What is colitis?
Pitfalls in the microscopic diagnosis

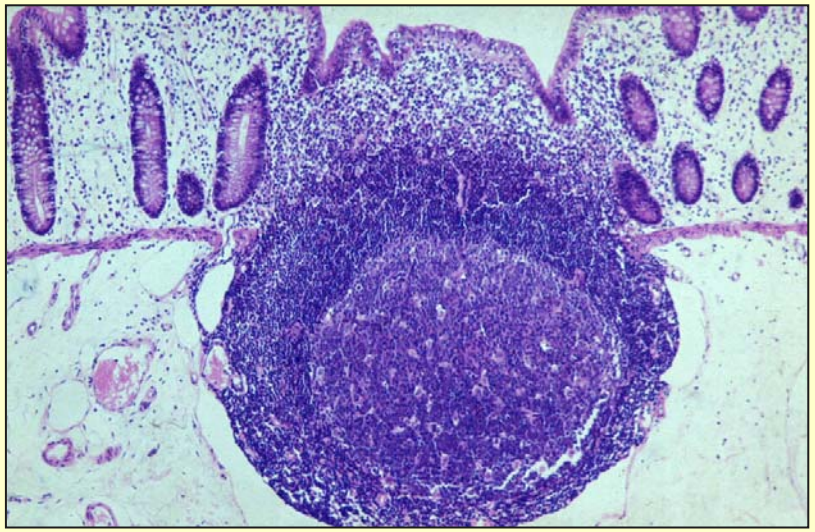
K. Geboes, KULeuven, 2004

Normal colon

- **Epithelium**
  - **Surface**
    - **Flat - regular**
  - **Crypts**
    - **Tubular – perpendicular base reaches muscularis mucosae**
    - **intercryptal distance and internal diameter similar**
  - **Cells**
    - **Columnar cells**

Normal colon

- Lamina propria
  - Immune competent cells
    - Organized lymphoid tissue
    - Lamina propria lymphocytes
    - Intraepithelial lymphcoytes
  - Extracellular matrix
- Muscularis mucosae



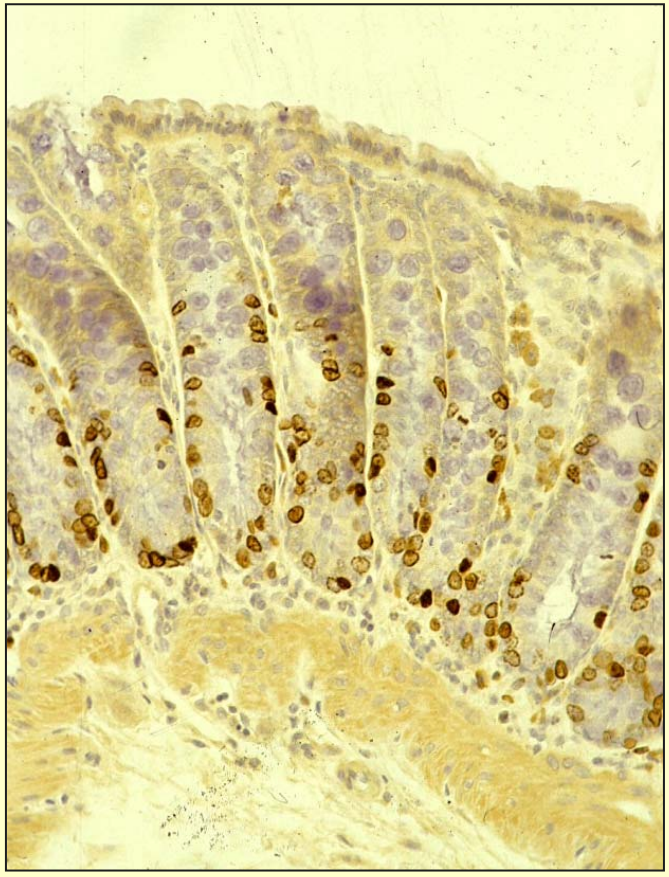
What is colitis? Statistical approach (morphometry)

- **Chronic inflammatory infiltration**
  total cellularity increase
- **Surface epithelial height to crypt epithelial height.**
  In normal mucosa the surface epithelial cell height exceeds the height of crypt epithelium
- **Redistribution of infiltrating cells so that there is a similar density in the basal third to that of the superficial third > IBD**

  Jenkins e.a. J Clin Pathol 1988; 41; 72-79

What is colitis?

- **The normal mucosa is a dynamic structure**
  - **Epithelial cell turnover**
  - **Traffic of immune competent cells**
- **A pure morphometric approach of one time point may have limitations**



Normal mucosa vs Colitis

- **Lamina propria cellular infiltrate : increase in intensity; composition & distribution**
- **Organized lymphoid tissue : stimulation**
- **Epithelium :**
  - **surface epithelium**
    - **terminally differentiated cells**
      DAMAGE & REPAIR (restitution)
  - **crypts**
    - **differentiating cells, proliferative compartment**
      INCREASED PROLIFERATION (mitotic activity)
  - **normal turnover : increased turnover**

Basic lesions : Inflammation

- **Inflammation pattern I**
  - **Patchy, focal**
  - **Diffuse**

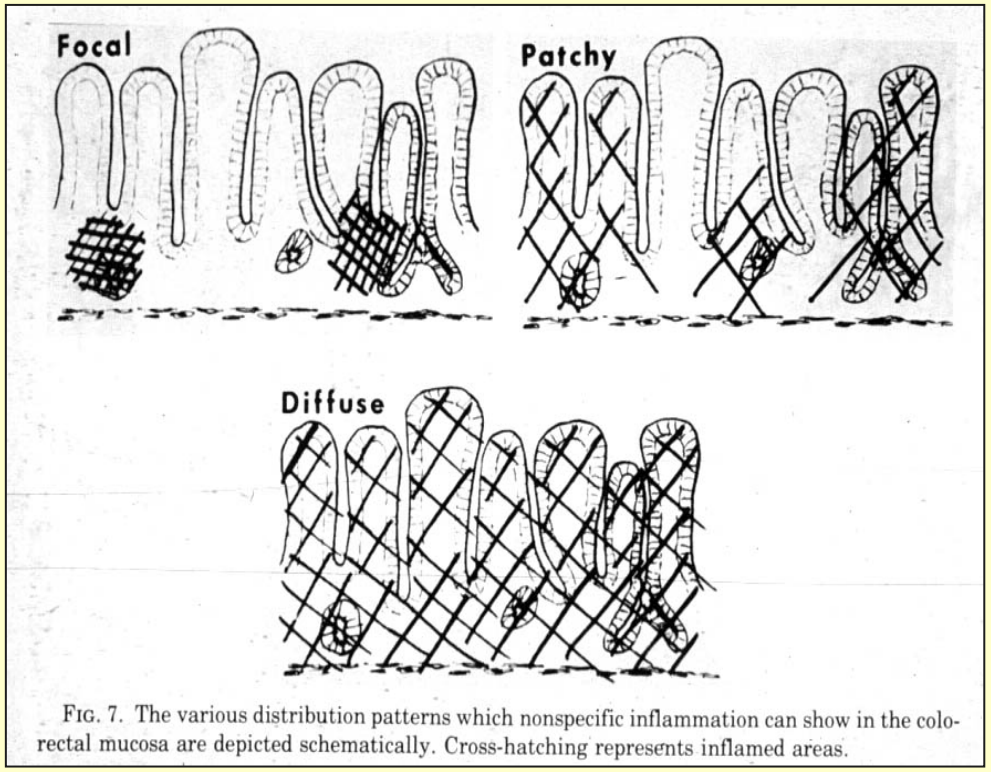
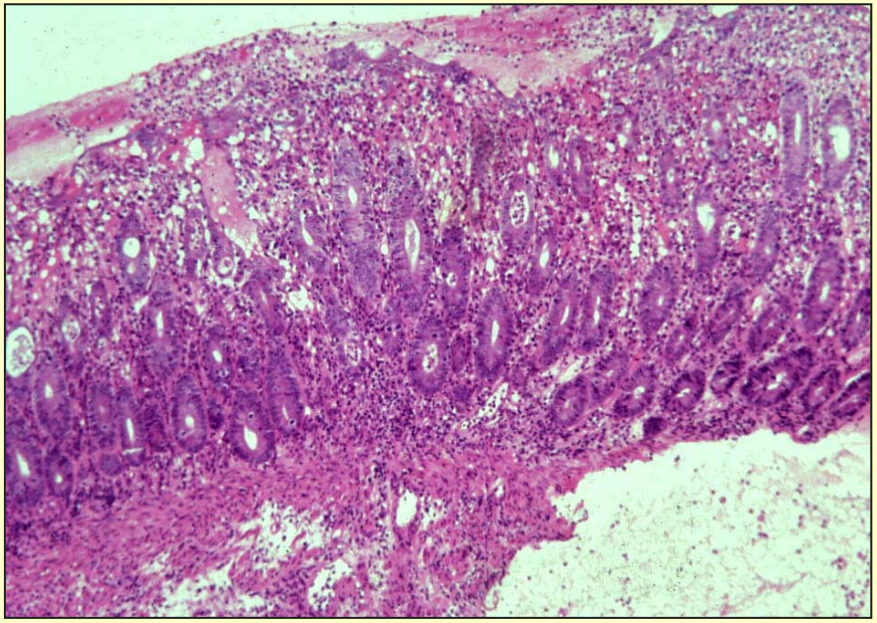


FIG. 7. The various distribution patterns which nonspecific inflammation can show in the colorectal mucosa are depicted schematically. Cross-hatching represents inflamed areas.

Basic lesions : Inflammation

- **Inflammation pattern II**
  - **Diffuse upper third (Infections such as Shigella colitis)**
  - **Diffuse transmucosal (IBD)**

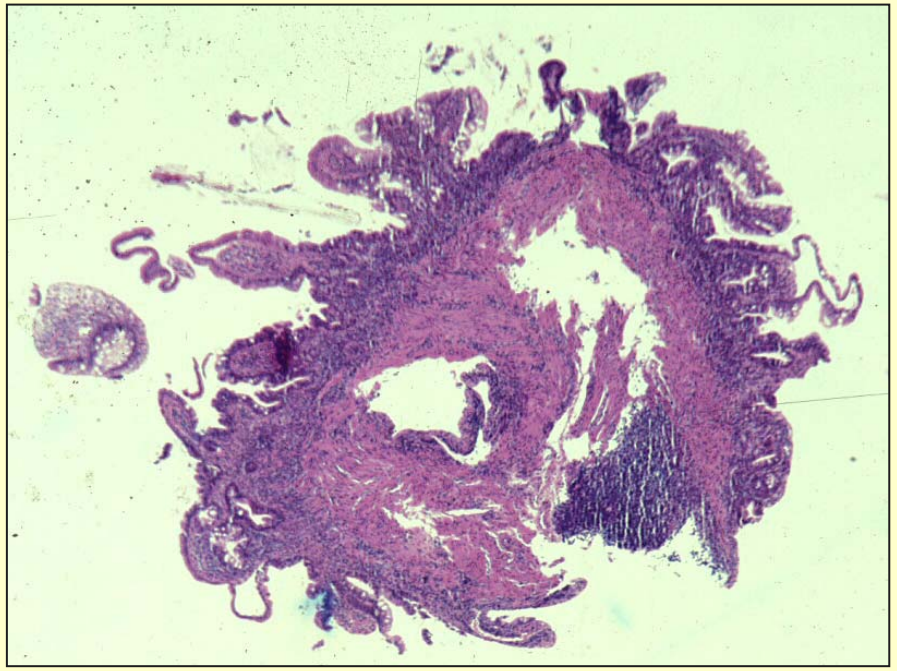


Basic lesions : Inflammation

- **Inflammation composition**
  - **Mononuclear**
  - **Mixed**
    - **Active disease when combined with epithelial damage**
  - **Eosinophils**
  - **Mast cells (tryptase)**

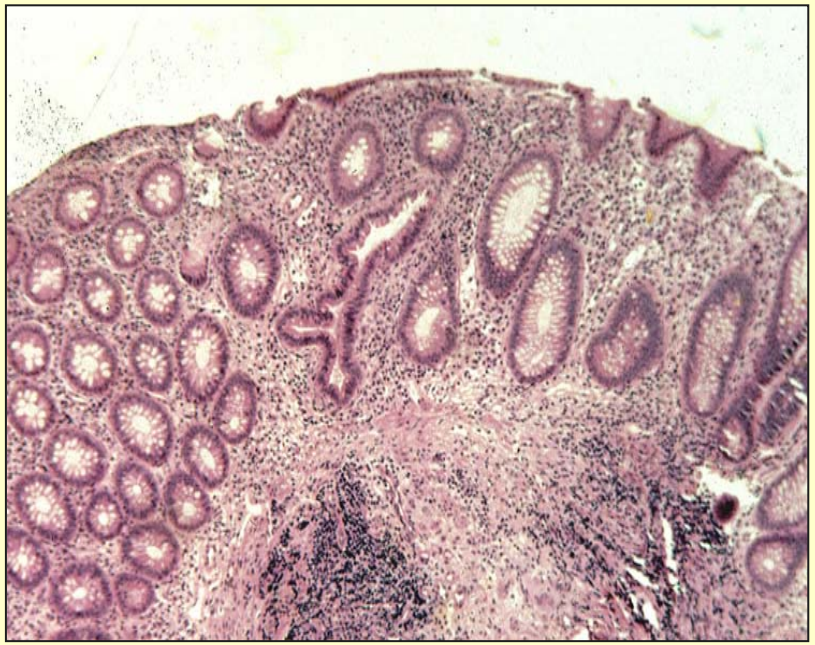
Basic lesions : Architecture

- **Surface**
  - **Flat or irregular**



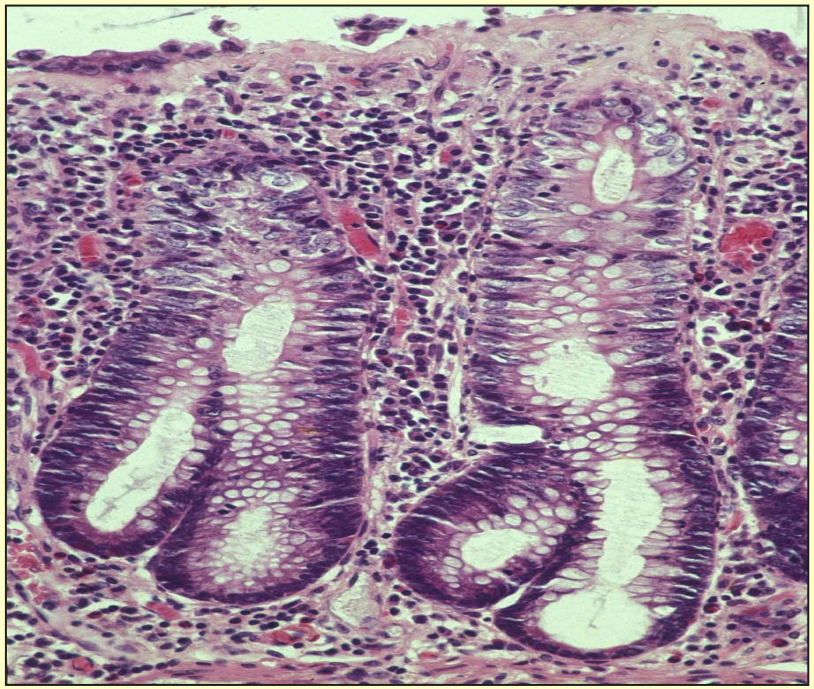
Basic lesions : Architecture

- Crypt architecture
  - Crypt density
    - 7/8 crypts per 1 mm mucosal length (IBD 4 to 5)
    - Closely packed
  - Variable or constant intercryptal distance

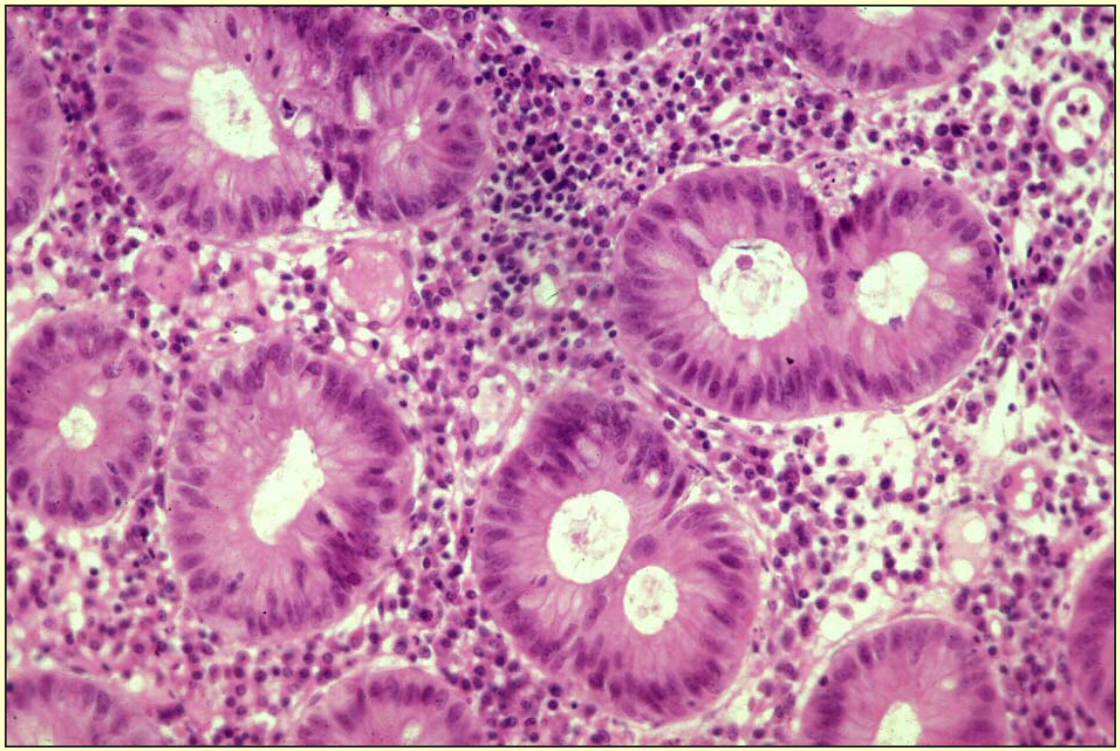


Basic lesions : Architecture

- Crypt architecture
  - Straight or branching tubes (infrequent branching < 10% may be normal)
  - Base reaching muscularis mucosae
  - Variable or constant internal diameter



Ulcerative colitis : Bifid crypts – transverse section



Basic lesions : Architecture

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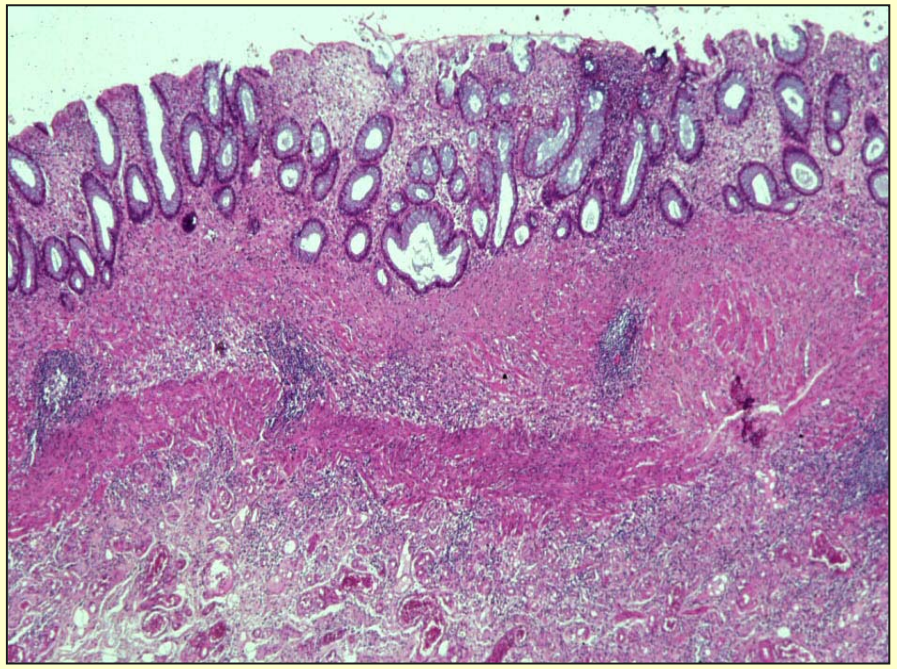
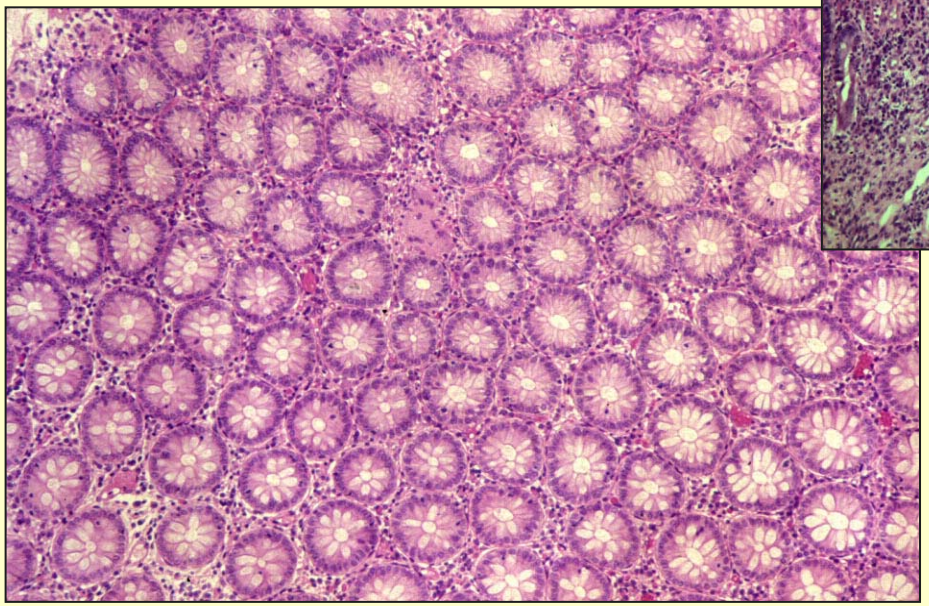
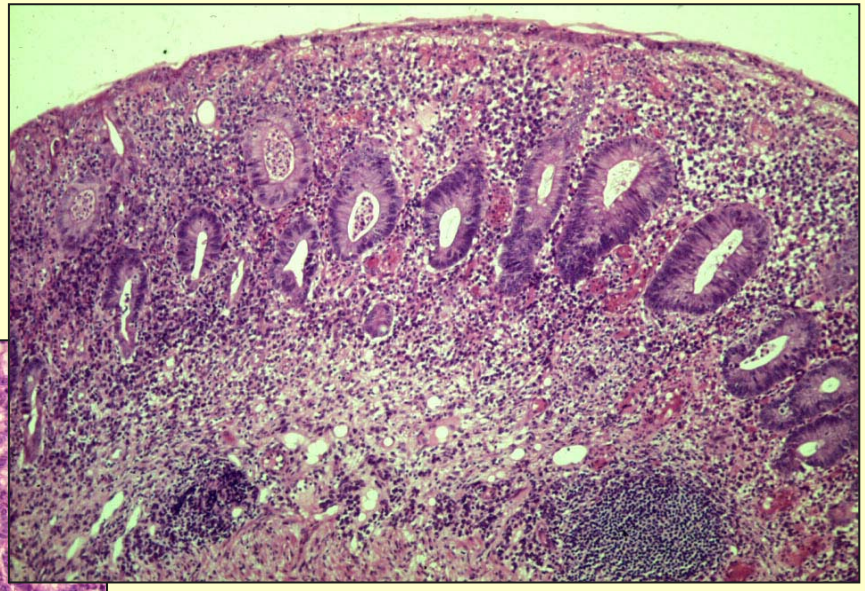
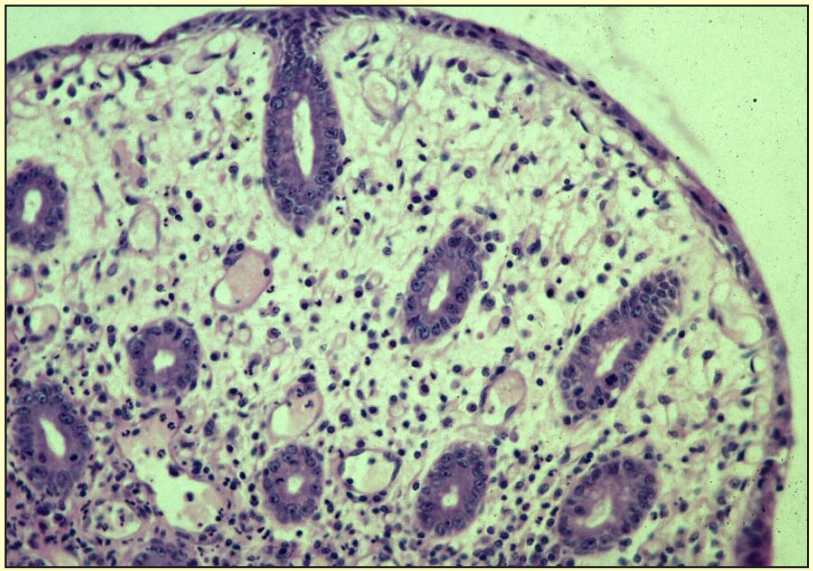


Regular crypts with solitary giant cell; UC – shortened crypts





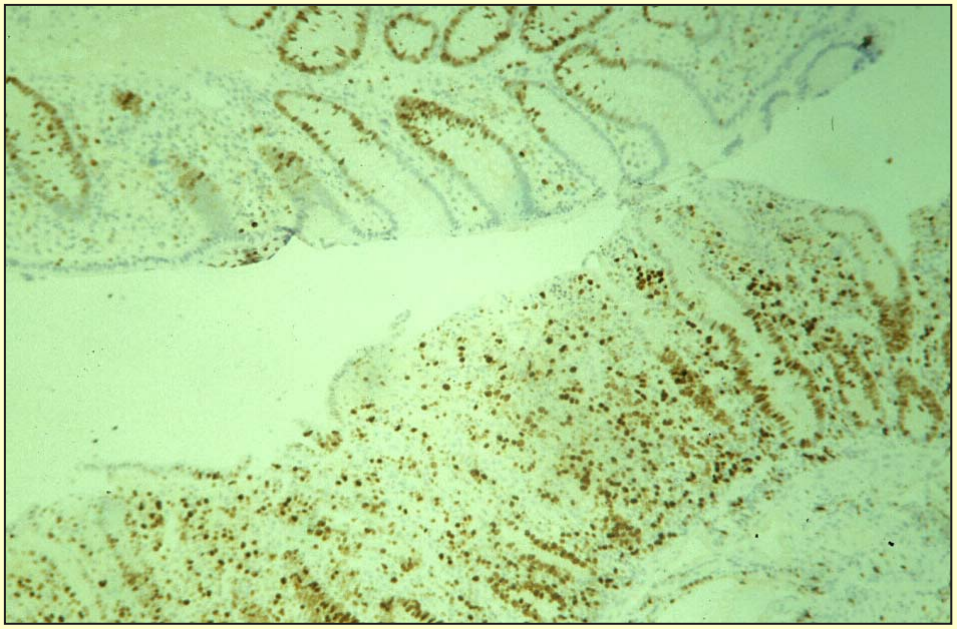
Basic lesions : Epithelial cells



- Restitution
- Mitotic activity

Basic lesions : Epithelial cells

- **Increased mitotic activity indicates repair : Ki67 in Ulcerative colitis : upregulation**



Basic lesions : Epithelial cells

- Metaplasia
  - Paneth cell metaplasia
  - Ulcer associated cell lineage

Clinical Situations

- **No clinical information**
  - **Non specific colitis**
- **Normal macroscopy**
  - **Microscopic colitis**
    - **Collagenous colitis; lymphocytis colitis; giant-cell colitis; microscopic colitis otherwise not specified (mos)**
- **Inflammatory diarrhoea**
  - **Infectious colitis**
  - **Drug-induced colitis**
  - **Inflammatory bowel disease**
  - **Miscellaneous**

No clinical information

"Non-specific inflammation"

Tsang & Rotterdam, Am J Surg Pathol 1999; 23: 423-30

- **Increase in inflammatory cells beyond what would be expected physiologically in the corresponding anatomic sites. Crypts may show reactive changes, such as an increase in mitoses and slight irregularity in shape.**
- **Lack of sufficient clinical data or distinctive histopathological features precludes further classification into specific etiologic types of colitis**

No clinical information

"Non-specific inflammation"

Tanaka & Riddell, Hepato-gastroenterol 1990; 37: 18-31

- **Predominantly chronic inflammatory cell infiltrate in the absence of architectural distortion and multiple basal lymphoid aggregates or plasma cells immediately above the muscularis mucosae.**
- **Such a pattern can be seen in resolving infections, complicated diverticular disease, drug-induced colitis and bile-salt malabsorption, but may include CD. However, it is currently impossible to make a positive diagnosis of CD in these circumstances, although in a patient with known CD the lesions may well represent local involvement**

Normal endoscopy

- Pts with clinical suspicion irritable bowel syndrome (IBS) and normal colon at endoscopy
- Mucosal inflammation present in 27% of pts with chronic diarrhoea and negative macroscopic findings
  - Whitehead R. Virch Arch Pathol Anat 1990; 47; 187

Prolonged Diarrhea
Normal endoscopy

No new case of IBD

Melanosis coli - Microscopic colitis

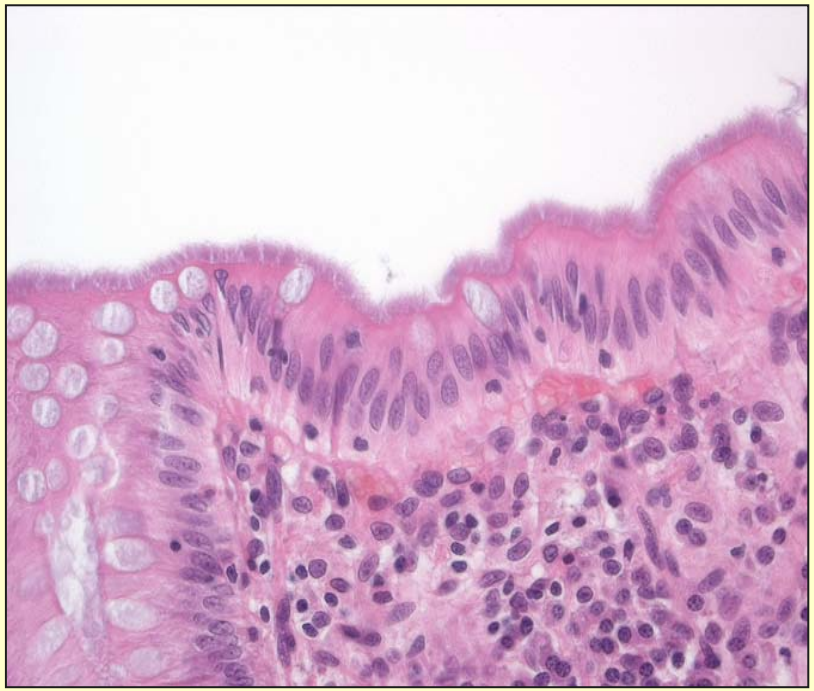
- 59 patients : colonoscopy for anemia : normal biopsy McIntosh e.a. Am J Gastroenterol 1992; 87; 1407
- 100 consecutive patients : symptoms ? : 22 pathologic biopsy Prior e.a. Dis Dis Sci 1987
- 111 patients : 20 pathologic biopsy, Marshall e.a. 1994

Normal endoscopy

- Infections
- Post infectious IBS
- Drug-related disease
- Microscopic colitis
  - Collagenous colitis
  - Lymphocytic colitis
    - Idiopathic
    - Infectious
    - Drug-related
  - Giant cell colitis
  - Microscopic colitis otherwise not specified

Human Intestinal Spirochetosis

- ♂ > ♀
- **Less common in children ?**
- **Usually asymptomatic**
- **Pathogen/commensal ?**
- **↑ incidence in homosexual men and immunocompromised (AIDS) pts**



Infections & Colitis

- **Enterohemorragic E. coli : important in western world**
- **lesions in terminal ileum and colon**
- **Microscopy**

Normal	Acute inflam	Ischemic type
12 / 31	10 / 31	5 / 11

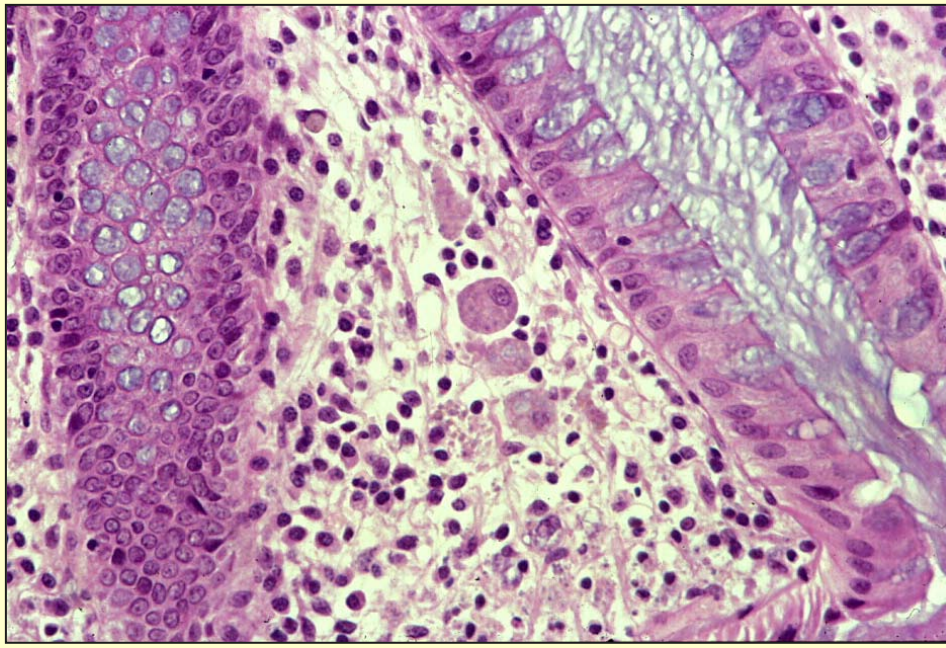
Combination	Pseudomembranous colitis
4/11	4 / 11

(Griffin e.a. Gastroenterology 1990, 99, 142; Kelly e.a. Am J Clin Pathol 1987, 88, 78)

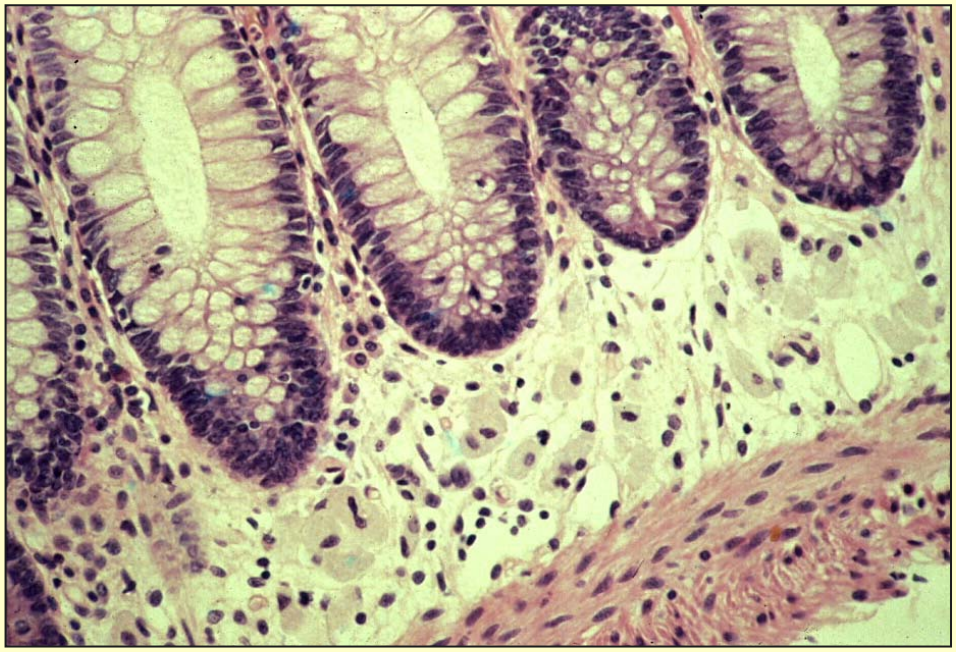
Infections & Colitis macrophages

- Lou e.a. Hum Path 1971; 2; 421

  Colonic histiocytosis : 34/50 (68%) consecutive rectal biopsies : small collections of PAS+ cells
- Bejarano e.a. Am J Surg Pathol 2000; 24; 1009 40% of biopsies +; associated changes point to healing phase

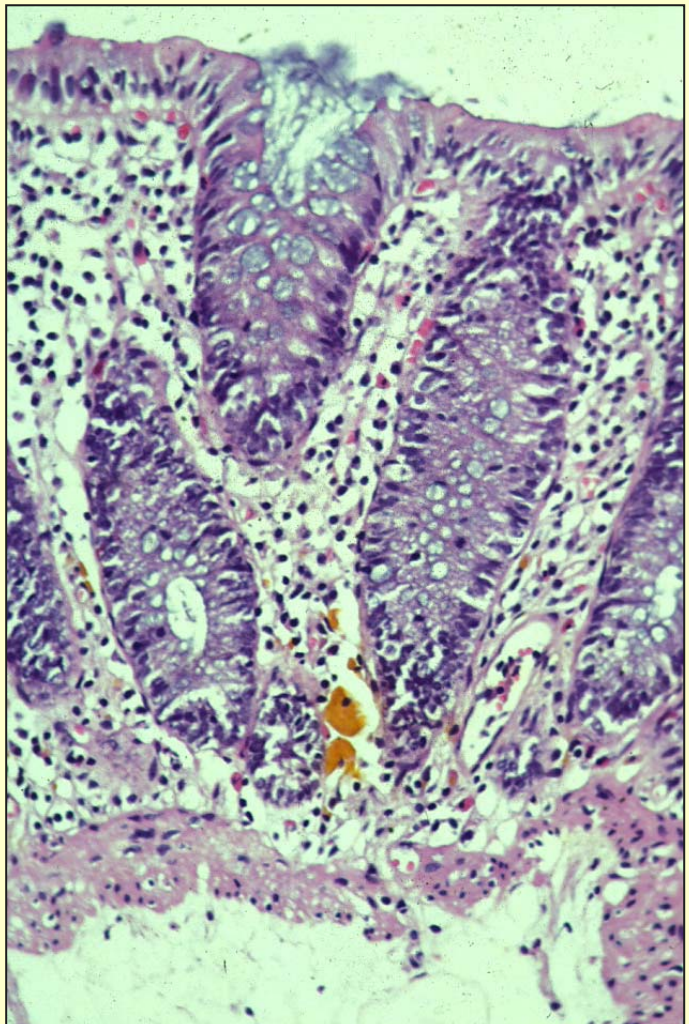


Macrophages (476367) or Storage diseases (698451)

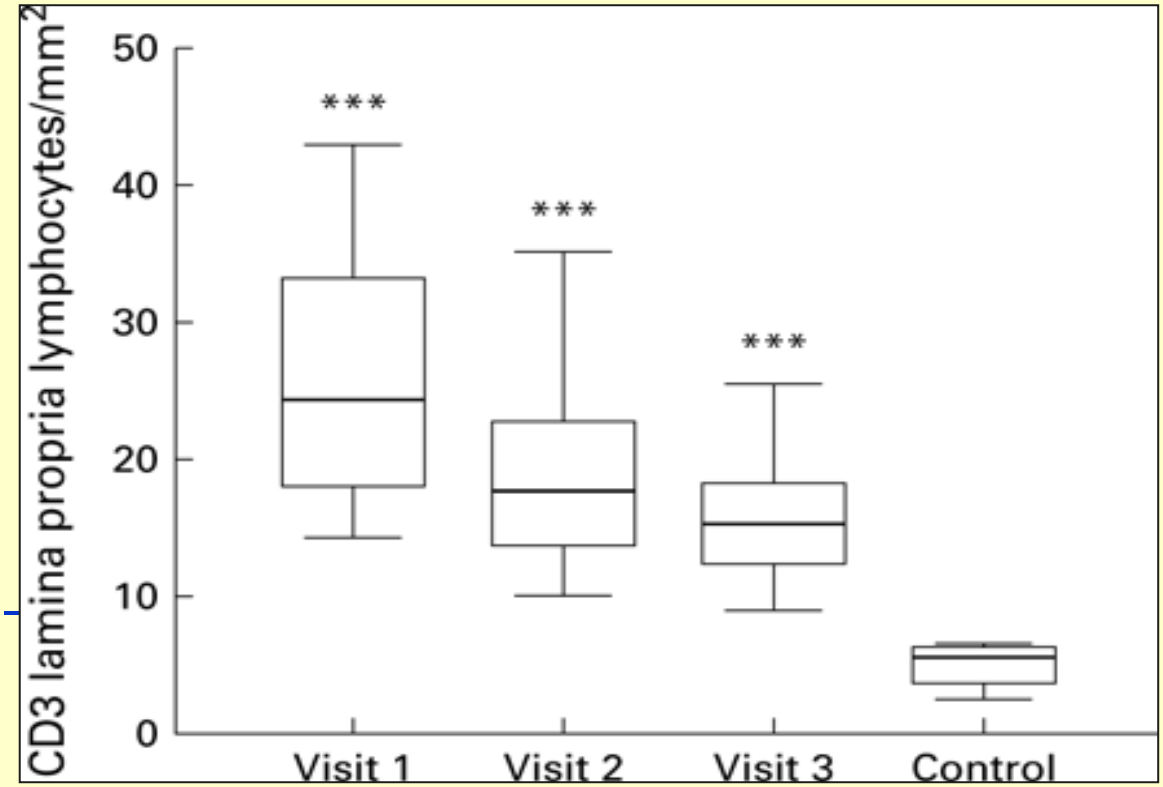


Infections & Colitis
macrophages

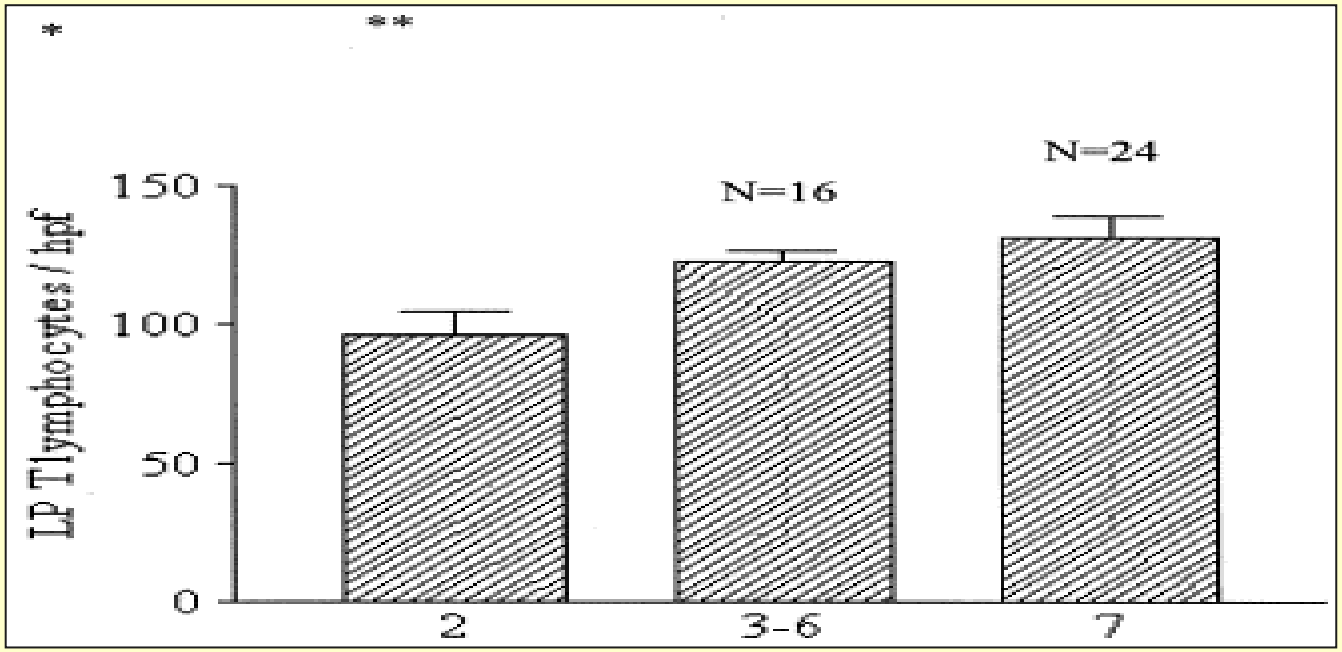
- **Bile salt colitis**
- **Storage diseases**



Post infectious IBS
25% of pts with Campylobacter colitis



CD3 staining lamina propria lymphocytes.
***p<0.001 v controls. Spiller e.a. Gut 2000; 47; 804



Lamina propria (LP) T lymphocyte counts per high power field (hpf) in 52 IBS patients with diarrheal symptoms. Lymphocyte scores increased with increasing frequency of diarrhea. *p = 0.04 *vs* 2 days/wk of loose stools. **p = 0.012 *vs* 2 days/wk of loose stools. (Dunlop e.a. Am J Gastroenterol 2003; 98; 1578)

Drug-Induced Colitis : The Problem

- Diarrhoea is a frequent adverse event of drugs
  - 7% of all drug adverse effects
  - 4.1% in 5,669 pts with lansoprazole
- More than 700 drugs have been implicated in causing diarrhoea
- Colitis is less common and associated with less drugs

Drug-Induced Colitis : Clinical Presentation

- **Acute Diarrhoea**
  - **Usually during the first days of treatment**
- **Chronic Diarrhoea**
  - **Can appear long time after start of drug**

Drug-Induced Colitis :Pathogenesis of diarrhoea (& colitis)

- **Secretory diarrhoea**
  - Antineoplastics, gold salts, biguanides, cardiac glycosides, prostaglandins
- **Shortened transit time**
  - Cisapride, erythromycin
- **Malabsorption of fat & carbohydrates**
  - Gold salts (auranofin) ..
- **Osmotic diarrhoea**
  - Lactulose, antacids, sugar substitutes

Drug-Induced Colitis :Pathogenesis of diarrhoea (& colitis)

- **Protein-loosing enteropathy**
  - **Antineoplastics, antibacterials**
- **Toxic and immunologic injury**
- **Promotion of infections**
  - **Antibacterials, antineoplastics, immunosuppressive agents..**
- **Allergic reaction**
- **Impairment of cell proliferation**

Drug-Induced Colitis : Patterns

- **Eosinophilic colitis**
  - **Aspirin**
  - **Psychotropic drugs (carbamazepine)**
  - **Ticlodipine**
- **Microscopic colitis (Lymphocytic more common)**
  - **Proton pump inhibitors**
  - **NSAIDs**
  - **Veinotonics**

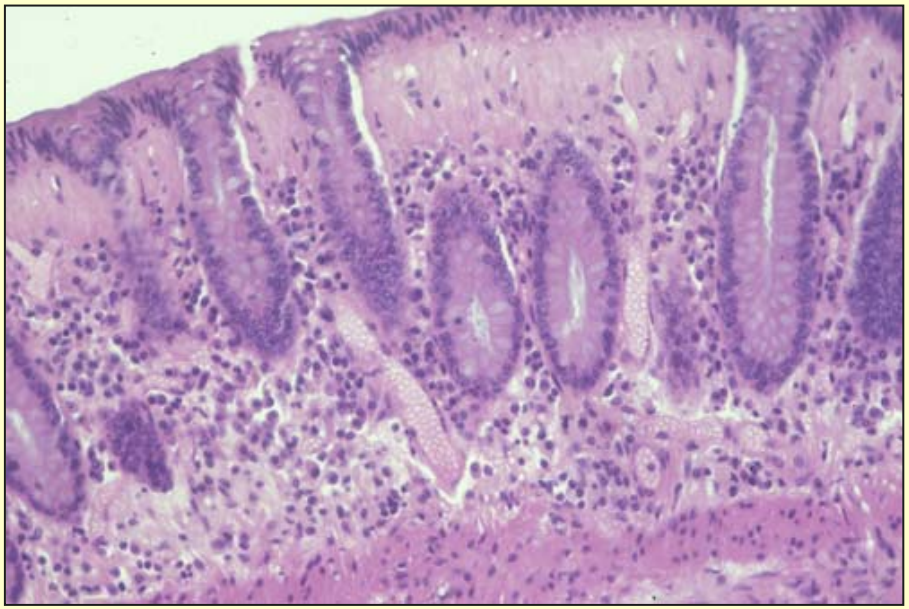
H2 receptor antagonists

Ticlodipine

Carbamazepine

Microscopic colitis

- **Collagenous colitis**
  - **Chronic watery diarrhoea**
  - **Discontinuous thickening of subepithelial collagen table**
  - **Multiple biopsies**
  - **Changes with treatment**



Microscopic colitis
Collagenous colitis

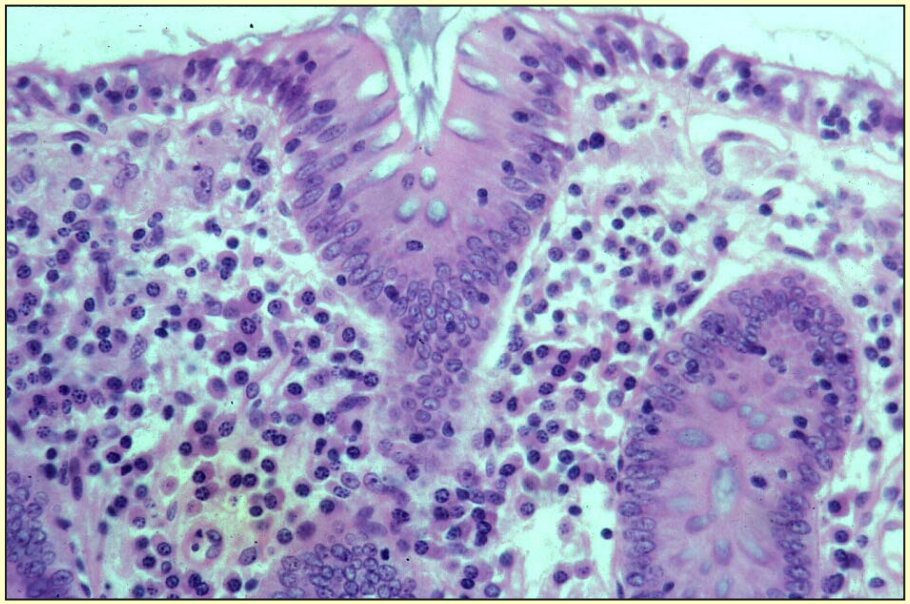
- Normal crypt architecture
- Increased subepithelial collagen band (nl 0-3 μm; more than 7, 10 or 15 to 20 μm)
- Increase number of intraepithelial lymphocytes (nl = 4/100)
- Increase of mononuclear cells in lamina propria
- Paneth cell metaplasia (more severe disease; relation with IBD?)

Microscopic colitis
Collagenous colitis

- Biopsies of the whole colon are required as sigmoid and rectum may fail to show significant thickening of collagen band
  - Jessurun e.a. Hum Pathol 1987; 18; 839
  - Offner e.a. Hum Pathol 1999; 30; 451
- Staining for tenascin may be useful for the diagnosis of minimal collagenous colitis
  - Muller e.a. Virch Arch 2001; 438; 435-41

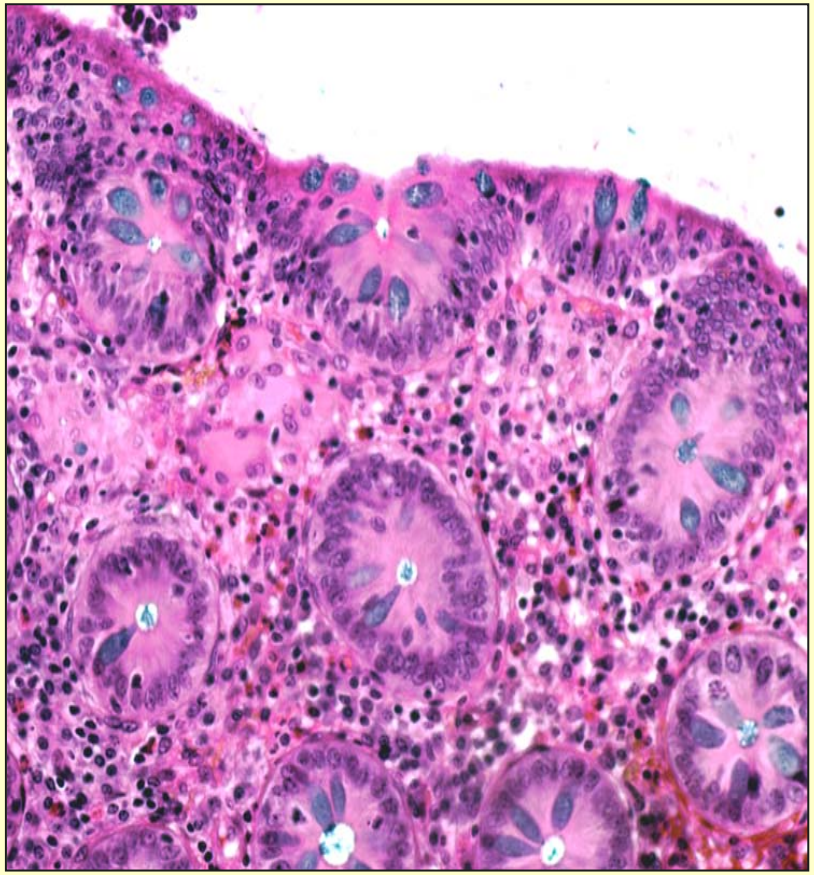
Microscopic colitis

- **Lymphocytic colitis**
  - **Normal architecture**
  - **Flattened – cuboidal surface ep cells**
  - **Increase in interepithelial lymphocytes (>20/100)**
  - **Increase in lamina propria cells**



Microscopic colitis

- **Microscopic colitis with giant cells**
  - Libbrecht e.a. Histopathology 2002; 40; 335
  - Sandmeier & Bouzourene Int J Surg Pathol 2004; 12; 45
- **Cryptal lymphocytic coloproctitis**
  - Rubio & Lindholm J Clin Pathol 2002; 55; 138



Microscopic colitis

Microscopic colitis not other wise specified (NOS)

Warren BF, Histopathology 2002; 40

in stead of nonspecific colitis

- **Patients with chronic diarrhoea and normal colonoscopy**
- **Increase in inflammatory cells in multiple biopsies**

Microscopic colitis & IBD

- **26 pts with a diagnosis of IBD and microscopic colitis (based on a review of 12 centres : 9 Europe; 3 North America)**
  - **Panaccione e.a. Gastroenterology 1999; 116: A833**
  - **Geboes IOIBD, unpublished**
- **Progression towards Ulcerative colitis**
  - **4 pts : elderly patients, pancolitis, Geboes IOIBD**
  - **Pokorny e.a. J Clin Gastroenterol 2001; 32; 435**
- **Progression towards Crohn's disease**
  - **2 pts : Geboes IOIBD**
- **Healing (?) after IBD**

Inflammatory diarrhea

Acute unclassified colitis (6 wks duration) Notteghem e.a.
Gastroenterol Clin Biol 1993, 17, 811-815

104 pts; follow-up : 2.5-3yrs

results :

- **16 Lost for follow-up**
- **88 - 46 (52.3%) > IBD**

  54% = UC 33% = CD
  13% = Unclass

  - 42 (47.7%) > no relapse

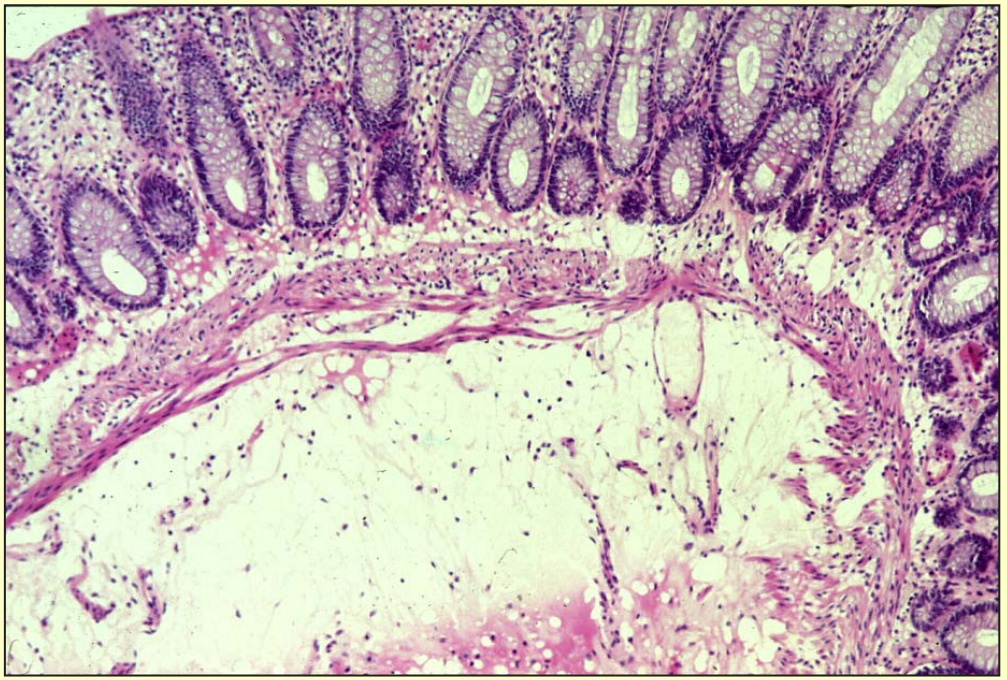
Infective-type colitis

Spectrum of microscopic features

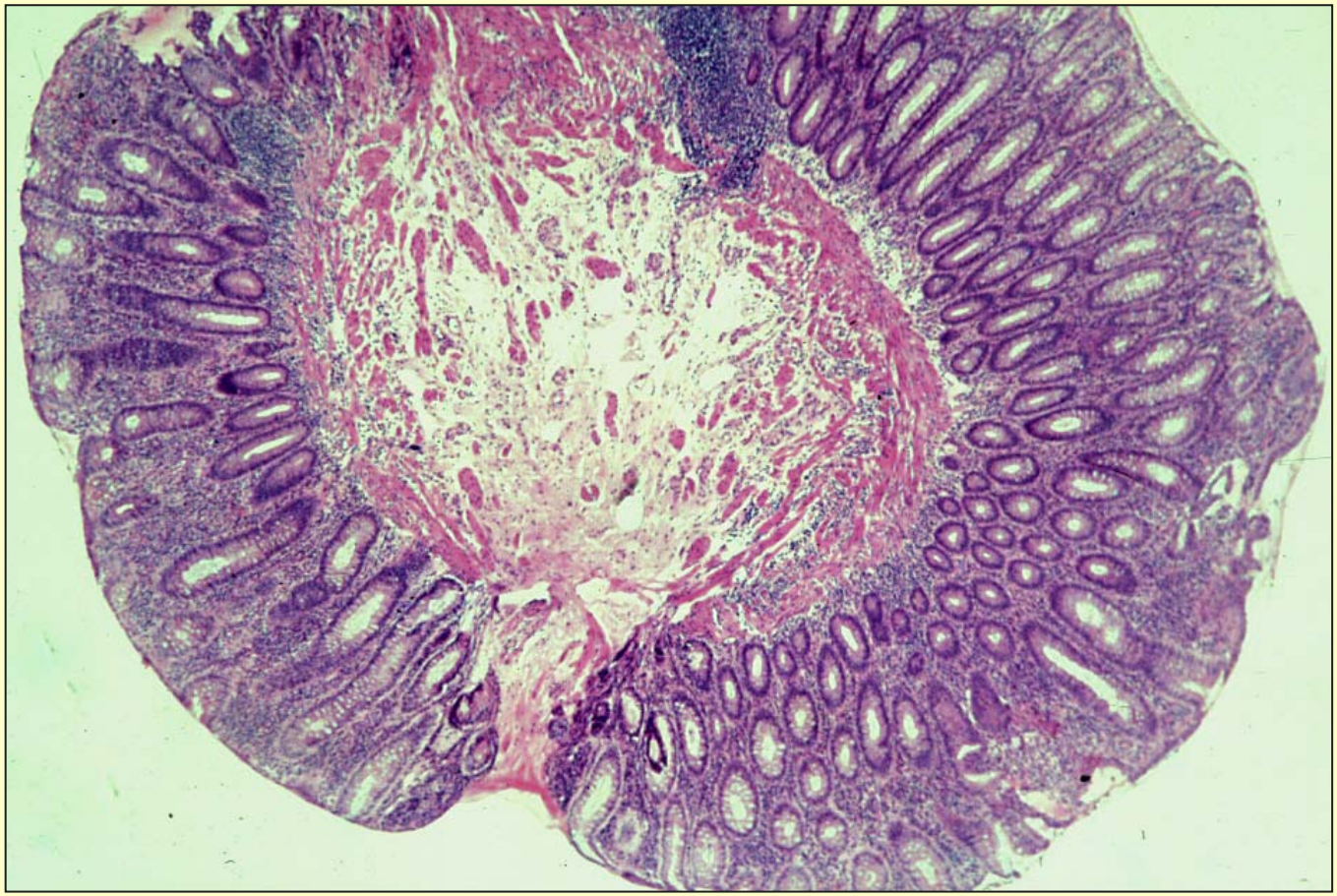
- normal biopsy — toxins
  - Vibrio ch; Klebsiella
- oedema
- active inflammation — invasion
  - Yersinia, Campylo
- fulminant lesions (extensive necrosis)
- residual lesions

Oedema

- **Drug-induced**
  - **Laxatives, enema**
- **Infections**



Infective-type colitis (593579)



Infective-type colitis
Microscopic features

- **Architecture**
  - **NORMAL (except ...) String of Pearls**
- **Inflammation**
  - **DISTRIBUTION : focal – patchy**
  - **COMPOSITION**
    - **NEUTROPHILS (active acute)**
      - **early (day 1-7) Superficial upper part of lamina propria & upper part of crypts**
    - **MONONUCLEAR CELLS**
      - **late (day 9, 10)**
      - **superficial (except...)**

IBD and infection at diagnosis

First attack of colitis

- **ASLC group** **78% + culture**
- **IBD group** **21% + culture**

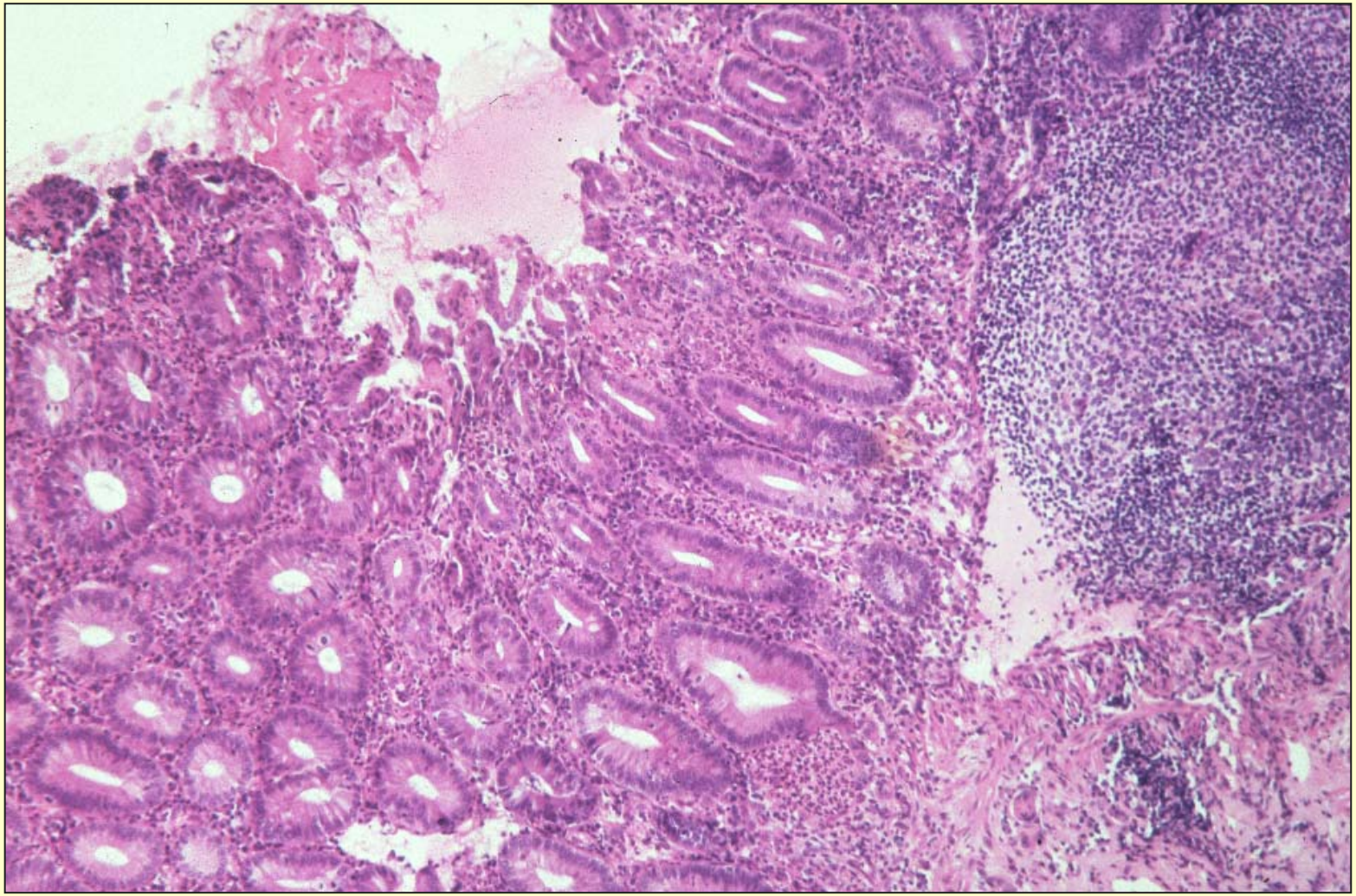
Schumacher e.a. Scand J Gastroenterol 1993, 28, 1077-85

IBD and superinfection at relapse

Species	CD	UC
• C. difficile	4	1
• Salmonella typhimurium	0	1
• Campylobacter jejuni	1	0
• Enteropathogenic E. coli	3	0
Initial nr of patients	49	15
Total nr positive	9(18%)	2(13%)

Weber e.a. J Clin Gastroenterol 1992, 14, 302-8

Amoebiasis



Colonoscopy in inflammatory diarrhea
Where to biopsy? How many?

Number of samples (Bentley e.a. J Clin Pathol 2002, 55; 955)

Material & Methods

25 pathologists

60 cases with follow up (rectal & full colonoscopic series)

Results

	Rectum	full series
Crohn's disease :	24%	> 64%
Ulcerative colitis :	64%	> 74%

Colonoscopy & biopsy in inflammatory diarrhea

- **Diagnostic accuracy : 92 – 96%**
  - **Pera e.a. Gastroenterology, 92; 1987**
  - **Dejaco e.a. Endoscopy 35; 2003**

    Clinical data, endoscopy and biopsy = accurate diagnosis in 96%
- **Endoscopy is the first-line procedure in the initial evaluation of patients with unexplained diarrhea and suspected IBD because of**
  - **Direct visual appreciation of lesions**
  - **The ability to collect biopsy samples**

D.D Chronic Idiopathic Inflammatory Bowel Disease - Acute Self Limiting (Infectious type) Colitis

- Surawicz e.a. 1984
- Nostrant e.a. 1987
- Schmitz-Moorman & Himmelman, 1988
- Therskildsen e.a. 1989
- Notteghem e.a. 1993
- Schumacher e.a. 1994

D.D Chronic Idiopathic Inflammatory Bowel Disease - Acute Self Limiting (Infectious type) Colitis

- Surawicz e.a. 1984 : 148 pts, (44) - (22 short course IBD, 82 long course, 26 CD)
  - 75% of CD : crypt distorsion
- Nostrant e.a. 1987 : 168 pts, (48) - (36 short course - 84 long course UC)
  - Histopathology differentiates ASLC from UC (crypt distorsion - plasmacytosis)
- Therskilden e.a. 1989 : 32 pts
  - lesions absent at 1 mth, no predictive value

D.D Chronic Idiopathic Inflammatory Bowel Disease - Acute Self Limiting (Infectious type) Colitis

Basic lesions

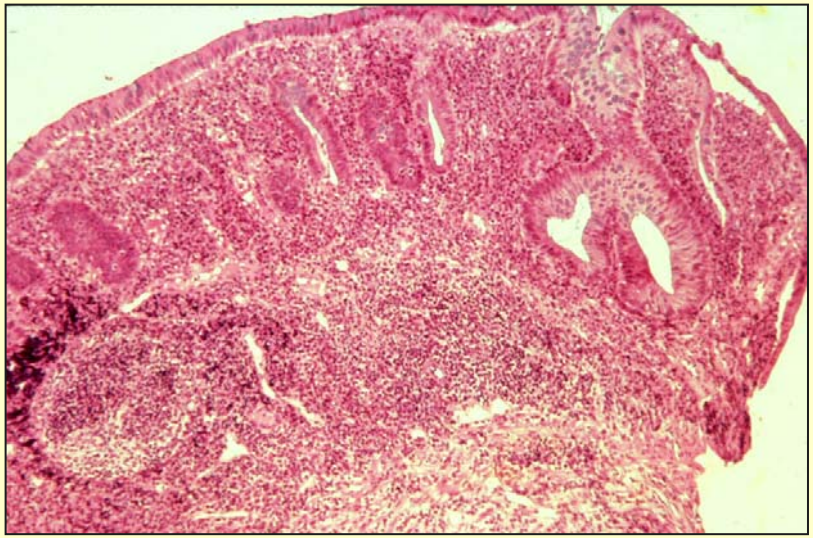
mucosal architecture

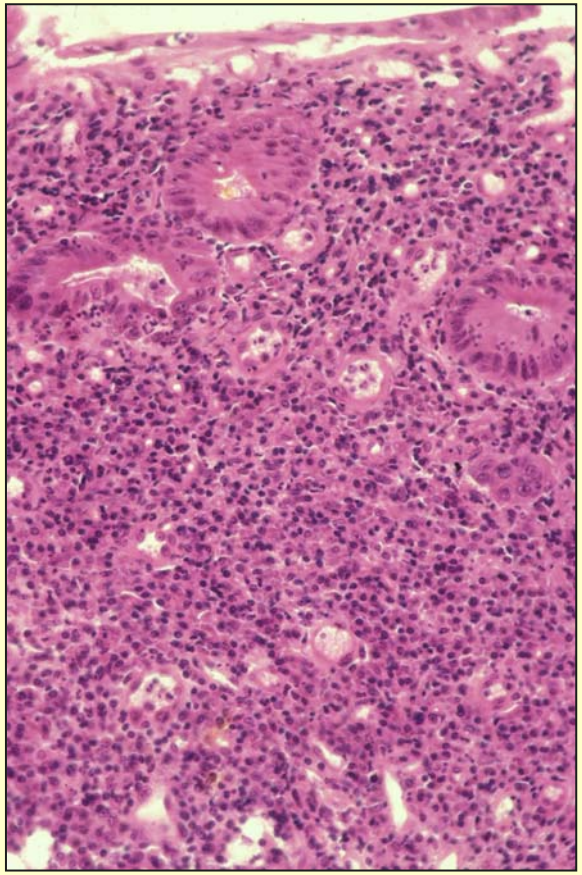
- regular - irregular surface
- crypt distorsion

inflammatory infiltrate

- basal plasmacytosis

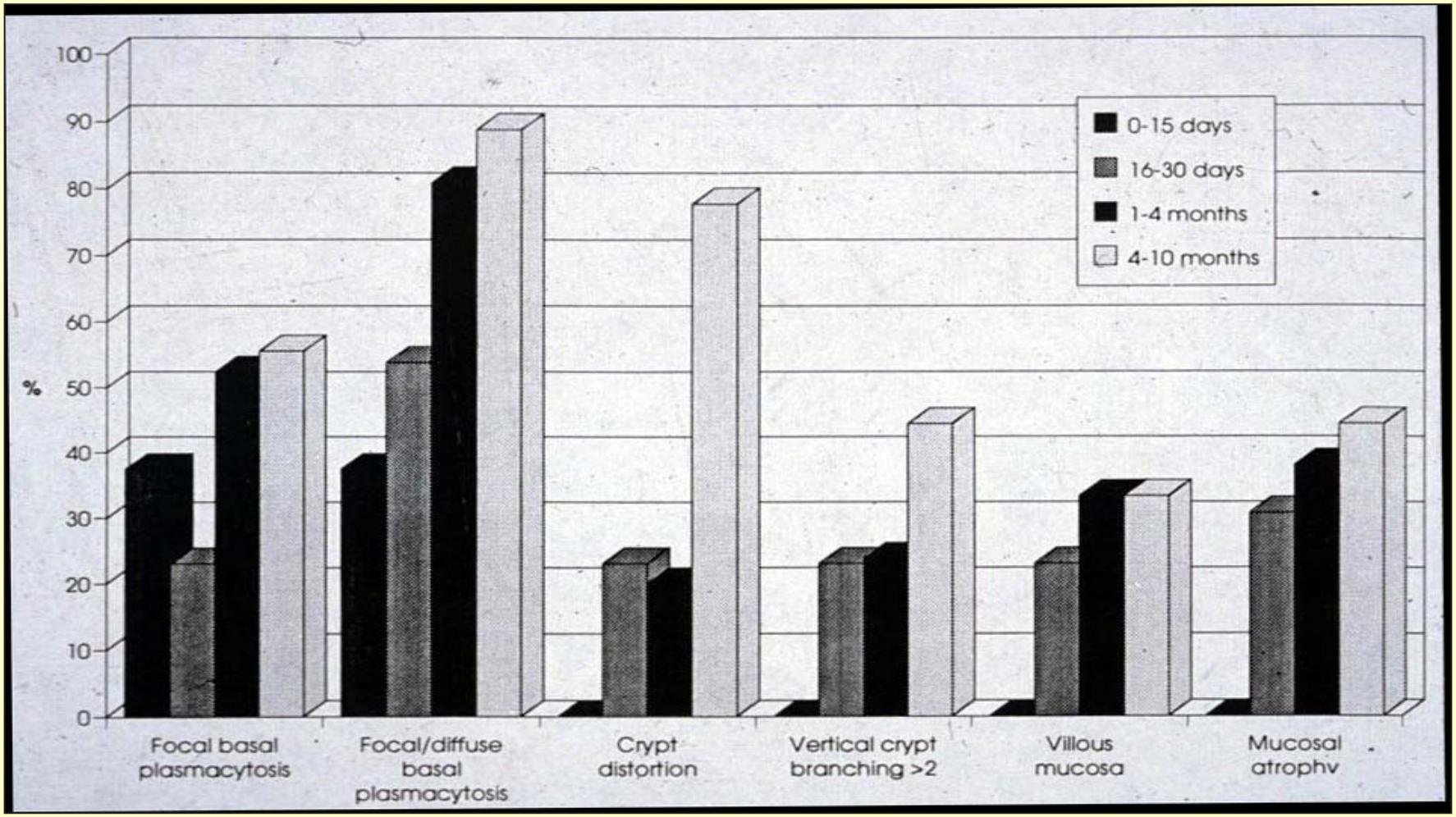
Chronic Idiopathic Inflammatory Bowel Disease
Ulcerative colitis





Biopsy Diagnosis & IBD - Evolution in Time

Schumacher e.a. Scand J Gastroenterol 1994



Colonoscopy in inflammatory diarrhea
Repeat Endoscopy!

- **Repeat endoscopy can help to establish a precise diagnosis**
  - **12 pediatric pts with indeterminate colitis > UC Markowitz Am J Gastroenterol 88; 1993**
  - **14% (out of 96) developed a pattern more consistent with UC**
    Langevin e.a. Am J Gastroenterol 15; 1992
- **Repeat biopsy can help to establish a precise diagnosis**

Drug-Induced Colitis : Lesions, type & distribution & evolution

- **Microscopy**
  - **Normal**
  - **Infectious-type colitis**
  - **IBD-like pattern**
  - **Specific features**
- **Variable**
  - **oedema**
  - **ischemic-type colitis**
  - **microscopic colitis**
- **Evolution**
  - **Complete remission after elimination of offending agent**

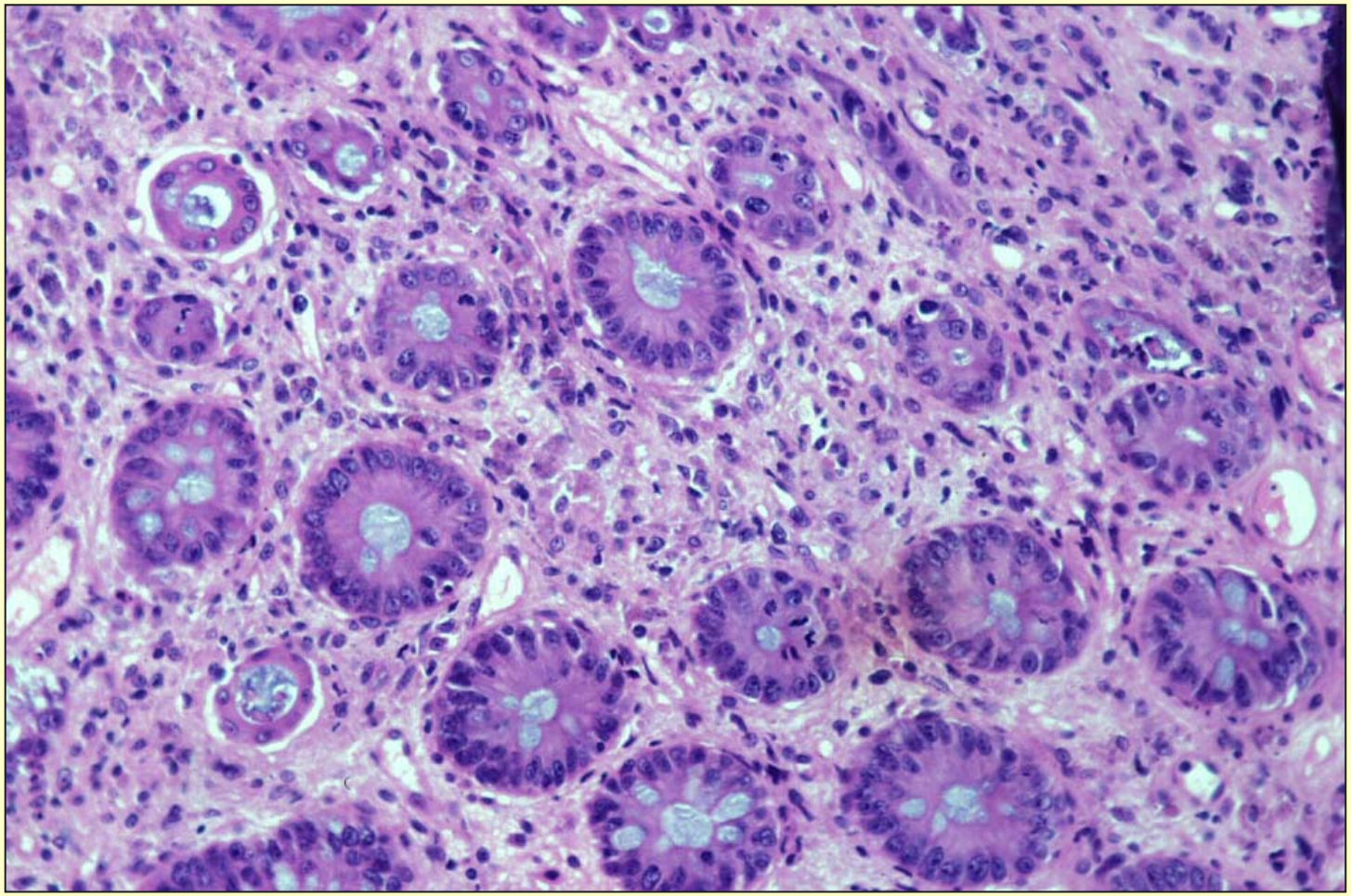
Drug-Induced Colitis : Patterns

- **Infective-type colitis**
  - **Antibacterials**
  - **NSAIDs**
  - **Cyclosporin**
- **Ischemic-type colitis**
  - **Cardiovascular drugs (diuretics, digoxin, antihypertensive drugs…)**
  - **Oral contraceptives**
  - **Ergot alkaloids**
  - **NSAIDS**

Drug-Induced Colitis : Patterns

- IBD-like pattern : Crohn's disease without granulomas
  - Mycophenolate mofetil
- IBD-like pattern : Crohn's disease with granulomas
  - Diclofenac
  - Clofazimine
- IBD-like pattern : Ulcerative colitis
  - Diclofenac
  - Amionogluthemide (antineoplastic agent)
- Graft-versus-host-like pattern (mofetil)

Graft-versus-host-disease (1070784)



Graft-versus-host-disease

- **Differential diagnosis**
  - **conditioning regimen**
  - **toxic drug reactions**
  - **primary infections**
- **Acute GVHD : focal crypt cell necrosis (apoptosis - “popcorn lesion”)**
- **Chronic GVHD : extensive crypt cell degeneration - loss of crypts**

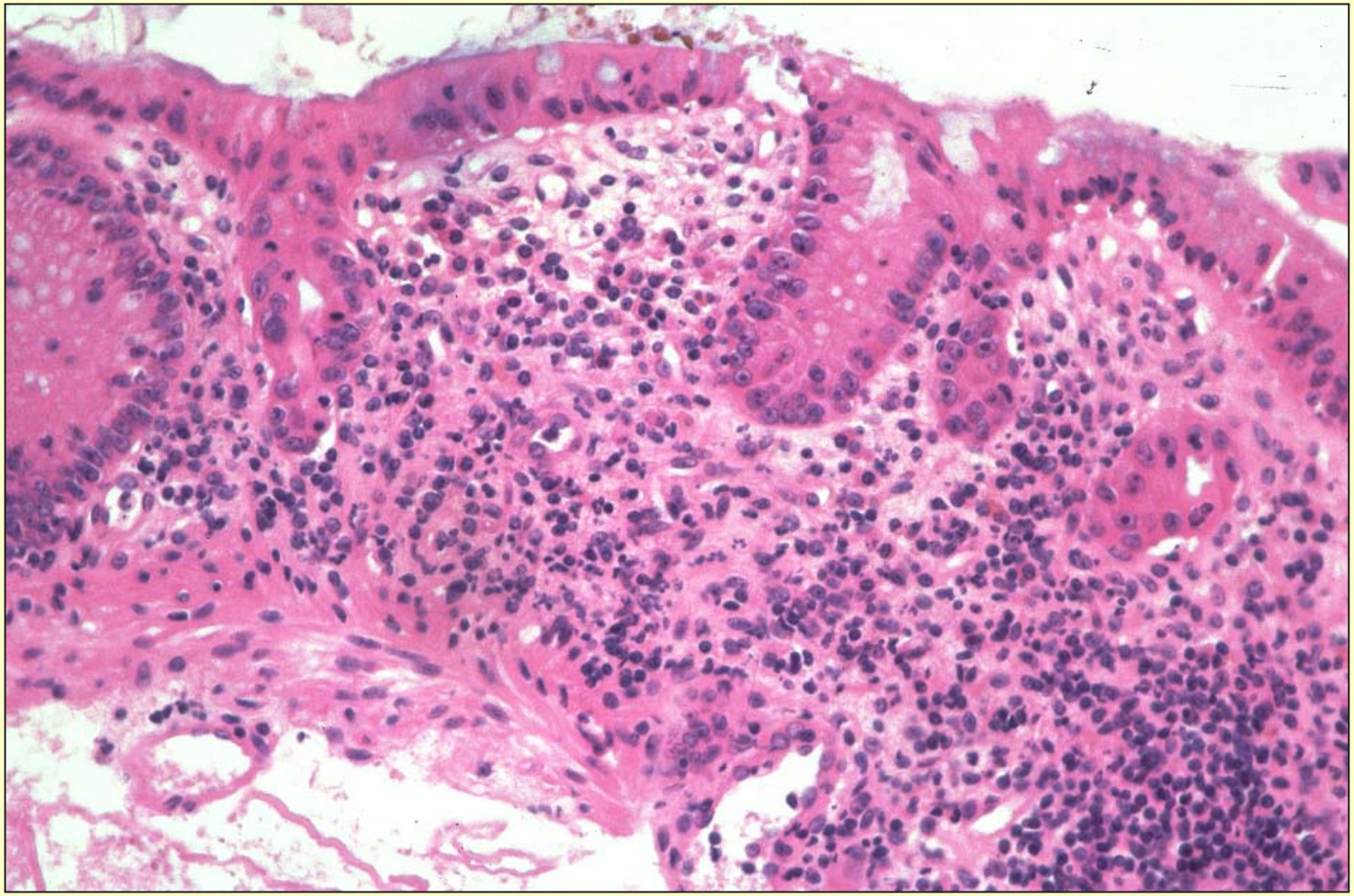
Mofetil Mycophenolate & Chronic diarrhoea

- **3/20 pts with Crohn's disease**

  Hafraoui e.a. Gastroentérol Clin Biol 2002, 26, 17

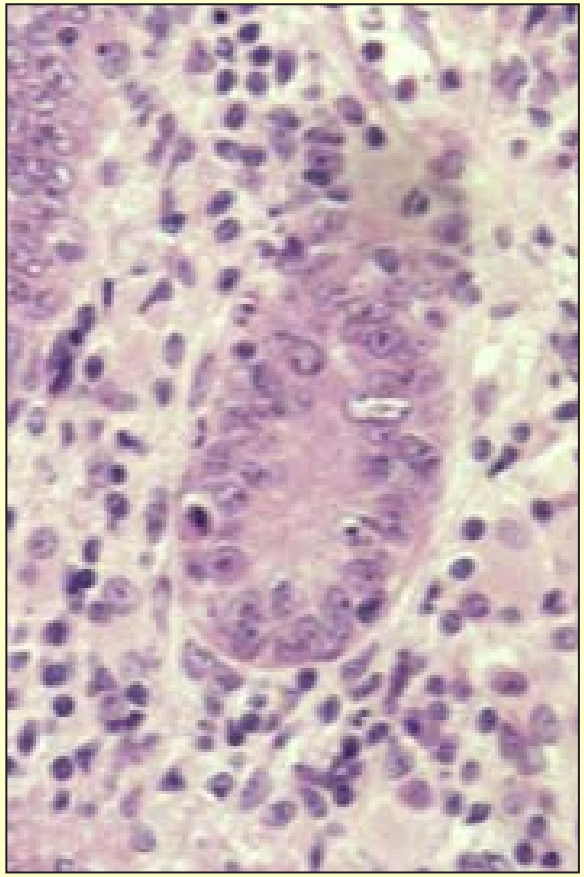
- **26 pts (mean age 41.5yrs) with cadaveric organ transplant > persistent afebrible chronic diarrhoea**
  - **13 infections (Campylobacter, CMV ..)**
  - **13 Crohn's-like morphology**

Mofetil Mycophenolate & Chronic diarrhoea



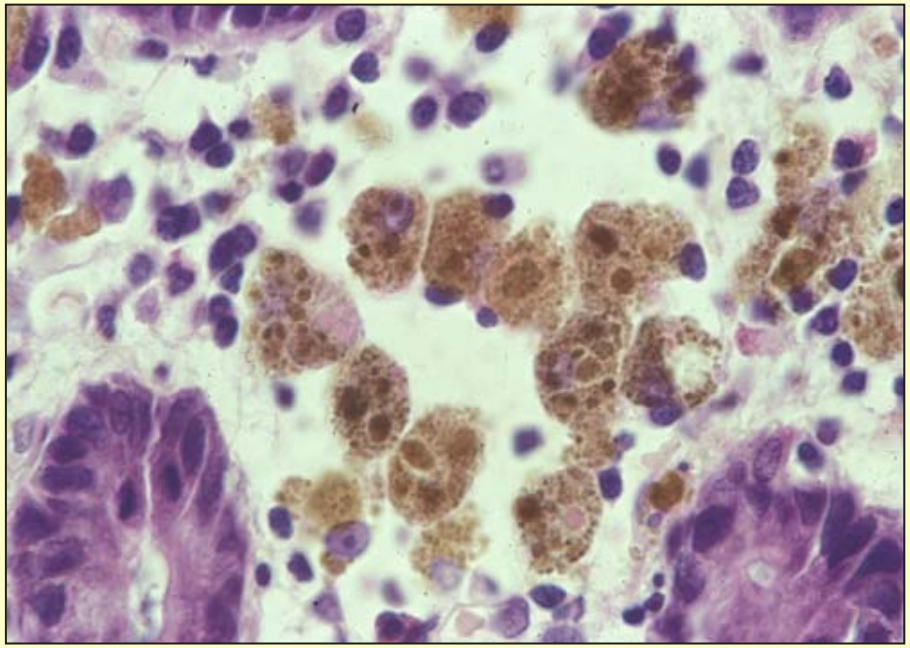
Drug-Induced Colitis : Patterns

- **Specific patterns**
  - **Pancreatic enzyme supplements and colonic strictures**
  - **Crypt epithelial cell apoptosis**
  - fluorouracil
  - NSAIDs (diclofenac, mefenamic acid)
  - Cyclosporin
  - Colchicine
  - Ranitidine
  - Ticlodipine



Drug-Induced Colitis : Patterns

- Specific patterns
  - Clofazimine and crystal-storing histiocytosis
  - (pseudo)melanosis coli
  - Kayexalate-sorbitol questran - colitis



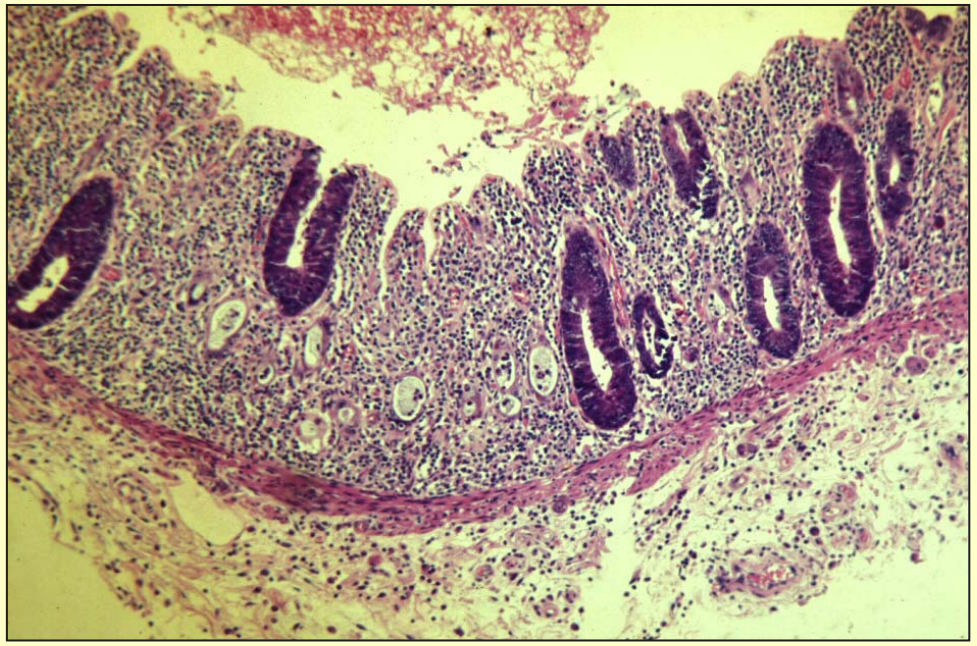
Drug-Induced colitis : Patterns
Kayexalat-sorbitol colitis

Miscellaneous

- **Architectural abnormalities**
  - **Transition points (rectum, caecum)**
  - **Post-surgery**
  - **Radiation**

Radiation-induced disease (662079/6)

- Acute
- Chronic
  - Loss of crypts
  - Fibrosis - hyalinization of stroma
  - vascular ectasias
  - limited inflammation

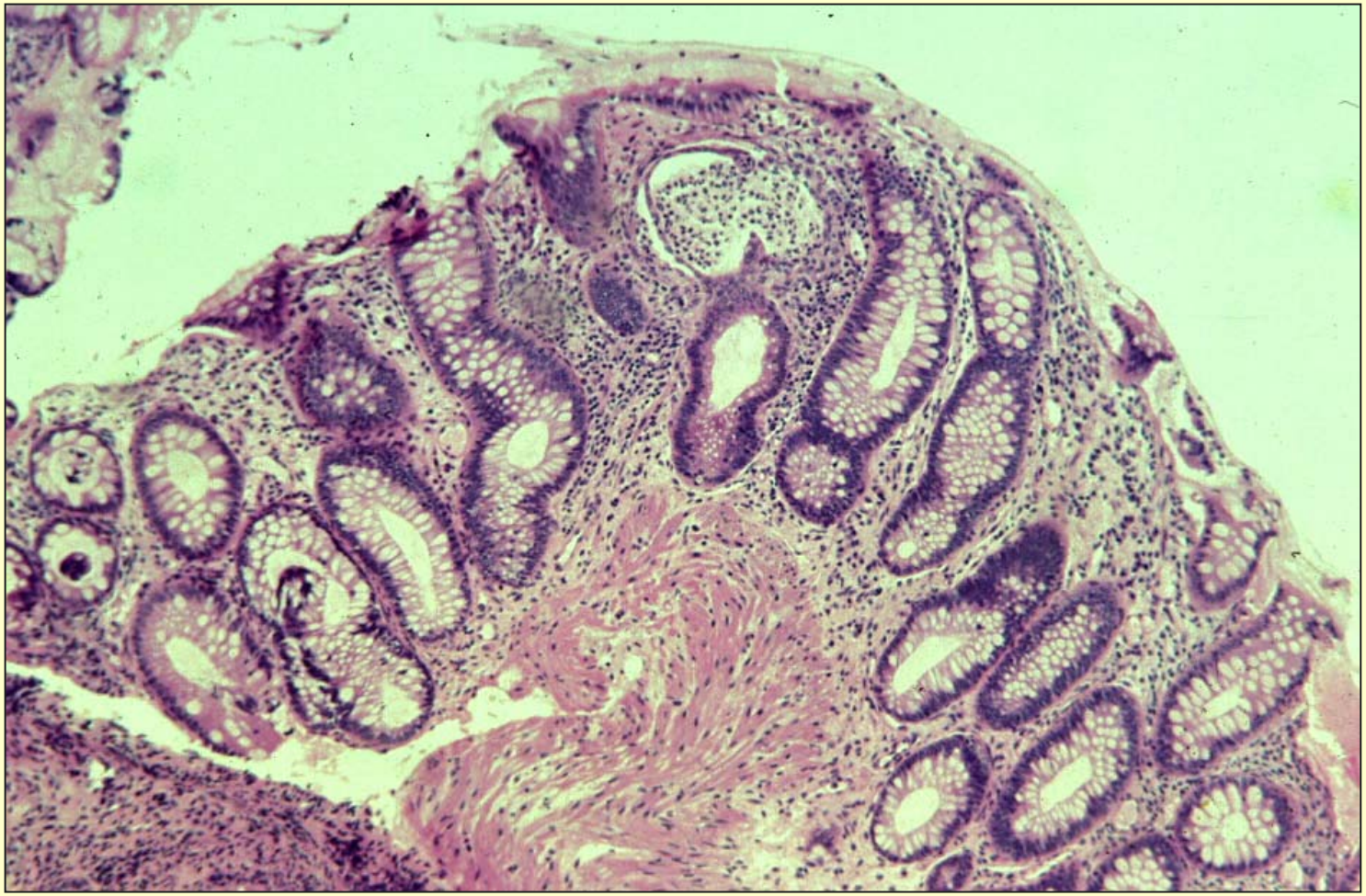


Focal active colitis

- Def : focal crypt injury by neutrophils
- 39 pts : no history of IBD (average follow up 20 mths)
- Results
  - 20 pts ASLC
  - 6 pts antibiotic associated colitis
  - 3 pts IBS
  - 2pts ischemic colitis
  - 1 pt radiation colitis
  - 7 incidental finding - no further diagnosis

Stern e.a. Gastroenterology 108; 1995, A922

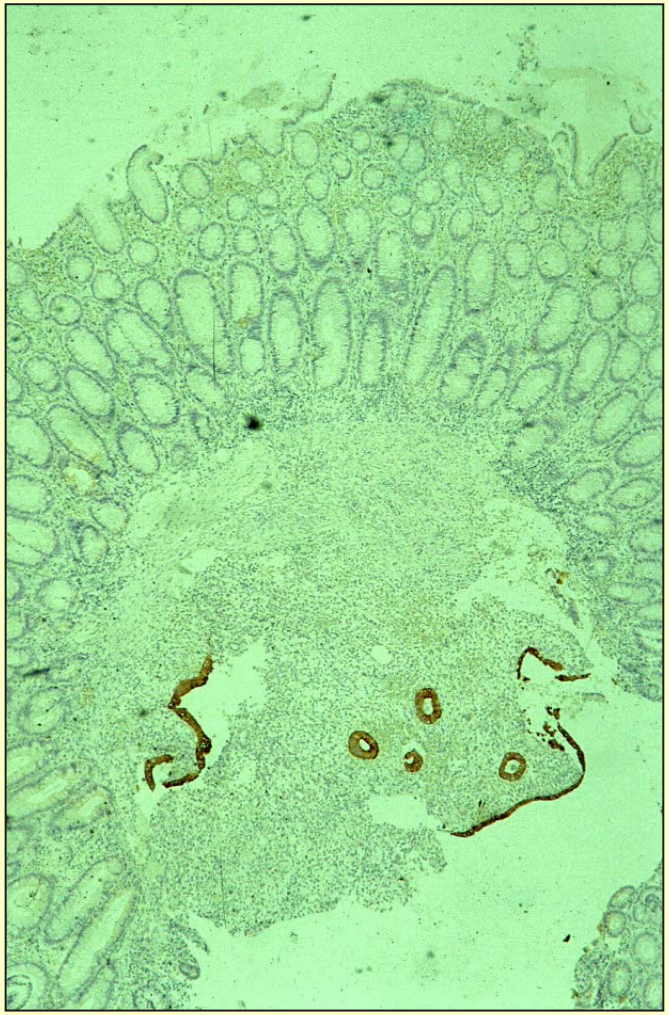
Focal active colitis (671857)

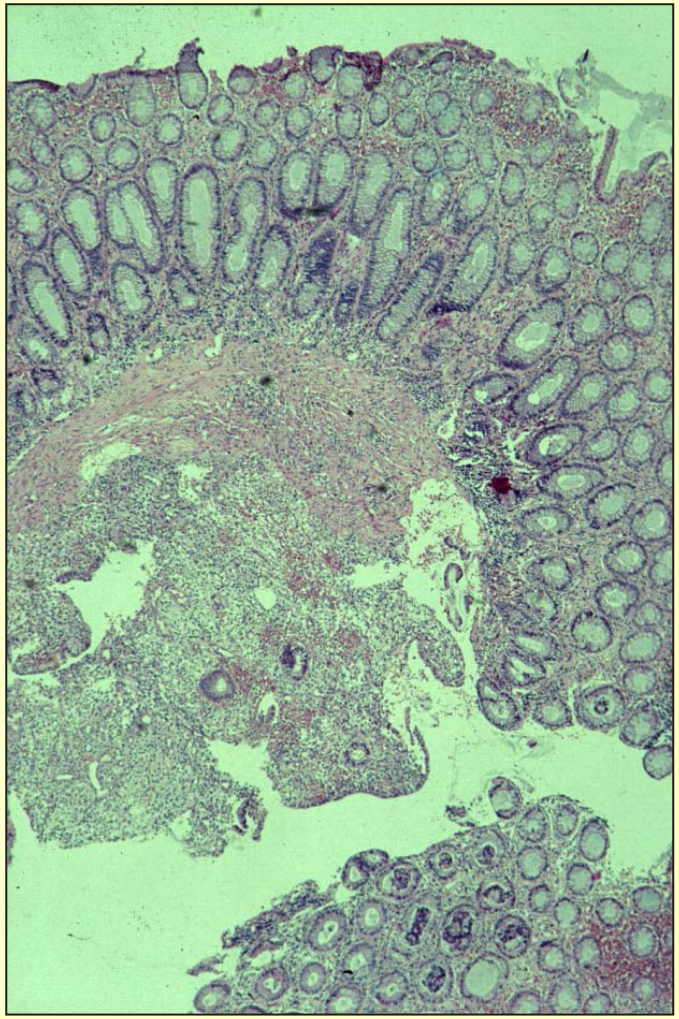


Endometriosis

- Intestinal endometriosis : prevalence
  - 3-37% of all endometriosis
- Anatomic distribution :
  - rectosigmoid 50-90%, caecum 2-5%, appendix 3-18%, small intestine 2-16%
- Asymptomatic Symptomatic
  - Ileal endometriosis : acute, chronic or recurrent distal small bowel obstruction
- (Small) Intestinal endometriosis
  - may mimic CD
  - may be associated with CD

Endometriosis (1036672) CK7





Diverticular disease-associated Colitis

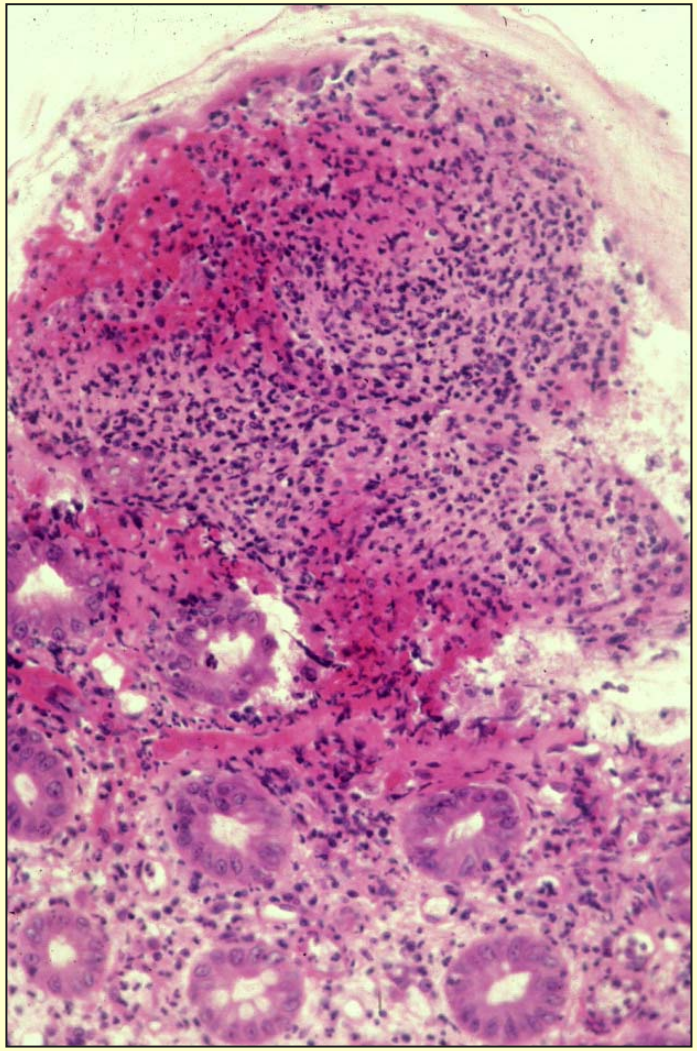
- Chronic colitis localized to the sigmoid colon and occurring in association with diverticular disease (Makapugay & Dean Am J Surg Pathol 1996, 20, 94-102; Ludeman & Shepherd Pathology 2002; 34; 568-572)
- Pathogenesis : multifactorial (mucosal prolapse, ischemia..)
- Microscopy
  - crypt distorsion, basal plasmacytosis > UC-like
  - fat wrapping, fissures - sinuses, granulomas > CD-like (Goldstein e.a. Am J Surg Pathol 2000, 24, 668-675)
  - no lesions proximal and distal
- Outcome
  - 3 / 23 > UC (Makapugay)
  - 2 / 25 > CD (Golstein)

Pseudomembranous colitis

- C. difficile induced
- Wide range of mucosal lesions (Rocca e.a. 1984)
  - No lesions 8%
  - Oedema & congestion 8%
  - Non-specific colitis 31%
  - Classic features 53%

Pseudomembranous colitis (678450/1)

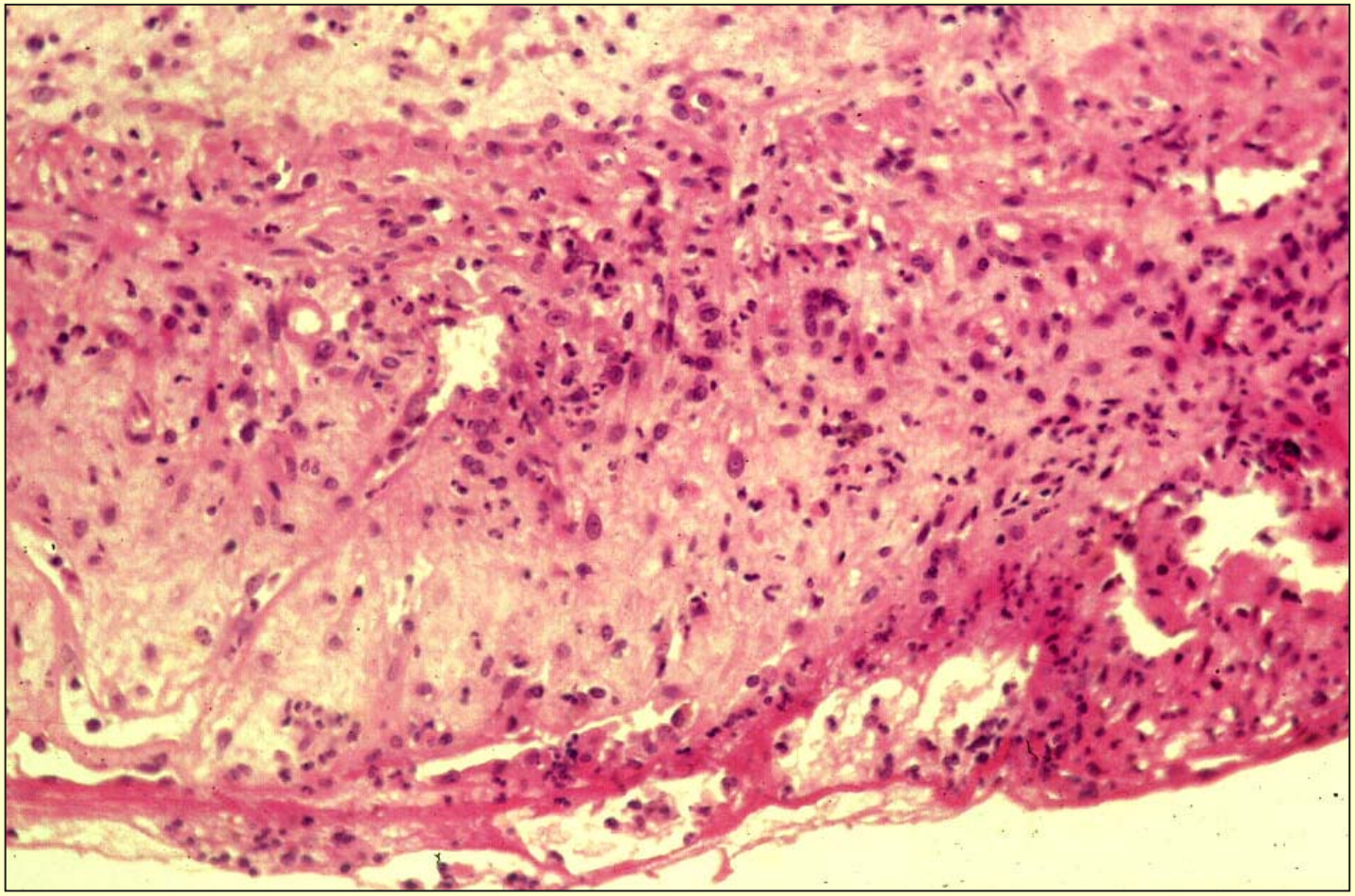
Pseudomembranous colitis (678138)



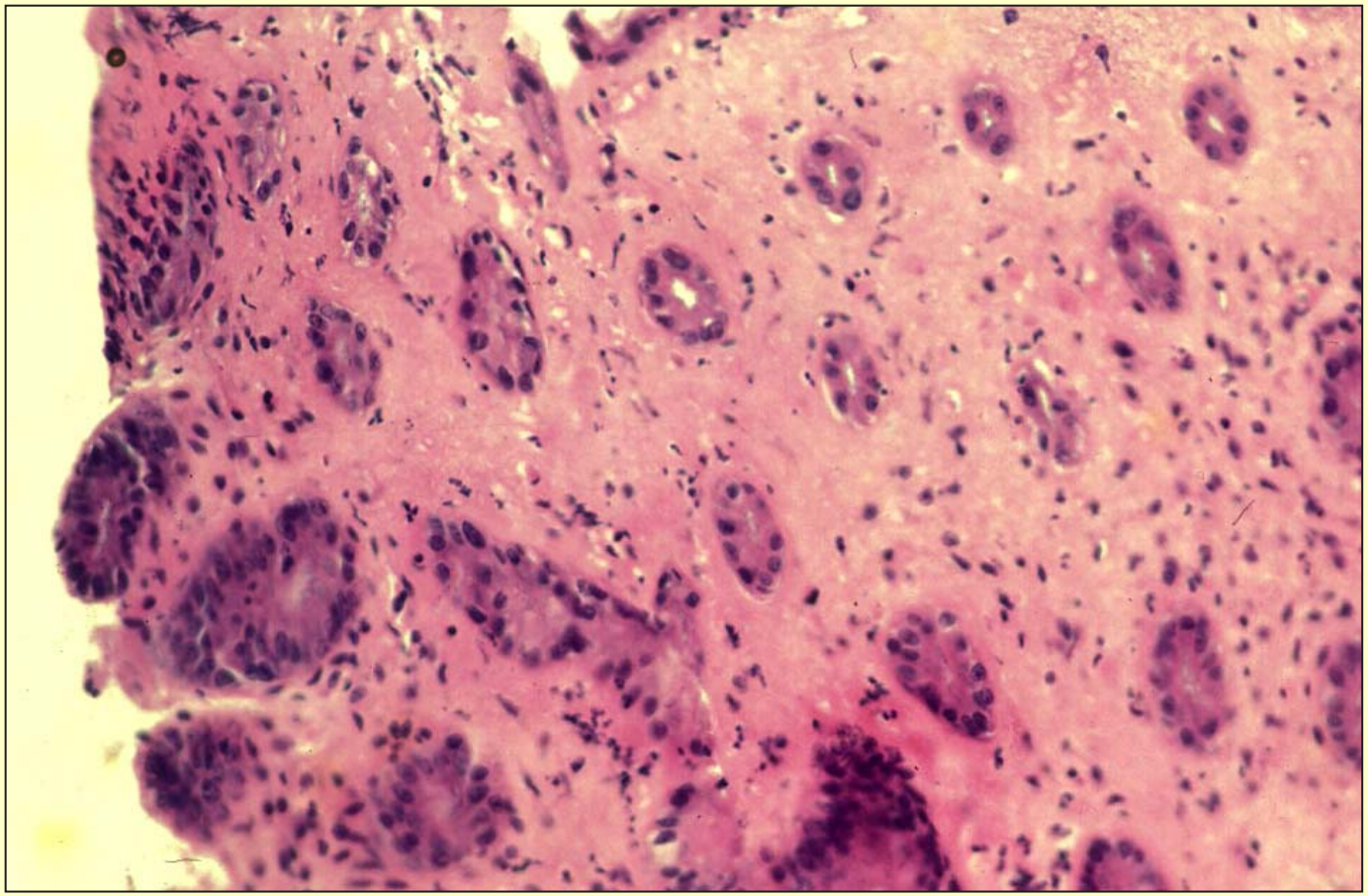
Pseudomembranous & Ischemic colitis (Digna & Greenson 1997)

- 25pts C. difficile 24 pts ischemic colitis
- Hyalinisation of lamina propria
  0/25 19/24
- Atrophic microcrypts
  6/25 18/24
- Lamina propria hemorrhage
  9/25 18/24

1021662 Ischemia & Pseudomembrane



683025 Ischemia : hyalinisation & atrophic crypts



IBD & Therapy

- **Improvement**
  - **Decrease of score**
  - Disappearance of activity defined by the presence of neutrophils?
- **Remission**
  - **Healing**
  - Disappearance of inflammation – persistent architectural abnormalities?
  - Normalisation has been observed in UC (and CD?)

Crohn's disease before and after remicade