Pathology Lectures

Gastro-esophageal reflux disease

Peptic Ulcer Disease

Pancreatitis

Diarrhea

Malabsorption

Inflammatory bowel disease-1

Inflammatory bowel disease-2

Colonic polyps and carcinoma-1

Colonic polyps and carcinoma-2

Cirrhosis

Cirrhosis

Cholecystitis

Tumors of liver and pancreas

Objectives

- Upon completion of this lecture the students will :

1. Know the two forms of idiopathic inflammatory bowel disease (IBD).
2. Describe the pathogenesis of IBD.
3. Compare and contrast Crohn disease and ulcerative colitis with respect to:

- clinical features and extraintestinal manifestations
- pathology (gross and microscopic features) of IBD.
- complications of IBD.(especially adenocarcinoma preceded by dysplasia)

Inflammatory Bowel Diseases

- Crohn's disease and ulcerative colitis.

- Although their causes are still not clear, the two diseases probably have an immunologic hypersensitivity basis.

Nucleotide-binding oligomerization domain-containing protein 1

Pathophysiology

Genetics: mutation in
NOD2…… susceptibility gene in Crohn disease.
……. Abnormal recognition and response to intracellular pathogens

Less effective at recognizing and combating luminal microbes

THEORY

Mucosal immune responses.

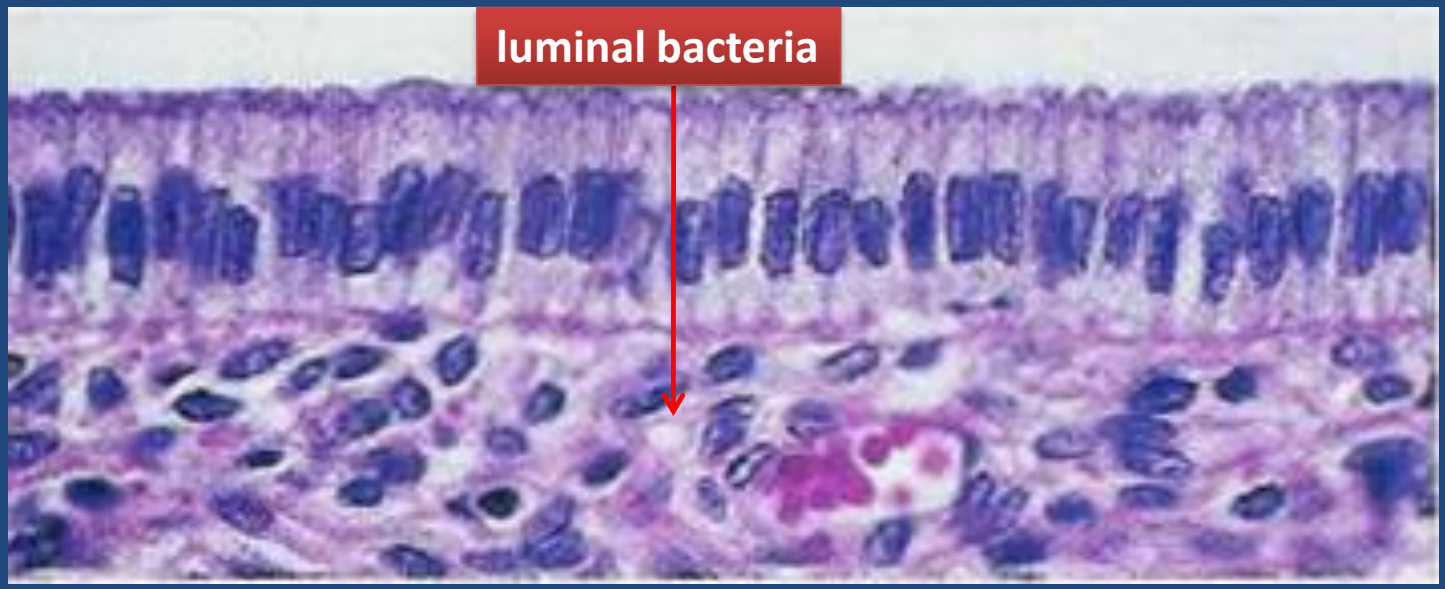
Abnormal intestinal epithelial tight junction barrier function

Transepithelial flux of luminal bacterial components activates immune responses

Immunosuppression is the mainstay of IBD therapy.

Inflammation

NOD2 **encodes a protein that binds to intracellular bacterial peptidoglycans**


luminal bacteria

Mutations in *NOD2* are seen in about 15% of Crohn's disease patients but are also seen in a smaller percentage of the general population,

so mutations in *NOD2* are neither necessary nor sufficient for the development of Crohn's disease

Pathophysiology

An *idiopathic disorder*

The pathophysiology of IBD is under active investigation.

Persons with IBD have a genetic predisposition for the disease.

Most investigators believe that the two diseases result from a combination of

1. ***Defects in host interactions with intestinal microbes***
2. ***Intestinal epithelial dysfunction***
3. ***Aberrant mucosal immune responses*.**

For unclear reasons, research suggests that smoking increases the risk of Crohn disease but reduces the likelihood of ulcerative colitis.

Clinical

The manifestations of IBD generally depend on the area of the intestinal tract involved.

Colon	Small intestine	Extraintestinal manifestations
Bloody diarrhea, Tenesmus	Abdominal pain Intestinal obstruction. Steatorrhea	Arthritis Eye manifestation Skin manifestation

Crohn's disease

- is a chronic inflammatory disorder that most commonly affects the ileum and colon but has the potential to involve any part of the gastrointestinal tract from the mouth to the anus.

Crohn's disease

Clinical Features

- Any age but has its highest incidence in young adults
- Extremely variable clinical feature.
  - Acute phase: fever, diarrhea, and right lower quadrant pain may mimic acute appendicitis.
  - Chronic disease : remissions and relapses over a long period of time.
  - Thickening of the intestine may produce an ill-defined mass in the abdomen.

Crohn's disease

- Sites of Involvement:

✓ Any part of the GIT from the mouth to the anus.

✓ ileum (30%) colon (20%).

✓ most commonly terminal ileum

✓ Commonly (75%) have perianal lesions such as abscesses, fistulas, and skin tags.

Crohn's disease

- **Gross Appearance:**
- Involvement is typically segmental, with skip areas of normal intestine between areas of involved bowel.

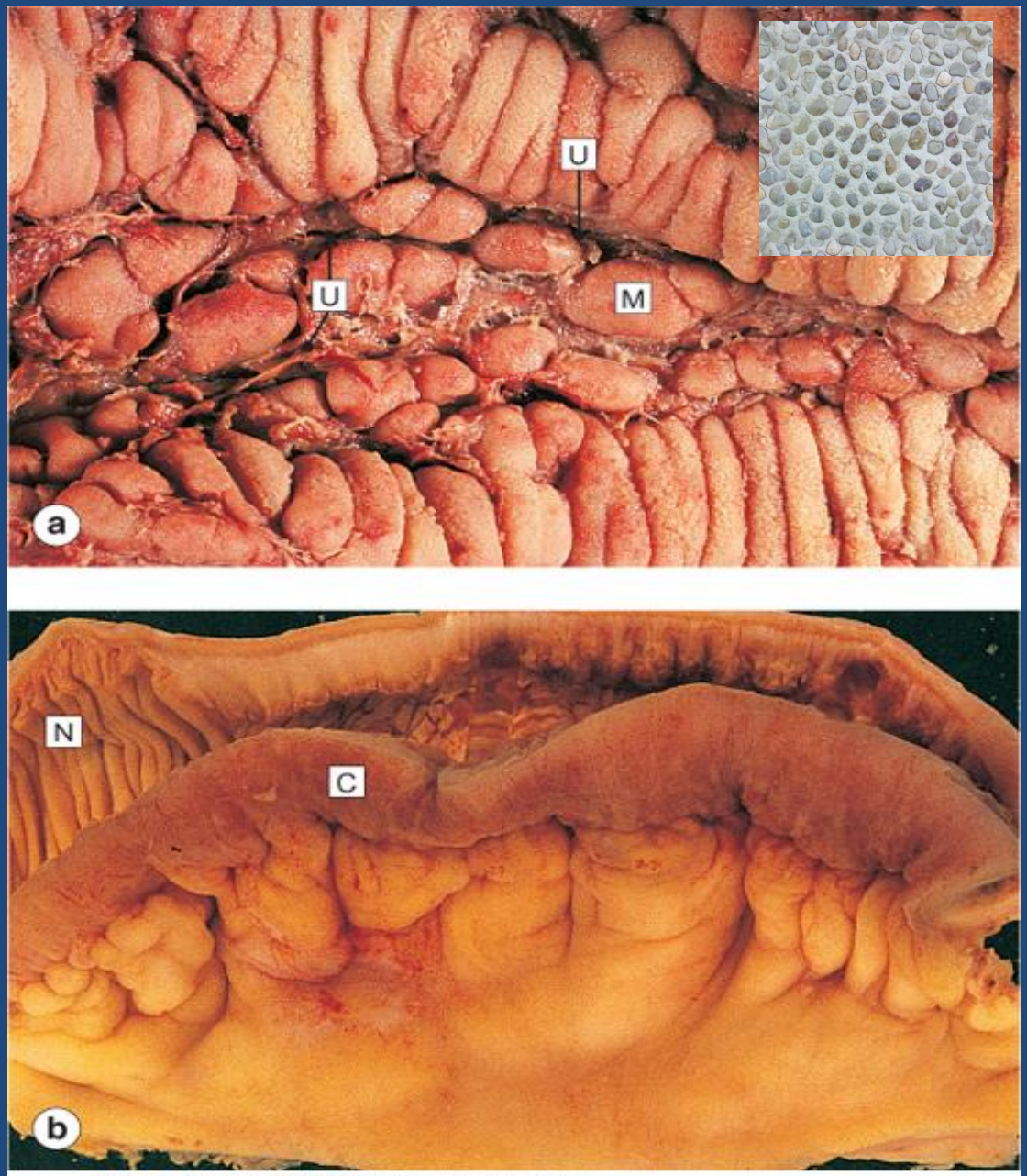
- Marked fibrosis causing luminal narrowing with intestinal obstruction.

- Fissures (deep and narrow ulcers that look like stabs with a knife that penetrate deeply into the wall of the affected intestine)

- fistulas (communications with other viscera).

Mucosa: longitudinal serpiginous ulcers separated by irregular islands of edematous mucosa. This results in the typical cobblestone effect.

FAT : In involved ileal segments, the mesenteric fat creeps from the mesentery to surround the bowel wall (creeping fat)



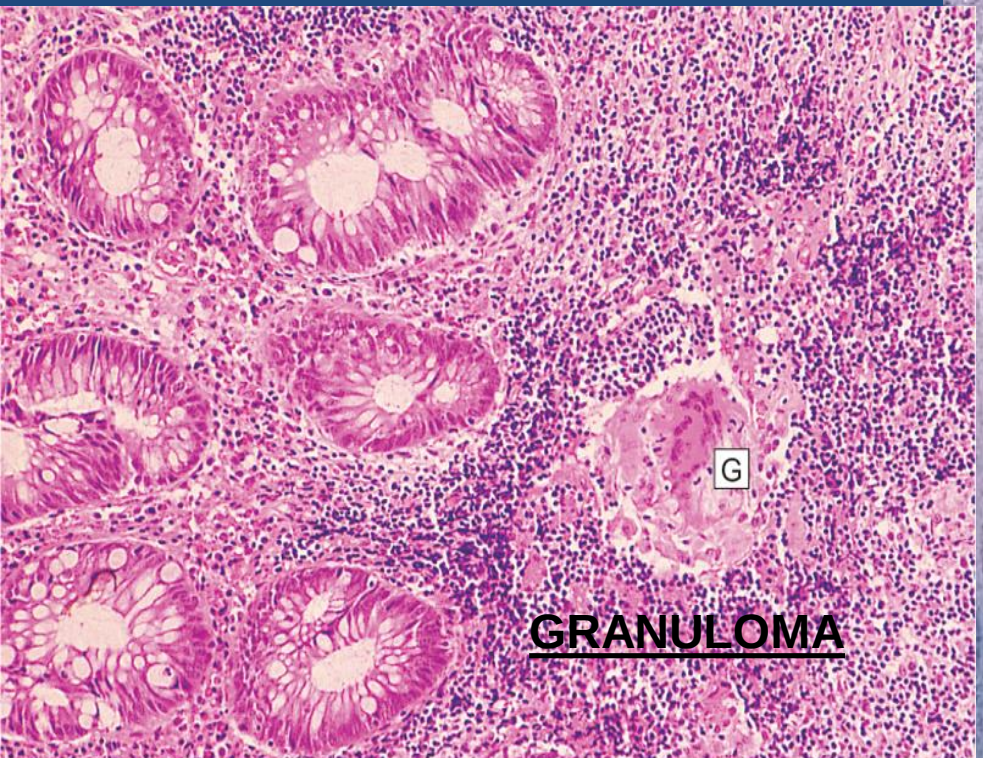
Crohn's disease

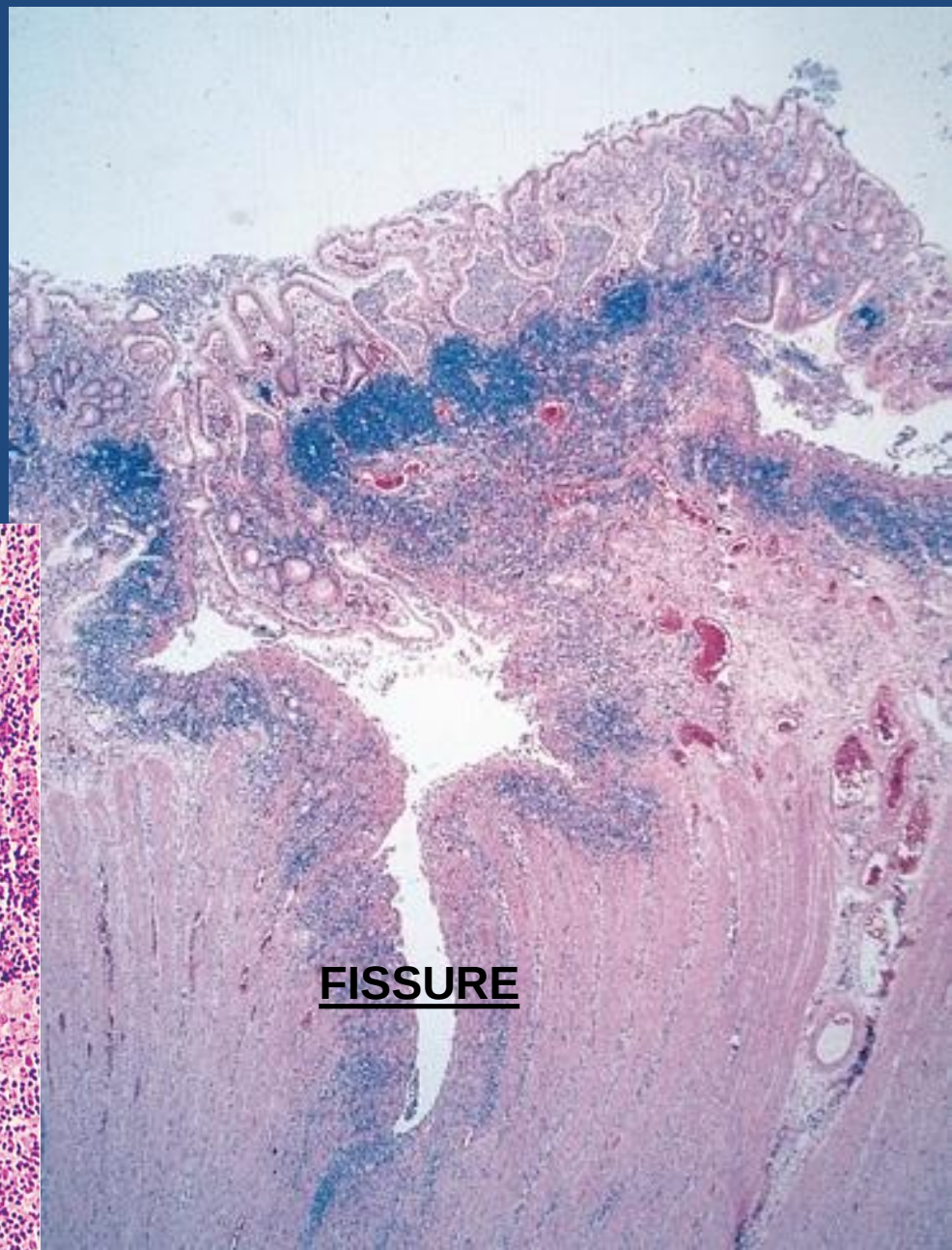
- **Microscopic Features**

1. Distortion of mucosal crypt architecture,
2. Transmural inflammation,
3. Epithelioid granulomas [60%].

- Fissure-ulcers and fistulas can be seen microscopically.

Crohn's Disease





Crohn's disease

- **Complications**

1. Intestinal obstruction
2. Fistula formation

a) between the ileum and the colon result in malabsorption
b) Enterovesical fistulas lead to urinary infections and passage of gas and feces with urine.
c) Enterovaginal fistulas produce a fecal vaginal discharge.

3. Extraintestinal manifestations (arthritis and uveitis)
4. Slight increased risk of development of carcinoma of the colon—much less than in ulcerative colitis.

Crohn's disease

- Summary
- Involvement of discontinuous segments of intestine (skip areas
- Can involve any part of GIT.
- Noncaseating epithelioid cell granulomas
- Transmural (full-thickness) inflammation of the affected parts

Ulcerative Colitis

- is an inflammatory disease of uncertain cause.
- It has a chronic course characterized by remissions and relapses.
- 20- to 30-year age group but may occur at any age

Ulcerative Colitis

- **Etiology**
- The cause is unknown
- Antibodies that cross-react with intestinal epithelial cells and certain serotypes of *Escherichia coli* have been demonstrated in the serum of some patients with ulcerative colitis.

Ulcerative Colitis

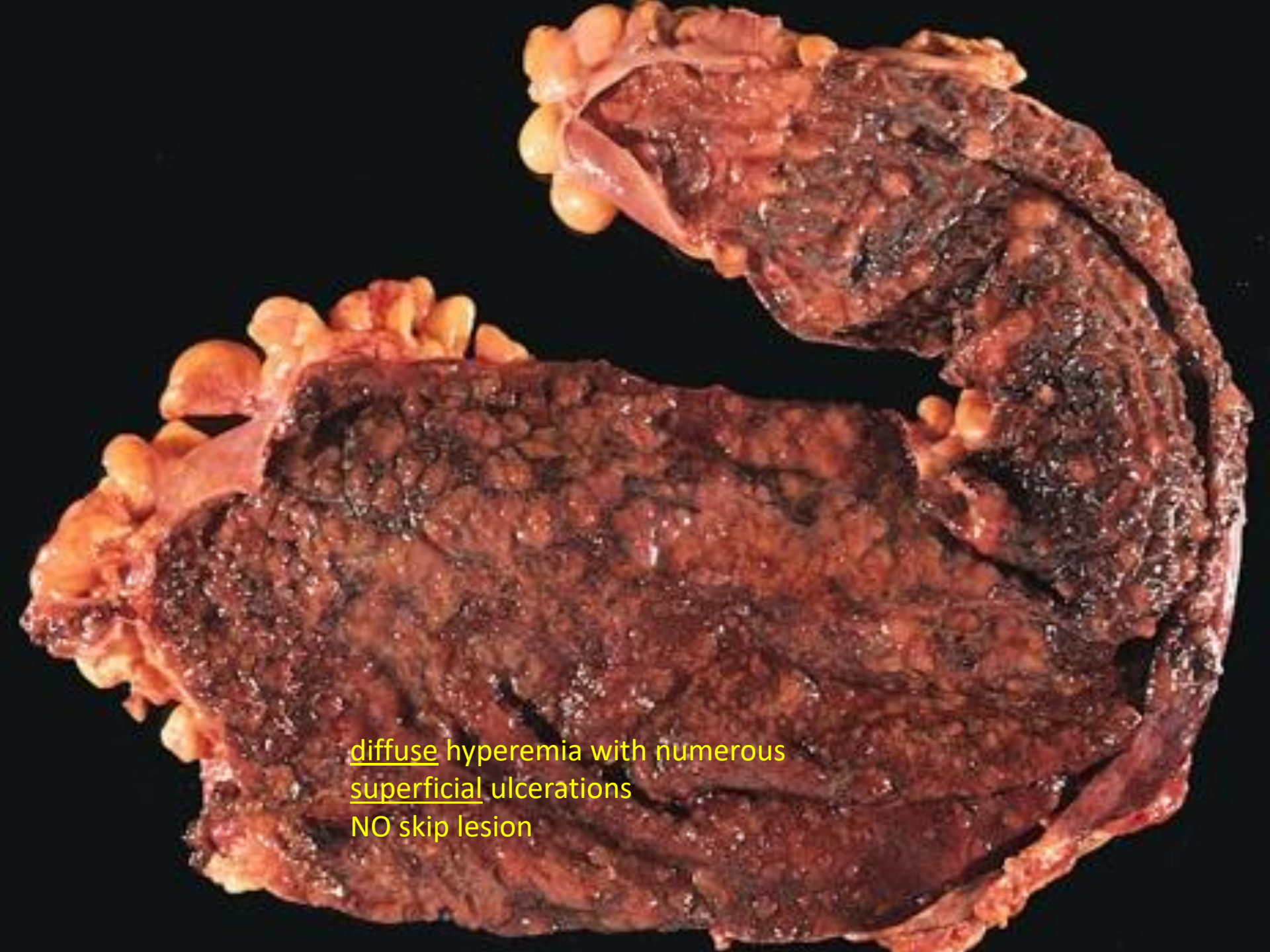
- **Clinical Features**
- In the acute phase and during relapse, the patient has fever, leukocytosis, lower abdominal pain, bloody diarrhea and mucus in the stool.
- The disease usually has a chronic course, with remissions and exacerbations.

Ulcerative Colitis

- **Sites of Involvement**
- Ulcerative colitis is a disease of the rectum, and the colon.
- Rectum is involved in almost all cases
- The disease extends proximally from the rectum in a continuous manner without skip areas.
- The ileum is not involved as a rule

Ulcerative Colitis

- **Gross Appearance**
- Involves mainly the mucosa (diffuse hyperemia with numerous superficial ulcerations in the acute phase.
- The regenerated or nonulcerated mucosa may appear polypoid (inflammatory pseudopolyps) in contrast with the atrophic areas or ulcers.


diffuse hyperemia with numerous
superficial ulcerations
NO skip lesion

Ulcerative Colitis

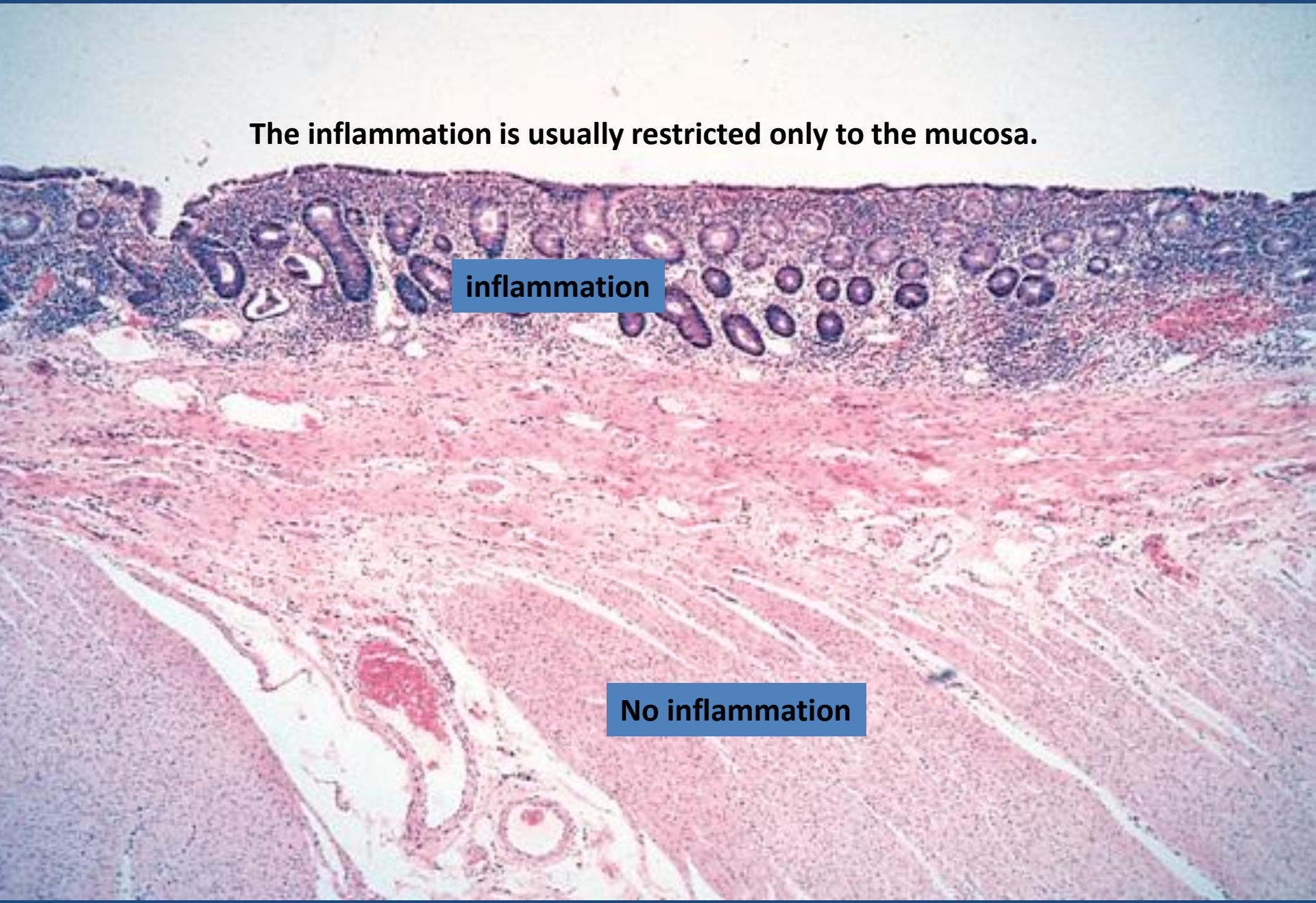
- **Microscopic Appearance**
- The inflammation is usually restricted to the mucosa.

- In the active phase….neutrophils (Cryptits, crypt abscess)

- In the chronic phase…..crypt atrophy and distortion

- Active inflammation correlates well with the severity of symptoms.

The inflammation is usually restricted only to the mucosa.



Ulcerative Colitis

- **Complications**

- Acute phase

1. Severe bleeding
2. Toxic megacolon (dilation of the colon, with functional obstruction)

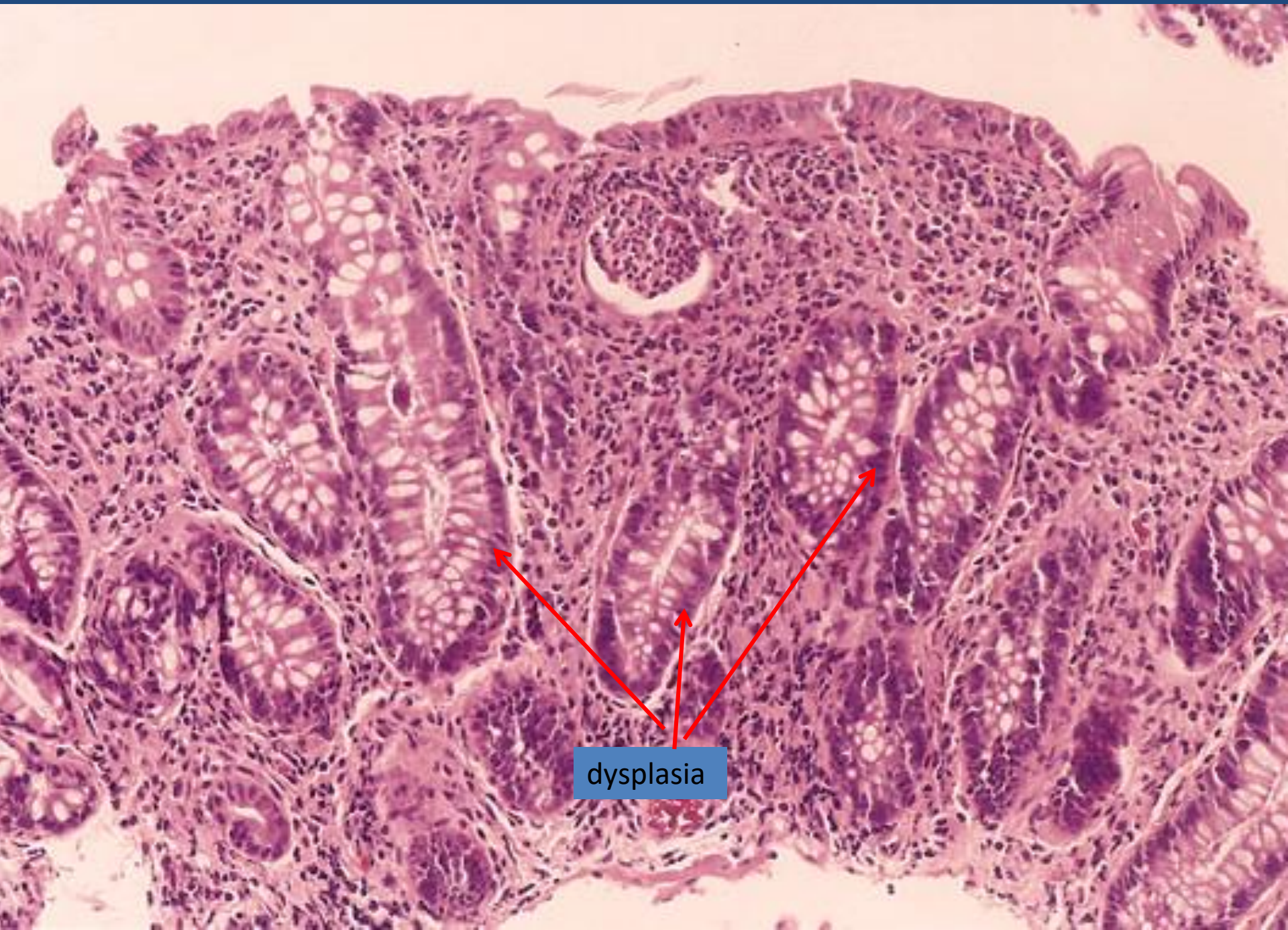
- Chronic ulcerative colitis

✓ Increase risk of developing colon carcinoma.
✓ The presence of high-grade dysplasia in a mucosal biopsy imposes a high risk of cancer and is an indication for colectomy.

- Extraintestinal manifestations

✓ occur more commonly in ulcerative colitis than in Crohn's disease.

1. Arthritis
2. Uveitis
3. skin lesions (pyoderma gangrenosum),
4. sclerosing pericholangitis (fibrosis around bile ducts), leading to obstructive jaundice.


dysplasia

Objectives

1. Know the two forms of idiopathic inflammatory bowel disease (IBD).

Crhon disease and ulcerative colitis

2. Describe the pathogenesis of IBD.

Theories

Autoimmunity

3. Compare and contrast Crohn disease and ulcerative colitis with respect to:

- clinical features and extraintestinal manifestations
- pathology (gross and microscopic features) of IBD.
- complications of IBD.(especially adenocarcinoma preceded by dysplasia)

Inflammatory bowel diseases summary

Crohn's disease	Ulcerative Colitis
• Any part of the GIT	• Colon only
• Skip areas of normal mucosa	• Diffuse involvement of mucosa
• Deep ulcers (fissure)	• Superficial ulcers
• Transmural inflammation	• Mucosal inflammation only
• Fistula formation	• Not seen
• Creeping mesenteric fat	• Not seen
• Fibrous thickening of wall	• Not seen
• Granulomas	• Not seen
• Dysplasia is rare	• Dysplasia is common
• Carcinoma is rare	• Carcinoma is more common (10%)

Inflammatory bowel diseases

1. Colon only 2. Diffuse involvement of mucosa 3. Superficial ulcers 4. Any part of the GIT 5. Skip areas of normal mucosa 6. Mucosal inflammation only 7. Fistula formation 8. Transmural inflammation 9. Granulomas 10. Deep ulcers (fissure) 11. Dysplasia is common 12. Carcinoma is more common (10%)	A. Crohn's disease B. Ulcerative Colitis

8 LECTURES

Colonic polyps and carcinoma-1

Colonic polyps and carcinoma-2

Objectives

- Upon completion of this lecture the students will

1. Know common types of intestinal polyps
2. Differentiate between the neoplastic and non-neoplastic polyps
3. Know the clinical presentation of left and right sided colon cancer, and the environmental factors that increase its risk
4. Understand the pathogenesis of colon cancer
5. Discribe the Pathological features of colon cancer

Tumors of the small and large intestines

Polyps
Carcinoma
Carcinoid tumor
Lymphoma

Polyps

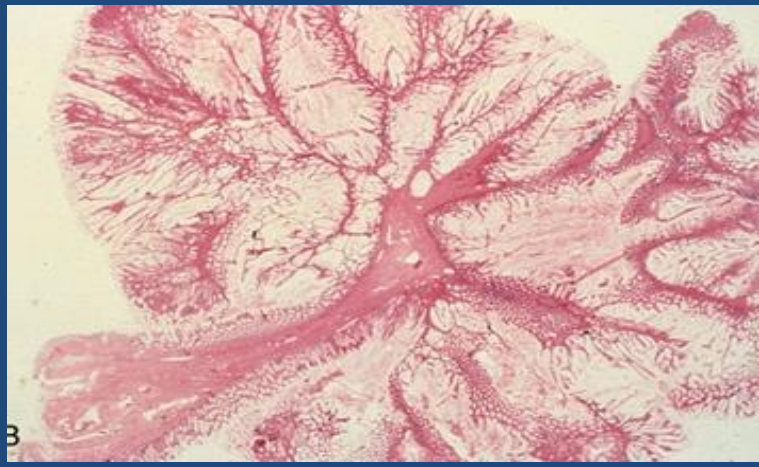
- ***Non-neoplastic polyps*** **90%**
  - Hyperplastic polyps
  - Hamartomatous polyps (Juvenile & Peutz-Jeghers polyps)
  - Inflammatory polyps
  - Lymphoid polyps

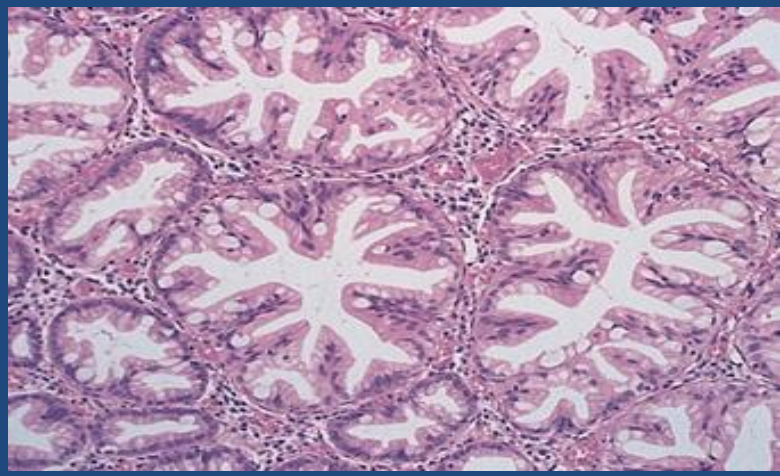
- ***Neoplastic polyps*** **10%**
  - Adenoma

Polyps

Hyperplastic Polyp

- Asymtomatic
- > 50% are located in the rectosigmoid
- Sawtooth surface
- Star shaped crypts
- Composed of well-formed glands and crypts lined by differentiated goblet or absorptive cells.





Hamartomatous polyps

- Juvenile polyps

Peutz-Jeghers polyps

Non-Neoplastic Polyp

Hamartomatous polyp

Juvenile Polyps (retention polyp)

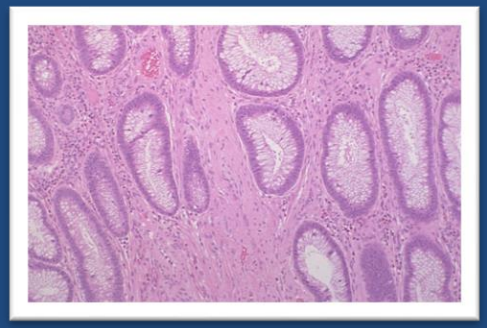
- Developmental malformations affecting the glands and lamina propria
- Commonly occur in children under 5 years old in the rectum.
- In adult called retention polyp.

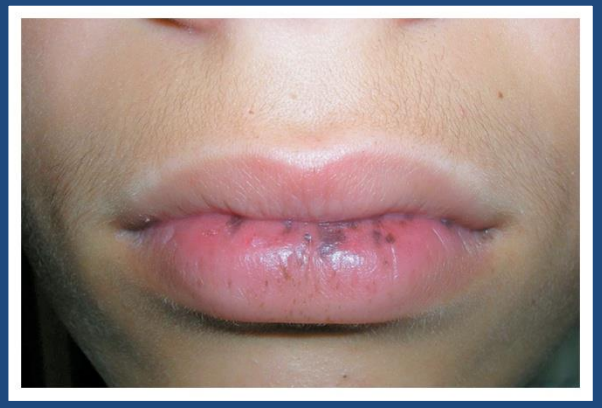
Non-Neoplatic Polyps

Hamartomatous Polyps

Peutz-Jehgers syndrome

- Rare, autosomal dominant
- hamartomatous polyps accompanied by mucosal and cutaneous pigmentation around the lips, oral mucosa, face and genitalia.
- Polyps tend to be large and pedunculated.
- Increased risk of developing carcinoma of the pancreas, breast, lung, ovary and uterus.

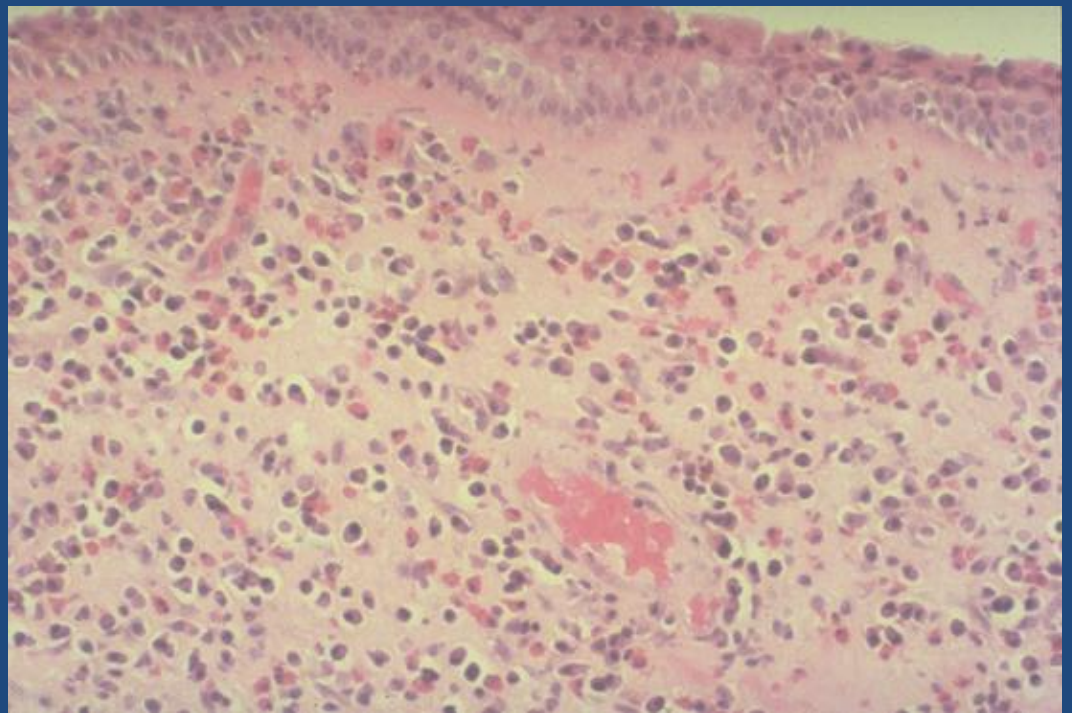




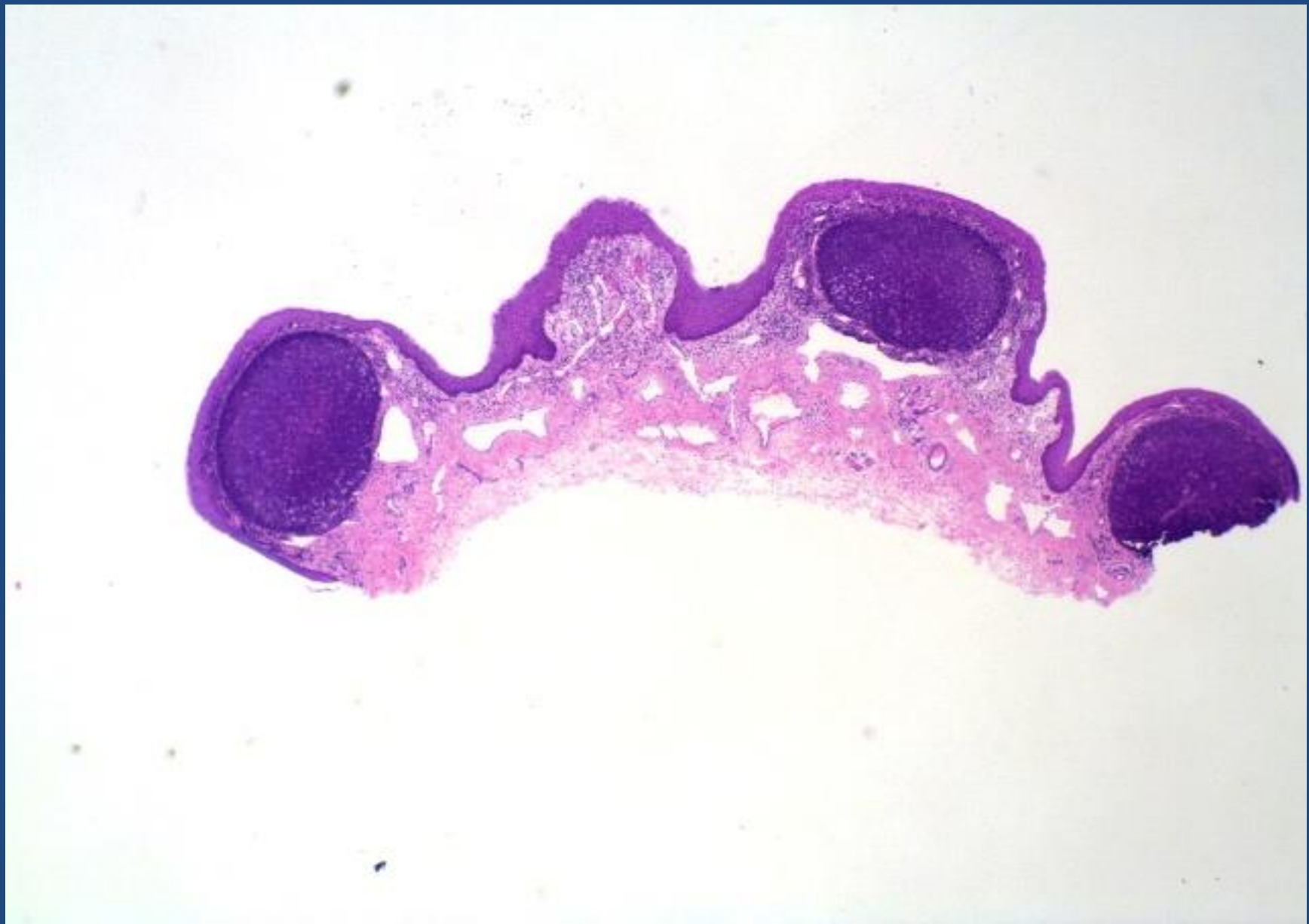
Non-Neoplastic Polyps

Inflammatory Polyps

- longstanding IBD, especially in chronic ulcerative colitis.
- Represent an exuberant reparative response to longstanding mucosal injury called pseudopolyps



4] Lymphoid polyps



Neoplastic Polyps (Adenomas)

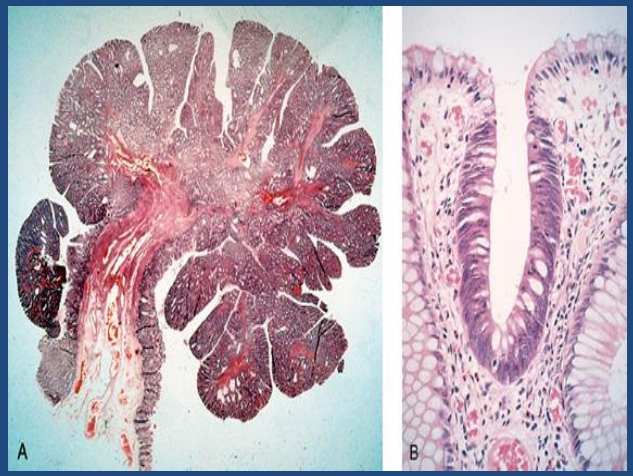
Adenomatous Polyp (adenoma)

- Occur mainly in large bowel.
- Spordic and familial
- Vary from small pedunculated to large sessile
- Epithelium proliferation and **dysplysia**
- Divided into:
  1. Tubular adenoma: less than 25% villous architecture
  2. Villous adenoma: villous architecture over 50%
  3. Tubulovillous adenoma: villous architecture between 25 and 50%.

Neoplastic Polyps

1] *Tubular adenoma*

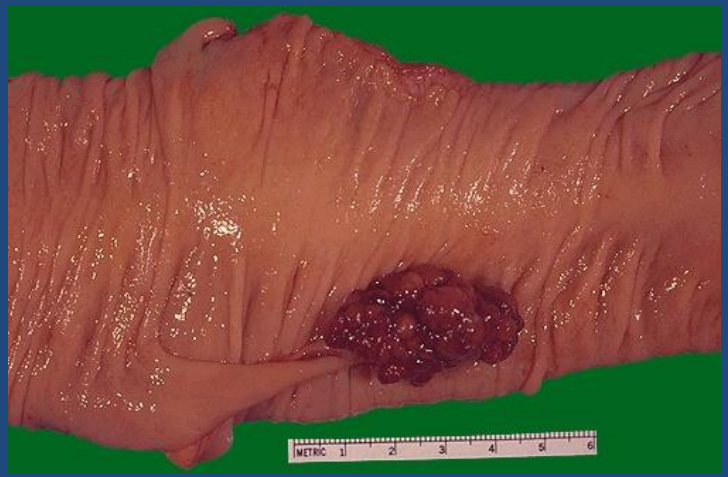
- Represents 75% of all neoplastic polyps.
- 75 % occur in the distal colon and rectum.

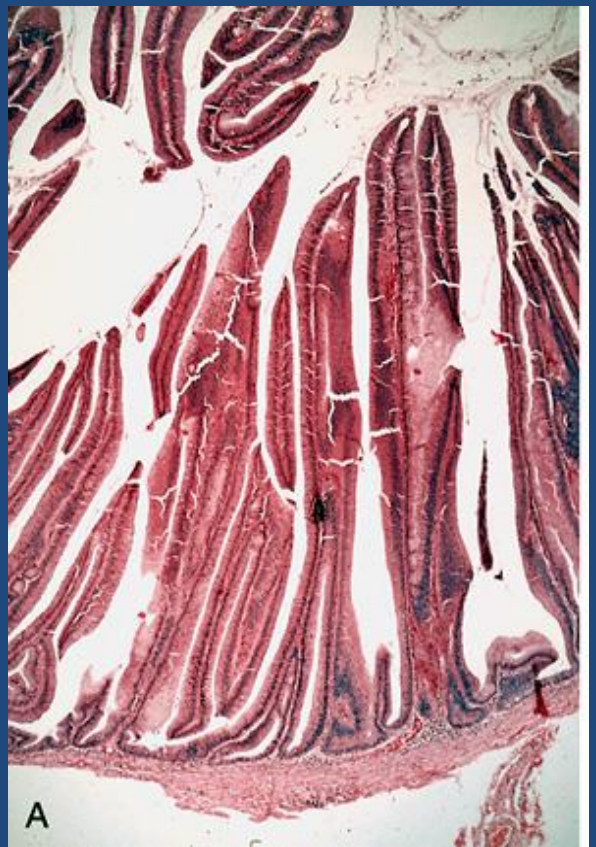


Neoplastic Polyps

Villous Adenoma

- The least common, largest and most ominous of epithelial polyps.
- Age: 60 to 65 years,
- Present with rectal bleeding or anemia, large ones may secrete copious amounts of mucoid material rich in protein.
- 75% located in rectosigmoid area.





3] ***Tubulovillous adenoma***

- Intermmediate in size, degree of dysplasia and malignant potential between tubular and villous adenomas.

Relationship of Neoplastic Polyps to Carcinoma

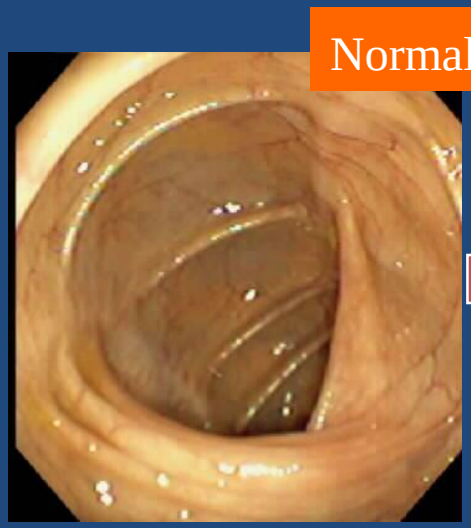
- Adenoma to carcinoma sequence is documented by several genetic alterations.
- The probability of carcinoma occuring in a neoplastic polyp is related to:

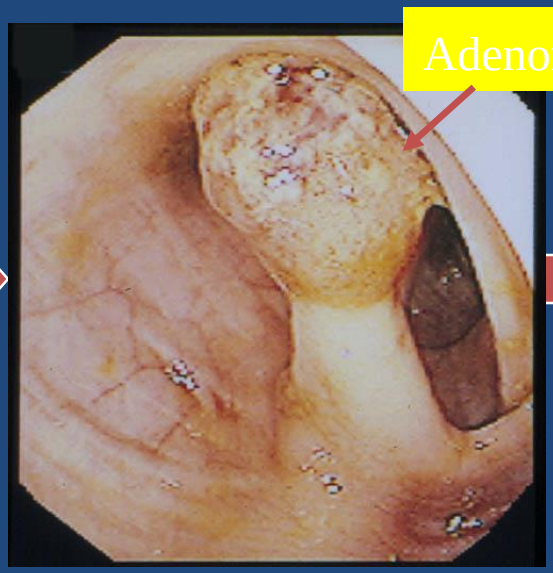
  1. The size of the polyp.

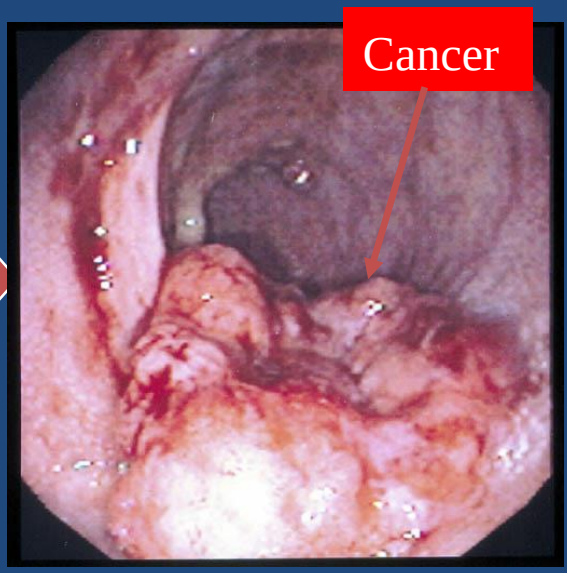
  2. The relative proportion of its villous features.

  3. The presence of significant cytologic atypia (dysplasia) in the neoplastic cells.

Adenoma to Carcinoma Pathway







APC loss

K-ras mutation

Chrom 18 loss

p53 loss

Normal Epithelium → Hyper-proliferation → Early Adenoma → Intermediate Adenoma → Late Adenoma → Cancer

Familial Polyposis Syndrome

- Patients have genetic tendencies to develop neoplastic polyps.

Familial polyposis coli (FPC)

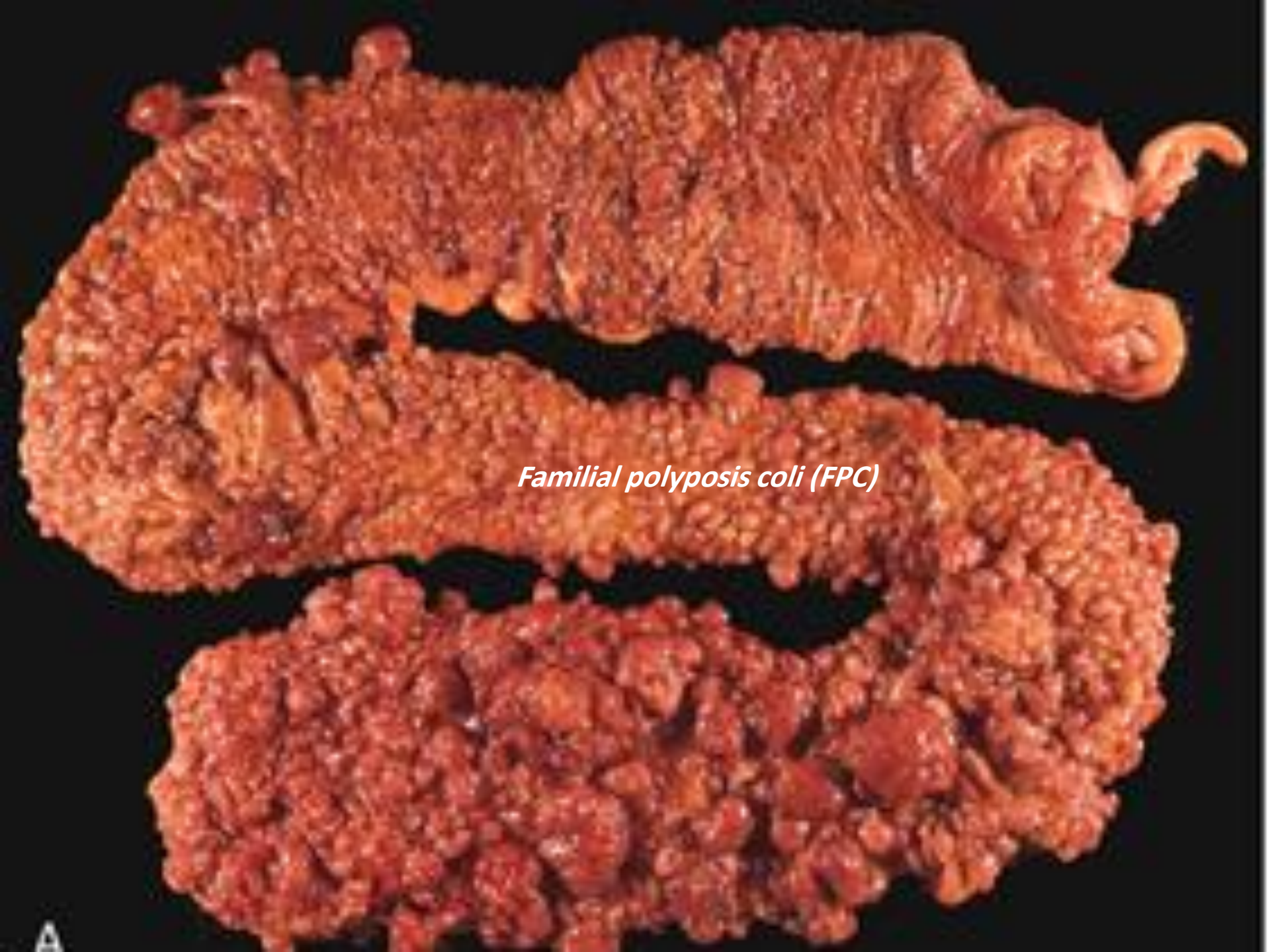
- Genetic defect of Adenomatous polyposis coli (*APC*).
- *APC* gene located on the long arm of chromosome 5 (5q21).
- *APC* gene is a tumor suppressor gene
- Innumerable neoplastic polyps in the colon (500 to 2500)
- Polyps are also found elsewhere in alimentary tract
- The risk of colorectal cancer is 100% by midlife.

Gardener's syndrome

- Polyposis coli, multiple osteomas, epidermal cysts, and fibromatosis

Turcot syndrome

- Polyposis coli, glioma and fibromatosis


Familial polyposis coli (FPC)
A

Malignant Tumors of Large Intestine

Adenocarcinoma

- **Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide.**
- Constitutes 98% of all cancers in the large intestine.

- Predisposing factors:

1. IBD, adenomas , polyposis syndrome.
2. Diet appears to play an important role in the risk for colon cancer:

- Low fibre diet.
- High fat content.
- Alcohol
- Reduced intake of vit A, C & E.

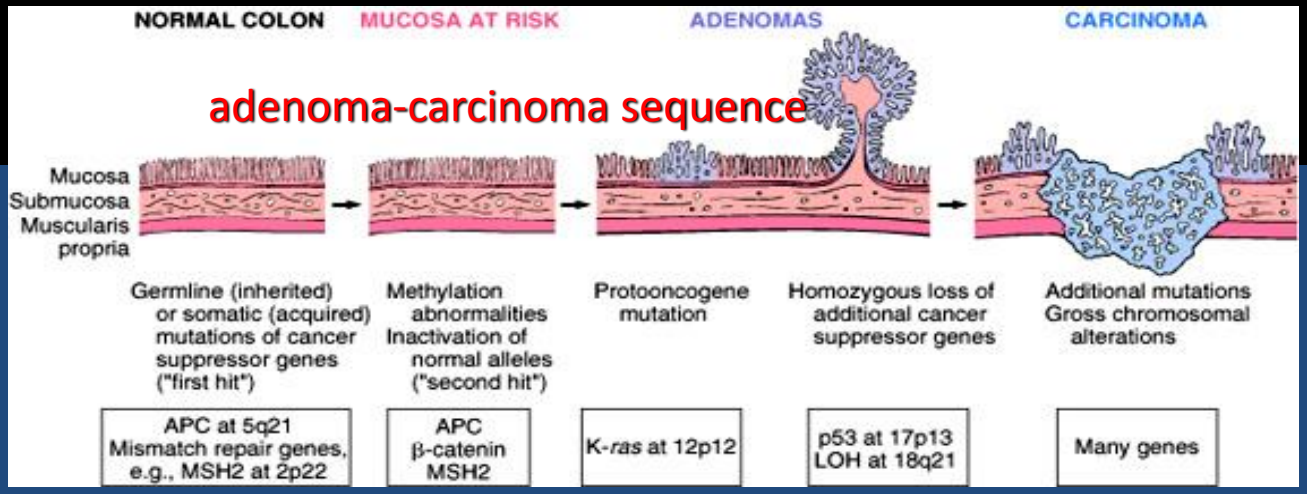
Adenocarcinoma of Large Intestine

Carcinogenesis

- Two pathogenetically distinct pathways for the development of colon cancer, both seem to result from accumulation of multiple mutations:

  1- The APC/B-*catenin pathway (85 %)*

  - chromosomal instability that results in stepwise accumulation of mutations in a series of oncogenes and tumor suppressor genes.



Malignant Tumors of Large Intestine
Adenocarcinoma

Carcinogenesis

2- The *DNA mismatch repair genes pathway:*

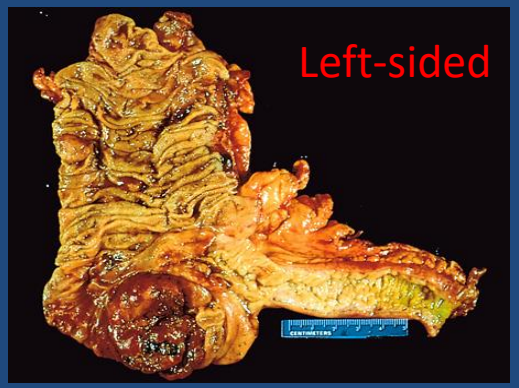
- 10% to 15% of sporadic cases.
- There is accumulation of mutations (as in the *APC/B-catenin schema)*
- Five DNA mismatch repair genes (MSH2, MSH6, MLH1, PMS1, AND PMS2)
- give rise to the ***hereditary non polyposis colon carcinoma (HNPCC)***

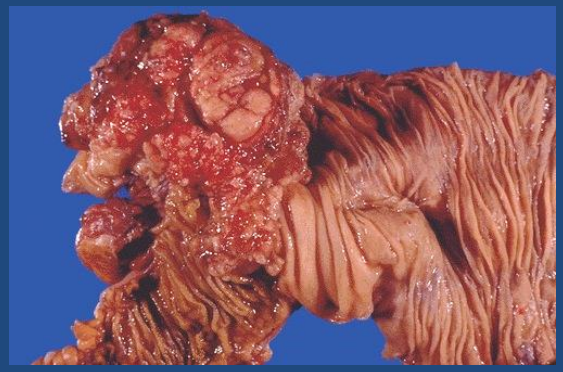
- Hereditary mutation of the *APC* gene is the cause of familial adenomatous polyposis (FAP), where affected individuals carry an almost 100% risk of developing colon cancer by age 40 years.

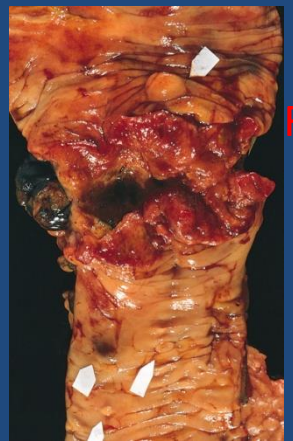
Colorectal Carcinoma

Morphology

- 70% are in the rectum, rectosigmoid and sigmoid colon.
- Left-sided carcinomas tend to be annular, encircling lesions with early symptoms of obstruction.
- Right-sided carcinomas tend to grow as polypoid, fungating masses, obstruction is uncommon.
- Mucinous adenocarcinoma secret abundant mucin that may dissect through cleavage planes in the wall.







Right-sided

Signs and symptoms

- If located closer to the anus: change in bowel habit, feeling of incomplete defecation, PR bleeding
- A tumor that is large enough to fill the entire lumen of the bowel may cause bowel obstruction

Tumor markers

A **tumor marker** is a substance found in the blood , urine or body tissues that can be elevated in cancer, among other tissue types.

Carcinoembryonic antigen (CEA)

Carbohydrate antigen (CA19-9)

Useful to assess disease recurrence (late stage)

CEA levels may also be raised in some non-neoplastic conditions like ulcerative colitis pancreatitis, cirrhosis COPD, Crohn's disease as well as in smokers

CA19-9 are raised in in patients with colon cancer and pancreatic cancer, esophageal cancer and hepatocellular carcinoma. Apart from cancer, elevated levels may also occur in pancreatitis, cirrhosis.

Tissue inhibitor of metalloproteinases 1 (TIMP1)

Early as well as late stage disease

Duke classification is used for staging

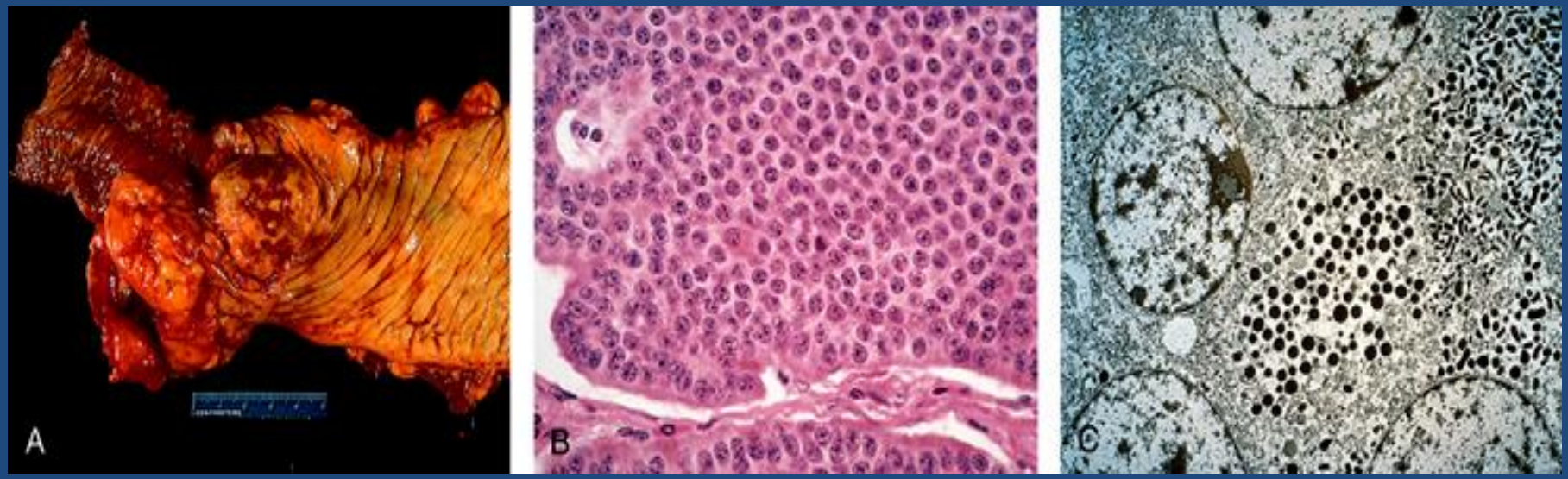
Malignant Small Intestinal Neoplasms

- In descending order of frequency:
- carcinoid, adenocarcinomas, lymphomas and leiomyosarcomas.

Small Intestinal Neoplasms

Carcinoid Tumors

- Neoplasms arising from endocrine cells found along the length of GIT mucosa.
- 60 to 80% appendix and terminal ileum: 10 to 20% rectum.
- Ultrastructral features: neurosecretory electron dense bodies in the cytoplasm



Small Intestinal Neoplasms

Carcinoid Tumor

Clinical features

- Asymptomatic
- May cause obstruction, intussusception or bleeding.
- May elaborate hormones: Zollinger-Ellison, Cushing's carcinoid or other syndromes.

Small Intestinal Neoplasms

Carcinoid tumor

Carcinoid syndrome

- 1% of carcinoid tumor & in 20% of those of widespread metastasis
- Paroxymal flushing, episodes of asthma-like wheezing, right-sided heart failure, attacks of watery diarrhea, abdominal pain,
- The principal chemical mediator is serotonin
- The syndrome is classically associated with ileal carcinoids with hepatic metastases.

Small Intestinal Neoplasms

Lymphoma

- Most often low-grade lymphomas arising in mucosal-associated lymphoid tissue (MALT) lymphoma or high-grade non-Hodgkin's lymphomas of B cell type.
- May occur in any part of the intestine;
- the ileocecal region is a favored site for Burkitt's lymphoma.

Objectives

1. Know common types of intestinal polyps

A- Non-neoplastic polyps no dysplasia

4 common types (hyperplastic, hamartomatous, inflammatory, lymphoid)

B- Neoplastic polyps there is dysplasia

3 types (tubular, tubulovilous, villous)

2. Know the clinical presentation of left and right sided colon cancer, and the environmental factors that increase its risk

- Left colon…frank bleeding, obstruction
- Right colon…iron diffecieny anaemia
- Tumor markers ……..CEA

3. Understand the pathogenesis of colon cancer

- Adenoma to Carcinoma Pathway
- Two genetic pathways APC/B-*catenin and DNA mismatch repair genes*
- Familial Polyposis Syndrome

4. Discribe the Pathological features of colon cancer

- Adenocarcinoma most common ……carcinoid tumor { neurosecretory granules}
- 70% are in the rectum and/or sigmoid
- Duke classification is used for staging