THE PATHOLOGY AND SIGNIFICANCE OF ILEITIS

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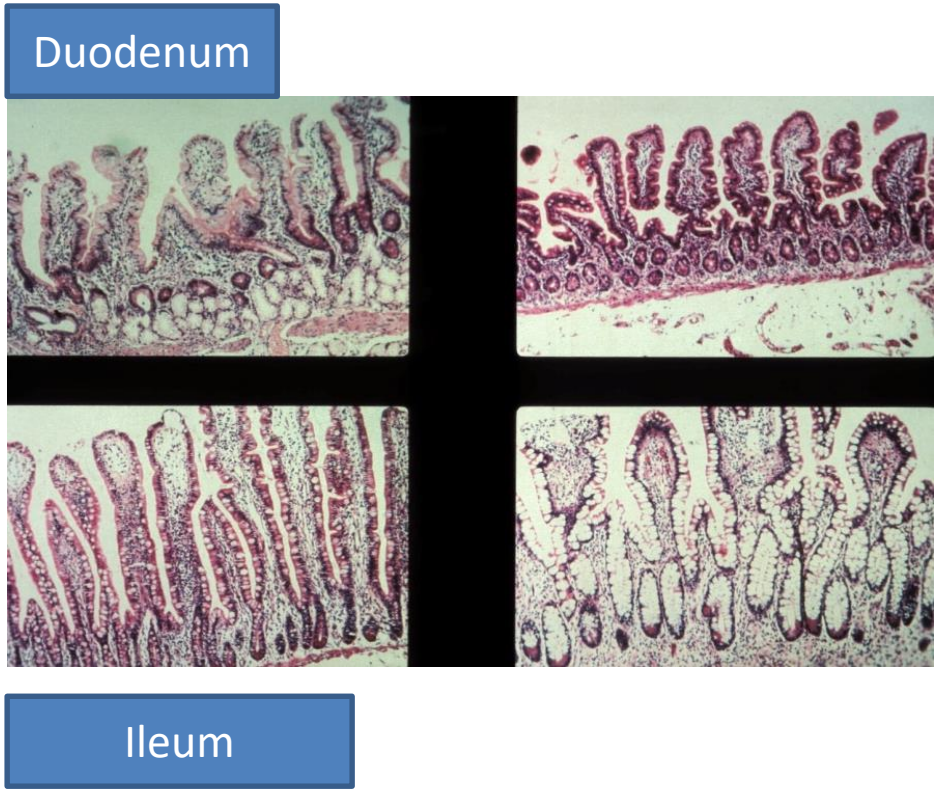
Normal small intestine Variations

- The ileum constitutes 2/5ths of the small intestine
- **The wall** is thinner
- **Mesenteric fat** is abundant
- More vascular loops
- More **Goblet** cells
- Adult ileal mucosal **stem cells** might be different from stem cells in other areas, for instance by inducing bile acid uptake and expression of the IBAT protein (Middendorp e.a. Stem cells 2014)
- **Lymphoid tissue**
- **Small intestinal tissue macrophages are different from those in the colon**

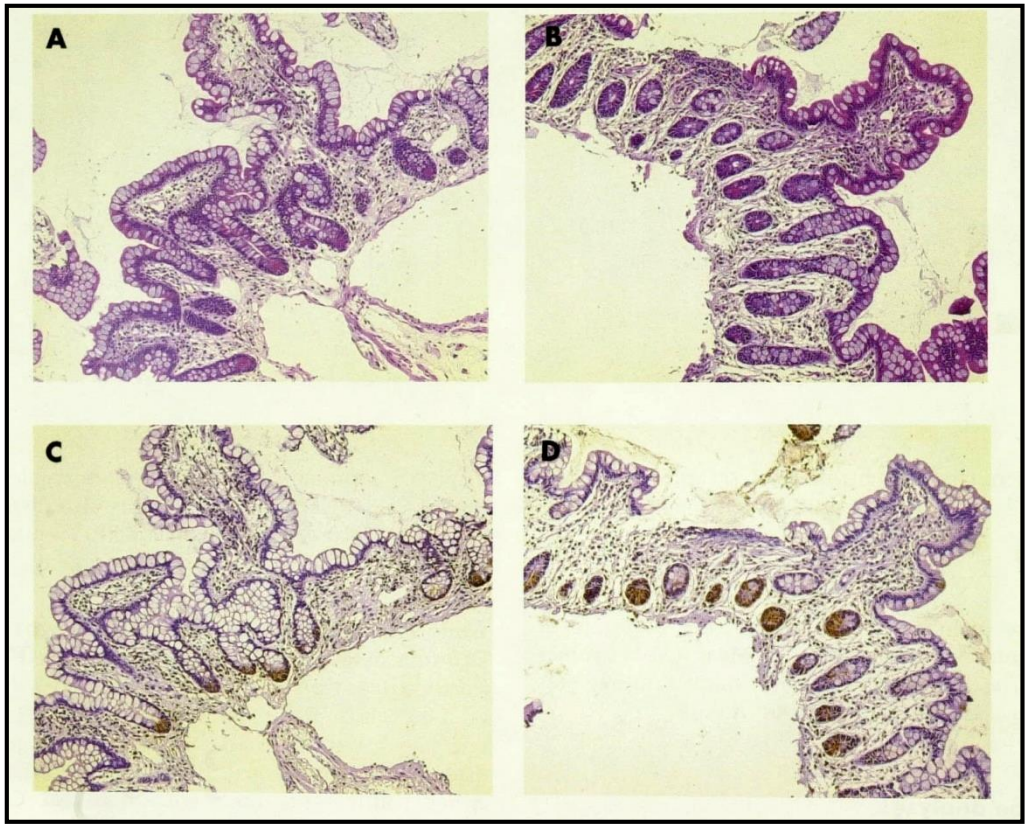


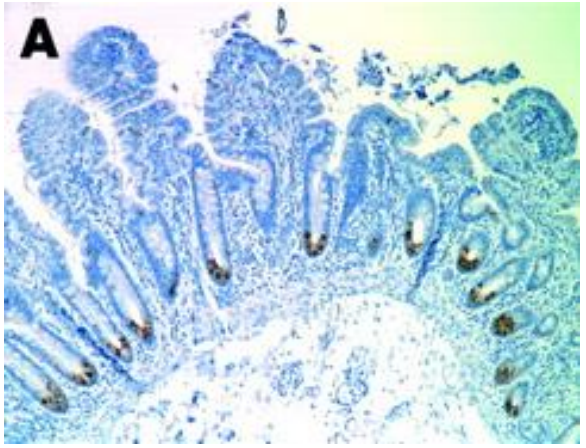
Defensin5 expression in ileum

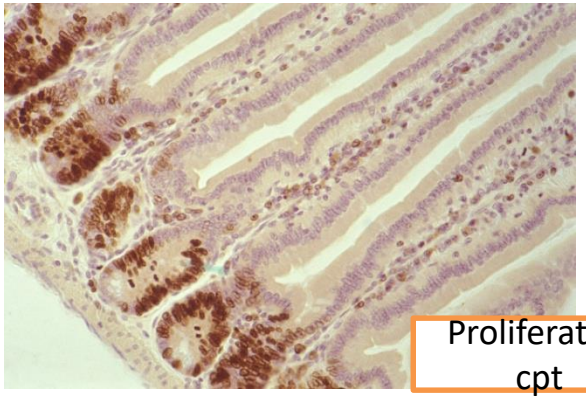
Decreased expression of human defensins 5 & 6 in ileum in CD

Wehkamp et al Gut 2004; 53: 1658

NOD2 expression in Paneth cells Gastroenterology 2003







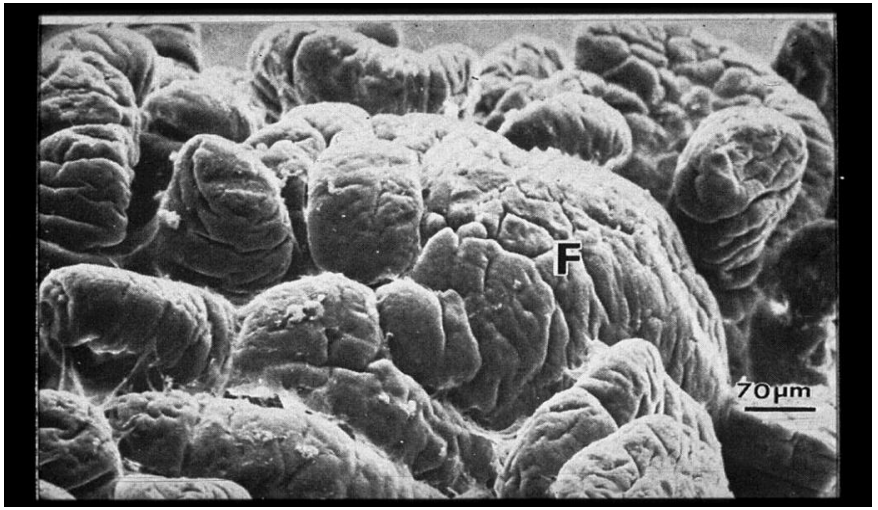
Proliferative cpt

Peyer's patches (lympho-epithelial complexes)
Normal structure

First description **1677**

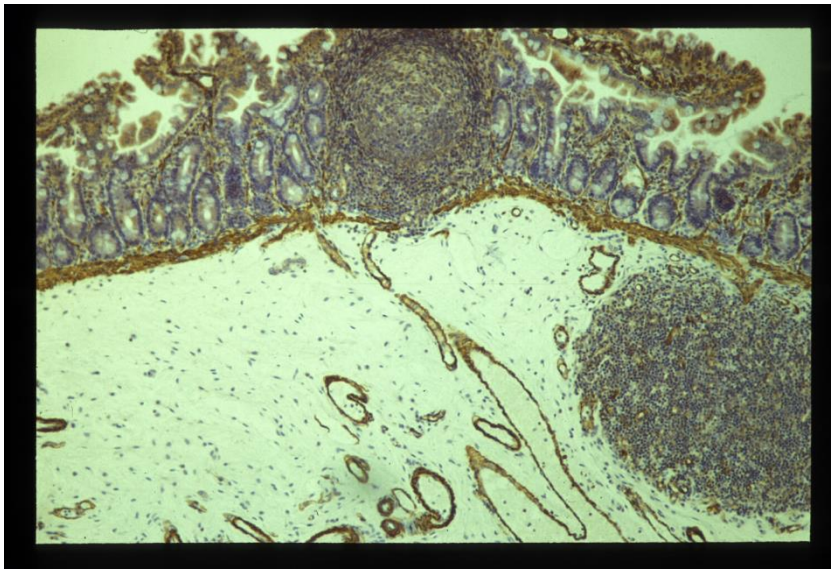
Diffusely present along the small intestine: antimesenteric

Numbers
-24 weeks : +/-45
-20 year : +/- 200
-95 year : +/- 100



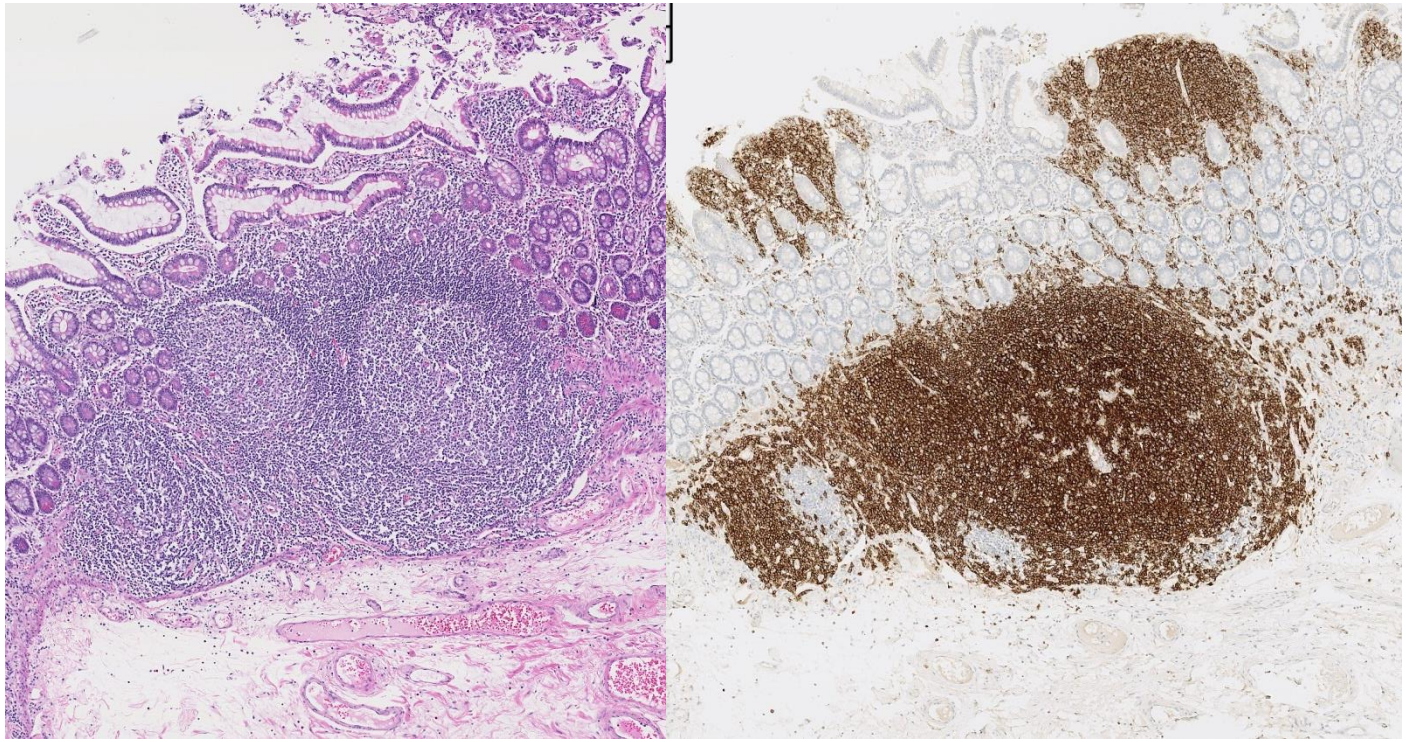
-Composition
Epithelial cells
- M cells
- FAE cells

Lymphoid components
- Subepithelial mixed zone
- Follicles



NODULAR LYMPHOID HYPERPLASIA

Common in children and adolescents



Ileitis : IBD or not?

- **Indications for biopsy : overview of historical and recent studies**

Clinical situations

Isolated ileitis

Lesions of colon and ileum

-**The challenge of isolated ileitis**
- **Histopathological features for the diagnosis of Crohn's disease**
- **Backwash ileitis**
- **Other causes of ileitis : differential diagnostic issues**
- **Miscellaneous**

Studies concerning biopsies of terminal ileum
History (1984-1995)

The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn's disease

G. Coremans, MD
P. Rutgeerts, MD
K. Geboes, MD
J. Van den Oord, MD
E. Ponette, MD
G. Vantrappen, MD
Leuven, Belgium

- Endoscopy of the terminal ileum :

– Successful	72 %	400 / 555
– Not successful	8 %	42
– Not tried	11 %	63
– Inadequate cleaning	9 %	50

- Ileoscopy valuable findings :

	29.5 %	118 / 400
abnormal :	5 %	

- In neoplastic diseases the diagnostic yiel
  unrewarding

(Börsch, Schmidt. Dis Col Rect. 1985)

- n = 2324 consecutive ileocolonoscopies
- n = 1648 (> 70 %) normal

Cuvelier, De Vos Acta Gastroenterol, 1995

Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of IBD?

Geboes e.a. Am J Gastroenterol 1998; 93; 201

257 consecutive patients
with clinical signs / suspicion of IBD
in whom ileoscopy with biopsy was performed

- Chronic diarrhoea
- Acute diarrhoea
  - Severe
  - > 2 weeks
  - Blood loss + / -
  - Fever
  - Malaise
- Abdominal pain
- Abnormal ileal radiology

Crohn's disease	43 %	111
Ulcerative colitis	25 %	63
ASLC (infectious type)	12 %	30
Inflammation (unclassified)	12 %	30
Ischemic disease	4 %	10
Non-specific ulceration (Bauhin)	2 %	5
Neoplastic disease	1 %	3
Drug induced	1 %	2
Adhesions	1 %	2
Endometriosis	< 1 %	1

More recent studies

Asymptomatic ileitis, past present and future. Greaves ML, Pochapin M. J Clin Gastroenterol 2006; 40: 281

Etiologies of this phenomenon, include subclinical Crohn's disease, nonsteroidal anti-inflammatory drugs and spondylarthropaties

The diagnostic value of endoscopic terminal ileum biopsies. McHugh e.a. Am J Gastroenterol 2007; 102: 1084

- **Biopsy of endoscopically normal mucosa is unlikely to yield diagnostically useful information, and is not encouraged as routine.**
- **However, when "ileitis," ulcers, or erosions are identified, biopsies can be very helpful.**

Ileitis when it is not Crohn's disease. Dilauro e.a. Curr Gastroenterol Rep 2010; 12: 249

- Ileitis may be caused by a wide variety of other diseases.
- These include infectious diseases, spondyloarthropathies, vasculitides, ischemia, neoplasms, medication-induced, eosinophilic enteritis, and others.
- The diagnosis of the specific etiology is suggested by a detailed history and physical examination, laboratory testing, and ileocolonoscopy and/or radiologic data.

Conclusion

Ileoscopy with biopsy is useful in carefully selected patients

These include : inflammatory diarrhea; presence of endoscopic lesions; anaemia…

Isolated active ileitis (IAI)

- **Typical CD in 8/28 pts (27%)**
  - **Goldstein Am J Surg Pathol 2006**
- **60 patients with IAI (O'Donnell et al 2013)**
  - **Repeat endoscopy**
  - **Serum analysis for ANCA, anti-OmpC, ASCA IgA, ASCA IgG, anti-Cbir**
  - **Results**
    - **No significant difference in the prevalence of antibodies between IAI cases and healthy controls**
    - **Endoscopy follow up in 43 pts**
      - **6/43 (14%) : definite Crohn's disease**
      - **18/43 (42%) : normal**
      - **11/43 (26%) : persistent IAI**
- **40 pts : no lesions in a median follow up of 3.2 yrs (82% NSAIDs)**
  - **Lengeling e.a Clin Gastroenterol Hepatol. 2003;**

Isolated ileitis Challenges

- NSAIDs ulc
- Adhesion
- Vascular diseases
- Infections
- Tumors Mass lesions :
  - neuroendocrine tumor of ileum
  - Metastasis

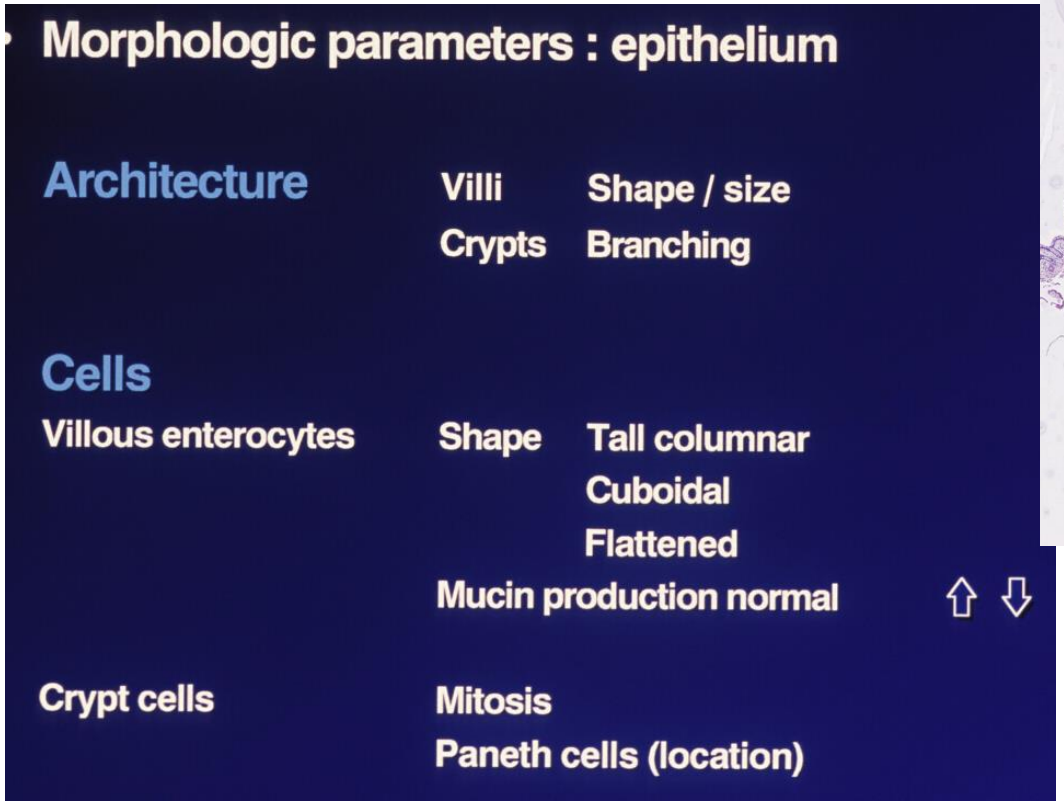
- Elderly patients; with a history of joint lesions
- Abdominal surgical history
- General symptoms/ systemic disease
- General symptoms

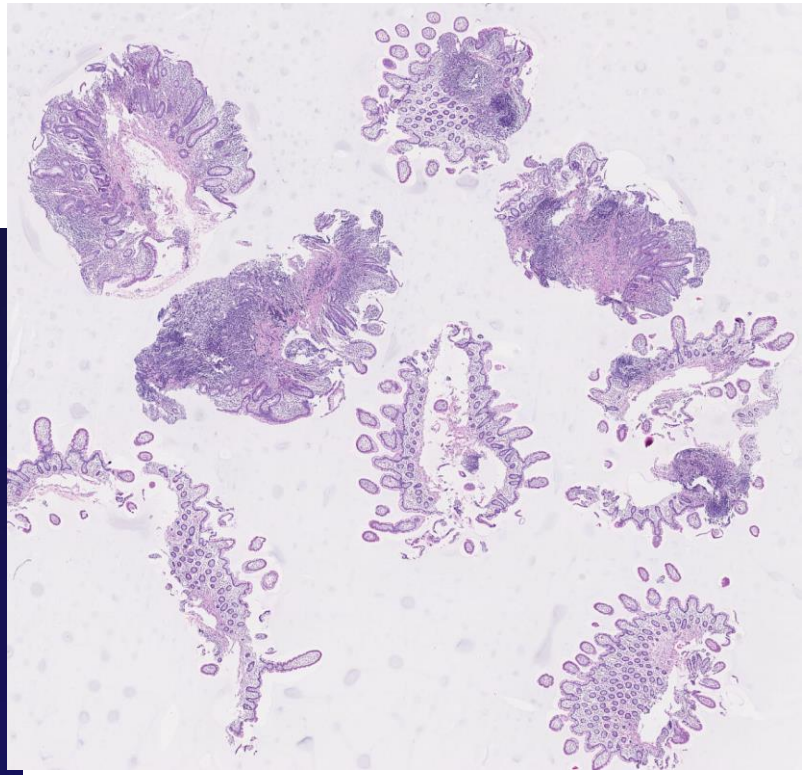
- No features of
  - Age of the patient
  - No malabsorption in clinical chemistry
  - Short history

Histopathological features for the diagnosis of Crohn's disease

Early lesions

Diagnostic lesions





- Based on multiple samples
- Heterogeneity of villous architecture

Early lesions in Crohn’s disease

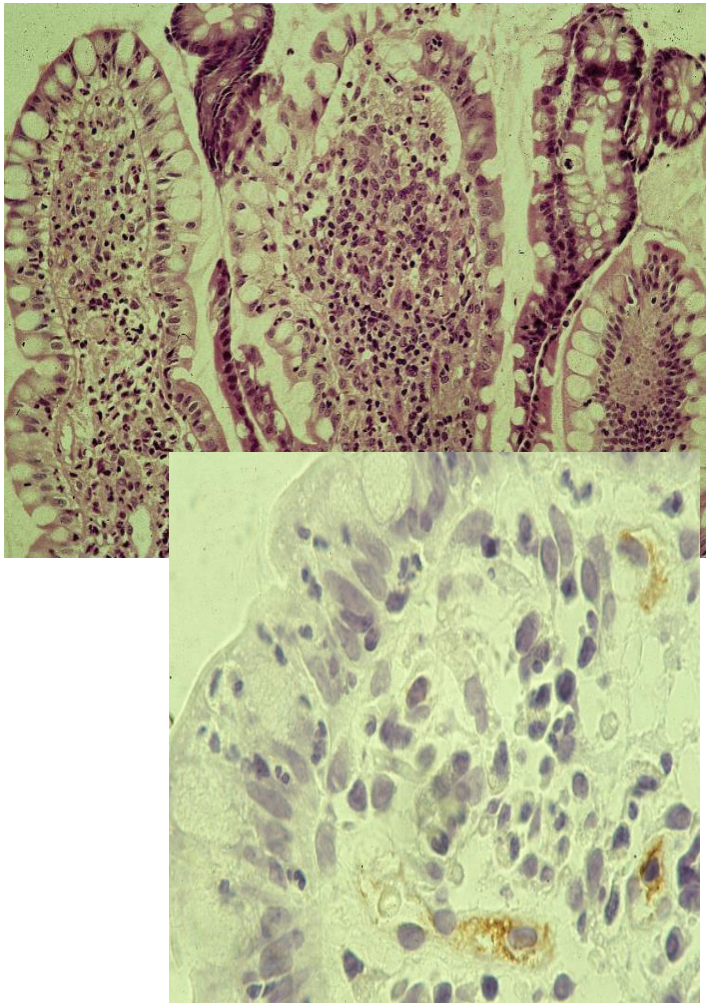
Early lesions in Crohn's disease are associated with inflammation

The only exception (?) are damage and rupture of small capillaries under- neath intact epithelium with subsequent loss of surface epithelial cells (the summit lesion)

Sankey, e. a. Early mucosal changes in Crohn's disease Gut, 34, 1993, 375

Although even then inflammation is common

Maunoury, e.a. Endoscopy 2000; 32: 700



Early Mucosal Lesions in Crohn's disease

2 : **Epithelial patchy necrosis or microulceration (loss of 1 – 6 epithelial cells)**

3 : Naked surface of the dome area overlying a lymphoid follicle (with loss of M cells)

4 : Aphthoid ulcer

Overlying a lymphoid follicle

Or not

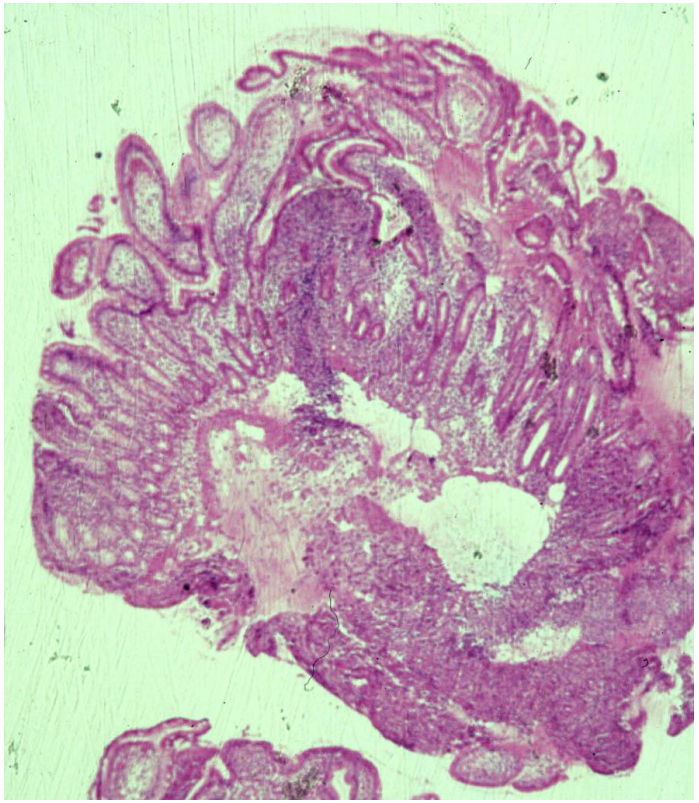
Diagnostic ! lesions

Ileal biopsy in IBD

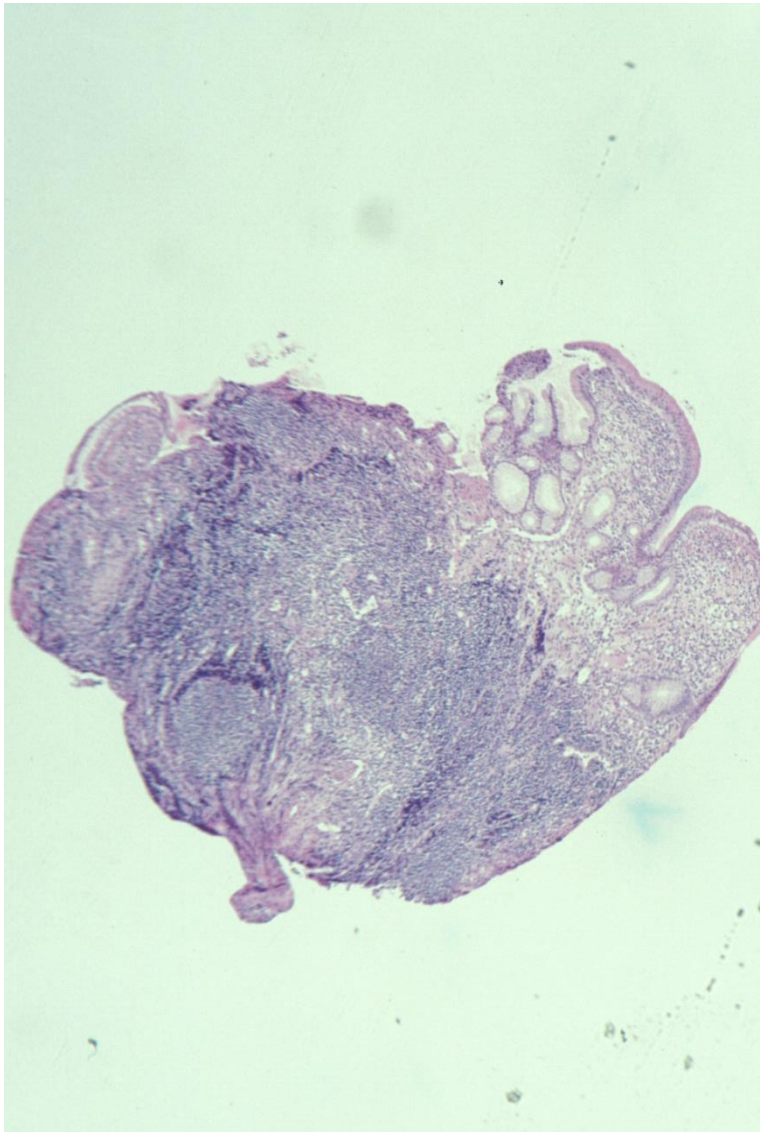
Mucoid metaplasia
Pseudopyloric gland metaplasia

Ulcer associated cell lineage (UACL)

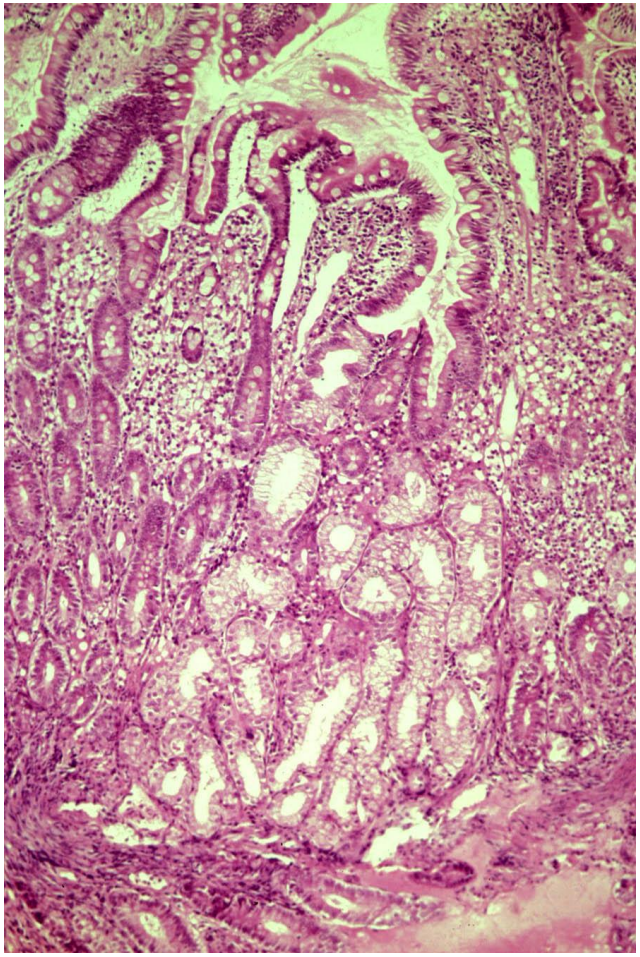
Re-epithelialisation -
regeneration subsequent to ulceration



Mucoid metaplasia



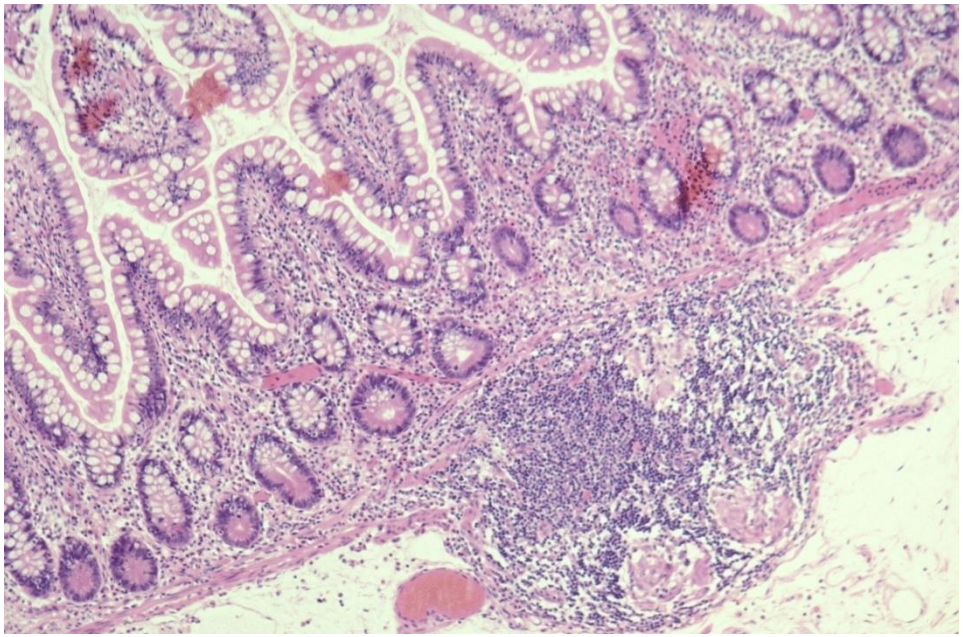
Not specific
Statiscally most common in Crohn's disease

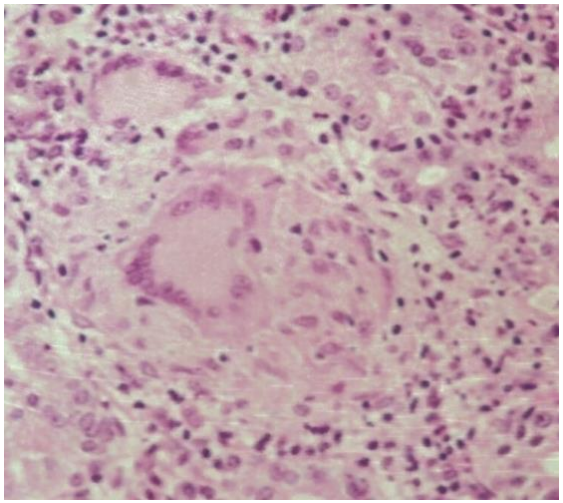


OTHER FEATURES

Granulomas

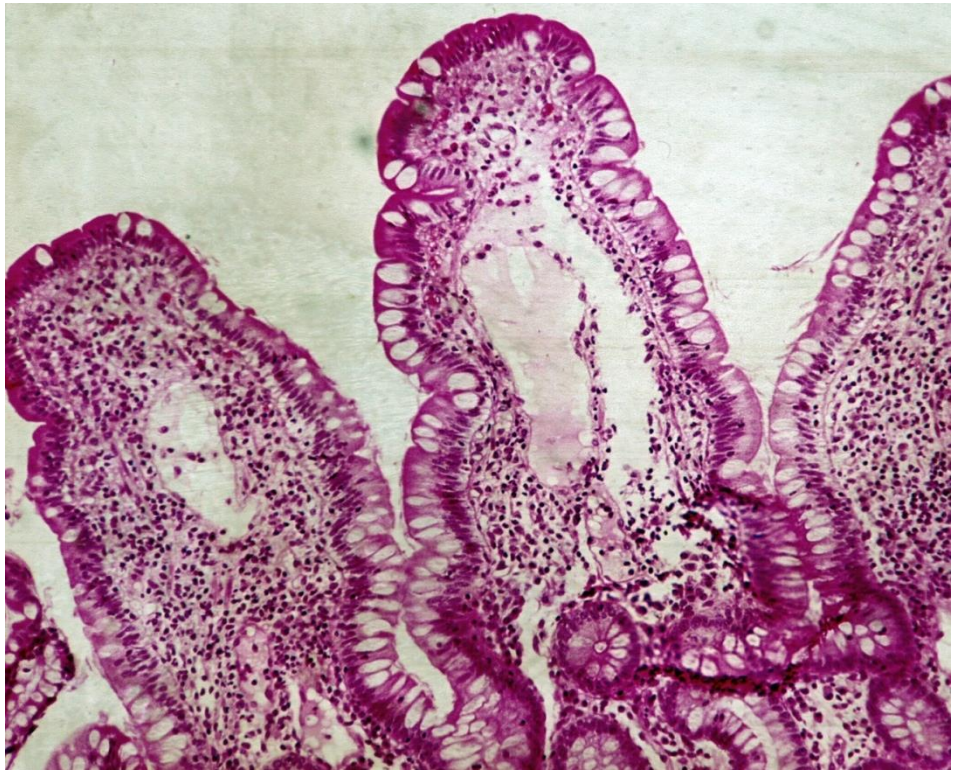
- Not specific
- Diagnosis of Crohn's disease in association with other lesion
- Frequency of finding : 3 – 56% for endoscopic samples
- Highest frequenty : children



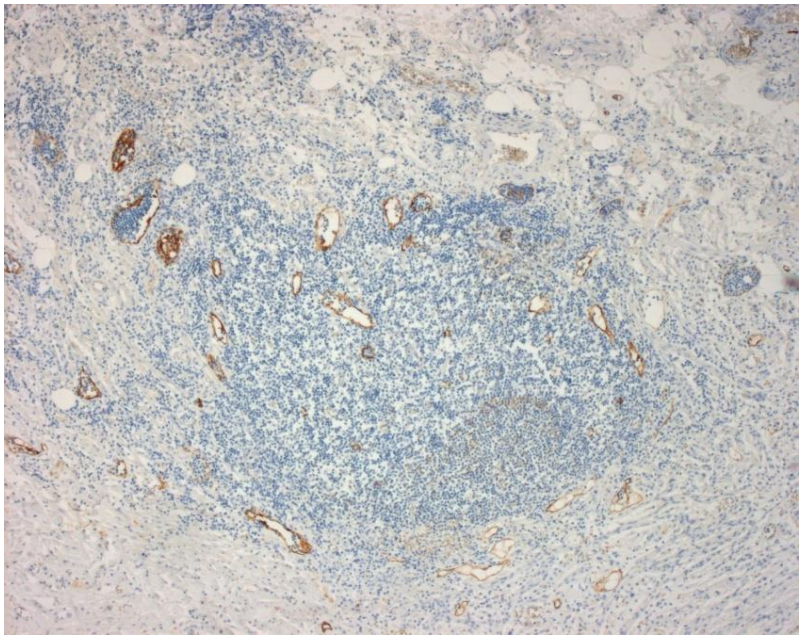


Lymphatics and Crohn's disease

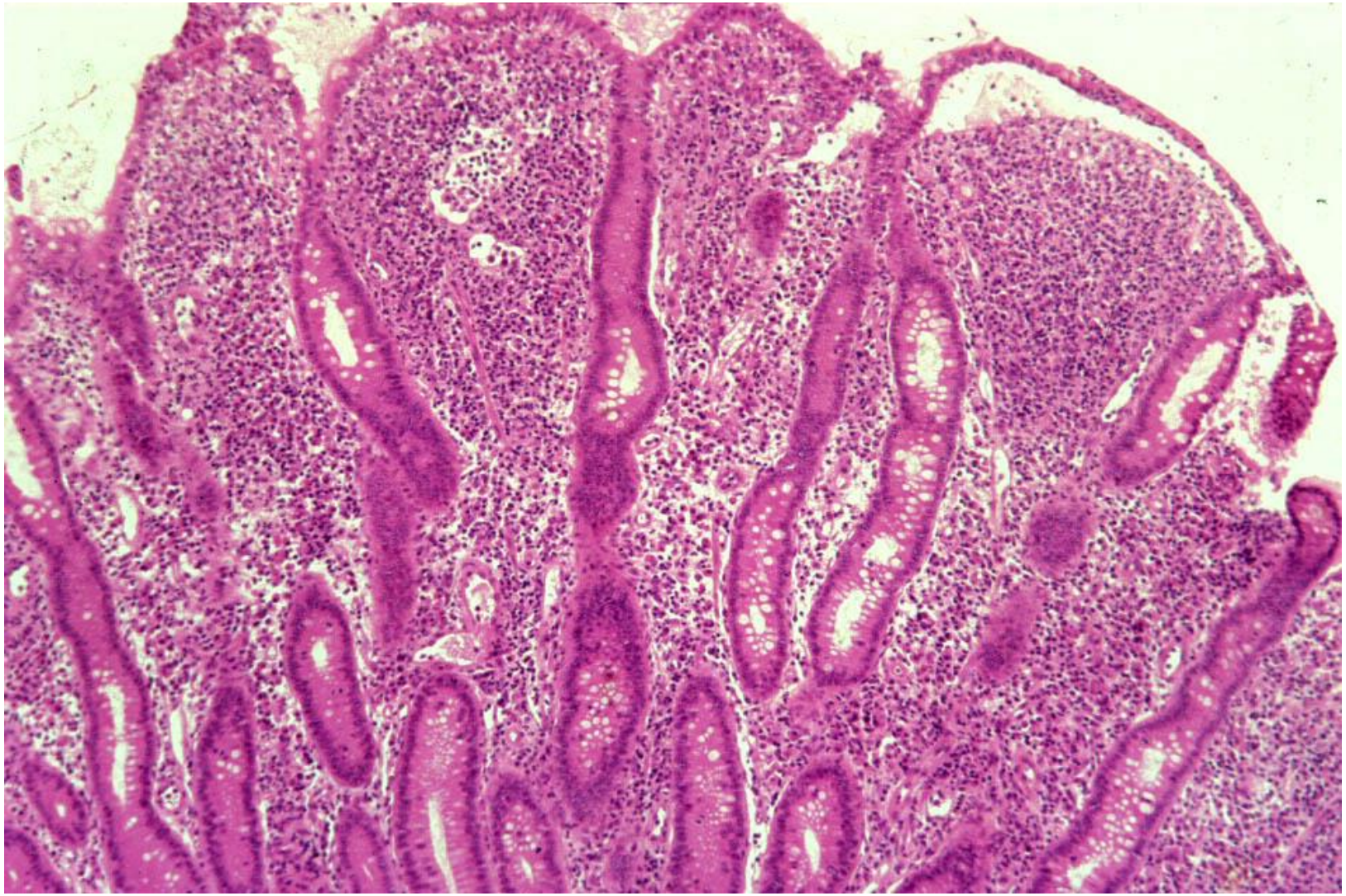
Dilated mucosal lymphatics

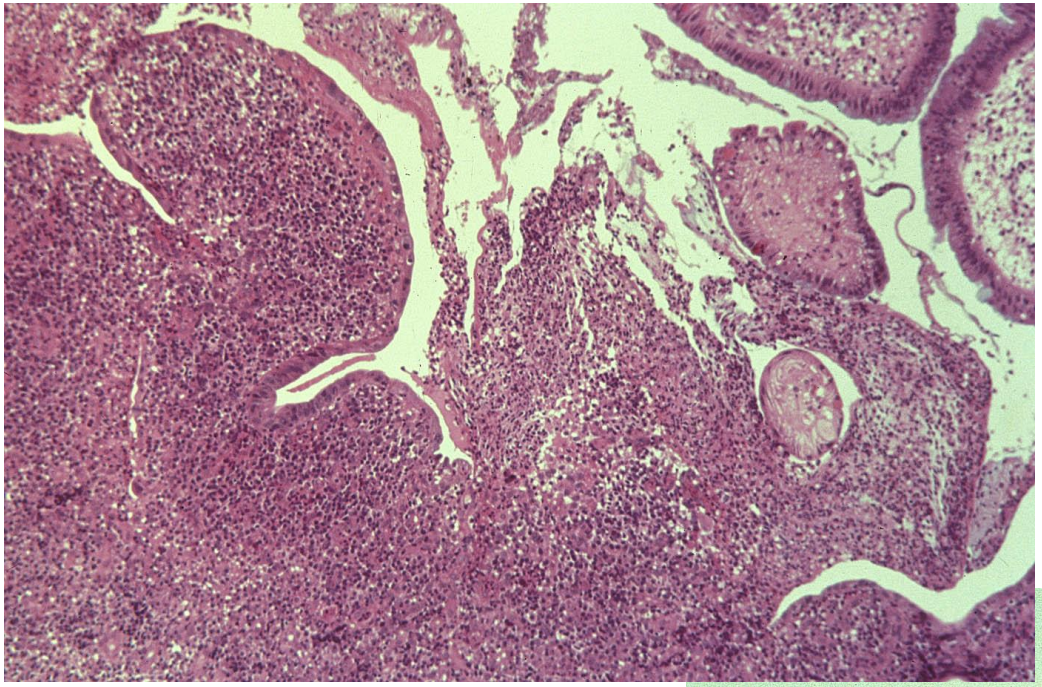


Increased numbers
Lymphagiogenesis

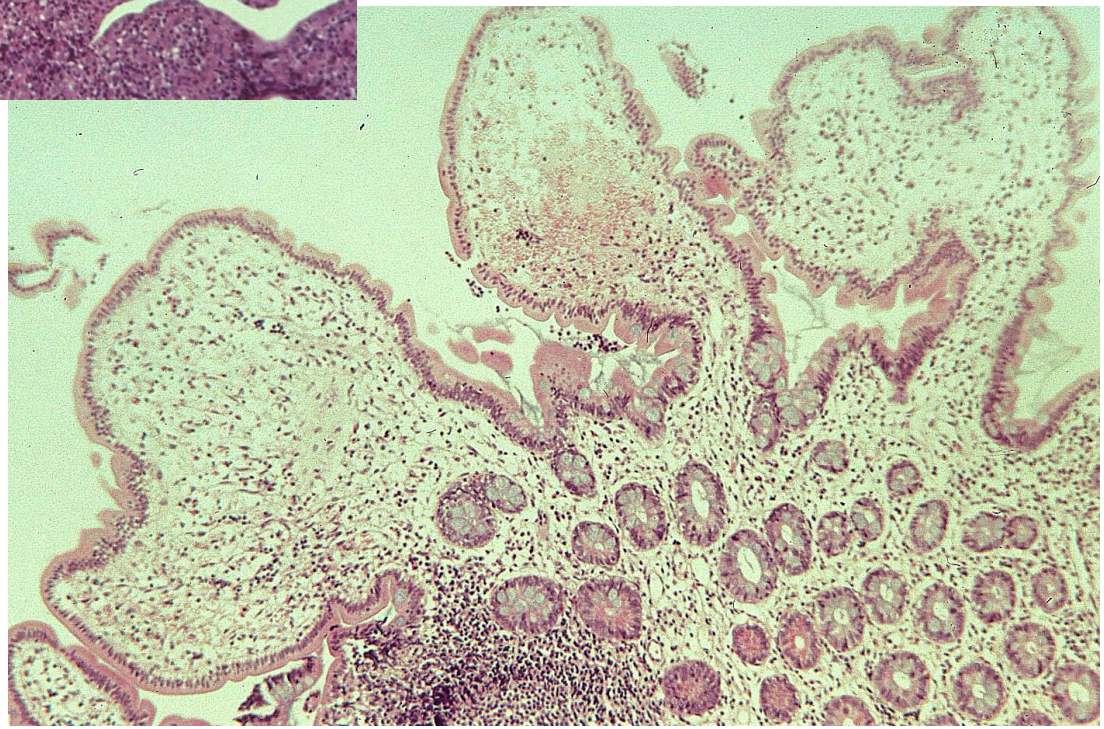


Active inflammation – chronic inflammation - dilated lymphatics





Active inflammation
(relation with treatment)



Histopathology and relapse

Inflammation (early postoperative lesions)

Eosinophils

Eosinophilic infiltration may occur in the neoterminal ileum within a few weeks of resection.

Rutgeerts et al Gut 1984; 25: 665

Mucosal expression of interleukin 5 (IL-5) an important eosinophilic activating factor is increased (in association with prominent eosinophilic infiltration) in early recurrence.

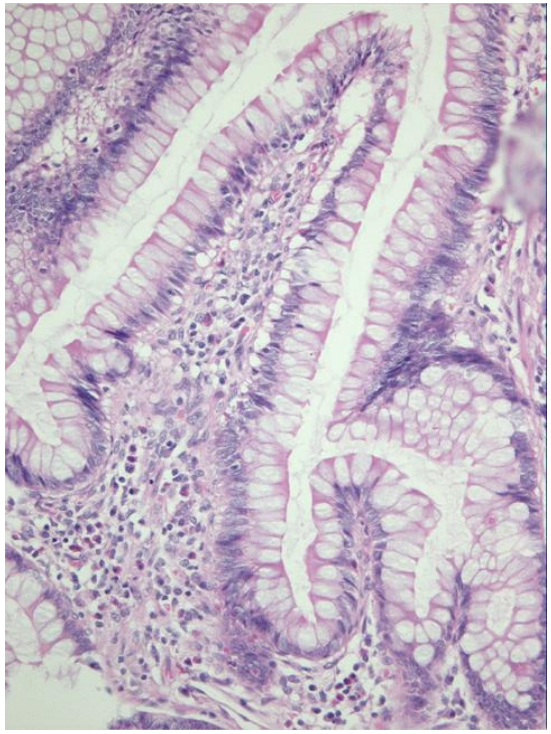
Dubucquoi et al Gut 1995; 37: 242

Hypercrinia – Mucin preservation and relapse

Ileum – Distinctive mucosal features

Increased proportion of goblet cells within the epithelium (Segal & Petras, in : Histology for Pathologists, 1992, p547-)

Ratio Goblet cells/absorptive enterocytes 1/1



Hypercrinia

Increased number of goblet cells

Endoscopic recurrence

18/22 endoscopic recurrence / 55.6% hypercrinia

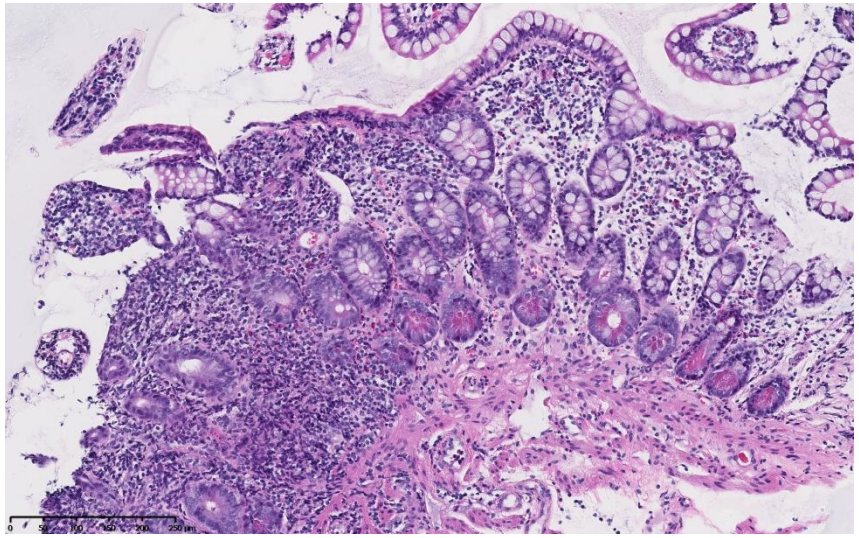
5 pts ratio goblet cells/enterocytes > 50%

5 pts ratio > 75%

10/12 recurrence / 60% hypercrinia

31/37 recurrence / 67.7% hypercrinia

Terminal Ileitis & Ulcerative colitis
Backwash ileitis ?



Definition (historical)

- Backwash : reflux of contents due to inflammation-induced malfunction of ileocecal valve
- Associated with pancolitis

But

Terminal ileitis in UC with mildly active disease!?

Terminal - Backwash ileitis

Goldstein & Dulsi Am J Clin Pathol 2006; 126:365

- Ileal lesions in continuity with colonic lesions
- Histology
  - Diffuse inflammation
  - Regular shortening of villi
- Correlation with extent of disease
- Disease activity correlates with level of cecal disease
- Frequency decreases
- Pathogenesis?
  - Terminology dates from barium enemas, when ileocecal valve was opened
  - **Primary manifestation of the disease (would explain terminal ileitis in patients with mildly active disease**

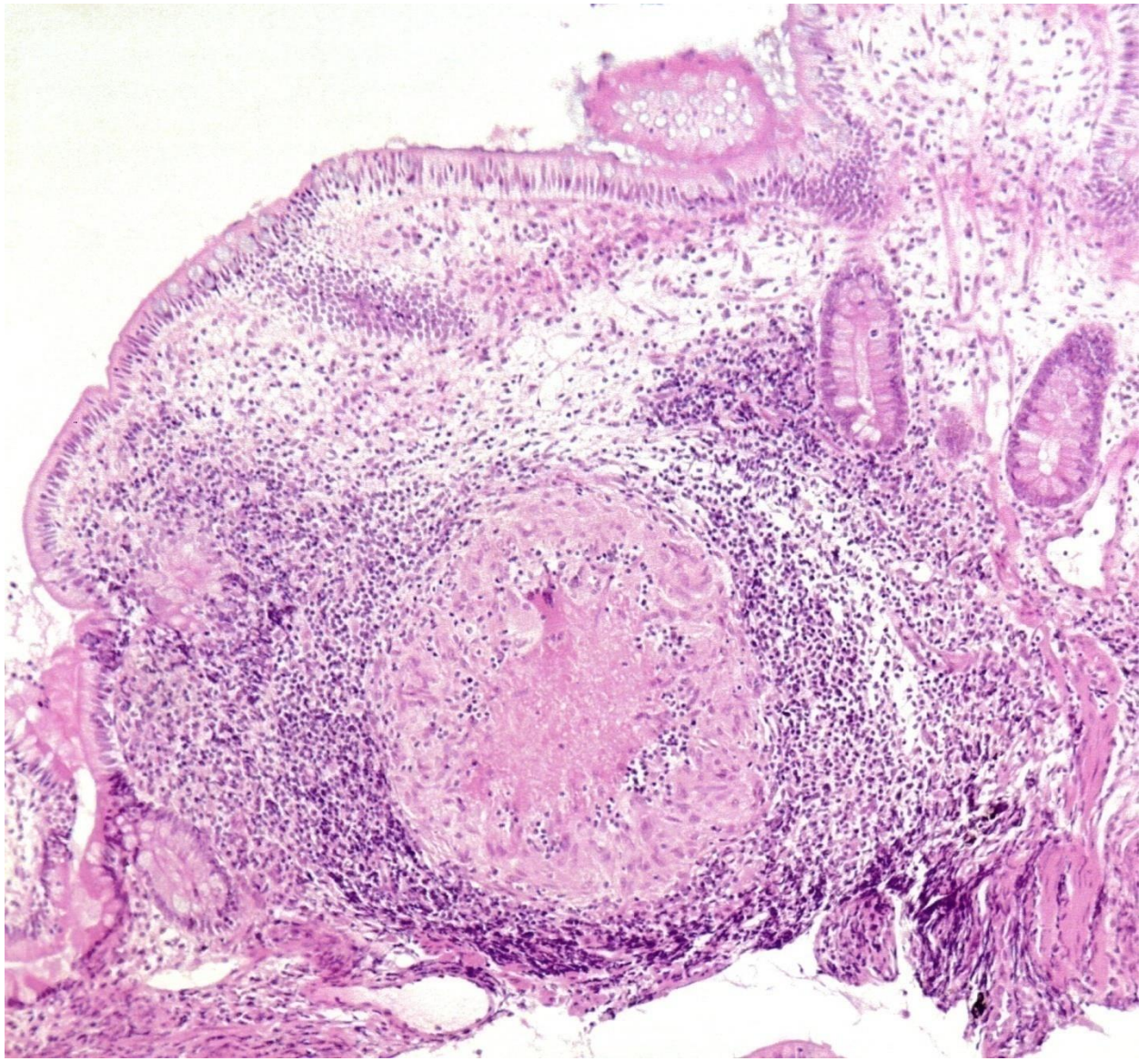
DIFFERENTIAL DIAGNOSTIC ISSUES

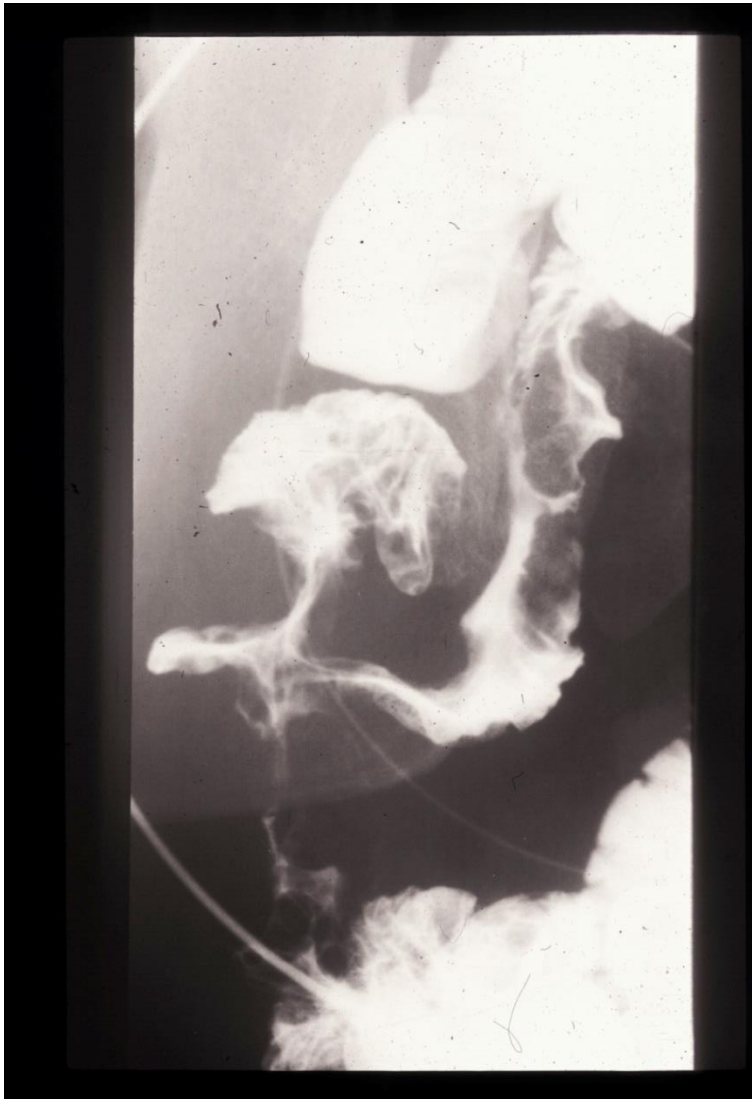
- **Other infections**
  - **Self-limited infections**
    - **Viral gastroenteritis occurs especially in the pediatric age group.**
    - **Bacterial pathogens are Shigella, Salmonella, Campylobacter, Yersinia, Escherichia coli, Clostridium difficile**
  - **Chronic infections**
    - **Mycobacteria**
- **Mimics of IBD**
  - **NSAIDS**
  - **Other DRUGS**
  - **Ileitis and spondylarthropaty**
  - **Tumor associated lesions**
    - **Primary**
    - **Metastatic**

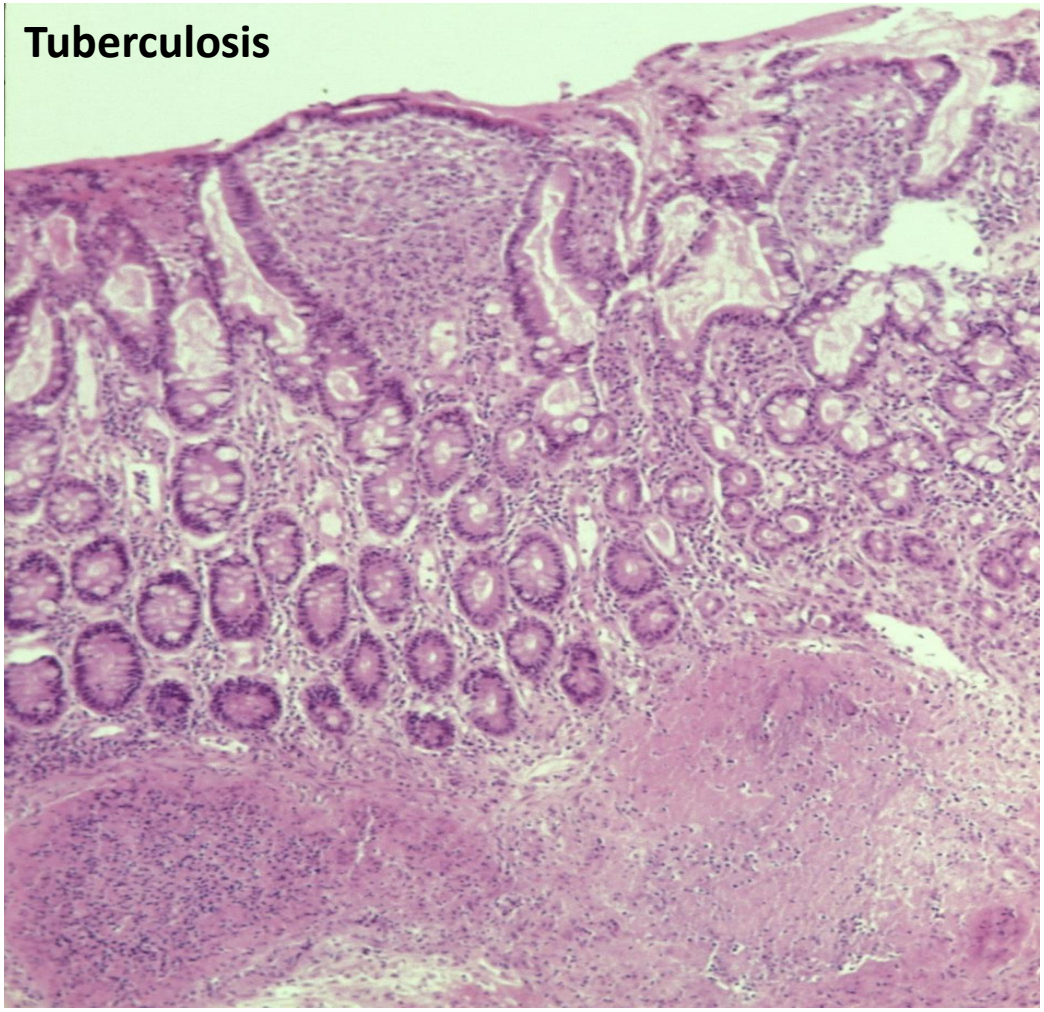
Granulomas

Not specific
Diagnosis of Crohn's disease in association with other lesion


VC 17.2.75






Tuberculosis

MIMICS OF IBD

NSAIDS

OTHER DRUGS

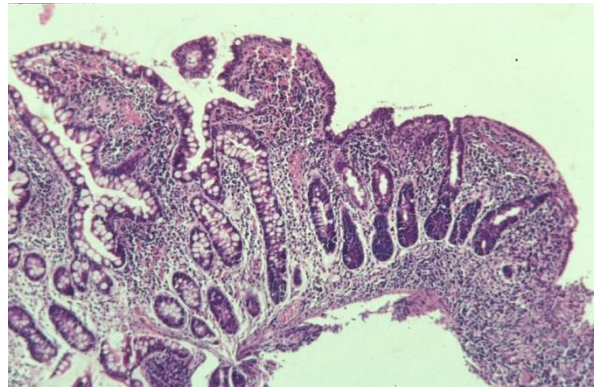
ILEITIS AND SPONDYLARTHROPATY

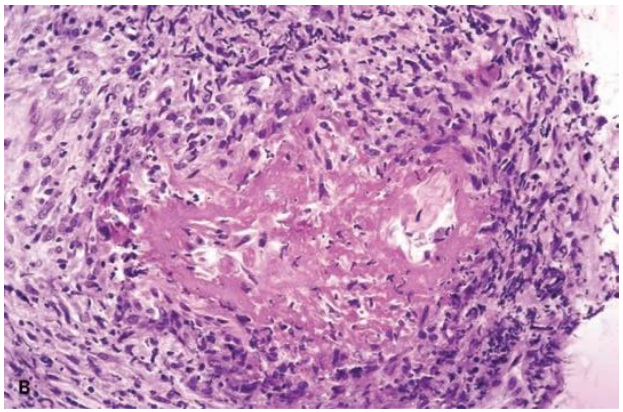
TUMOR ASSOCIATED LESIONS

PRIMARY

METASTATIC

VASCULITIS





NSAIDs

Clinical history

Tumor associated lesions

Patients are usually older

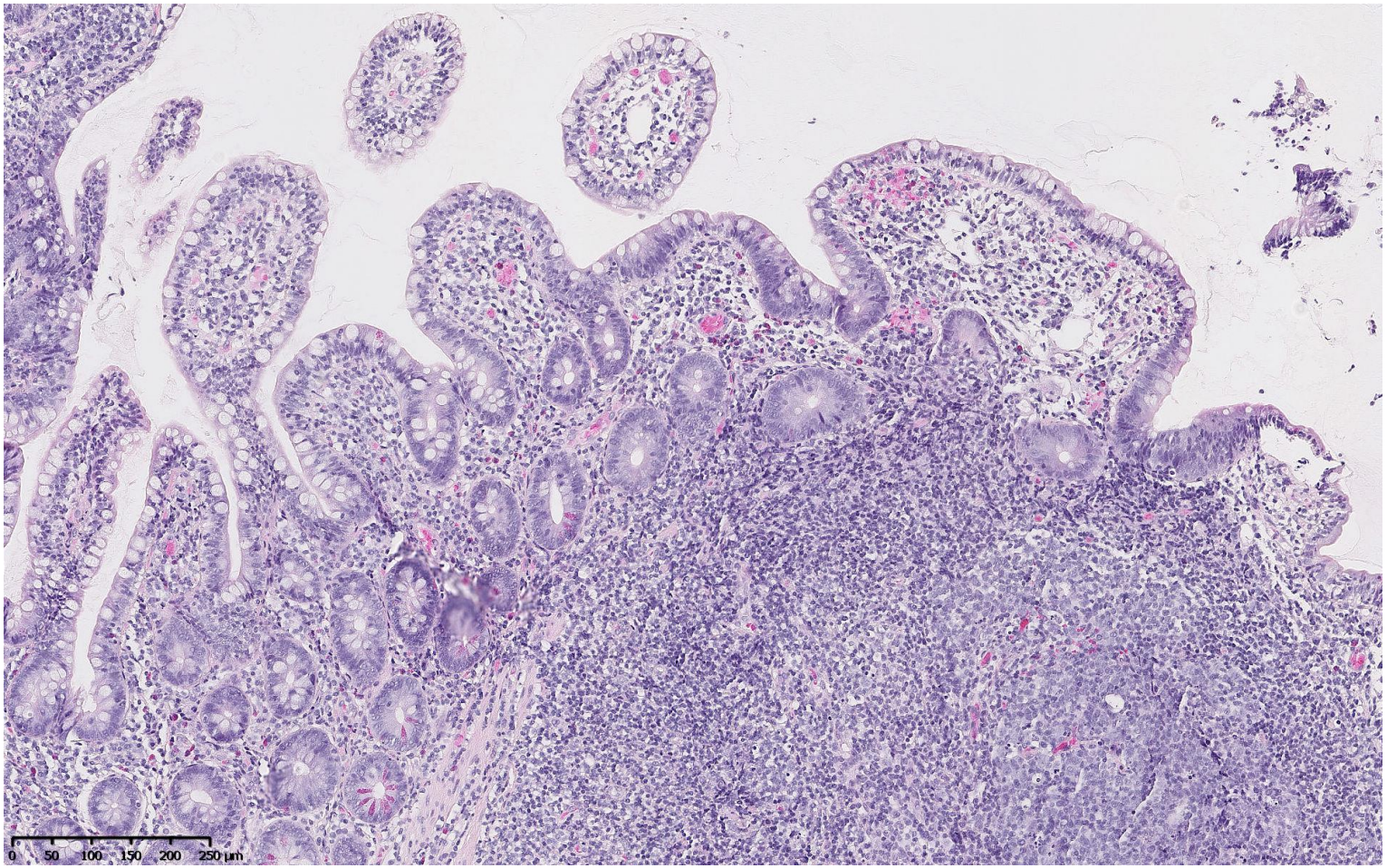
Spondylarthropathy

Associated lesions

Other Drugs

- Olmesartan medoxomil, an angiotensin II receptor antagonist
  - 25 cases out of a series of 12.935 or 0.19%.
  - Lesions are observed usually one to two years after the start of the medication.
  - Woman are slightly more affected.
  - Increased collagen deposition can be noted.
- Ipilimumab, a humanized monoclonal antibody developed to reduce and overcome cytotoxic T-lymphocyte antigen 4 (iatrogenic autoimmune enteropathy)
- Imatinib mesylate (treatment of GIST)
- Mycophenolate mofetil (MMF)

Olmesartan



INFLAMMATION & SPONDYLARTHROPATHY

Histopathology of intestinal inflammation related to reactive arthritis Cuvelier e.a. Gut 1987

65% reactive arthritis; 57% ankylosing spondylitis (n = 232)

Long-term evolution of gut inflammation in patients with spondylarthropathy De Vos e.a. Gastroenterology 1996

Evolution towards CD : 7% (n = 49)

Female patient

°1944

Clinical History

Stenosis of a renal artery and the celiac trunk

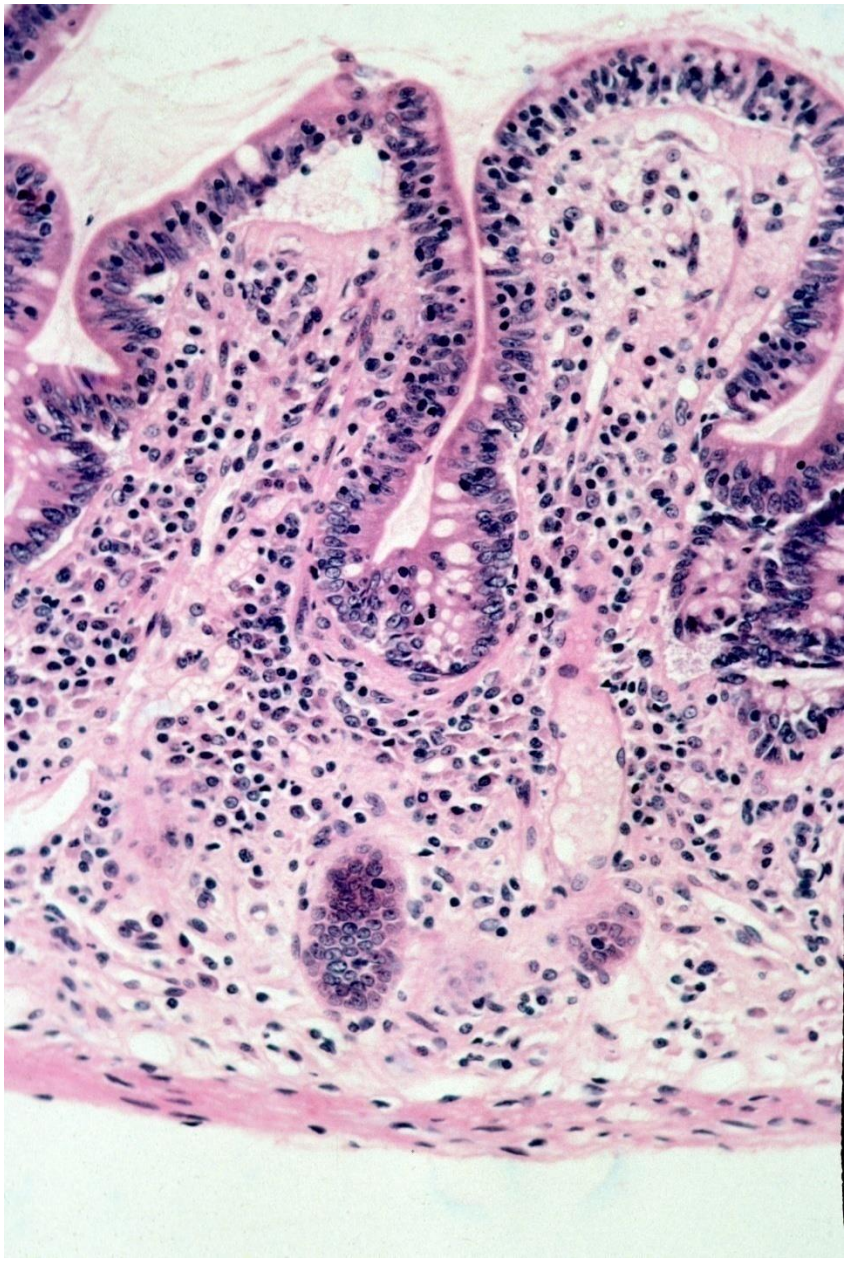
Arterial hypertension

Migraine

Treatment : Cafergot, omeprazole, tiberal, plavix (clodipogrel)

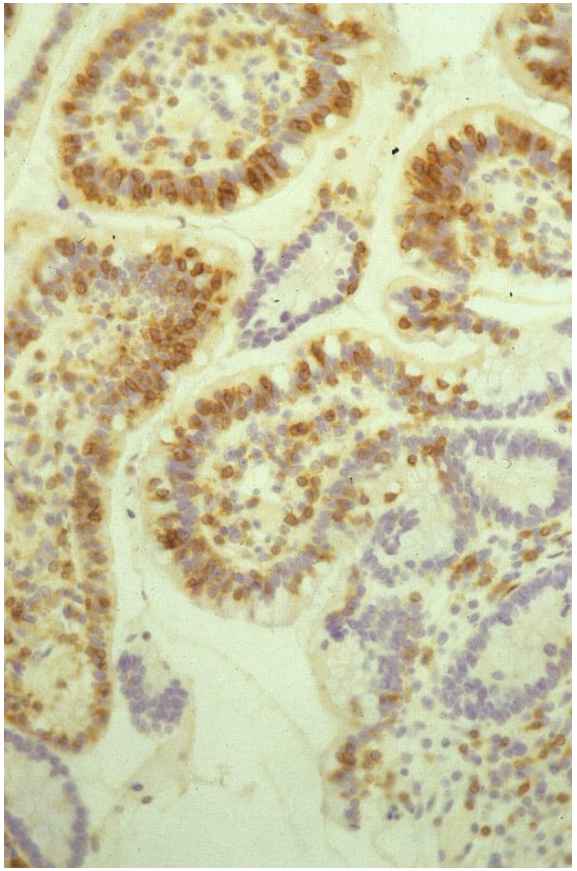
Current complaints : headache and diarrhea

Endoscopy : Ischemia? > normal aspect

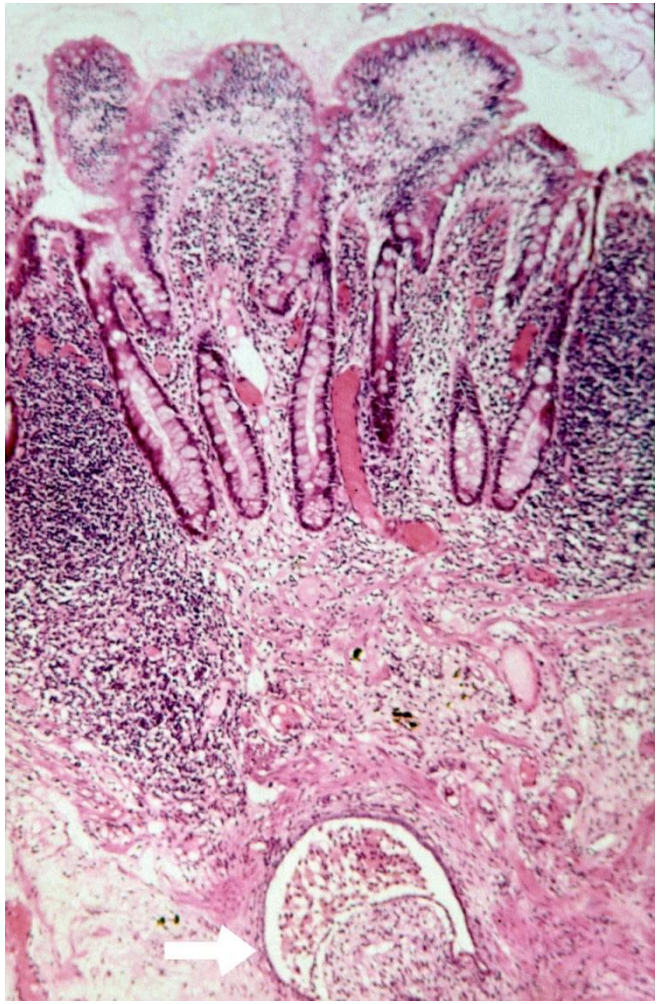


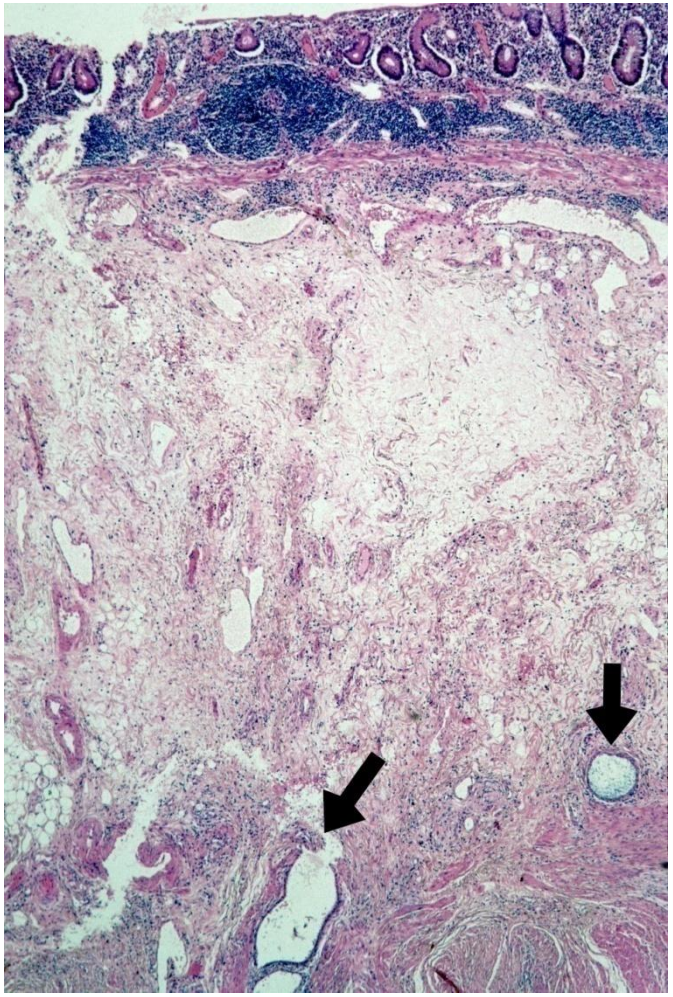
Microscopic colitis
Histology – Small Intestine

Duodenal abormalities in up to 70% (7% antiendomysial antibodies)
Ileal abnormalities in up to 15%
Primary Ileal villous atrophy



Endometriosis





Crohn's disease and endometriosis

Craninx e.a. Eur J Gastroenterol Hepatol 2000; 12: 217

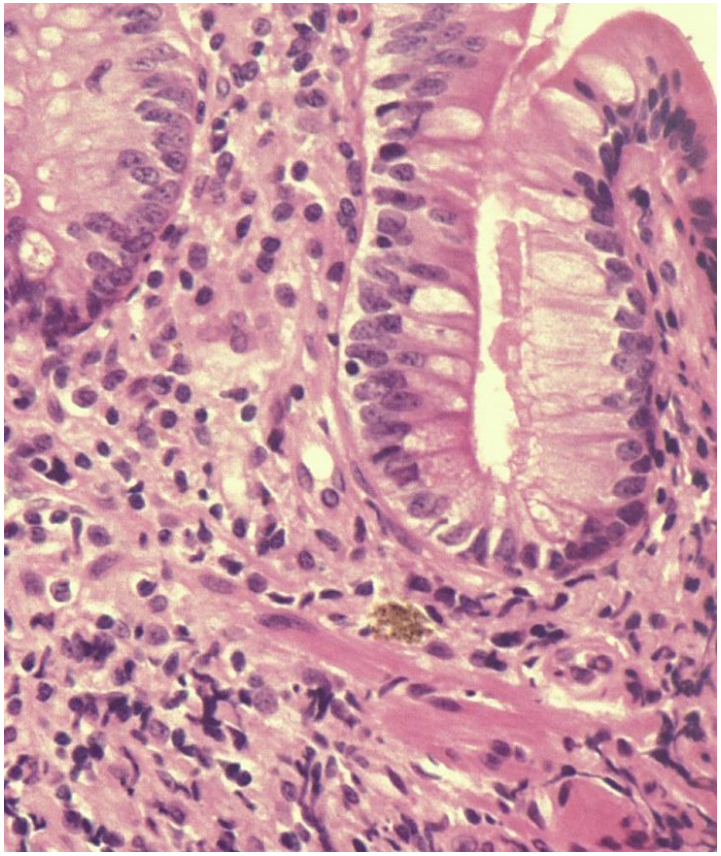
- In Crohn's disease endometriosis of the terminal ileum seems more common
- Endometriosis can mimic Crohn's disease
- Endometriosis can occur simultaneously

- 8 female pts : surgery for Crohn's disease of terminal ileum (n=7) or colon (n=1)
- Intestinal endometriosis of the ileum (n=6); colon (n=2)

Miscellaneous

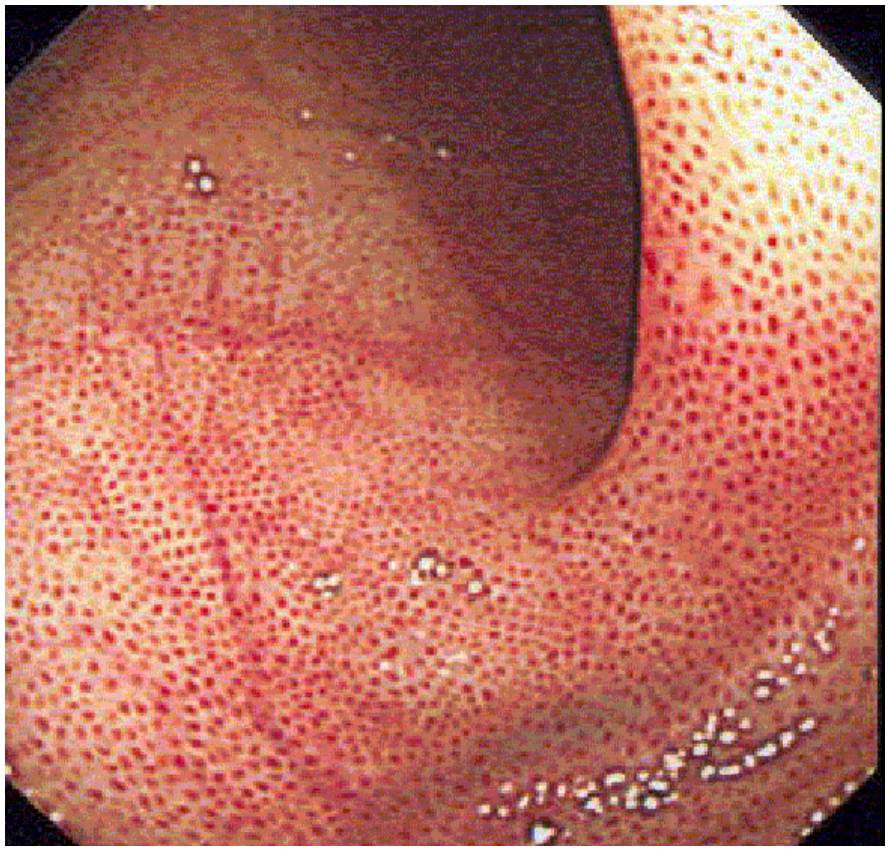
Athmospheric/food additives dust

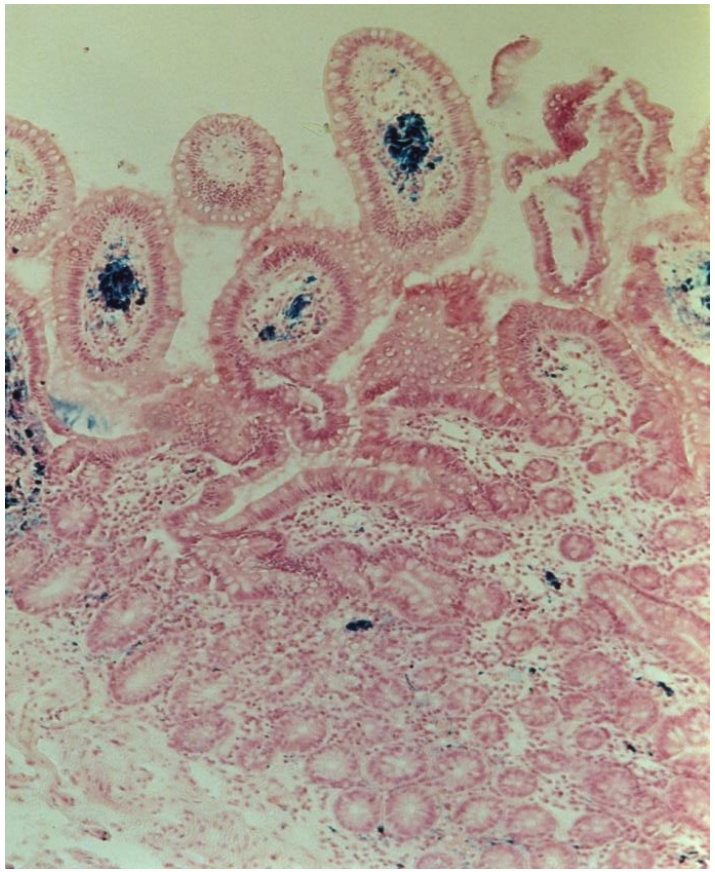
Particularly in macrophages associated with Peyer's patches (situated in the base) in the small intestine
In stroma
Appearance : dark brown or black (pigment rich in aluminium, silicon and titanium)
Frequency 34/42 (over 6 yrs of age) (Shepherd e a Hum Pathol 1987; 18: 50)
Sampling through M cells
Powell e.a. Gut 1996; 38: 390



Miscellaneous

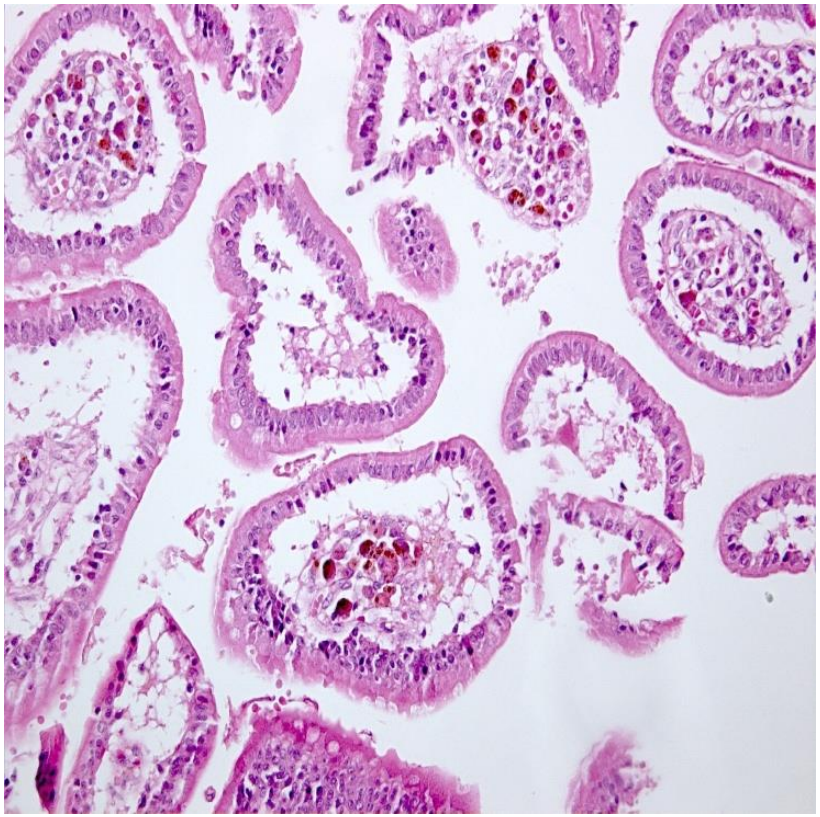
Ileum – Deposition of iron





Miscellaneous

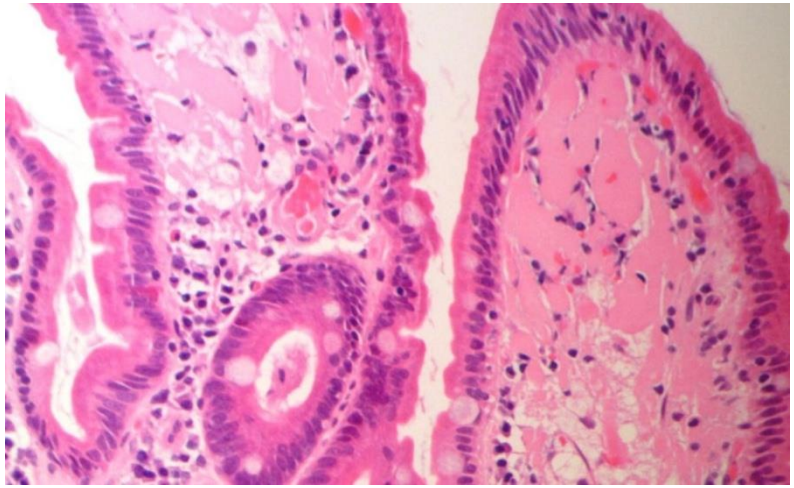
Bile pigment (ileum)

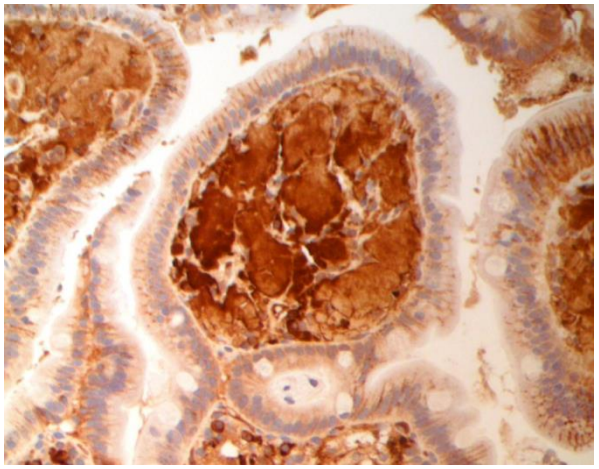


Miscellaneous

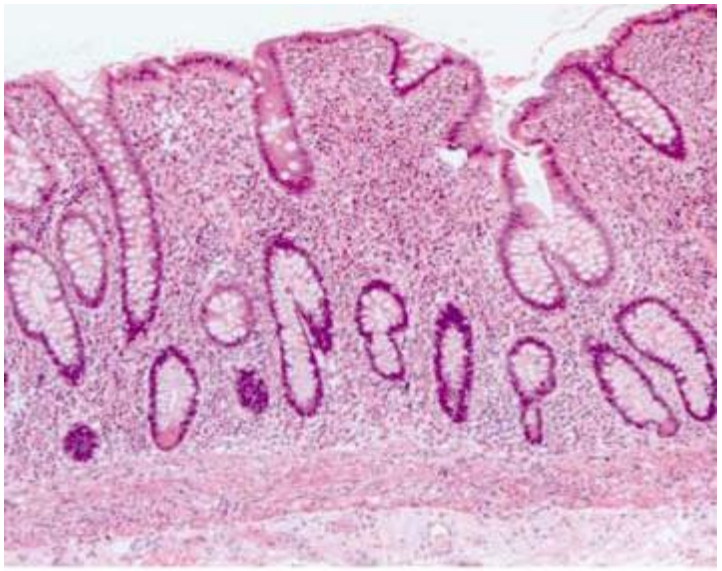
Waldenström's Macroglobulinemia

Staining for kappa light chain

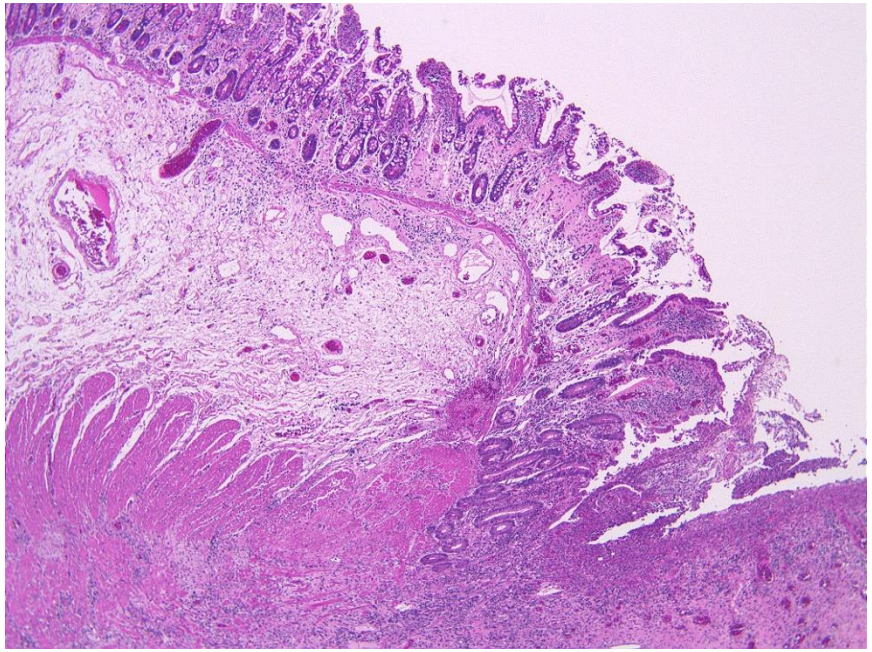




Systemic mastocytosis

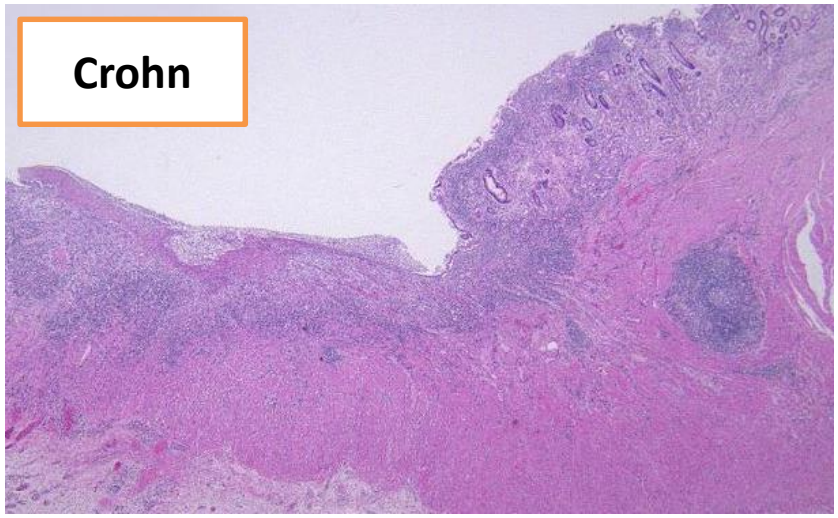


Behçet disease
Can involve Ileum (& colon)



Endoscopic biopsies can hardly differentiate

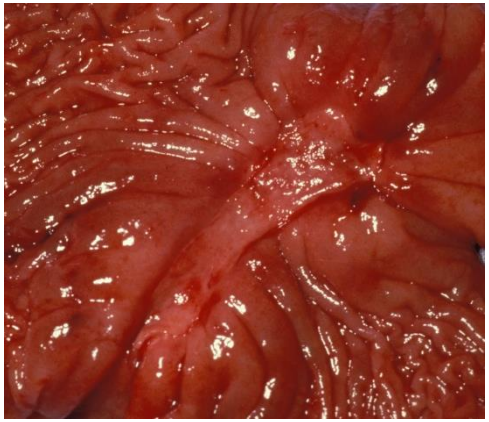
Crohn



Behçet

- Ulcers on opposite side of the mesentery
- Unrelated to the site of M-cells or lymphoid tissue
- Changes limited to mucosa adjacent to ulcers

Ulceration in small bowel



- Isolated non-specific ulcer
  - Rare (40/100,000 pts)
  - Mainly ileum (at 100 cm of the valve)
  - Male preponderance
- Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)
- Idiopathic chronic ulcerative enteritis (ICUE)
- Chronic non-specific multiple ulcers of the intestine
  - Four candidate mutations in the solute carrier organic anion transporter family, member 2A1 (SLCO2A1) gene, encoding a prostaglandin transporter, were identified (Hosoe e.a. J Crohn Colitis 2017)

Conclusions

- Ileal biopsies can provide information in patients with endoscopic features of ileitis and clinical symptoms of (inflammatory diarrhea)
- Isolated active ileitis is not always Crohn's disease
- So-called backwash ileitis is not yet well understood
- Various conditions may induce either isolated ileitis or ileitis in association with colitis
- These include infections, drugs but also less common conditions (mass lesions…)

Iatrogenic autoimmune-like enteritis Pathophysioloy

- CTLA-4 is expressed on regulatory T cells and patients receiving treatment with anti-CTLA-4 show abnormal numbers of regulatory T cells in intestinal biopsies
- Enterocytes can express MHC class II (like normal antigen presenting cells) but lack expression of the costimulatory molecules (CD80 and CD86) needed to activate naïve T-cell
  - Yet, under certain conditions, they can express other costimulatory markers such as PD-L1 (programmed cell death)
  - Blockade of PD-L1, the ligand of PD-1, leads to the development of autoimmune enteritis.
- AIE-like enteritis can develop following severe depletion of gut microbiota from antibiotic therapy, consistent with the idea that commensal microorganisms play an important role in regulating gut immunity