IATROGENIC AND DRUG INDUCED PATHOLOGY IN THE SMALL INTESTINE

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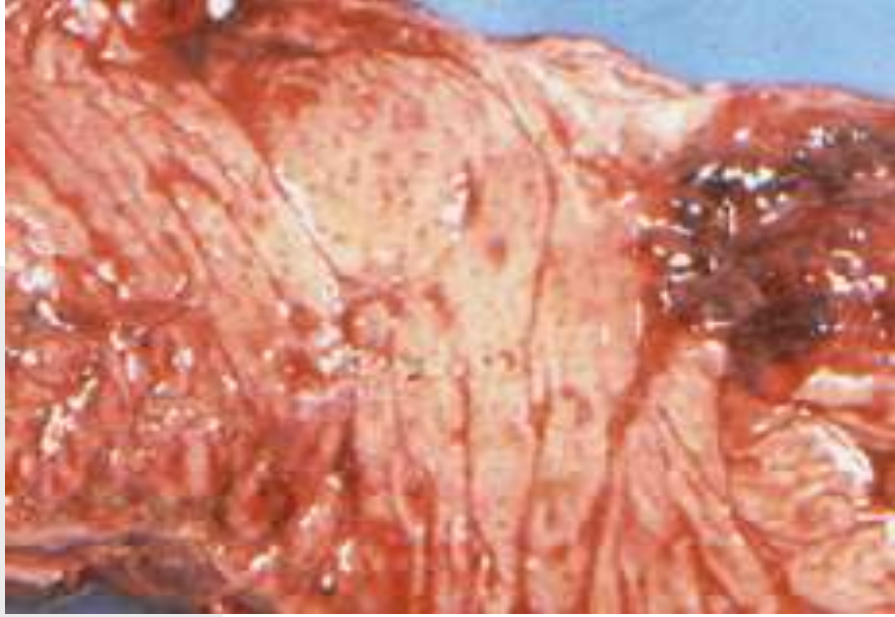
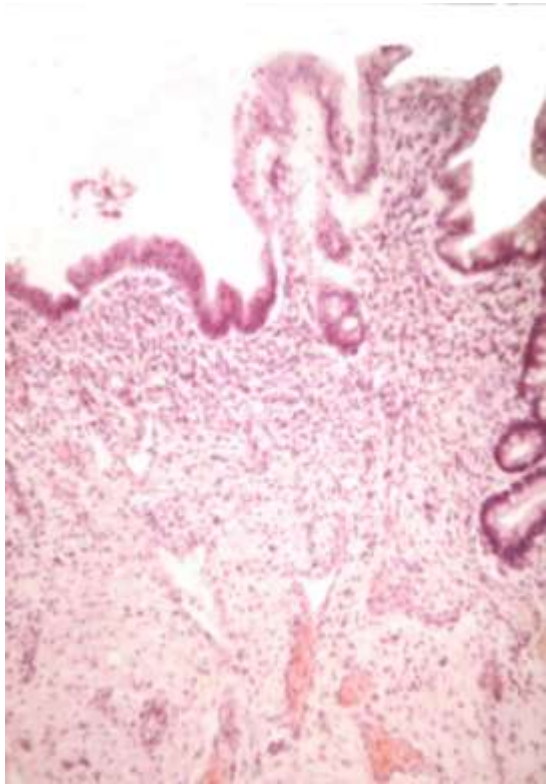
Content

- Iatrogenic pathology
  - Radiation
  - Chemotherapy
  - Graft-Versus-Host disease
  - Changes following surgical procedures
  - Transplantation
- Drug-induced pathology
  - NSAID
  - Enteric-coated K^+ supplements





Radiation induced enteritis

- Complication of abdominal/pelvic irradiation
- Life-threatening complications: fistulas, strictures, chronic malabsorption
- Increasing incidence because of combined chemotherapy and radiation
- Acute and chronic forms exist

Radiation induced enteritis

- Severity ~ anatomical features, host mechanism, type of therapy
- Severity of acute radiation enteritis likely to determine severity of chronic disease
- Radiobiology
  - $OH^{\cdot}$ and other free radicals are formed
  - Cells most vulnerable in G2 and M phases

Radiation induced enteritis

- Rapidly proliferating tissues e.g. crypt epithelial cells, are very sensitive, undergo apoptosis and are shed from villus
- Acute effect: diarrhoea
- Concurrent chemotherapy may enhance apoptosis and exacerbate G-I symptoms

Radiation: molecular biology

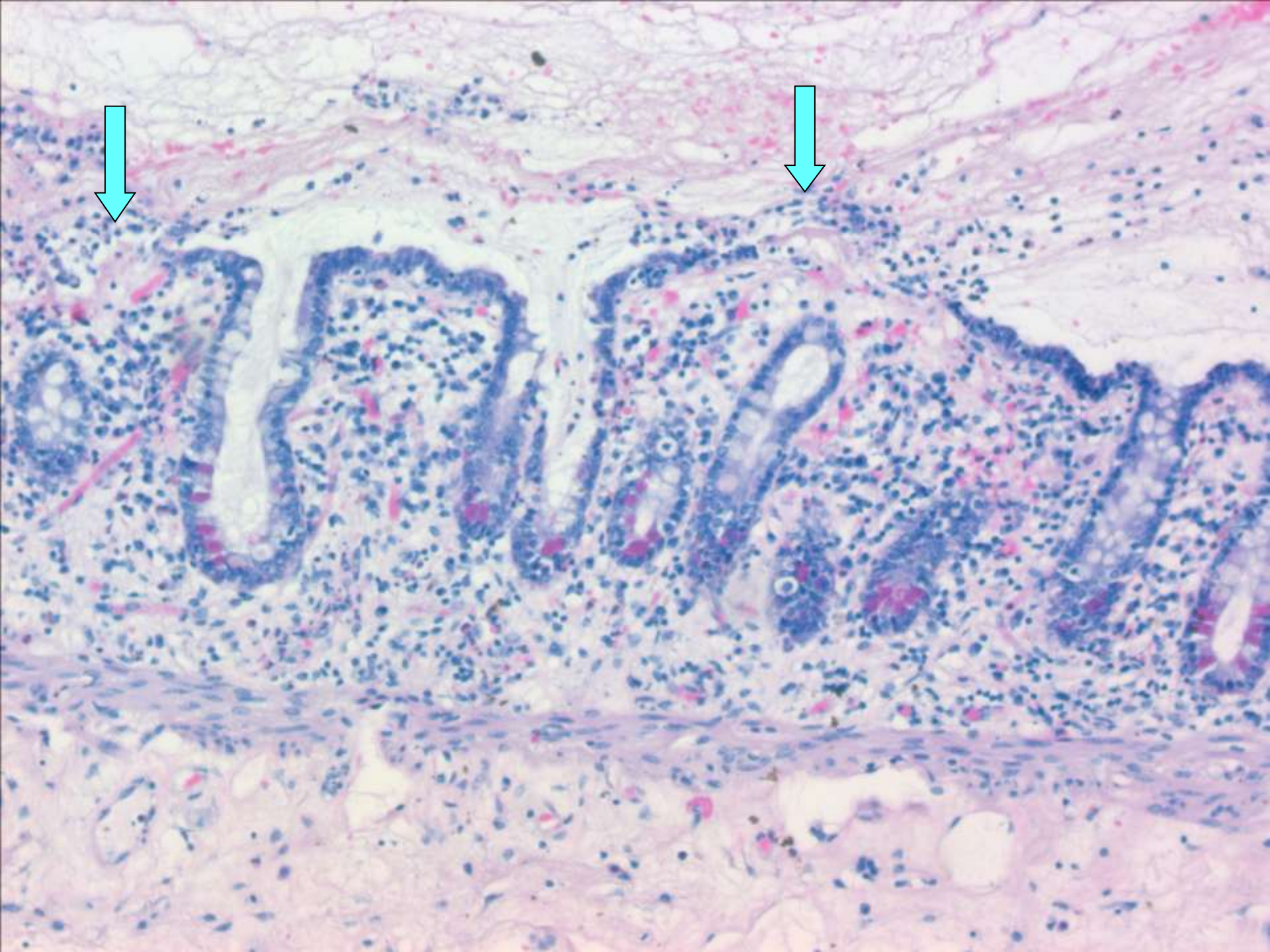
- Apoptosis:
  - in crypt stem cells after 1-5 cGy, dose dependent
  - ↑ *p53* expression in stem cell region → *p53* dependent apoptosis
  - small intestinal stem cells more sensitive than colonocytes (more *bcl-2*)
- 5% risk of complications at 5 y after 4500-5000 cGy

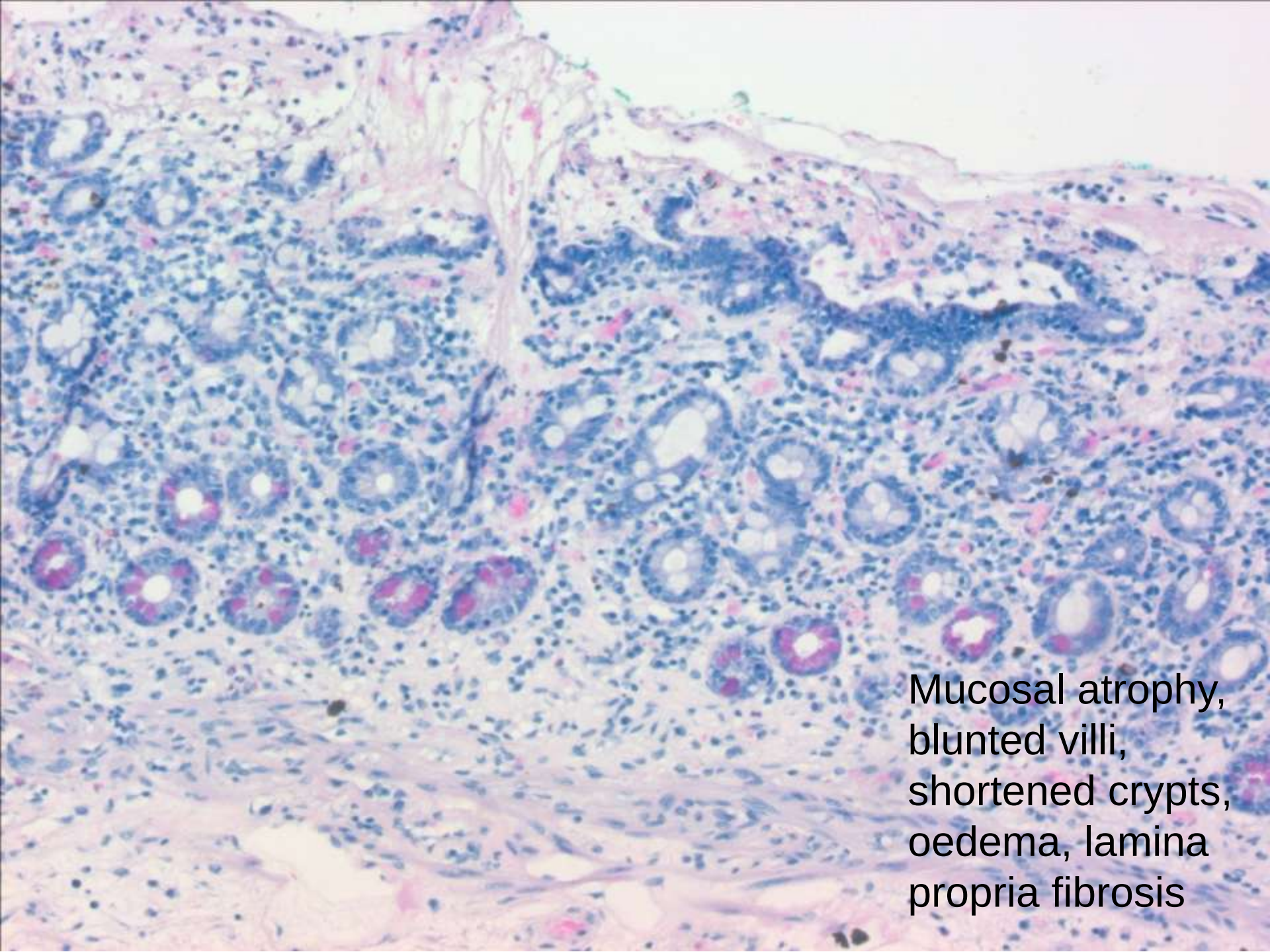
Radiation effect: molecular biology

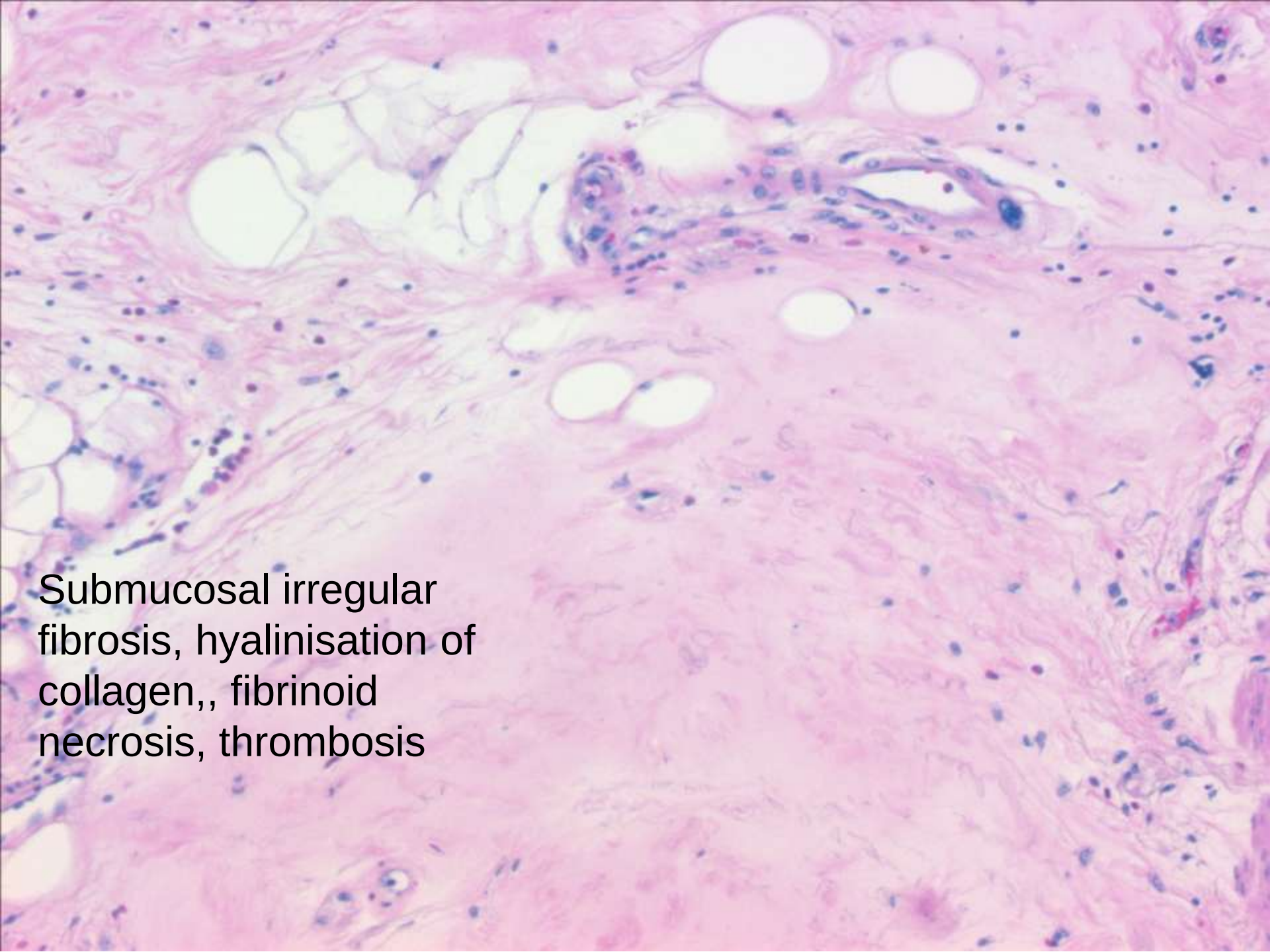
- Activates translation of TGF-ß gene
  - TGF-ß1: implicated in pathogenesis of fibrosis
  - TGF-ß1 primarely in intestinal villus, at top of colonic crypts
- TGF-ß overexpressed after radiation
  - ↑↑ expression of collagen and fibronectin genes, chemotaxis of fibroblasts
  - inhibits ECM degradation

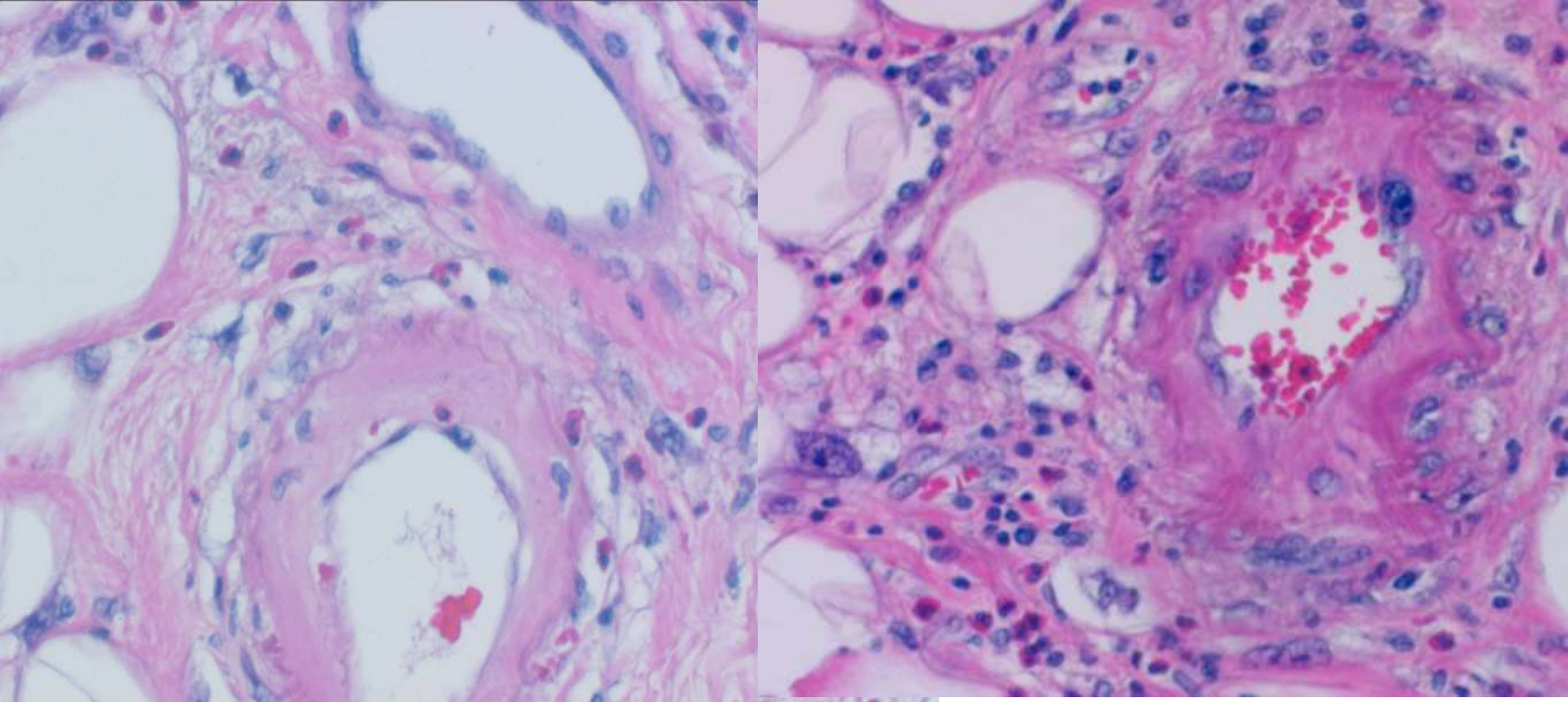
Radiation effect: histopathology

- ↑ collagen deposition, progressive occlusive vasculitis → narrowing of lumen, stricture, serosal thickening, ulceration, necrosis, occasional perforation

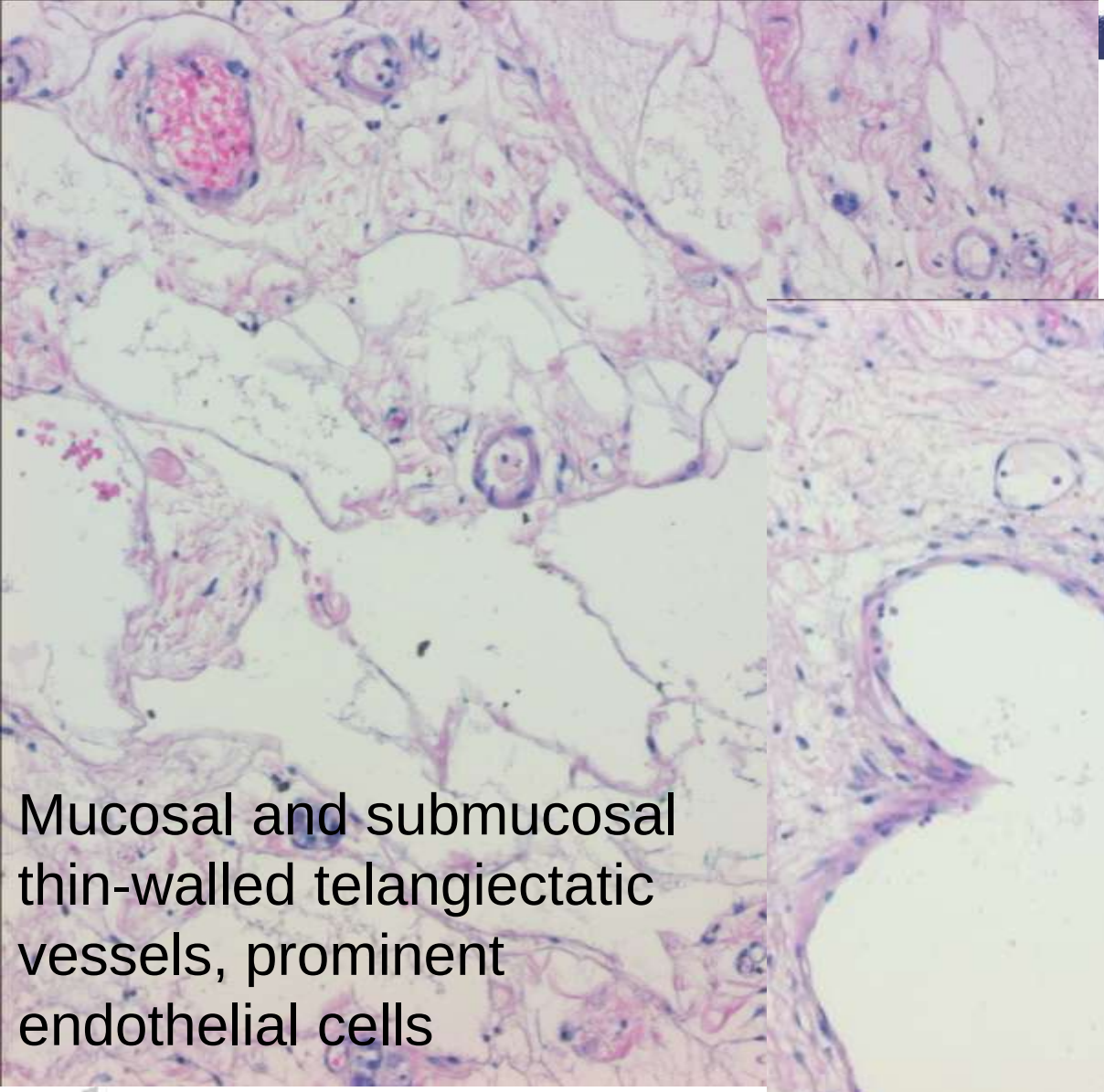



Mucosal atrophy, blunted villi, shortened crypts, oedema, lamina propria fibrosis

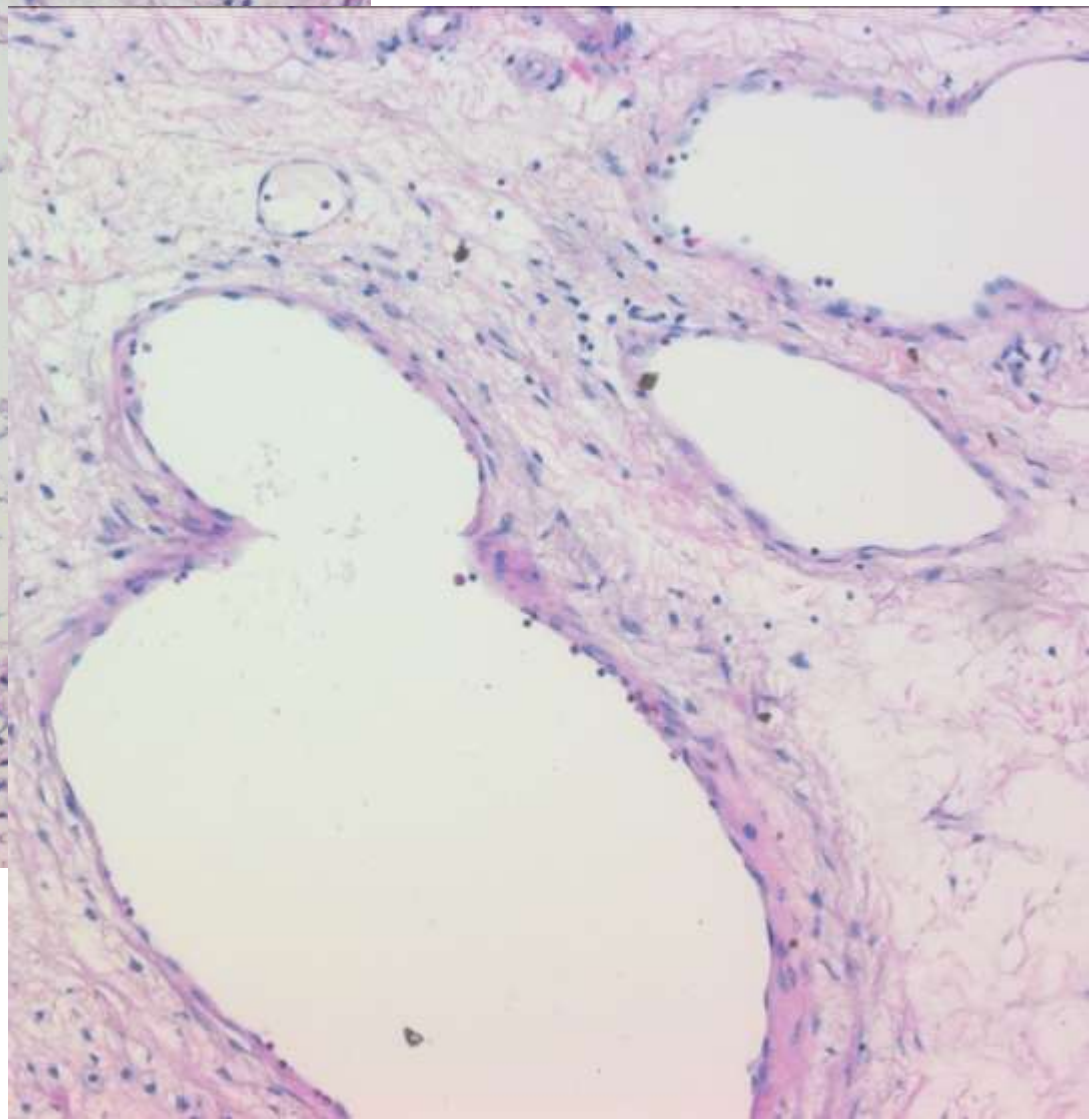

Submucosal irregular fibrosis, hyalinisation of collagen,, fibrinoid necrosis, thrombosis



Vascular hyalinisation, myointimal hyperplasia, increased collagen, narrowing of lumen

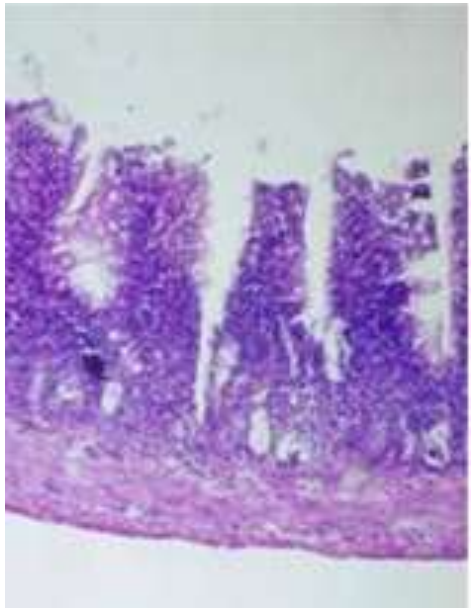


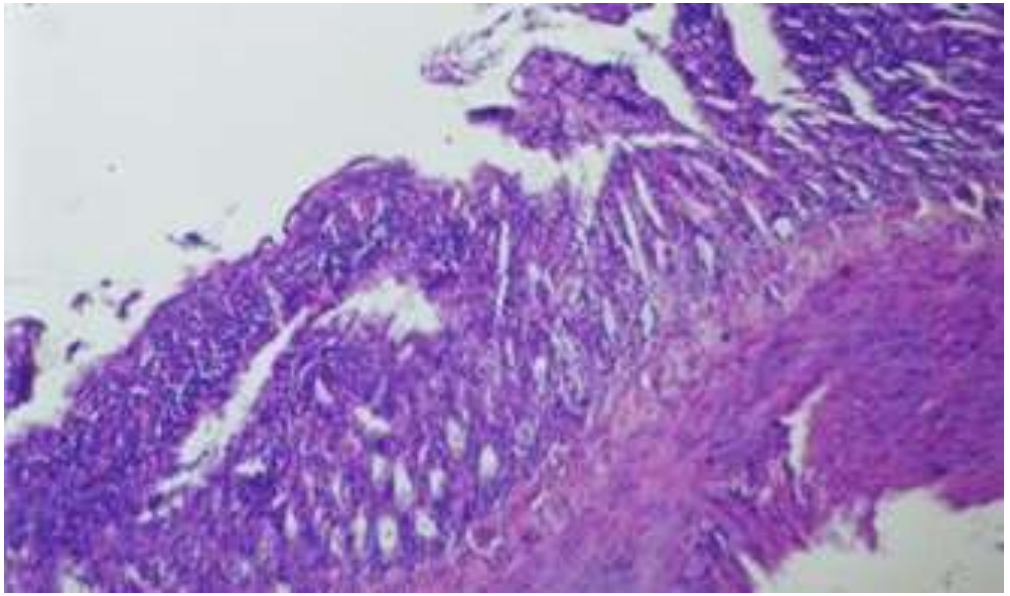
Mucosal and submucosal thin-walled telangiectatic vessels, prominent endothelial cells



Lesions induced by chemotherapy

- Cyclophosphamide, methotrexate, 5-FU
- May be exacerbated by radiotherapy
- ~ acute radiation damage: ↑ apoptosis, ↓ mitotic activity and villous blunting, atrophy and erosions





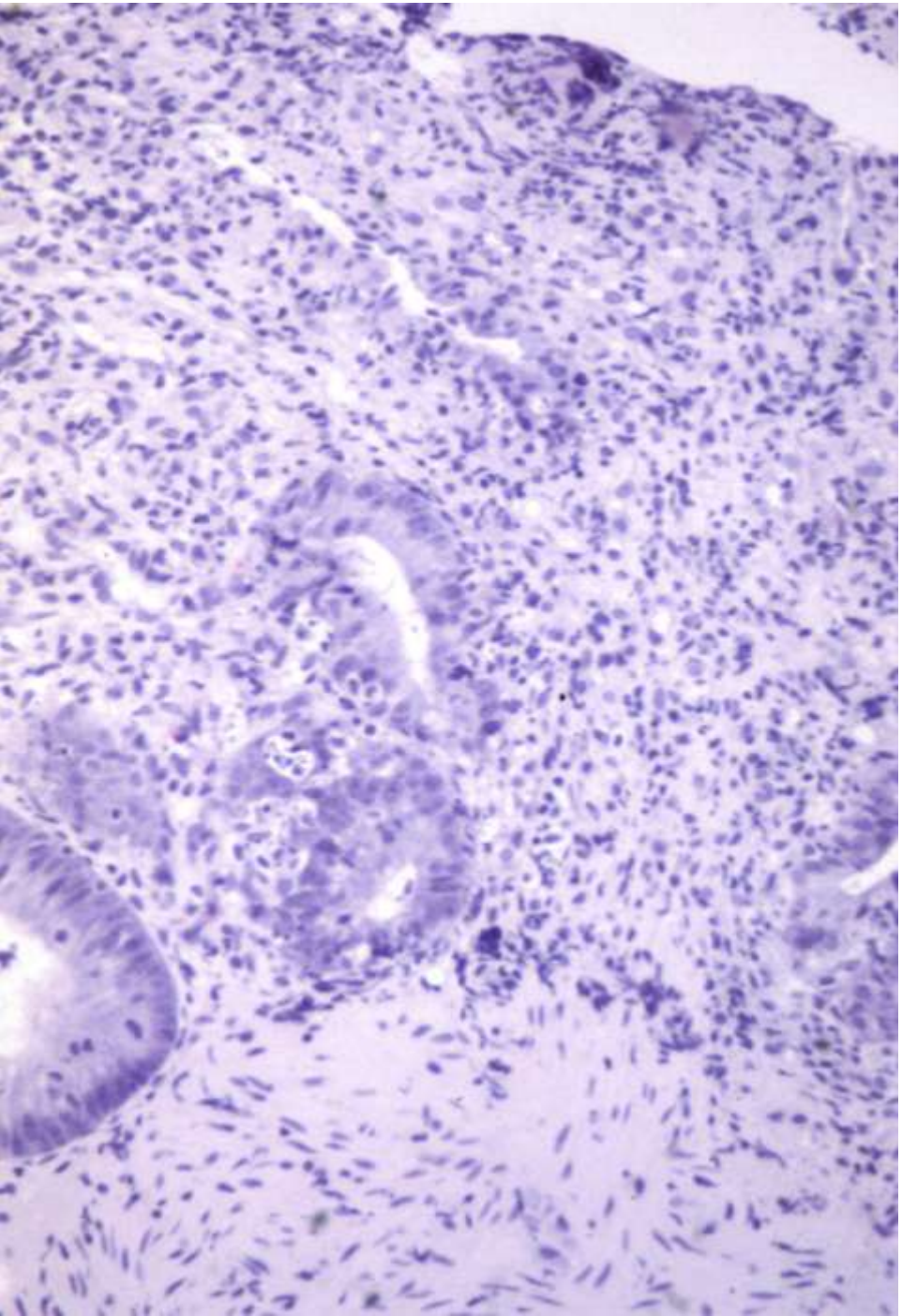
Jej. 12h: epithelial shedding, ↓ crypts

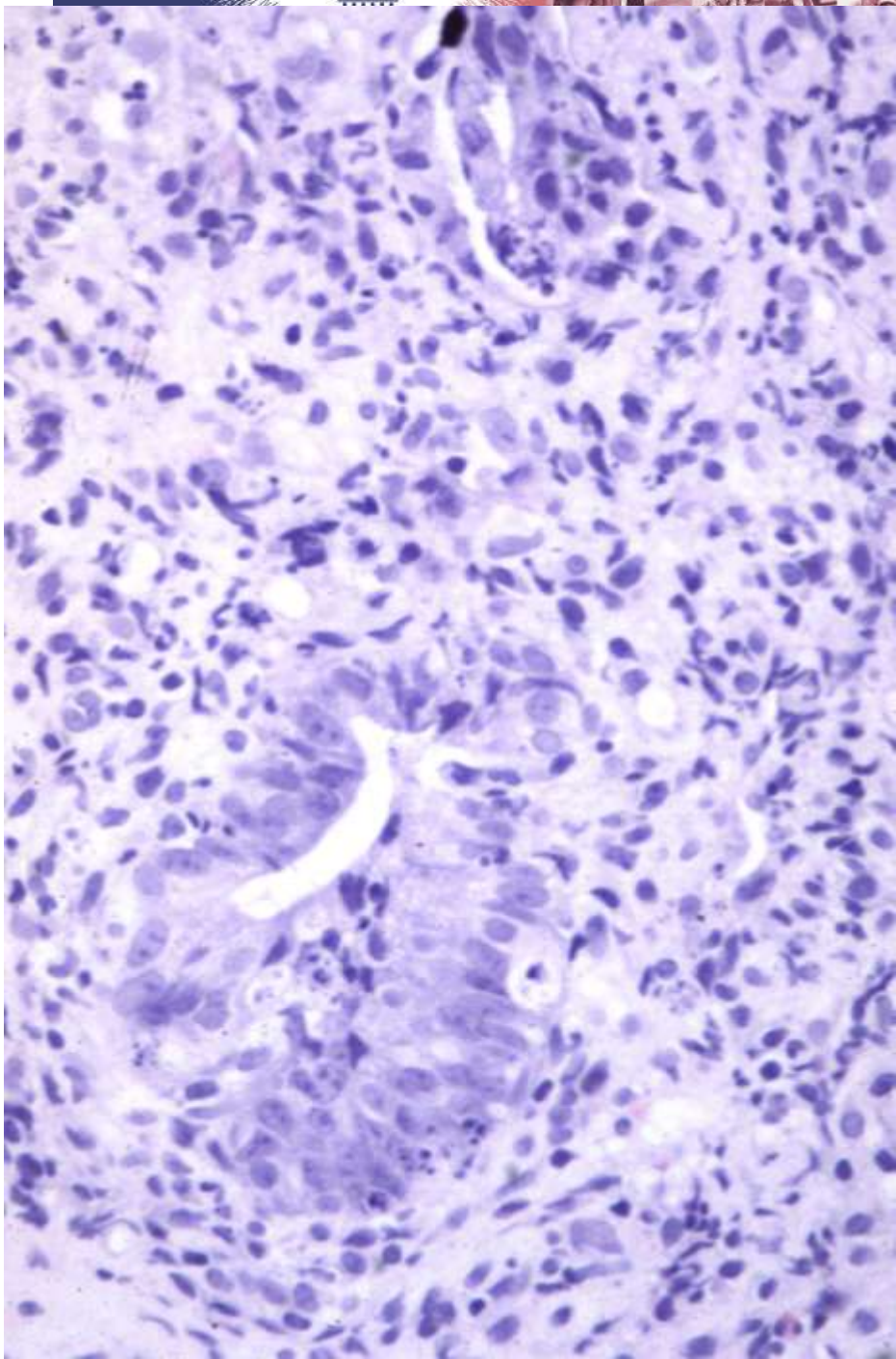
Ileum 24h: destruction of villi, ↓ crypts

Kolli et al. Arch Toxicol 82:763-70; 2008

Acute Graft-Versus-Host Disease

- Complication of bone marrow Tx
- Donor CD8+ T cells attack host epithelial cells $\rightarrow$
  - apoptotic epithelial cells
  - lymphocytes infiltrating epithelium, villlous atrophy, crypt destruction
  - surface erosions, ulcerations





Mucosal changes following surgery

- Diversion
- Ileostomy
- Continence restoration
- Ileo-anal anastomosis with ileal reservoir (pouch)
- (Transplantation)

Diversion colitis

- In normal diverted bowel
- In IBD, U.C. and CD
- In pelvic ileal reservoir and diversion pouchitis
- Histology: cryptitis, crypt abscesses, diffuse inflamed mucosa, basal granulomas may occur. Cave: CD!
- Histological lesions very soon after defunctioning

Diversion colitis in pelvic reservoir, diversion pouchitis

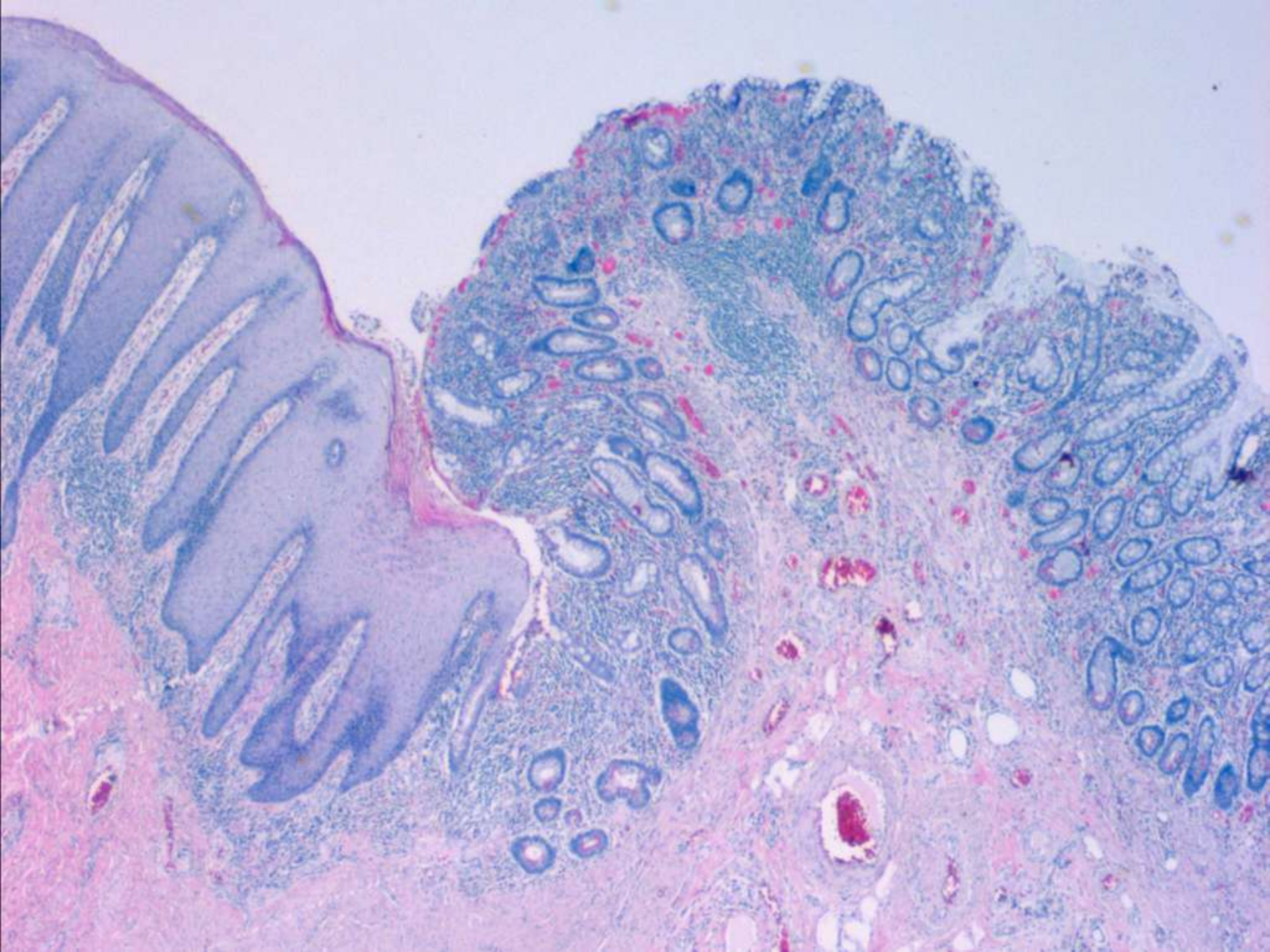
- Pouchitis: diarrhoea, discharge, fever, resembles acute UC histologically
- Cause unknown
- Pouch responds to faecal diversion like the rectum: pronounced lymphoid hyperplasia and superficial erosions

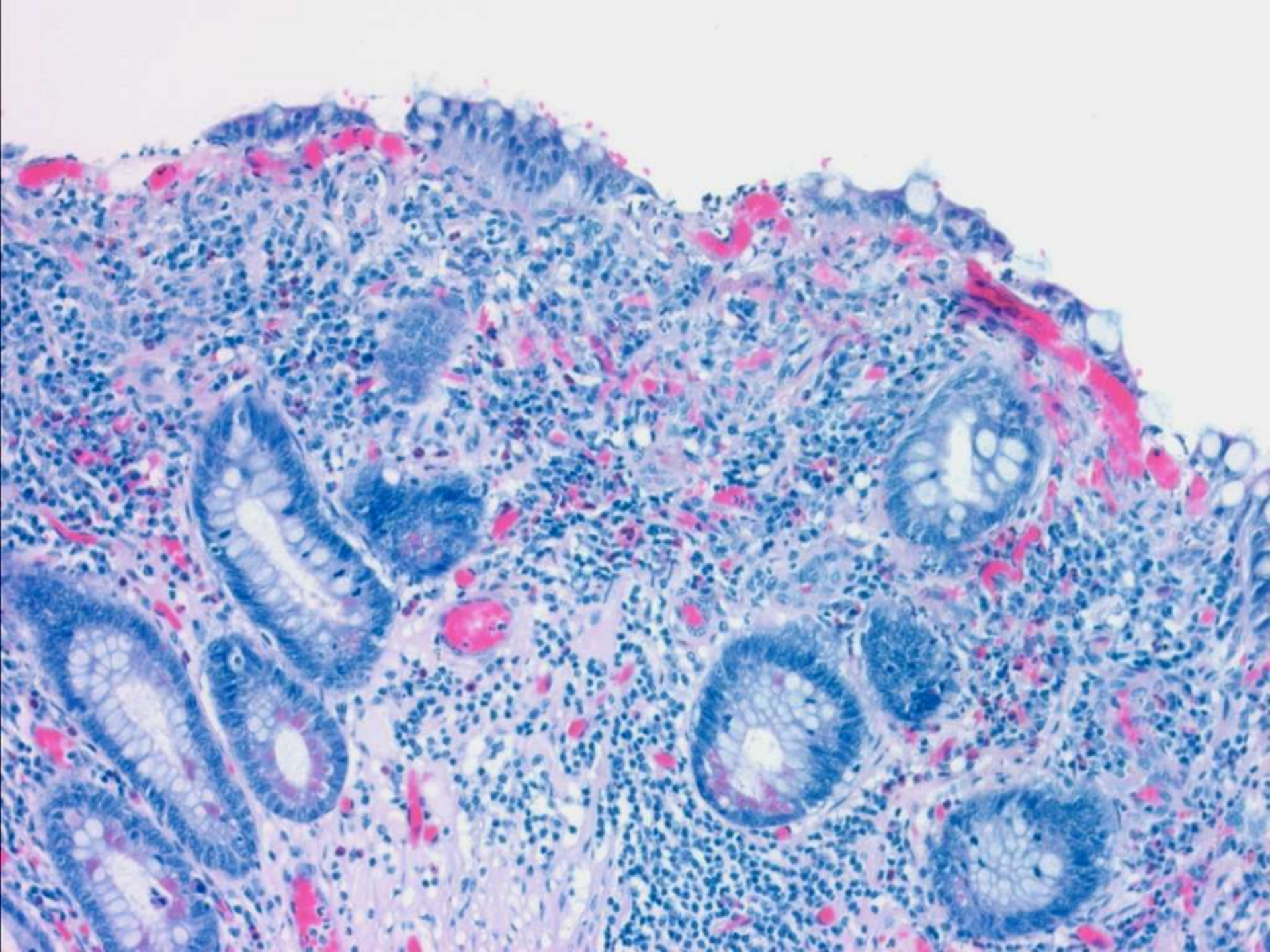
Pathogenesis

- Harig et al. (N Engl J Med 1989): absence of bacterial fermentation-producing short chain fatty acids (butyric acid)
- Local supply of short chain fatty acids results in endoscopic and histologic improvement

Ileostomy

- Mechanical and ischaemic aetiology of lesions
- Superficial erosions, villous atrophy
- Ulcerations may occur
- Mucosal prolapse, increase of fibromuscular cells
- Obstructive ileitis
- Dysplasia and carcinoma (rare)



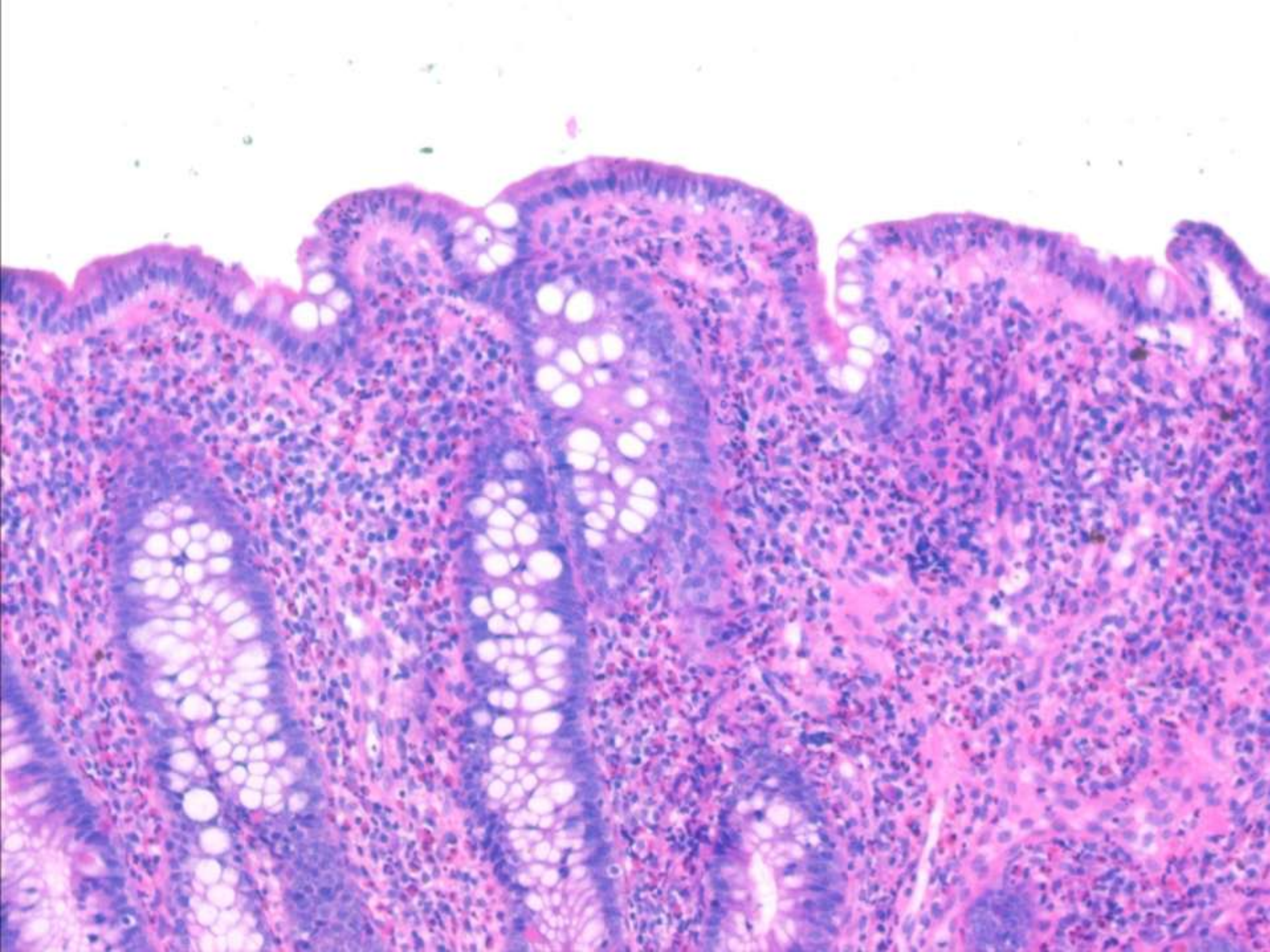


Pouchitis

- In U.C., FAP, total colectomy
- To be restricted to chronic relapsing inflammatory condition with
  clinical: pain, ↑ stool, urgency, discharge, fever, other systemic effects
  endoscopical: ↑ vascularity, contact bleeding, ulceration
  histological: active inflammation, ulceration

Pouchitis

- May be patchy, most in posterior and inferior part of pouch
- Chronic active inflammation, ulceration, villous atrophy ~ c.u.c.
- Evidence that pouchitis is mostly resurgent u.c.



Drug-induced pathology

- NSAID enteropathy: most occurring type
- Enteric-coated K^+ supplements e.a. can cause ulceration, erosion
- Eosinophilic enteritis occasionally in RA patients: ulceration, eosinophils, chronic inflammation, crypt abscesses

NSAID enteropathy

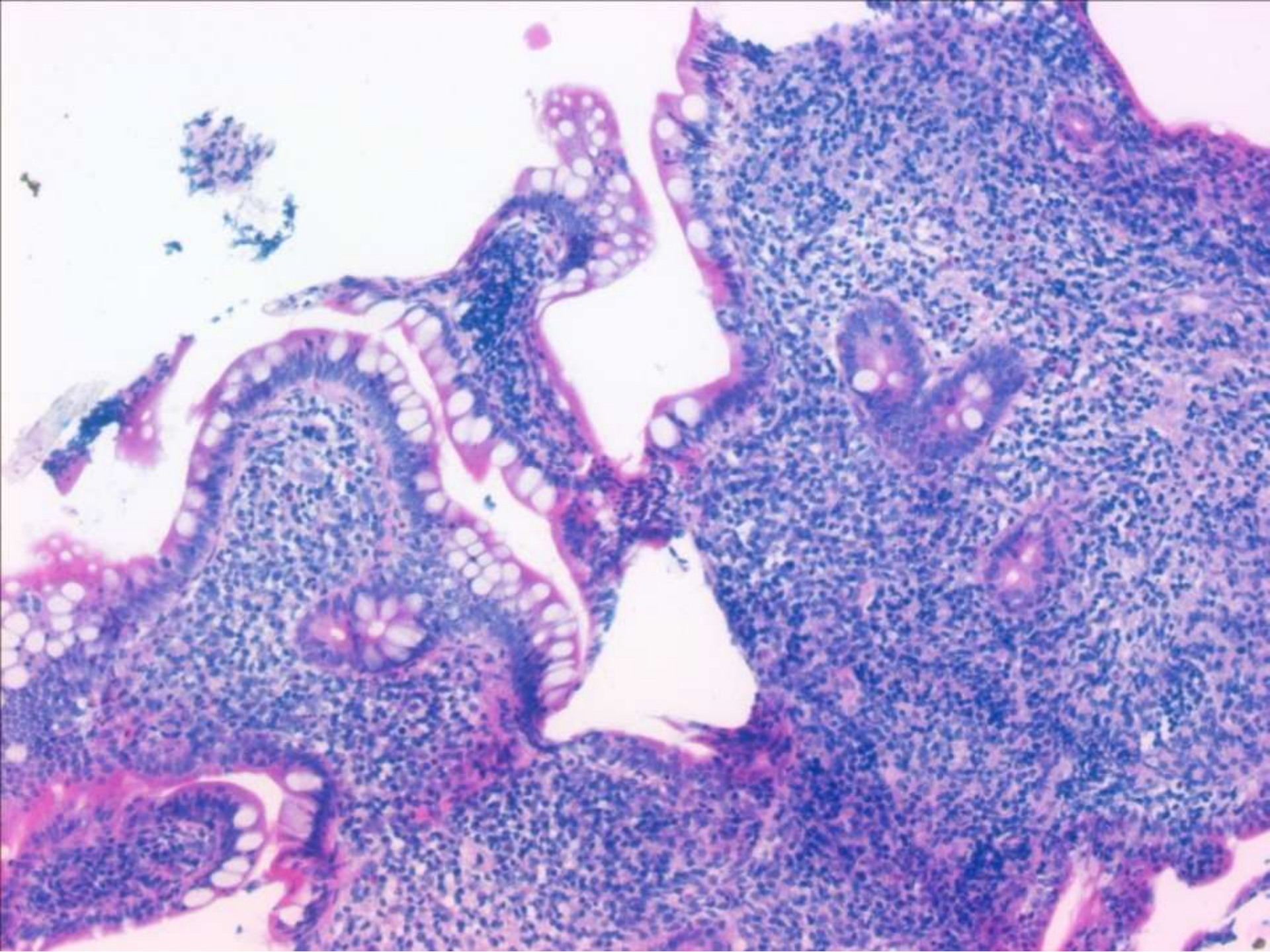
- More common in small intestine than in stomach
- Not life-threatening but complications need to be investigated
- To be distinguished from Crohn's disease (CD) and spondyloarthropathy related (SpA) ileitis

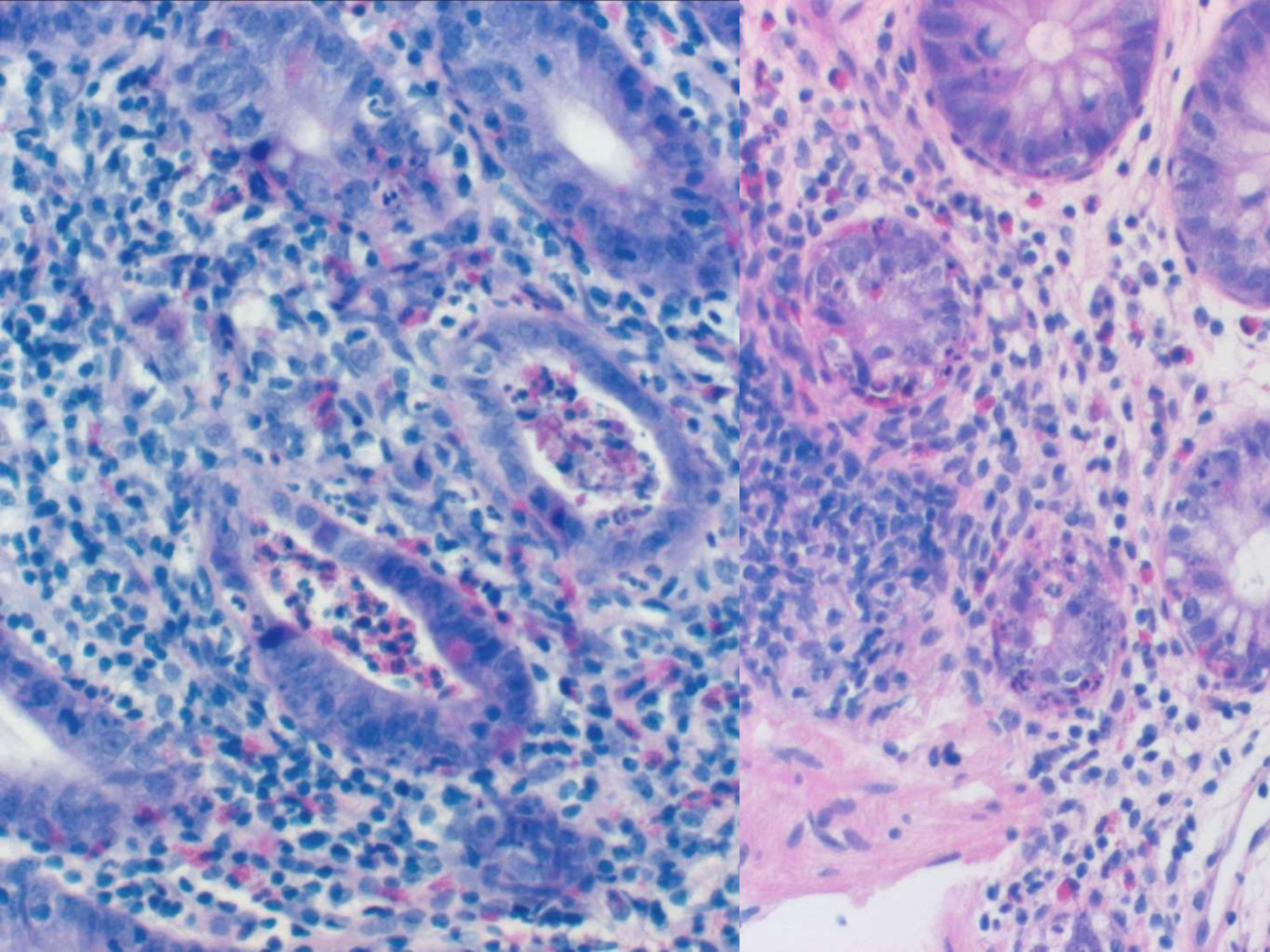
NSAID enteropathy: definition

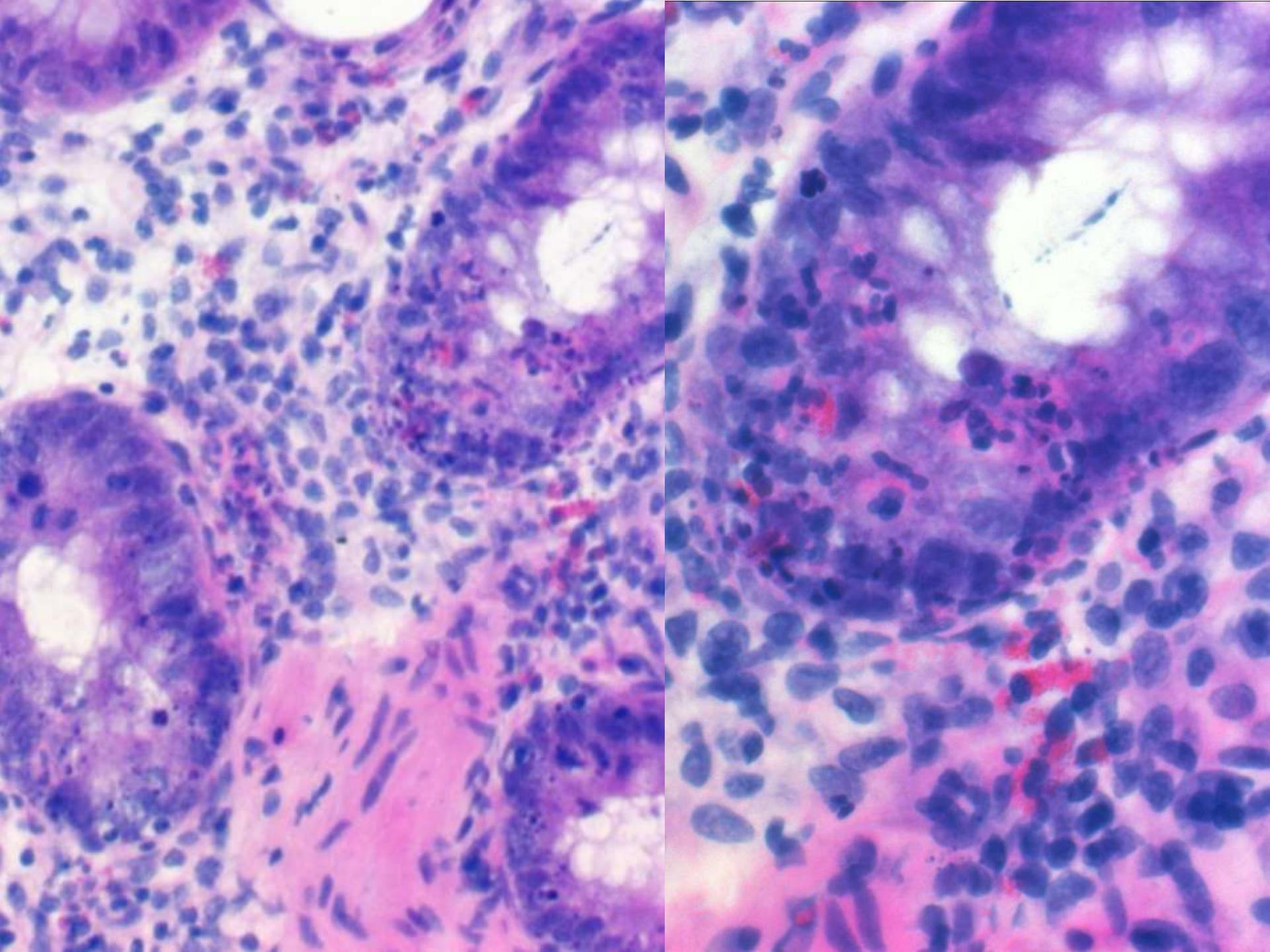
- Underdiagnosed entity!
  - Randall (Clin Gastroent Hepatol 2003): 33/40 ulcerative ileitis due to NSAID
- Symptoms absent, mild, non-specific, ignored by many clinicians
- Clinical difficulties in documenting small intestinal pathology
- Overlap with CD

NSAID enteropathy: diagnosis

- Approach: inflammatory markers in stools, enteroscopy, surgery, post-mortem (highest prevalence using faecal markers)
- Mucosal haemorrhagic blebs (in 20-40%), discrete small intestinal ulcers at endoscopy (in > 40%)
- Biopsy confirmation



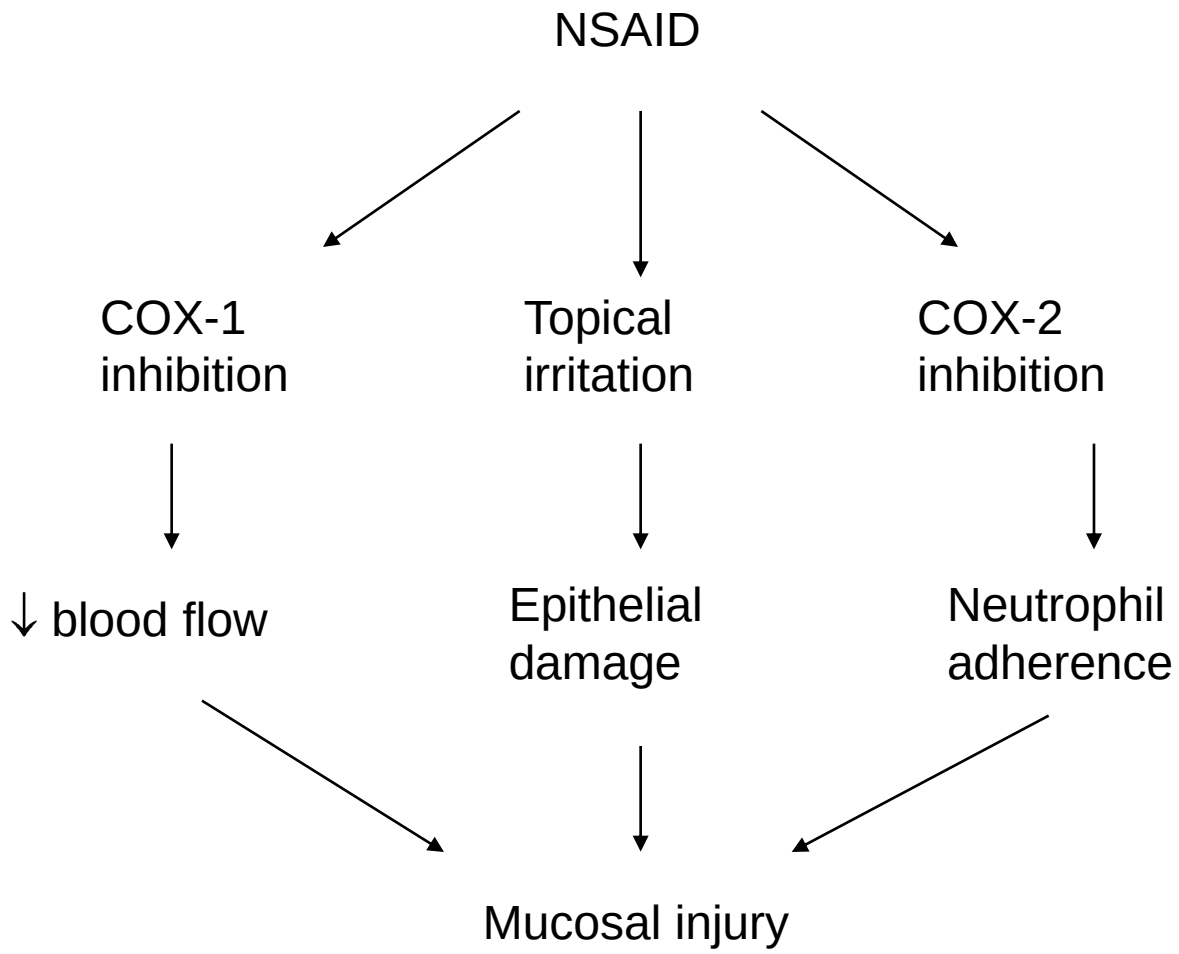




NSAID enteropathy: pathogenesis

- Anti-inflammatory effects: inhibition of prostaglandin (PG) synthesis
- PG synthesis via cyclo-oxygenase (COX-1, predominant form in GI tract; and COX-2, rapidly upregulated in response to various stimuli)
- COX-2 inhibition → impairment of healing and angiogenesis

NSAID enteropathy: pathogenesis



After *JL Wallace*

NSAID enteropathy: complications

- Bleeding may → iron deficiency anaemia
- Protein loss → hypoalbuminaenia
- Ileal dysfunction similar to ileal CD
- Small intestinal ulcers: asymptomatic in >25% of patients on NSAIDs
  - may be associated with perforation, obstruction
  - can be found at severe bleeding
- Strictures in small intestine, diaphragm disease

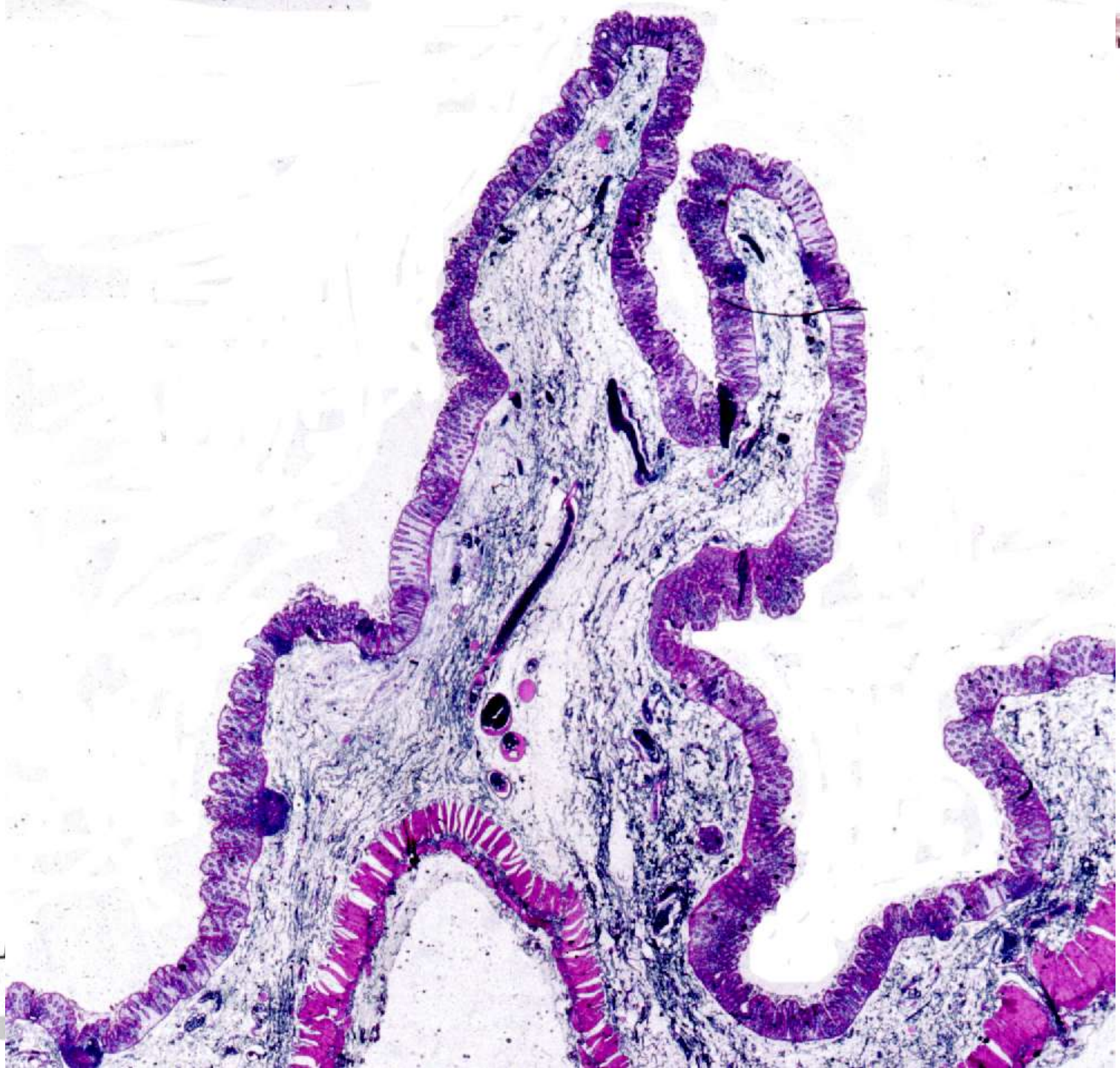
NSAID enteropathy: complications

- Diaphragm disease:
  - web-like septa narrowing the lumen
  - septal fibrosis in submucosa
  - intermingled with muscularis mucosae
  - mild villous blunting, superficial erosions

- Dd: CD, TBC, ischaemia, coeliac disease, lymphoma e.a.

Diaphragm disease

I. Bjarnason, *Gastroenterol 1993*



Dd. NSAID enteropathy, SpA, CD

	NSAIDs	SpA ileitis	Crohn's D
Dis location Males	Mid small int Not sex related	Ileitis 90%	Ileitis e.a. 60%
Symptoms Ileal histol.	Asymptom. Normal	Asymptom. CD-like	Symptom. CD features
NSAIDs effect on symptoms	Yes	No	May cause relapse

Sodium Polystyrene Sulfonate (Kayexalate) induced G-I tract necrosis

- Specific morphologic features of kayexalate!
  - Rhomboid, triangular, non-polarizable crystals
  - Basophilic crystals form mosaic pattern
  - Adherent to surface epithelium or within sloughed inflammatory exudates
  - Red with PAS and acid fast stain

Kayexalate

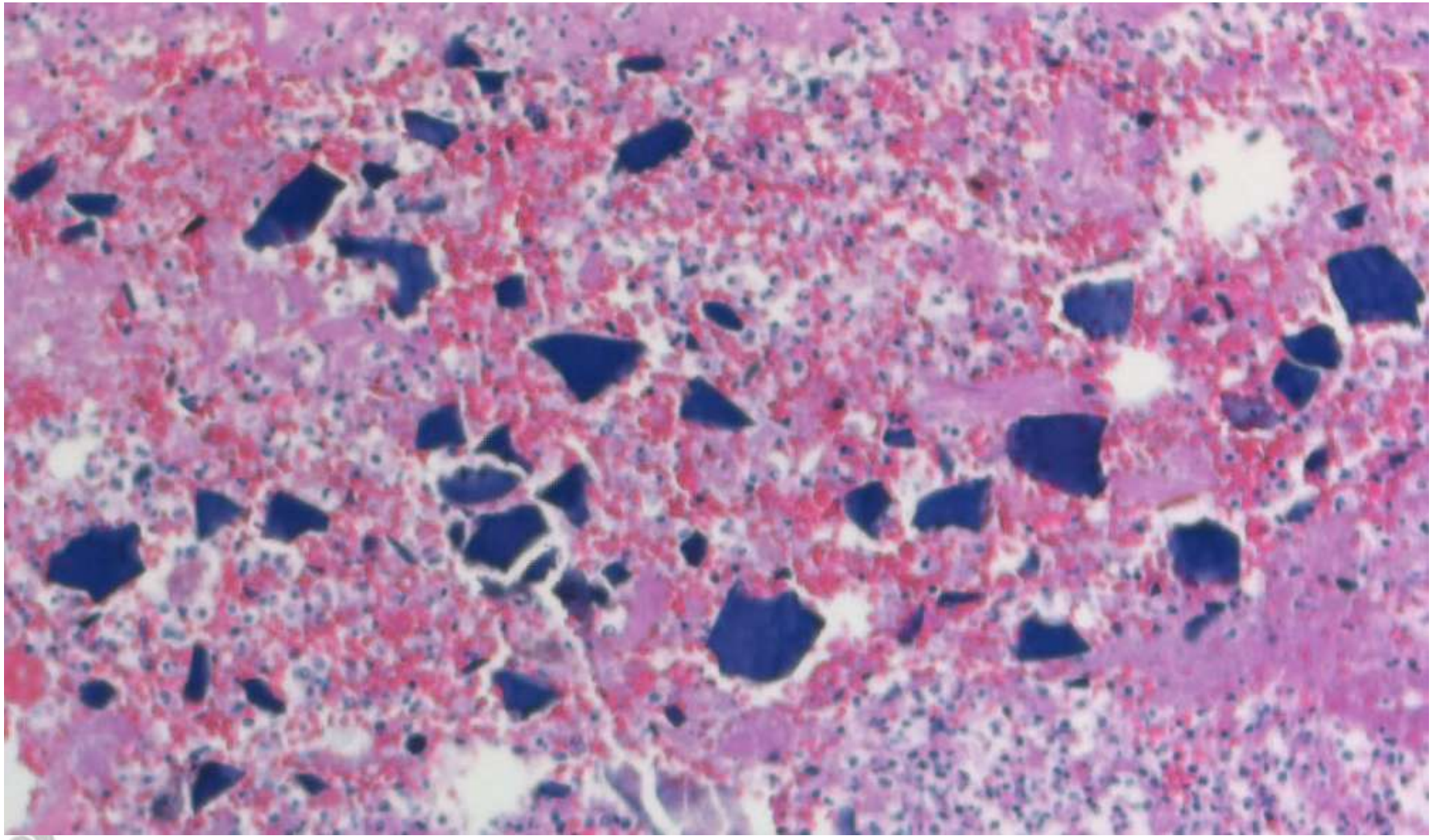
- Cation exchanging resin, given to patients with hyperkalaemia
- Binds and excretes sodium ions for potassium in large intestine, administered **topically** with sorbitol, an osmotic laxative
- **Orally** administered releases sodium ions in the stomach, binds hydrogen ions, exchanges hydrogen for potassium in small and large intestine

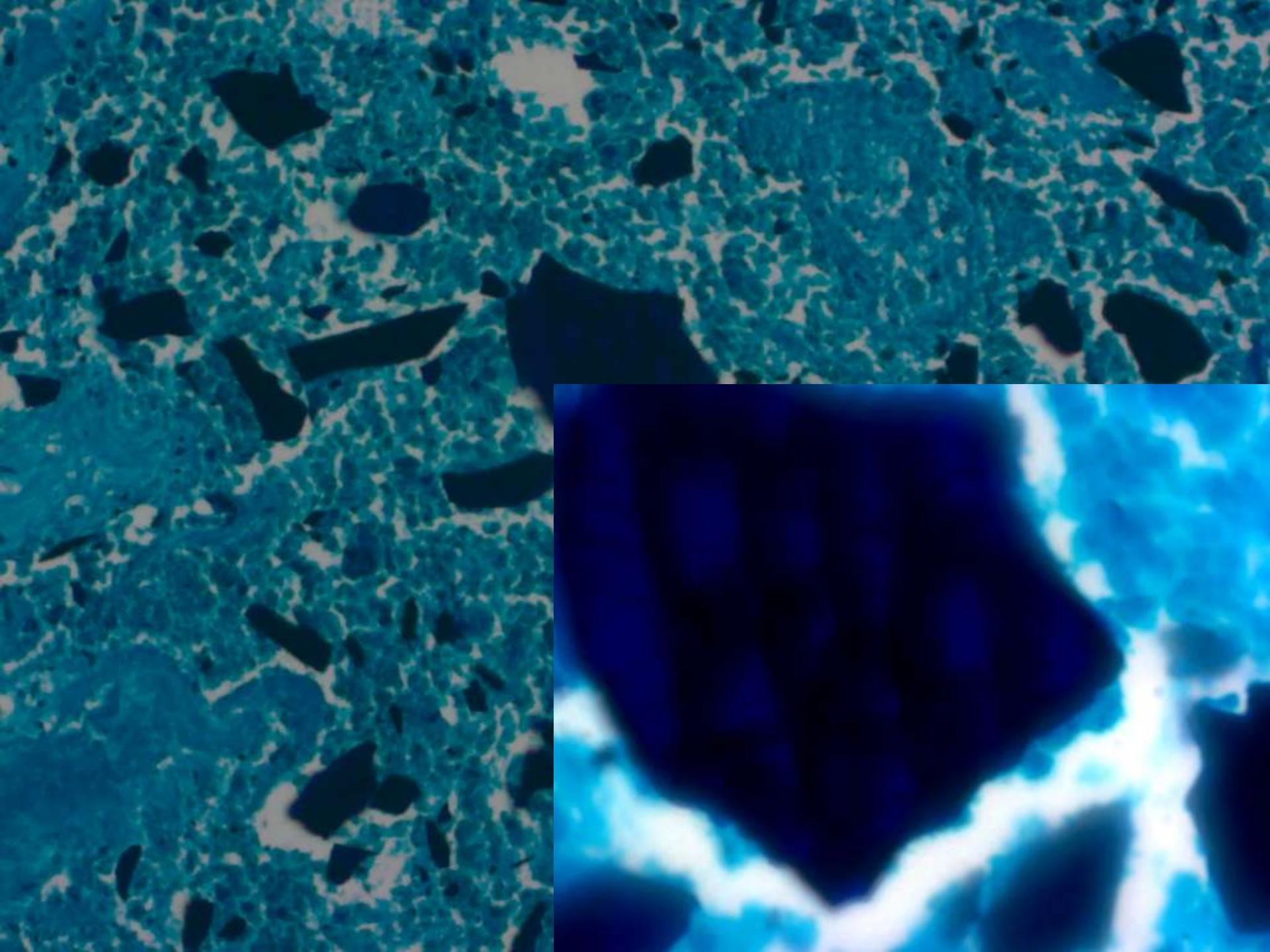
Pathogenesis

- Sorbitol induces ischaemic necrosis
- Uraemic patients are most susceptible to the vascular shunting induced by the osmotic load and vascular instability
- Hyperosmotic load may directly damage mucosa, cause vasospasm of intestinal vasculature, exacerbate inflammation through elevated PG levels

Sodium Polystyrene Sulfonate (Kayexalate) induced necrosis

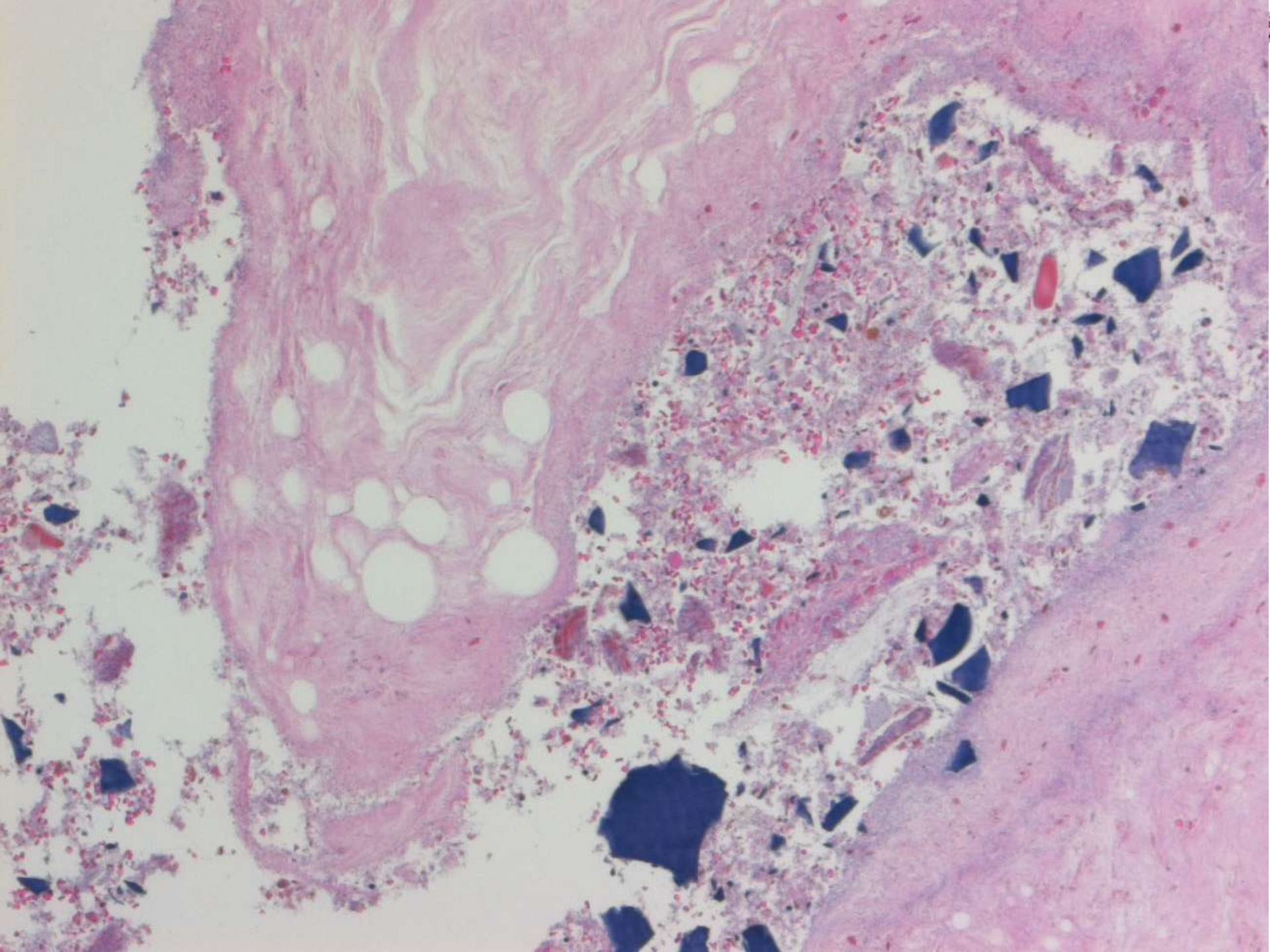
- Differential diagnosis
  - **Cholestyramine**,
    - bile acid binding resin sometimes used in treatment of *C. difficile* colitis,
    - **lacks mosaic pattern** and **pink** stain on acid fast stain

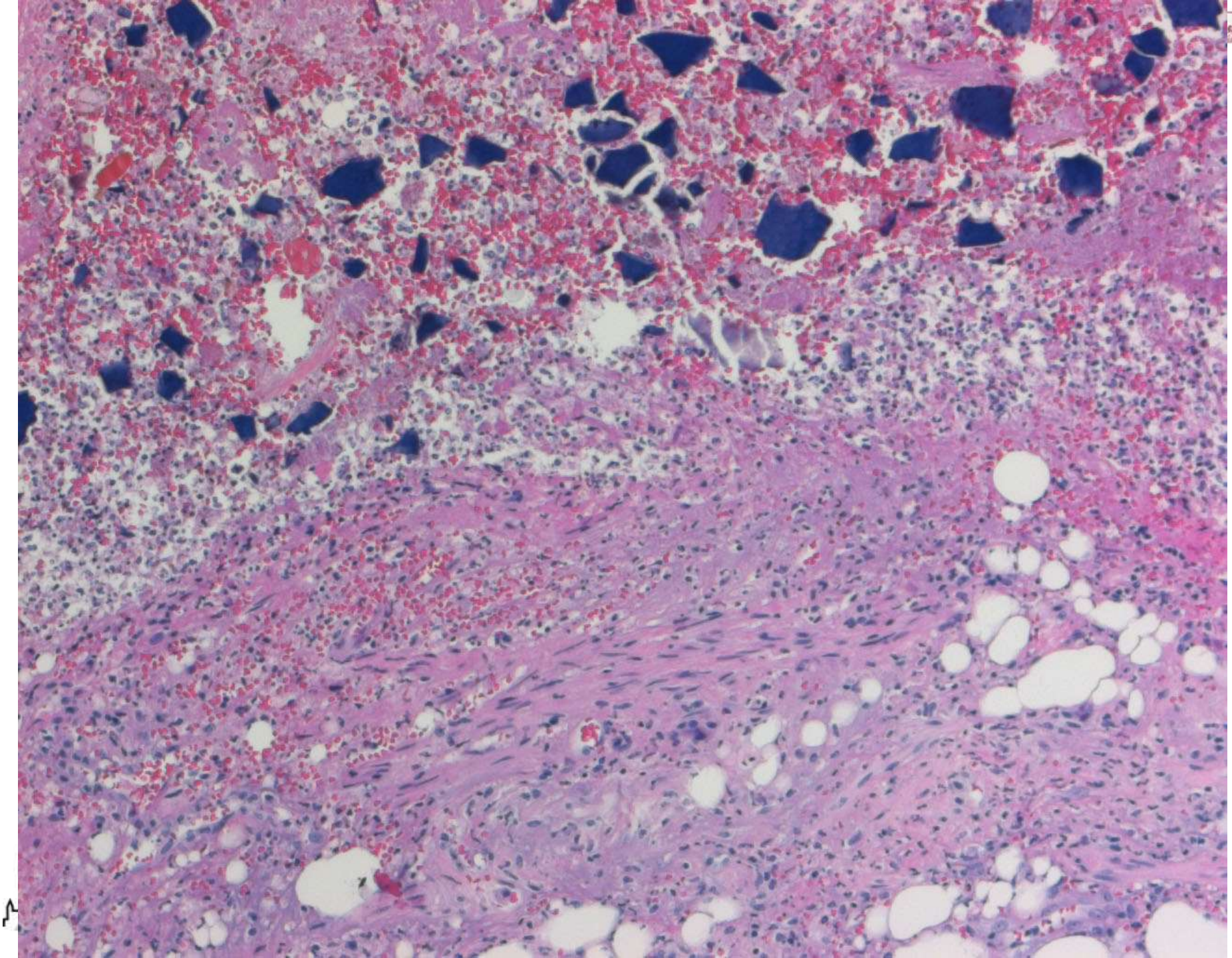




Kayexalate induced pathology in G-I tract

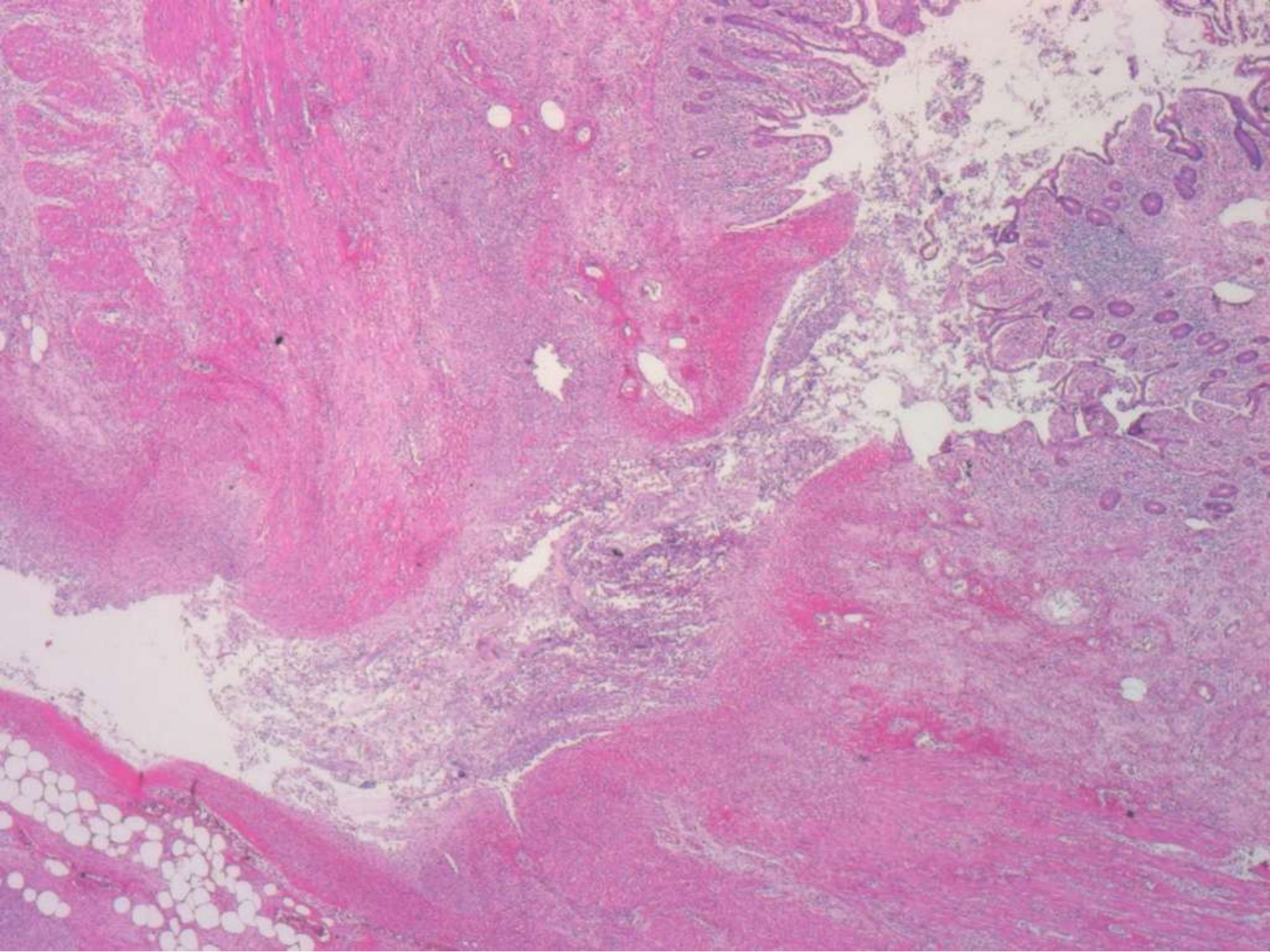
- Ulcers and erosions in oesophagus, stomach, small intestine (reversible, no serious sequelae)
- Ischaemic colitis
- Perforating appendicitis
- Enema more hazardous than oral preparations

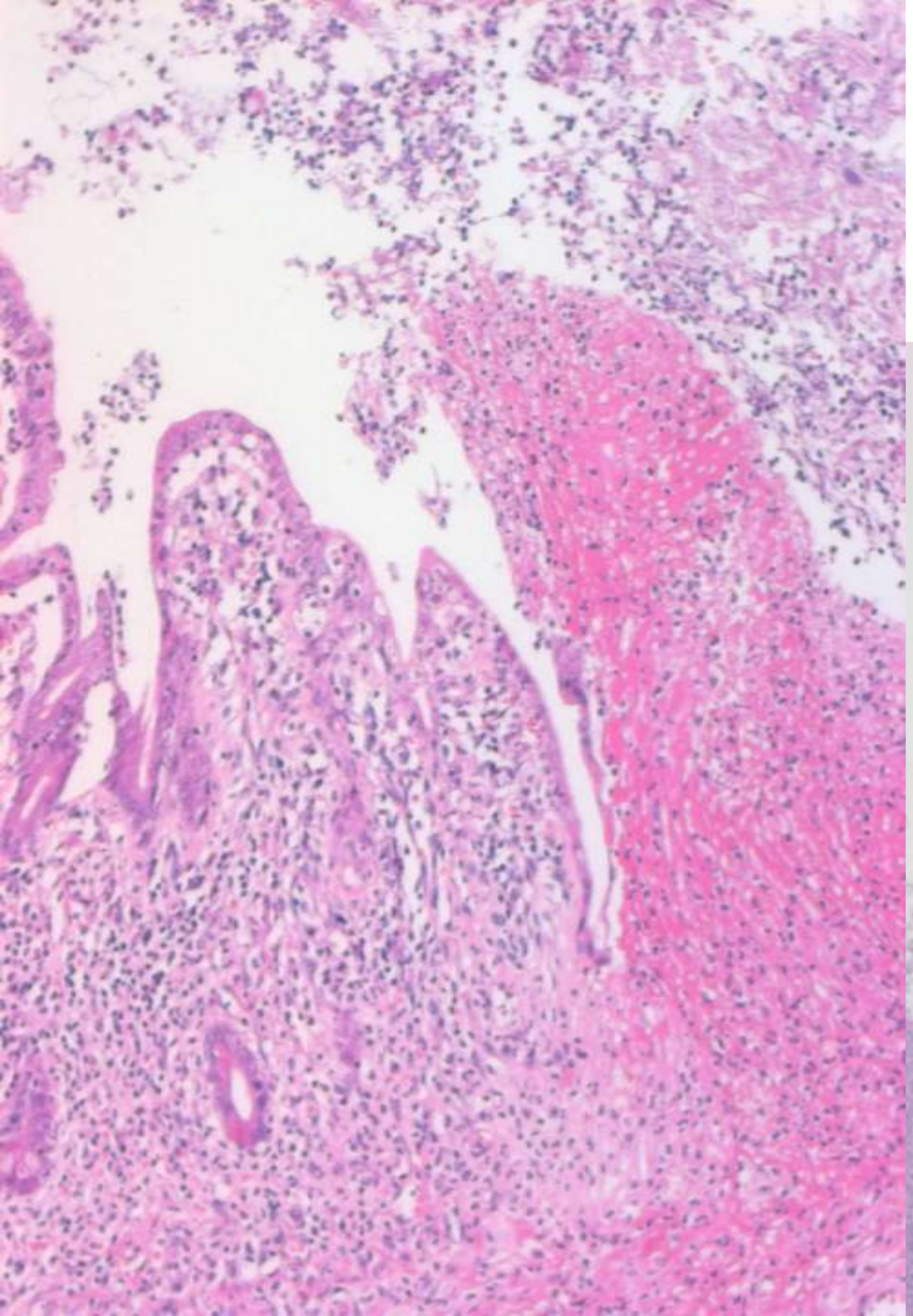




Bizarre “drugs”

- Confused 86-y-old lady
- Small intestinal ulcers





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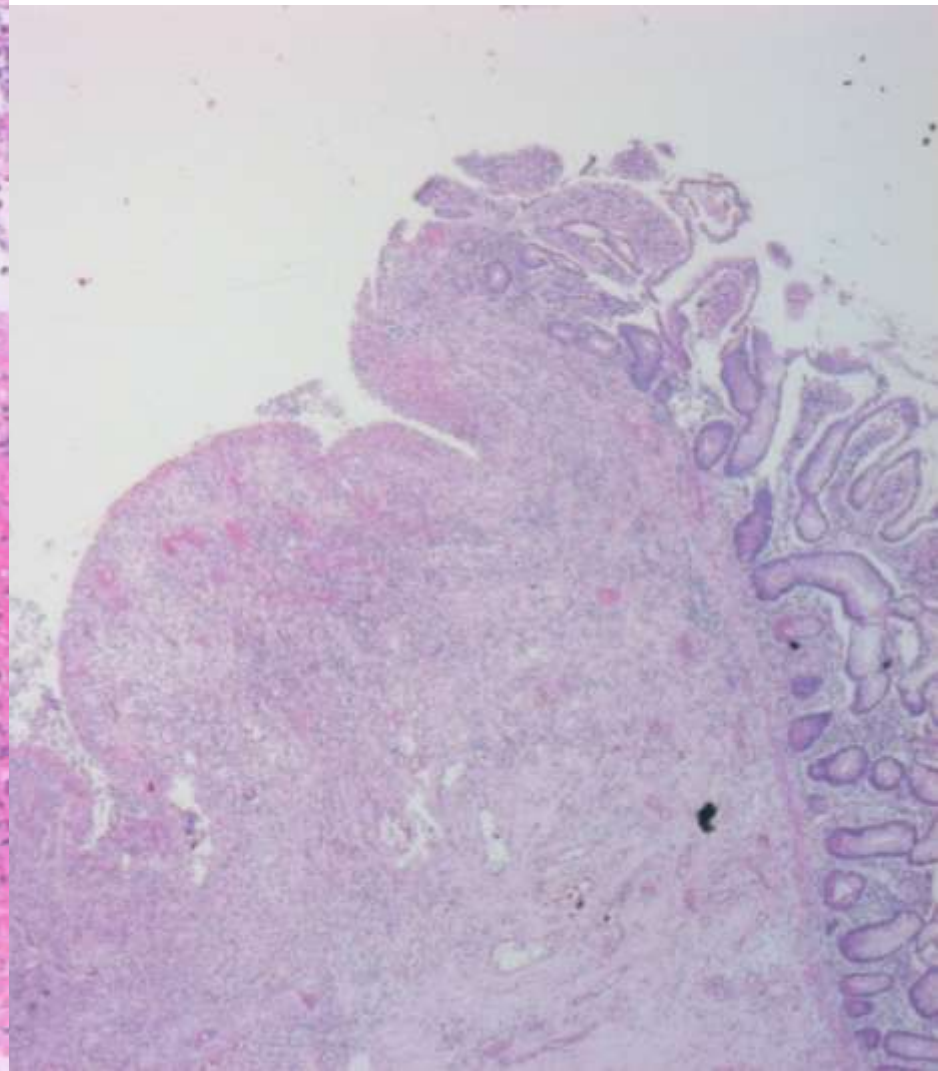

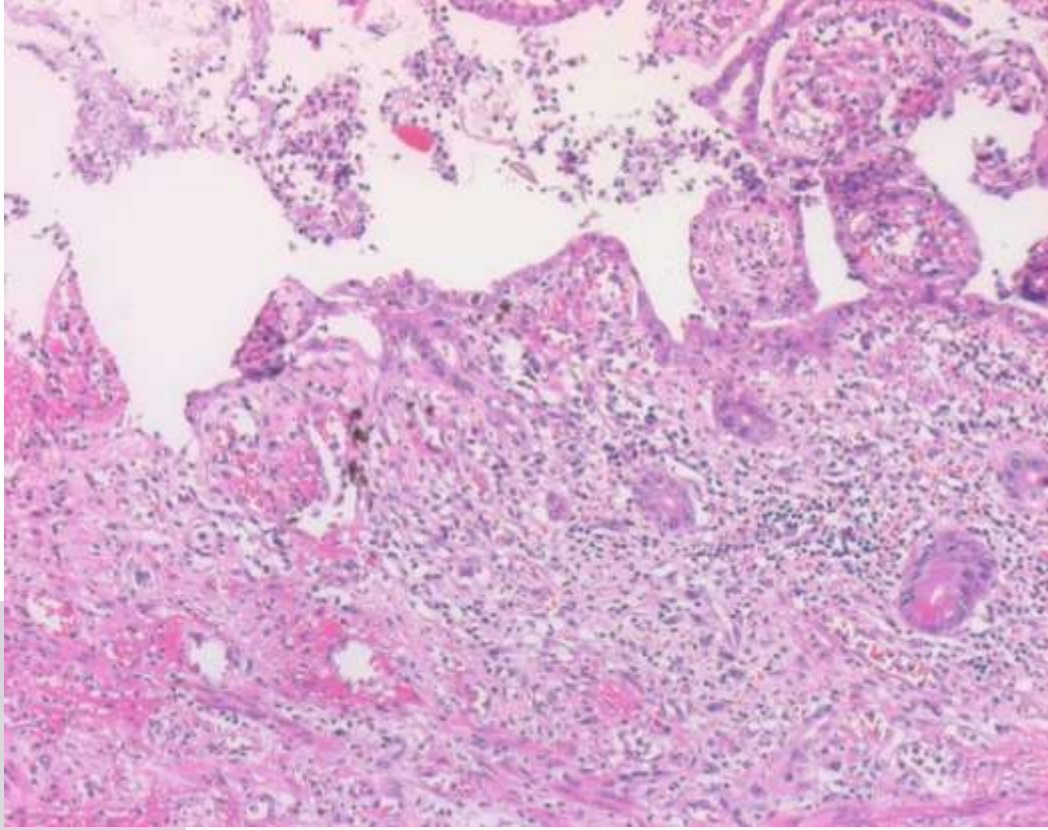

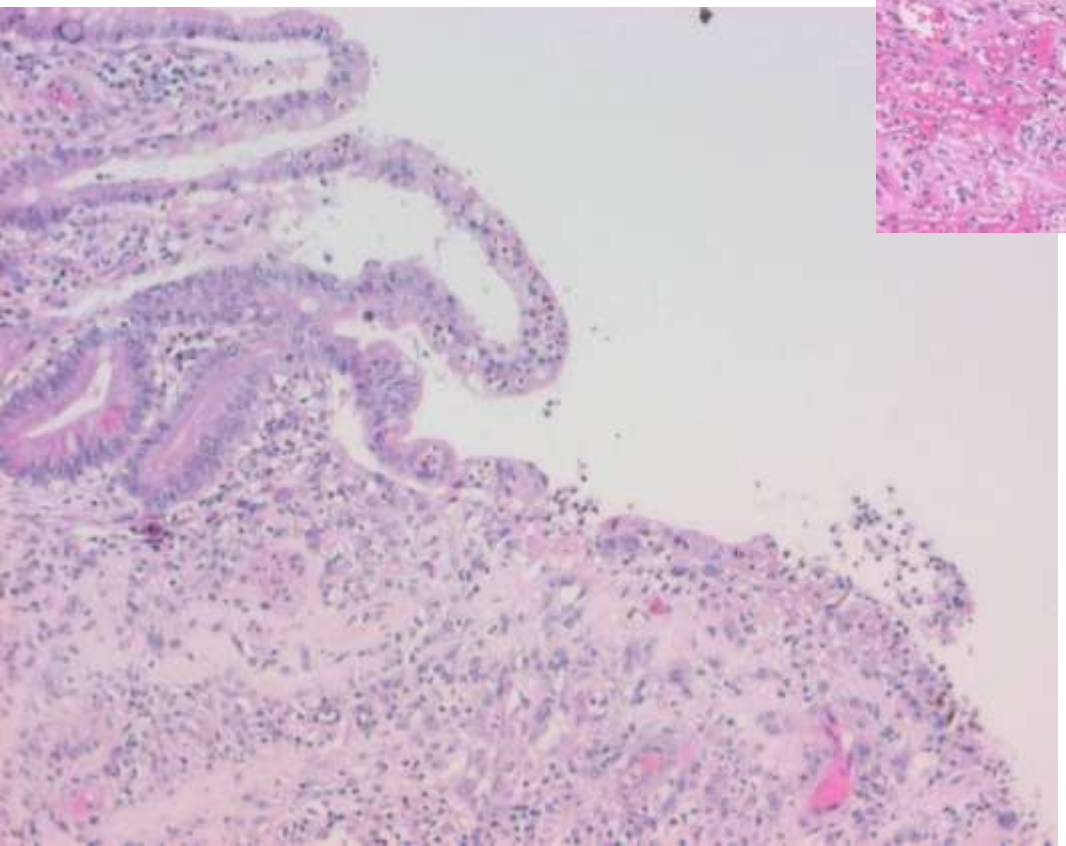

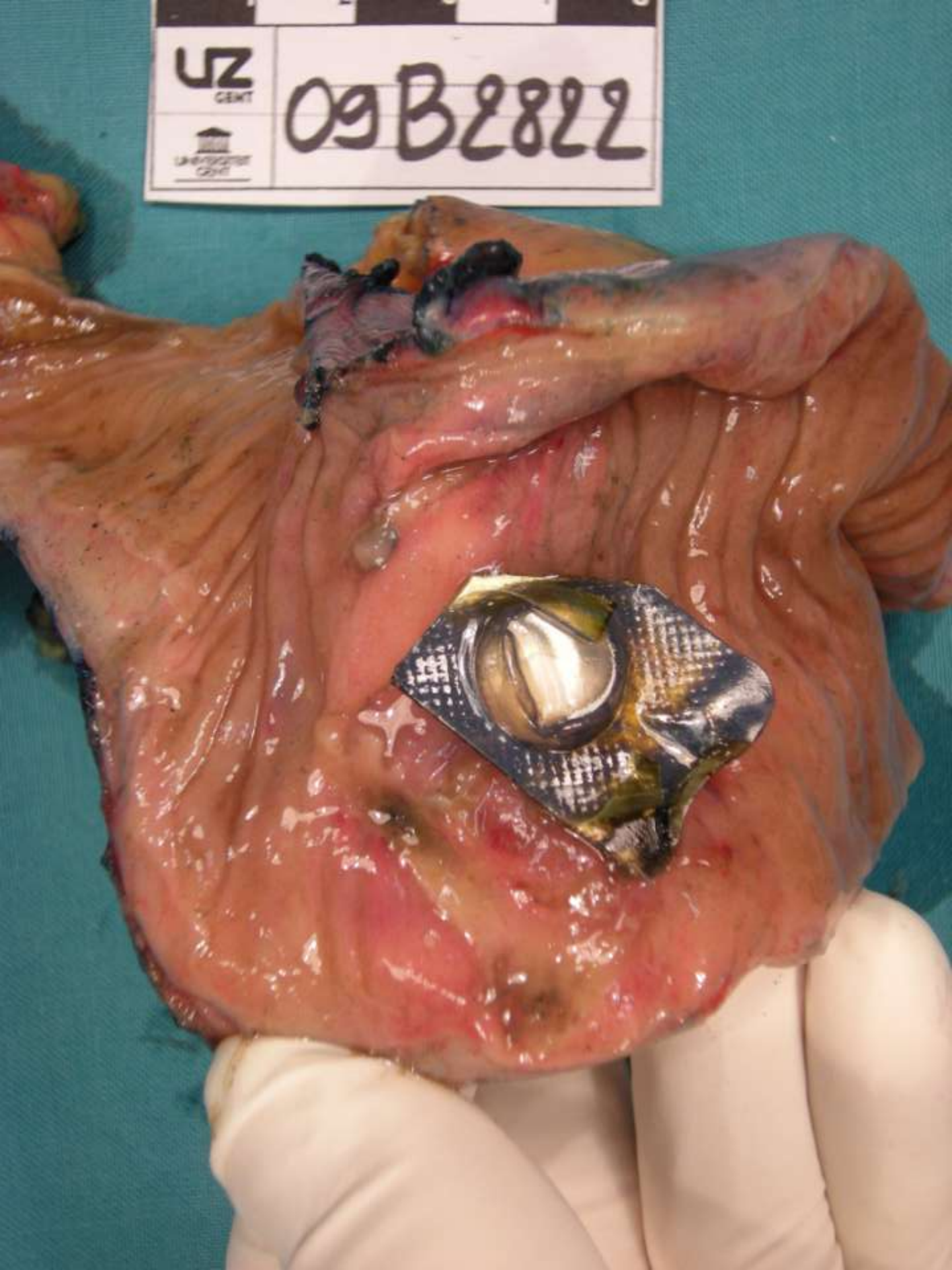
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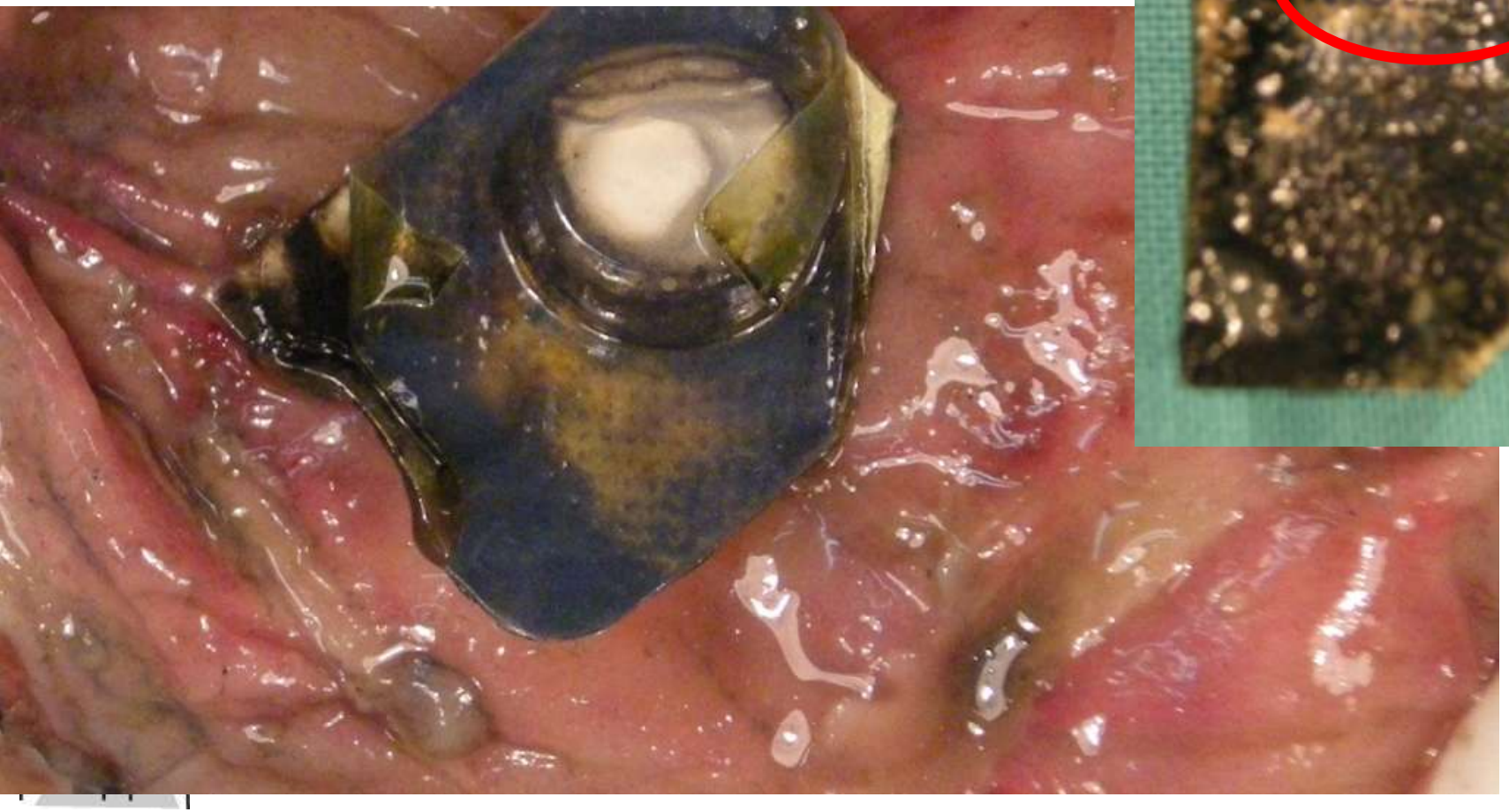

General conclusions

- If small intestinal ulceration is present consider
  - Crohn's disease
  - iatrogenic causes
  - acute infections
  - SpA
- Knowledge of clinical context helps
- NSAID-induced ileal ulcers very common

Conclusions

- Examination of biopsies may help in
  - Evaluation of small intestinal inflammatory processes
  - Elucidation of IBD
- Wide spectrum of inflammatory and infectious diseases and
- Miscellaneous diseases - including iatrogenic and drug induced - can be diagnosed