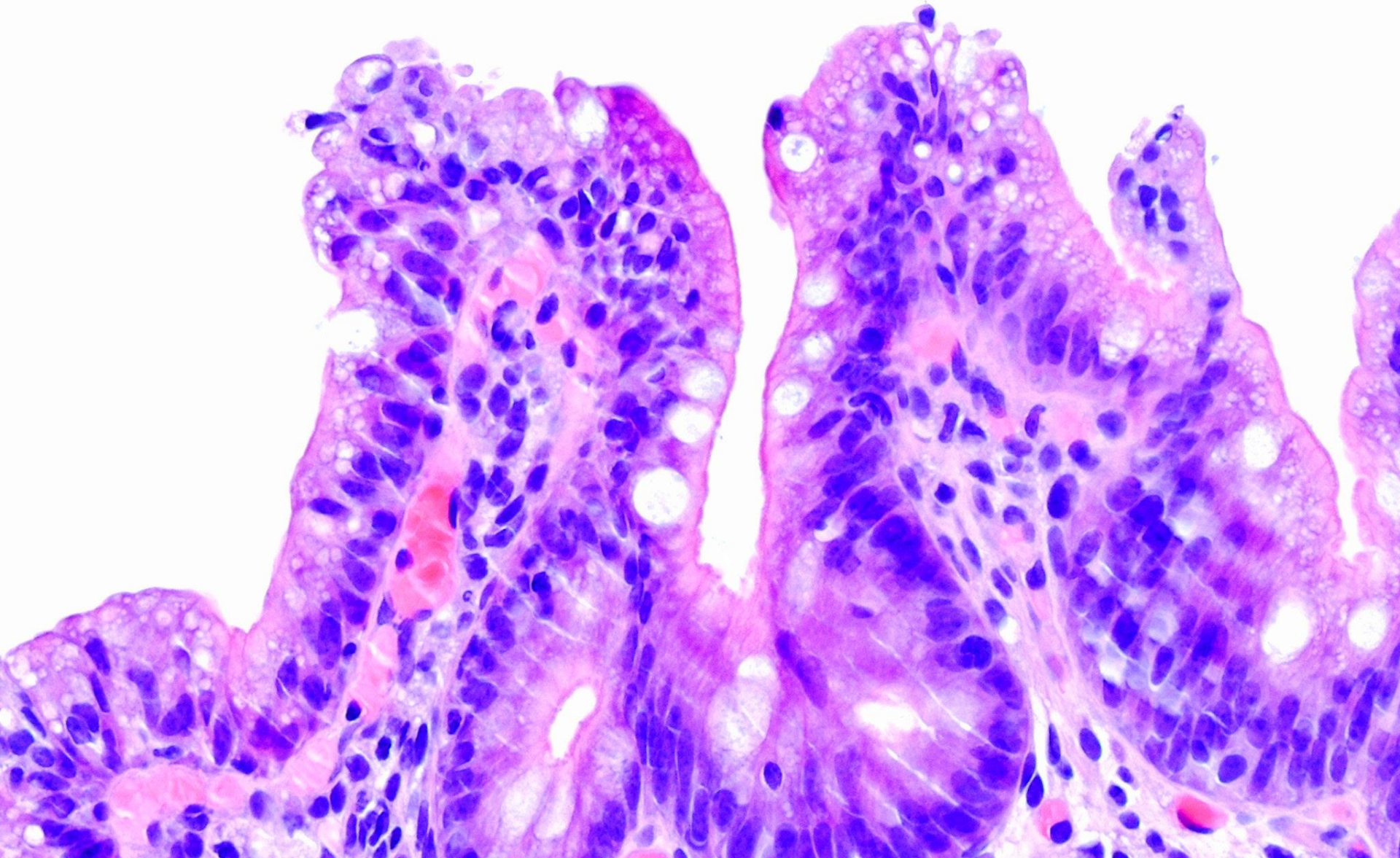
Tufting enteropathy



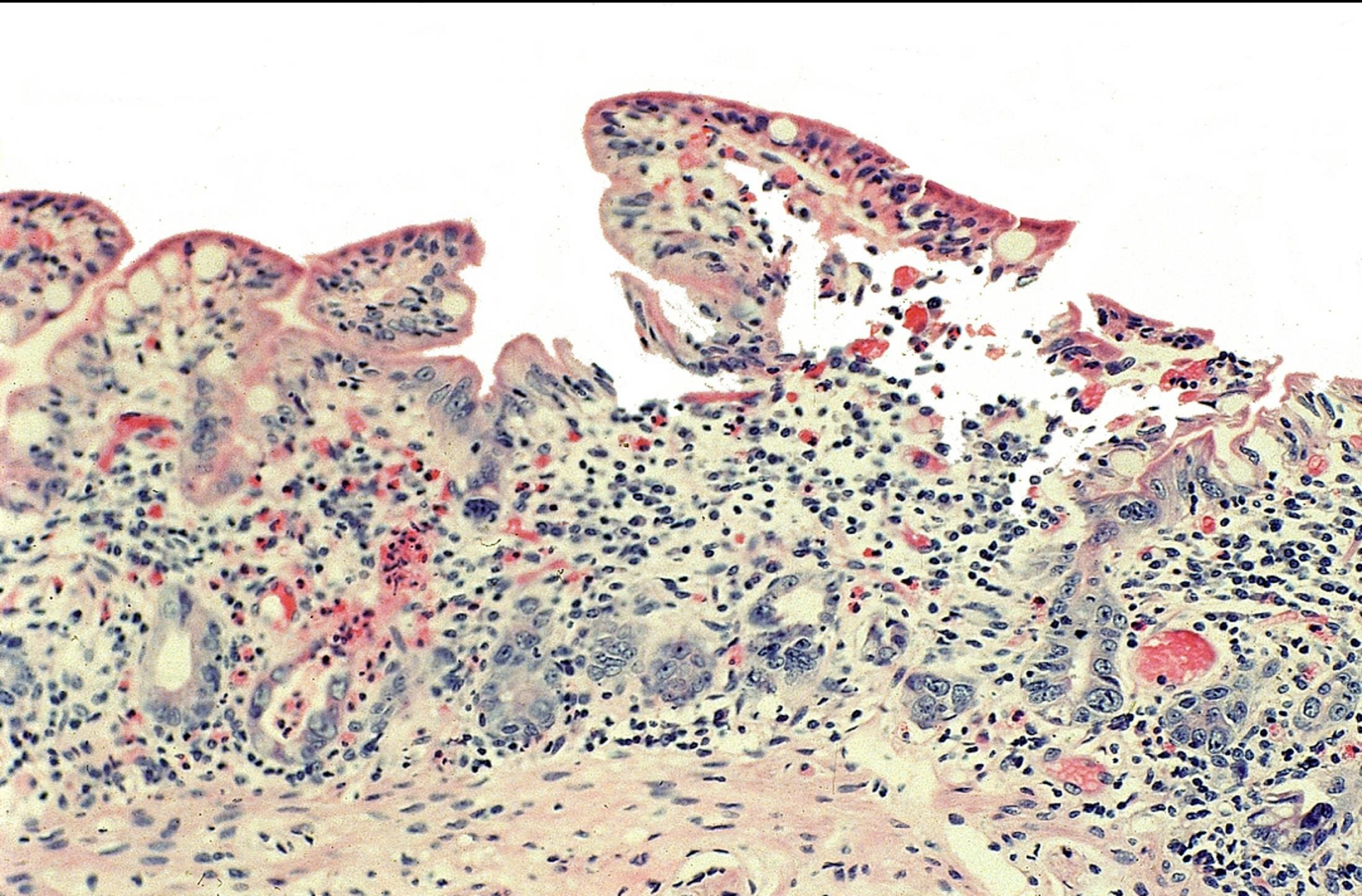
Tufting enteropathy

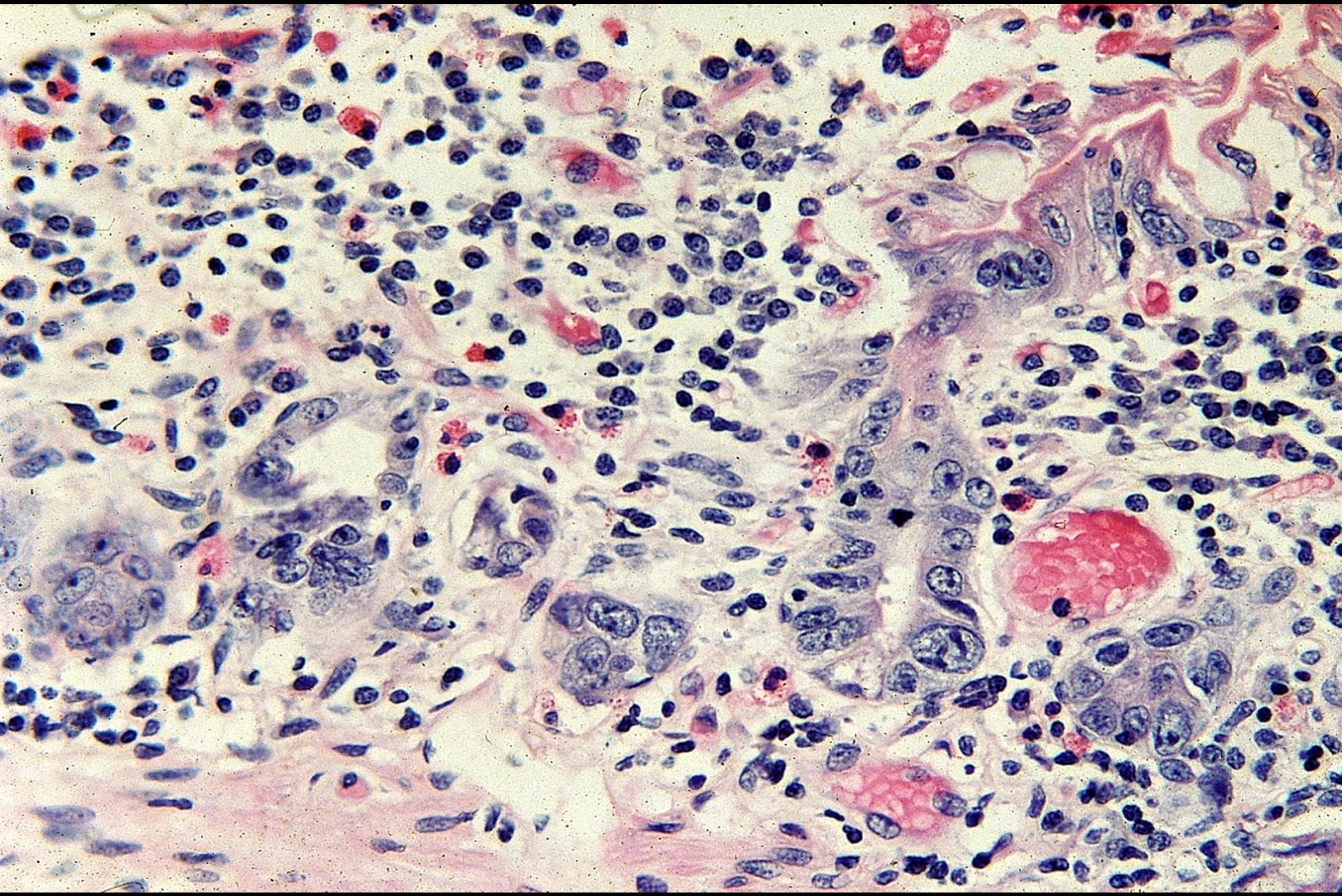


Tufting enteropathy

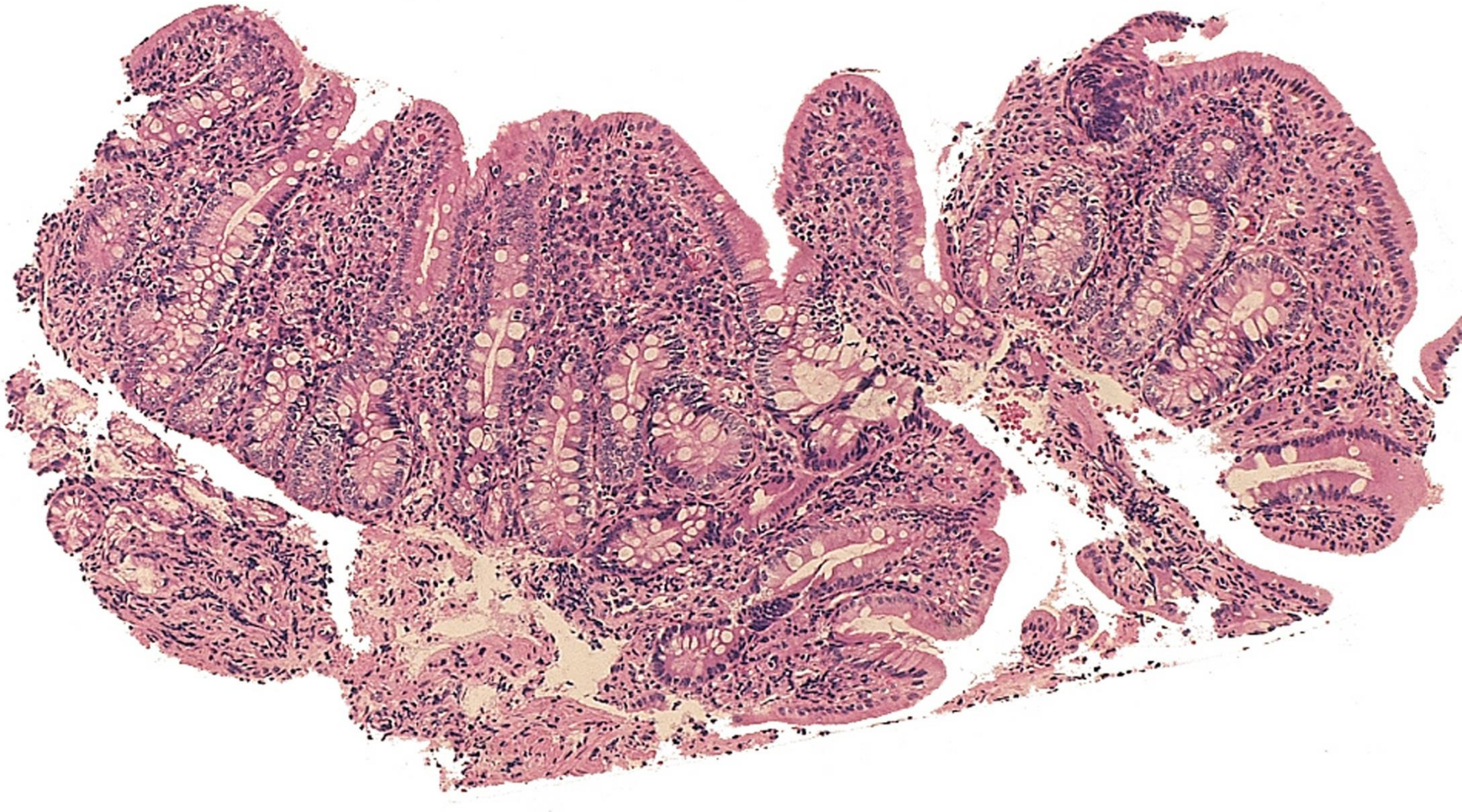


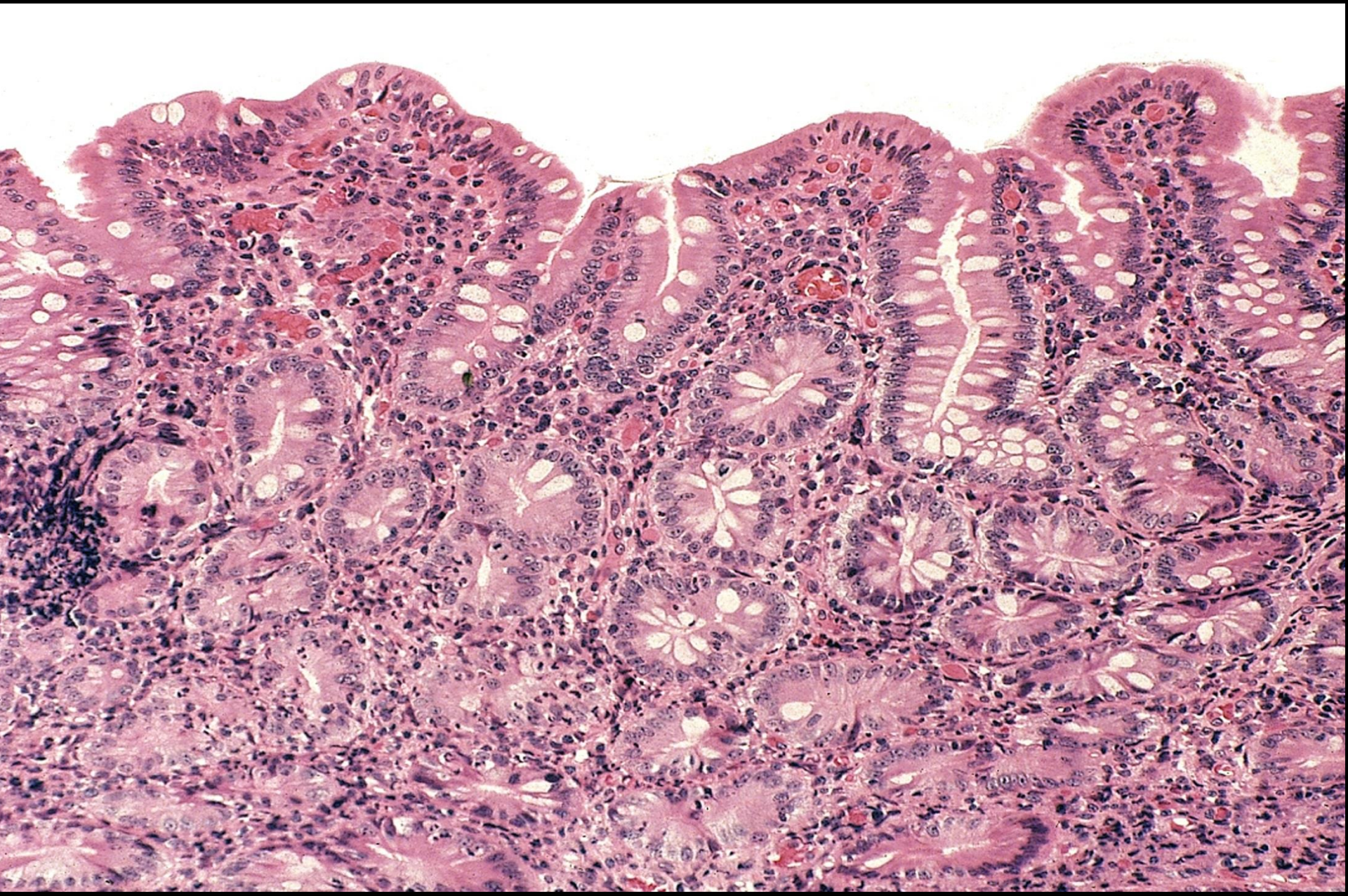
8 y.o. F treated with procarbazine, CCNU, and vincristine for recurrent medulloblastoma





5-week-old F with failure to thrive and a 3-week history of watery diarrhea





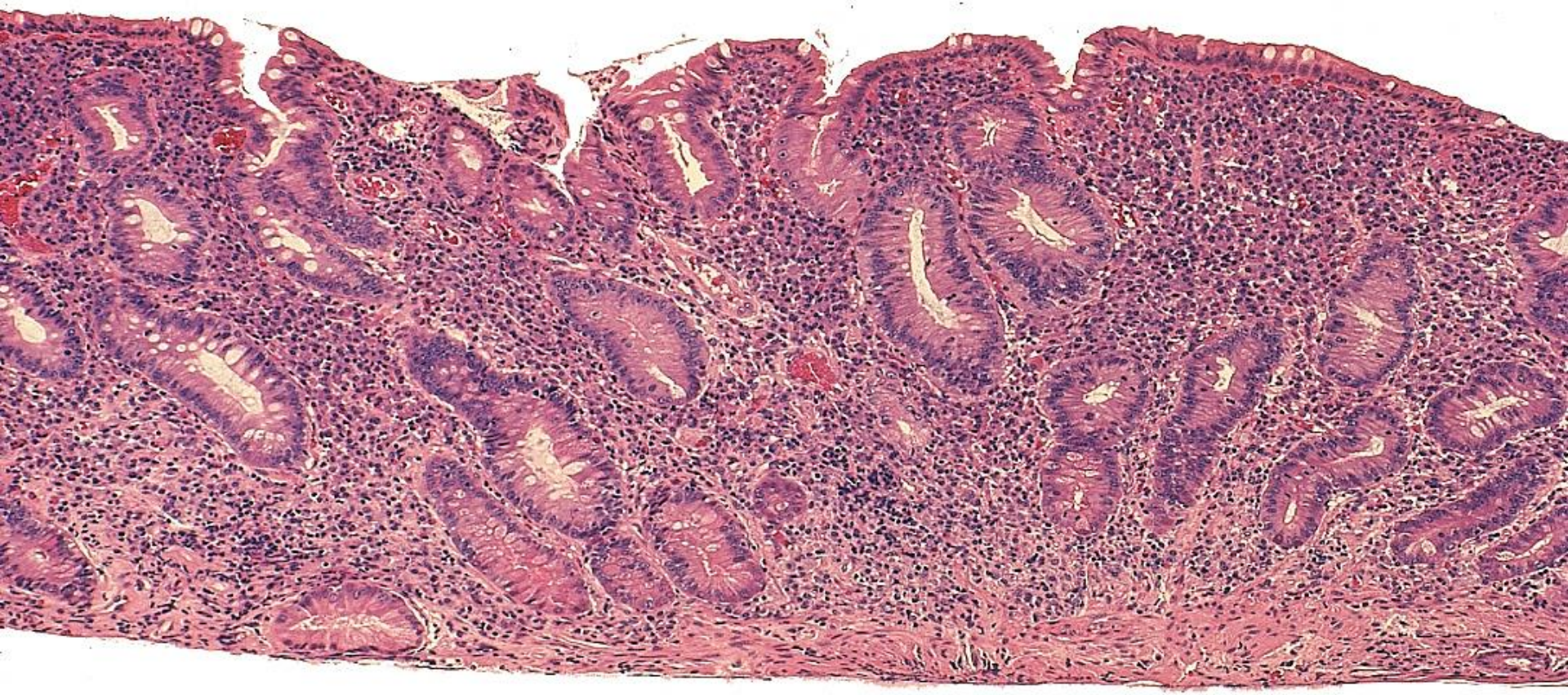
Cow's Milk Protein Intolerance

- Immune reaction to a variety of peptides within cow's milk
- Metabolic acidosis and blood in stool in severe cases
- Peripheral blood eosinophilia uncommon
- Tissue eosinophilia uncommon
- Can effect small or large bowel or both
- No specific test – RAST testing often performed
- Re-challenge necessary for definite diagnosis

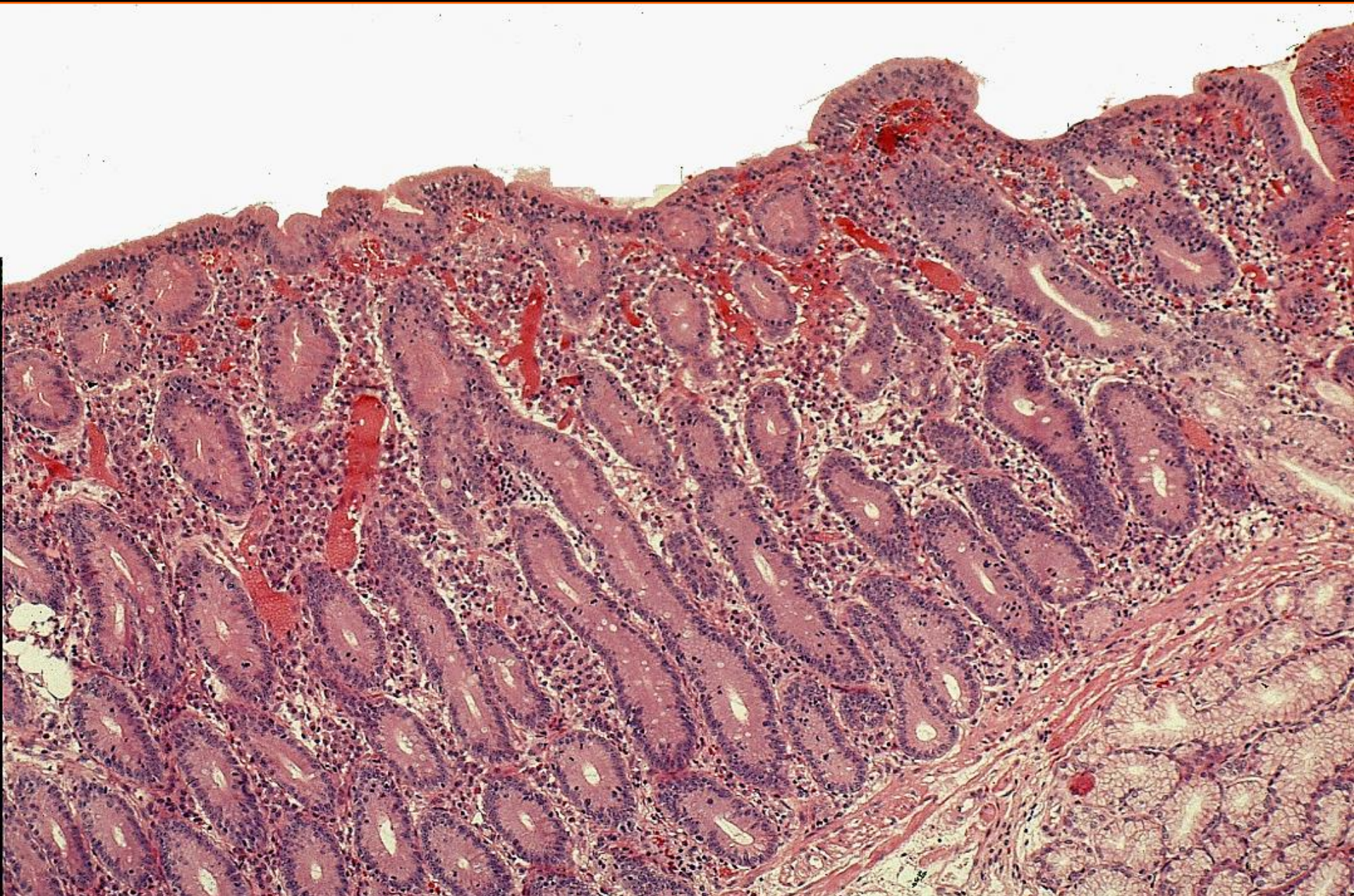
Variable Villous Blunting with Crypt Hyperplasia

- Viral enteritis
- Tropical sprue
- Bacterial overgrowth
- Zollinger-Ellison syndrome
- Whipple disease
- Mycobacterium avium intracellulare
- CMV infection
- Cryptosporidium
- Isospora
- Microsporidium

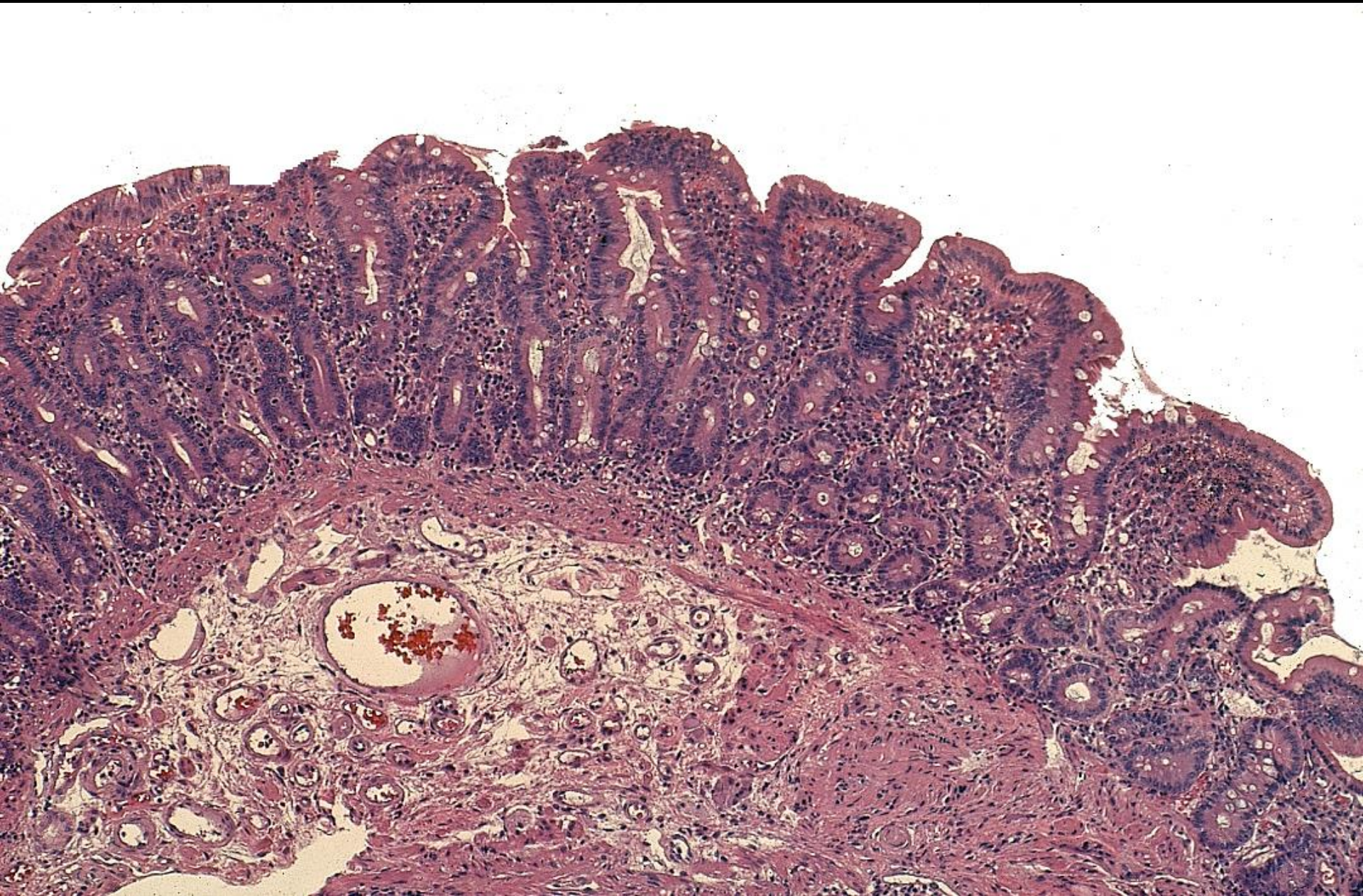
Viral Enteritis

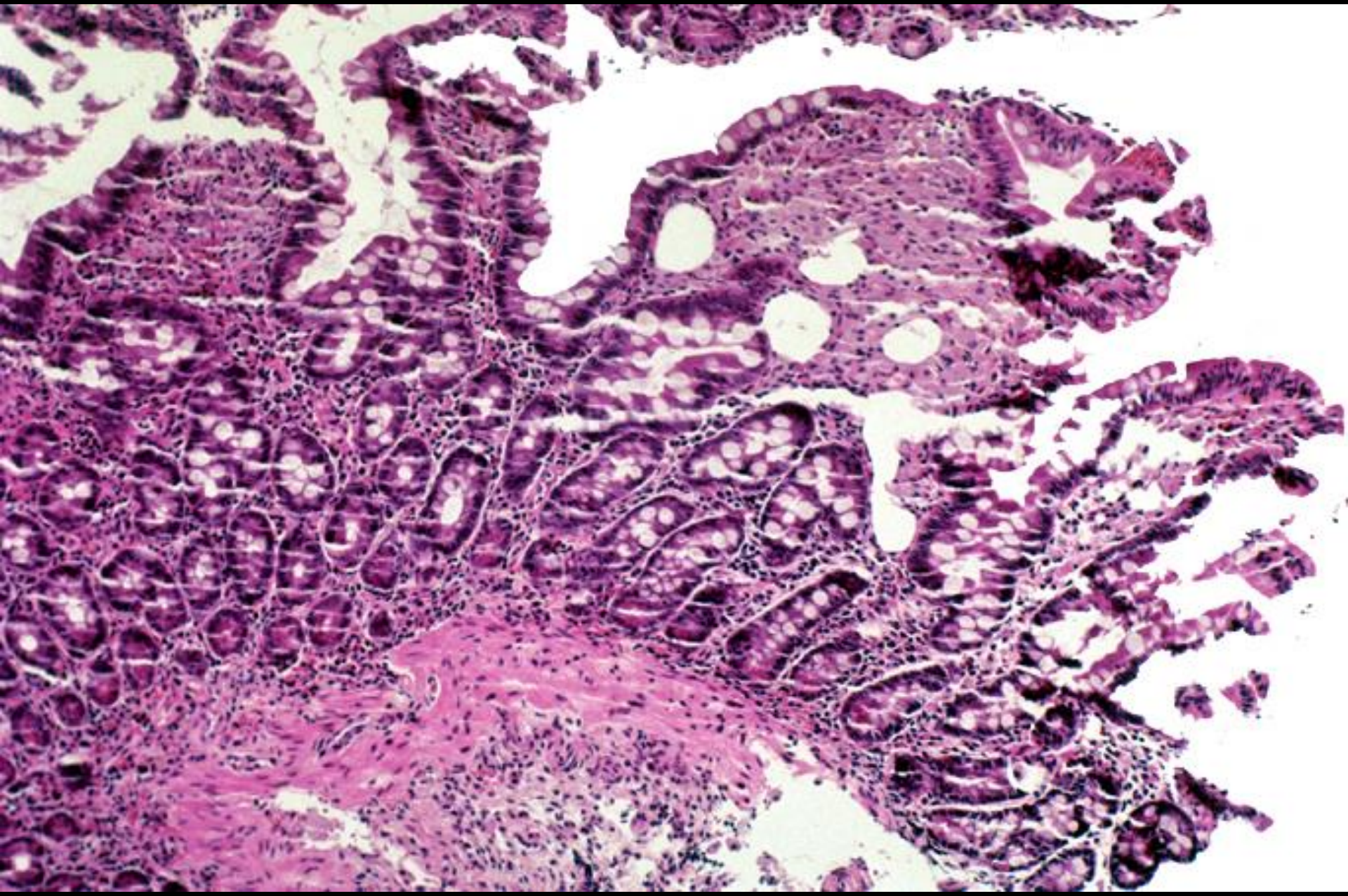


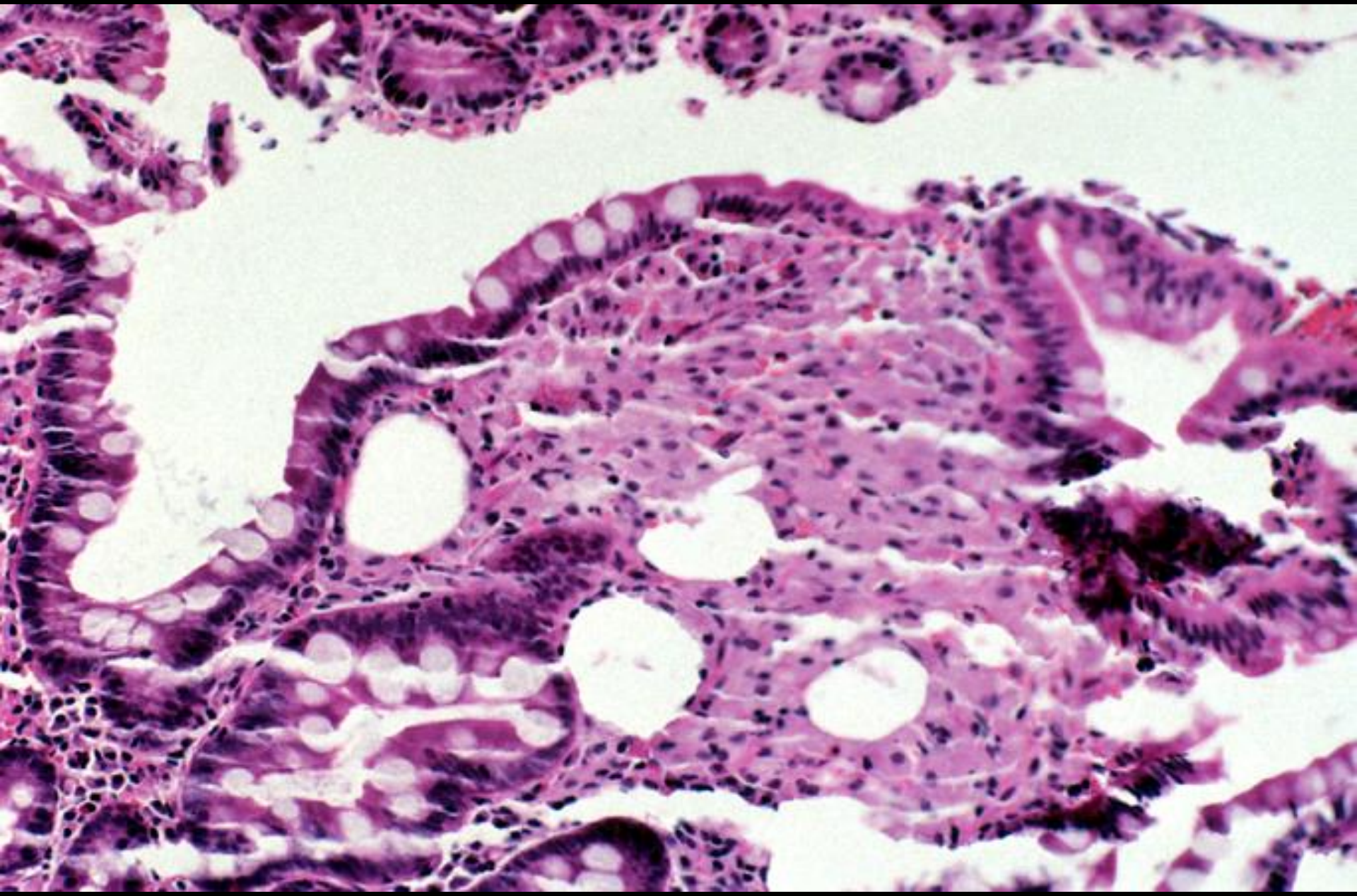
Tropical Sprue



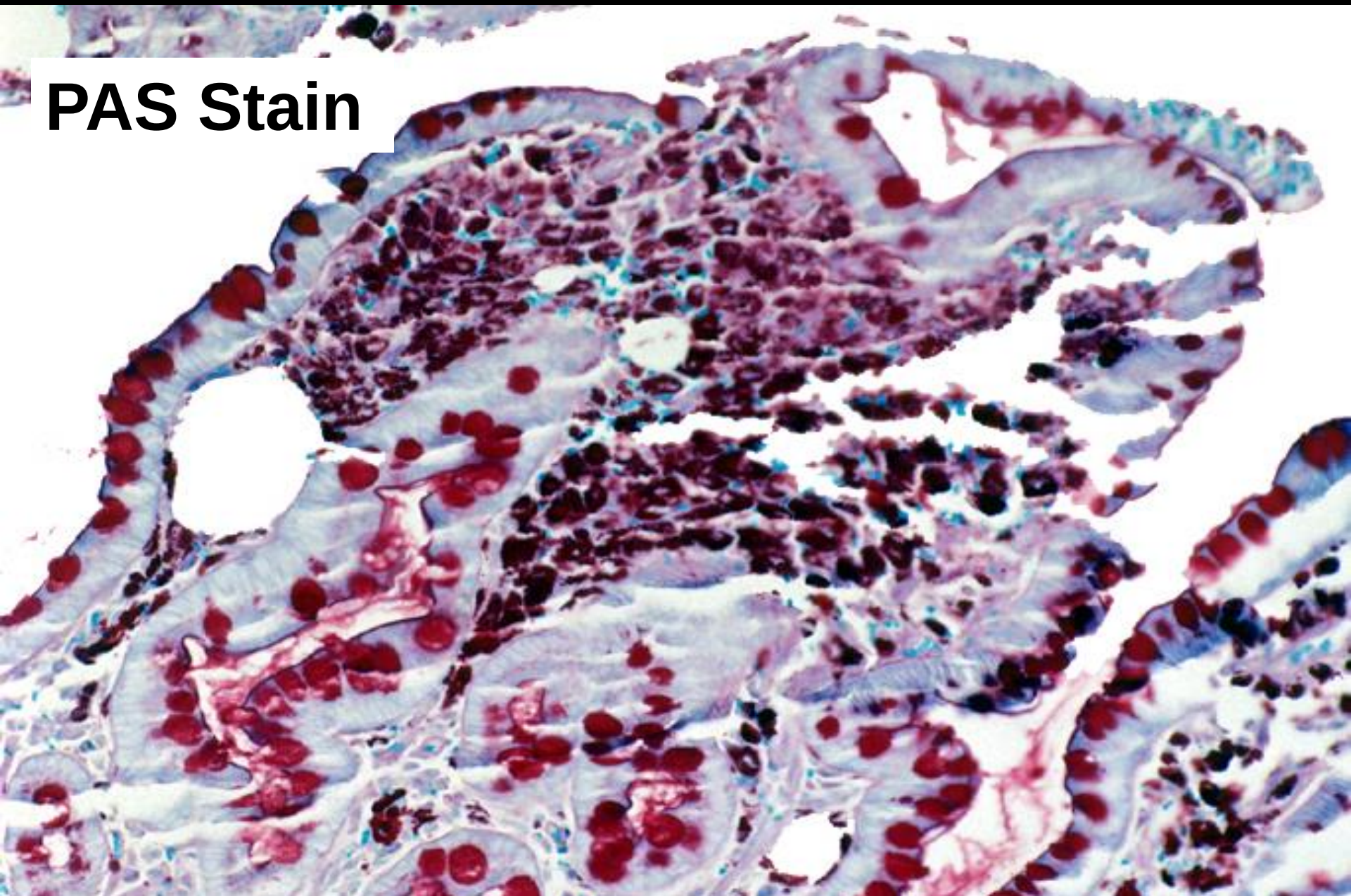
Bacterial Overgrowth



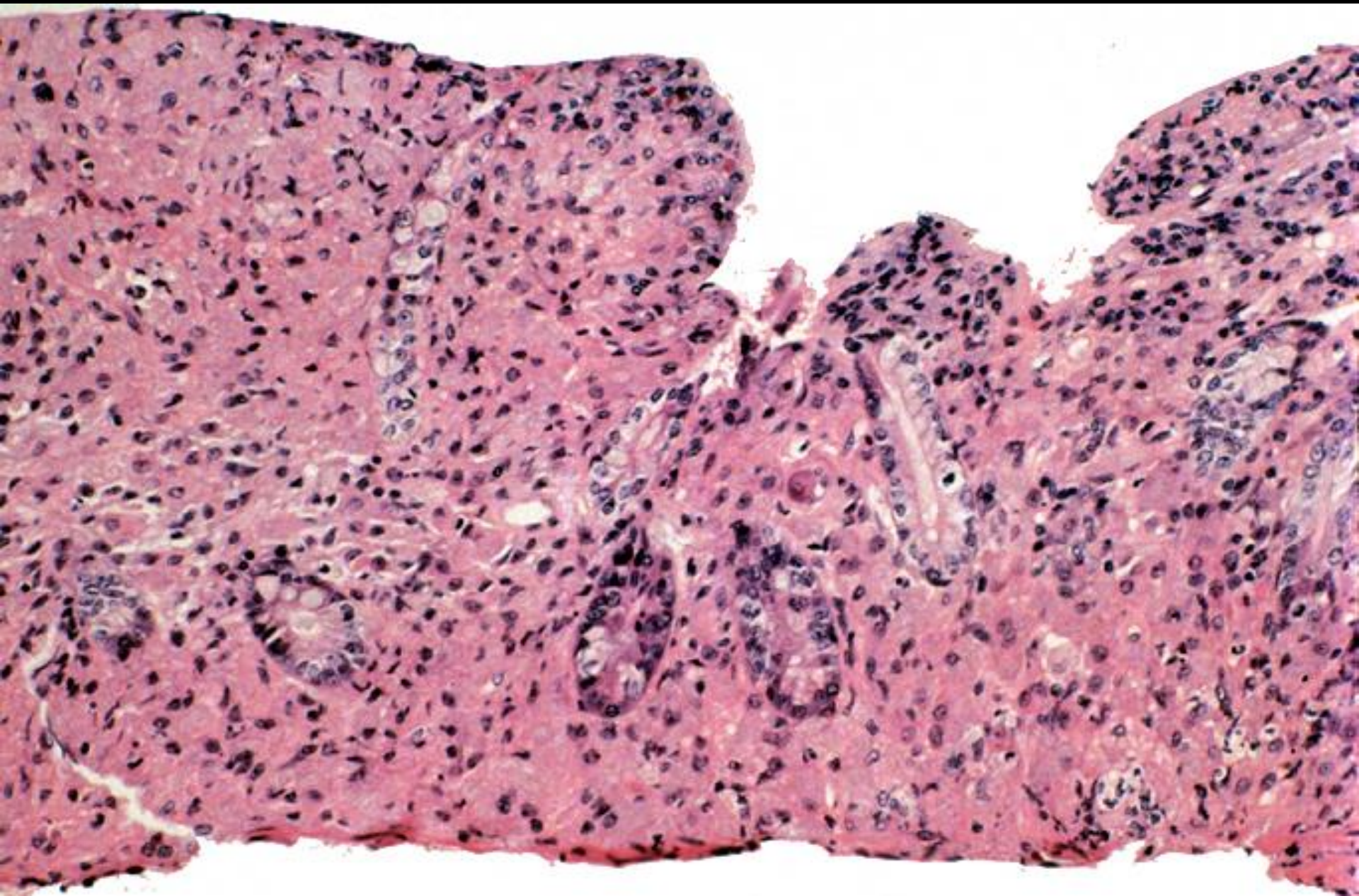




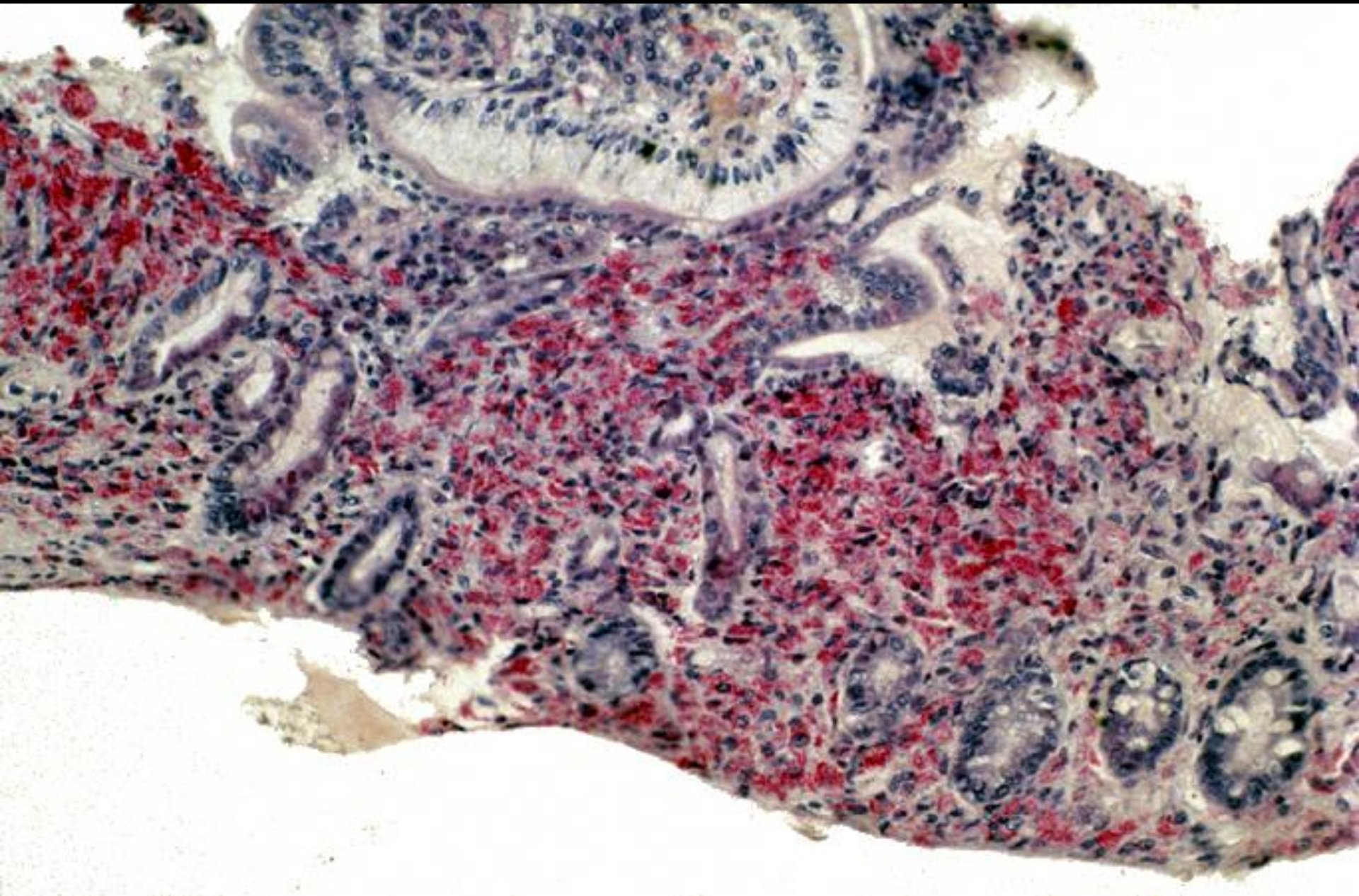
Whipple's Disease



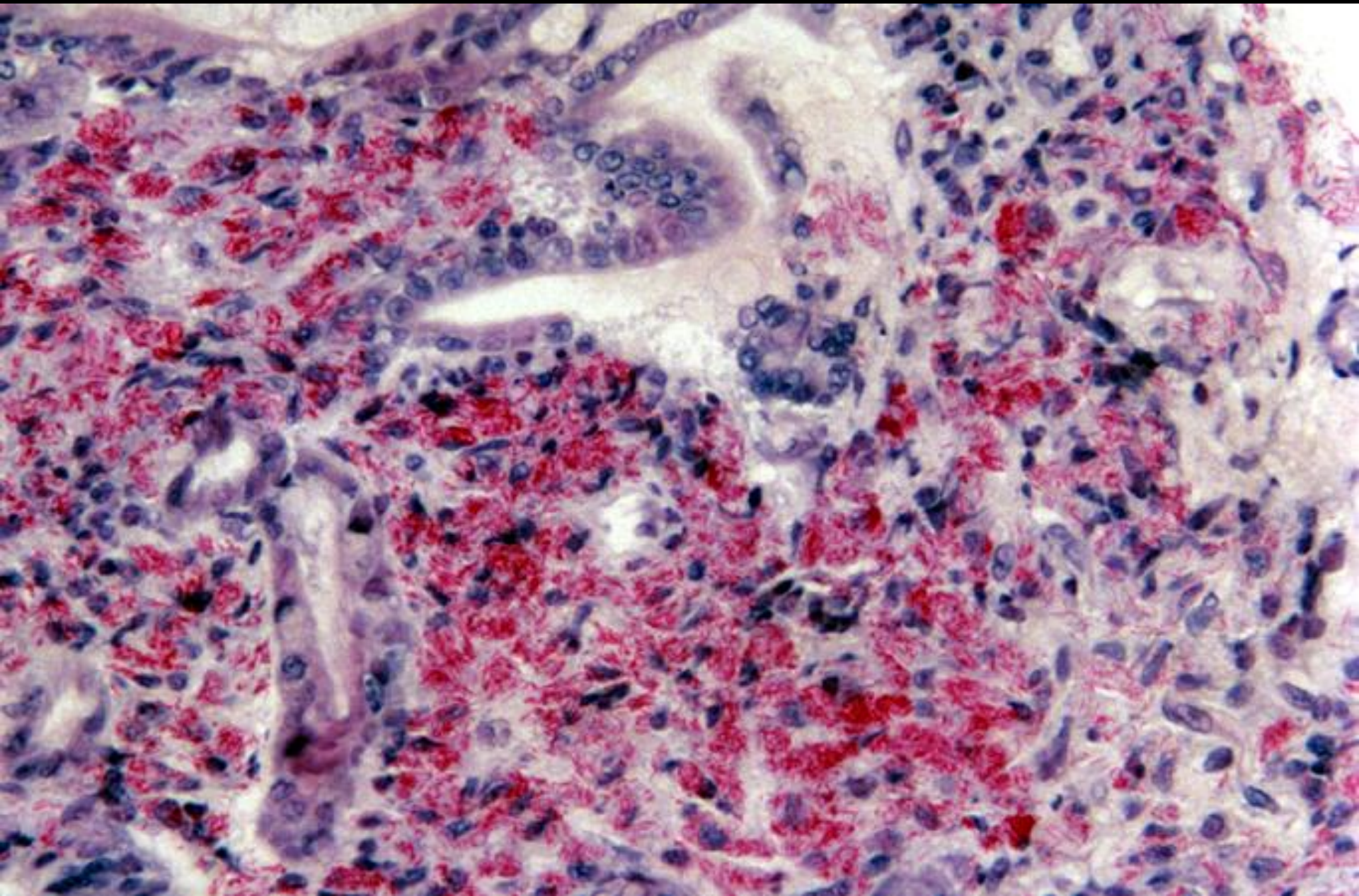
23 y.o. Male with AIDS

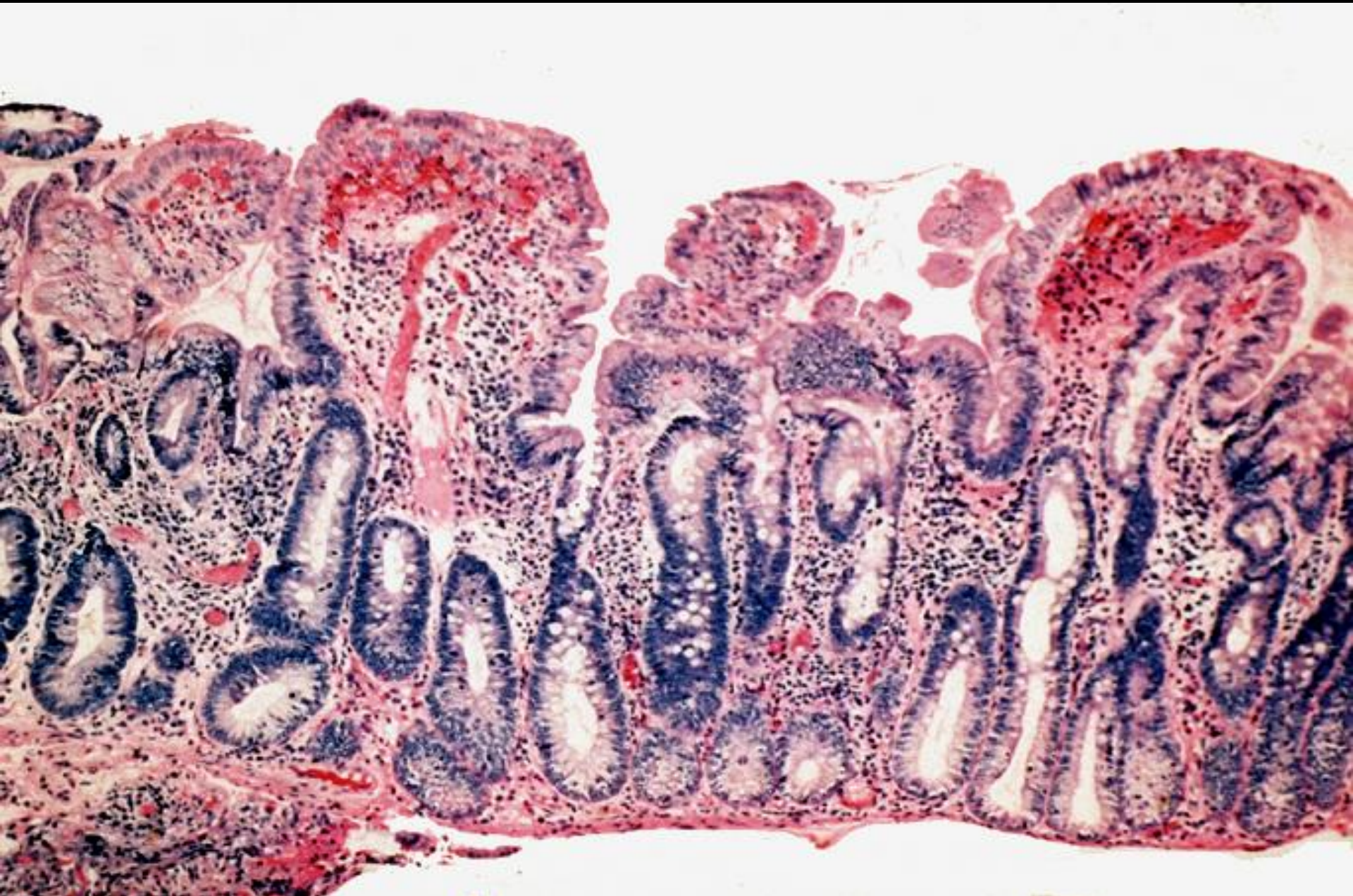


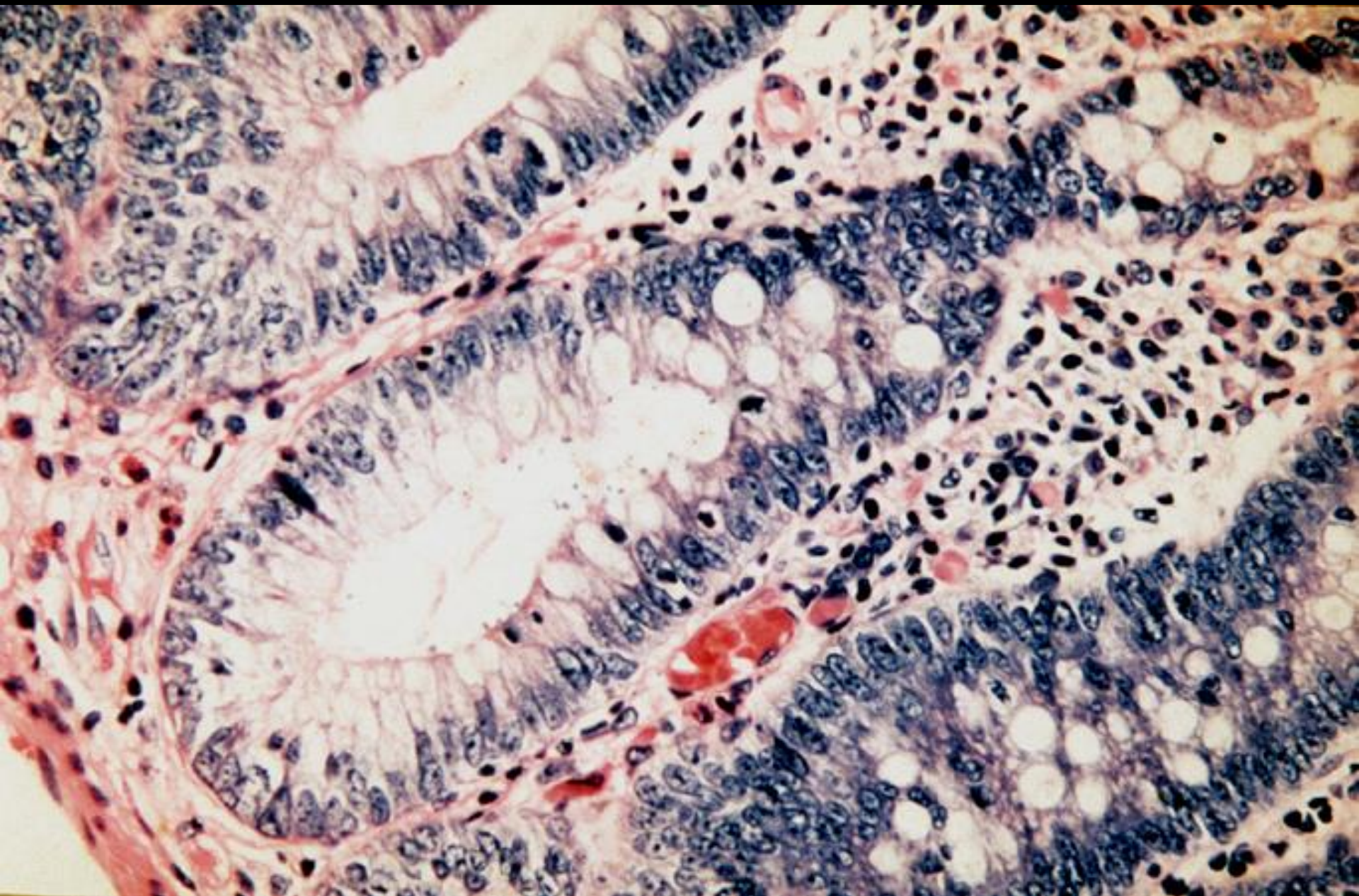
Fite Stain

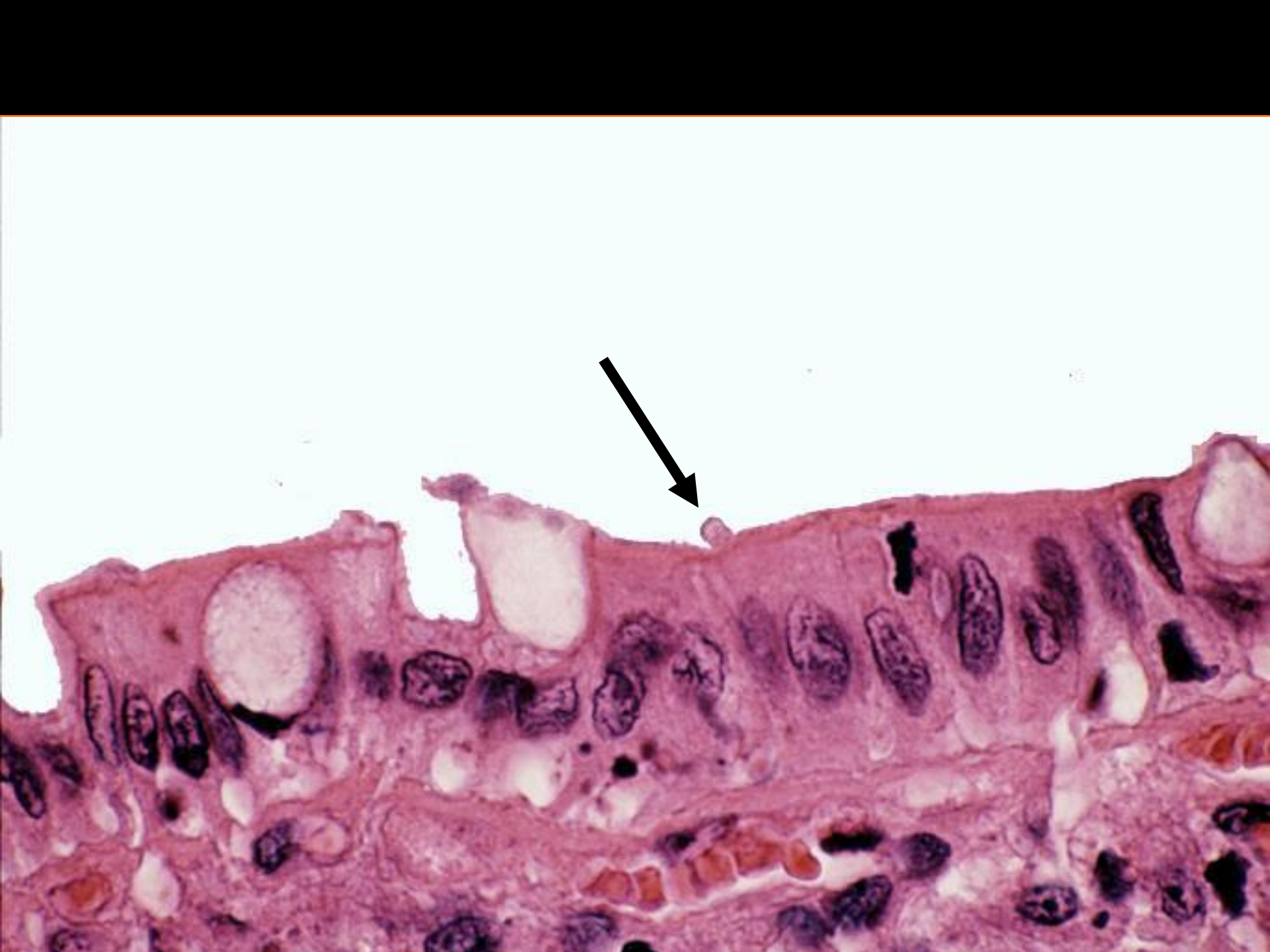


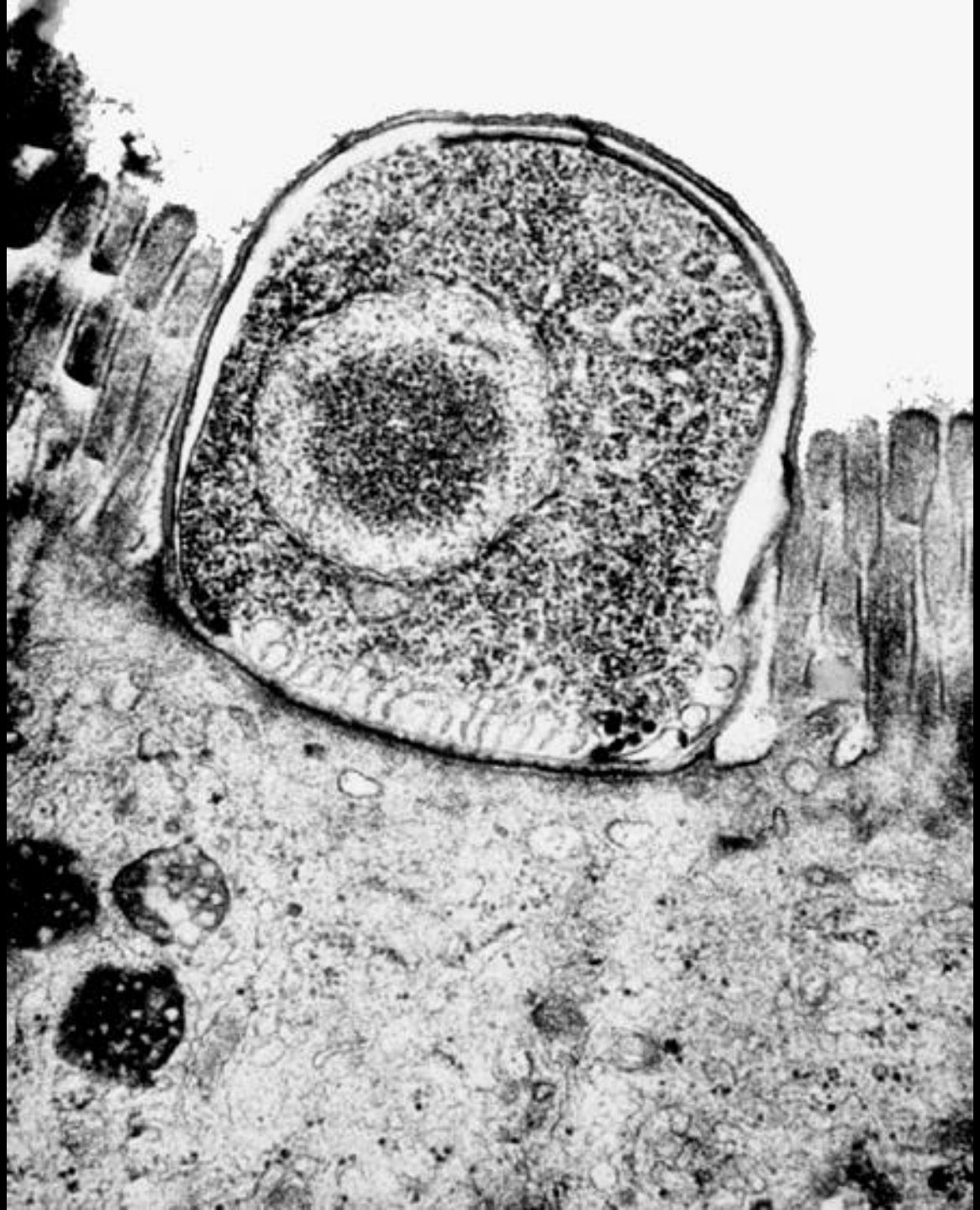
Mycobacteria Avium Intracellulare







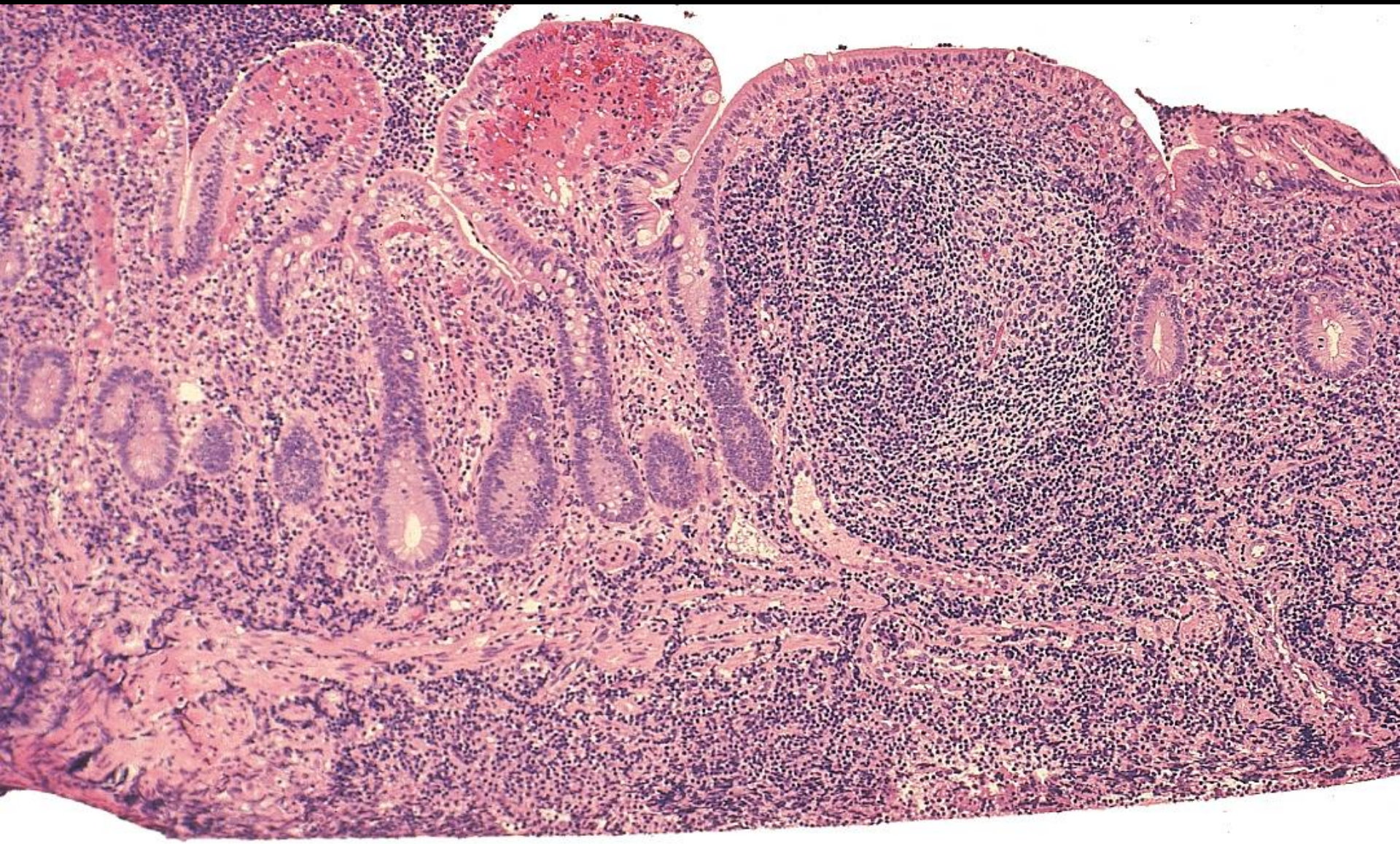


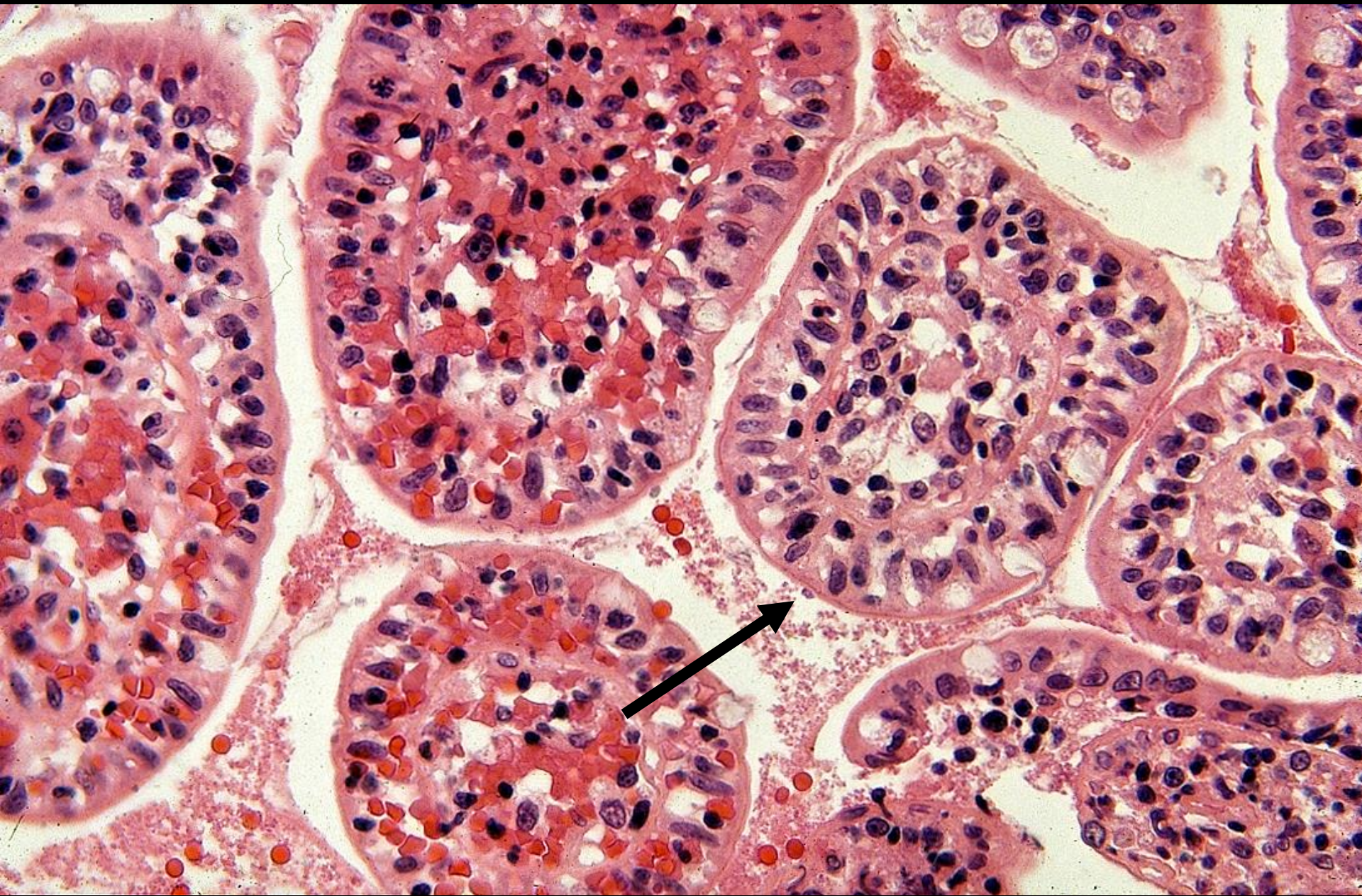


Normal Mucosal Architecture

- Celiac disease
- Cryptosporidium
- Giardia
- Eosinophilic gastroenteritis
- Lymphangectasia
- Abetalipoproteinemia
- Systemic mastocytosis
- Amyloidosis

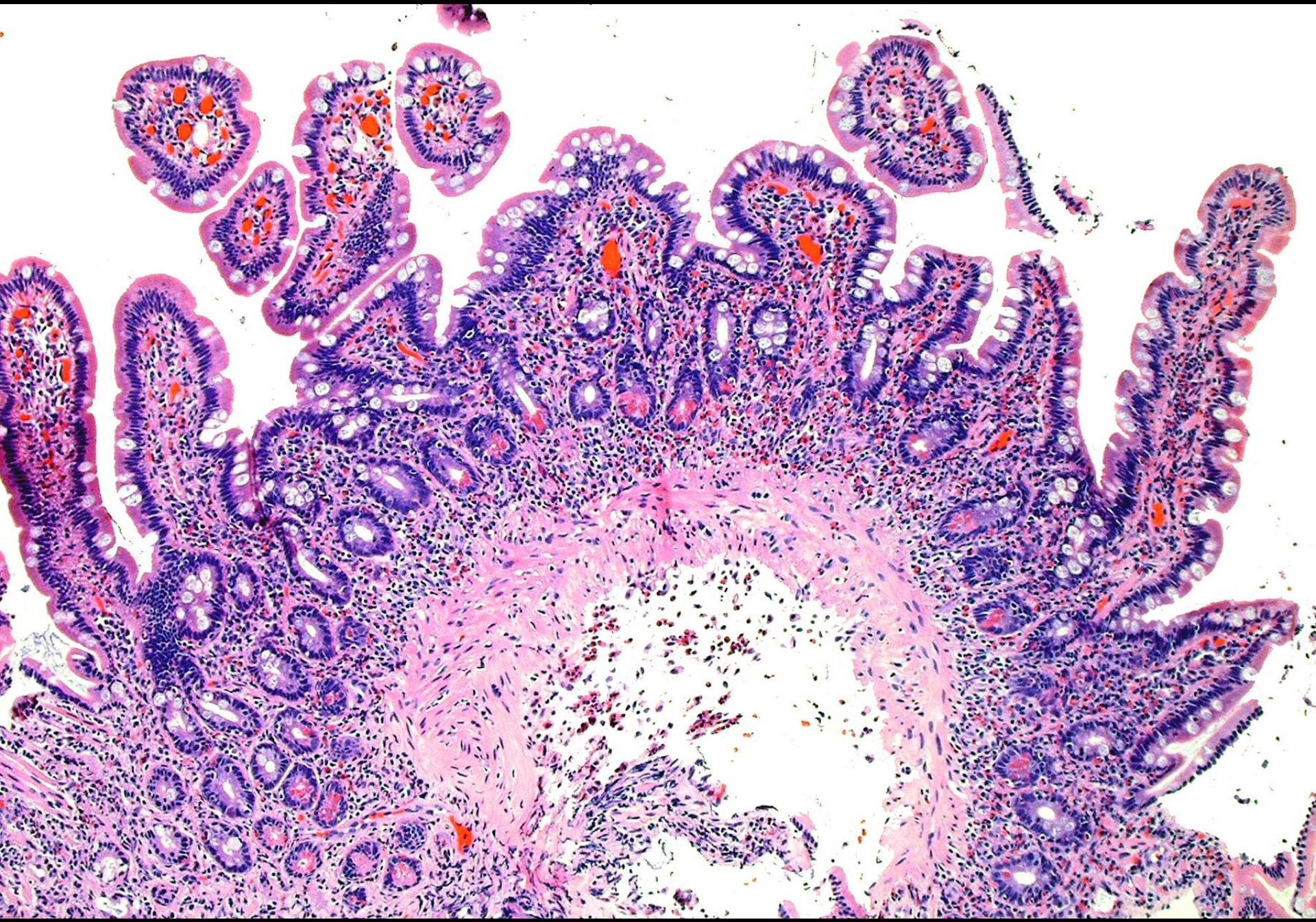
Terminal Ileal biopsy in a patient with diarrhea

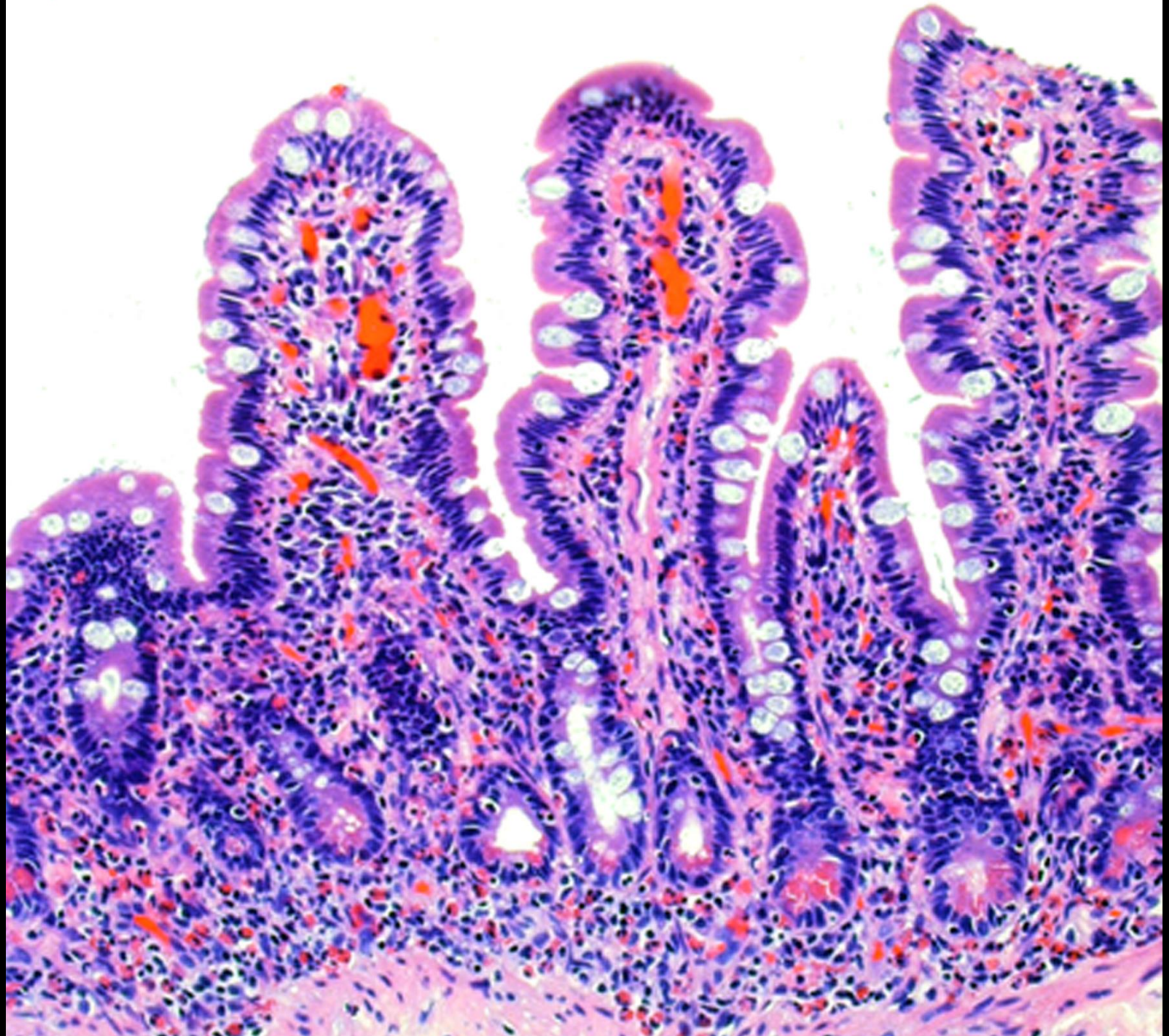


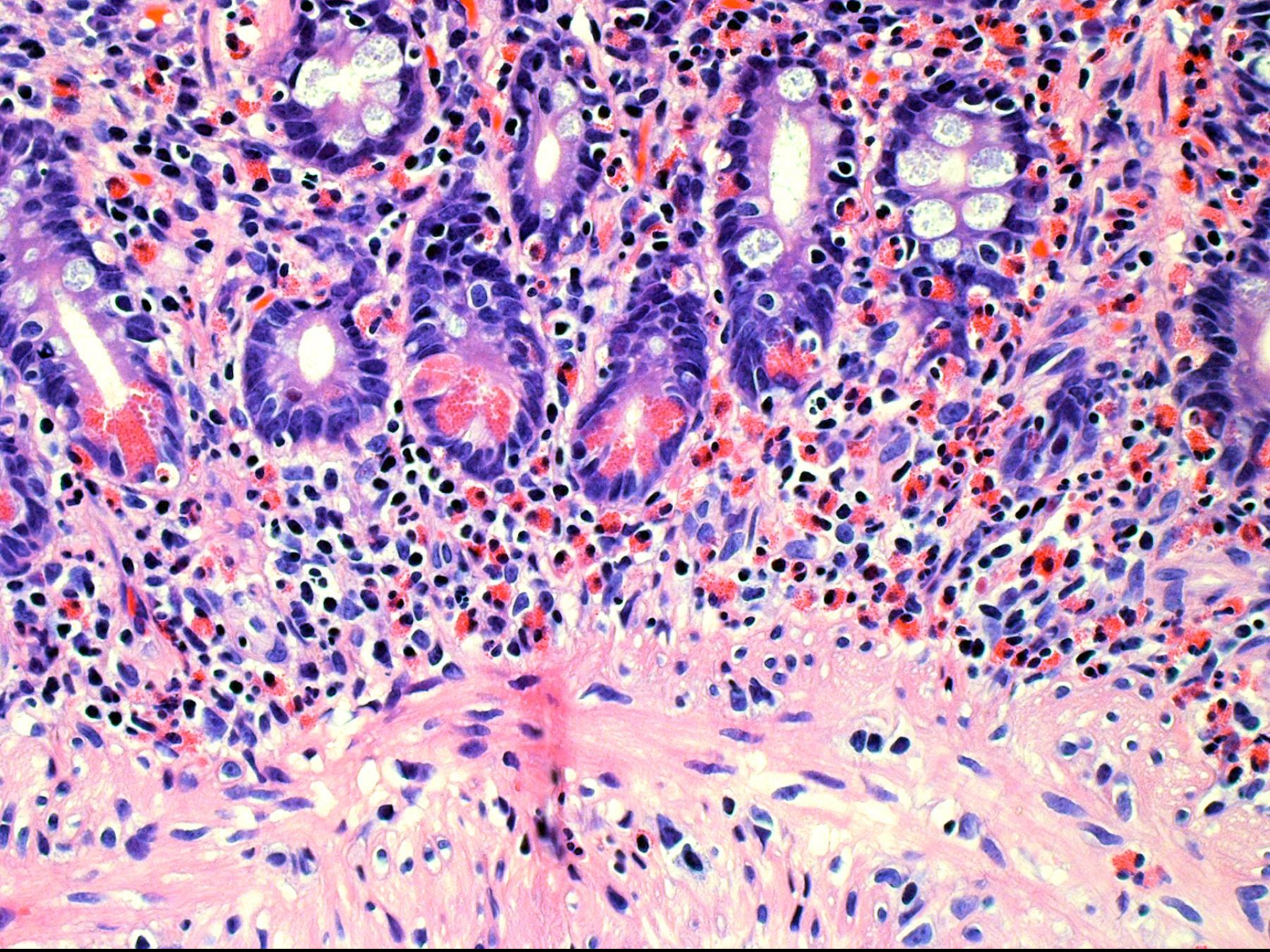


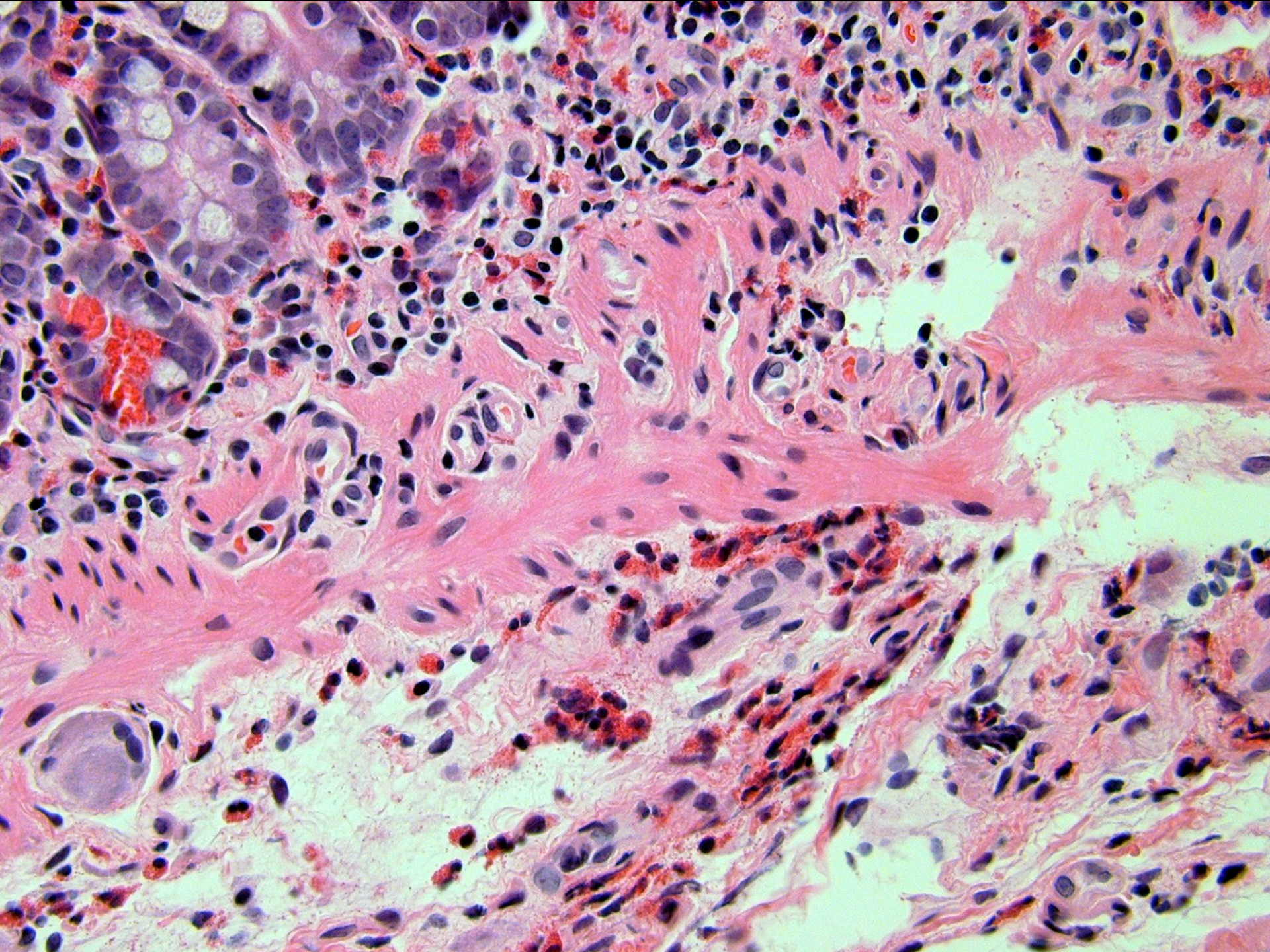
Clinical History

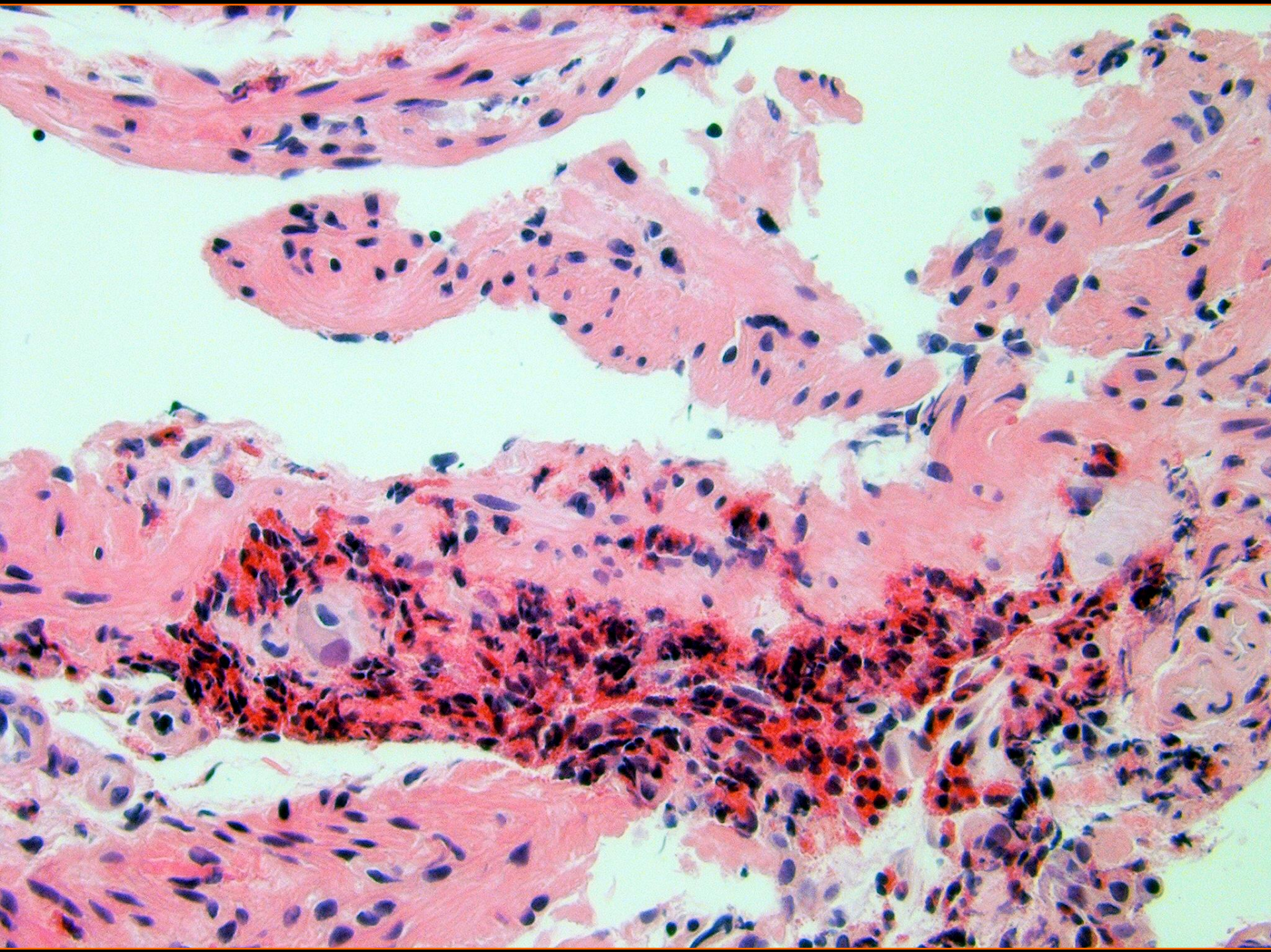
- 40 y.o. F with sudden onset of abdominal pain
- She also reports mild intermittent diarrhea
- Similar episodes in the past but extensive work-up has been negative
- Colonoscopy and upper endoscopy with biopsies two years ago were reportedly normal
- No medications except for Tylenol during the painful episodes

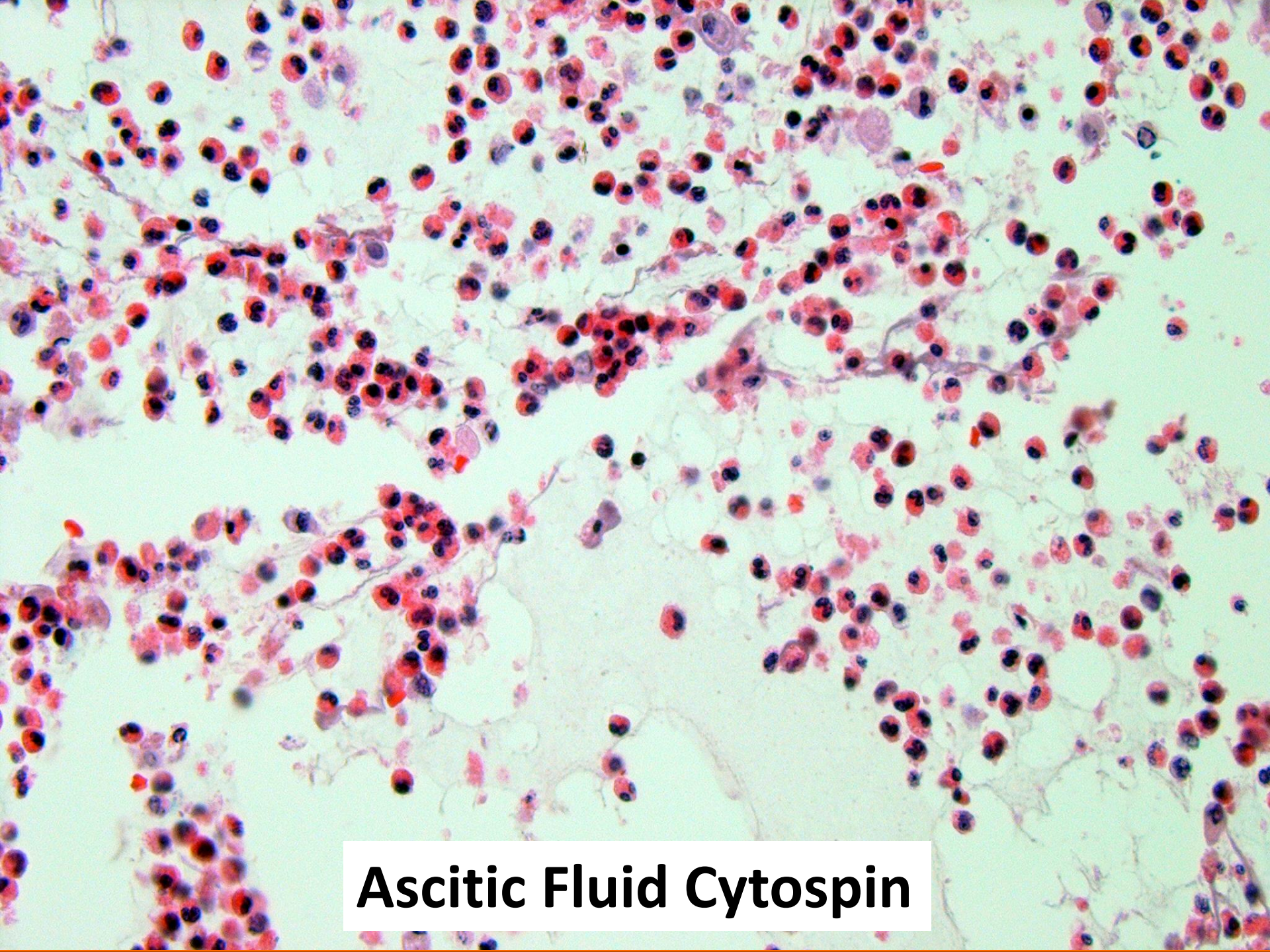




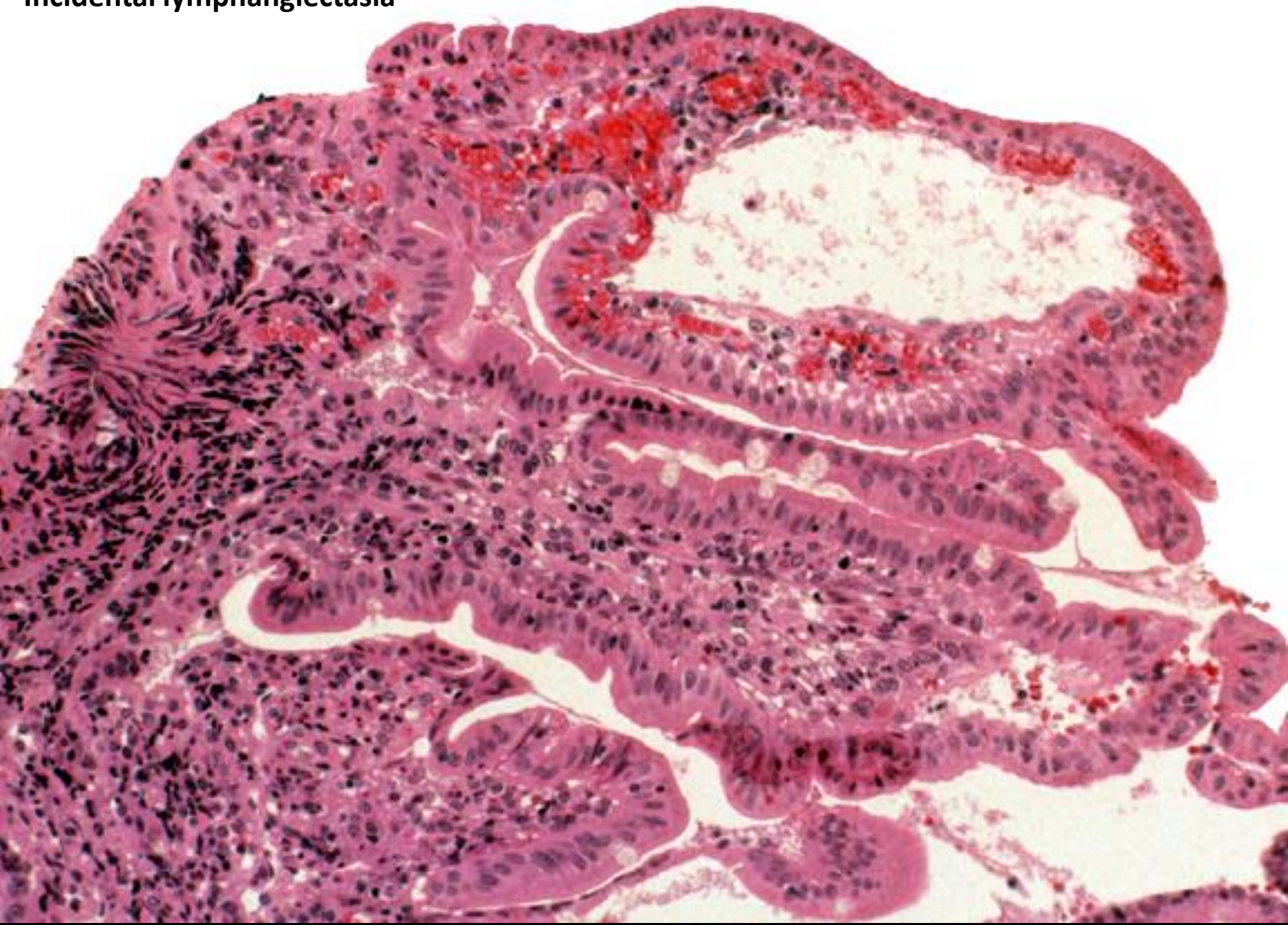


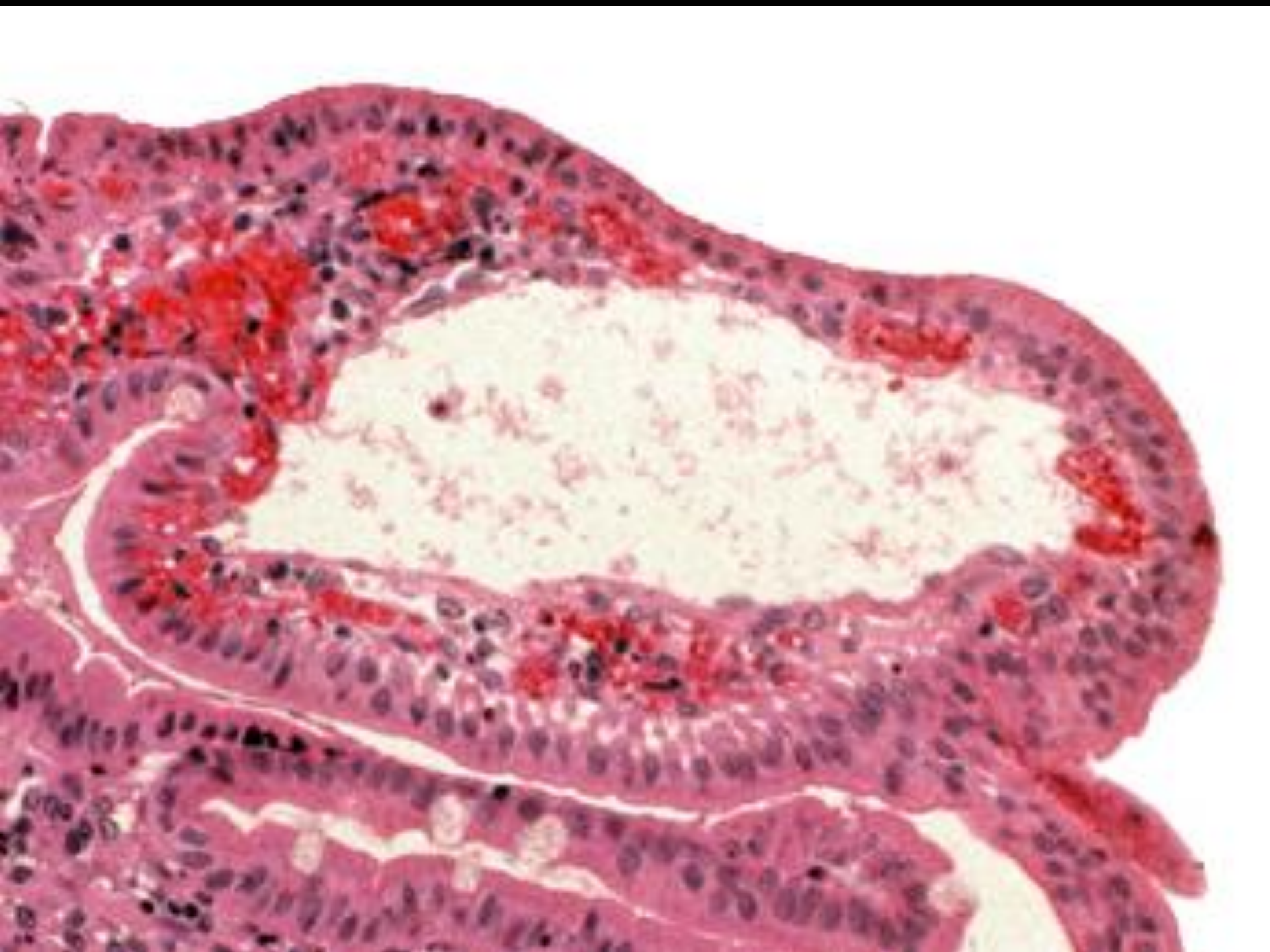


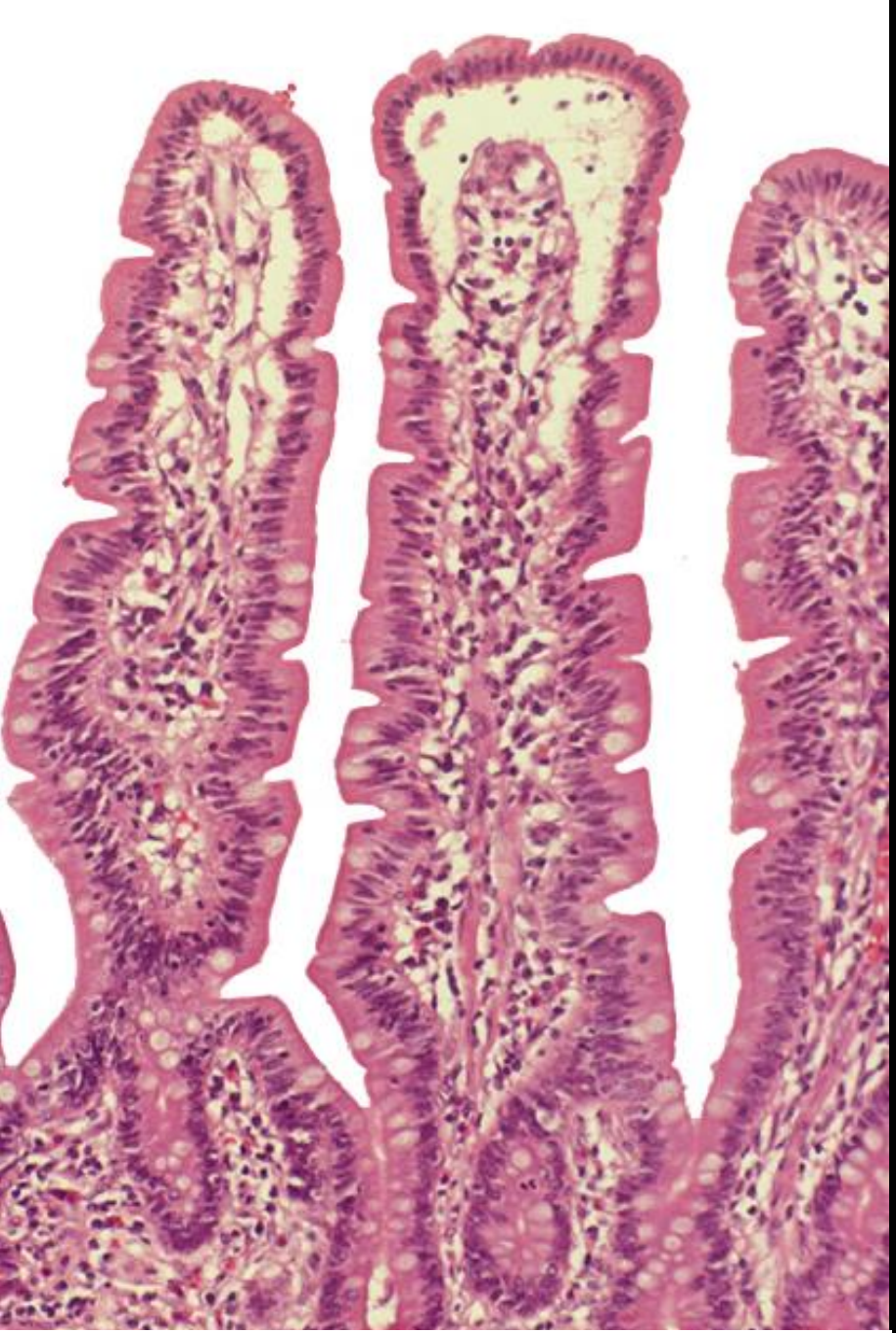



Ascitic Fluid Cytospin

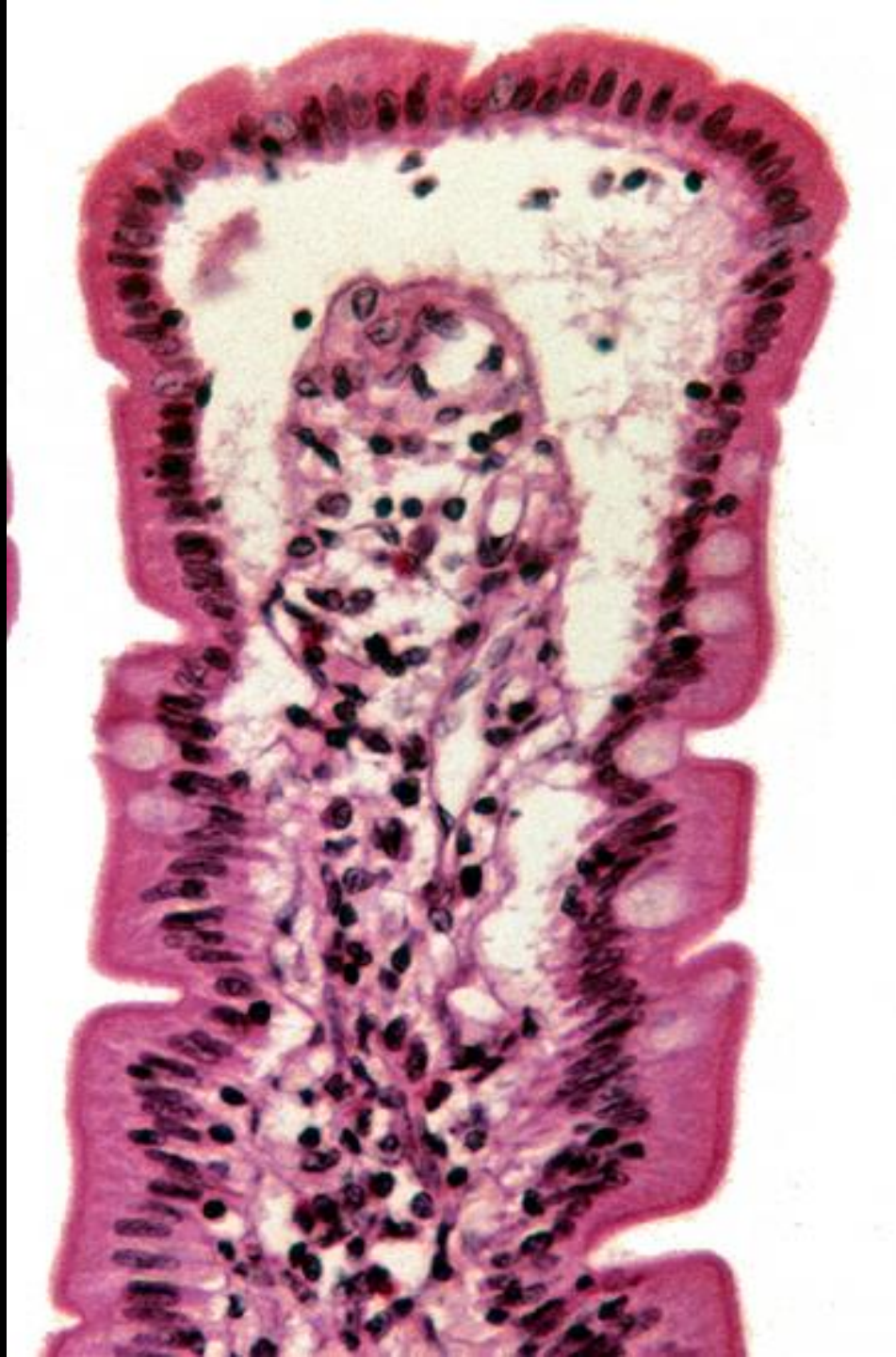
Incidental lymphangiectasia

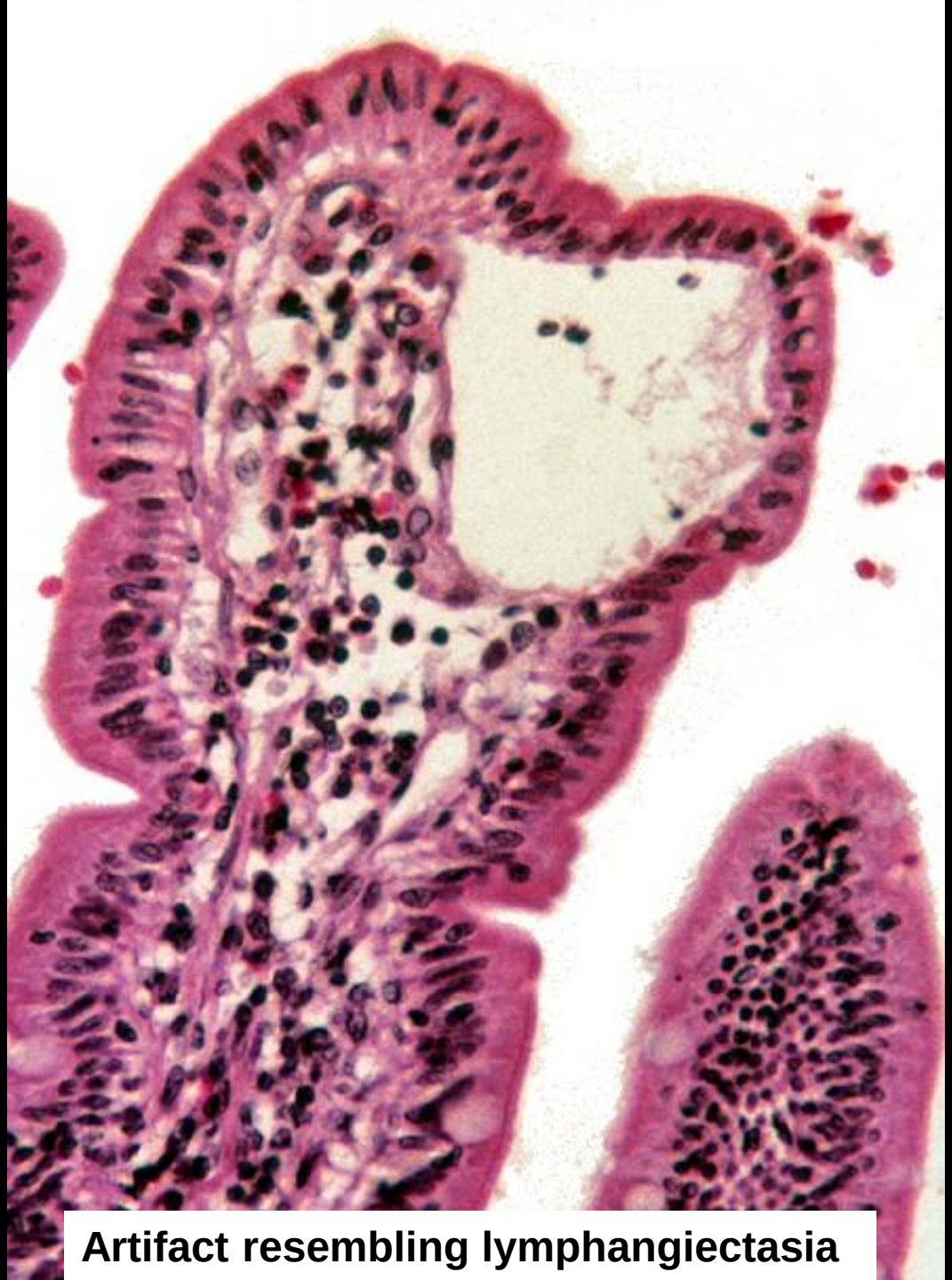




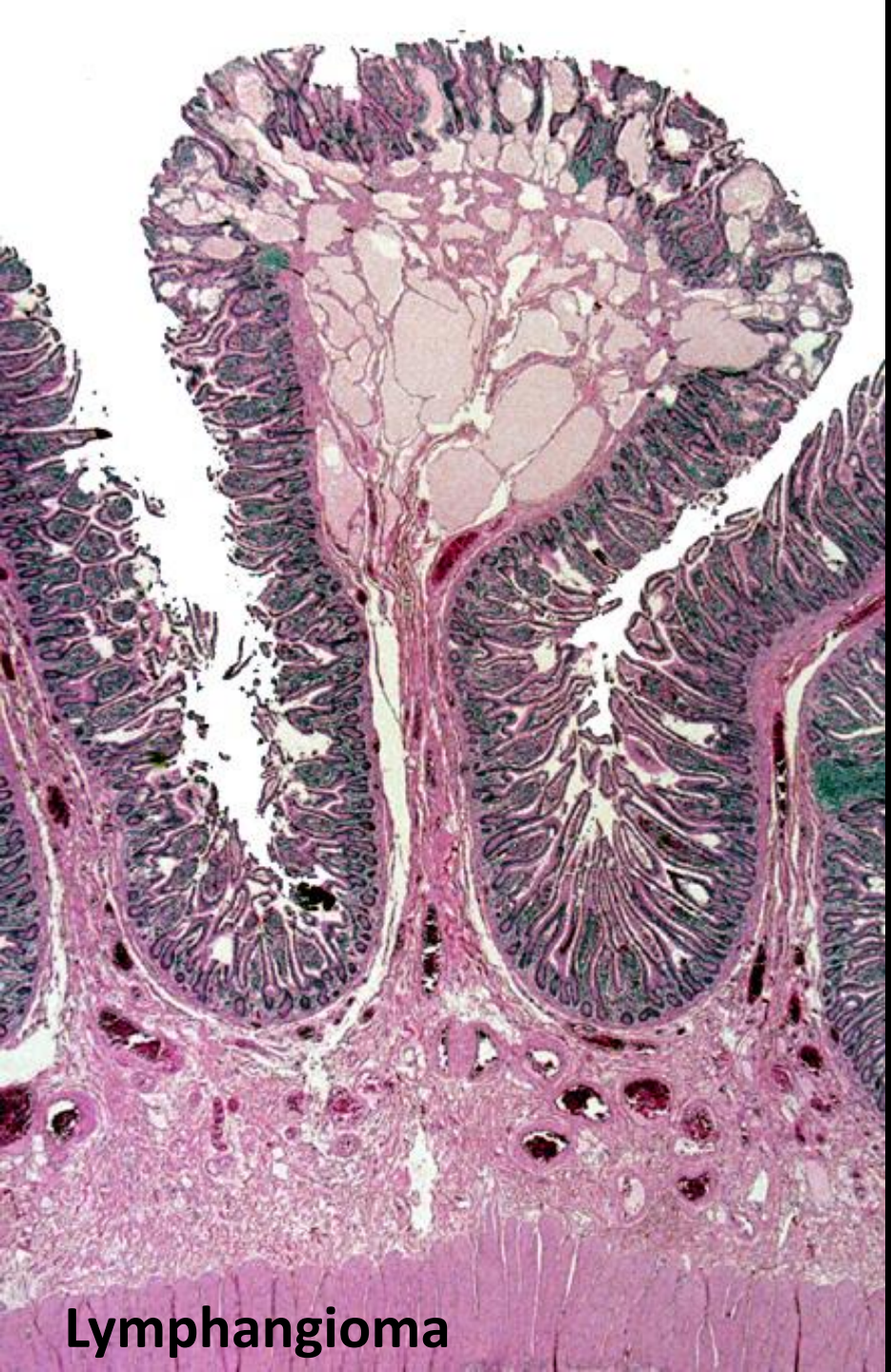


Artifact resembling lymphangiectasia

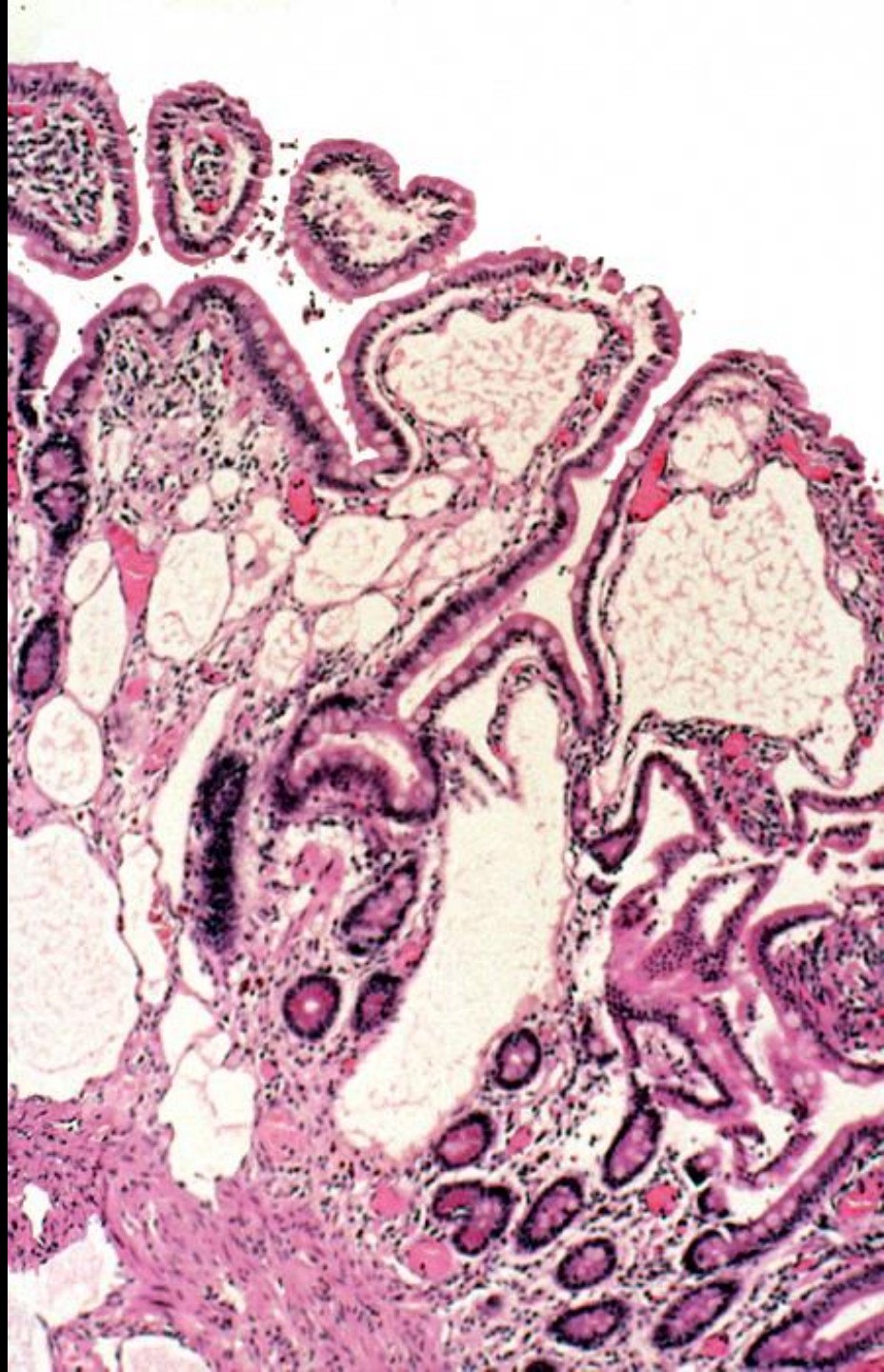




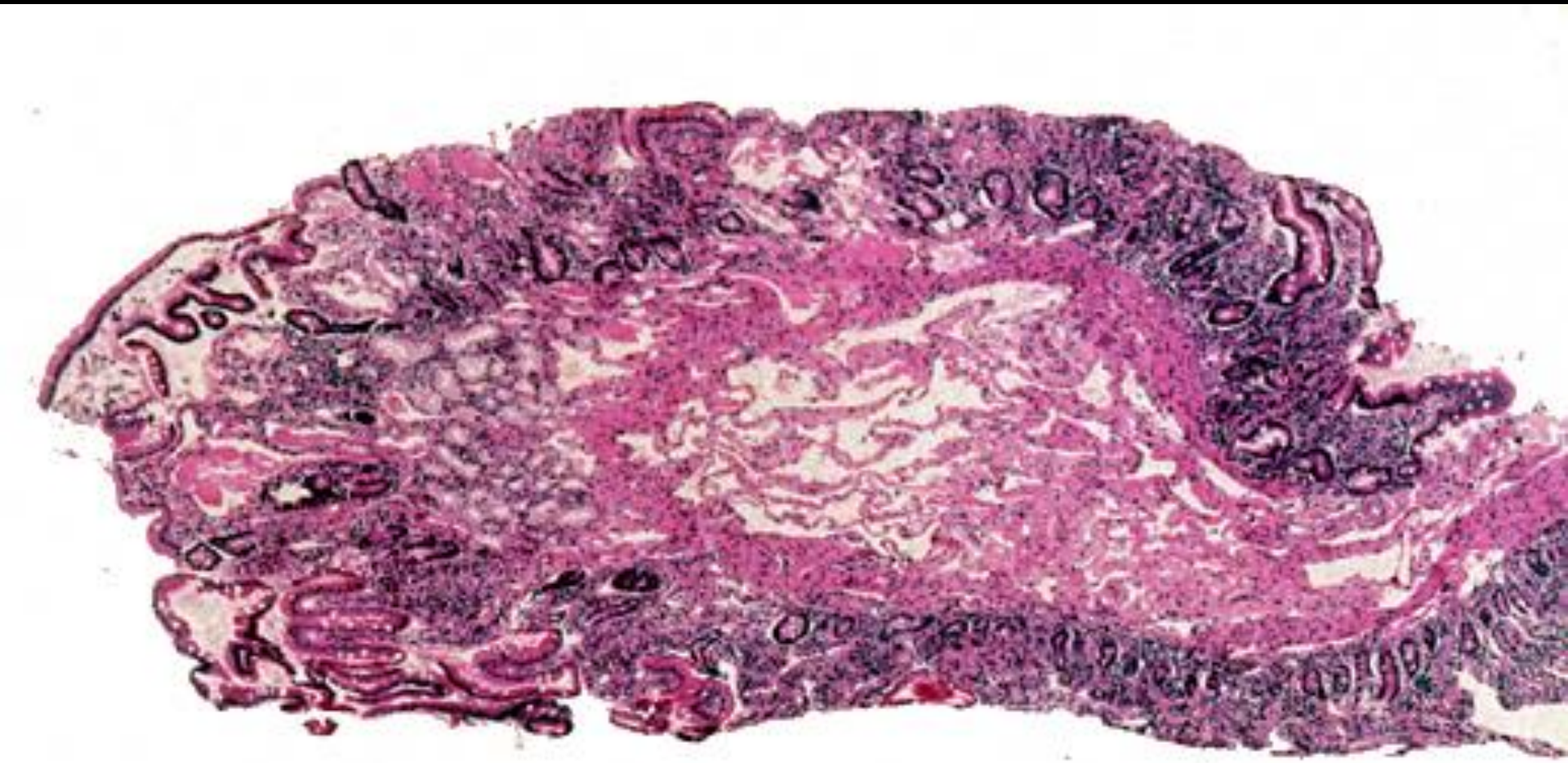
Artifact resembling lymphangiectasia



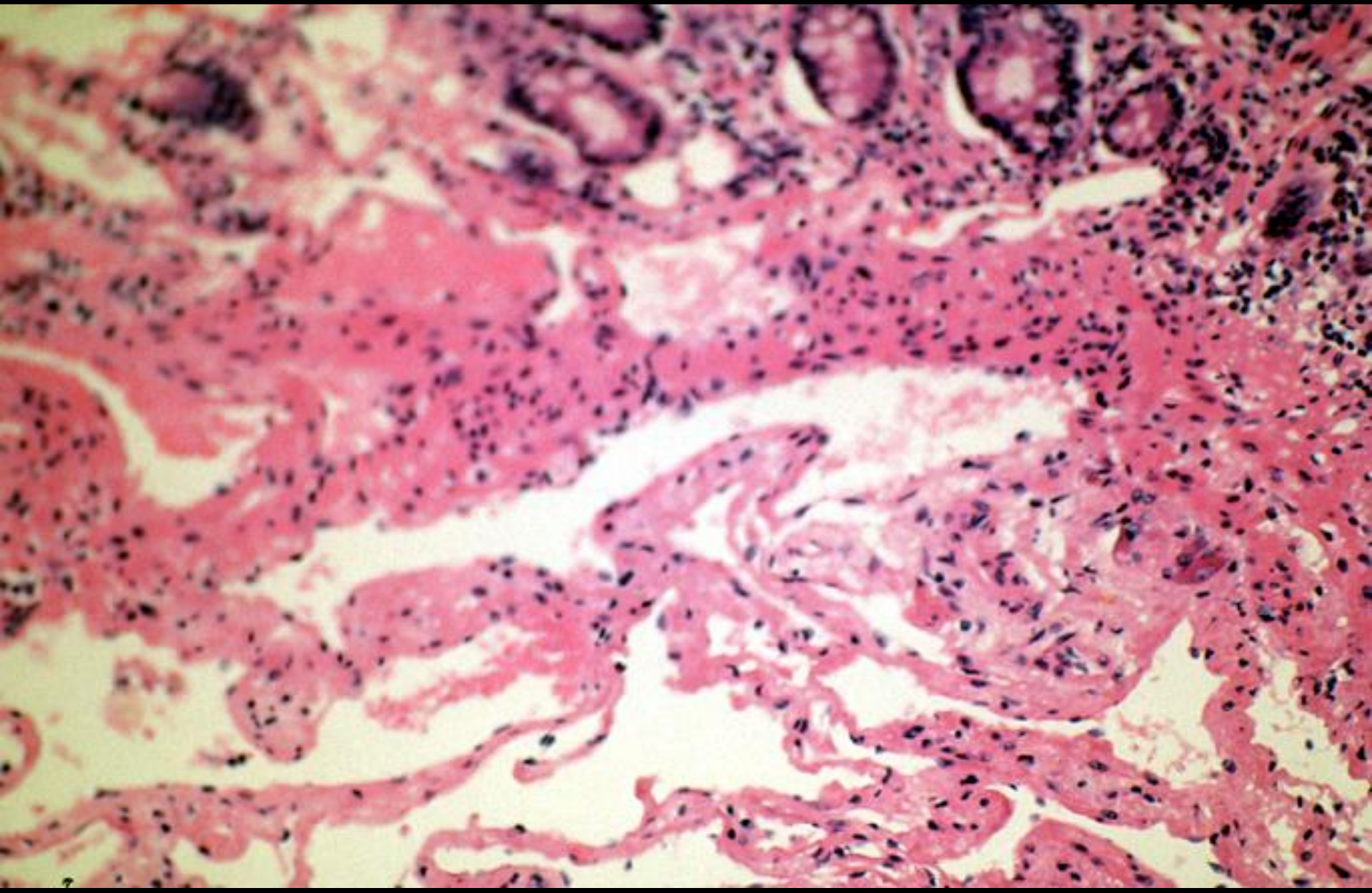
Lymphangioma



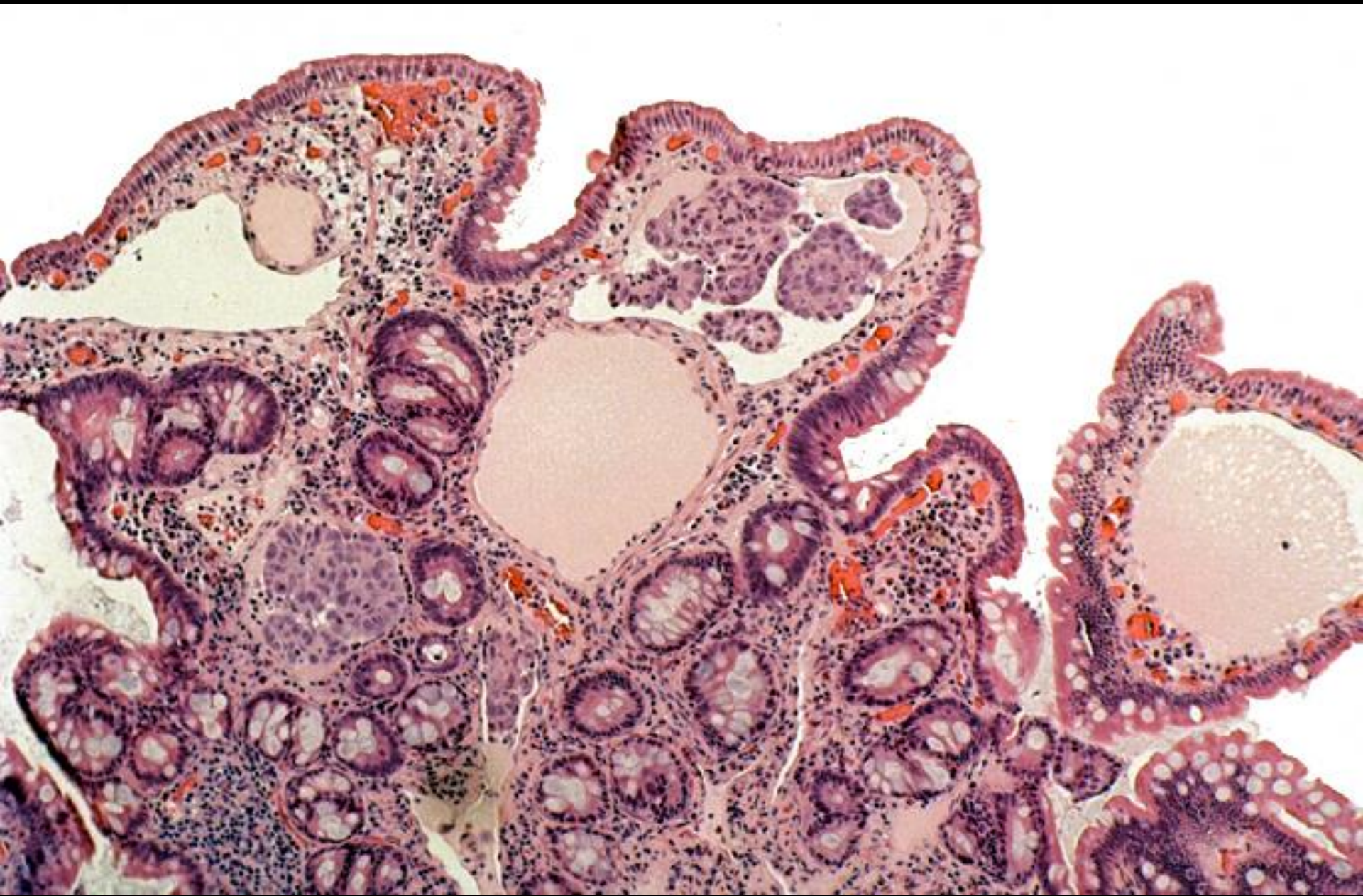
Lymphangioma

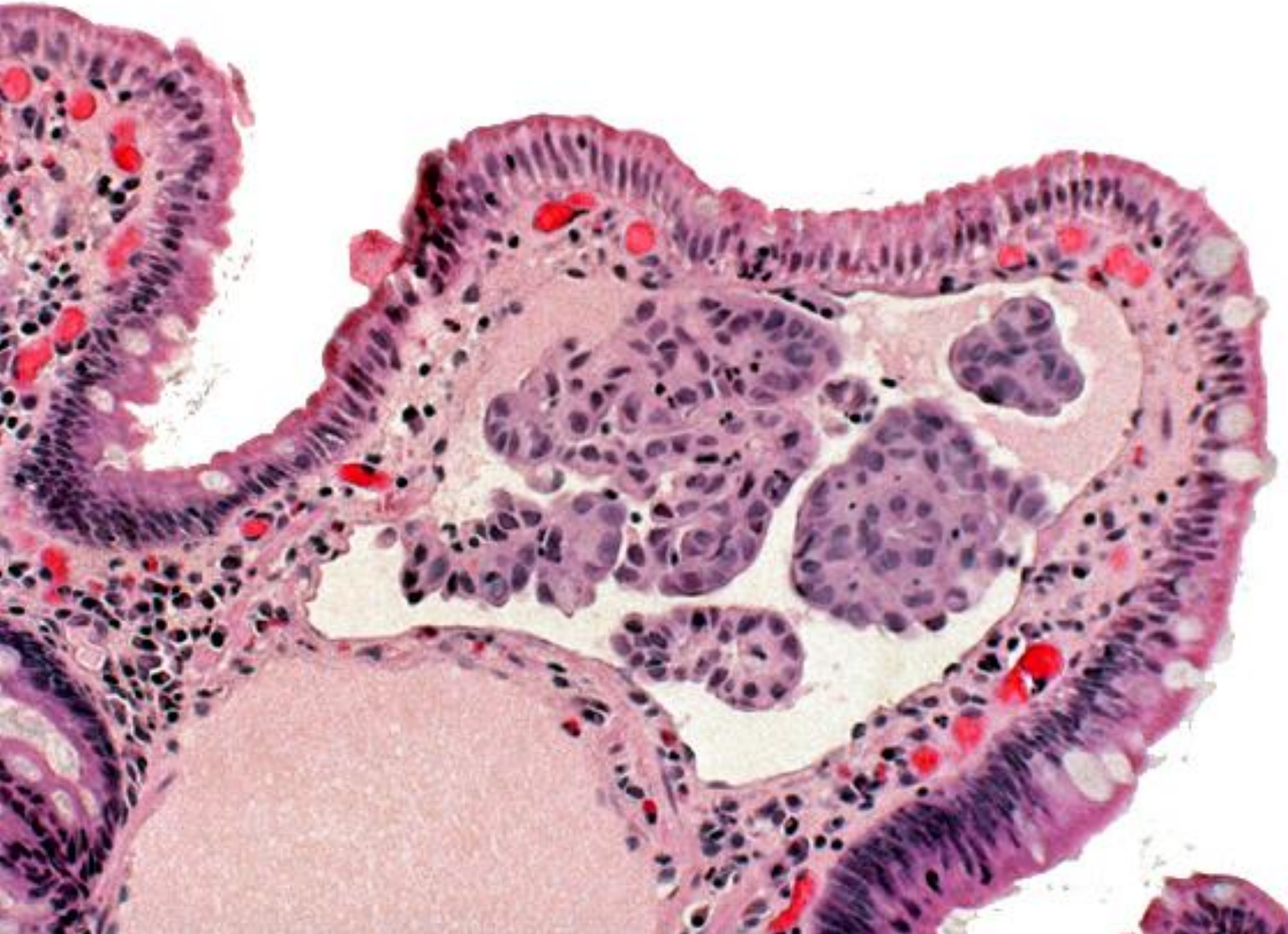


Lymphangioma



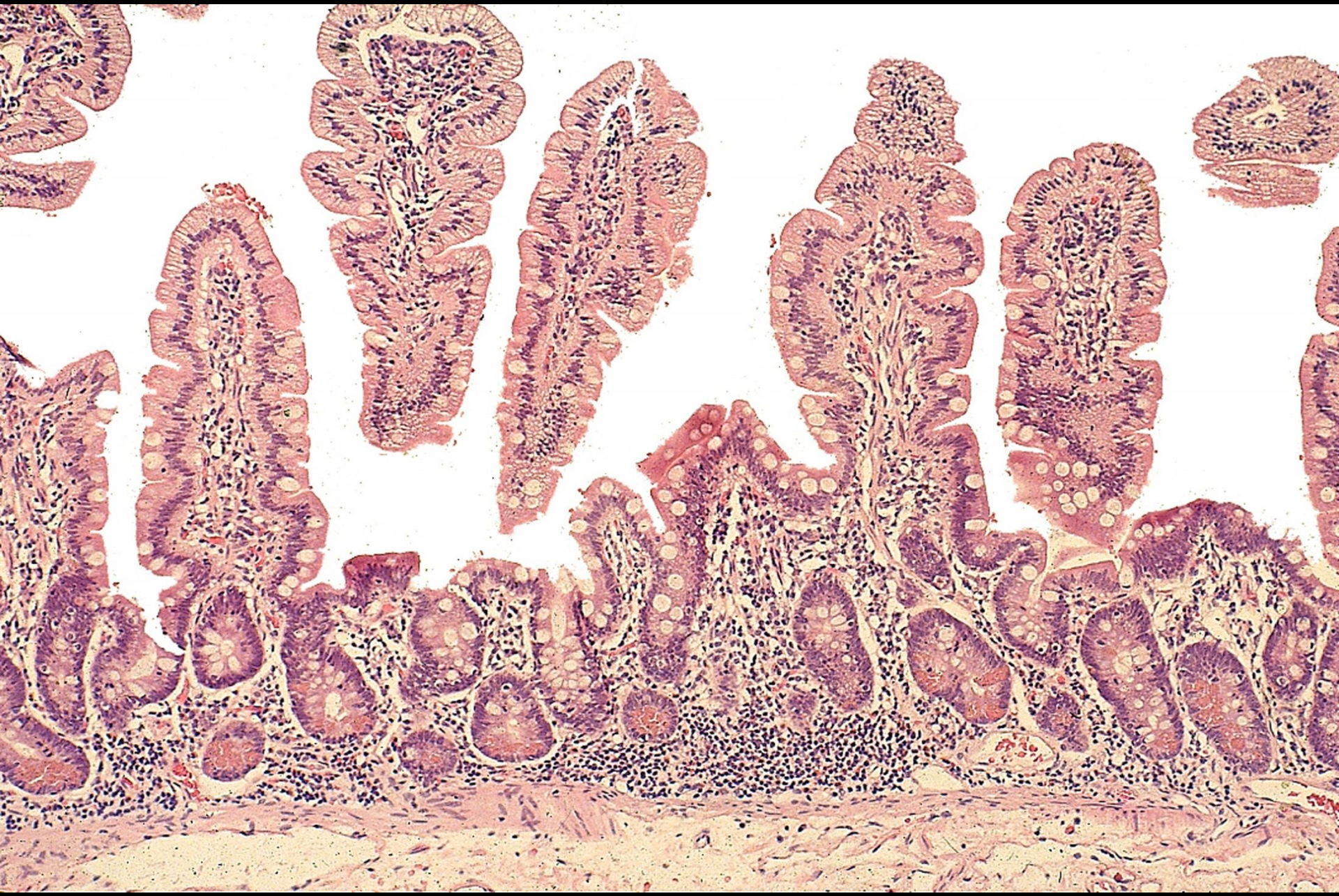
Lymphangiectasia due to pancreatic cancer infiltrating the root of the mesentery

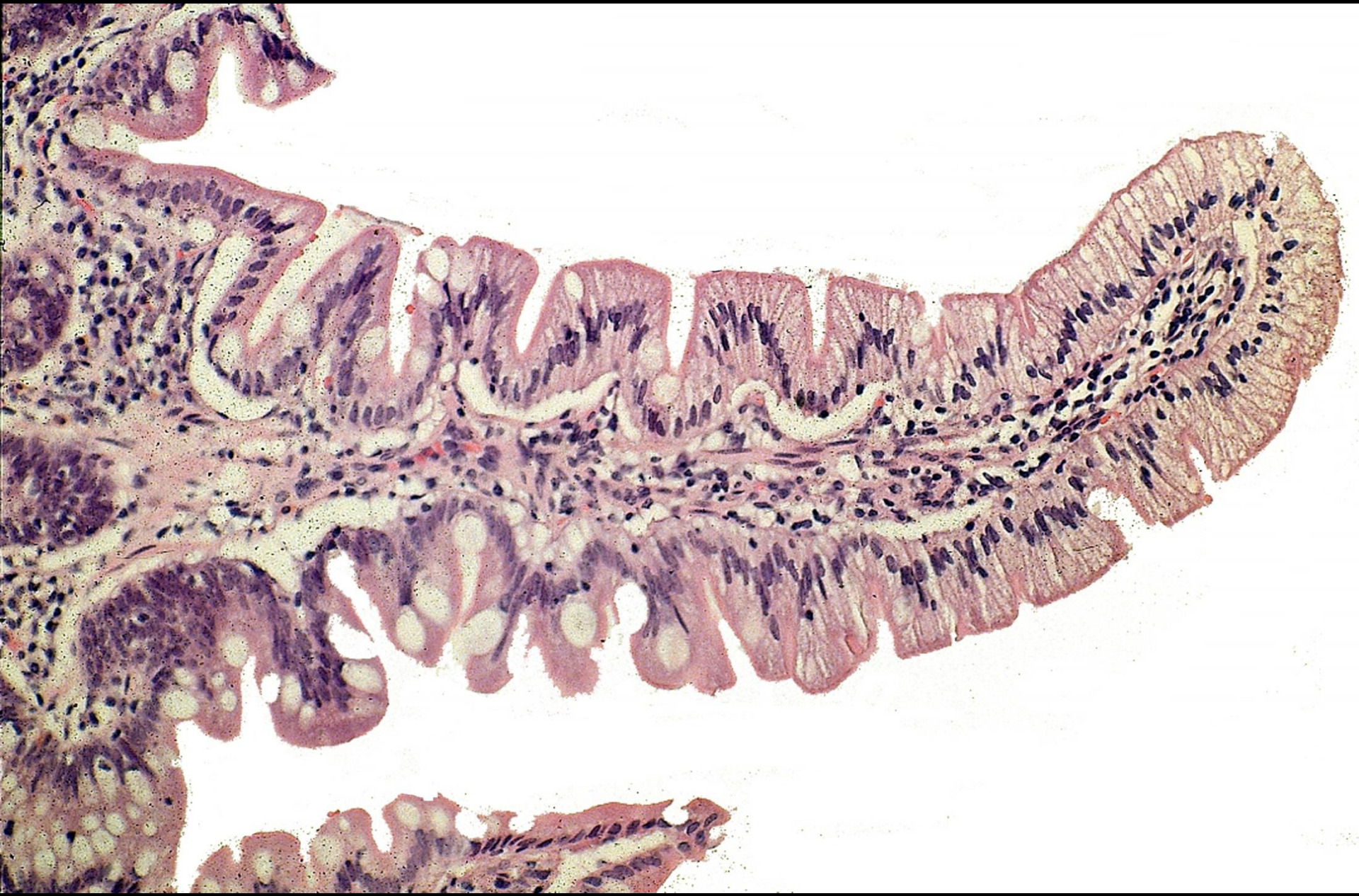




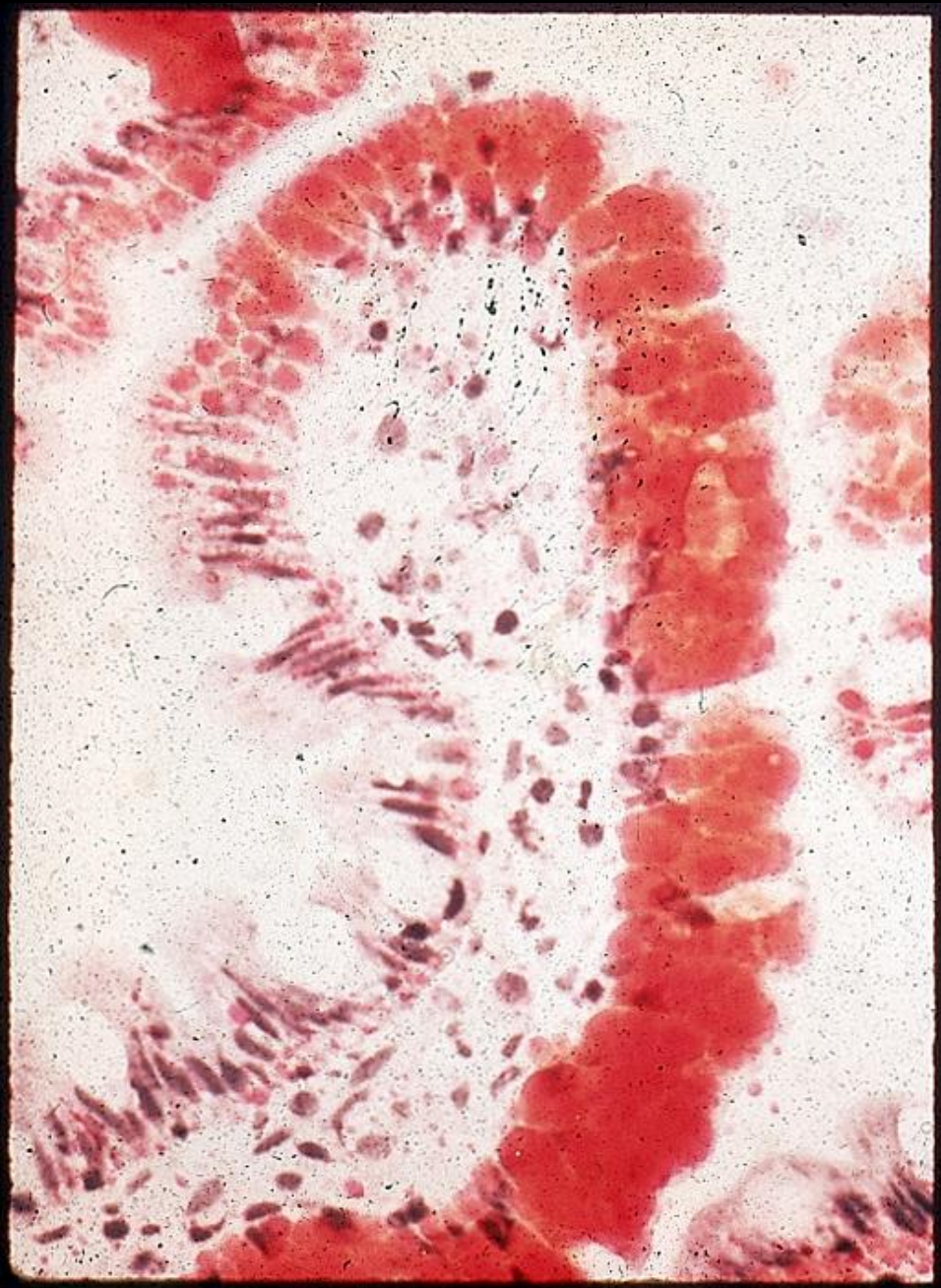
Clinical History

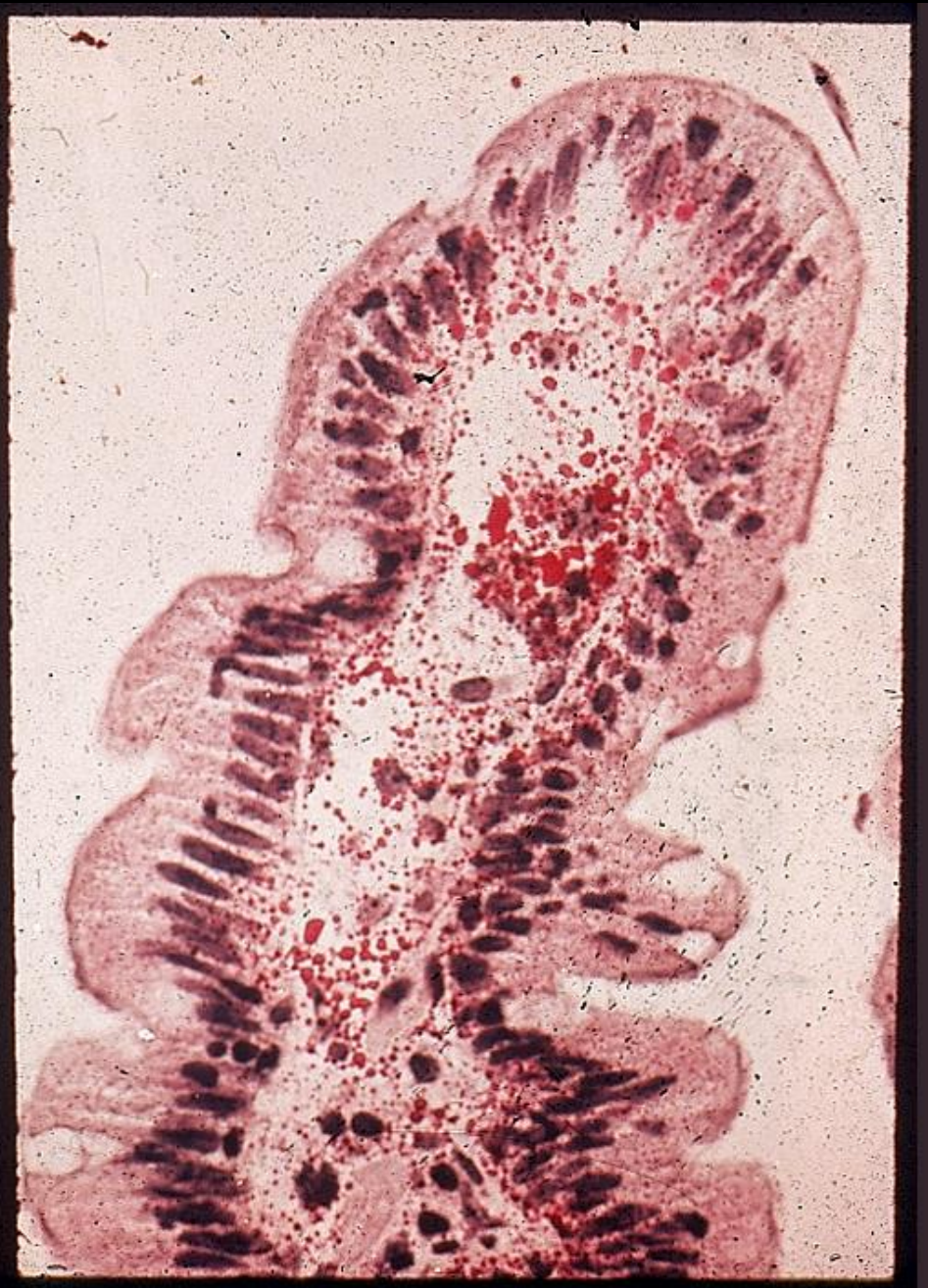
- 8-month-old F with diarrhea and failure to thrive
- Physical exam: listless & generalized mild hypotonia
- 72-hour stool collection reveals severe steatorrhea
- Liver chemistry tests mildly elevated



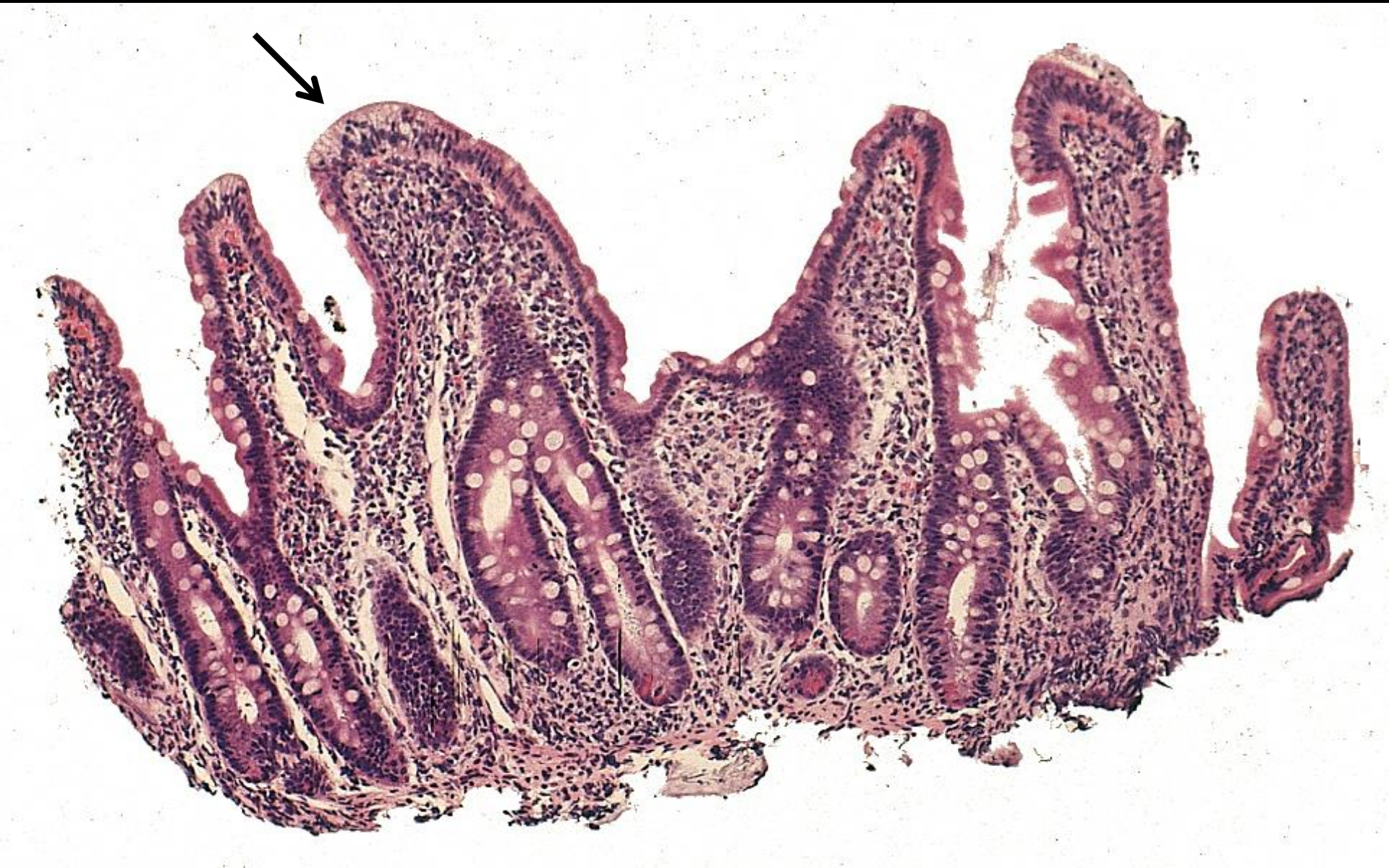


abetalipoproteinemia





Normal physiologic change due to not being NPO before endoscopy



Summary

- As much clinical history as possible
- As many biopsies as possible
- Some conditions have distinctive features, but many do not
- Many conditions produce an increase in IELs
- Cooperation between endoscopist and surgical pathologist is essential