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MediTec

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Erasmus+ Programme
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These lectures were prepared and performed for the students.

we published them in the MediTec websites to wider our educational aims.

With thanks to our team member Prof. Ismail Matalkeh for his efforts.

DRUG INDUCED GASTROINTESTINAL TRACT LESIONS

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SCHOOL OF MEDICINE
JORDAN UNIVERSITY OF SCIENCE & TECHNOLOGY

Iatrogenic Gastrointestinal Tract Lesions

- Pathological lesions induced by the act of the medical professionals
- Increasing in number
- Variable histological changes
- Can mimic some genuine GI lesions
- Can impose further difficulties in accurate Diagnosis
- Awareness of these lesions is important for the practicing pathologists and other physicians

Iatrogenic Gastrointestinal Tract Lesions

- Drugs, enemas and suppositories
- Surgery related lesions
- Radiotherapy related lesions
- Immunosuppression related lesions
- Radiological media related lesions
- Laser therapy related lesions
- Instrumentation related lesions

Iatrogenic Gastrointestinal Tract Lesions

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Human Pathology (2007) 38, 527–536

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

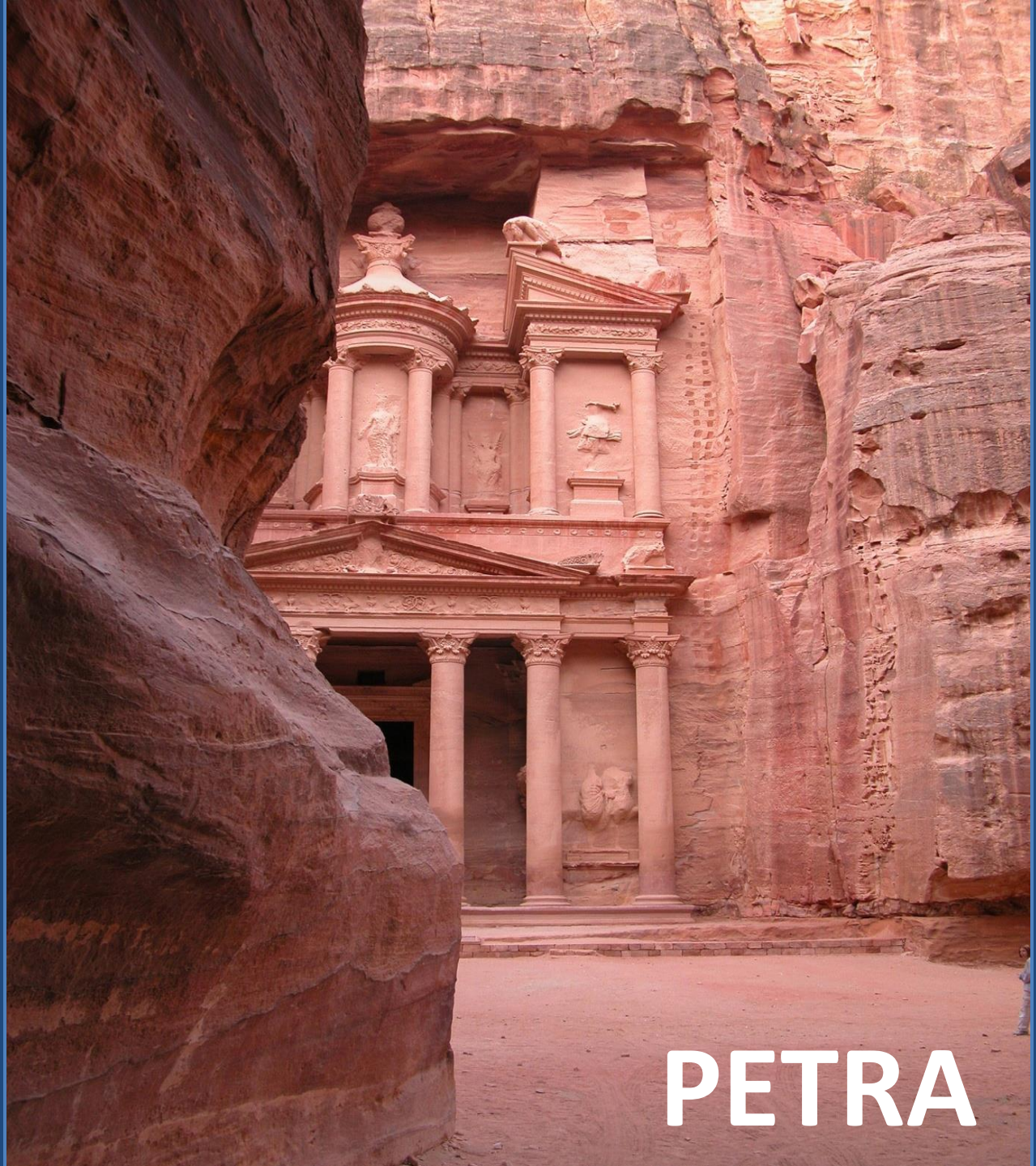
Progress in pathology

Pathological effects of drugs on the gastrointestinal tract: a review

Jeremy R. Parfitt MD, David K. Driman MBChB, FRCPC*

Table 1 Morphological classification of drug-induced pathology of the GI tract

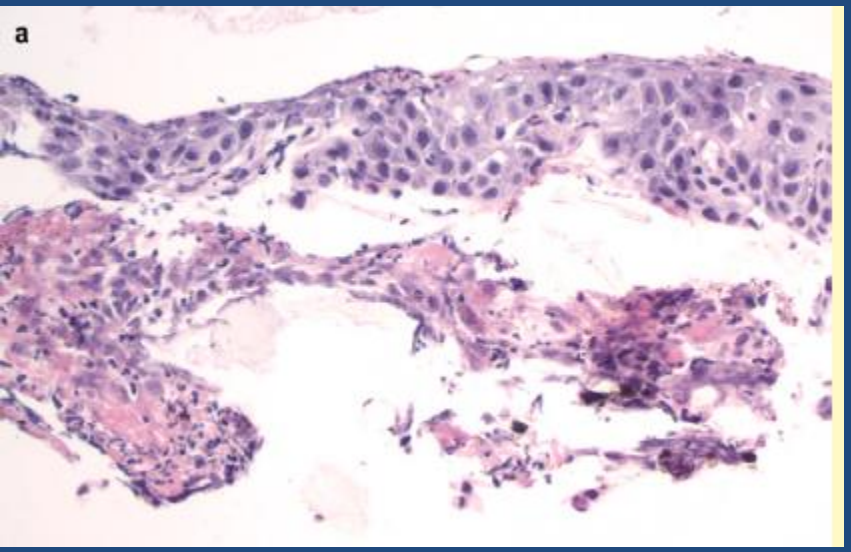
Esophagus	
Erosions and ulcers	KCl, alendronate, doxycycline, quinidine, iron, Kayexalate, Taxol
Strictures	KCl, alendronate
Stomach	
Parietal cell hypertrophy and hyperplasia	PPIs
Fundic gland cysts and polyps	PPIs
Erosions and ulcers	NSAIDs, KCl, alendronate, iron, Kayexalate, HAIC, SIR, colchicine
Reactive gastropathy	NSAIDs
Epithelial atypia mimicking dysplasia	HAIC, SIR, colchicine, Taxol
Apoptosis	PPIs, colchicine
Small intestine	
Erosions and ulcers	NSAIDs, KCl, iron, Kayexalate, colchicine
Strictures	KCl
Diaphragms	NSAIDs
Large intestine	
Erosions and ulcers	NSAIDs, KCl
Strictures	KCl, pancreatic enzyme replacement
Microscopic colitis	PPIs, ticlopidine, ranitidine, simvastatin, flutamide, carbamazepine, paroxetine, sertraline, penicillin V, Cyclo 3 Fort, NSAIDs
Pseudomembranous colitis	Antibiotics, PPIs
Neutropenic enterocolitis	Cytosine arabinoside, cisplatin, vincristine, adriamycin, 5-FU, mercaptopurine
Malakoplakia	Corticosteroids
Sigmoid diverticular perforation	Corticosteroids
Ischemic colitis	Digitalis, diuretics, BCP, ergotamine, cocaine, Kayexalate, glutaraldehyde, sumatriptan, α-interferon, dopamine, methysergide, and NSAIDs
Focal active colitis	NaPO4, NSAIDs
Epithelial atypia mimicking dysplasia	IV cyclosporin
Apoptosis	NSAIDs, NaPO4, melanosis, 5-FU

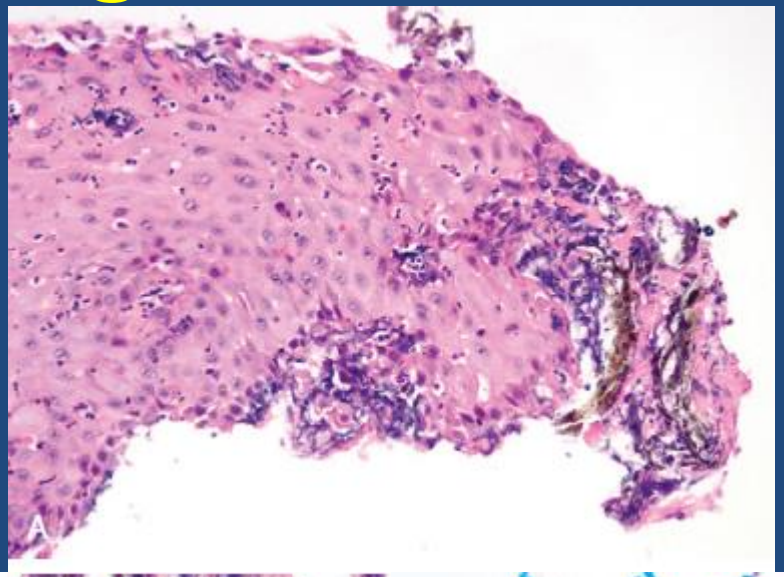

PETRA

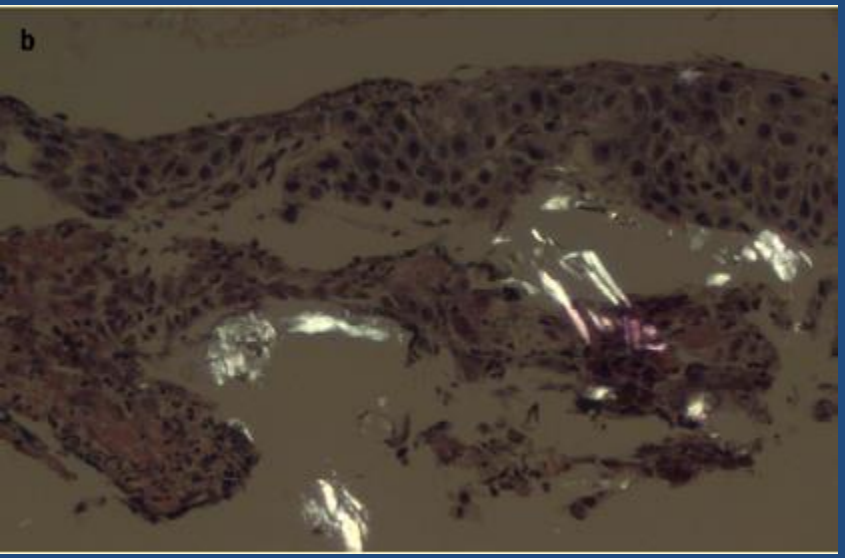
Pill esophagitis

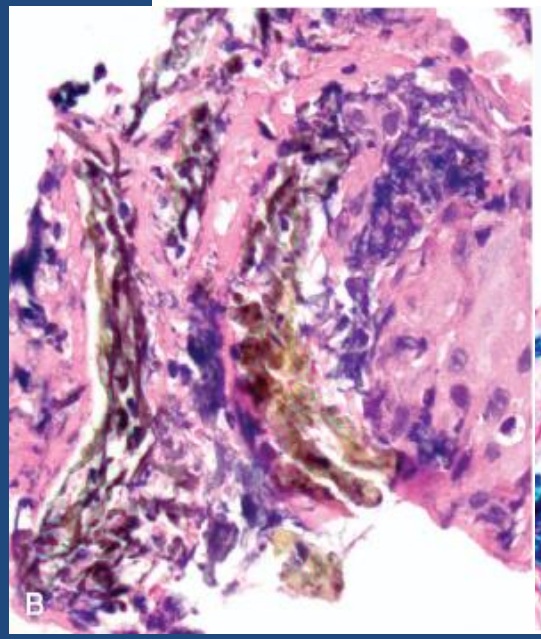
- Secondary to caustic injury caused by retention of a pill in the esophagus
- Often associated with failure to consume adequate amounts of liquid with tablet or capsule medications
- Supine position before bedtime
- Women & elderly
- Antibiotics (particularly Doxycycline, Tetracycline and Clindamycin)
- NSAIDs, Potassium Chloride, Iron supplements, Ascorbic acid and Alendronate

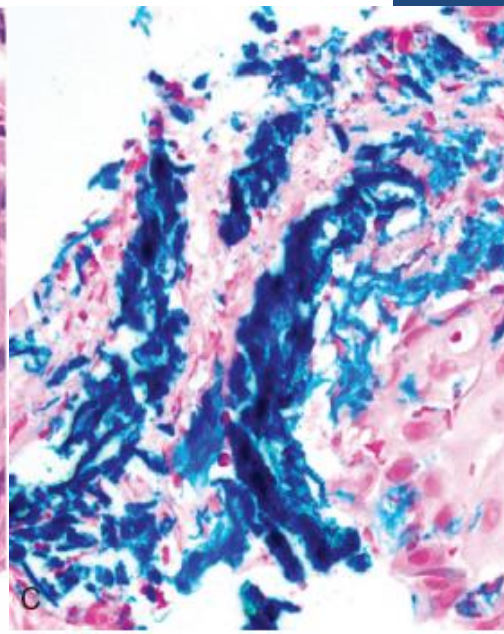
Pill esophagitis





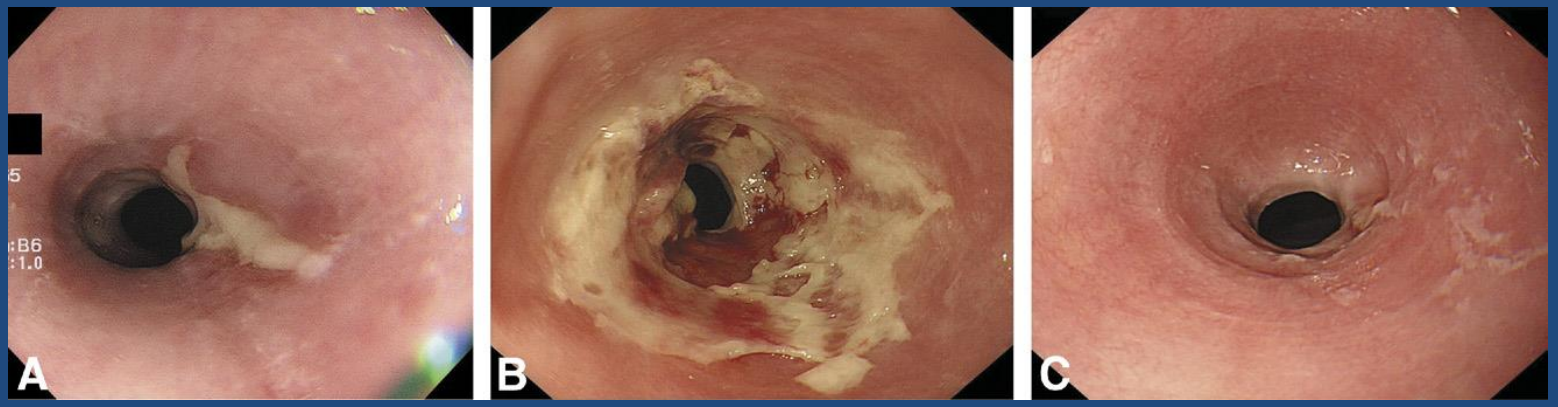




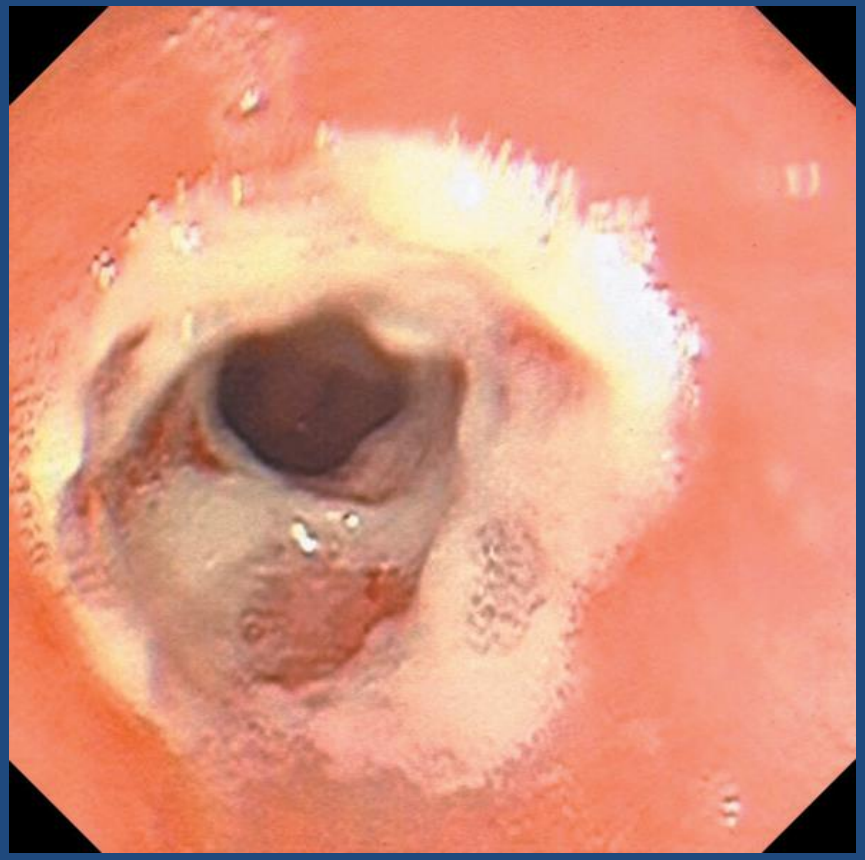


ALENDRONATE

- Second-generation bisphosphonate, has the potential to cause ulcers within the esophagus and stomach, as well as occasional esophageal strictures.



Bisphosphonates: common cause of oesophagitis and ulceration in the elderly



Alendronate

UM QAIS

Gastric Injury : Common Drugs

Drug (or Drug Family)	Predominant Pathology
NSAIDs/aspirin Alcohol	Erosions Ulcers Reactive gastropathy
Proton pump inhibitors	Parietal cell hypertrophy and hyperplasia Fundic gland cysts and polyps
Iron	Erosions with Fe^{++} deposits
Kayexalate	Crystal deposition (rhomboid or triangular, nonpolarizable, basophilic crystals adherent to the surface epithelium or within sloughed inflammatory exudate)
Cholestyramine	Crystal deposition (similar to Kayexalate crystals)
Colchicine/Taxol	Abundant metaphase mitoses (especially "ring" mitoses); epithelial pseudostratification; loss of polarity; increased apoptosis in pit epithelium
Chemotherapy	Mucosal sloughing, enlarged gland cells with normal N/C ratio, gland loss
Hepatic arterial infusion chemotherapy (HAIC)/ selective internal radiation (SIR) sphere therapy	Ulceration with nuclear atypia; numerous enlarged, bizarre-shaped nuclei with vesicular chromatin, and large, irregular nucleoli
Bisphosphonates (Alendronate)	Ulcerations (rare in the stomach, most commonly in the esophagus)
Corticosteroids	Possibly increased acid secretion, synergistic ulcerogenic effect when combined with aspirin and NSAIDs

NSAIDs

- Most widely prescribed drug in the world (7.7%)
- Age is an added risk factor

  Multiple-drug regimens

  Co-morbidities

  Age-associated changes in pharmacokinetics an pharmacodynamics

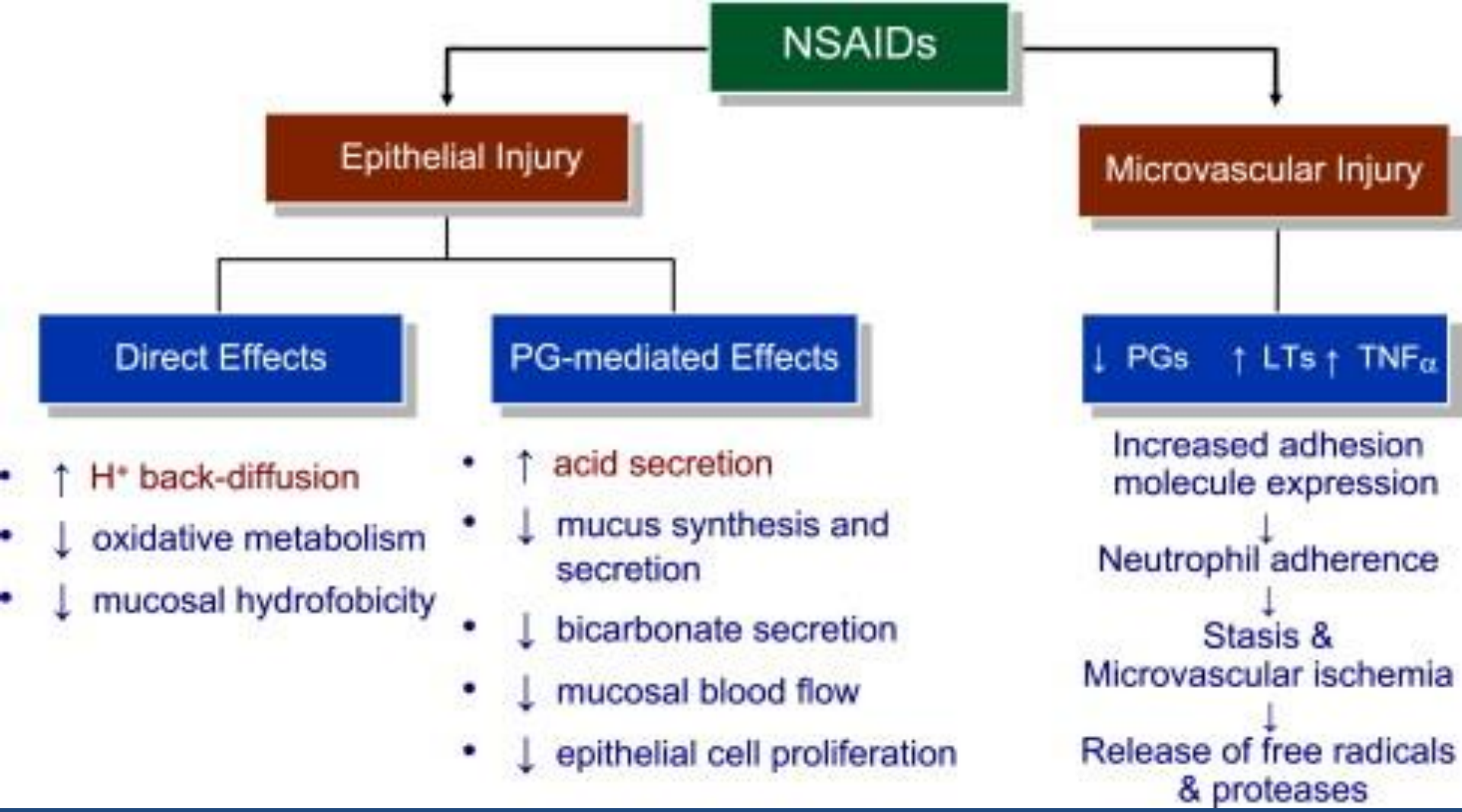
NSAIDs and the Stomach

NSAID gastropathy is more common with the following risk factors:

1. Use of older NSAIDs such as, in order of decreasing gastric toxicity, Piroxicam, Naproxen, Sulindac, Indomethacin, Diclofenac, and Ibuprofen.

   Newer NSIADs such as Nabumetone, Oxaprocin, and Etodolic acid have a much lower gastric toxicity.

2. Increasing age
3. Female sex
4. Concurrent use of other ulcerogenic substances such as corticosteroids and anticoagulants

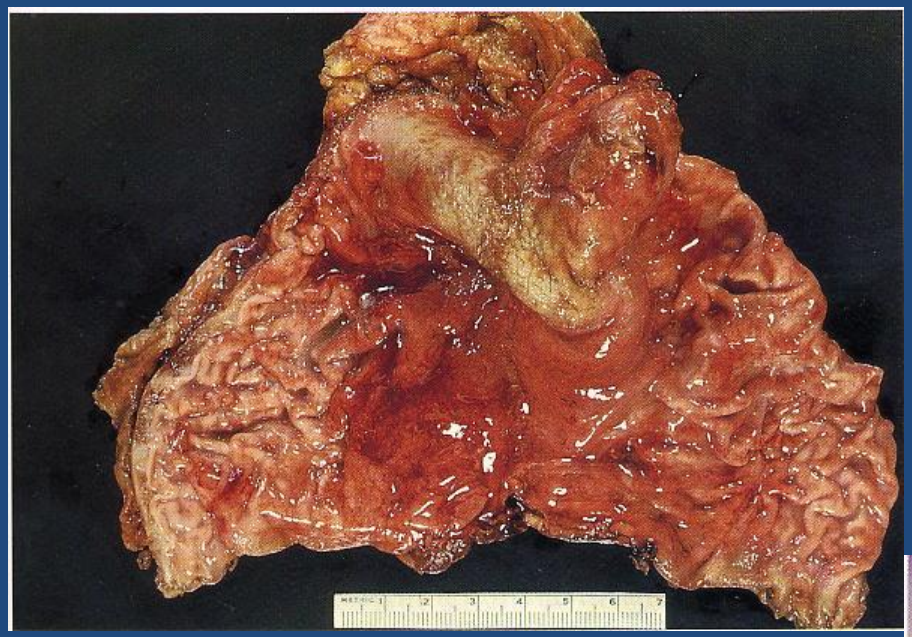


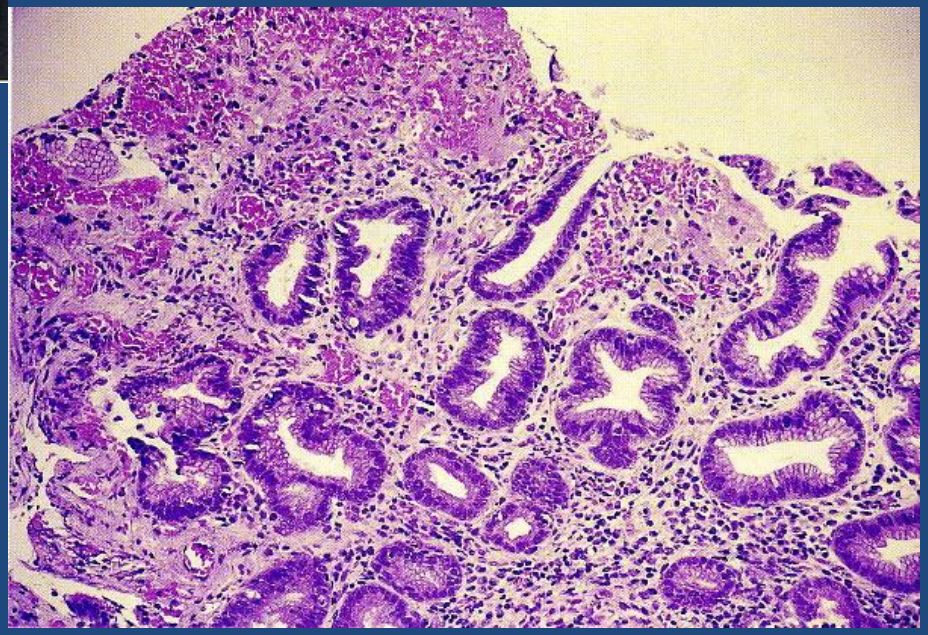
Scarpignato, Carmelo, Gastroenterology Clinics of North America

NSAIDs and the Stomach

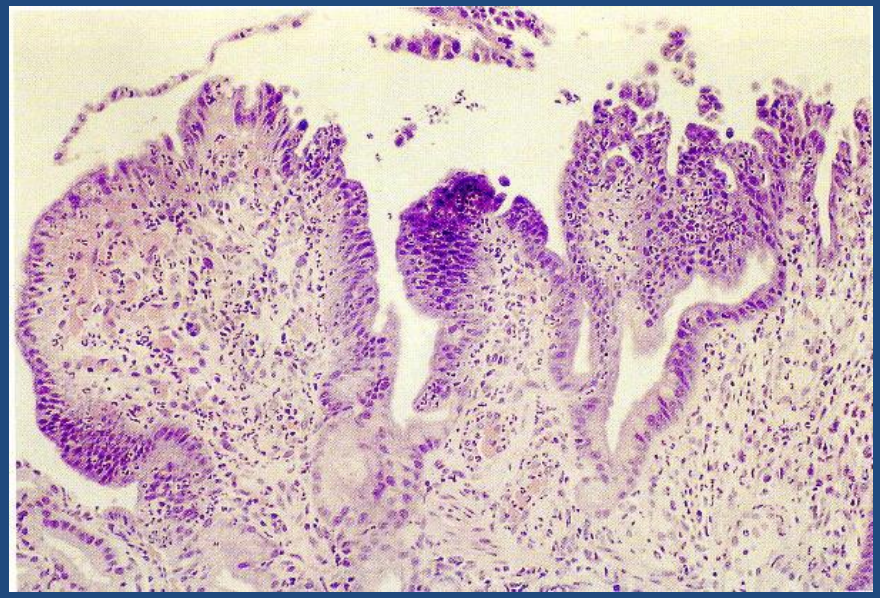
- Acute erosive gastritis
- Reactive gastropathy
- Prepyloric ulcers
- Cicatrizing submucosal fibrosis and prepyloric diaphragm
- Lymphocytic gastritis

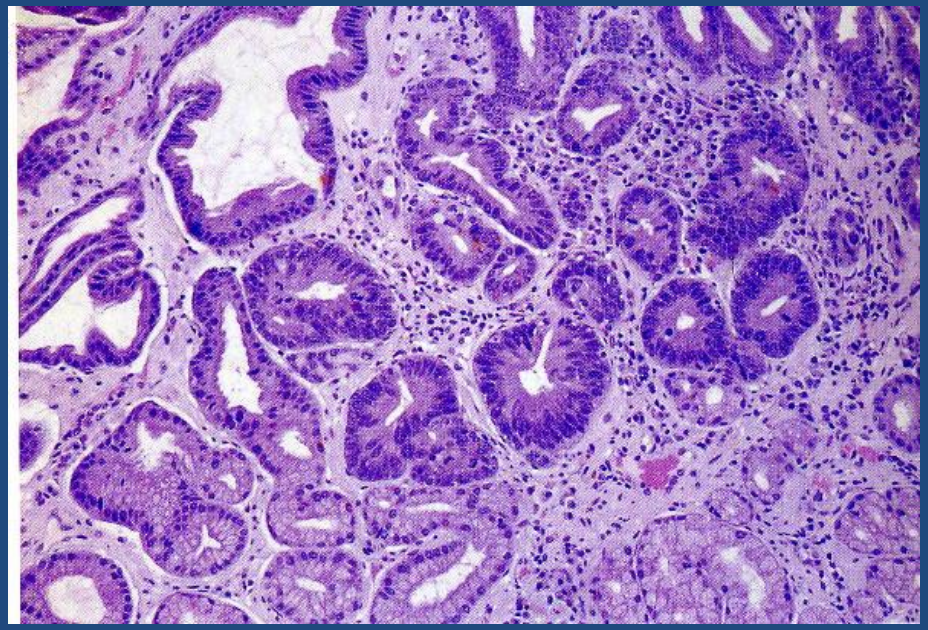
Acute Erosive or Haemorrhagic Gastritis



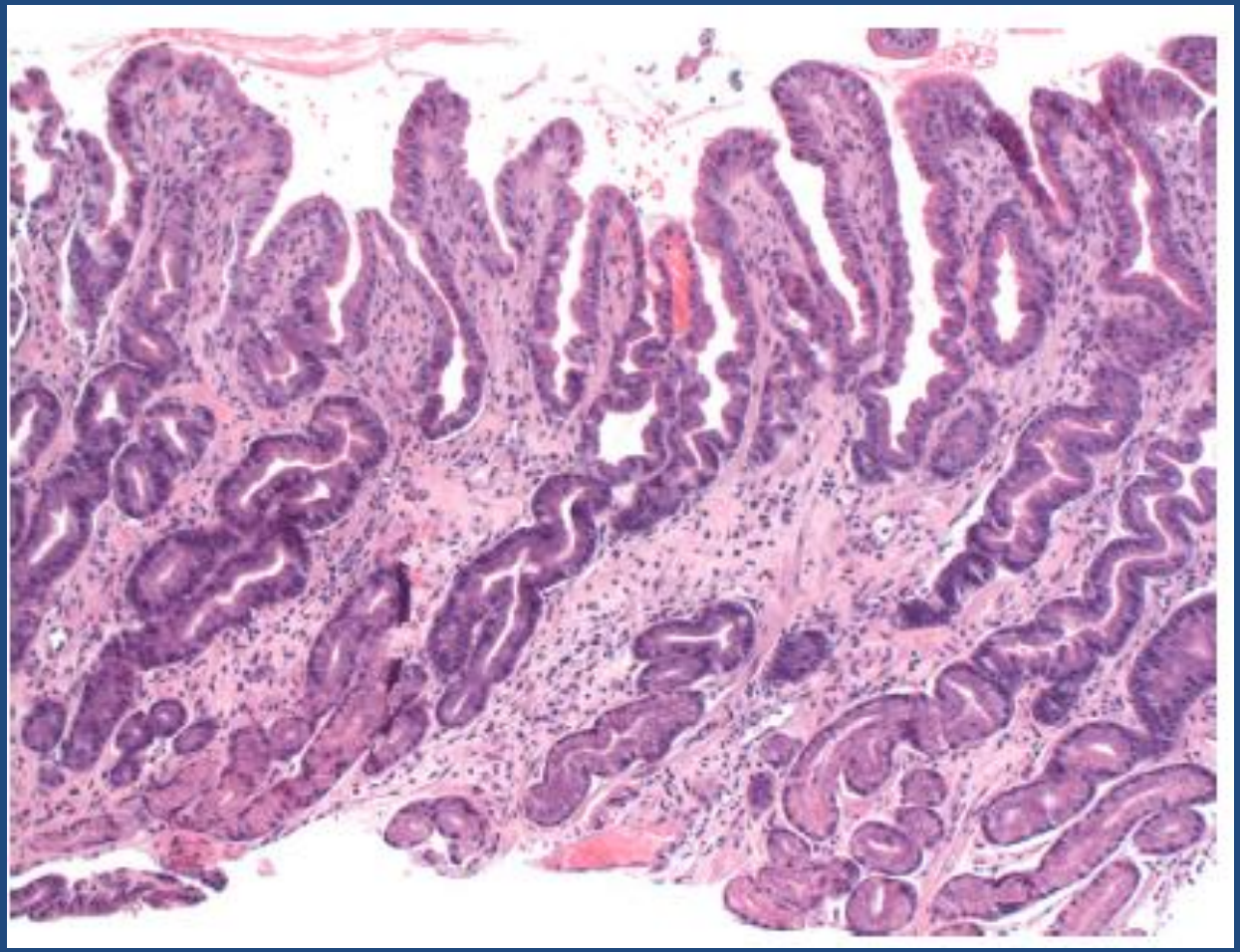


Acute Erosive or Haemorrhagic Gastritis





Reactive Gastropathy



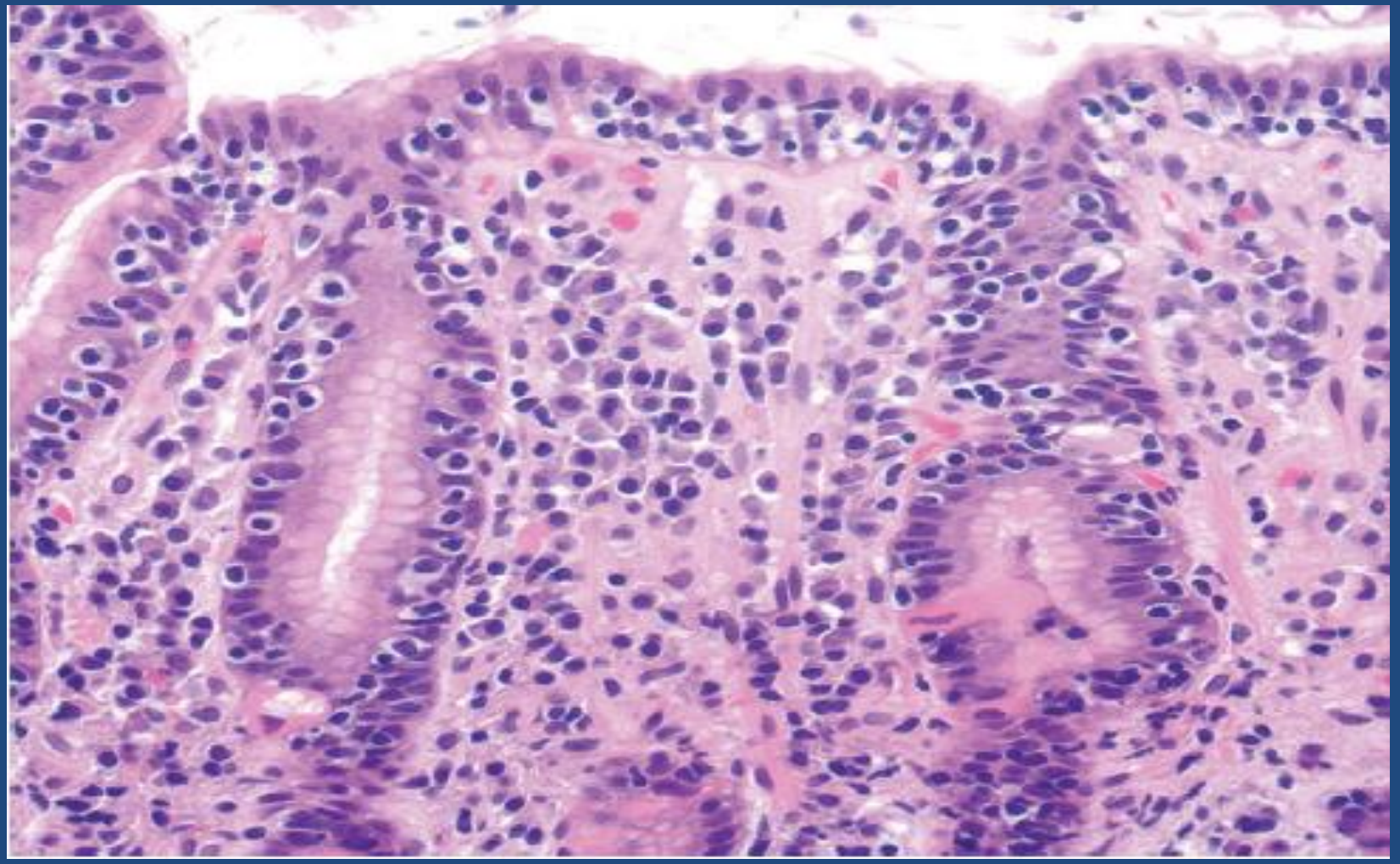
NSAID Gastropathy Manifestations

- Most commonly as dyspepsia and epigastric pain
- Serious consequences such as hemorrhage, chronic peptic ulcers, and perforation can occur
- It occurs within the first few weeks of initiating treatment, but may also be seen with long term use

NSAID Associated Ulcers

- Often multiple
- Characteristically prepyloric
- Presence of the features of reactive gastropathy in the immediate adjacent mucosa is a helpful clue to the aetiology.
- The use of NSAID suppositories does not prevent the formation of prepyloric ulcers.

NSAIDs: Lymphocytic Gastritis

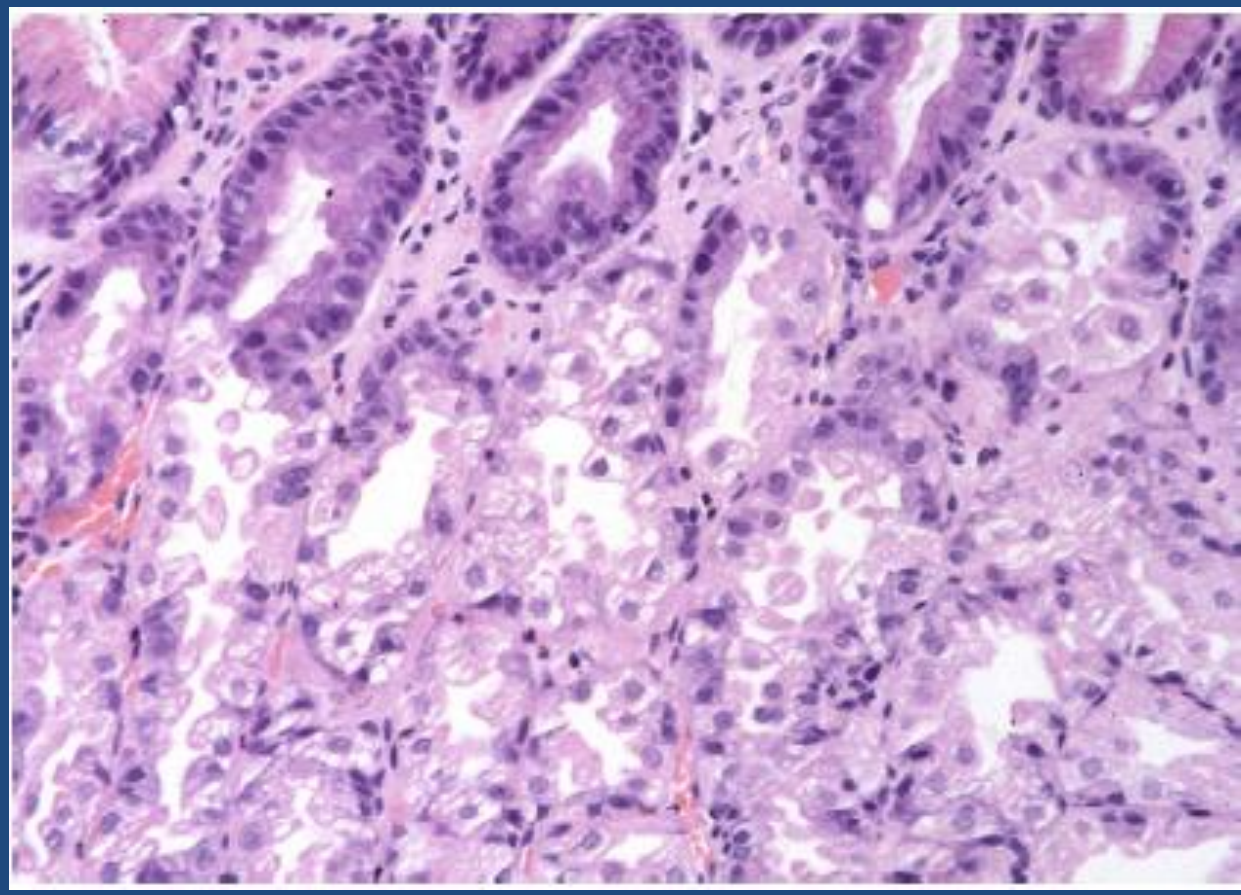


PROTON PUMP INHIBITORS (PPIs)

- Hyperplasia and hypertrophy of parietal cells
- Hyperplasia of ECL cells
- Oxyntic gland dilatation
- Parietal cell “snouting”
- Parietal cell cytoplasmic vaculation
- Fundic gland polyps.
- Atrophic gastritis with intestinal metaplasia

Parietal Cell Hyperplasia

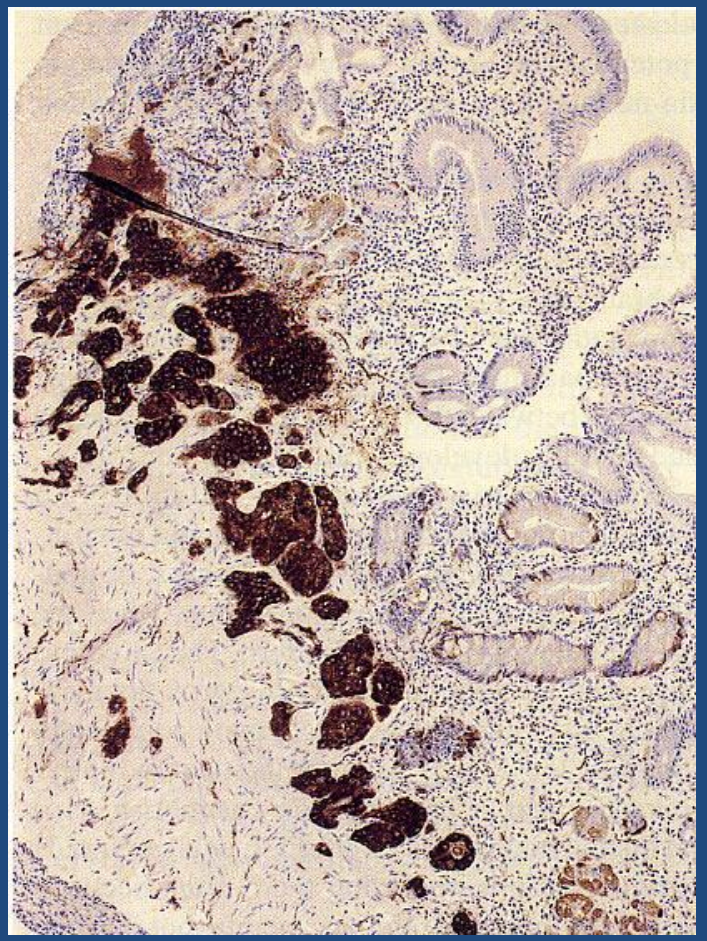
Protrusion of parietal cells into the gland lumens, creating Serrated appearance



Omeprazole-Induced changes

Omeprazole-Induced changes

Omeprazole-Induced changes



IRON INDUCED INJURY

Histopathology 2008, **53**, 311–317. DOI: 10.1111/j.1365-2559.2008.03081.x

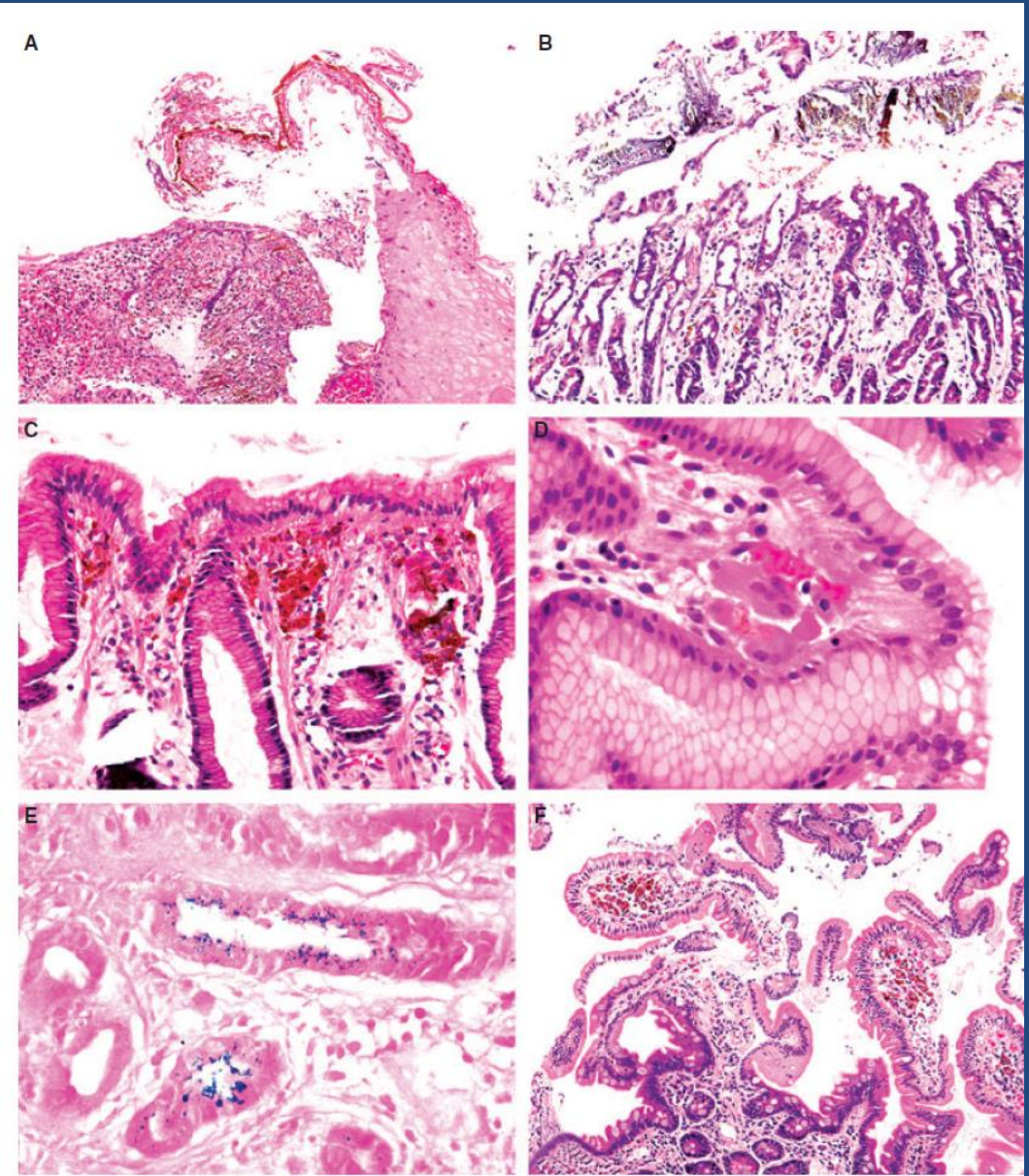
Iron-induced mucosal pathology of the upper gastrointestinal tract: a common finding in patients on oral iron therapy

P Kaye,[1,2] K Abdulla,[1] J Wood,[2] P James,[1] S Foley,[2] K Ragunath[2] & J Atherton[2]
[1]*Department of Cellular Pathology, and* [2]*Wolfson Digestive Diseases Centre, Nottingham University Hospitals and NHS Trust and University of Nottingham, Nottingham, UK*

Table 1. Patterns of iron deposition

Pattern	Name	Description
A	Luminal	Iron deposited in a crystalline form, often in a linear fashion over intact or eroded epithelium
B	Lamina propria	Granular iron present, usually in large amounts, within lamina propria and/or granulation tissue with overlying intact or ulcerated epithelium
C	Epithelial	Iron within glandular or surface epithelial cells
D	Reticuloendothelial	Iron in histiocytes within lamina propria

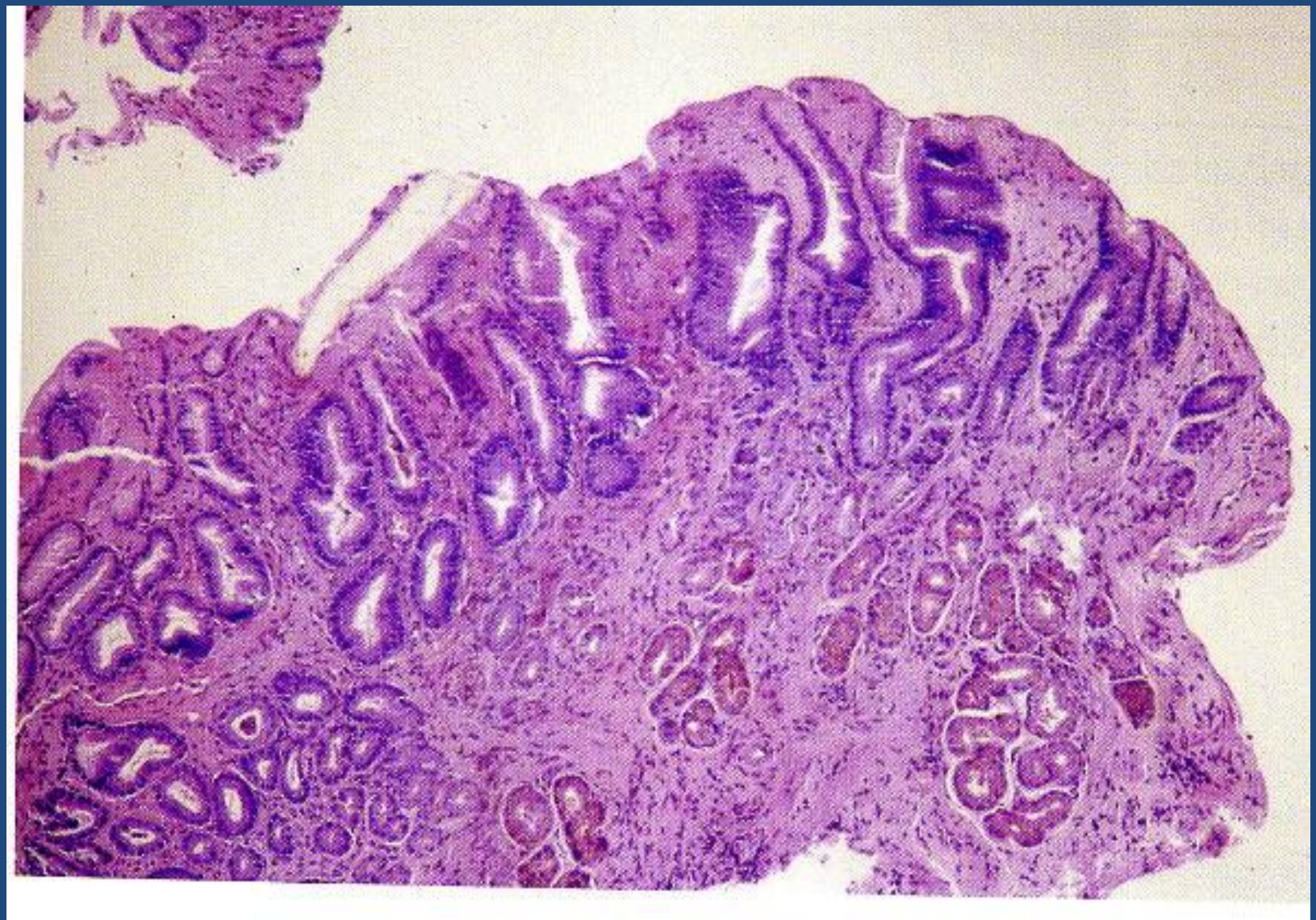
IRON INDUCED INJURY



Gastric Hemosiderosis

- In patients ingesting large amounts of iron medications
- Hemosiderin pigment in gastric epithelial cells and lamina propria macrophages.
- Little clinical significance and does not indicate that the patient suffers from hemochromatosis.
- The diagnosis of hemochromatosis must only be considered in patients with clinical evidence of the disease.

Gastric Hemosiderosis



Iron Tablet Induced Gastric Erosion

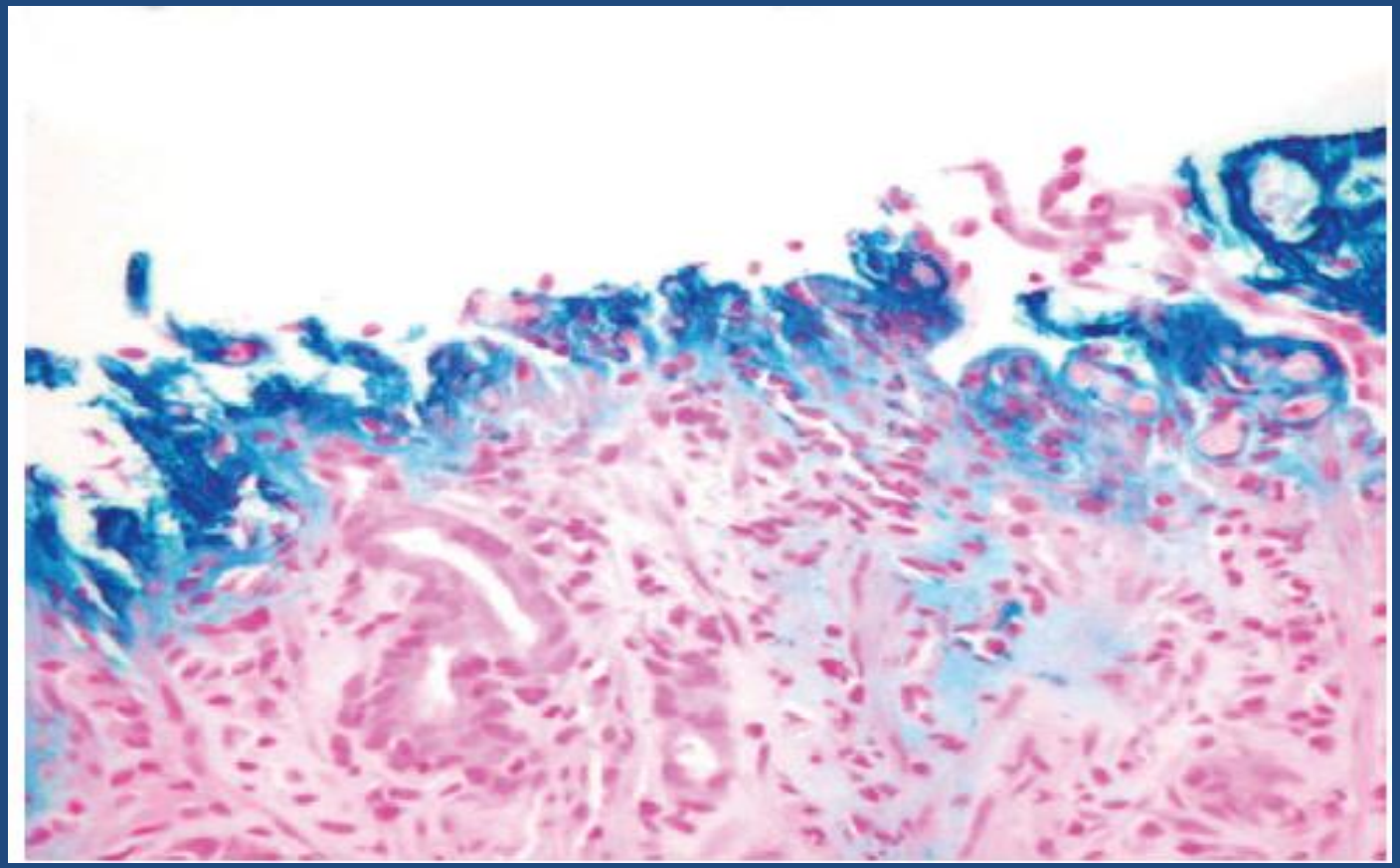
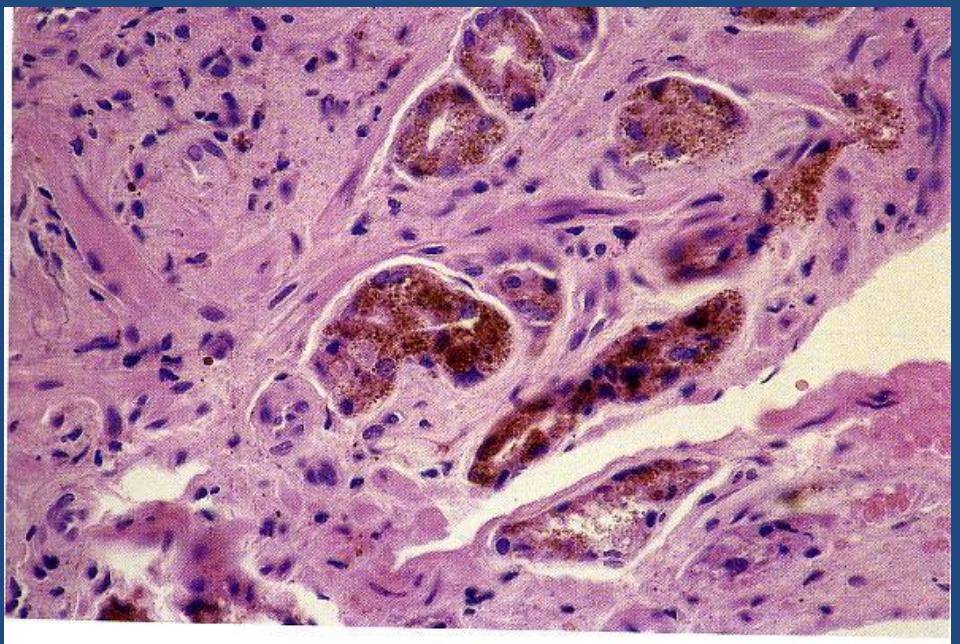
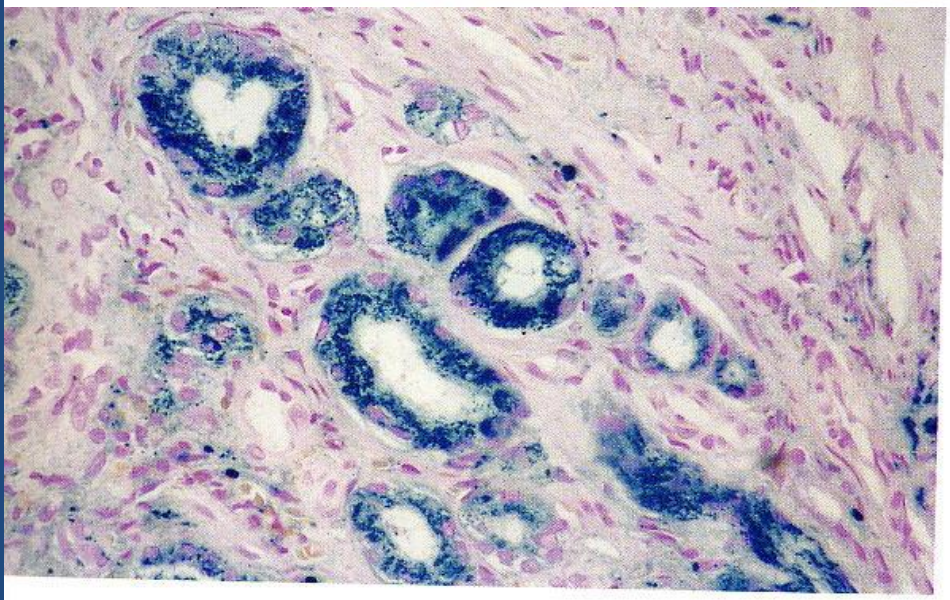
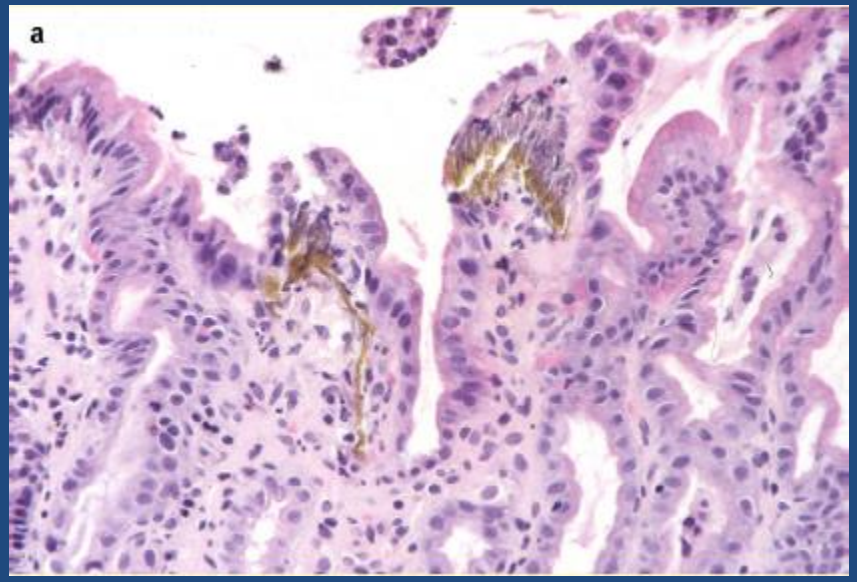


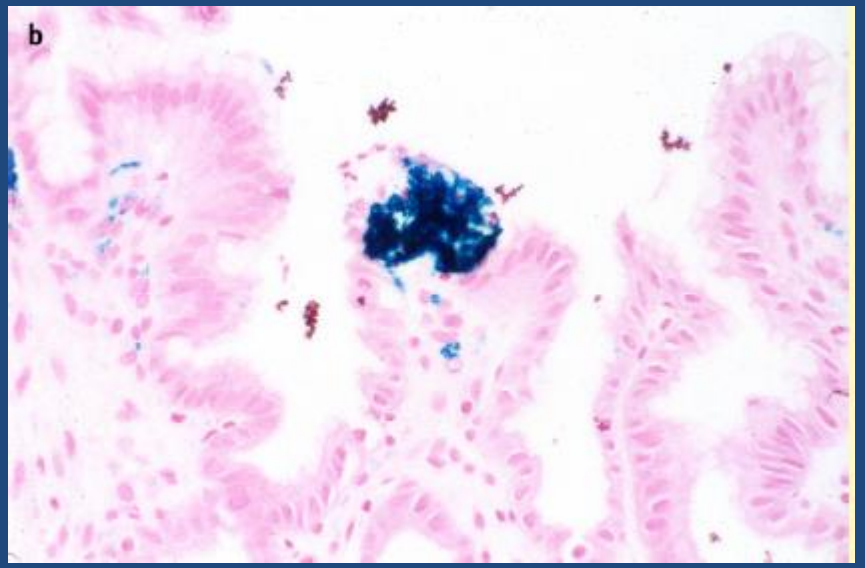
FIGURE 12-47 Mucosal erosion associated with chronic iron tablet intake. The ferrous nature of the pigment in the erosion is highlighted by a Prussian blue stain.

Gastric Hemosiderosis



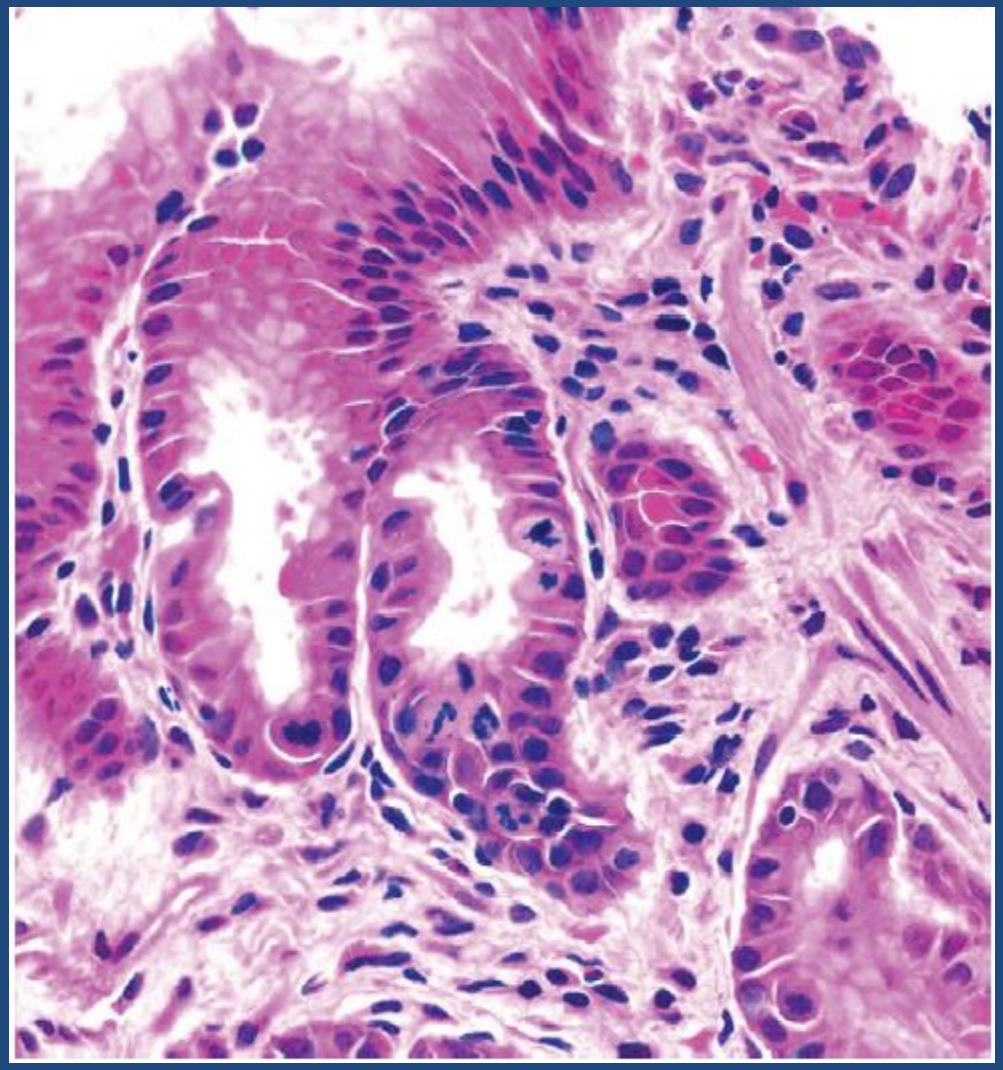






Gastric injury in Cholchicine

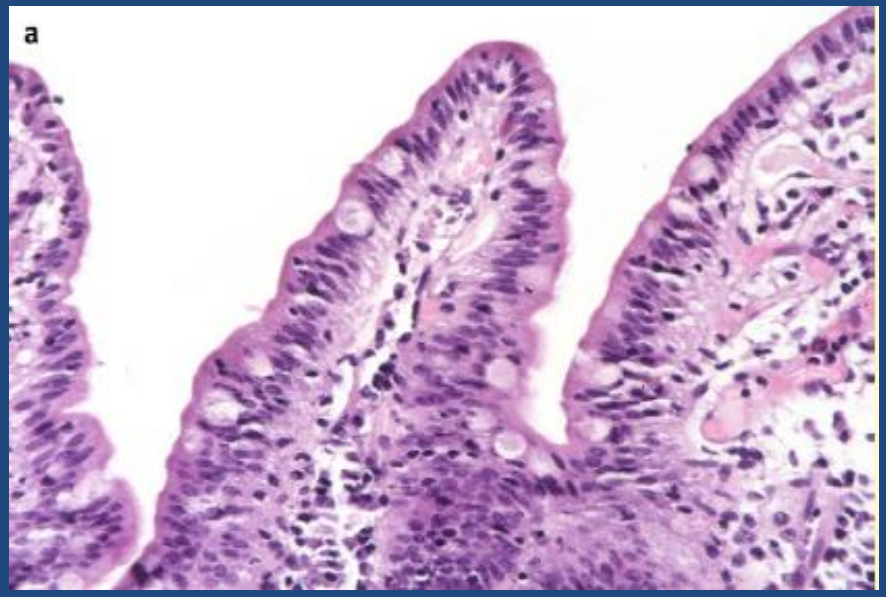
- Pseudostartification
- Loss of polarity
- Prominent Metaphase mitosis
- Apoptosis
- Mimic dysplasia

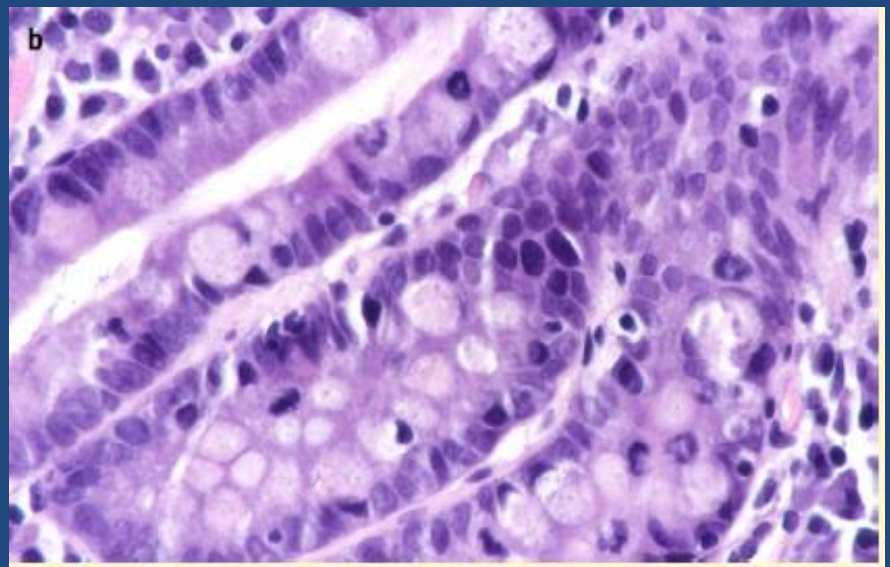


Duodenal Bx in Colchicine Toxicity

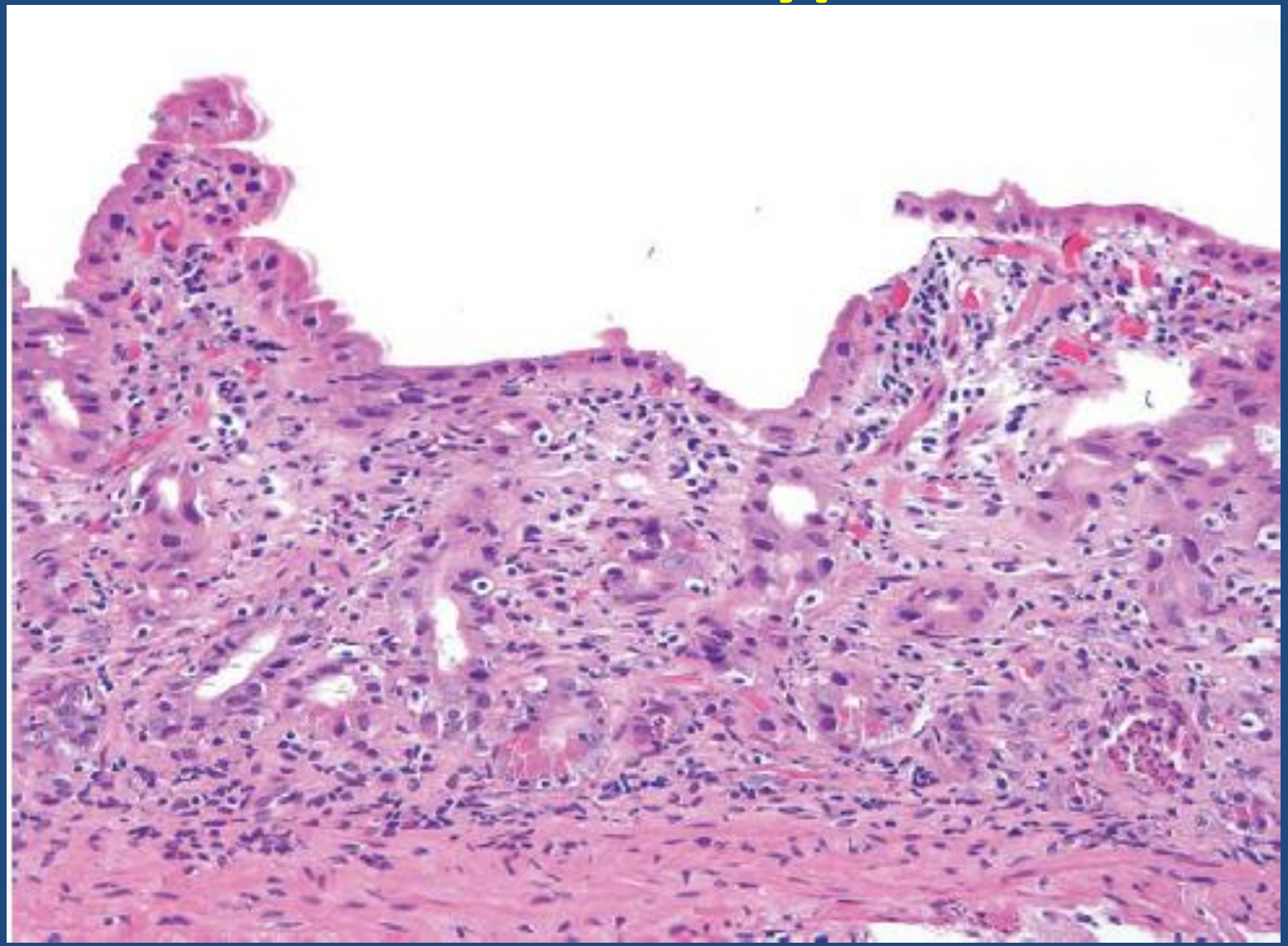
Villous blunting and pseudostratification of epithelial nuclei.

In the crypts, numerous mitoses are arrested in metaphase, and several assume a characteristic ‘ring’ pattern.





Duodenum: Chemotherapy-induced Reactive Atypia

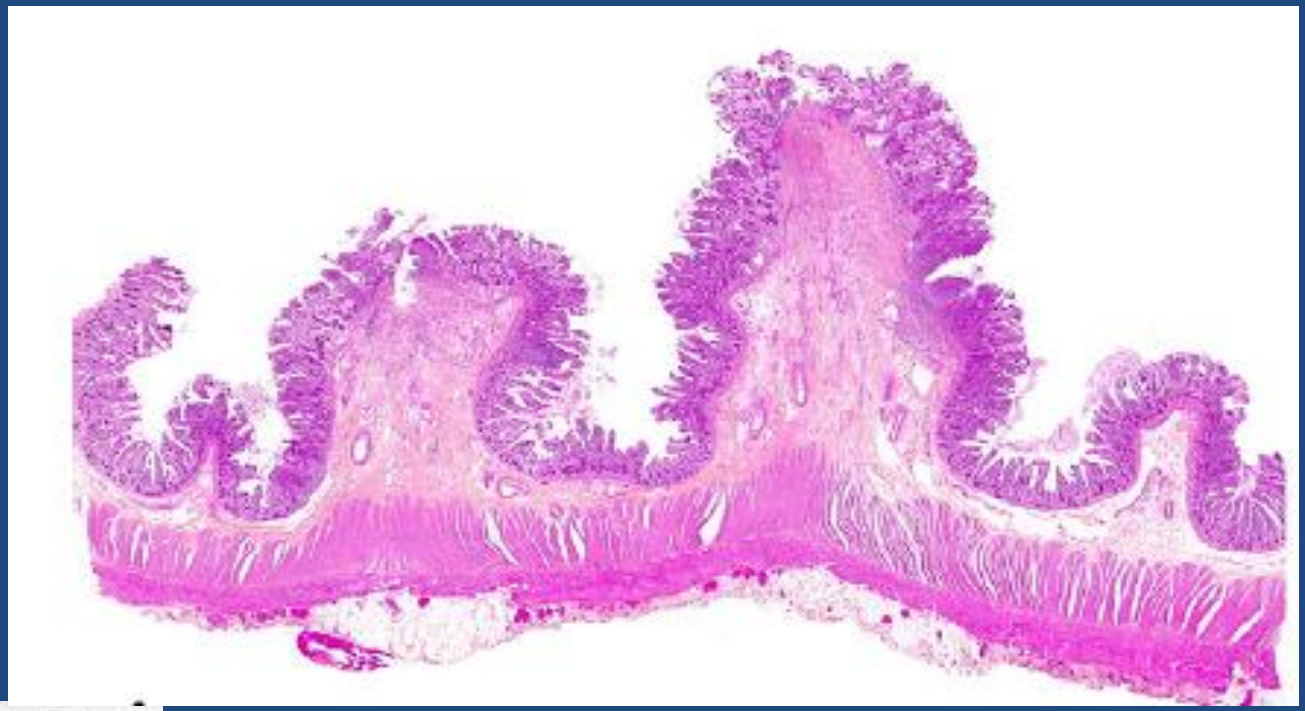


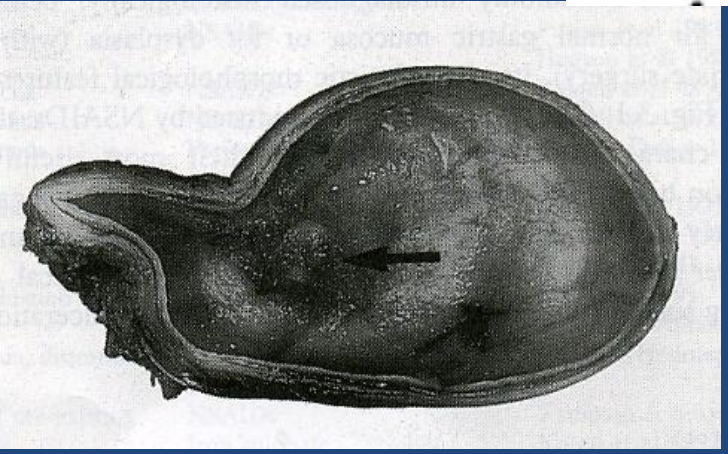
NSAID Associated Diaphragm Disease

- Ulceration of the antrum with subsequent cicatrizing submucosal fibrosis and the formation of prepyloric diaphragms

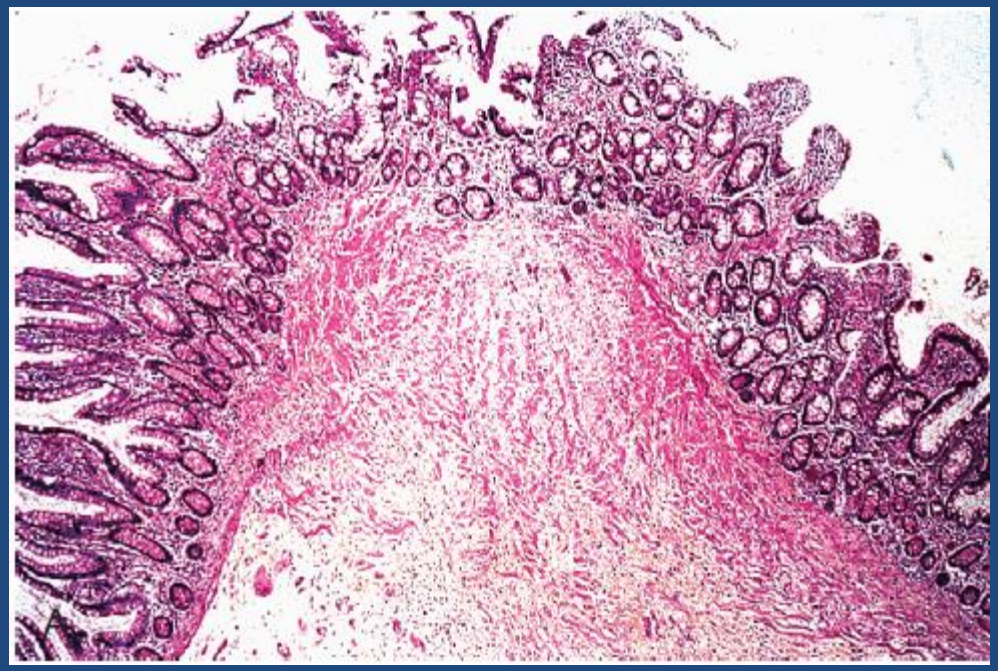
- More commonly seen in the small bowel.

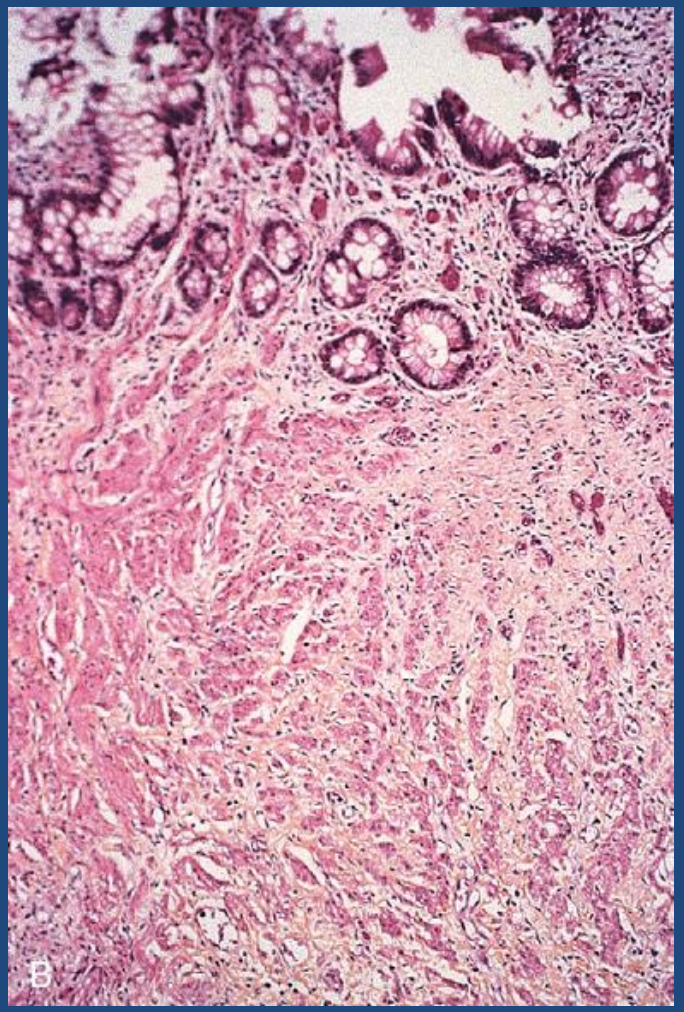
NSAID Associated Diaphragm Disease





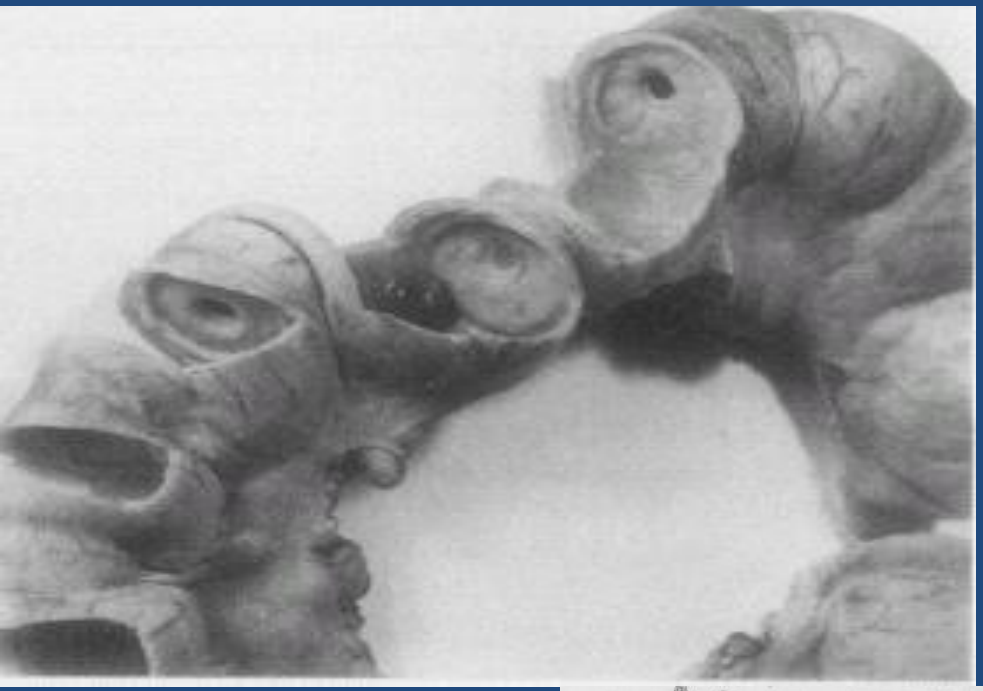
NSAID Associated Diaphragm Disease

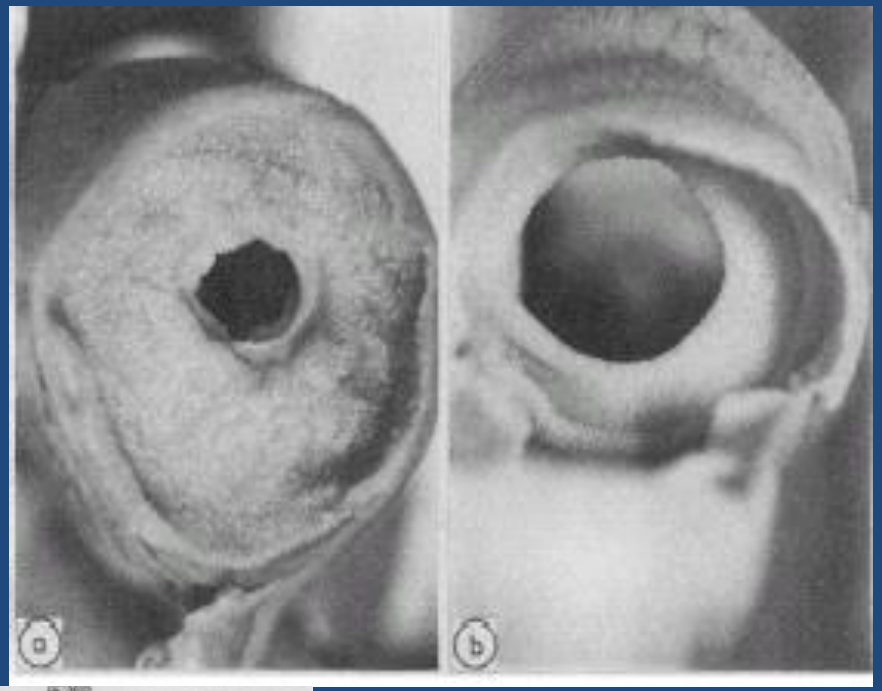


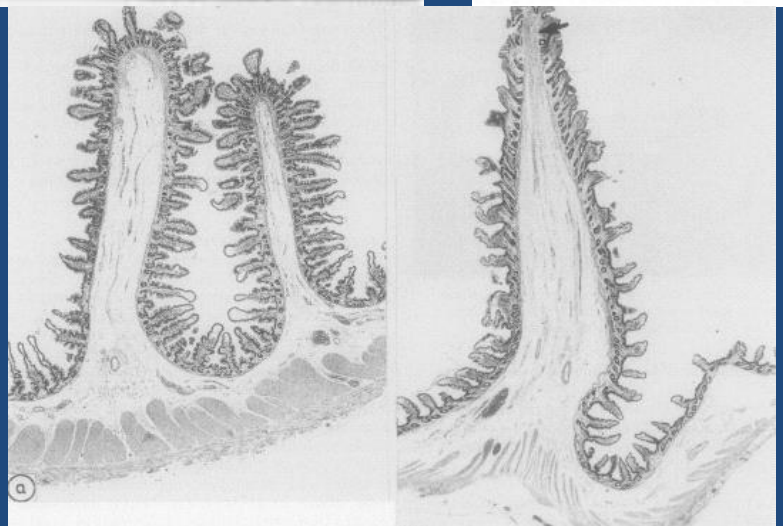


- Thin fibrous septa that form luminal diaphragm
- Sub mucosal fibrosis
- Reactive changes

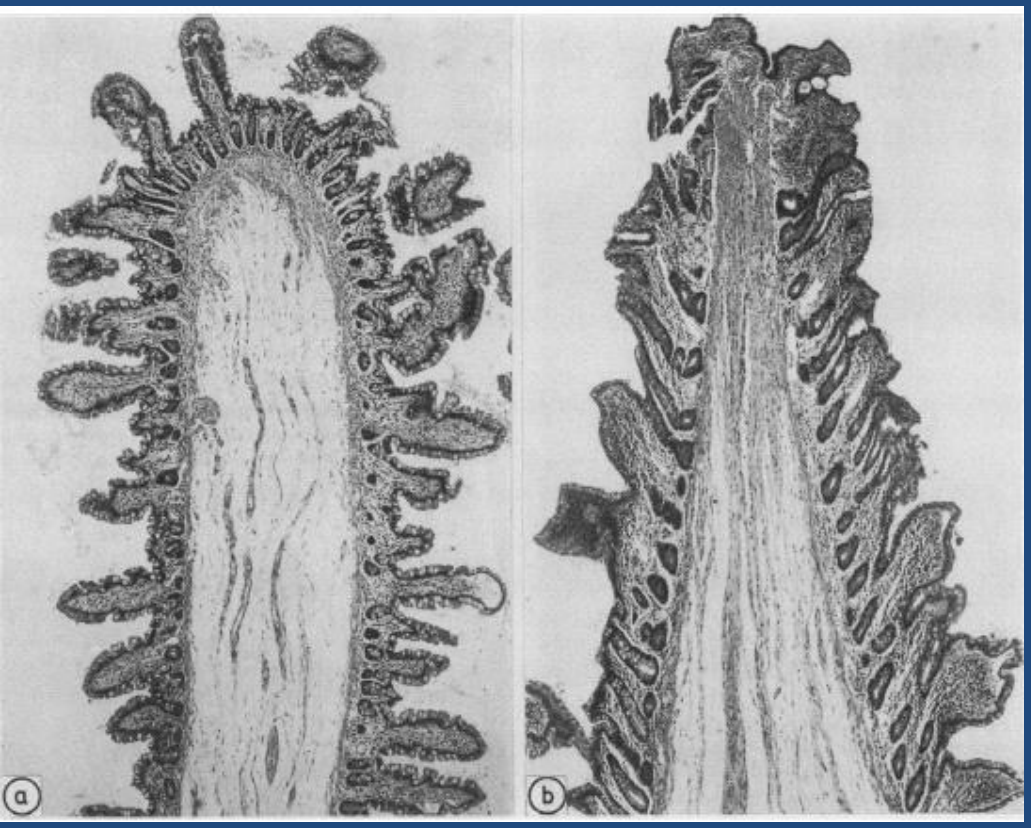
Small Intestinal Diaphragm Disease

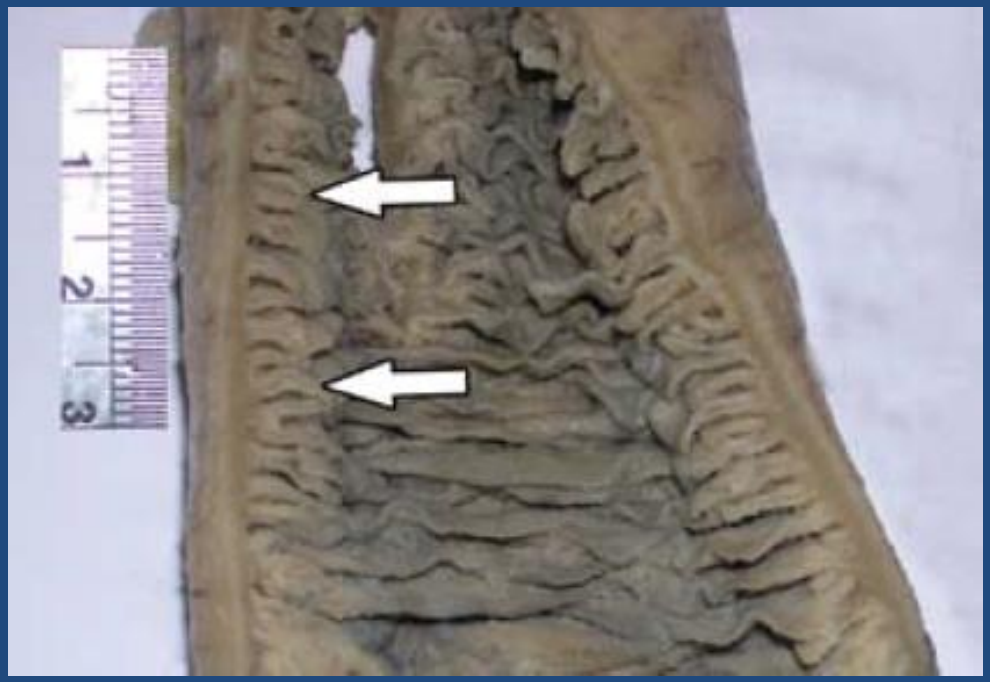


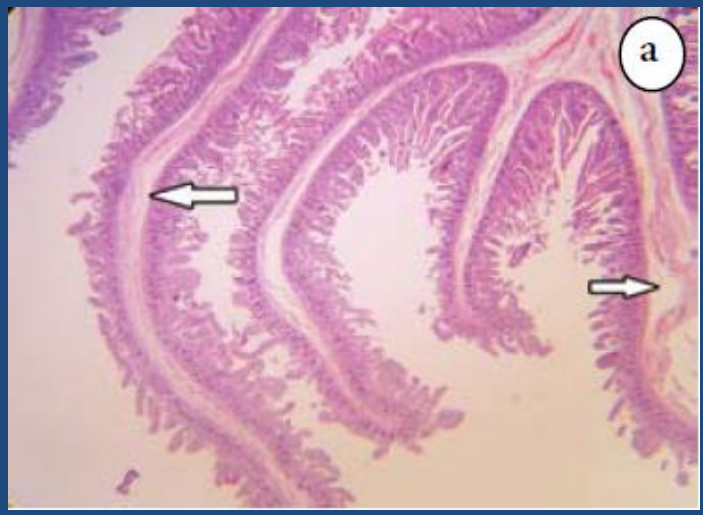


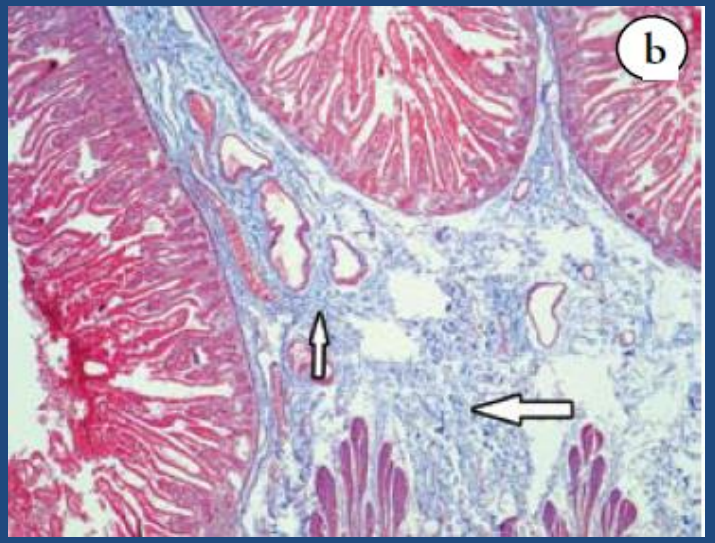


Small Intestinal Diaphragm Disease









Case Reports

Diaphragm disease of the jejunum

Raji H. Al-Hadithi, Mohammed S. Alorjani, Samir M. Al-Bashir, Ismail I. Matalka

Saudi Med J 2009; Vol. 30 (5)

Drug-Induced Small Intestinal Lesions

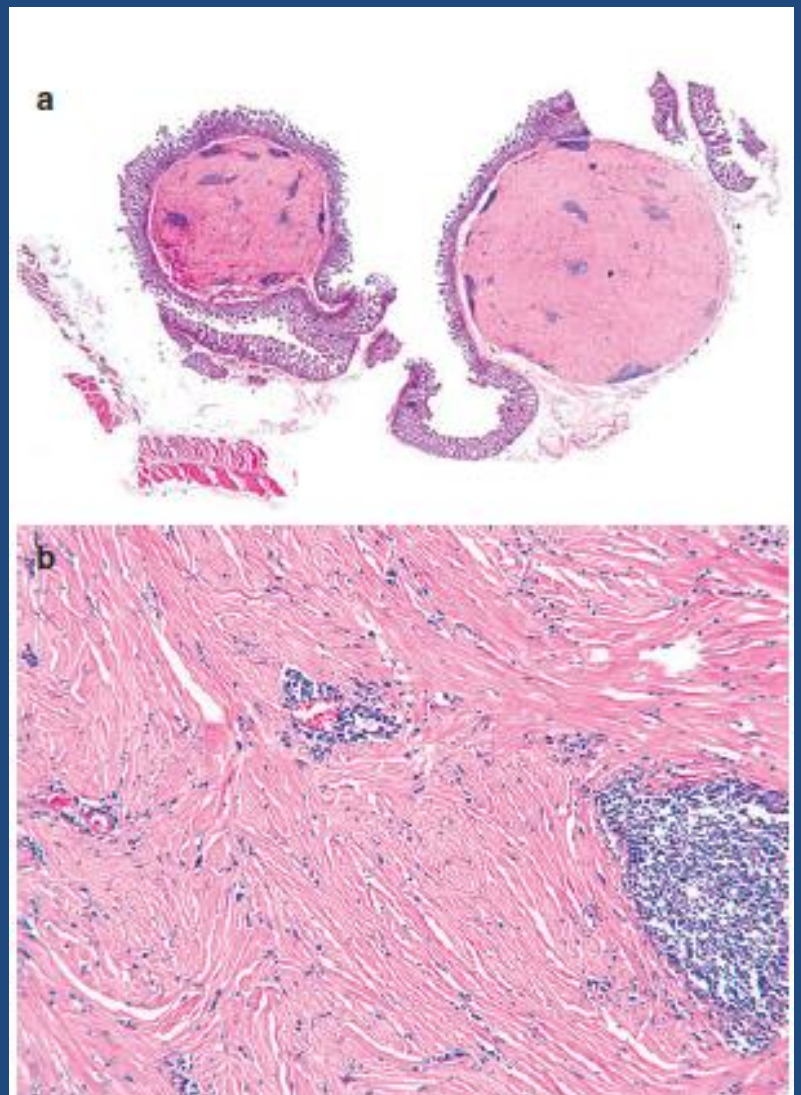
- Duodenal ulcers = NSAIDs **(Davies & Brightmore 1970)**
- Jejunal ulcers & Diaphragm Disease = NSAIDs (Lang et al 1988)
- Ileal ulcers = NSAIDs and potassium Chloride (Lang et al 1988 and Leyonmarck & Raf 1985)
- Ileal Inflammation and malabsorption = Mefenamic acide (Marks & Gleeson 1975)

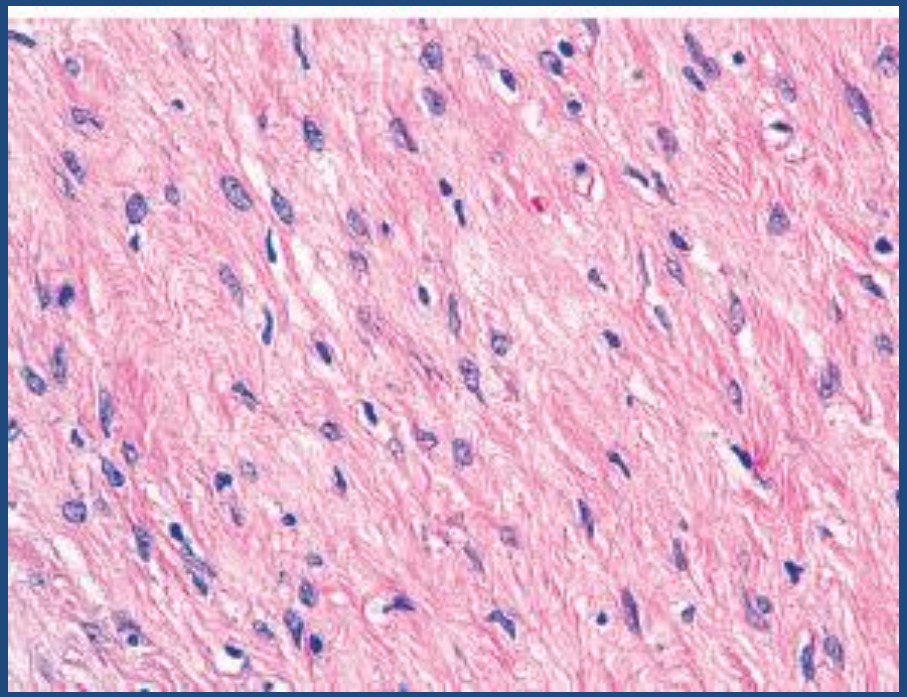
Clinical & Pathological Significance

- **To be differentiated from Crohn's disease**
- **To be differentiated from ischemic enteritis**

NSAID-associated submucosal fibrous nodules of the small intestine

Histopathology, 2007, 51, 405–432.



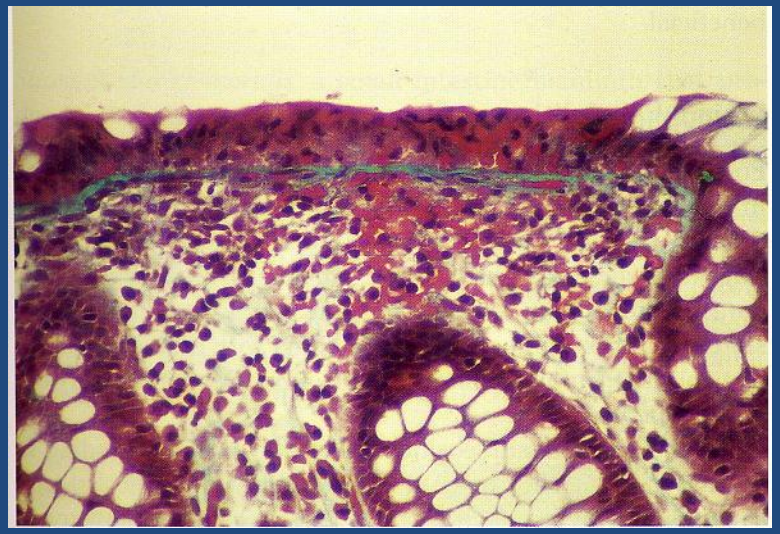


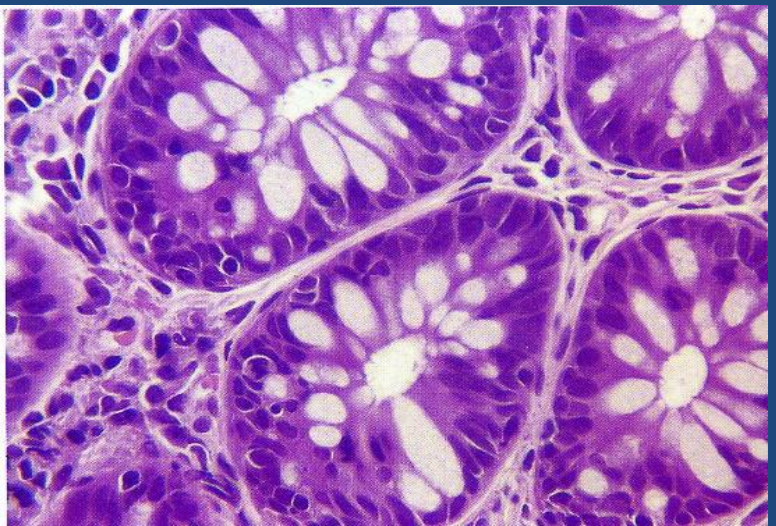
WADI MUJIB

NSAIDs and Colon

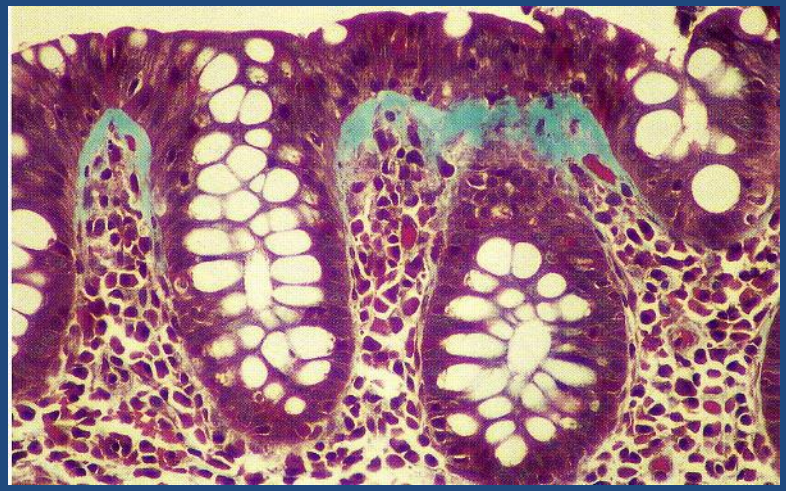
- Ulceration (Hudson et al 1993)
- Colonic diaphragms (Fellows et al 1992, Pucius et al1993)
- Microscopic colitis (Kingham et al 1982)
- Lymphcytic colitis (Lazenby et al 1989)
- Collagenous colitis (Lindstrom 1976)
- Potent inducers of apoptosis in the crypt epithelium (Lee 1993)
- Exacerbation of pre-existing UC (Kawai et al 1992)

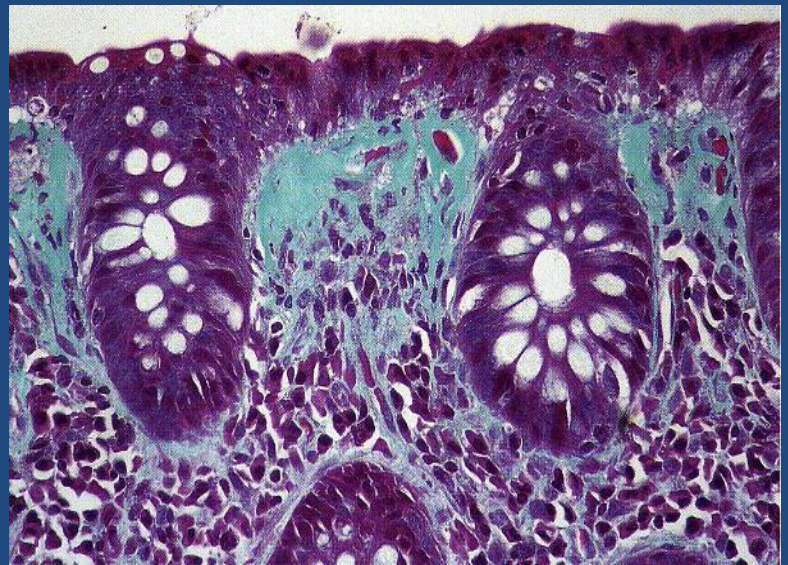
Lymphocytic Colitis



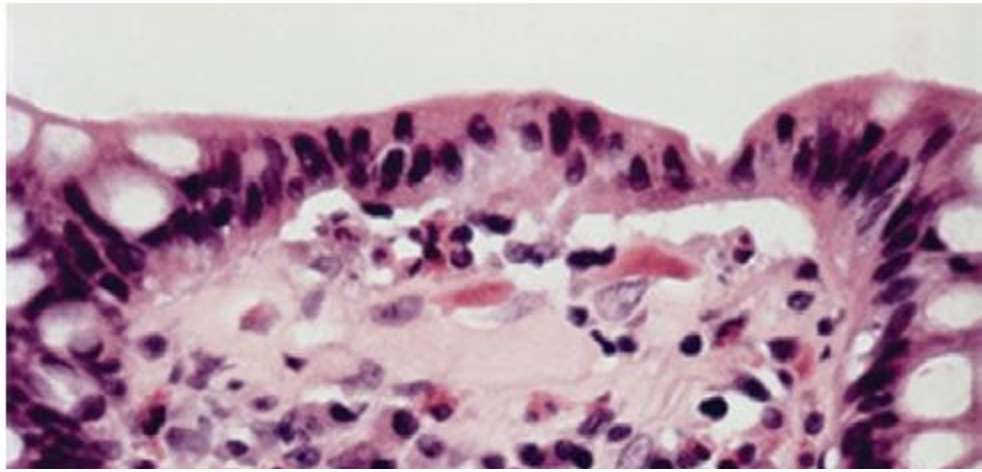


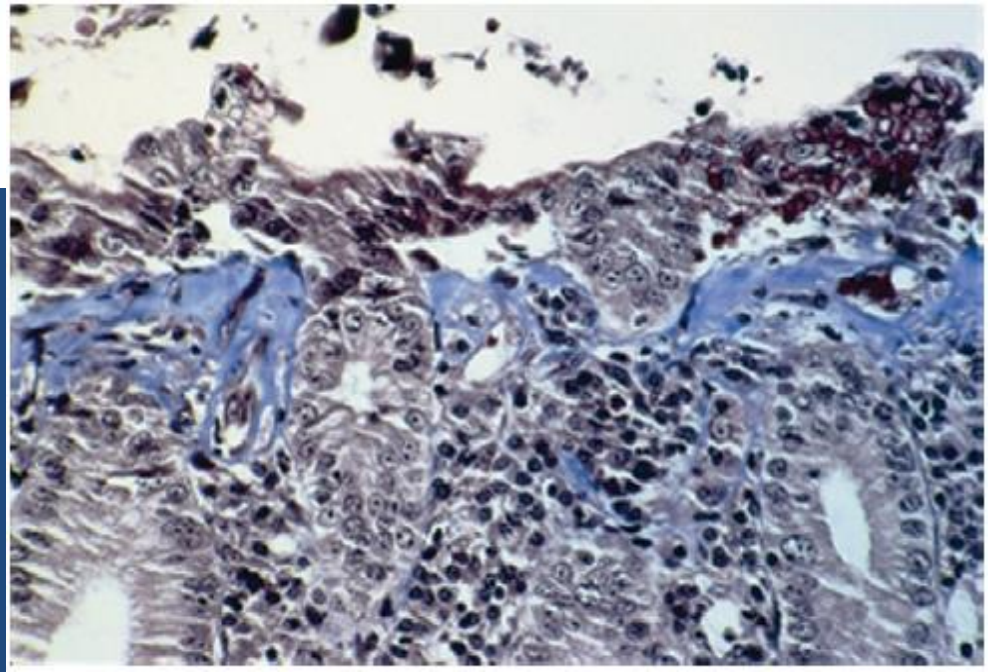
Collagenous Colitis





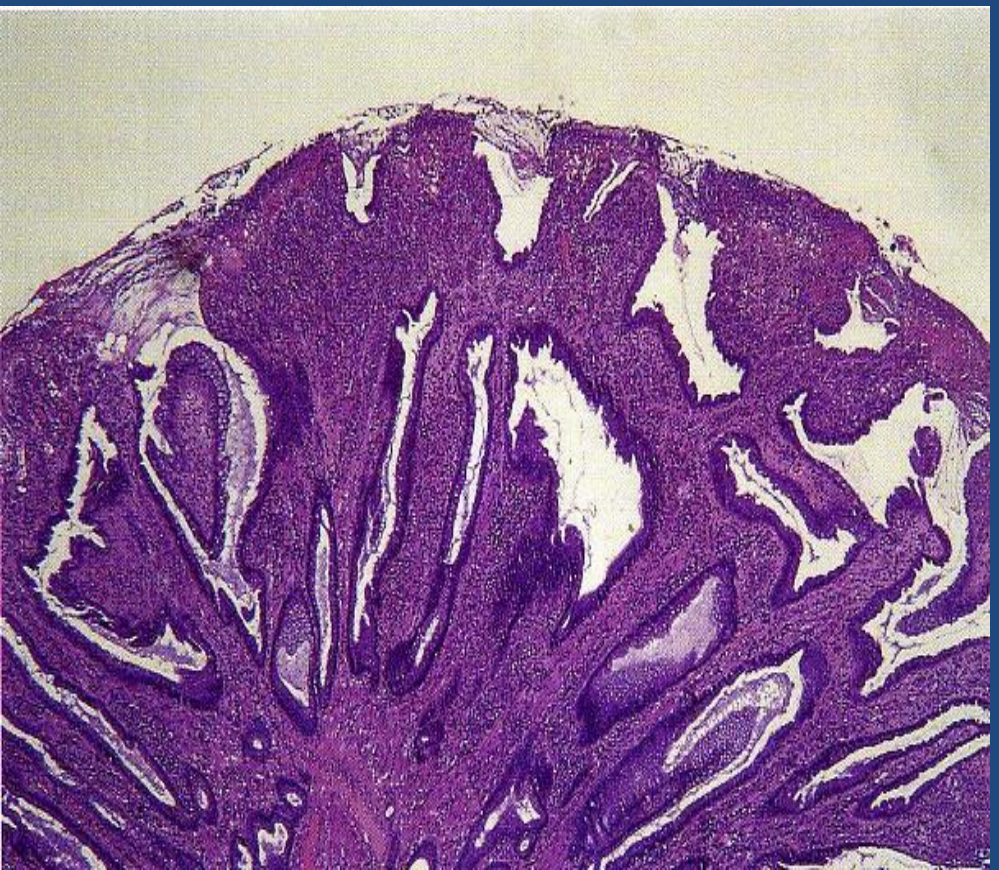
Collagenous Colitis

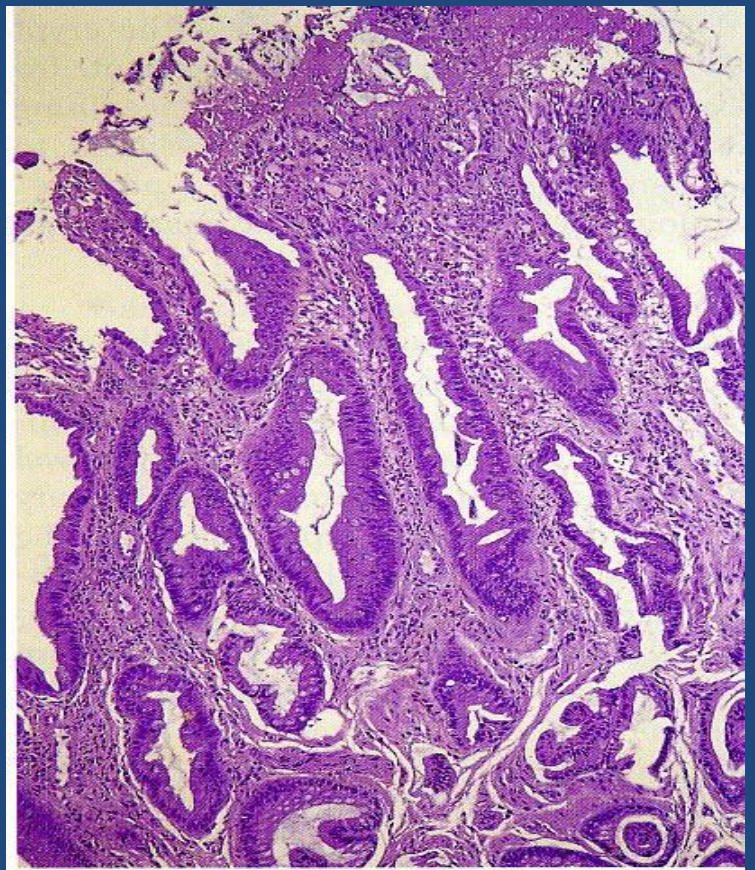




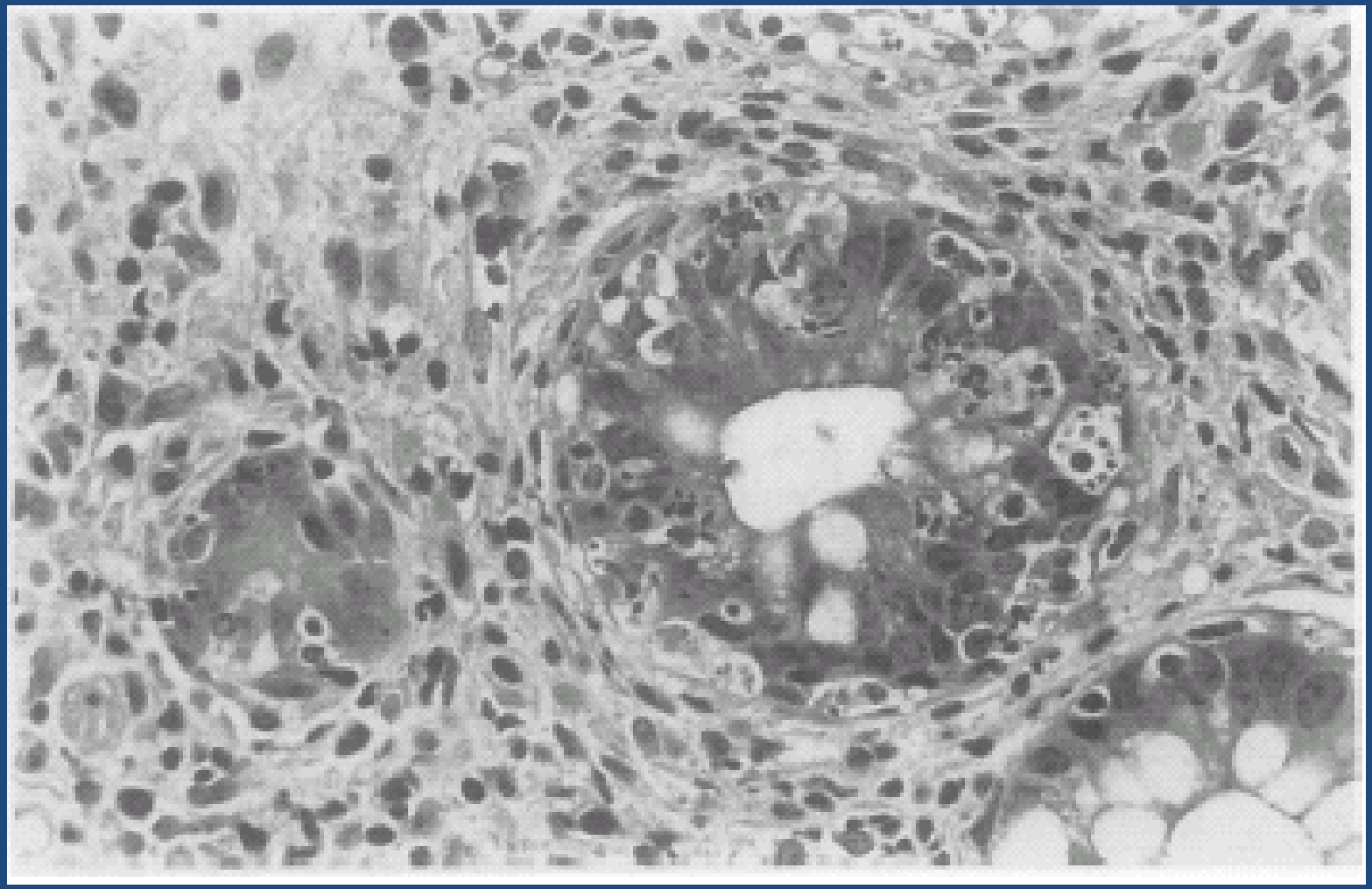
NSAIDs and Analgesic Containing Suppositories

Mucosal damage of the rectum and mucosal prolapse syndrome-like features. (Fenzy & Bogomoletz 1987)





NSAID assoiciated Apoptosis



Lee 1993

DANA

HOUFA




Focal active colitis

- 45% patients immunosuppressed, 40% taking NSAIDs
- Follow-up (1-74 mths, mean = 25 mths)
  - acute self-limited infectious colitis (45%)
  - incidental finding (25%)
  - irritable bowel syndrome (14%)
  - ischaemia (10%)
  - antibiotic associated colitis (5%)
- No patient developed CIBD

Greenson et al, 1997

Focal active colitis

		infective/ self-limited	drugs	IBS	incidental	CIBD
Greenson et al, 1997	USA 42 cases adults	45%	14% (NSAIDS and Abs)	14%	26%	0
Volk et al, 1998	USA 31 cases adults	48%	?	10% ischaemic colitis	29%	13% (all CD)
Xin et al, 2003	USA 31 cases all children	31%	0%	0%	27.6%	31% (8 CD; 1 UC)
Shetty et al, 2011	UK 90 cases adults	19%	24% (NSAIDS and Abs)	33%	8%	16% (10 CD, 2 UC, 2 IBDU

Focal active colitis

- Up to half of all the patients have self-limited disease (likely infective)
- Strong but variable association with drugs (esp NSAIDs, PPIs and antibiotics) in adults
- Occasionally ischaemia, immunosuppression
- About one quarter incidental finding or associated with IBS
- Up to 15% (higher in children) will have CIBD – much more commonly CD

Focal Active Colitis

Histopathology 2011, **59**, 850–856. DOI: 10.1111/j.1365-2559.2011.04019.x

Focal active colitis: a prospective study of clinicopathological correlations in 90 patients

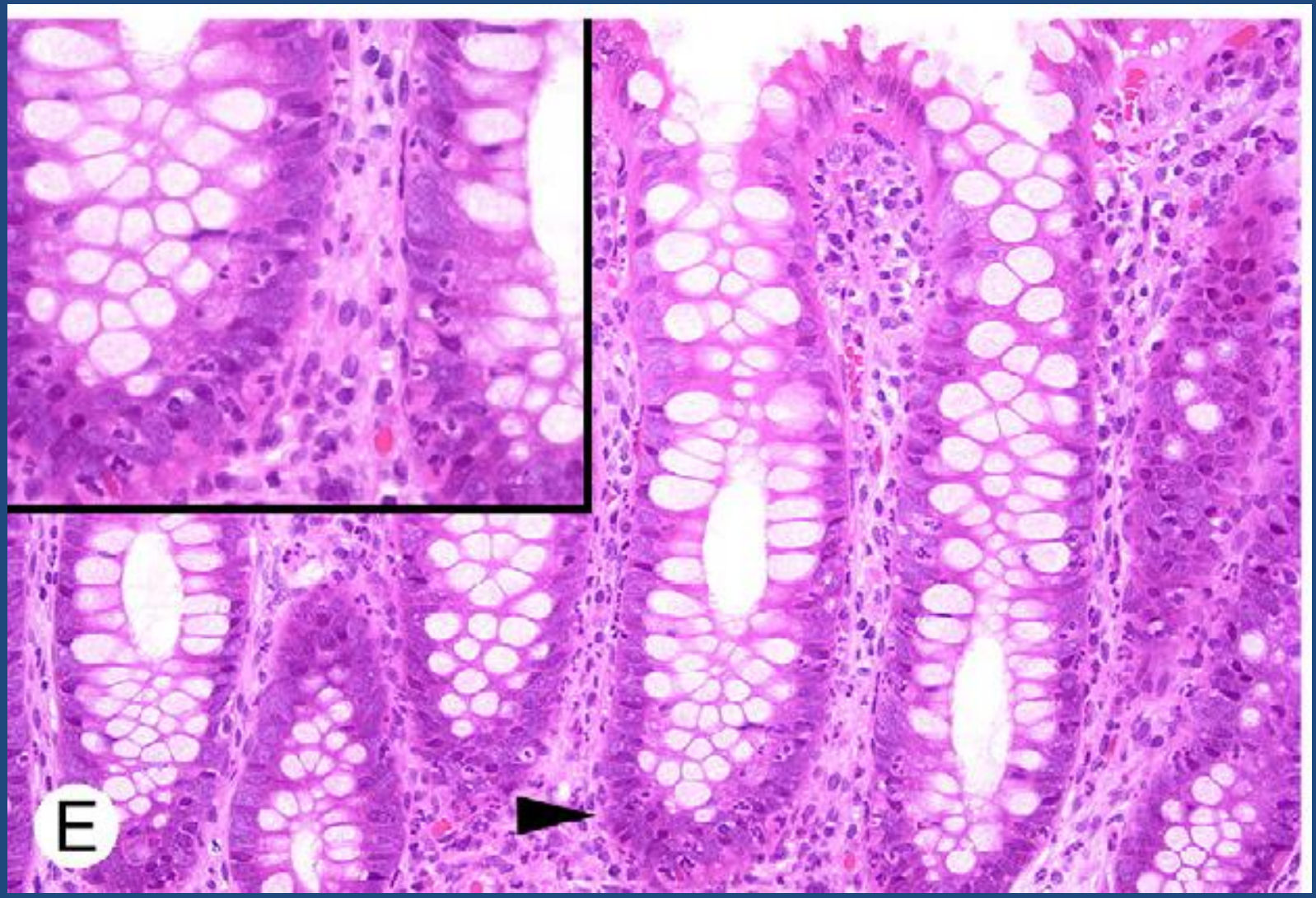
Sharan Shetty,[1] Salim M Anjarwalla,[2] Jyoti Gupta,[2] Chris J W Foy,[1] Ian S Shaw,[1] Roland M Valori[1] & Neil A Shepherd[2]

[1]*Departments of Gastroenterology and South West Research Design Service, Gloucestershire Royal Hospital, Gloucester, UK, and* [2]*Gloucestershire Cellular Pathology Laboratory, Cheltenham General Hospital, Cheltenham, UK*

- In 24% of patients drugs,especially NSAIDs, were implicated
- Infection was a probable cause in 19%.
- In 14 patients (15.6%), predominantly women, a diagnosis of chronic inflammatory bowel disease was ultimately made.
- A specific subtype of FAC, termed basal FAC, was significantly associated with drugs.

Focal Active Colitis

Focal Active Colitis

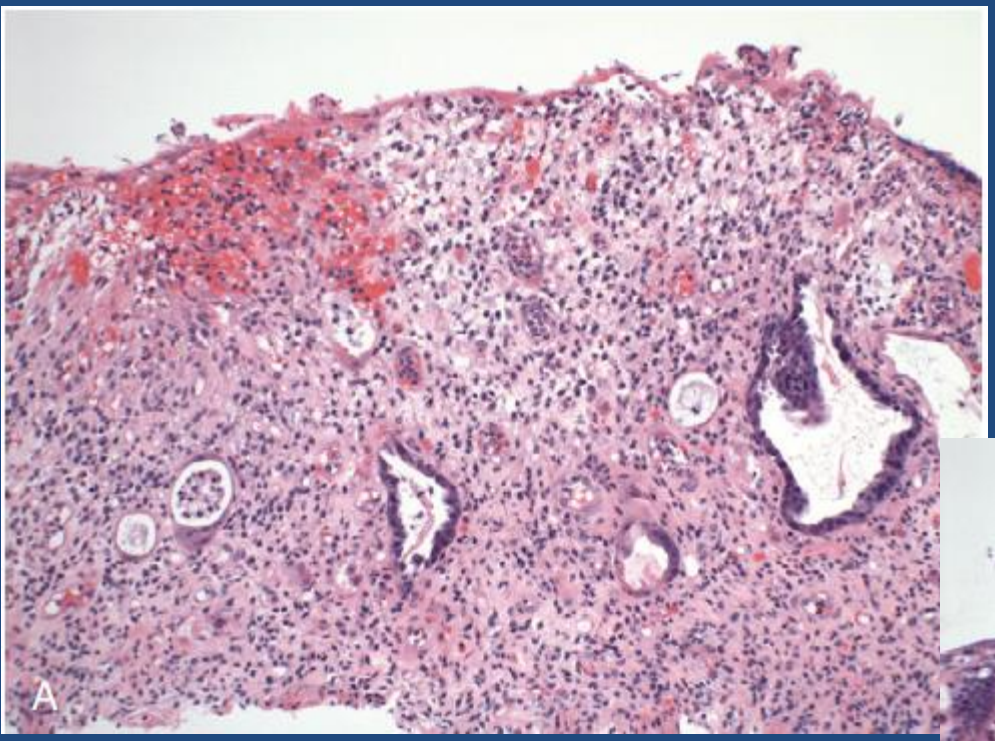


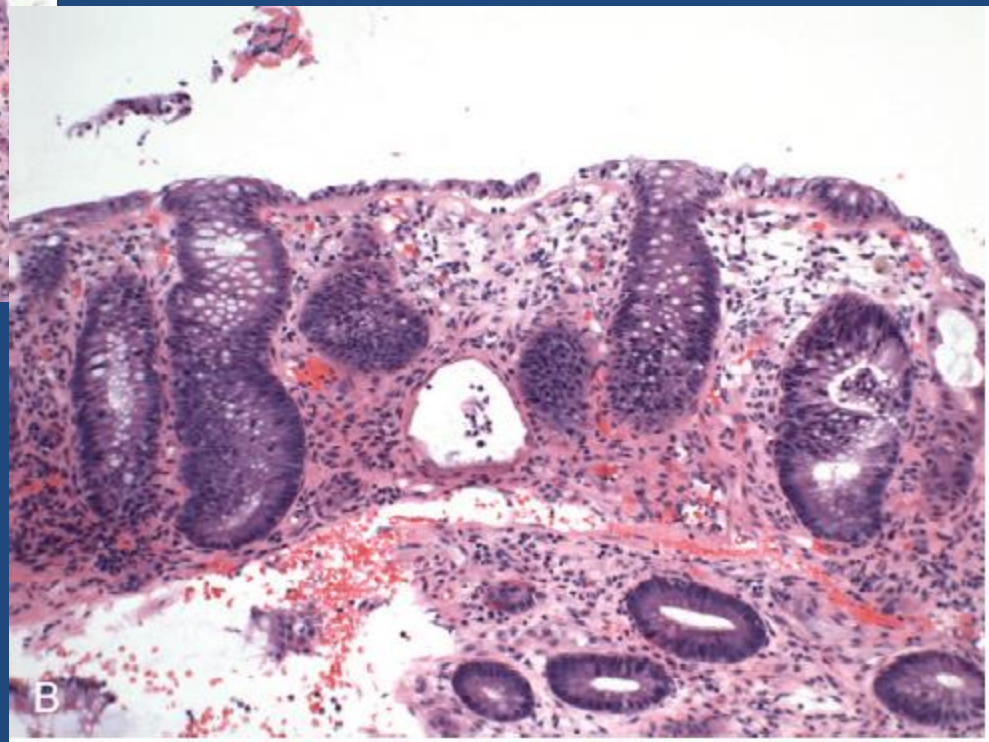
HOUFA-NORTH JORDAN

Other Drugs

• Alpha-methyldopa.	IBD-like acute colitis
• Gold therapy.	Eosinophilic colitis
• Anthraquinone laxative abuse.	Melanosis
• Long term laxative abuse.	Muscular and neural atrophy
• 5-fluorouracil	Acute epithelial necrosis, crypt regeneration, and distortion
• Bowel preparation drugs	Infective colitis like
• Penicillamine, antibiotics	Chronic inflammation

Chemotherapy Induced Colitis





- Crypt Loss
- Edema & Hemorrhage of L.P
- Apoptosis & Reg. changes

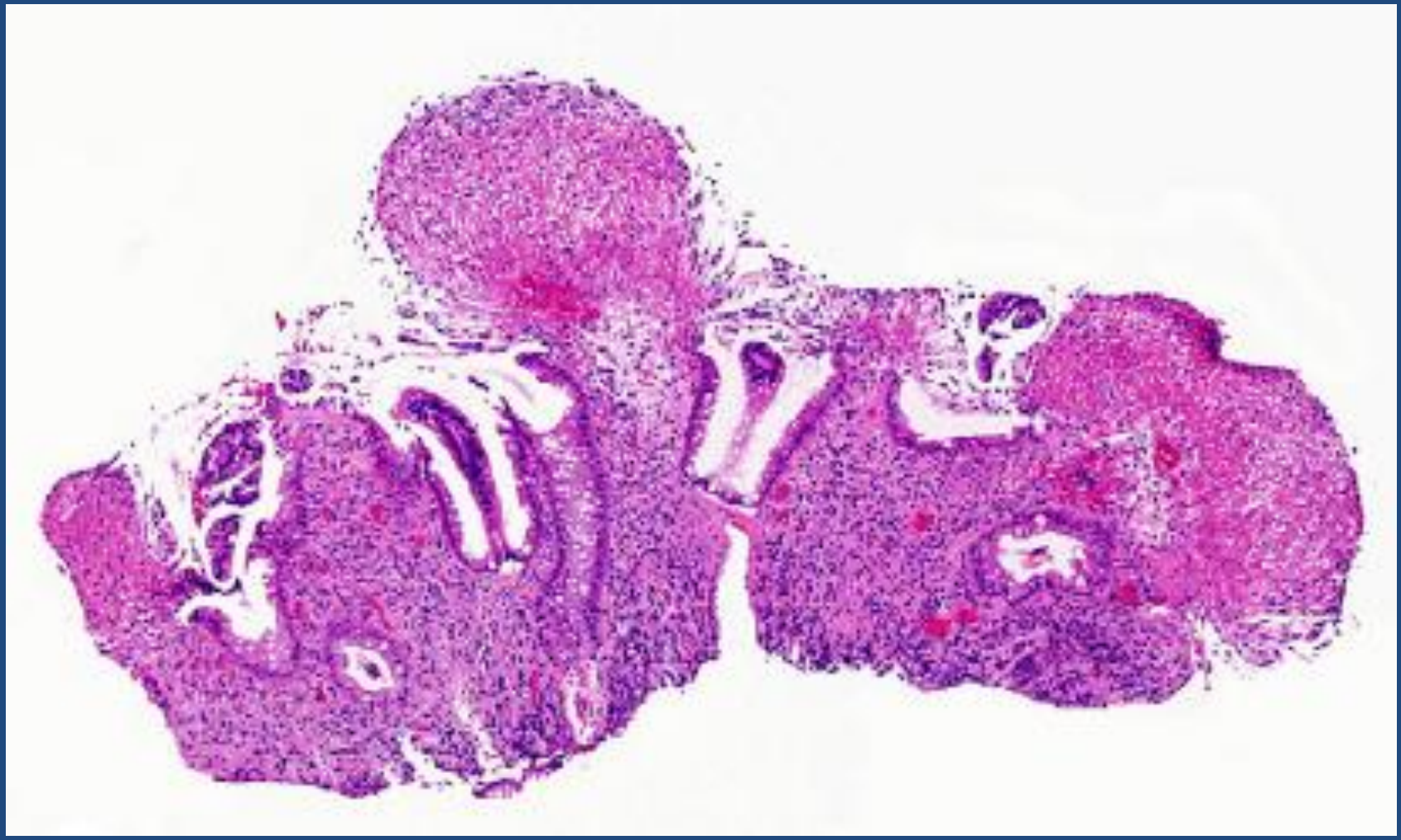
ANTIBIOTICS

- Pseudomembranous colitis , due to C difficile, has been traditionally considered synonymous with antibiotic-associated colitis because antibiotics, most commonly penicillins, clindamycin, cephalosporins, and trimethoprim-sulfamethoxazole, account for most of the cases.

- Antibiotic associated hemorrhagic colitis (AAHC) = Acute Colonic ischemia

- Interestingly, only 37% of C difficile cases were prescribed antibiotics within 90 days before diagnosis.

Pseudomembranous colitis



POTASIUM CHLORIDE

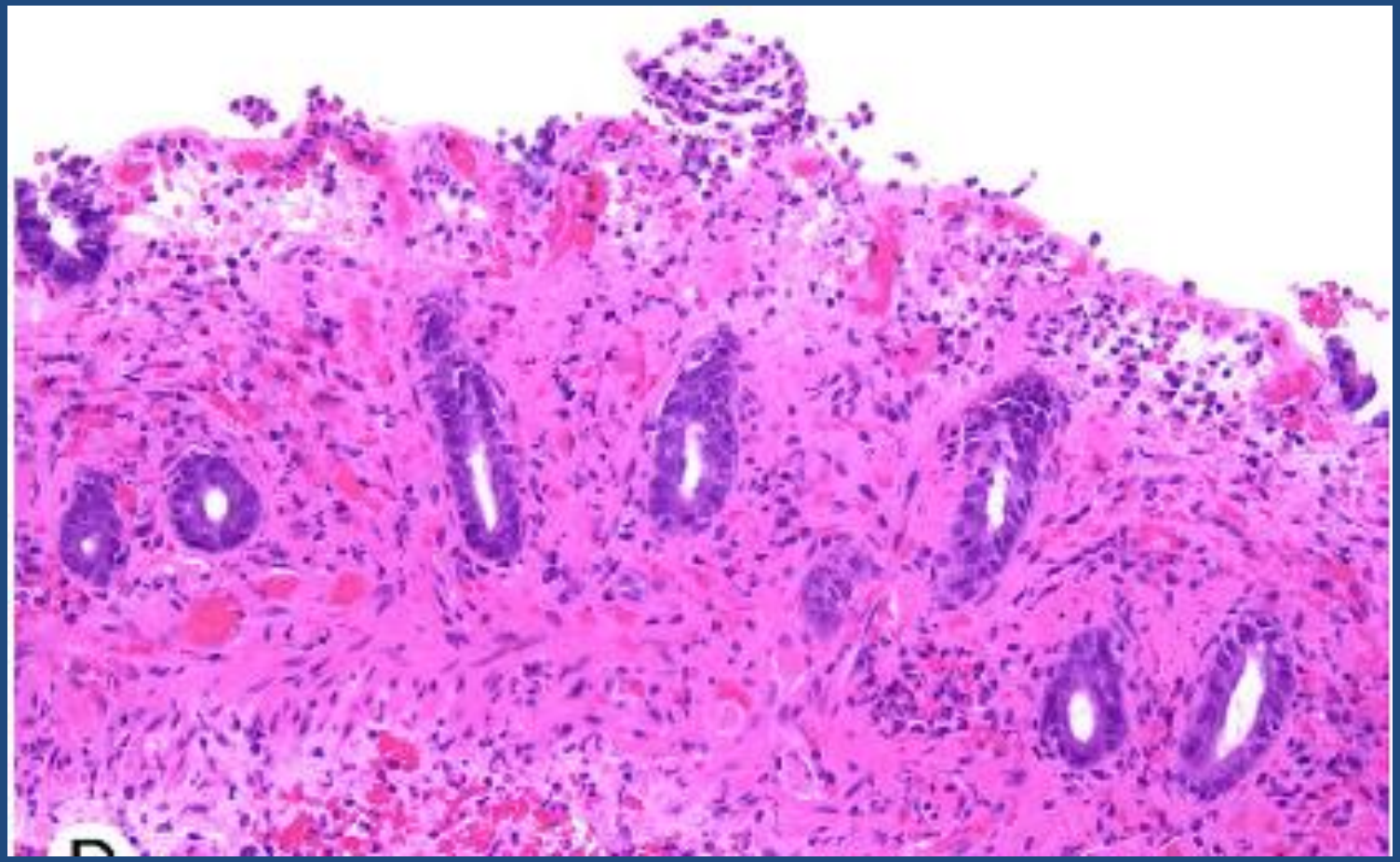
- The earliest reports of drug-related GI injury described the effects of oral potassium chloride (KCl), which may cause ulcers and strictures throughout the GI tract .

- Toxicity is mainly due to the irritation of localized high salt concentrations

DRUG INDUCED ISCHEMIC COLITIS

- Digitalis and diuretics
- Estrogens, ergotamine, and cocaine
- Kayexalate
- Glutaraldehyde

DRUG INDUCED ISCHEMIC COLITIS

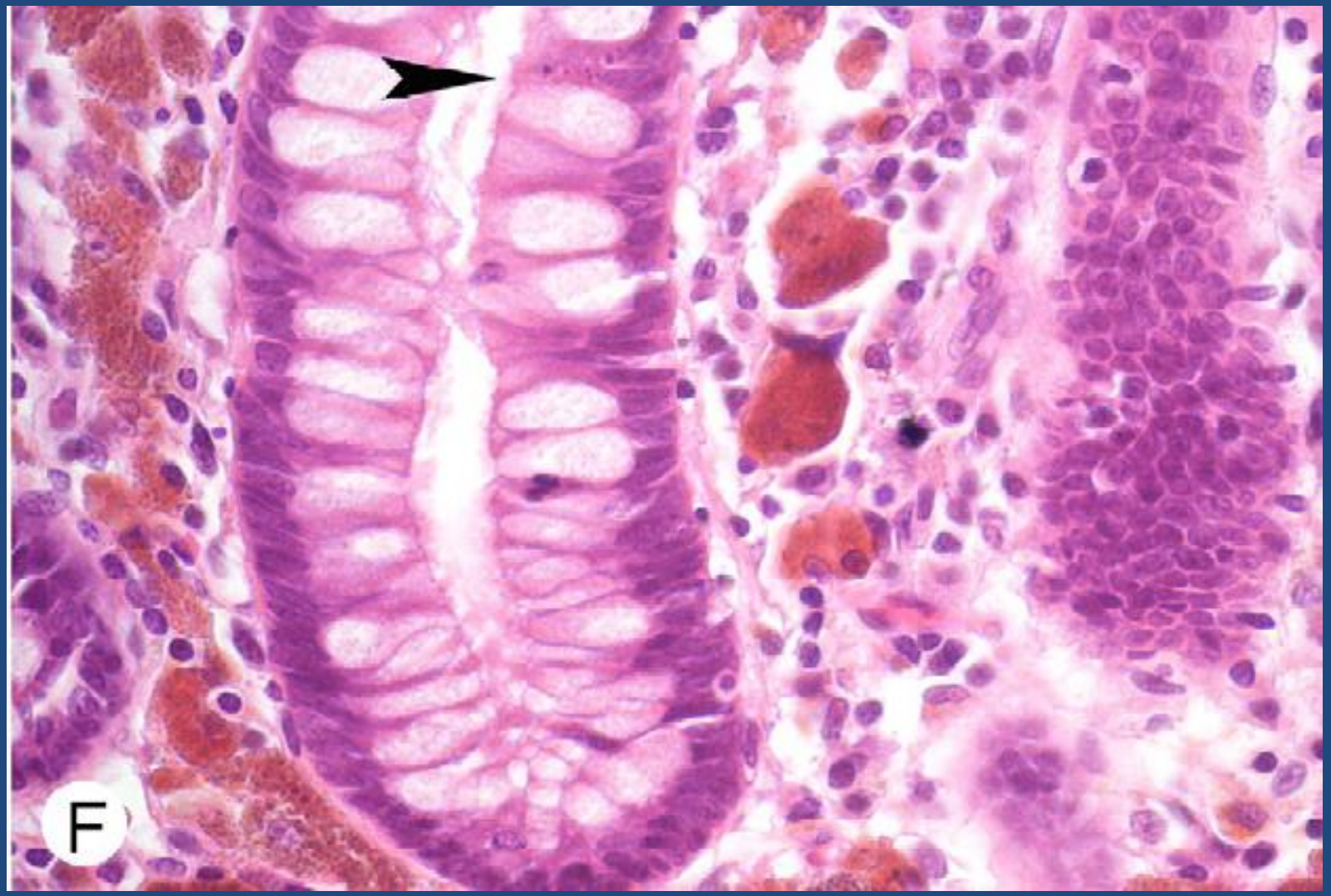


ENEMAS & LAXATIVES

- Melanosis Coli

- Apoptotic Colopathy (Bowel preparation)

Melanosis Coli



Preparation Artifacts

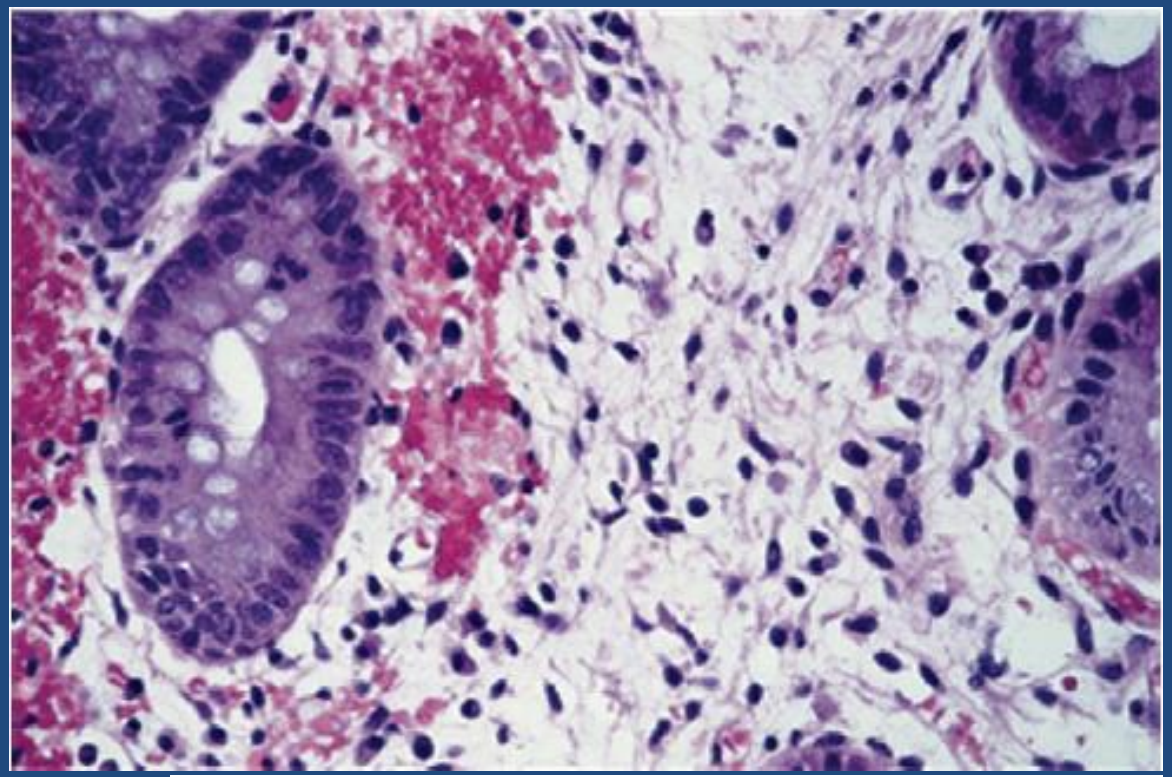
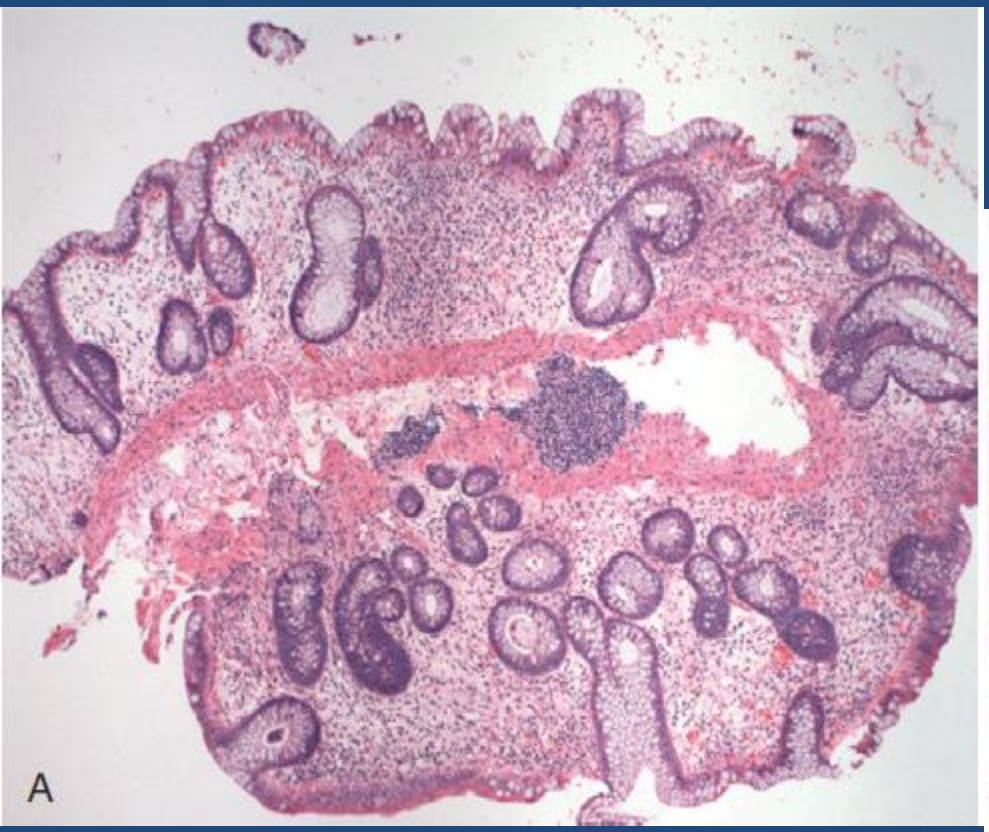


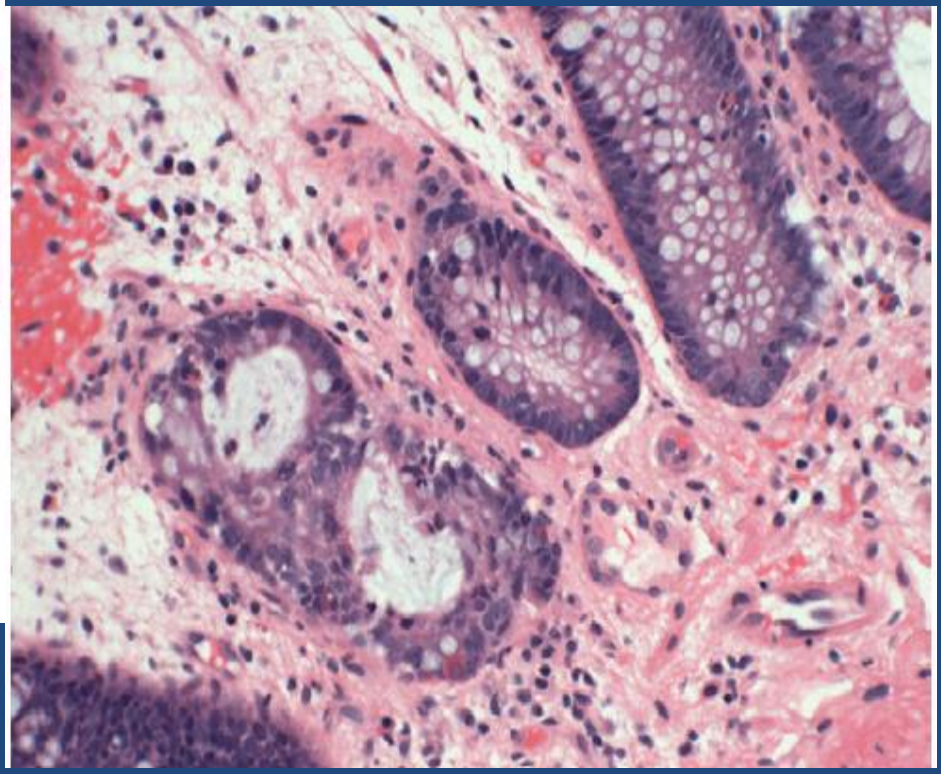
FIGURE 14-55 Enema effect causes edema of the lamina propria with extravasated red blood cells, many of which are lysed.

Mycophenolate Colitis

- Mycophenolic acid (MPA) is an immunosuppressant drug commonly used in patients undergoing solid organ transplant.
- Its pattern of inducing injury in the colon is well-known and features prominent crypt apoptosis that mimics graft-versus-host-disease.
- The injury pattern in the upper gastrointestinal (GI) tract is less extensively documented

Mycophenolate Colitis





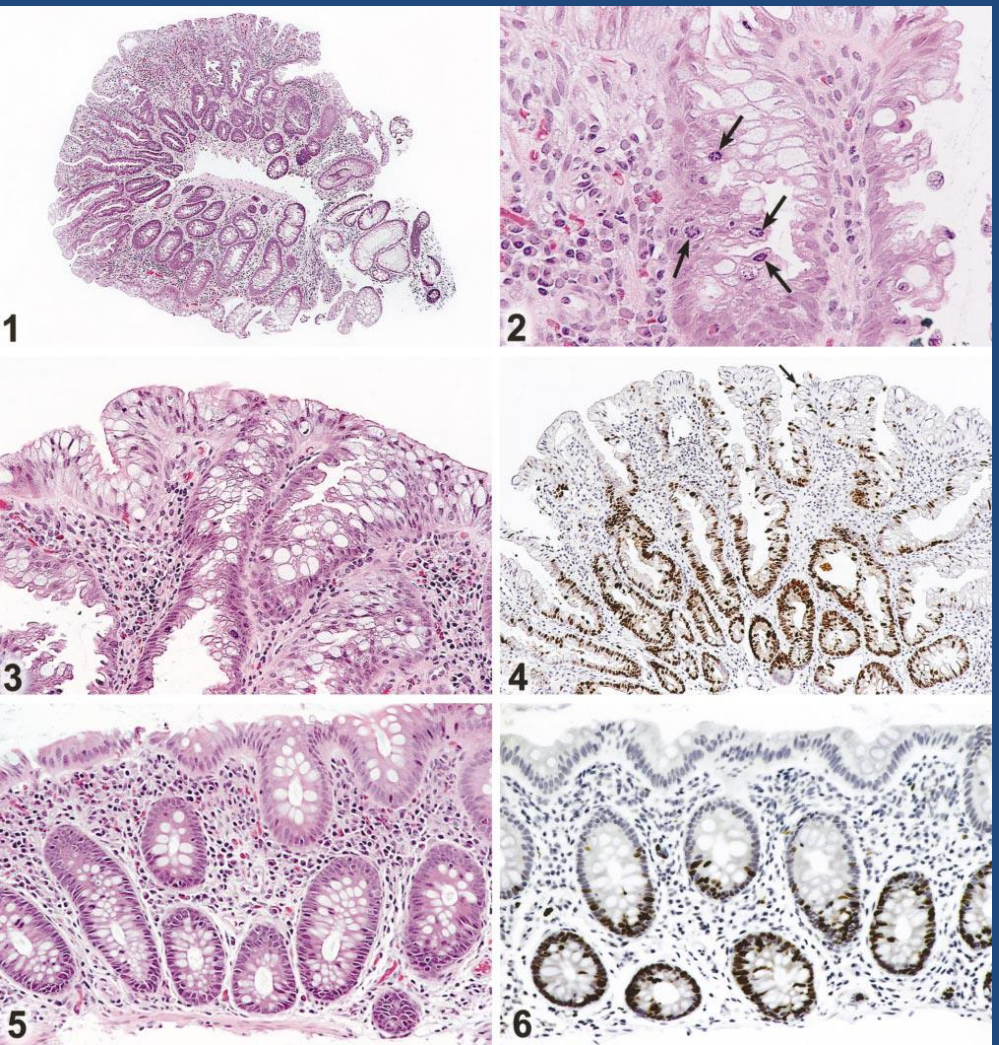
Crypt dropout, atrophy, and distortion

Minimal inflammation and reactive crypt changes

Apoptosis and GVHD like features

Colchicine Effect in a Colonic Hyperplastic Polyp
A Lesion Mimicking Serrated Adenoma

Michael Torbenson, MD; Elizabeth A. Montgomery, MD; Christine Iacobuzio-Donahue, MD, PhD; John H. Yardley, MD; Tsung-Teh Wu, MD, PhD; Susan C. Abraham, MD



Abundant metaphase mitoses.
Nuclear pseudostratification.
Loss of polarity.

Arch Pathol Lab Med—Vol 126, May 2002

Gastrointestinal Tract Epithelial Changes Associated With Taxanes: Marker of Drug Toxicity Versus Effect

American Journal of Surgical Pathology:
March 2008 - Volume 32 - Issue 3 - pp 473-477

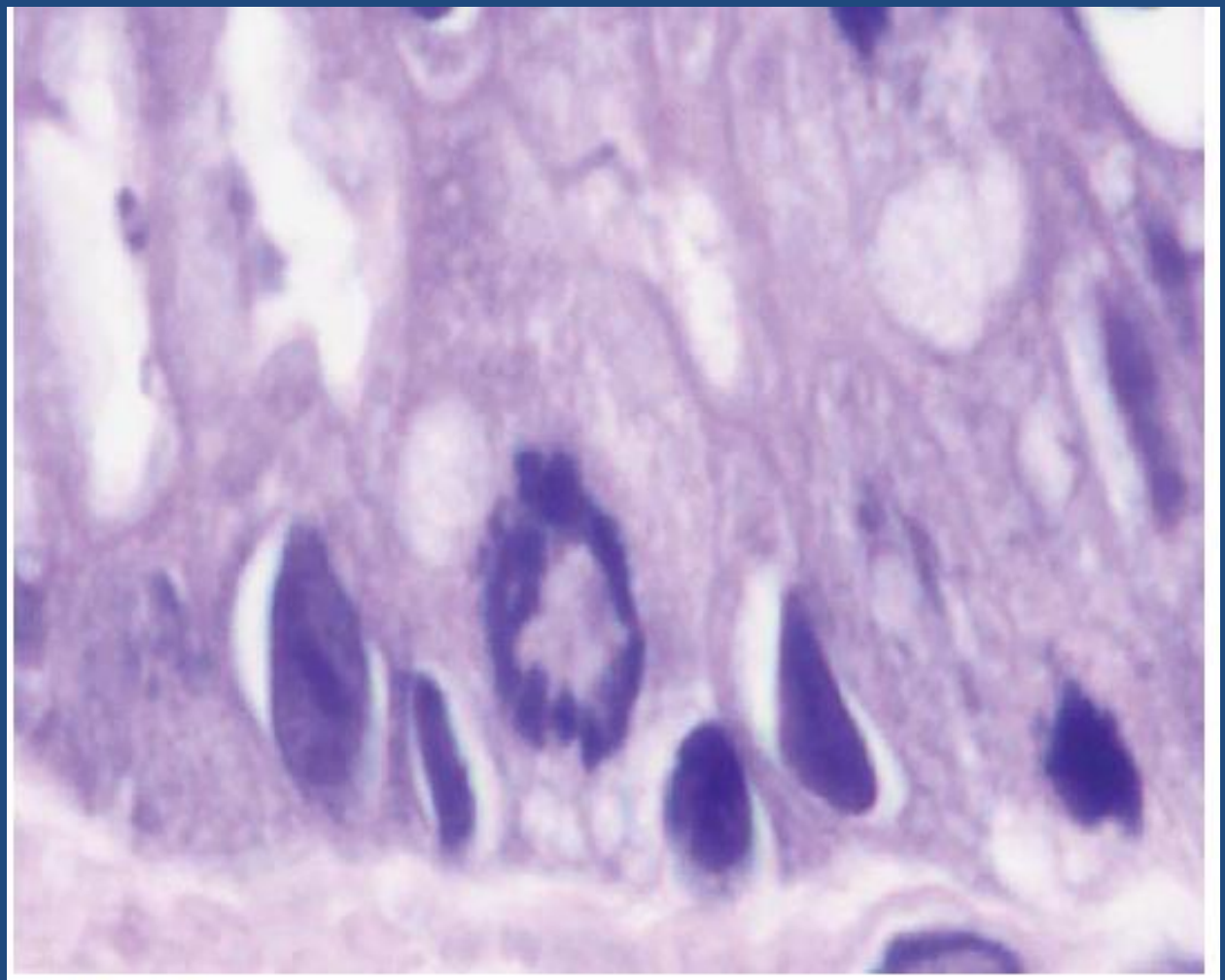


FIGURE 1. Prominent ring mitosis seen in the antrum of a patient on taxane chemotherapy.

Gastrointestinal Tract Epithelial Changes Associated With Taxanes: Marker of Drug Toxicity Versus Effect

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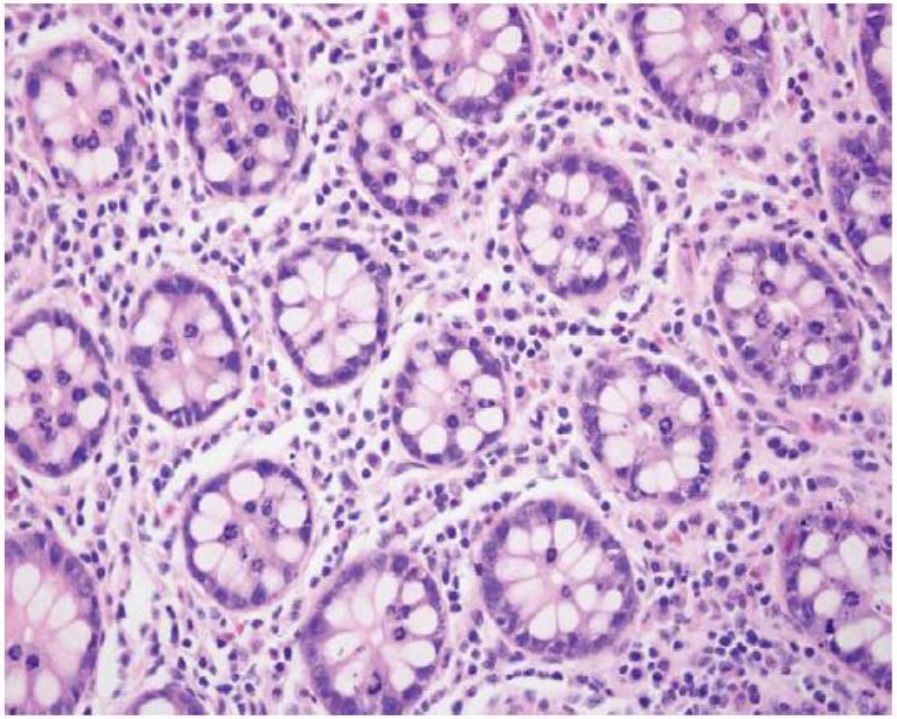

FIGURE 3. Numerous ring forms identified in the appendix.

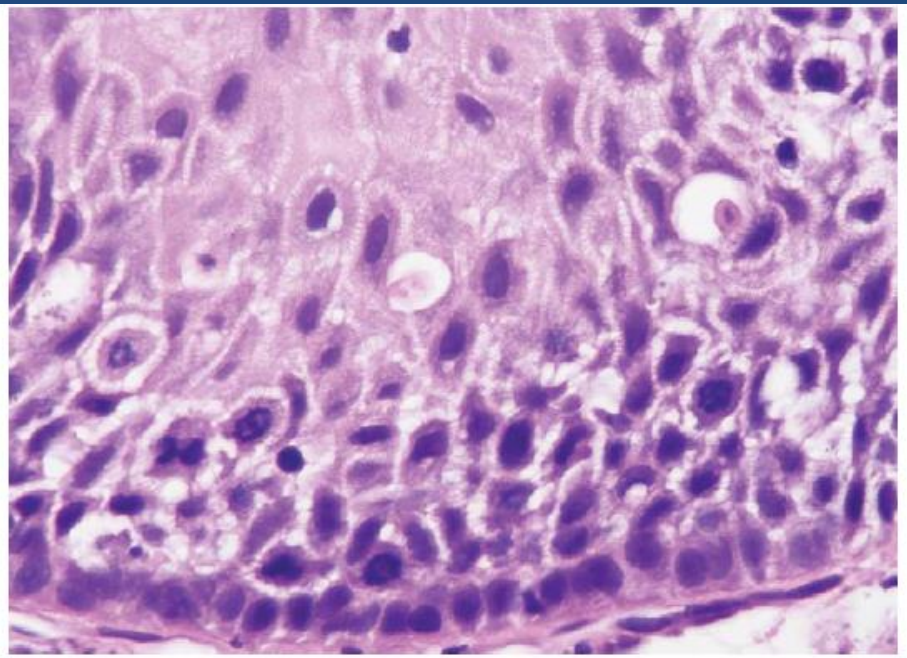

FIGURE 5. Increased apoptosis within the basal proliferative zone of the esophagus. In this high-power image, many ring mitoses can be seen.

Gastrointestinal Tract Epithelial Changes Associated With Taxanes: Marker of Drug Toxicity Versus Effect

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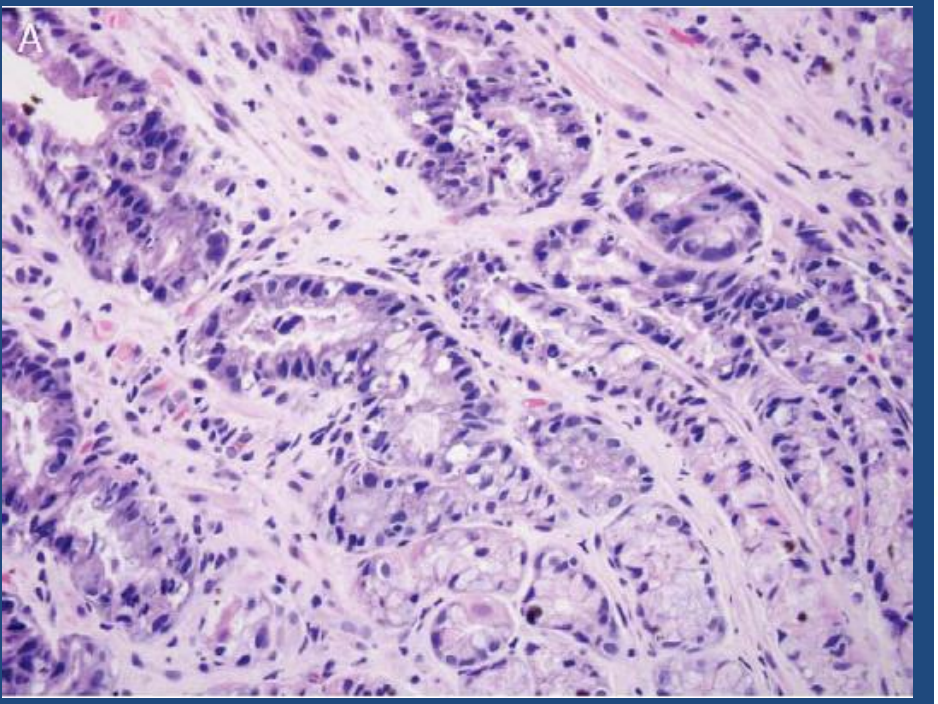


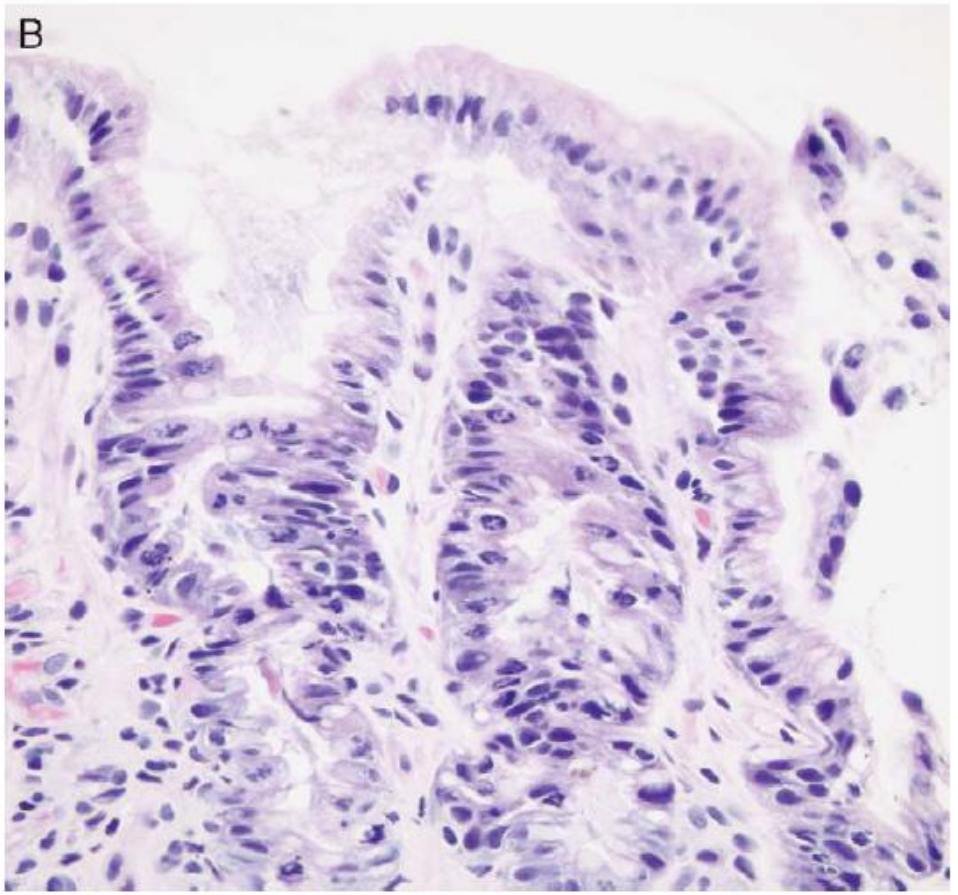


FIGURE 6. Notice the "busy" appearance of the gastric neck region with apoptosis (A), an appearance that can mimic epithelial dysplasia. However, in contrast to the pattern in dysplastic lesions, the abnormal area is restricted to the proliferative compartment. Note that the surface consists of a monolayer of mature epithelium (B).

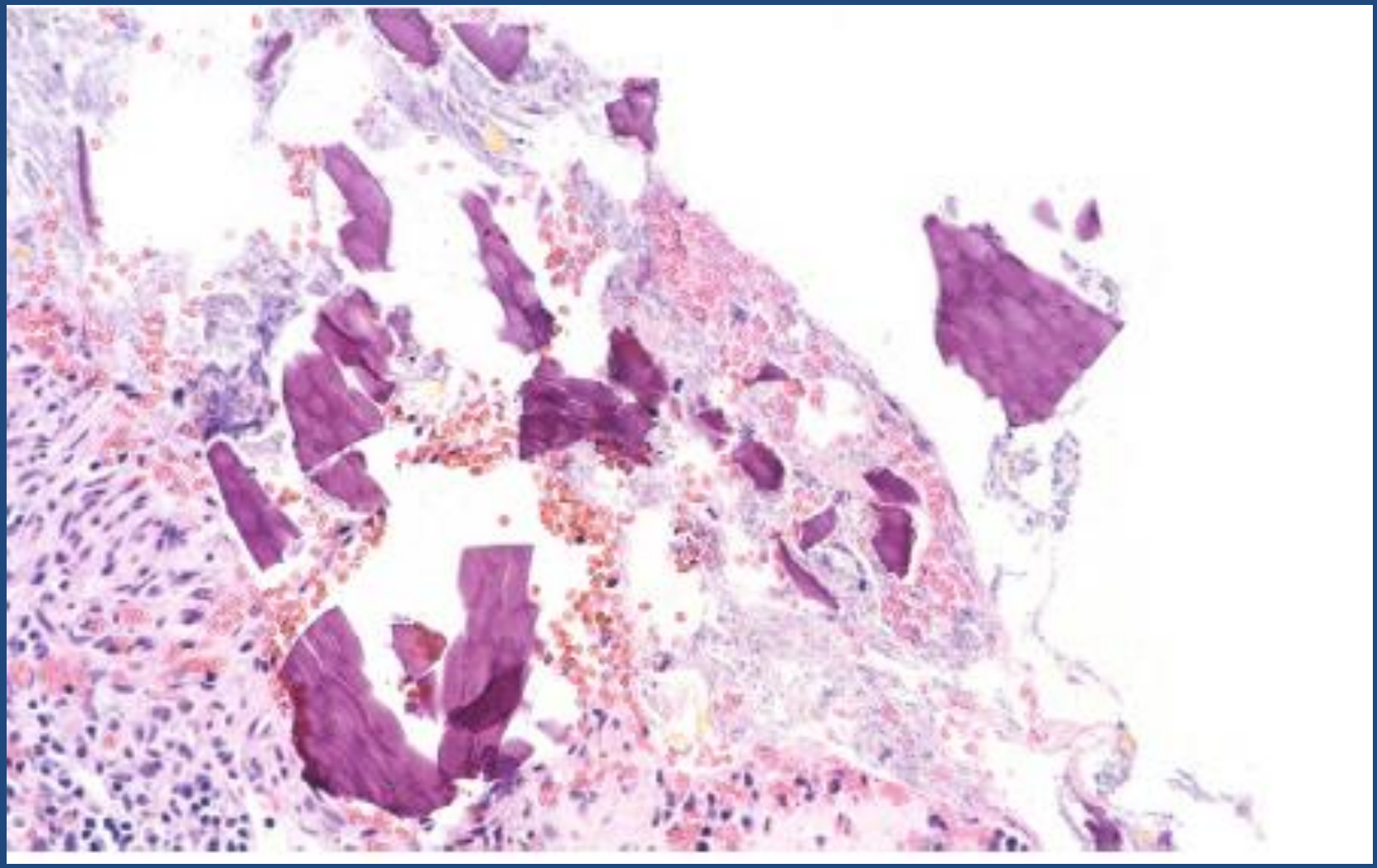
Kayexalate

- Cation-exchange resin, used to manage hyperkalaemia in renal failure

- When administered with sorbitol, Kayexalate has been associated with colonic necrosis that may necessitate surgical resection and can result in death.

- Characteristic Kayexalate crystals in the setting of colonic ulceration or perforation. The basophilic crystals have a ‘mosaic’ pattern that can be appreciated on haematoxylin and eosin stain, but is accentuated on acid-fast, PAS/Alcian blue and Diff-Quik stains

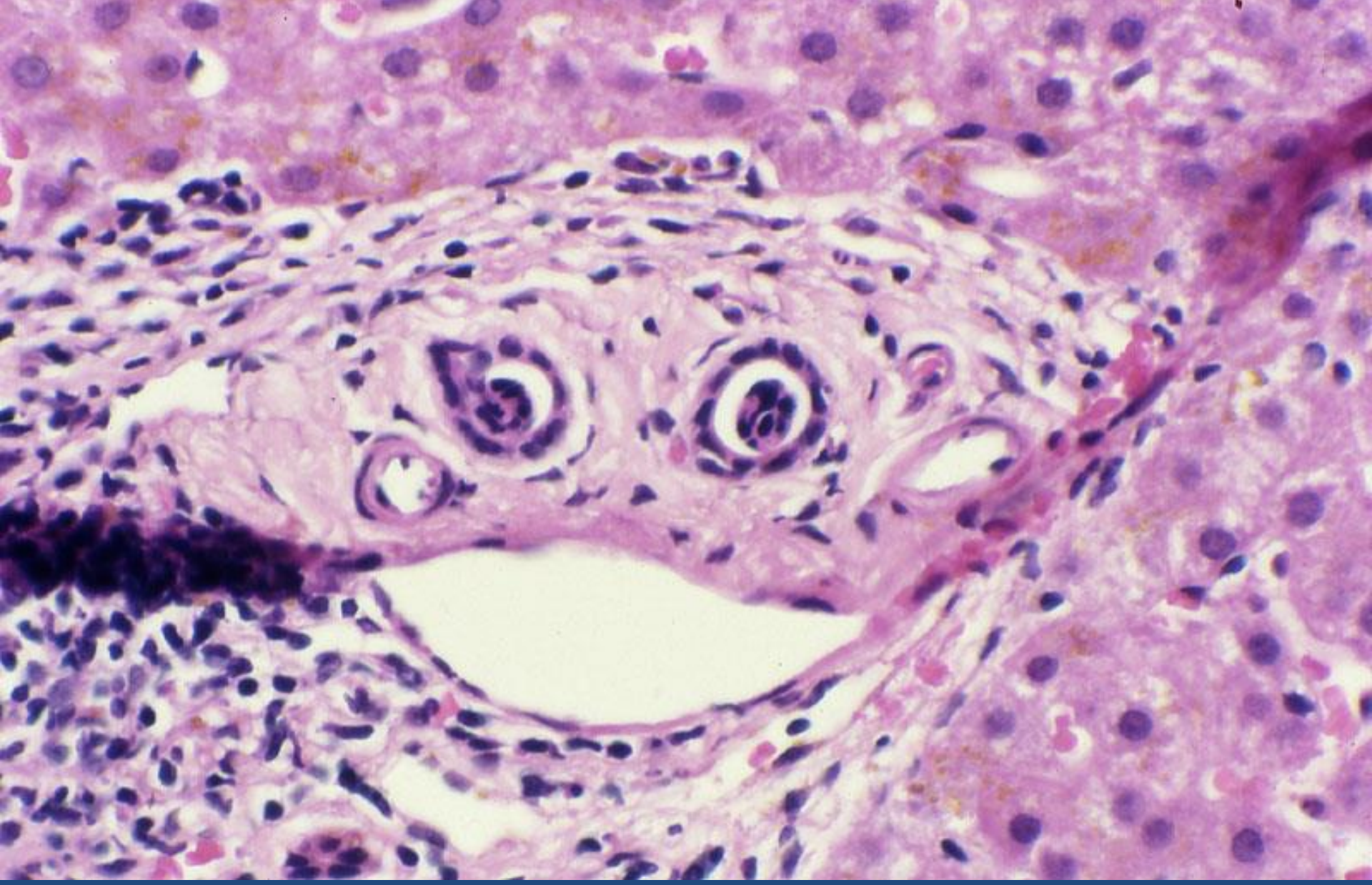
Kayexalate



Necrosis of the Gastrointestinal Tract in Uremic Patients as a Result of Sodium Polystyrene Sulfonate (Kayexalate) in Sorbitol: An Under recognized Condition
American Journal of Surgical Pathology: January 1997 - Volume 21 - Issue 1 - pp 60-69

Conclusions

- Drugs can produce a wide range of pathology in the upper and lower gastrointestinal tract.
- One must maintain a high index of suspicion for PPIs and NSAIDs as a cause for drug-induced GI pathology.
- Although there is an overwhelming number of drugs that are associated with adverse GI effects, there is a limited number of characteristic injury patterns that should prompt consideration of drug-induced GI pathology.



THANK YOU

Thank You