

Small and Large Intestinal pathology, part 3

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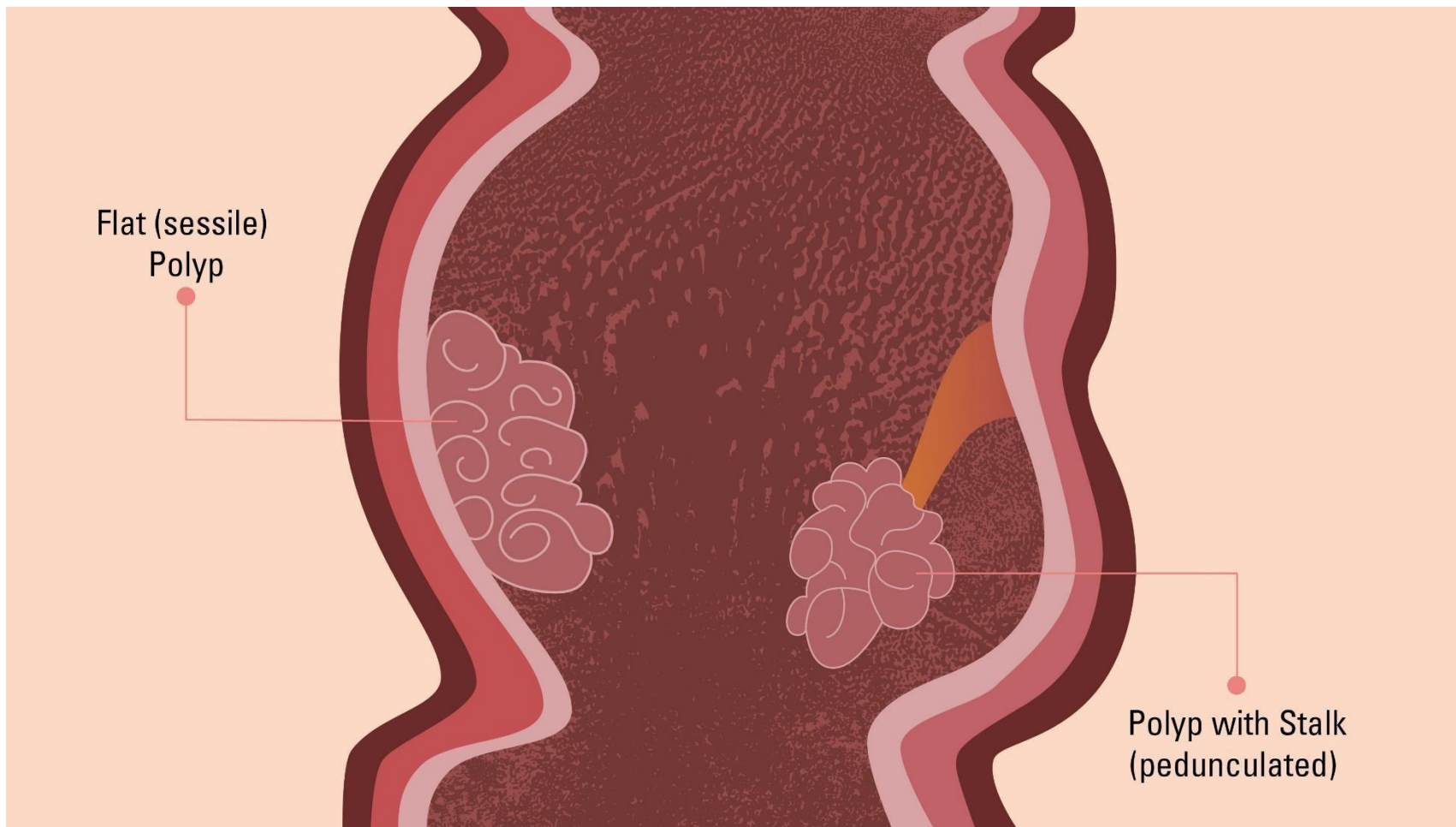
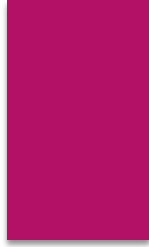
Diseases of the intestines

- ▶ Intestinal obstruction
- ▶ Vascular disorders
- ▶ Malabsorptive diseases and infections
- ▶ Inflammatory bowel disease.
- ▶ **Polyps and neoplastic diseases**

COLONIC POLYPS AND NEOPLASTIC DISEASE

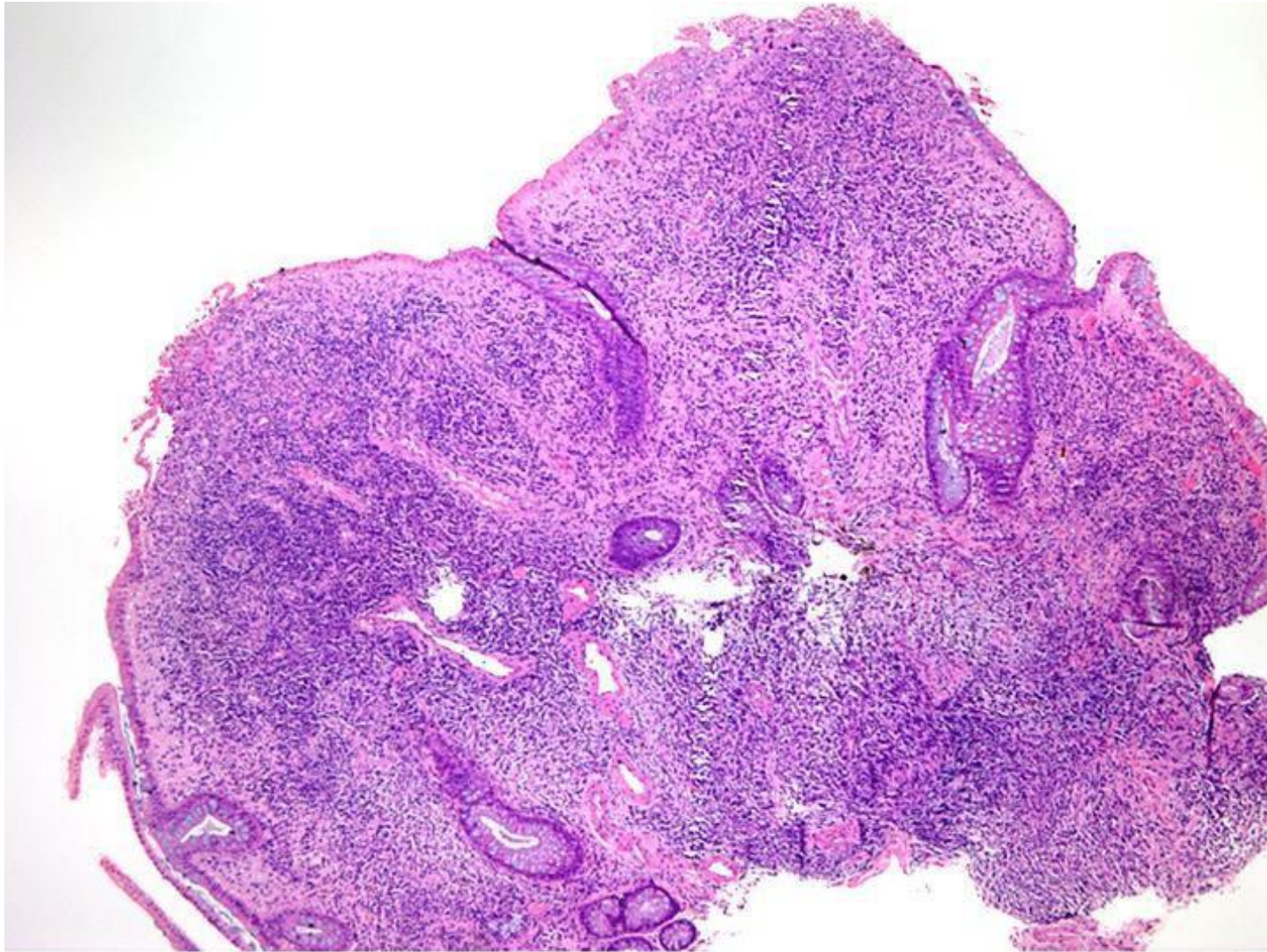
- ▶ Colon is most common site for polyps
- ▶ *Sessile polyp*: no stalk
- ▶ *Pedunculated polyp*: stalk.

- ▶ *Neoplastic polyps*: adenoma.
- ▶ *Non neoplastic polyps*: inflammatory, hamartomatous, or hyperplastic



Inflammatory Polyps

- ▶ *Solitary rectal ulcer syndrome.*
- ▶ Recurrent abrasion and ulceration of the overlying rectal mucosa.
- ▶ Chronic cycles of injury and healing give a polypoid mass of inflamed and reactive mucosal tissue.



4x: low power, dense inflammation in lamina propria

Hamartomatous Polyps

- ▶ Sporadic or syndromic.
- ▶ Disorganized, tumor-like growth composed of mature cell types normally present at that site.

- ▶ Juvenile Polyps
- ▶ Peutz-Jeghers Syndrome

Juvenile Polyps

- ▶ Most common hamartomatous polyp

- ▶ **Sporadic are solitary.**

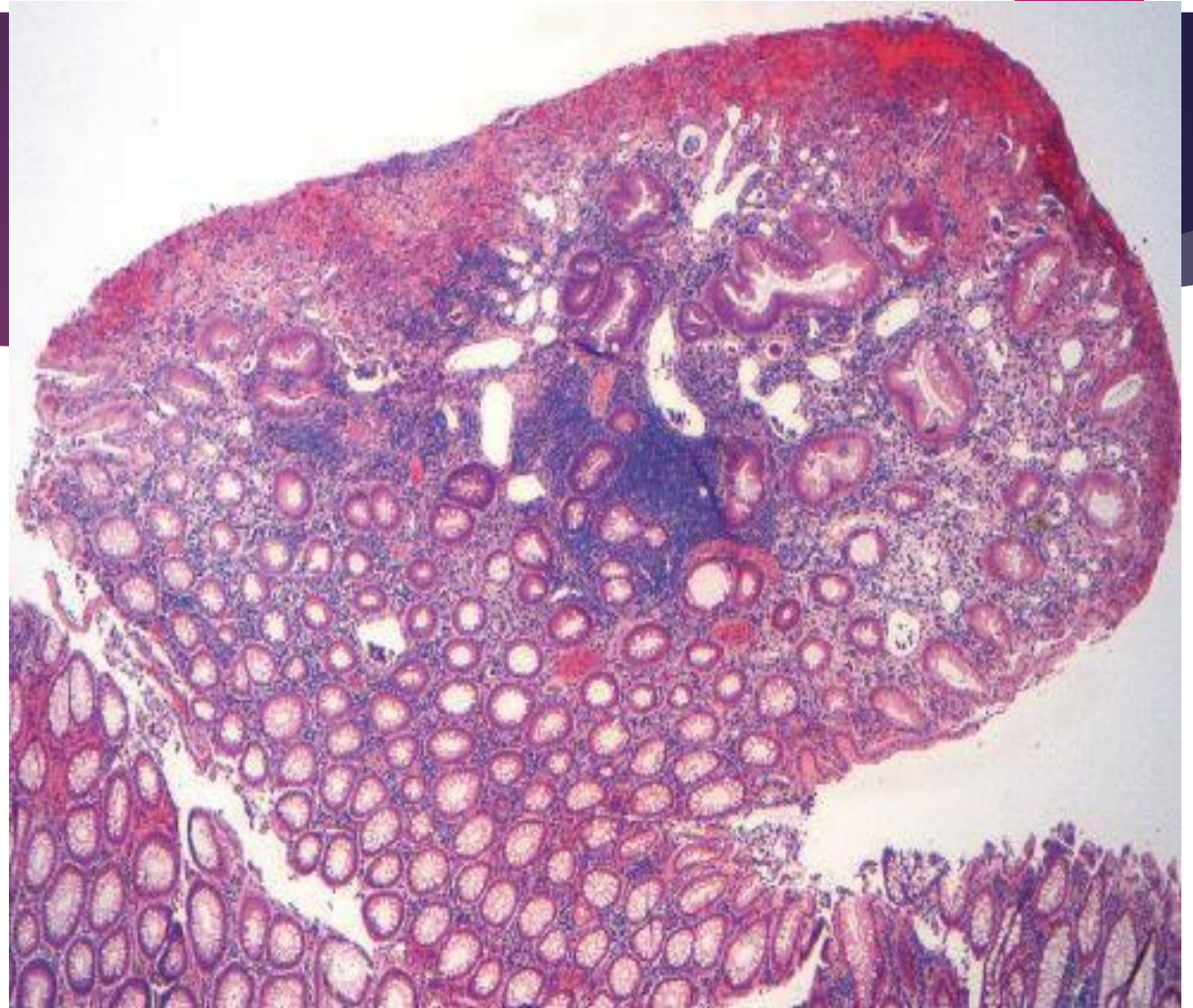
Children younger than 5 years of age
Rectum.

- ▶ **Syndromic are multiple.**

3 to as many as 100. Mean age 5 years
Autosomal dominant syndrome of juvenile polyposis
Transforming growth factor- β (TGF- β) mutation.
Increased risk for colonic adenocarcinoma.

Juvenile Polyps

- ▶ Pedunculated
- ▶ Reddish lesions
- ▶ Cystic spaces on cut sections
- ▶ Dilated glands filled with mucin and inflammatory debris.
- ▶ Granulation tissue on surface.



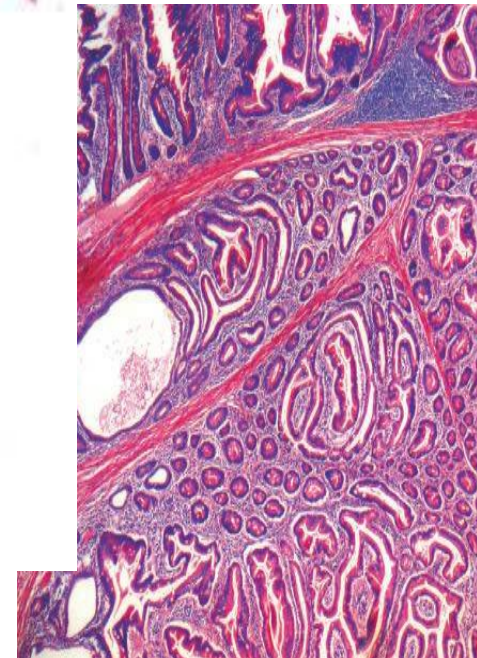
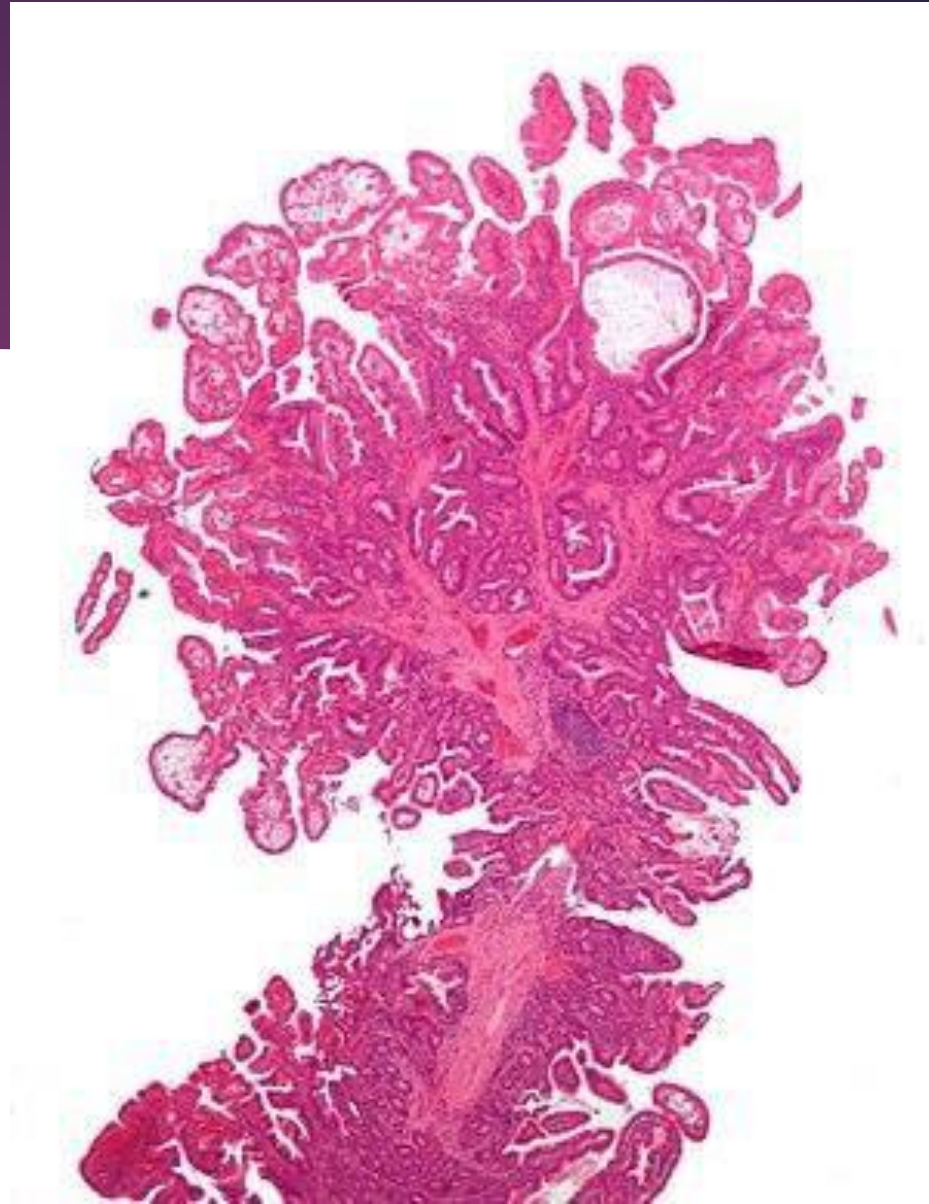
Peutz-Jeghers Syndrome

- ▶ Autosomal dominant, rare
- ▶ Mean age: 10-15 years.
- ▶ Multiple gastrointestinal hamartomatous polyps
- ▶ Most common in the small intestine.
- ▶ Mucocutaneous hyperpigmentation
- ▶ Increased risk for several malignancies: colon, pancreas, breast, lung, ovaries, uterus, and testes,

- ▶ *LKB1/STK11* gene mutation.

Peutz-Jeghers polyp

- ▶ Large.
- ▶ Arborizing network of connective tissue, smooth muscle, lamina propria
- ▶ Glands lined by normal-appearing intestinal epithelium
- ▶ Christmas tree pattern.



Mucocutaneous pigmentation



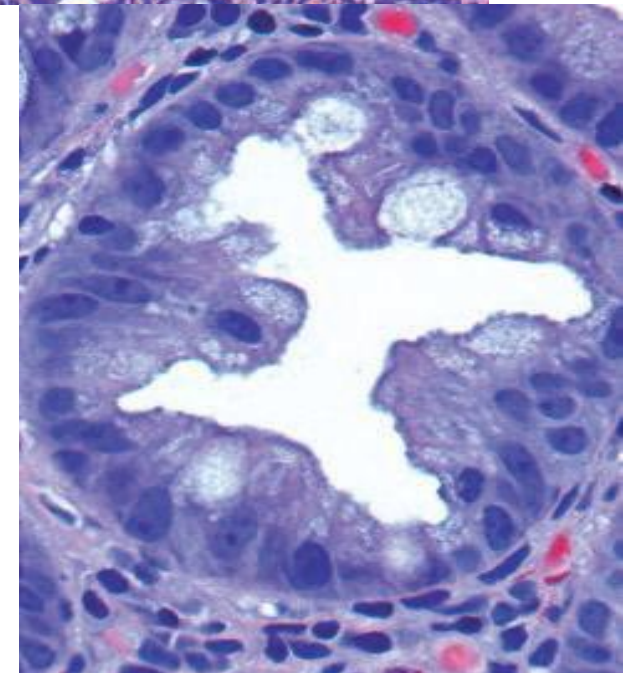
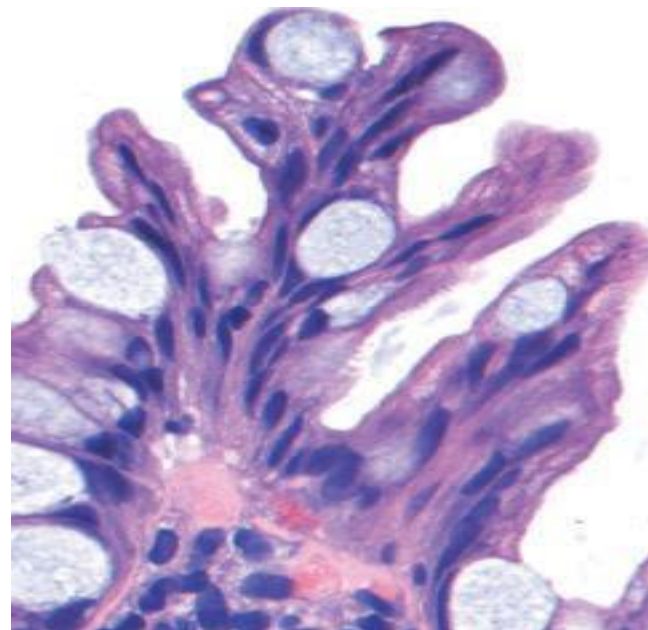
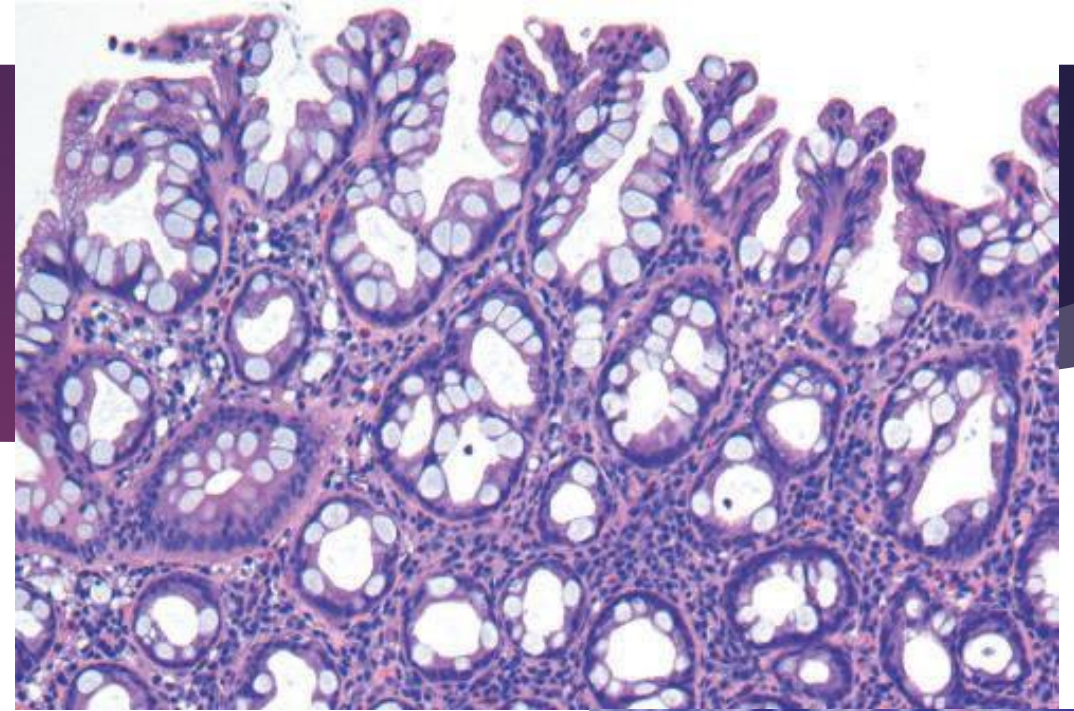
Hyperplastic Polyps

- ▶ Common
- ▶ 5th-6th decade.
- ▶ Decreased epithelial turnover and delayed shedding of surface epithelium >>> pileup of goblet cells & epithelial overcrowding
- ▶ **No malignant potential**

Hyperplastic polyp

- ▶ Left colon
- ▶ Rectosigmoid.
- ▶ Small < 5 mm
- ▶ Multiple

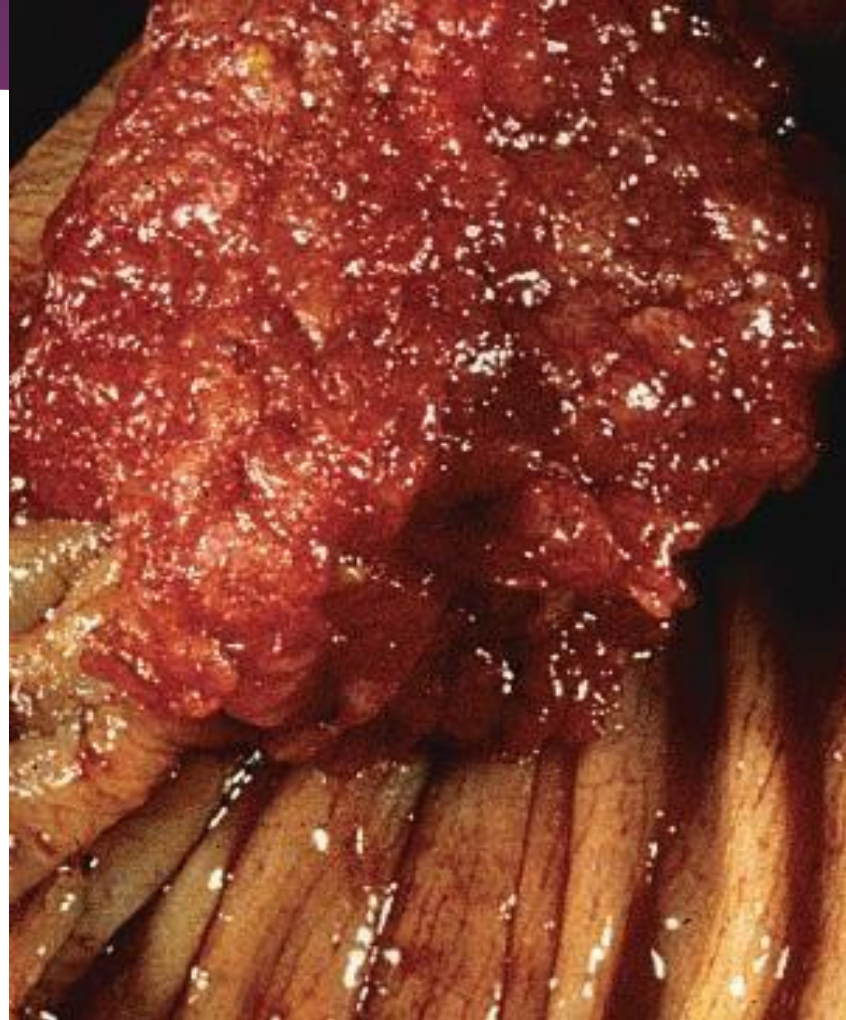
- ▶ Crowding of goblet & absorptive cells.



Adenomas

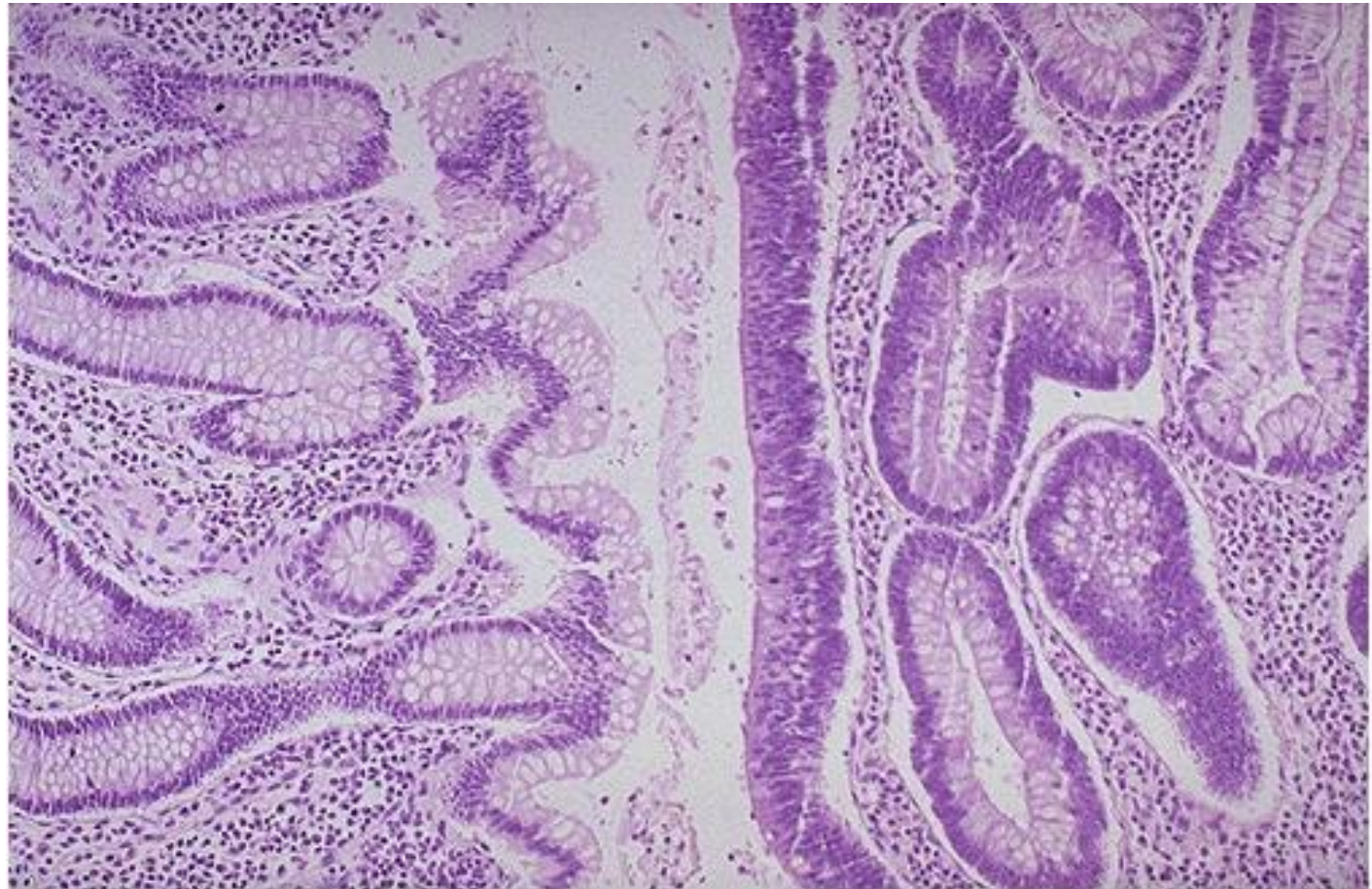
- ▶ Most common and clinically important
- ▶ *Increase with age.*
- ▶ *Definition: presence of epithelial dysplasia (low or high).*
- ▶ **Precursor for majority of colorectal adenocarcinomas**
- ▶ ***Most adenomas DO NOT progress to carcinoma.***
- ▶ *USA: screening colonoscopy starts at 50 yrs.*
- ▶ *Earlier screening with family history.*
- ▶ **Western diets and lifestyles increase risk.**

Pedunculated or sessile

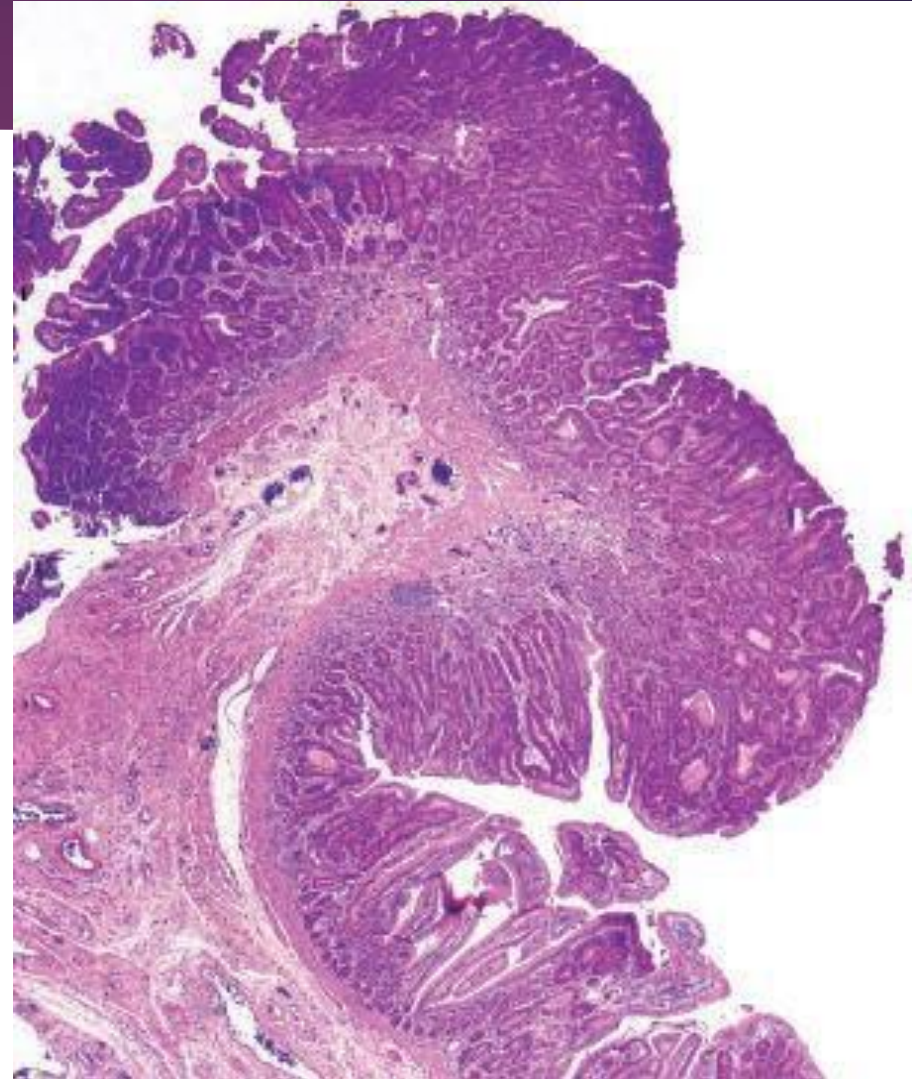
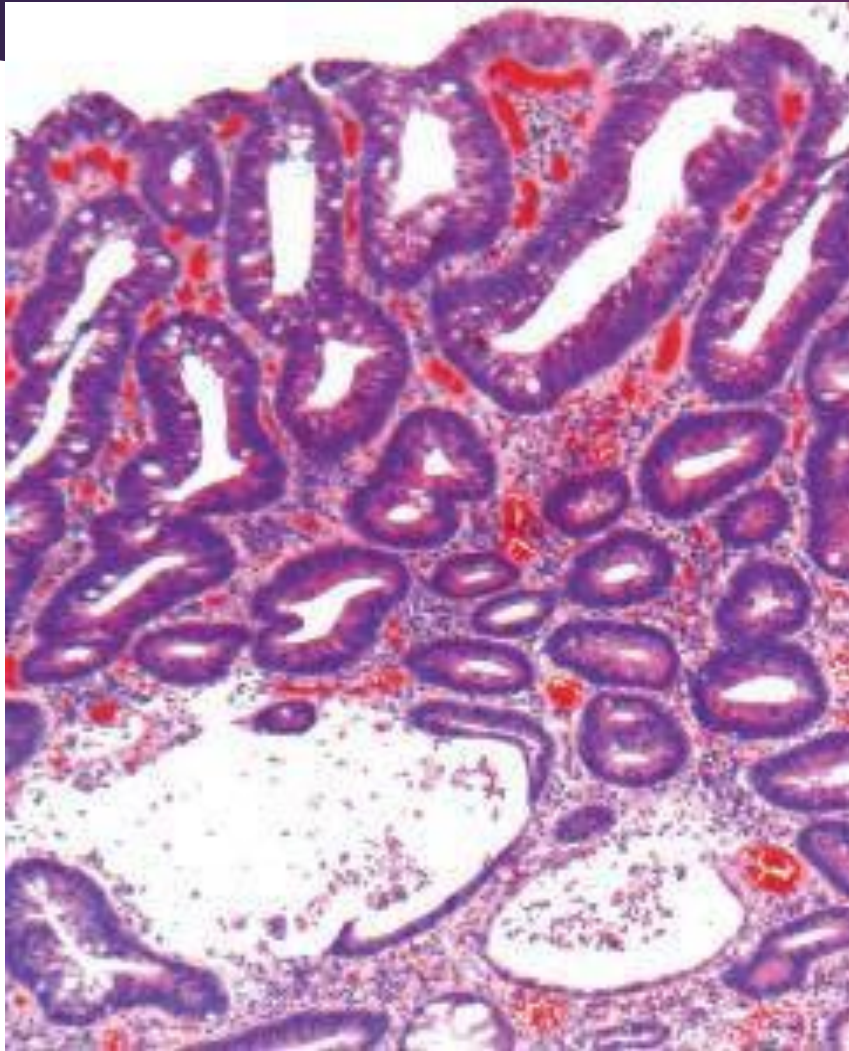


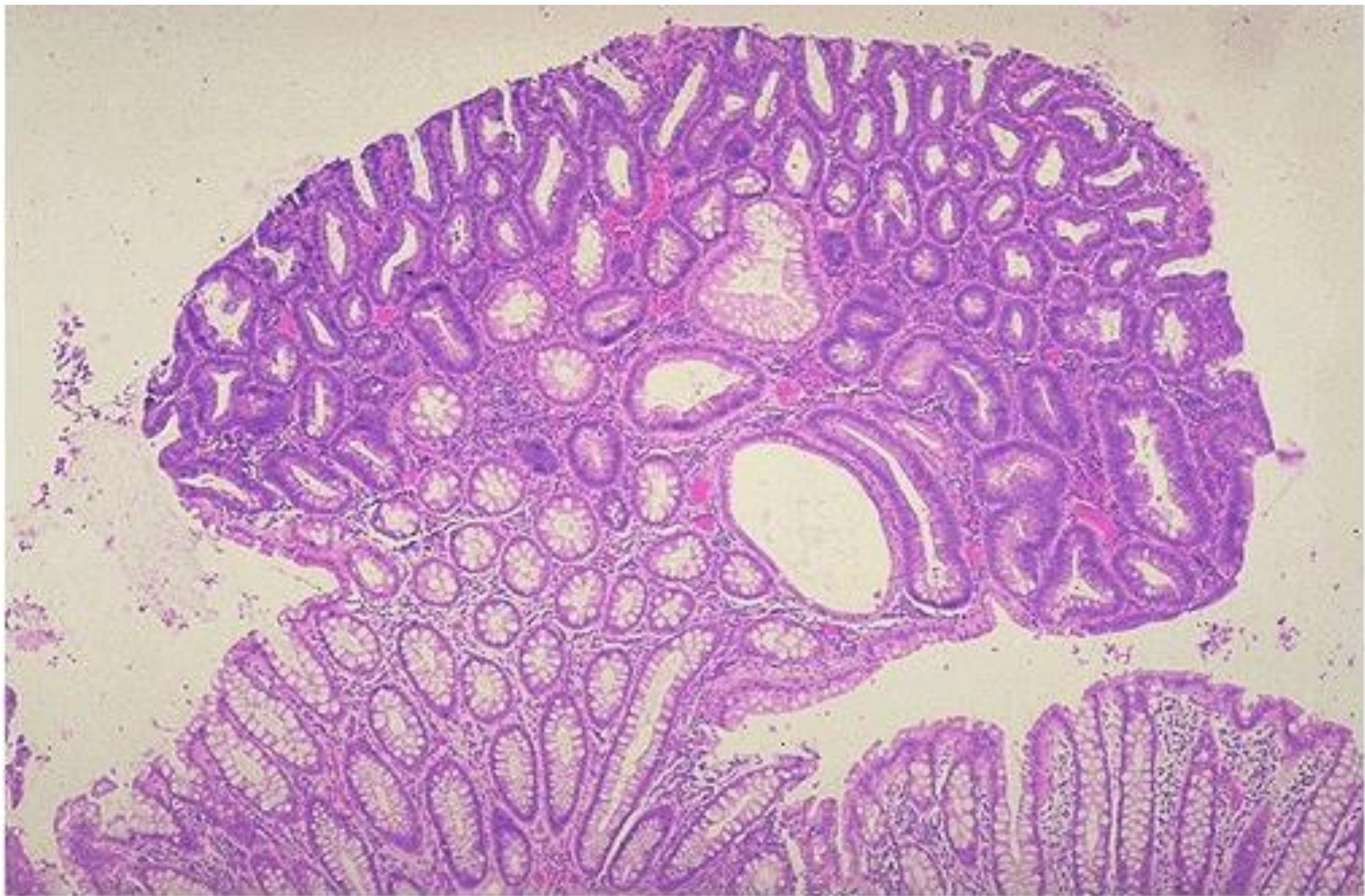
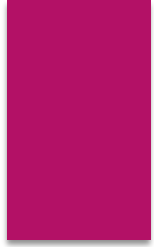
Colon adenoma

- ▶ **Hallmark: epithelial dysplasia**
- ▶ **Dysplasia: nuclear hyperchromasia, elongation, stratification, high N/C ratio.**
- ▶ **Size : most important correlate with risk for malignancy**
- ▶ **High-grade dysplasia is the second factor**

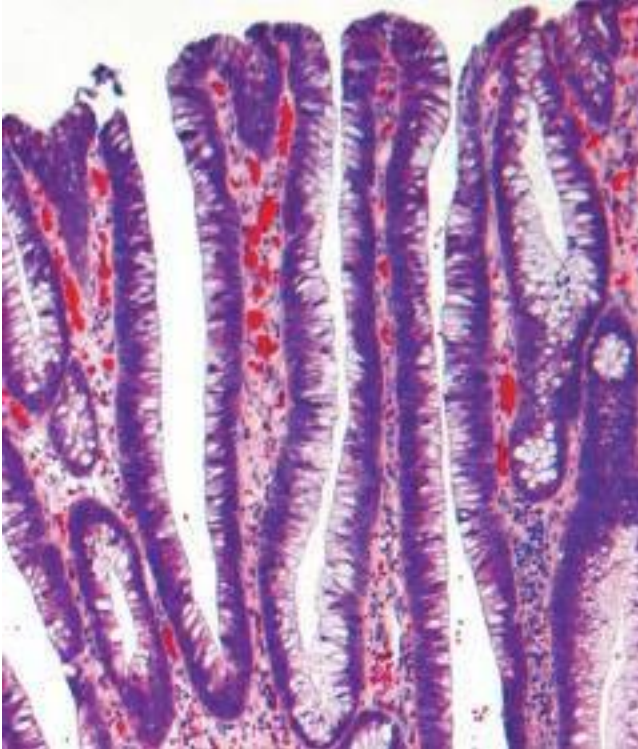


Tubular adenoma





Villous adenoma.

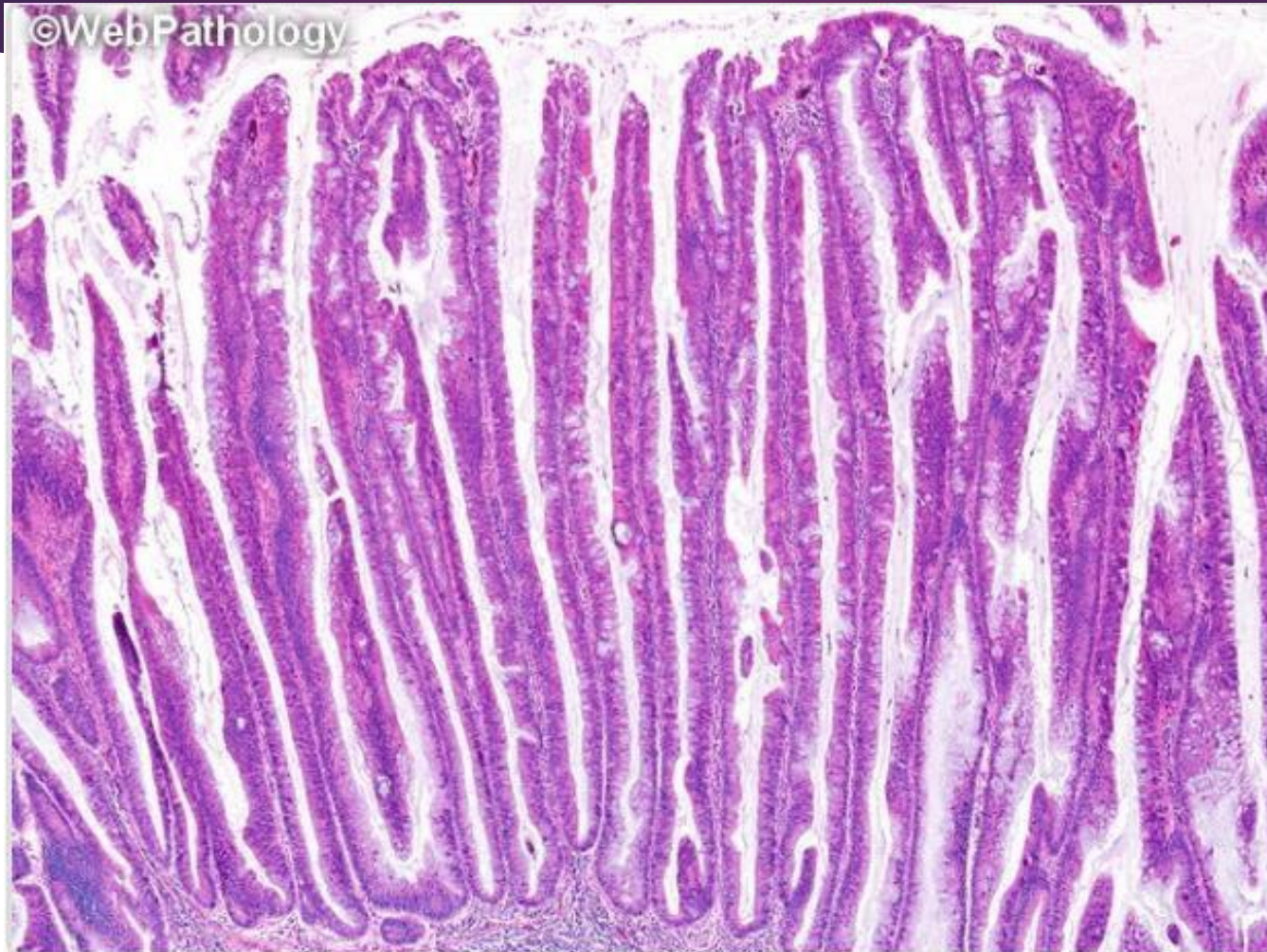


- ▶ Long slender villi.
- ▶ More frequent invasive foci

- ▶ **Architecture:**

- ▶ Tubular.
- ▶ Tubulovillous.
- ▶ Villous.

Villous adenoma



Familial Syndromes

- ▶ Syndromes associated with colonic polyps and increased rates of colon cancer
- ▶ Genetic basis.

- ▶ **Familial Adenomatous Polyposis (FAP)**
- ▶ **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**

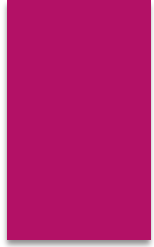
Familial adenomatous polyposis FAP

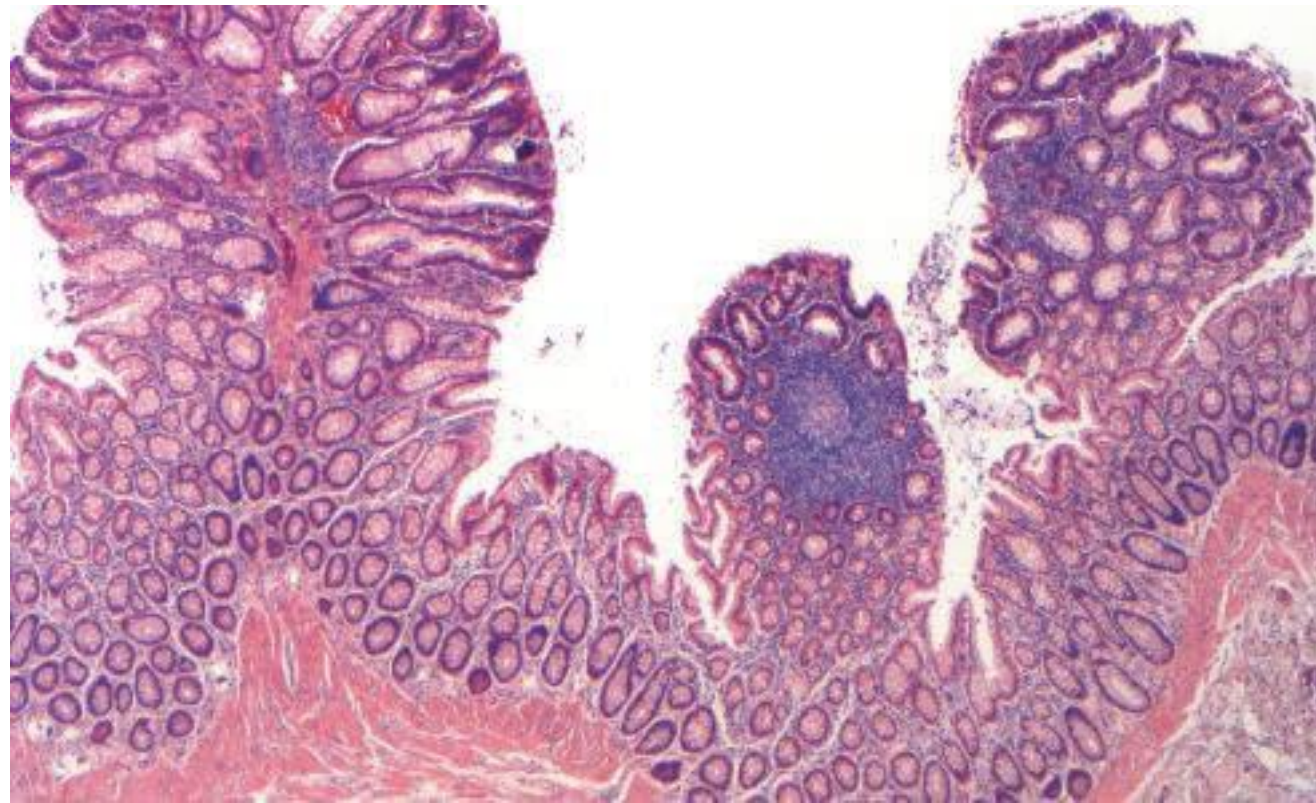
- ▶ Autosomal dominant.
- ▶ Numerous colorectal adenomas: teenage years.
- ▶ Mutation in APC gene.
- ▶ At least 100 polyps are necessary for a diagnosis of classic FAP.
- ▶ Morphologically similar to sporadic adenomas
- ▶ 100% of patients develop colorectal carcinoma, IF UNTREATED, often before age of 30.
- ▶ Standard therapy: prophylactic colectomy before 20 Year of age.
- ▶ Risk for *extraintestinal manifestations*,



▶ Variants of FAP: Gardner syndrome and Turcot syndrome.

- ▶ **Gardner syndrome:** intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.
- ▶ **Turcot syndrome:** intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)





Hereditary Nonpolyposis Colorectal Cancer: HNPCC, *Lynch syndrome*

- ▶ Clustering of tumors: **Colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin**
- ▶ Colon cancer at younger age than sporadic cancers
- ▶ Right colon with excessive mucin production .
- ▶ Adenomas are present, **BUT POLYPOSIS IS NOT.**

- ▶ **Inherited germ line mutations in DNA mismatch repair genes.**
- ▶ Accumulation of mutations in *microsatellite DNA (short repeating sequences)*
- ▶ Resulting in *microsatellite instability*
- ▶ Majority of cases involve either *MSH2* or *MLH1*.

Cecal polyps in HNPCC.



Colonic Adenocarcinoma

- ▶ Most common malignancy of the gastrointestinal tract
- ▶ Small intestine is uncommonly involved by neoplasia.
- ▶ Peak: 60 to 70 years
- ▶ 20% under 50 years.
- ▶ Developed countries lifestyles and diet.
- ▶ **Low intake of vegetable fiber and high intake of carbohydrates and fat.**
- ▶ Aspirin or other NSAIDs have a protective effect.
- ▶ Cyclooxygenase-2 (COX-2) promotes epithelial proliferation.

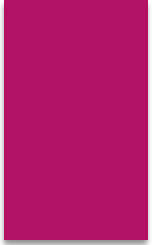
Pathogenesis

- ▶ Heterogeneous molecular events.
- ▶ Sporadic >>>> familial.
- ▶ **Two pathways:**
- ▶ **APC/ β -catenin pathway >> increased WNT signaling**
- ▶ **Microsatellite instability pathway >> defects in DNA mismatch repair**

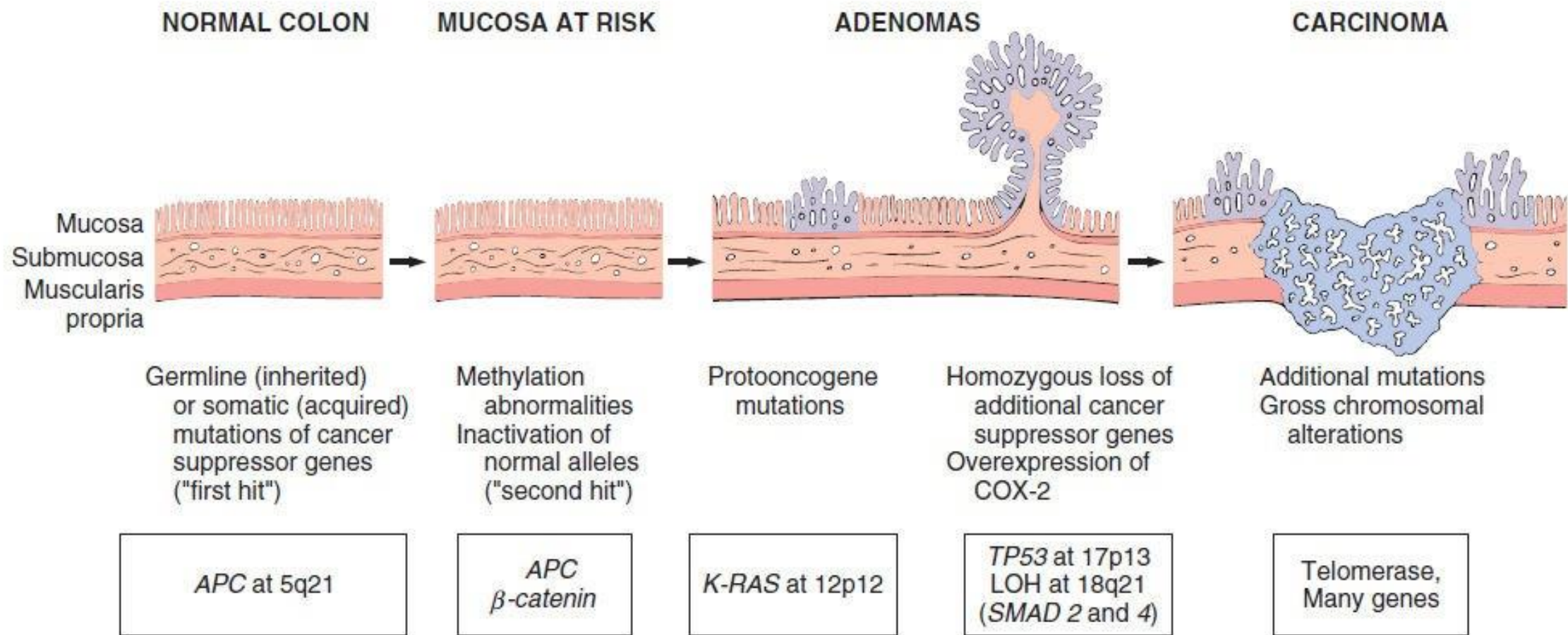
- ▶ Stepwise accumulation of multiple mutations

The APC/β-catenin pathway: chromosomal instability

- ▶ *Classic adenoma carcinoma sequence.*
- ▶ **80%** of sporadic colon tumors
- ▶ Mutation of the APC tumor suppressor gene: EARLY EVENT
- ▶ *APC is a key negative regulator of β-catenin, a component of the WNT signaling pathway.*
- ▶ *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).*

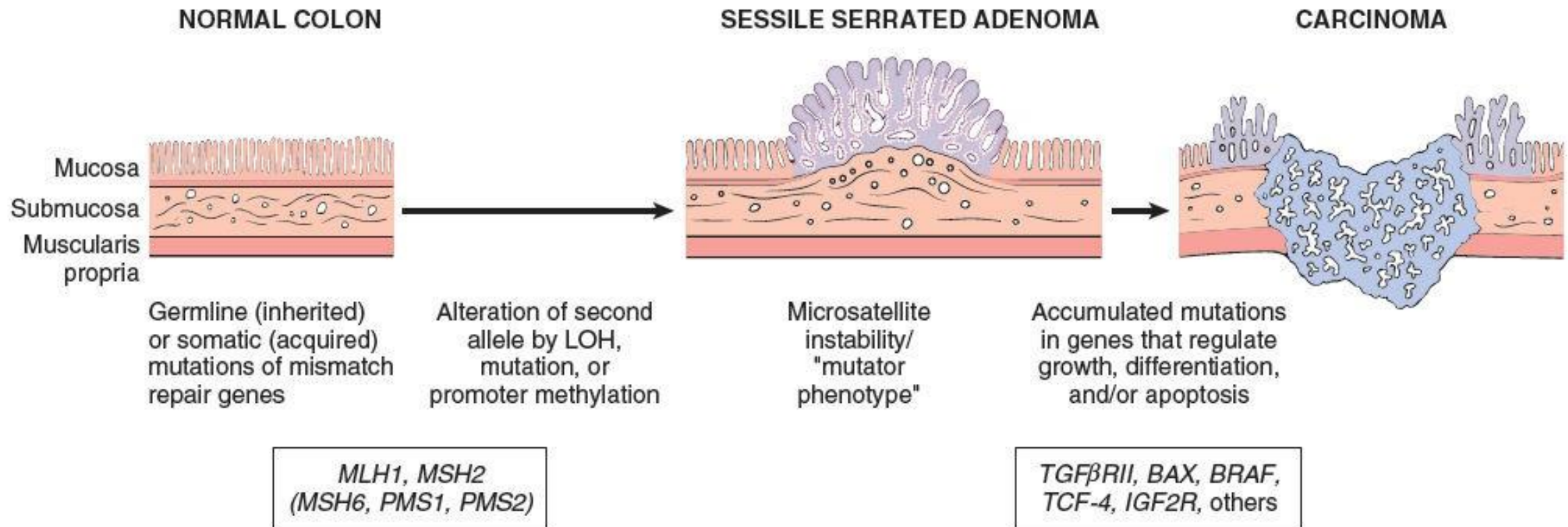
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- ▶ *Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.*
 - ▶ *Additional mutations >> activation of KRAS (LATE EVENT) >> inhibits apoptosis.*
 - ▶ *SMAD2 and SMAD4 mutations (tumor suppressor genes.)*

 - ▶ **TP53 is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
 - ▶ TP53 inactivation mutation
 - ▶ Expression of telomerase also increases as the tumor advances.



The microsatellite instability pathway

- ▶ DNA mismatch repair deficiency
 - ▶ Loss of mismatch repair genes
 - ▶ Mutations accumulate in microsatellite repeats
 - ▶ *Microsatellite instability*
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- ▶ Silent if microsatellites located in noncoding regions
 - ▶ Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes)



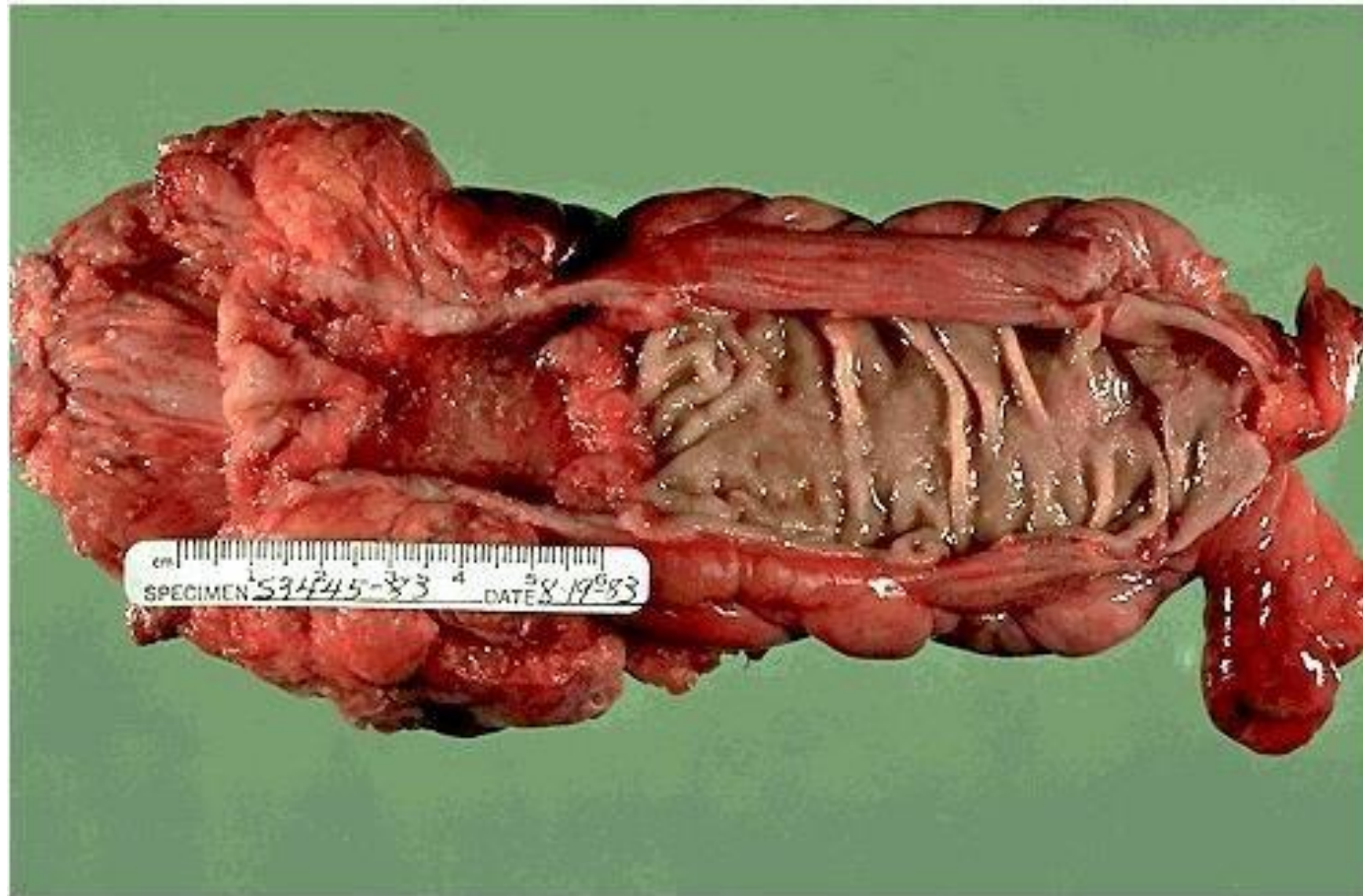
Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	<i>APC</i>	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	<i>MSH2, MLH1</i>	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	<i>APC</i>	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	<i>MSH2, MLH1</i>	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

MORPHOLOGY

- ▶ **Macroscopic:**
- ▶ Proximal colon tumors: polypoid, exophytic masses
- ▶ Proximal colon: rarely cause obstruction.
- ▶ Distal colon: annular lesions “napkin ring” constrictions & narrowing

- ▶ **Microscopic:**
- ▶ Dysplastic GLANDS with strong desmoplastic response.
- ▶ Necrotic debris are typical.
- ▶ Some tumors give abundant mucin or form signet ring cells.

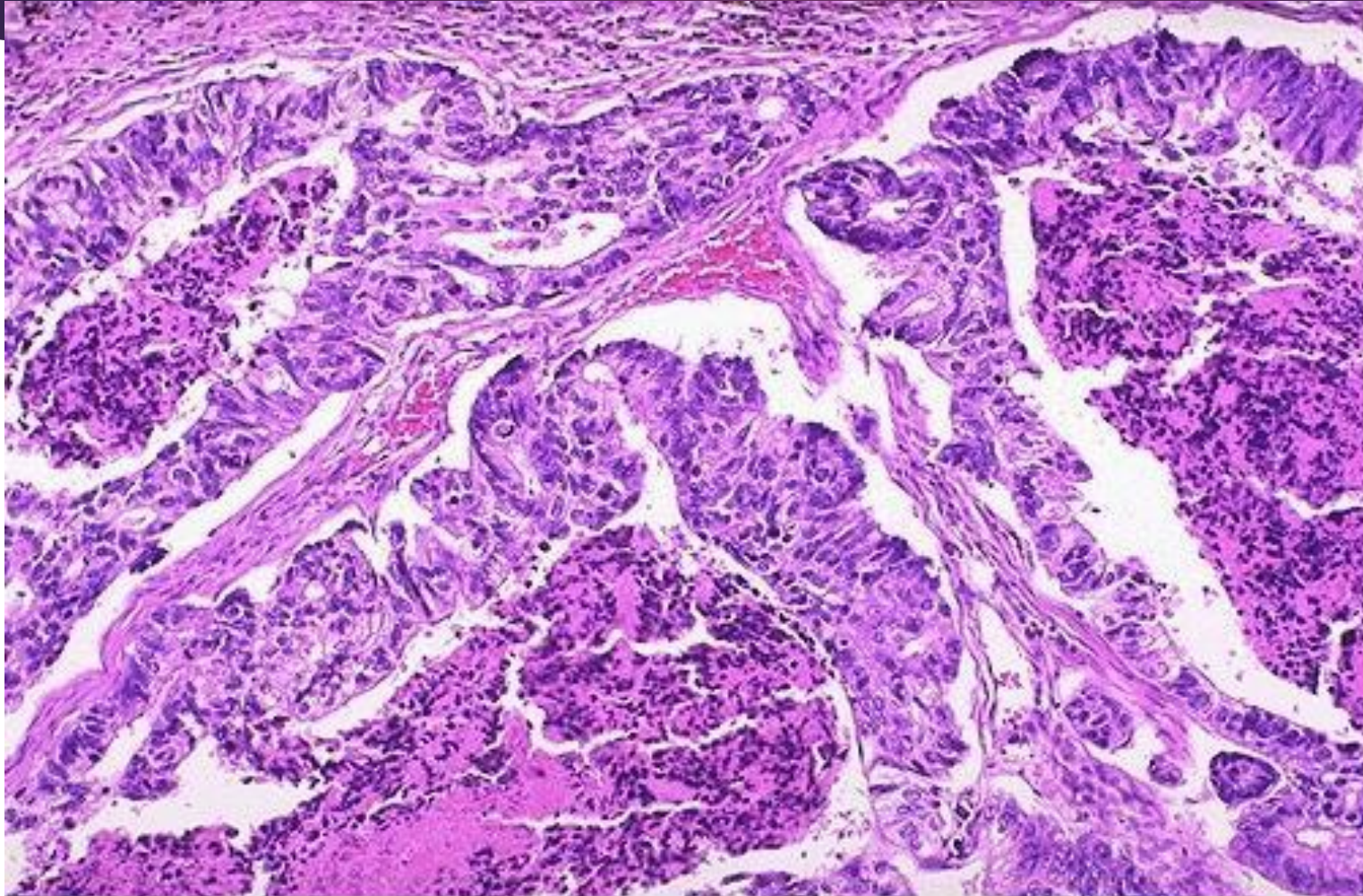
Rectosigmoid adenocarcinoma, napkin ring



Exophytic adenocarcinoma




Adenocarcinoma with necrosis



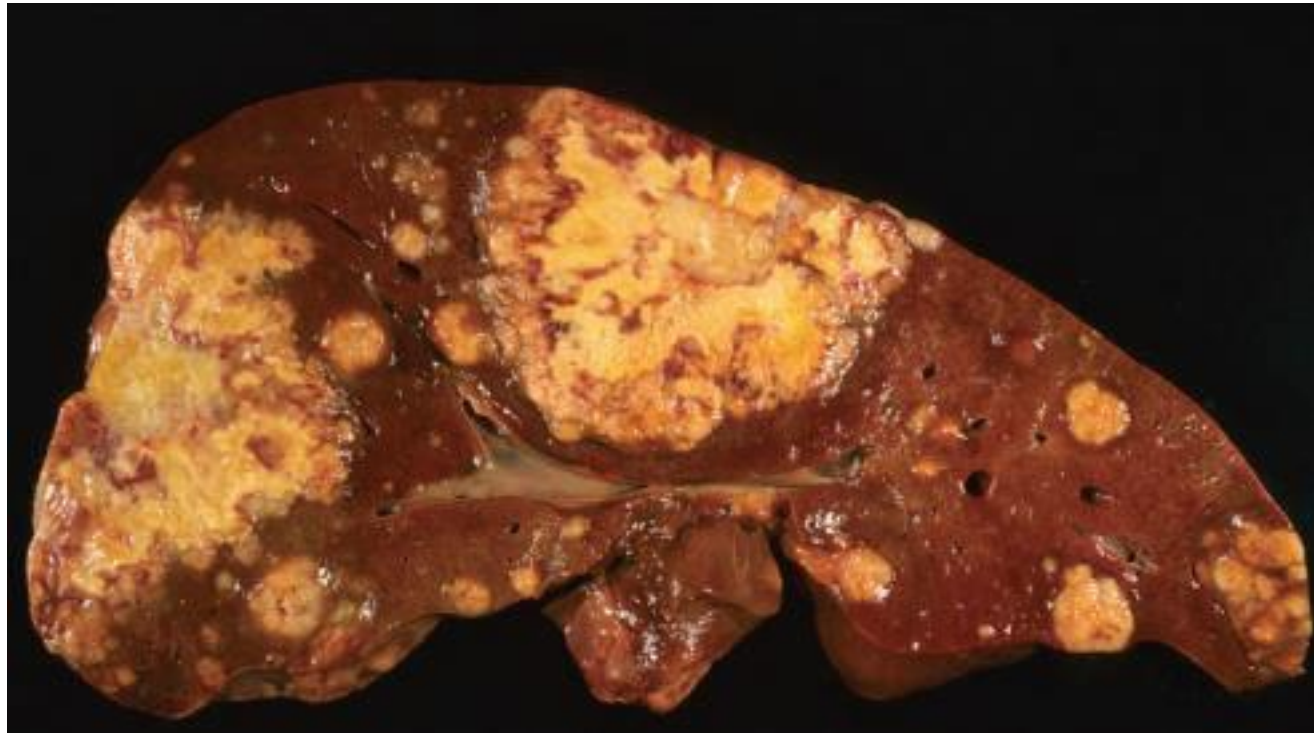
Clinical Features

- ▶ Endoscopic screening >> cancer prevention
- ▶ Early cancer is asymptomatic !!!!!!!!
- ▶ Cecal and right side cancers: *Fatigue and weakness (iron deficiency anemia)*
- ▶ **Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.**

- ▶ *Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.*

- 
- ▶ Poor differentiation and mucinous histology >> poor prognosis
 - ▶ *Most important two prognostic factors are*
Depth of invasion
Lymph node metastasis.
 - ▶ *Distant metastases (lung and liver) can be resected.*

Liver metastasis.



Appendix

- ▶ Normal true diverticulum of the cecum

- ▶ ACUTE APPENDICITIS
- ▶ TUMORS OF THE APPENDIX

ACUTE APPENDICITIS

- ▶ Most common in adolescents and young adults.
- ▶ May occur in any age.
- ▶ Difficult to confirm preoperatively

- ▶ DDX:

Mesenteric lymphadenitis,

Acute salpingitis,

Ectopic pregnancy,

Mittelschmerz (pain associated with ovulation),

Meckel diverticulitis.

- ▶ Luminal obstruction in 50-80% of cases >> increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
 - ▶ *Obstruction by fecalith, less commonly : gallstone, tumor, worms....*
- ▶ Diagnosis requires neutrophilic infiltration of the muscularis propria
- ▶ **Acute suppurative appendicitis >> more severe >> focal abscess formation.**
- ▶ **Acute gangrenous appendicitis >> necrosis and ulceration.**

Clinical Features

- ▶ Early acute appendicitis: periumbilical pain
- ▶ Later: pain localizes to the right lower quadrant,
- ▶ Nausea, vomiting, low-grade fever, mildly leukocytosis.
A classic physical finding is *McBurney's sign* (McBurney's point).
- ▶ Signs and symptoms are often absent, creating difficulty in clinical diagnosis.

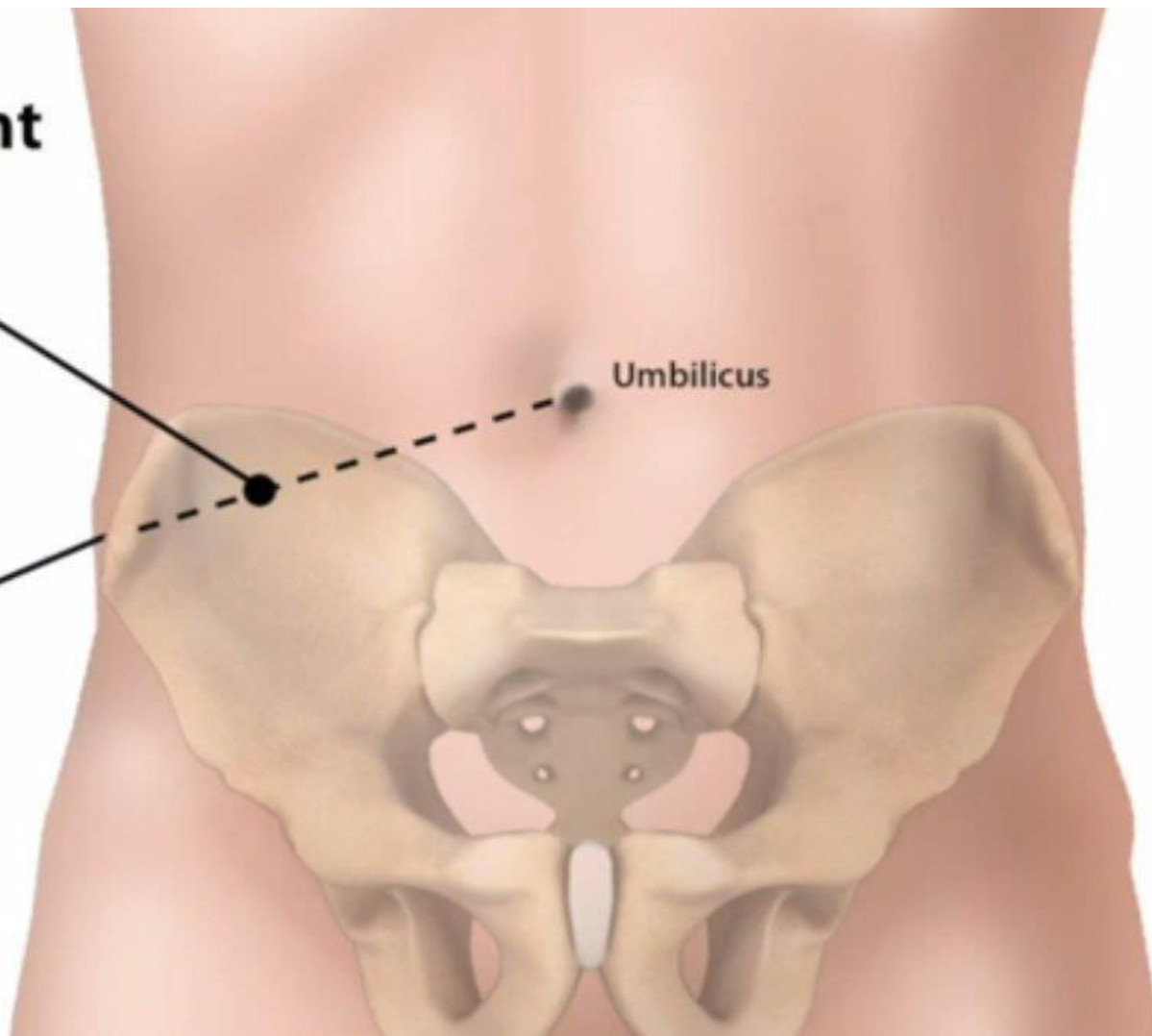


McBurney's Point

2/3 of the way from
umbilicus to ASIS

Anterior Superior Iliac Spine

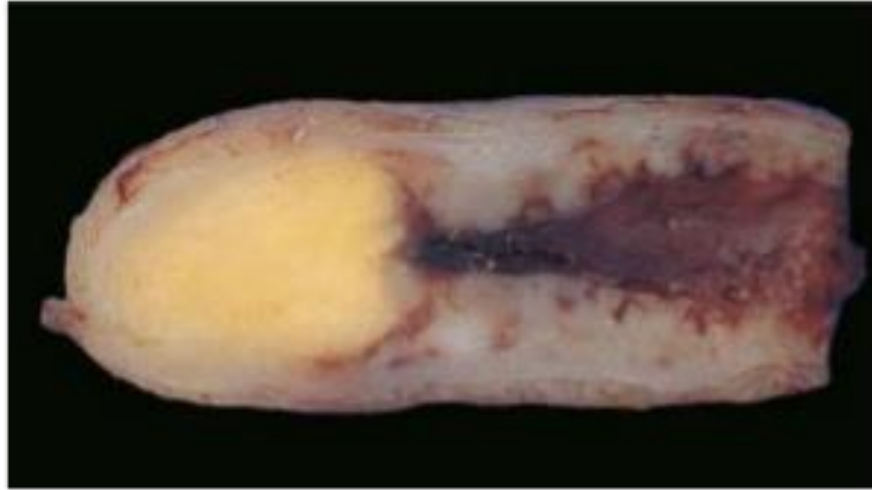
Umbilicus



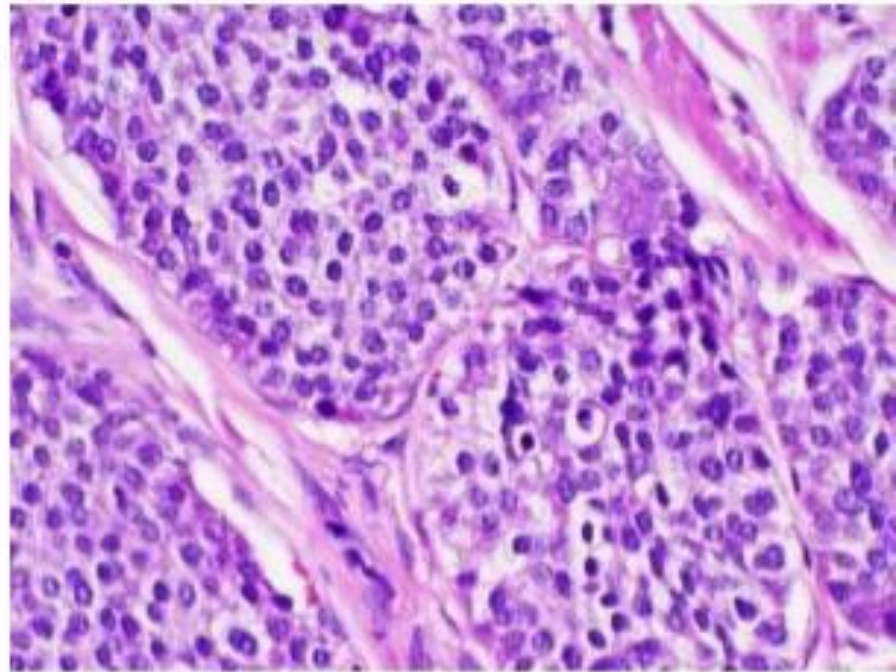
TUMORS OF THE APPENDIX

- ▶ The most common tumor: *carcinoid* (neuroendocrine tumor)
- ▶ Incidentally found during surgery or on examination of a resected appendix
- ▶ Distal tip of the appendix
- ▶ Nodal metastases & distant spread are rare.

Carcinoid tumor



Gross



Microscopic