

# **Drug-Induced colitis**

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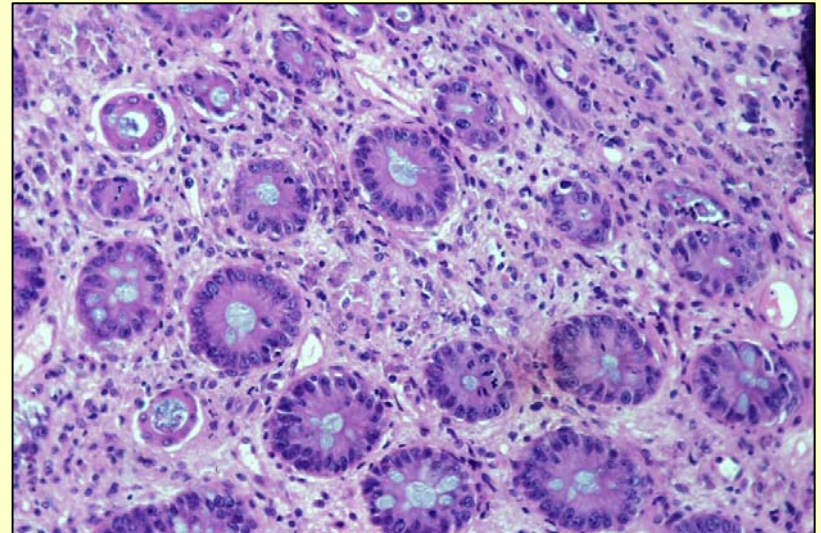
# Iatrogenic & Drug-induced pathology of the colon

## 1 Surgery

- Adhesions
- Motility disorders
- Short bowel syndrome

## 2 Graft-versus-host-disease

- Acute >
- Chronic



# Iatrogenic & Drug-induced pathology of the colon

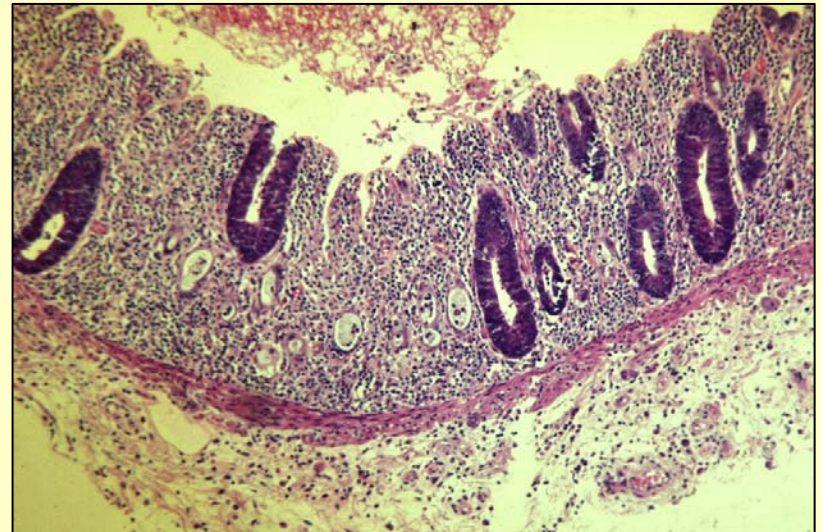
## 3 Radio-chemotherapy

- Radiation rectitis

- Acute >
- Chronic

## 4 Drugs

- Bowel preparation for investigations
  - Oedema
  - Focal active colitis
- Systemic or local treatment



# Drug-Induced Colitis : The Problem

- **Constipation is a frequent adverse event**
  - **> 280 drugs induce constipation in >3% of patients treated**
  - **Morphologic lesions : uncommon**
- **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**
  - **80 cases registered in France in 1984-1994!**

# Drug-Induced Colitis : The Problem

- **Prospective study : 59pts with inflammatory diarrhoea**
  - **35 drug-induced**  
Siproudhis e.a. Gastroentérol Clin Biol 1998, 22, 778
- **Prospective study : 88 consecutive pts with acute unclassified colitis**
  - **46 (52.3%) IBD**
  - **42 (47.7%) no relapse (50% drug-induced)**  
Notteghem e.a. Gastroentérol Clin Biol 1993, 11, 811

# **Drug-Induced Colitis : Clinical Presentation**

- **Acute Diarrhoea**
  - Usually during the first days of treatment
- **Chronic Diarrhoea**
  - Can appear long time after start of drug
- **Watery or inflammatory diarrhoea**
- **Colitis**
  - Inflammatory / Ischemic

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



# Drug-Induced Colitis :Pathogenesis of diarrhoea & colitis

- Clinical features and morphology can be influenced by the immune status of the patients
  - Immune competent
  - Immune disturbed
    - De novo colitis (UC) – flare up of colitis (UC) following liver transplantation for primary biliary cirrhosis
    - Colitis in transplant patients

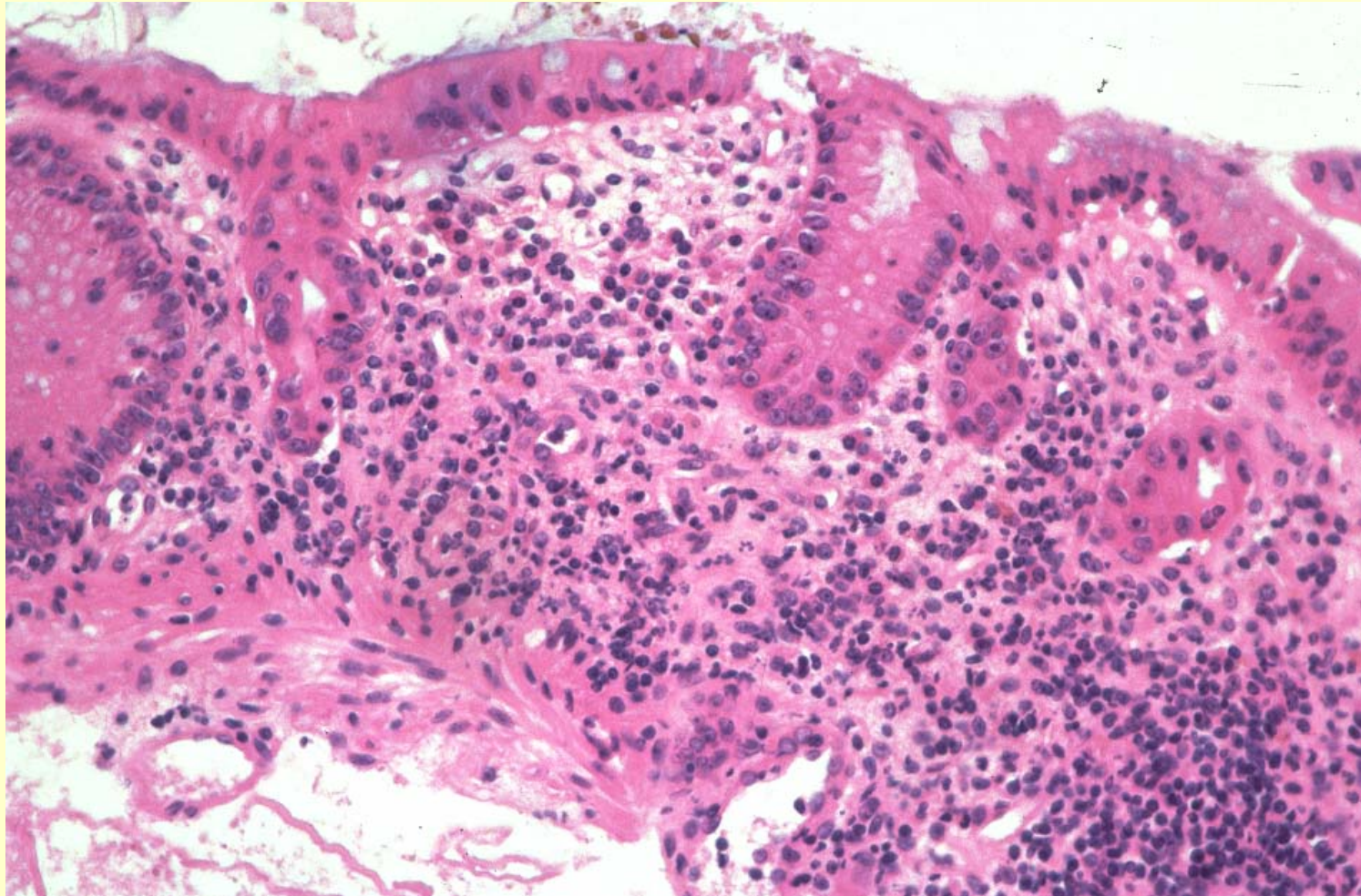
# **Mofetil Mycophenolate & Chronic diarrhoea**

- **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 afebrile chronic diarrhoea**
  - **13 infections (Campylobacter, CMV ..)**
  - **13 Crohn's-like morphology**

# Mofetil Mycophenolate & Chronic diarrhoea



# Mofetil Mycophenolate & Chronic diarrhoea

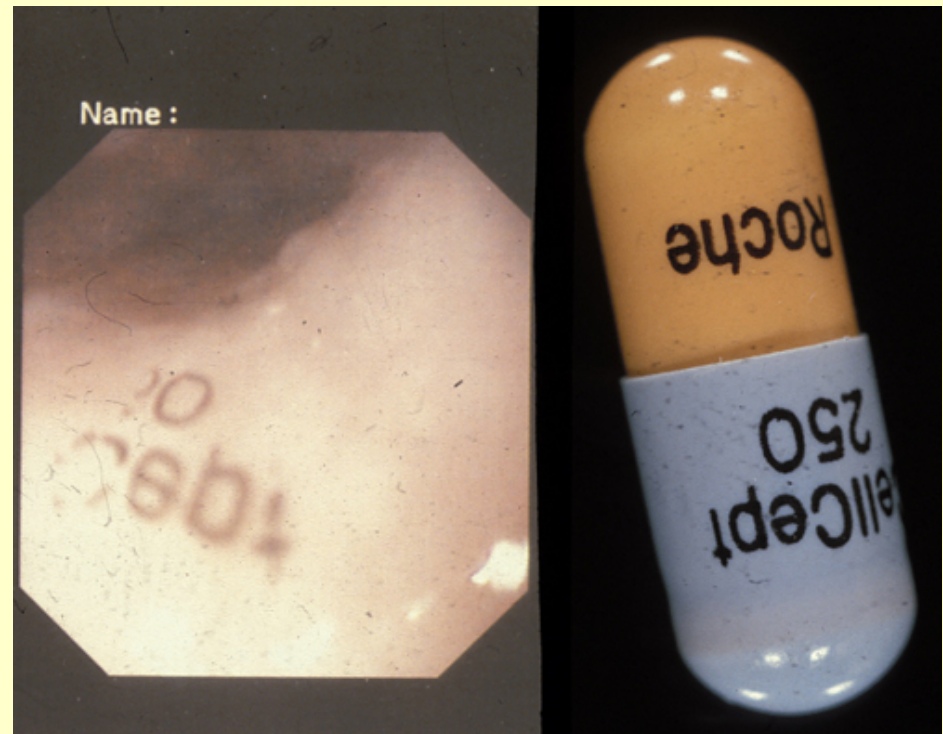
- **MMF is converted in its active metabolite : mycophenolic acid (MPA). MPA inhibits inositol-monophosphate dehydrogenase (IMPDH) which is necessary for the guanine synthesis in B- and T-lymphocytes**
- **MMF (experimentally)**
  - **impairs healing of left-sided colon anastomoses (Zeeh J e.a. Transplantation, 71, 1429-35, 2001)**
- **MMF (in humans) can induce**
  - **Graft-versus-host-disease pattern (Papadimitriou et al. Transplant Proc 2001)**
  - **Crohn's-like pattern (Dalle et al. Colorectal Dis 2004)**

# Mofetil Mycophenolate & Chronic diarrhoea : Mechanism

- MMF is converted into mycophenolic acid (MPA) and metabolized into 2 inactive metabolites
- A small part of this metabolite enters the biliary system (enterohepatic recirculation) – deconjugated and reabsorbed by enterocytes and metabolized into acyl glucuronide (AcMPA)
- **AcMPA**
  - **Promotes release of IL-6 & TNF $\alpha$**
  - **Causes impaired cell division by binding to elements of the cytoskeleton such as tubulin – individual variability**
    - **Responsible for impaired healing – explains ulcers in diclofenac treated patients and MMF treated patients**
  - **Binds to membrane proteins of enterocytes**

# Drug-Induced Colitis :Pathogenesis

- **Vascular impairment**
  - Cocaine & others
  - Anticoagulants
  - Reduced splanchnic flow due to cardiovascular drugs
  - Thromboses (oestrogens – progestagens)
- **Physical event**
  - Entrapment of pil



# Drug-Induced Colitis :Pathogenesis

- **Physical event**

- **Entrapment of pil**

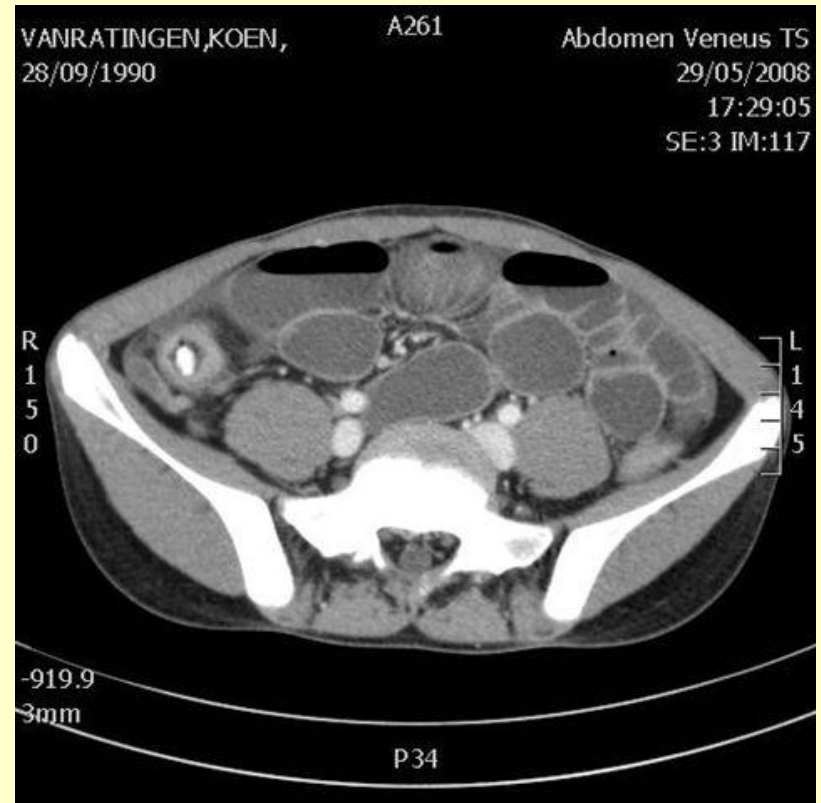
**Male pt; 17yrs; abdominal complaints for some months; lab : ferriprive anemia > treatment : vitamins, iron**

**Hospitalisation for subobstruction with vomiting**



# Drug-Induced Colitis :Pathogenesis

- **Physical event**
  - Hospitalisation for subobstruction with vomiting**
  - Final diagnosis : Crohn's disease with stricture**
  - Symptoms partly due to entrapment of vitam pill**







# Drug-Induced Colitis

## Lesions of the large Intestine: Type (1)

- **Erosions and ulcers**
  - NSAIDs, KCL
- **Strictures**
  - KCL, Pancreatic enzyme replacement
- **Microscopic colitis**
  - Variety of drugs
- **Pseudomembranous colitis**
  - Antibiotics, neoplastic agents, PPIs

# Drug-Induced Colitis

## Lesions of the large Intestine: Type (2)

- **Neutropenic enterocolitis**
  - Cytosine arabinoside, cisplatin, vincristine, adriamycine, mercaptopurine, -FU
- **Malakoplakia**
  - Corticosteroids
- **Sigmoid diverticular perforation**
  - Corticosteroids

# Drug-Induced Colitis

## Lesions of the large Intestine: Type (3)

- **Ischemic colitis**
  - Digitalis, diuretics, ergotamine, cocaine, Kayexalate, glutaraldehyde, sumatriptan,  $\alpha$ -interferon, dopamine, methysergide, NSAIDs
- **Focal active colitis**
  - NaPO<sub>4</sub>, NSAIDs
- **Epithelial atypia mimicking dysplasia**
  - IV cyclosporin
- **Apoptosis**
  - NSAIDs, NaPO<sub>4</sub>, Laxatives, -FU

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

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

# **Drug-Induced Colitis :Pathogenesis of diarrhoea & colitis**

**Occasionally combination of mechanisms**

**Same drug : different lesions or combinations**

- Erythromycin**
  - Transit time via motilin receptor**
  - Bacterial overgrowth (antibiotic)**

# NSAIDs & Colitis

- **Significant clinical problem**
  - **Elderly patients**
  - **2 months – 5 yrs after onset of treatment**
  - **Diarrhoea, blood in the stool**
  - **Small intestine and colon**
- **Pathogenesis**
  - **Decreased mucosal prostaglandins**
  - **Enterohepatic circulation**

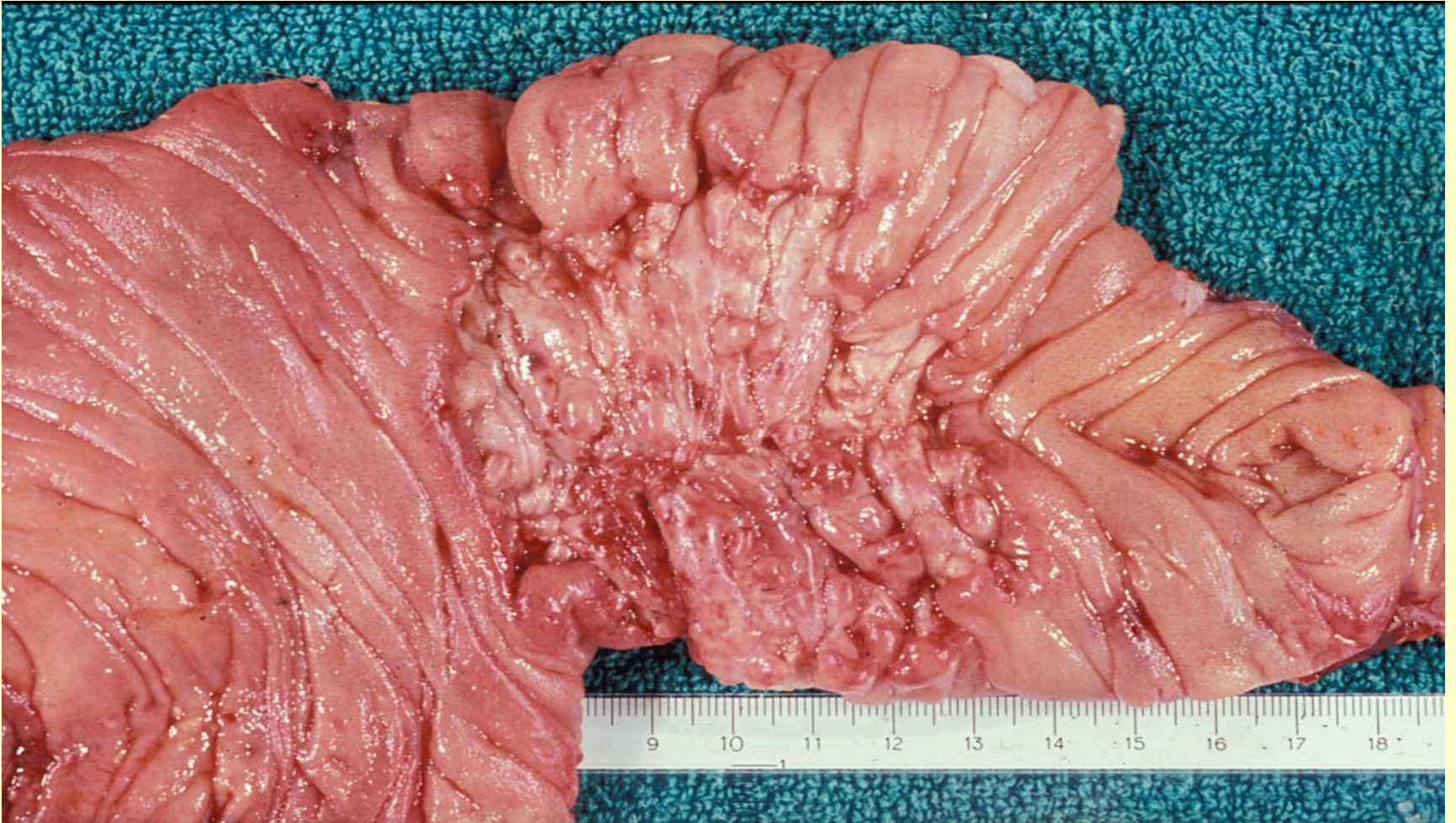
# NSAIDs & Colitis

Gibson e.a. Arch Internal Med 1992, 152, 625

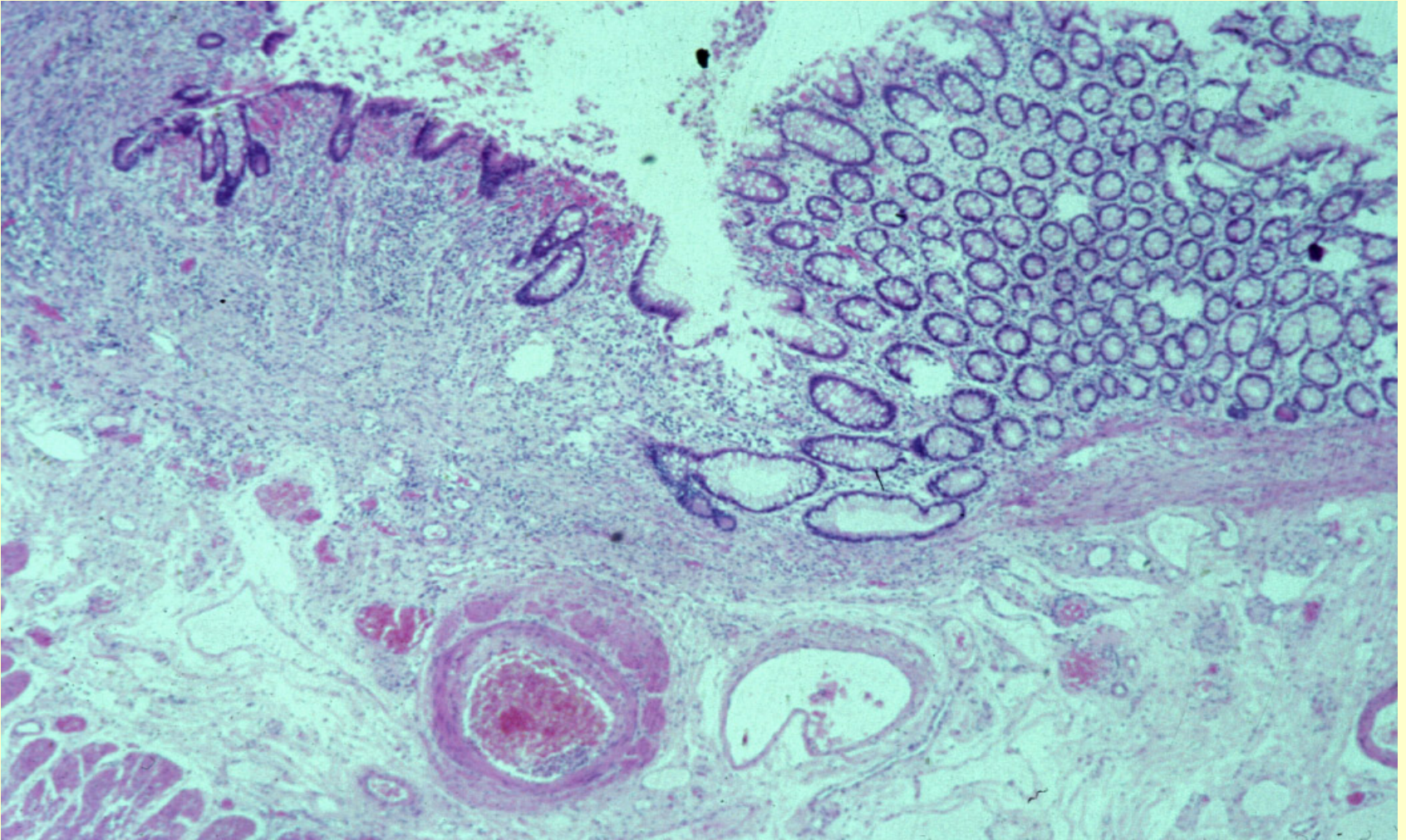
- **Non-specific ulceration : caecal,**
  - **Oxyphenbutazone, slow-release diclofenac, ibuprofen, distal ulcers naproxen**
- **Constipation & perforation**
  - **Indomethacin, ketoprofen, naproxen**
- **Hypersensitivity reaction (allergic colitis with eosinophils)**
  - **aspirin**
- **De novo colitis**
- **Focal active colitis**
- **Reactivation of quiescent IBD**



# NSAIDs & Non-specific ulceration

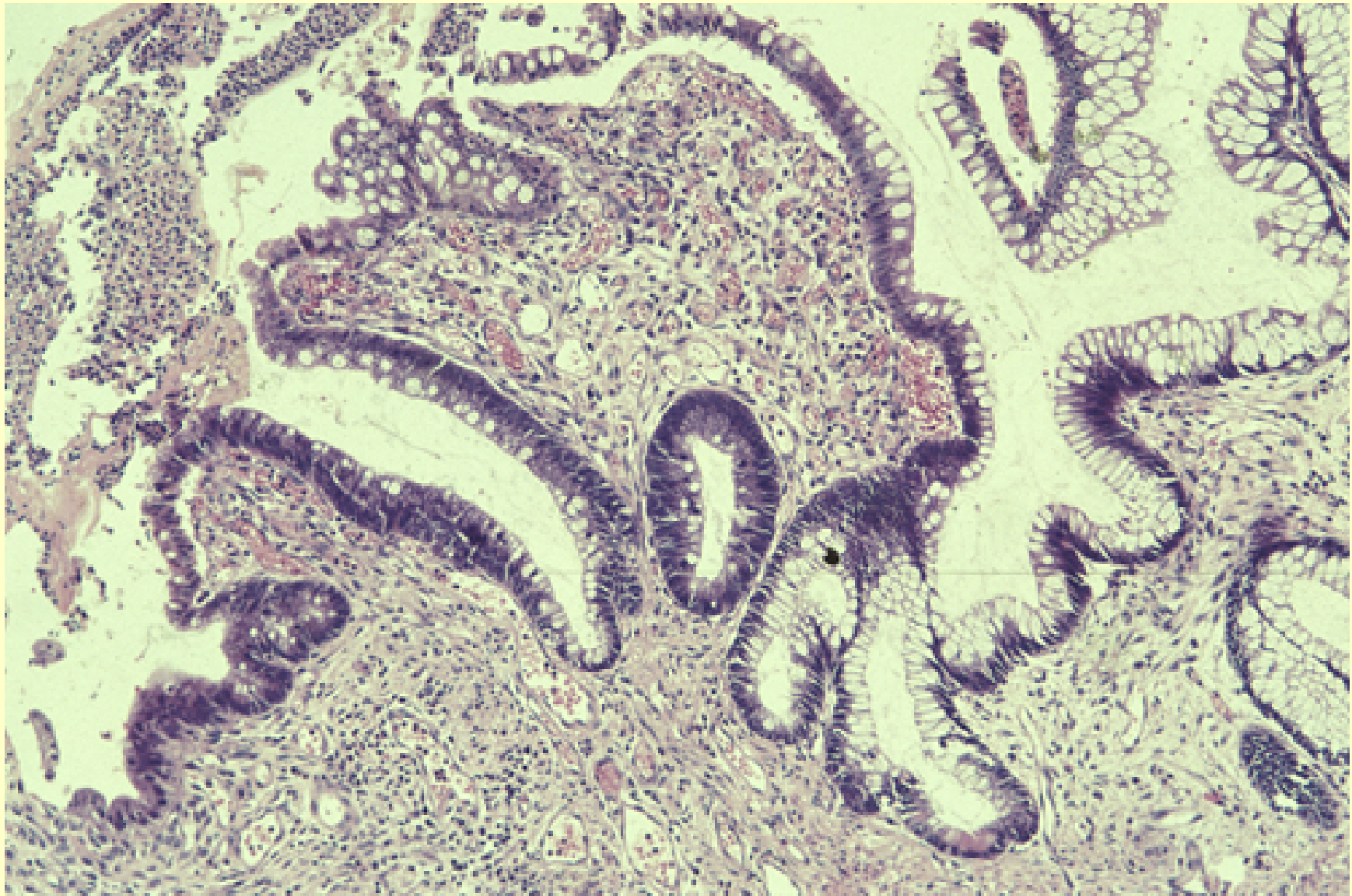


# NSAIDs & Non-specific ulceration



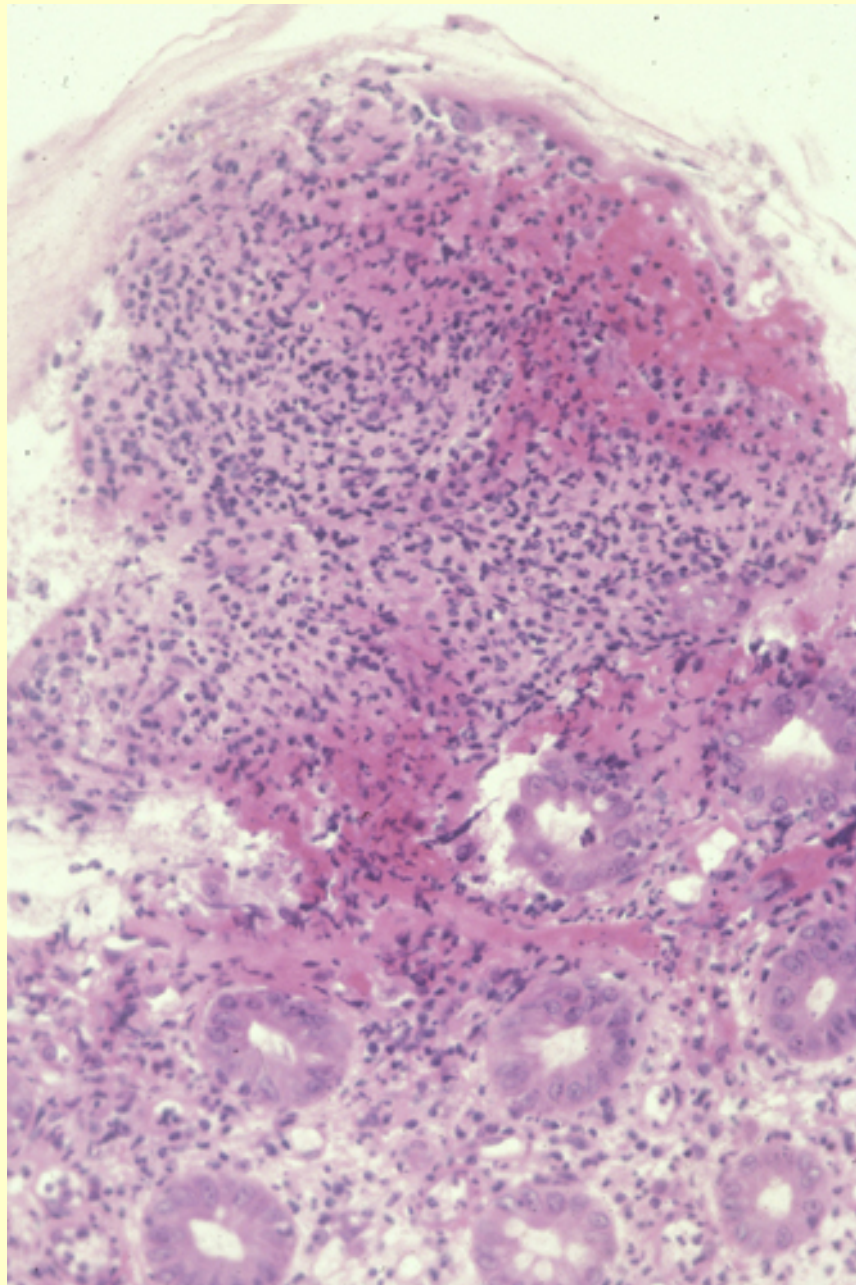
# NSAIDs & Colitis : Morphology

- **Architecture**
  - **Distorsion**
- **Epithelium**
  - **Well preserved**
- **Inflammation**
  - **Chronic**
  - **Basal plasmacytosis = absent**
  - **Limited active inflammation**



# **Antibacterials & Colitis**

- **Normal**
- **Oedema**
- **Infective-type colitis**
- **Pseudomembranous colitis**

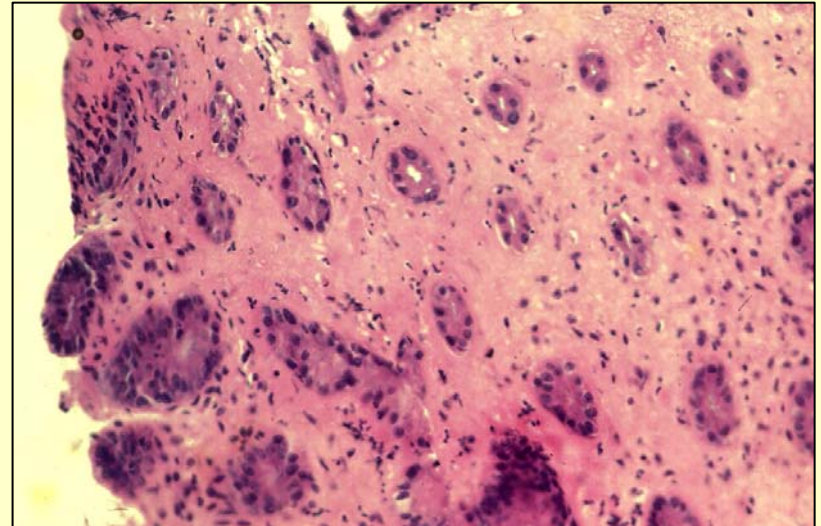


# Drug-Induced Colitis : Patterns

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

# Ischemic colitis in Young patient etiology

- Drugs
- Vasculitis
- Infections
- Hypovolemic/hypoperfusion syndrome
- Coagulopathy
- Anorexic behaviour





# Ischemic colitis in Young patient etiology

- Preventza OA et al. J Gastrointest Surg 2001; 5: 388-392
- N : 39 young adults (25 female) presenting with ischemic colitis
  - 13 oral contraceptives    19 : unknown etiology
  - 4 vasoactive drugs
  - 4 vascular thrombi
  - 2 vasculitis
  - 4 hypovolemia

# Pharmacologic agents and Colon Ischemia

- **Vasoconstriction – arterial spasm – non-occlusive ischemia**
- **Vasopressin – Terlipressin**
- **Decongestants**
  - Pseudoephedrine (segmental ischemic colitis, involving the splenic flexure)
- **Ergot alkaloids - Methysergide maleate**
- **Illicit/ Controlled drugs**
  - Cocaine
  - Amphetamines (Methamphetamine = speed, ...)
  - Antibiotic-associated hemorrhagic colitis
    - Antibiotics
  - Appetite suppressants : phentermine
  -
- **Chemotherapeutic agents**
  - Vinca alkaloid and taxane classes (inhibition of microtubule assembly/ischemic colitis)
- **Anticoagulants**
  - Bleeding – intramural hematoma (relation with cholesterol crystal embolism)
- **NSAIDs**
  - Non-selective NSAIDs
  - Selective cyclooxygenase inhibitors (rofecoxib, meloxicam)
- **Migraine headache medication**
  - Serotonin receptor agonists (naratriptan, sumatriptan, Alosetron hydrochloride, Tegaserod)

# Pharmacologic agents and Colon Ischemia

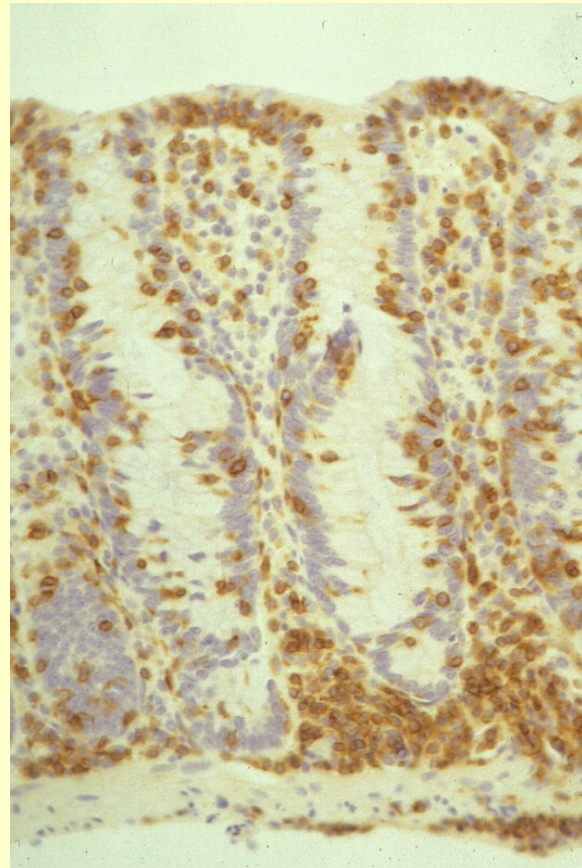
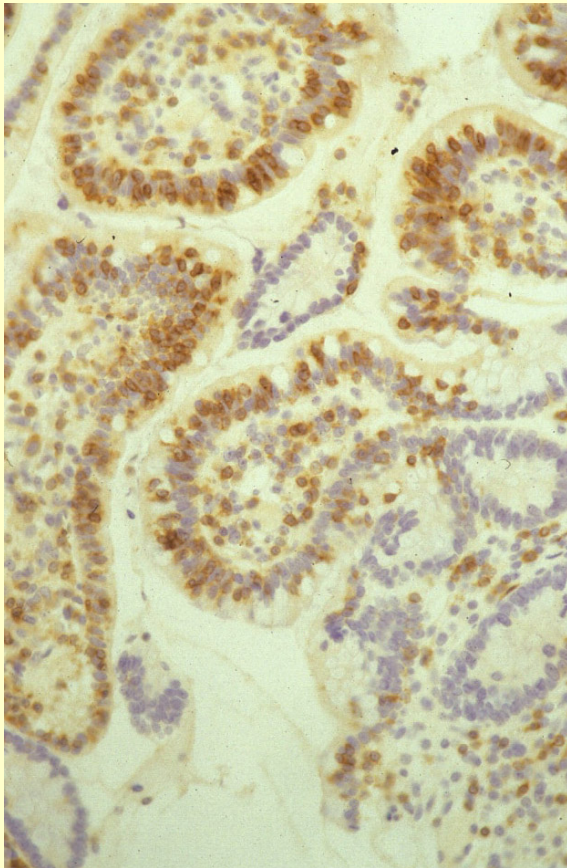
- Hyperlipemic agents
  - Statins
- Hormonal therapies
  - Flutamide (anti-androgenic)
  - Estrogens and oral contraceptives
- Hypotensive and hypovolemic drugs
  - Anti-hypertensive drugs (reserpine, methyldopa..)
  - Diuretics
  - Digoxin
  - Laxative osmotic agents
- Ganglion blockers – alpha-adrenergic blockers, catecholamines
- Anti-arrhythmic drugs
- Psychotropic drugs
  - Tricyclic antidepressants, Phenothiazines, barbiturates



# Lymphocytic ileo – colitis : Case History

- *Female patient*                      °1944
- *Clinical History*
  - *Stenosis of a renal artery and the celiac trunk*
  - *Arterial hypertension*
  - *Migraine*
  - *Treatment : Cafergot, omeprazole, tiberol, plavix (clodipogrel)*
  - *Current complaints : headache and diarrhea*
- *Endoscopy : Ischemia?*                      > *normal aspect*

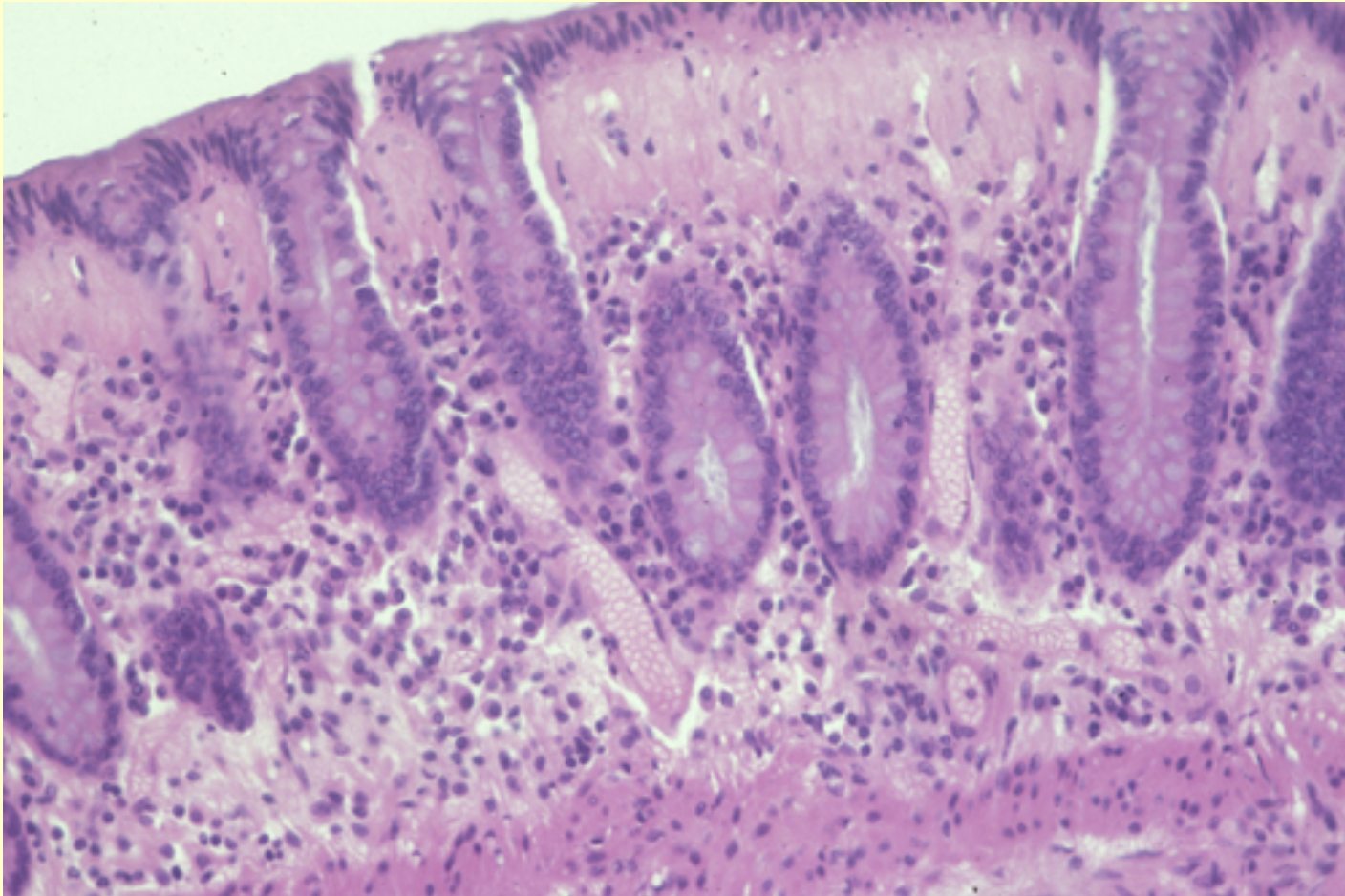
# Lymphocytic ileo - colitis



# Conditions associated with lymphocytic colitis

- **Enteric infections**
- **Gluten**
- **Autoimmune diseases**
- **Drugs**
  - Alpha-glucosidase inhibitor (diabetes)
    - Acarbose
  - Anticoagulants
    - Ticlodipine
    - Clodipogrel
  - H2 receptor antagonists
    - Rantidine
    - Cimetidine
  - Proton pump inhibitors
    - Lansoprazole
  - Cholesterol lowering agents
    - Simvastatin
  - Antiepileptic drugs
    - Carbamazepine
  - Anti Parkinson drug
    - Levodopa benserazide
  - NSAID
    - Piroxicam beta
  - cyclodextrin
    - Anti-serotonin agent
      - Oxetorone
    - Selective serotonin reuptake inhibitors
      - Sertraline
      - Paroxetine
    - Anti-androgenic
      - Flutamide
    - Phlebotonic drugs
      - Flavonoid extract
      - Cyclo 3 fort
      - Vinburnine
    - Ferrous sulphate (Tardyferon)
    - Antipsychotic
      - Clozapine (collagenous colitis)

# Collagenous colitis





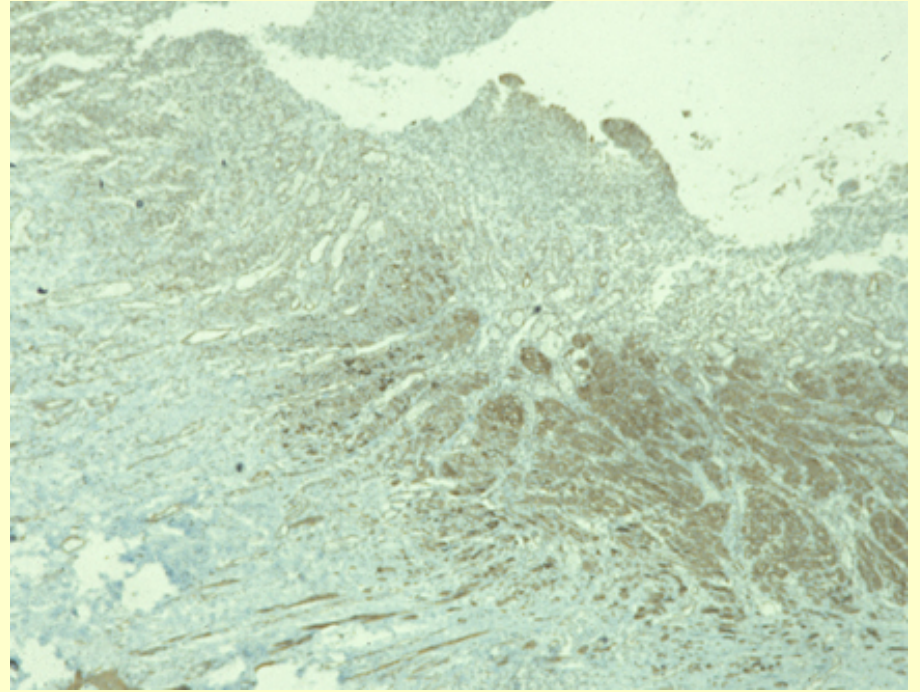
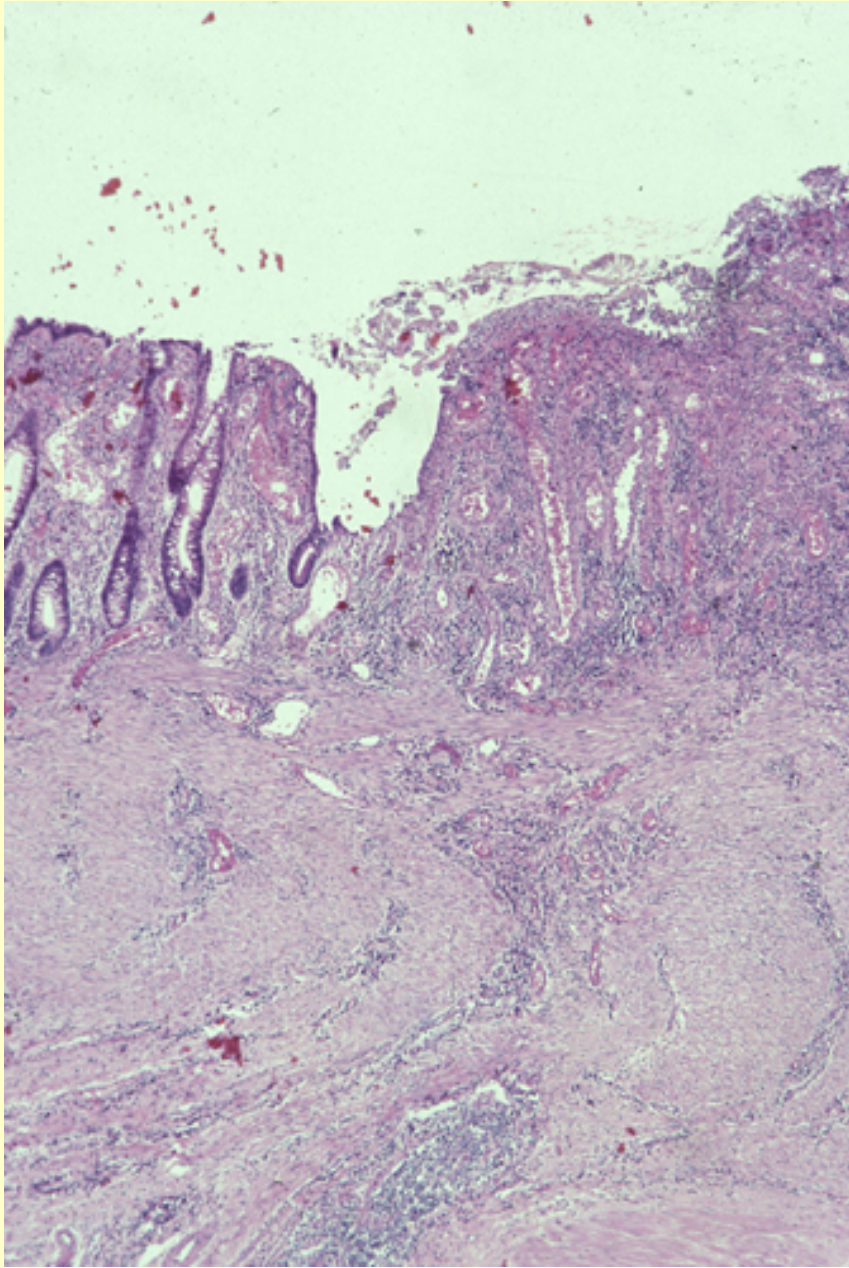
# Drug-Induced Colitis : Patterns

- **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)

# Drug-Induced Colitis : Patterns

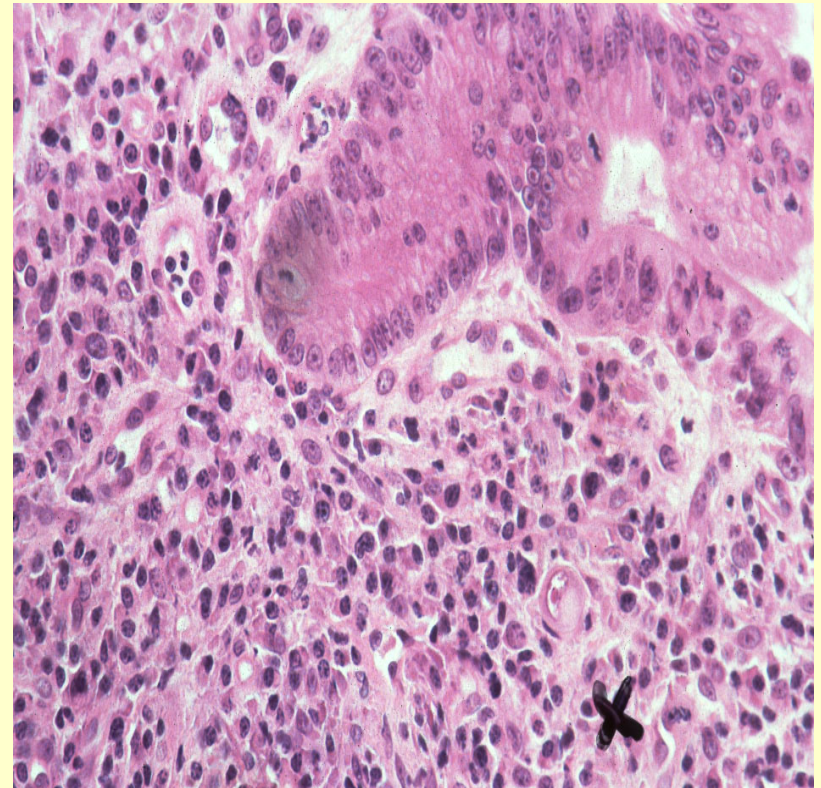
- Non-specific ulcer
- Colon
  - NSAIDs
  - Antineoplastic agents (methotrexate)
- Rectum
  - Suppositories (analgesics ...)





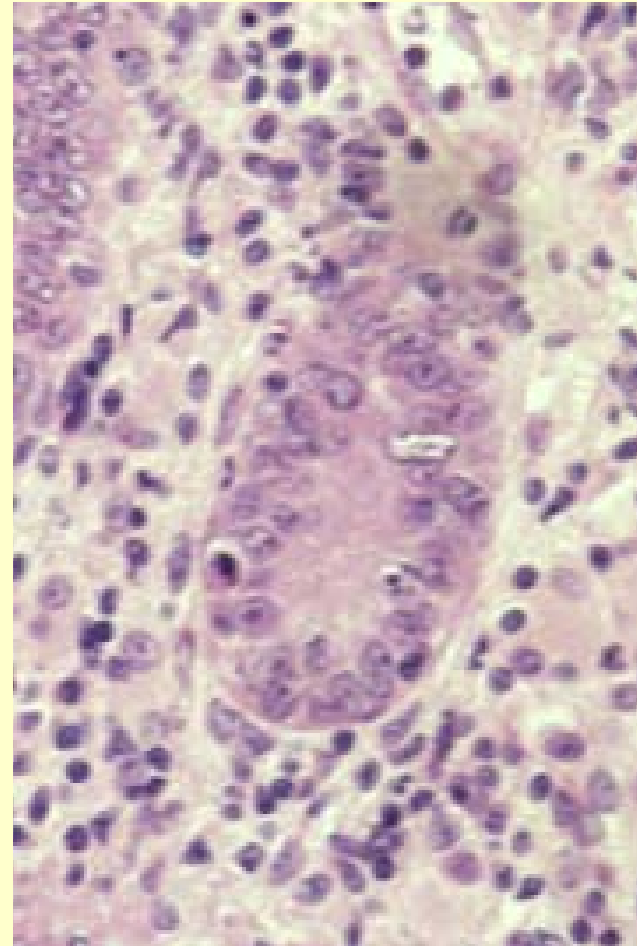
# Drug-Induced Colitis : Patterns

- **Surinfections**
- **Opportunistic infections (CMV...)**
- **Neutropenic colitis**



# Drug-Induced colitis : Patterns

- **Specific patterns**
  - **Crypt epithelial cell apoptosis**
  - fluorouracil
  - NSAIDs (diclofenac, mefenamic acid)
  - Cyclosporin
  - Colchicine
  - Ranitidine
  - Ticlopidine
  - Mofetil

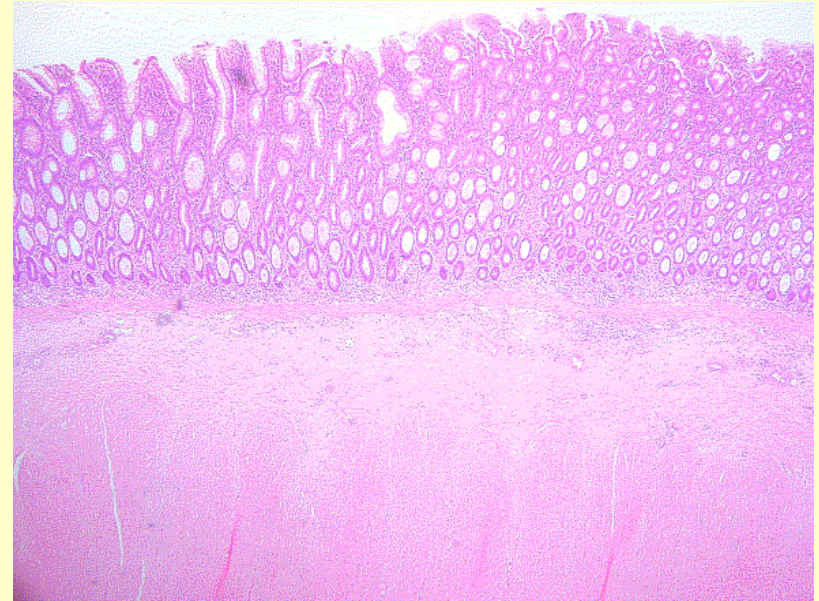


# Drug-Induced colitis : Patterns

- **Specific patterns**
  - **Surface epithelial cell apoptosis**
    - Contact laxatives (with or without pseudomelanosis)

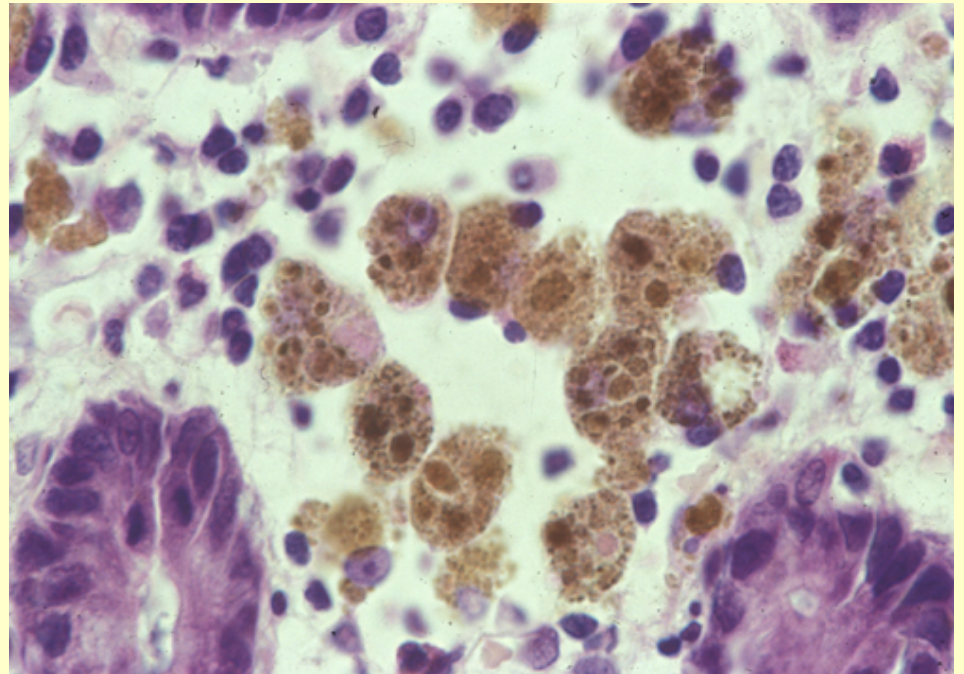
# Drug-Induced colitis : Patterns

- **Specific patterns**
  - **Pancreatic enzyme supplements and colonic strictures**



# Drug-Induced colitis : Patterns

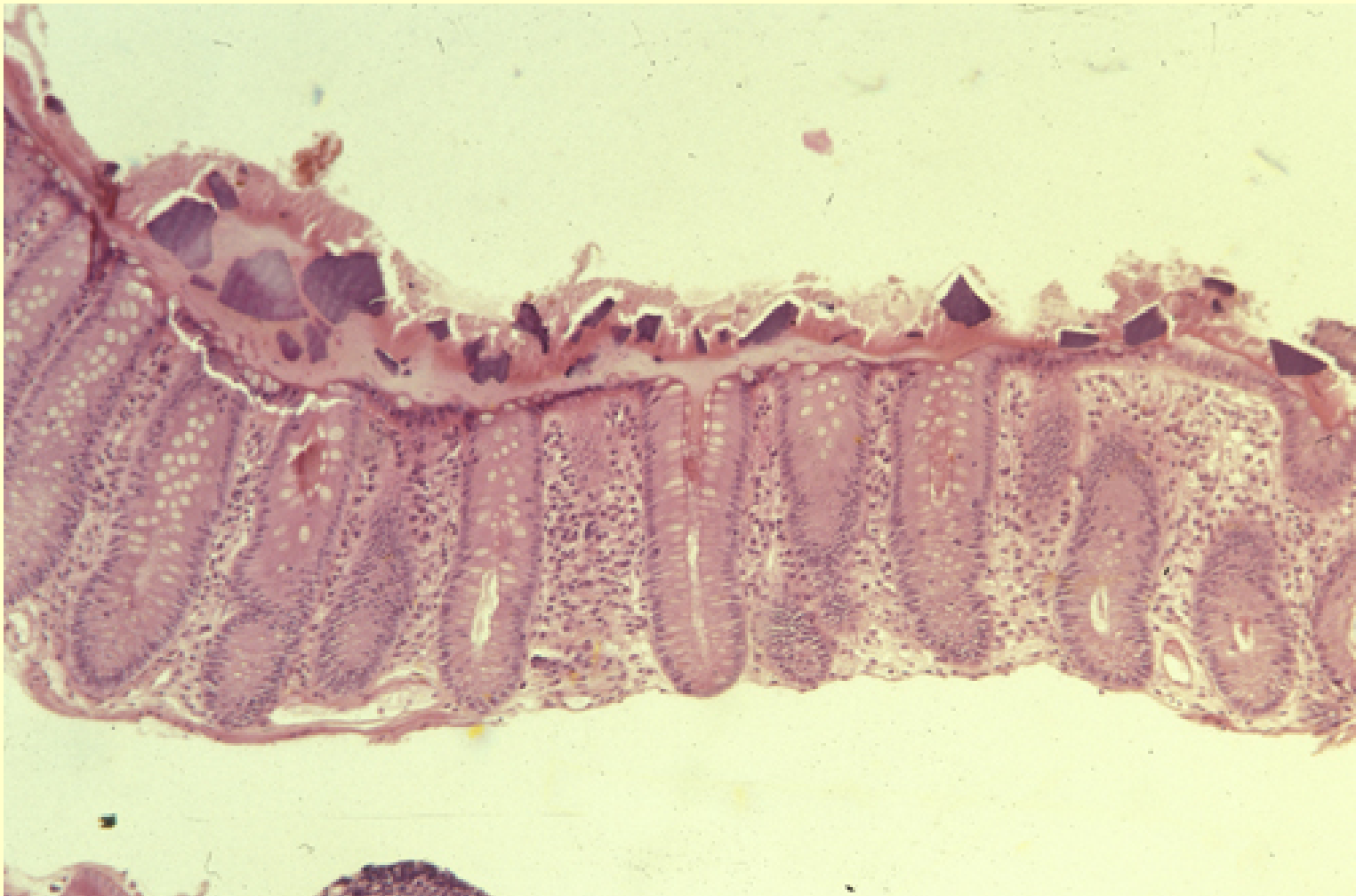
- **Specific patterns**
  - Clofazimine and crystal-storing histiocytosis
  - (pseudo)melanosis coli
  - Kayexalate-sorbitol colitis





# Drug-Induced colitis : Patterns

## Kayexalat-sorbitol colitis



# **Drug-Induced colitis : Diagnosis & conclusion**

- **THINK**
- **CLINICO-PATHOLOGICAL COLLABORATION**
  - **Clinical history**
  - **Relationship in time between onset of symptoms and start of drug and resolution after withdrawal**
- **CHALLENGE**