

Harvard-MIT Division of Health Sciences and Technology

HST.121: Gastroenterology, Fall 2005

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Gastrointestinal Neoplasms

Neoplastic Diseases of the Stomach

- **Mucosal polyps**
 - Hyperplastic (regenerative) polyps
 - Cystic fundic gland polyp
 - Inflammatory fibroid polyp
 - Polyposis syndromes
 - Adenomas
- **Gastric adenocarcinoma**
 - Variants: Adenosquamous; lymphoepithelial; hepatoid; parietal cell
- **Neuroendocrine tumors**
- **Stromal tumors**
- **Lymphomas**

Overview of the Lecture

- **Epithelial tumors**
 - **Epithelial polyps**
 - **Colorectal ACA**
 - **Gastric ACA**
 - **Esophageal ACA**
 - **Esophageal SCC**
- **Neuroendocrine tumors**
- **Lymphomas**
- **Gastrointestinal stromal tumors**

The Art of Terminology!

- A **tumor** is a mass lesion without reference to tissue composition or malignant potential
- GI tumors typically present as protrusions of mucosal tissue into the lumen (**polyps**); Polyps may have a broad base (**sessile polyps**) or be attached to the wall by a stalk (**pedunculated polyps**)
- Over the years, the term tumor has *almost* become synonymous with a **neoplastic** growth

The Art of Terminology

- A **neoplasm** is the new (new onset) growth (overgrowth) of a specific cell or tissue type, which may or may not form a tumor
- Based on their natural history, neoplasms may be **benign**, **malignant**, or **locally aggressive**
- If the new growth consists of benign indigenous cell or tissue elements, it may be called a **hamartoma** or a **hyperplasia**

The Art of Terminology

- **In the GI tract, dysplasia implies the presence of pre-malignant epithelial abnormalities** (this is not necessarily true for other organs)
- Dysplasia has a cytological spectrum from mild to severe (or from low-grade to high-grade)
- **Carcinoma** indicates the presence of severe dysplasia, which may be confined by the basement membrane (**carcinoma-in-situ**) or invade through the basement membrane (**invasive carcinoma**)

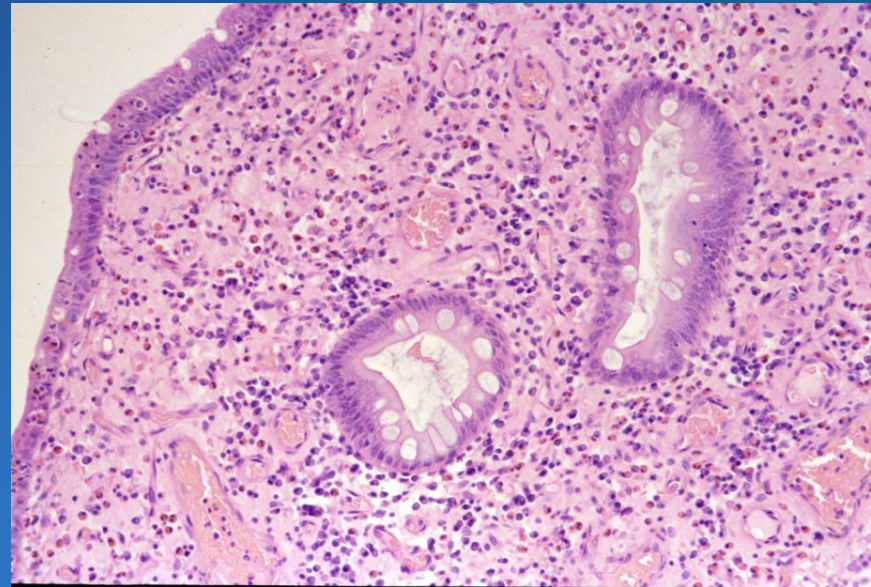
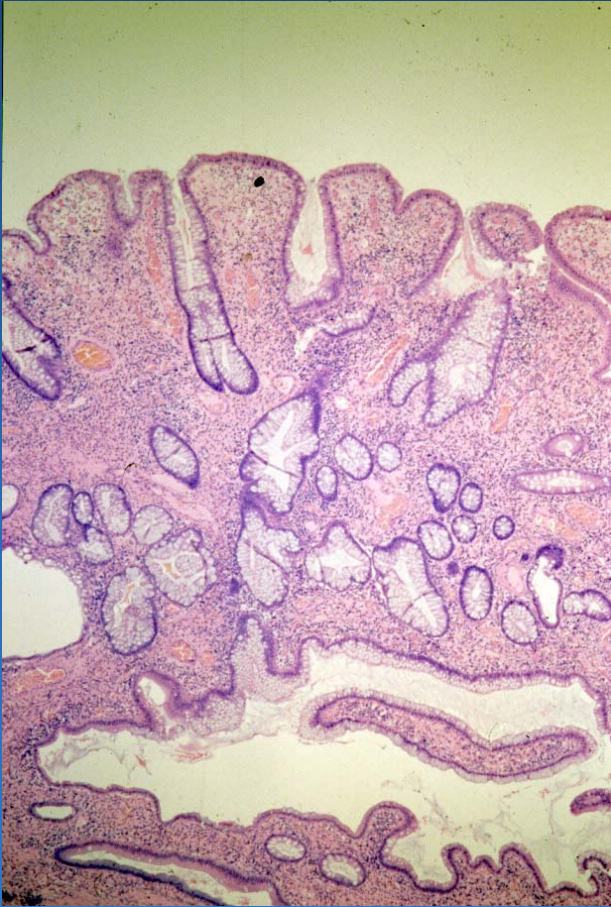
Epithelial Polyps

- **Inflammatory polyps**
 - **Inflammatory (pseudo)polyps**
 - **Sporadic juvenile polyps**
- **Hamartomatous polyps**
 - **Juvenile polyposis syndrome**
 - **Peutz-Jeghers syndrome**
- **Hyperplastic polyps**
- **Adenomas**

Juvenile Polyps and Polyposis

- Juvenile polyps consist of abnormal epithelial glands nested in an inflammatory background
- Sporadic polyps (also called **retention polyps**) are typically found in the rectosigmoid of children presenting with blood in stools
- Juvenile polyposis syndrome may be sporadic or familial (AD) and is associated with an increased risk of ACA and extraintestinal manifestations

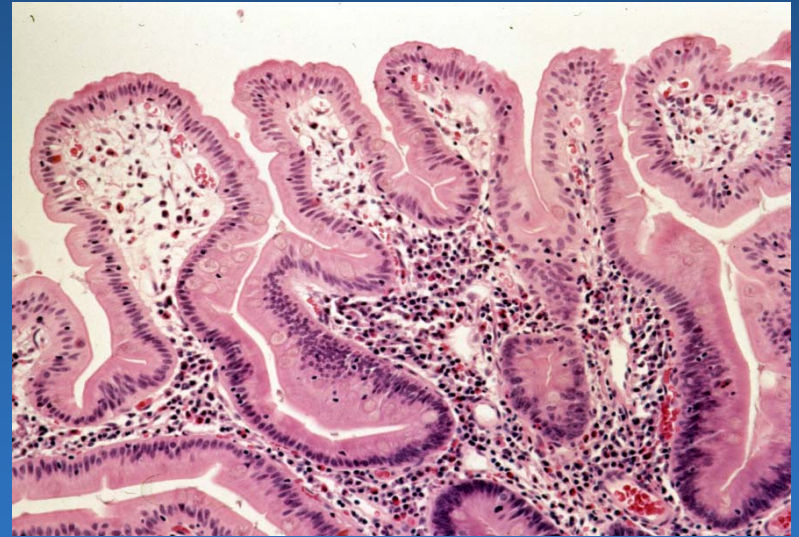
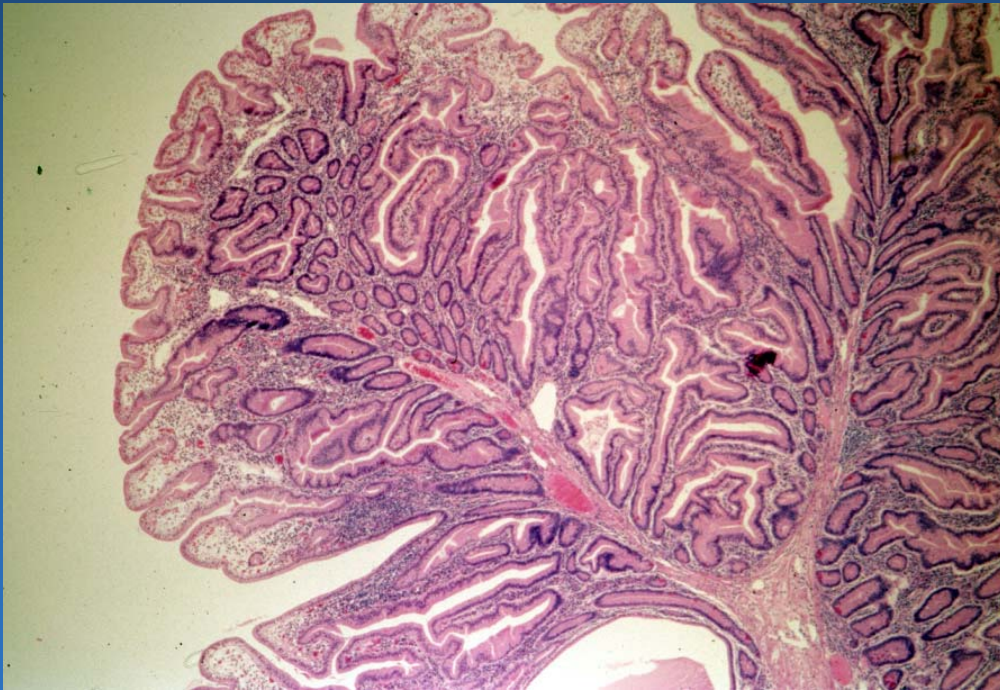
Juvenile polyp



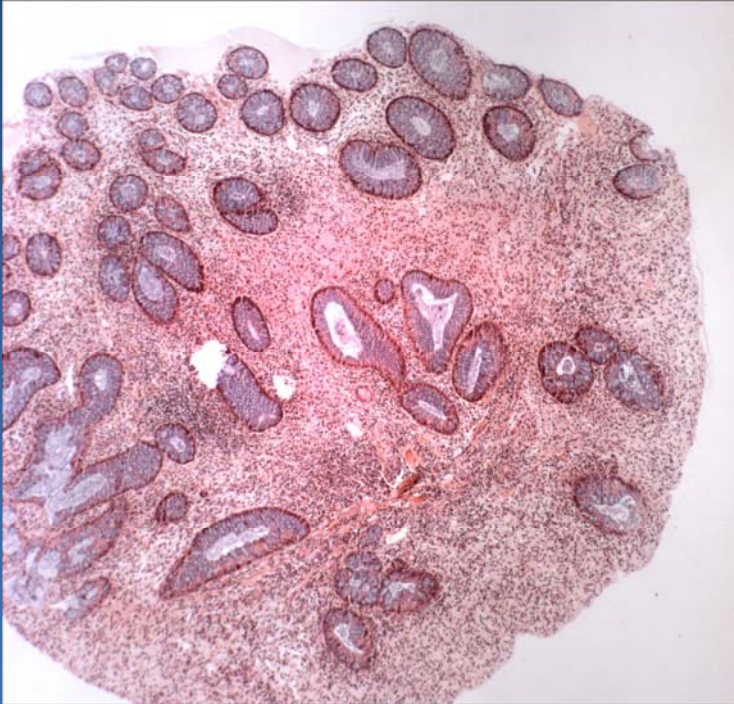
Hamartomatous Polyps

- Polyps consist of indigenous epithelial elements with an arborizing muscular framework and little to no inflammation
- **Peutz-Jeghers syndrome** is an AD disease with gastrointestinal hamartomatous polyps and mucocutaneous pigmented macules
- Molecular defect: STK11/LKB1 gene (serine-threonine kinase)
- PJS patients have an increased risk of gastro-intestinal neoplasms and neoplasms of many other organs including ovaries, testes, cervix, breast, thyroid, biliary tree, and urogenital tract

Peutz-Jeghers polyp



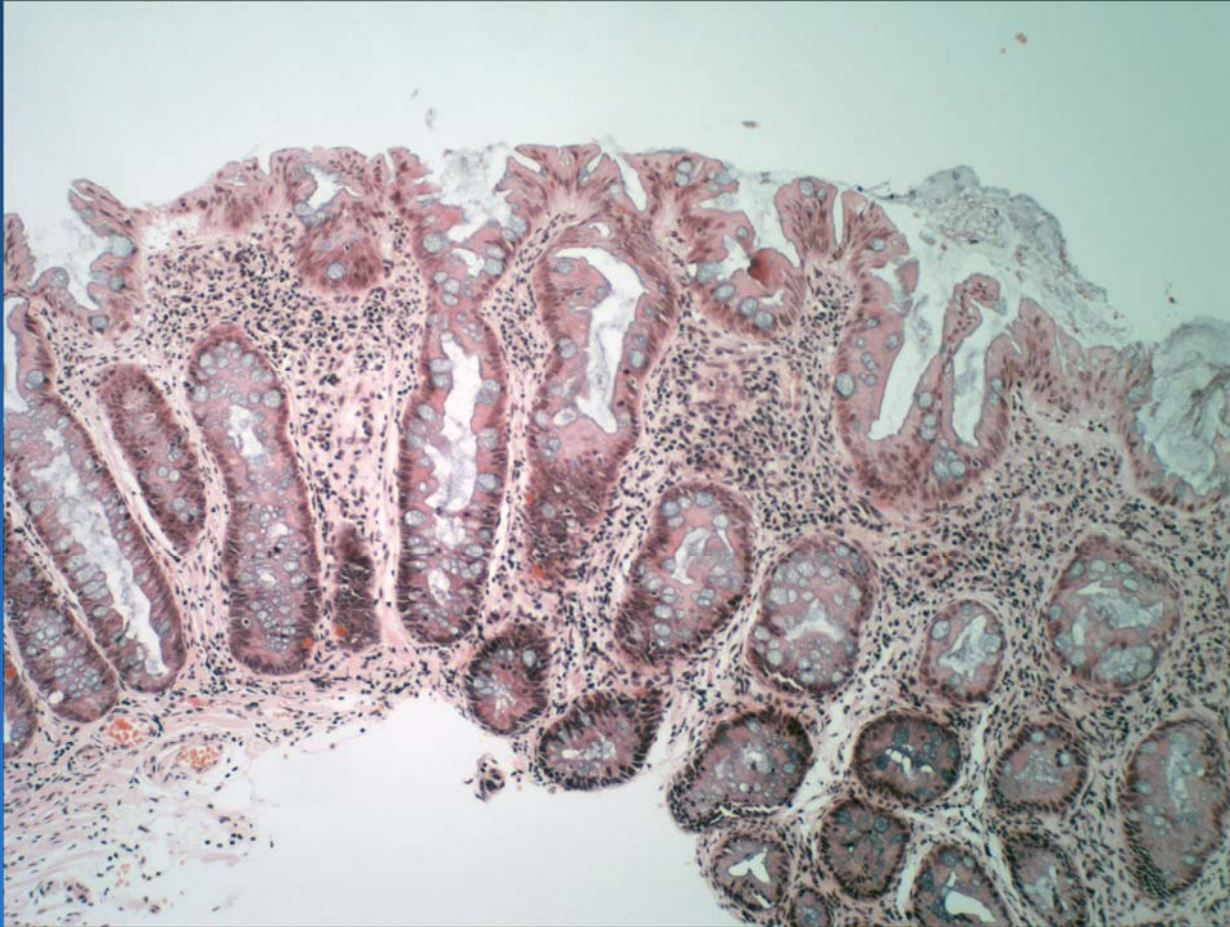
Cowden's syndrome- ganglioneuroma



Hyperplastic Polyps

- **The most common type of colorectal polyp**
- **Hyperplastic polyps are typically small and sessile protrusions of “hypermature” colonic epithelium with little inflammation and no muscular component**
- **Large hyperplastic polyps are much less common, but may be associated with an increased risk of dysplasia and ACA**
- **“Serrated neoplasia pathway”- methylation silencing of tumor suppressor genes**

Hyperplastic polyp



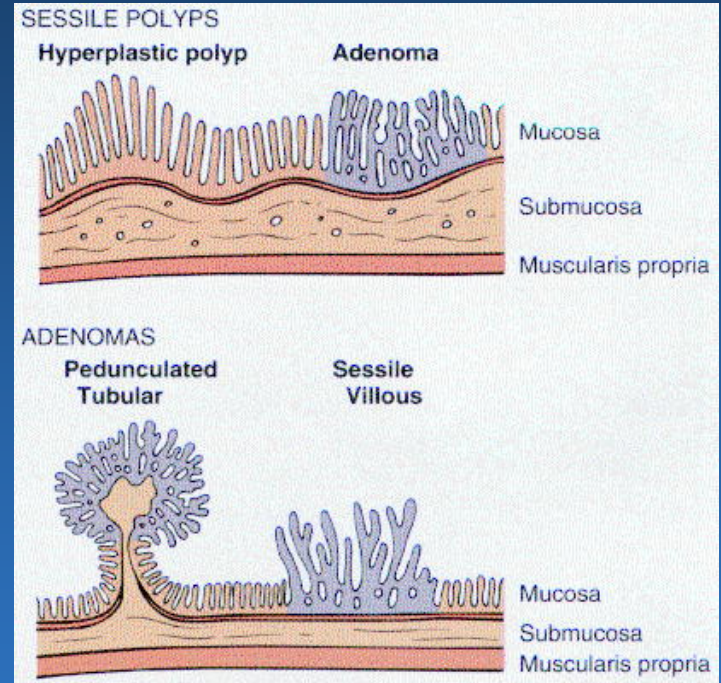
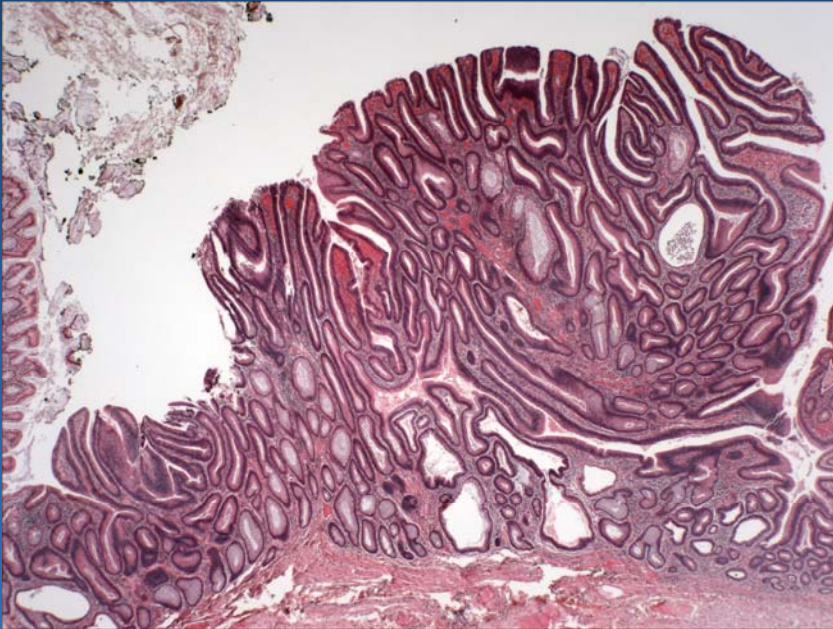
Adenomas

- **Adenomas are benign but dysplastic epithelial neoplasms of the GI tract**
- **Adenomas are common lesions, occurring in 25-50% of individuals over the age of 60**
- **Most adenomas (~90%) are colonic**
- **Most colonic adenomas (~75%) are in the rectosigmoid**
- **Most adenomas (~75%) are single**

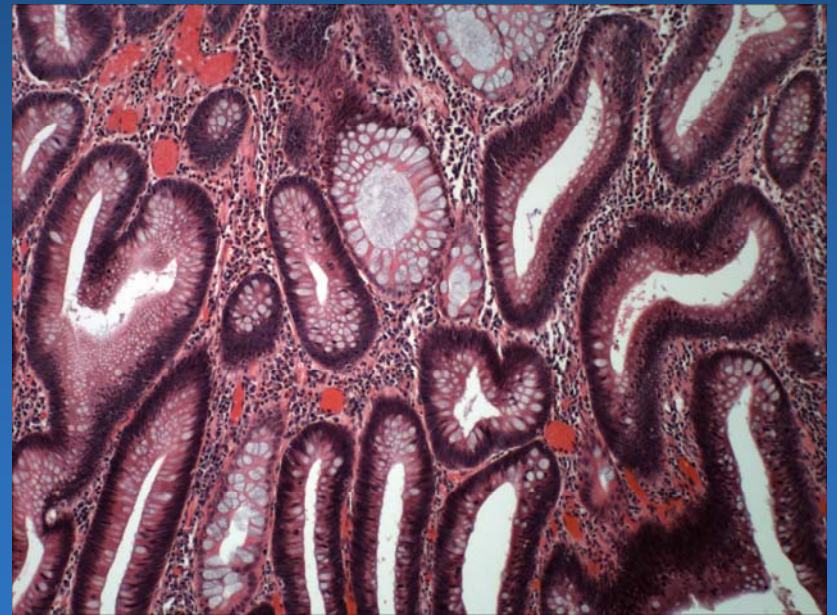
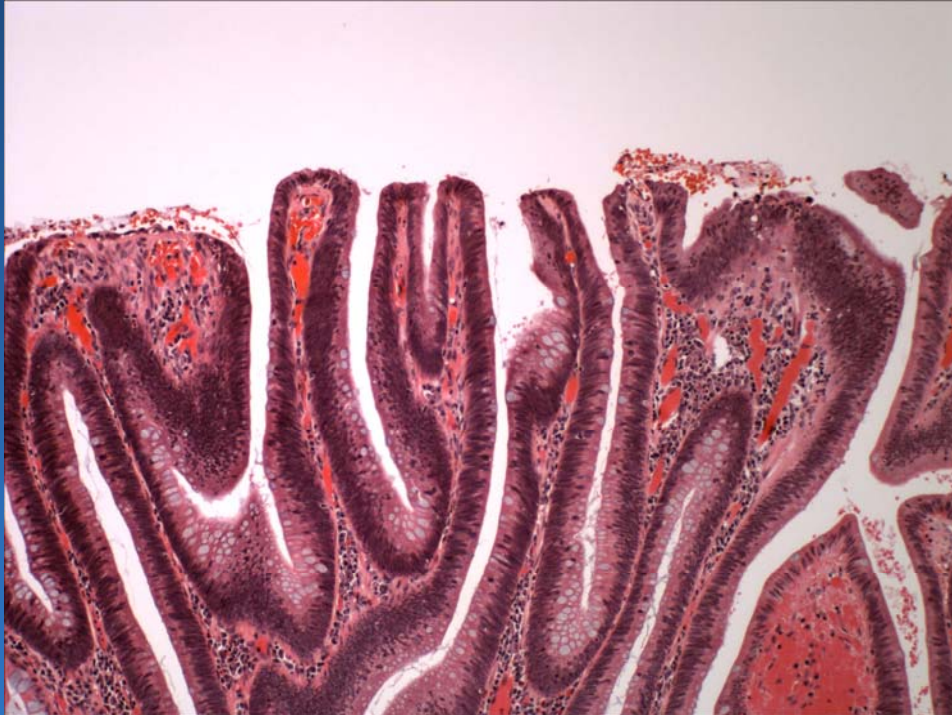
Classification of Adenomas

- Adenomas are divided into three types based on their glandular architecture
 - Tubular (most common)
 - Villous (least common)
 - Tubulovillous
- The above three types are histological variants of the same neoplastic process

Adenoma



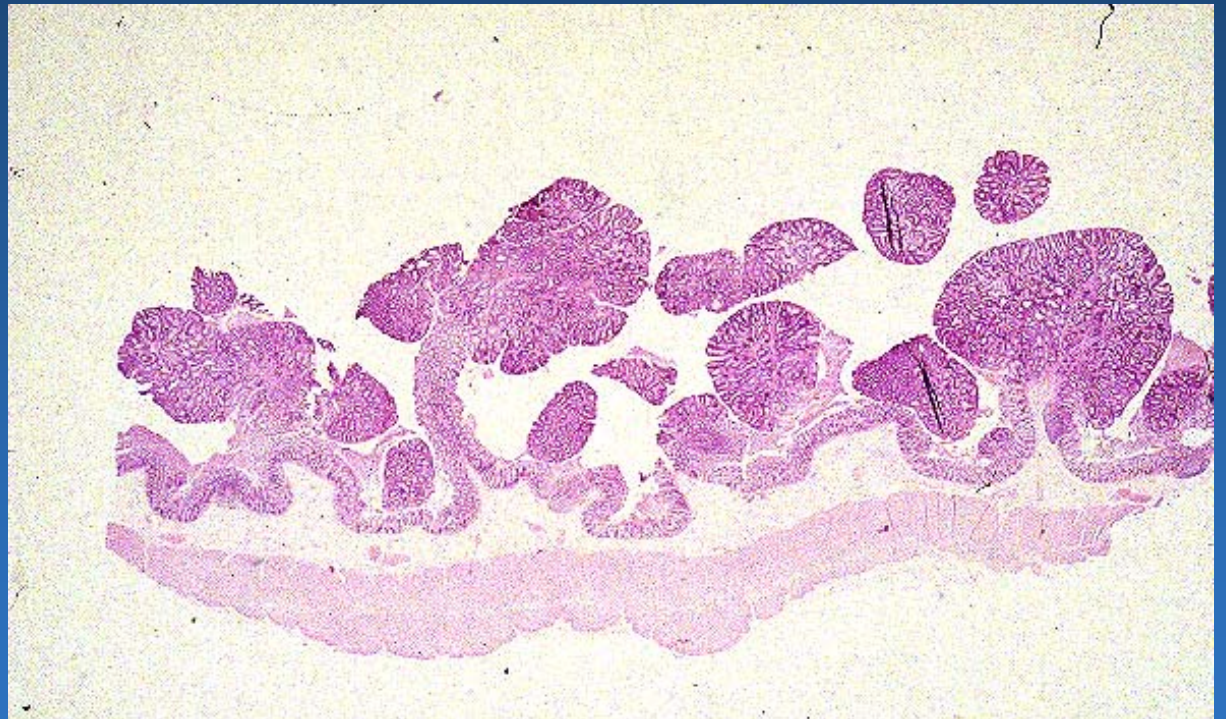
Colorectal adenoma



Familial Adenomatous Polyposis

- **AD disease characterized by progressive development of hundreds of adenomatous polyps (primarily colonic)**
- **Incidence of 1 in 10,000 live births**
- **Inherited in 80% of cases**
- **Associated with 100% risk of ACA**
- **Associated with mutations of APC gene (5q21)**

Familial adenomatous polyposis



APC Genotype-FAP Phenotype Associations

- Mutations in exons 3, 4, and distal 15 are associated with **Attenuated FAP** (also known as **Flat Adenoma Syndrome**)
- Mutations in codons 1309/1328 of exon 15 are associated with an early aggressive FAP
- Mutations in distal portion of exon 15 are weakly associated with **Gardner's Syndrome** (FAP + desmoids + osteomas + other)
- Mutations between exons 9 and 15 are associated with CHRPE

The APC Gene

- APC is a basolateral membrane protein that functions as a tumor suppressor protein presumably through interactions with β -catenin (a cytoskeletal protein that can exert a suppressive effect on cellular proliferation through the Wnt signaling pathway)
- Numerous mutations of the APC gene have been described in FAP; Somatic APC mutations are critical in sporadic colorectal carcinogenesis

APC Gene in Colorectal Carcinogenesis

Normal Epithelium



APC gene (5q loss or mutation)

Proliferative Epithelium



Methylation Abnormalities

Early Adenoma



k-Ras gene (12p mutation)

Intermediate Adenoma



DCC/SMAD (18q loss)

Late Adenoma



p53 gene (17p loss)

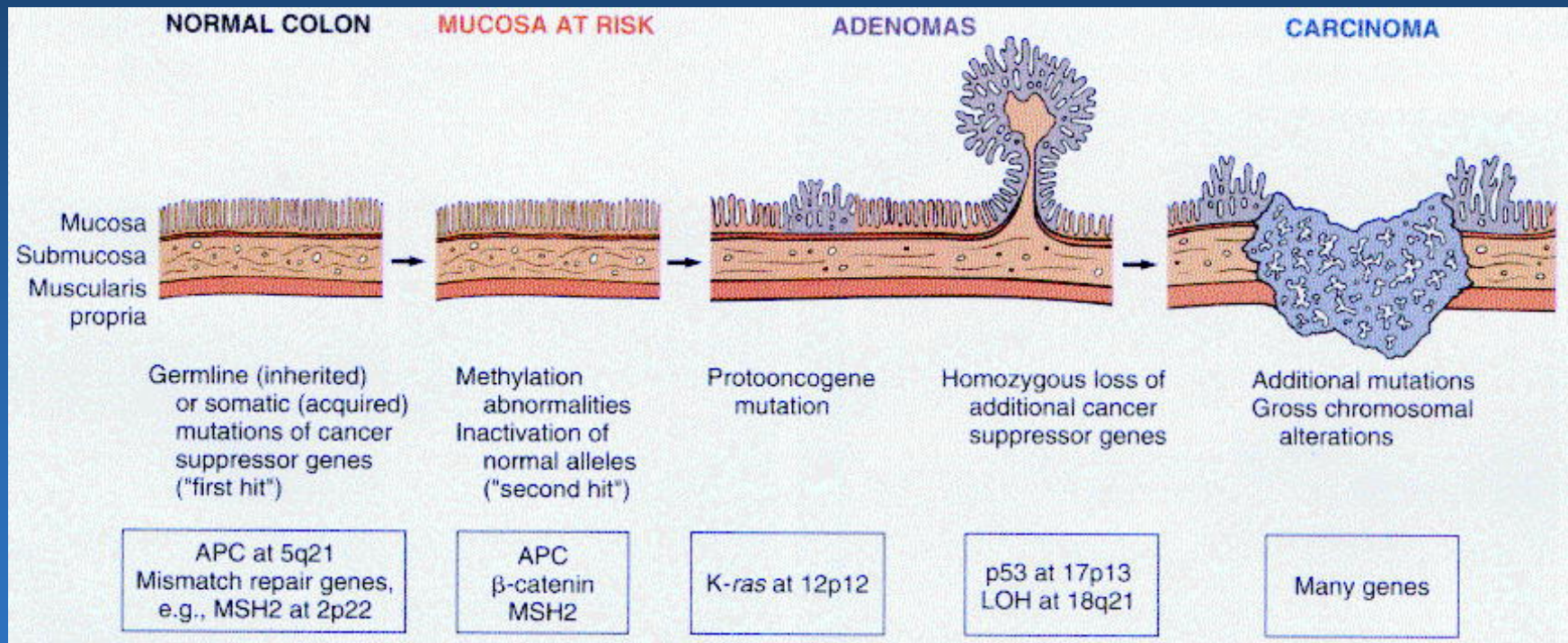
Invasive Carcinoma



Other mutations

Metastases

Colorectal carcinoma- progression

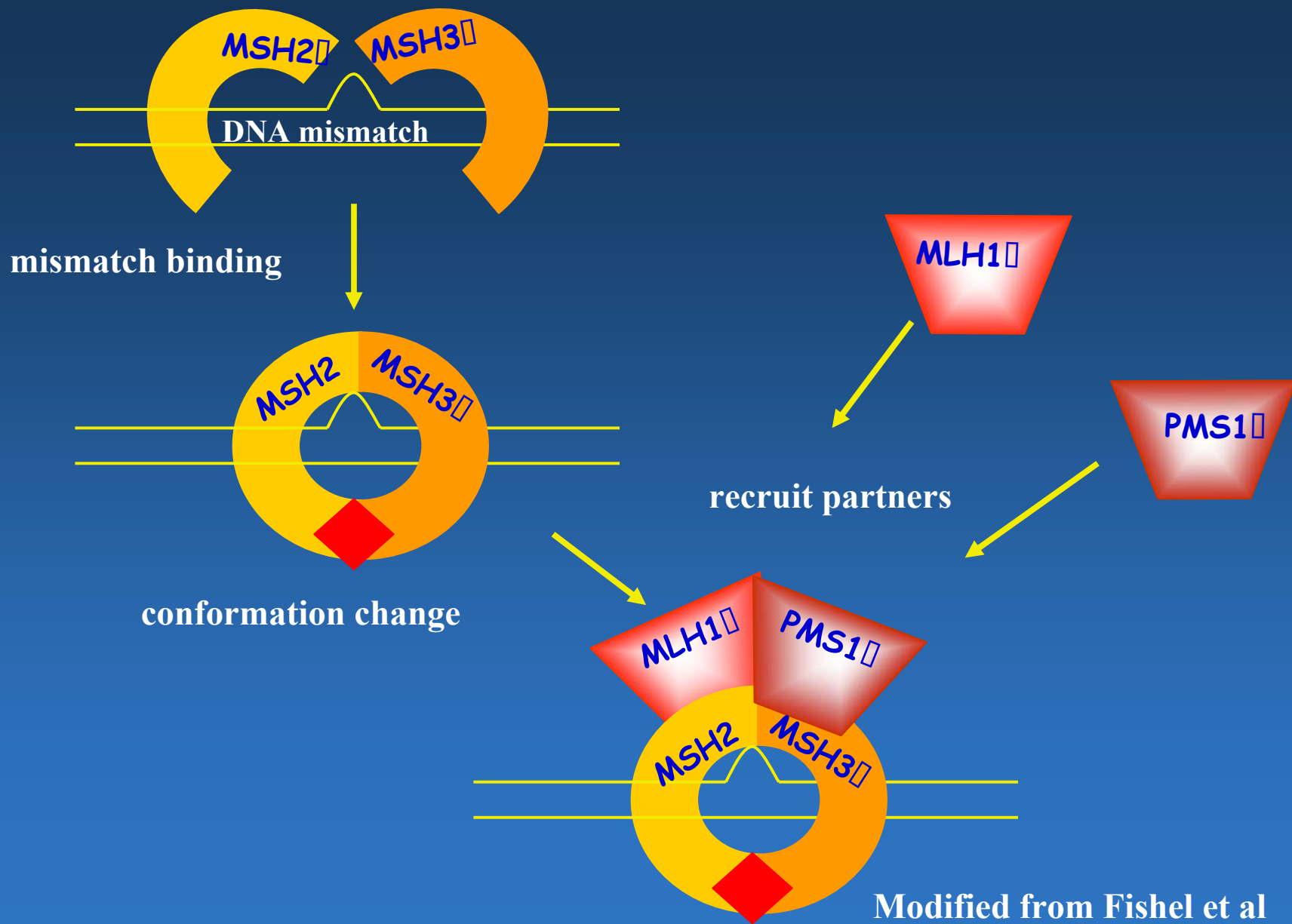


Genomic Instability in CRC

- **Chromosomal instability** (majority of CRCs): Allelic losses, translocations, and other gross chromosomal abnormalities in key regulatory proteins
- **Microsatellite instability** (minority of CRCs): Increased intragenic mutations due to instability of short tandemly repeated DNA sequences (microsatellites)

Microsatellite Instability (MSI)

- Nucleotide mismatches that “normally” occur when DNA polymerase inserts the wrong base in the newly synthesized DNA are typically repaired by mismatch repair enzymes
- Defects in the process of mismatch repair lead to MSI (instability in >40% of loci)
- Mutations in DNA mismatch repair (MMR) genes (primarily MSH2 & MLH1) are found in sporadic CRCs with MSI and in families with HNPCC



Modified from Fishel et al
Cancer Research 61:7369;2001

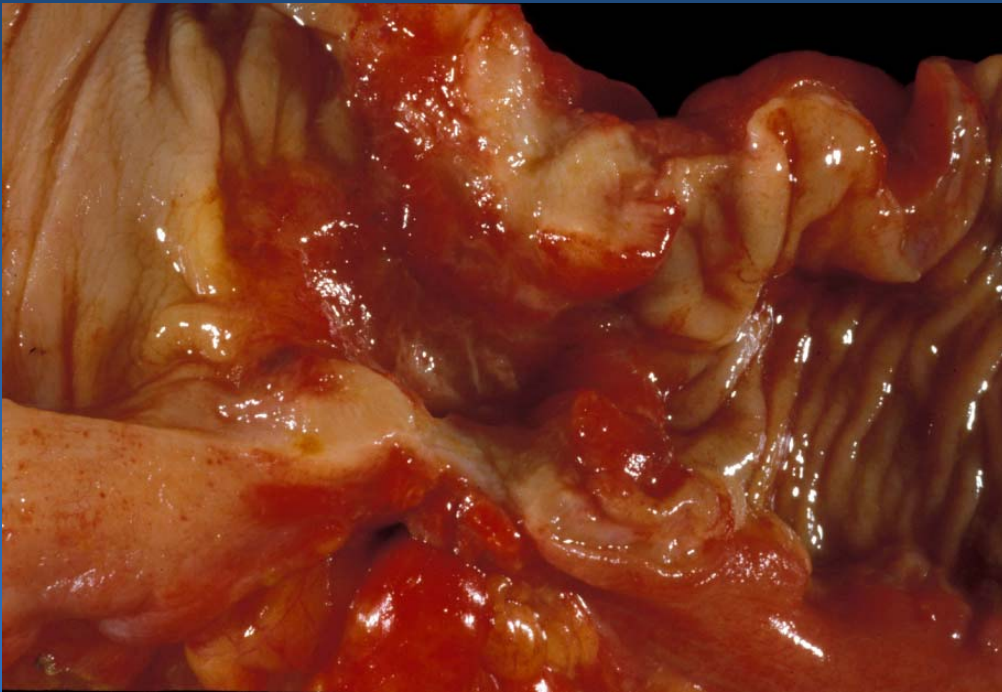
Hereditary Non-Polyposis Colorectal Cancer

<p>Original International Collaborative Group criteria (the Amsterdam Criteria)</p>	<ol style="list-style-type: none"> 1. Three relatives with colorectal cancer (CRC), one a first-degree relative of the other two 2. CRC involving at least 2 generations 3. ≥ 1 CRC diagnosed before the age of 50y
<p>Modified Amsterdam Criteria</p>	<ul style="list-style-type: none"> • In very small families: <ol style="list-style-type: none"> 1. Two CRC's in first-degree relatives 2. CRC involving at least 2 generations 3. ≥ 1 CRC diagnosed before the age of 50y • In families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusually early onset of CRC or endometrial cancer
<p>NCI Workshop (Bethesda Guidelines)</p>	<ul style="list-style-type: none"> • Cancer in families that fulfill Amsterdam criteria • Two HNPCC-related cancers • CRC or endometrial cancer before the age of 45 • CRC and a first-degree relative with CRC and/or HNPCC-related cancer and/or colorectal adenoma; one of the cancers before the age of 45 and adenoma before the age of 40 • Right-sided CRC with "undifferentiated" histology before the age of 45 • Signet-ring-cell-type CRC before the age of 45 • Adenomas before the age of 40

Colorectal Adenocarcinoma (CRC)

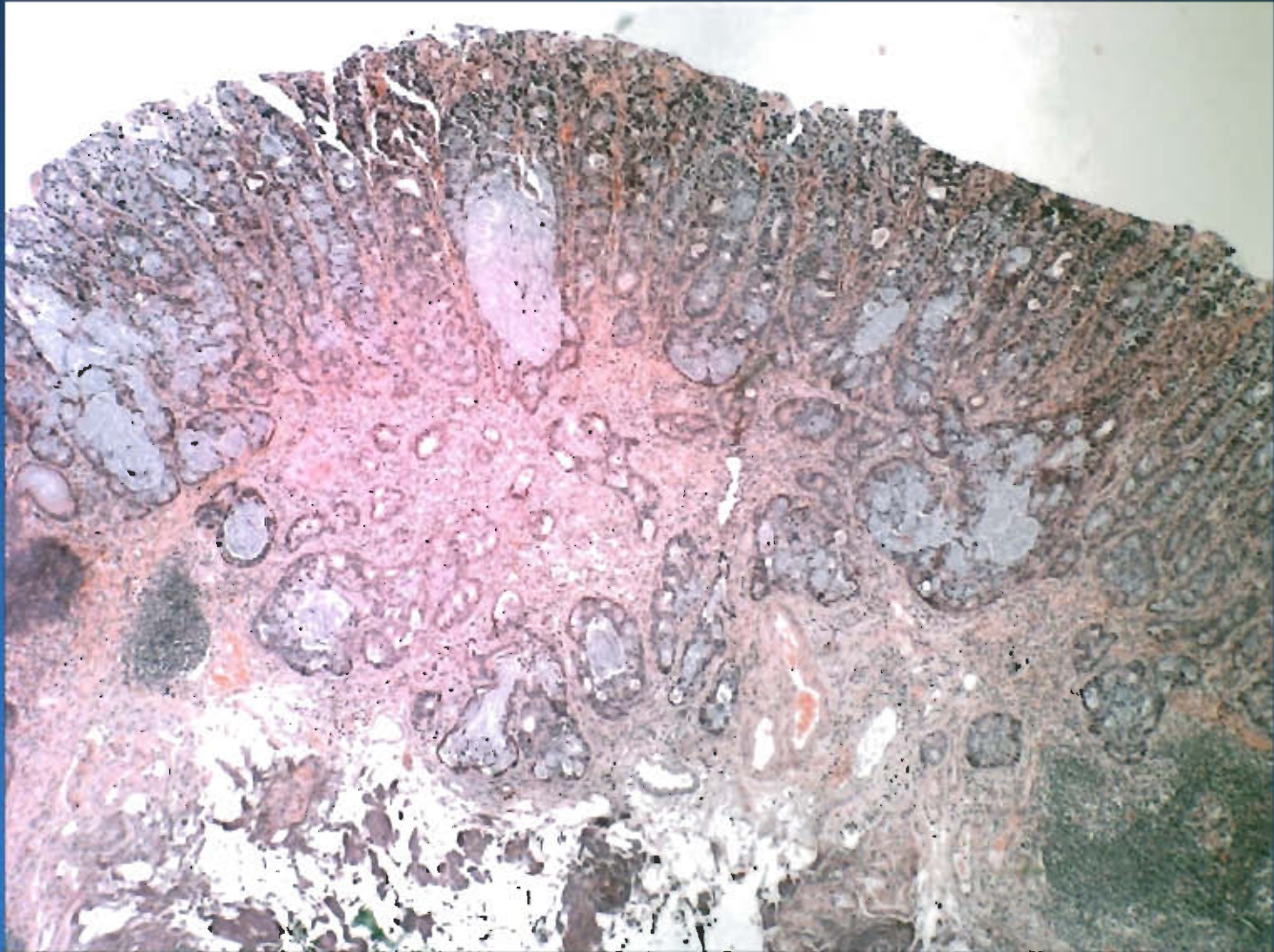
- In 1999, CRC was the third most common carcinoma and the third leading cause of cancer deaths in the US
- Greater than 130,000 new cases per year
- Rare before the age of 40
- M:F ratio of 1 (but ~2 for rectal cancers)
- Risk factors: ? environmental, ? diet
- Five-year survival ~65% in 1994

Colorectal carcinoma- gross

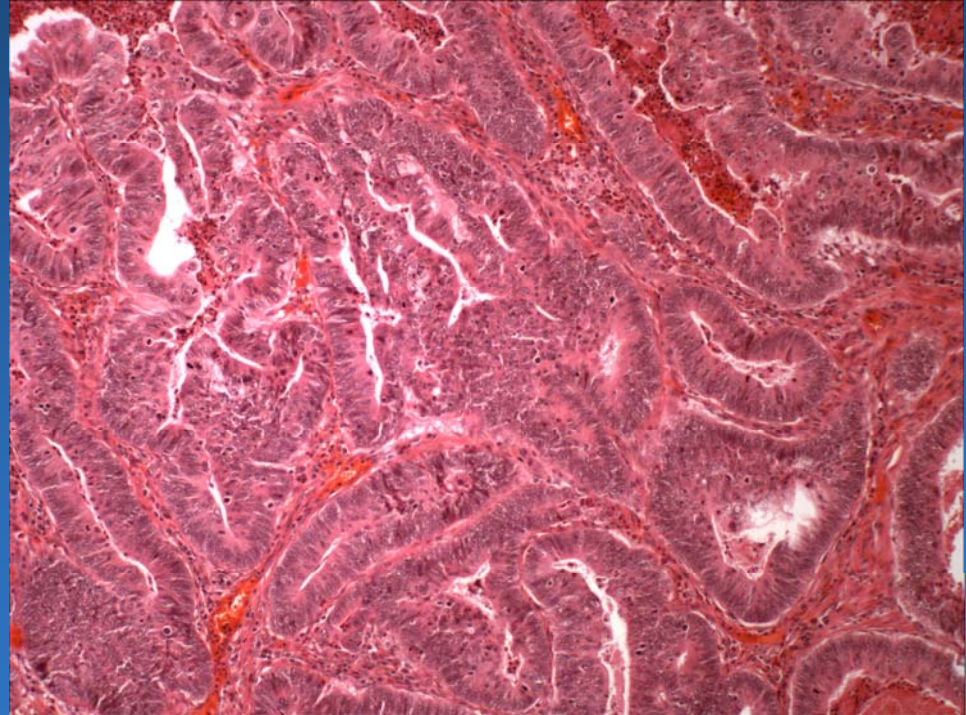
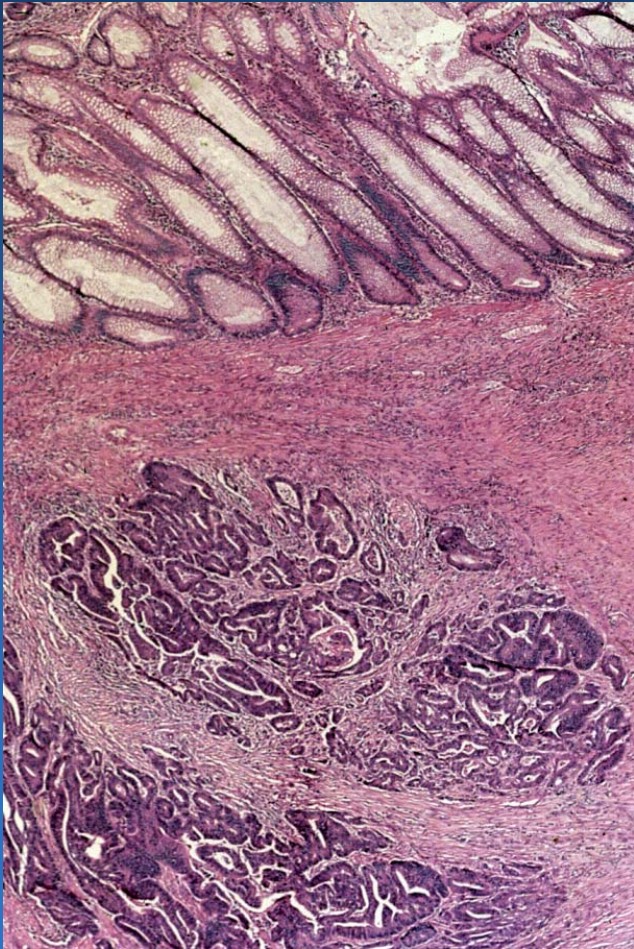


Pathology of CRC

- Most CRCs are in the rectosigmoid
- Left-sided tumors tend to produce “**napkin-ring**” lesions and present with obstruction
- Right-sided tumors tend to be large and centrally necrotic polypoid masses
- Most tumors are gland-forming and well- to moderately-differentiated; ~10% are **mucinous**
- Survival generally related to **depth of invasion, nodal status, and metastases**



Colorectal adenocarcinoma



Gastric adenocarcinoma

- **Worldwide variation in incidence (e.g. high in Japan)**
- **Incidence falling in U.S. over last 50 years**
- **Most common 50-70 years, M>F**
- **Causative factors:**
 - **dietary carcinogens**
 - **familial**
 - **chronic inflammatory conditions**
- **Aggressive tumors with poor prognosis (15% 5 year survival)**

Genetic Progression in Gastric Neoplasia

- 5q21 deletion/APC inactivation
- 17p13 deletion/p53 mutation
- MLH1 methylation

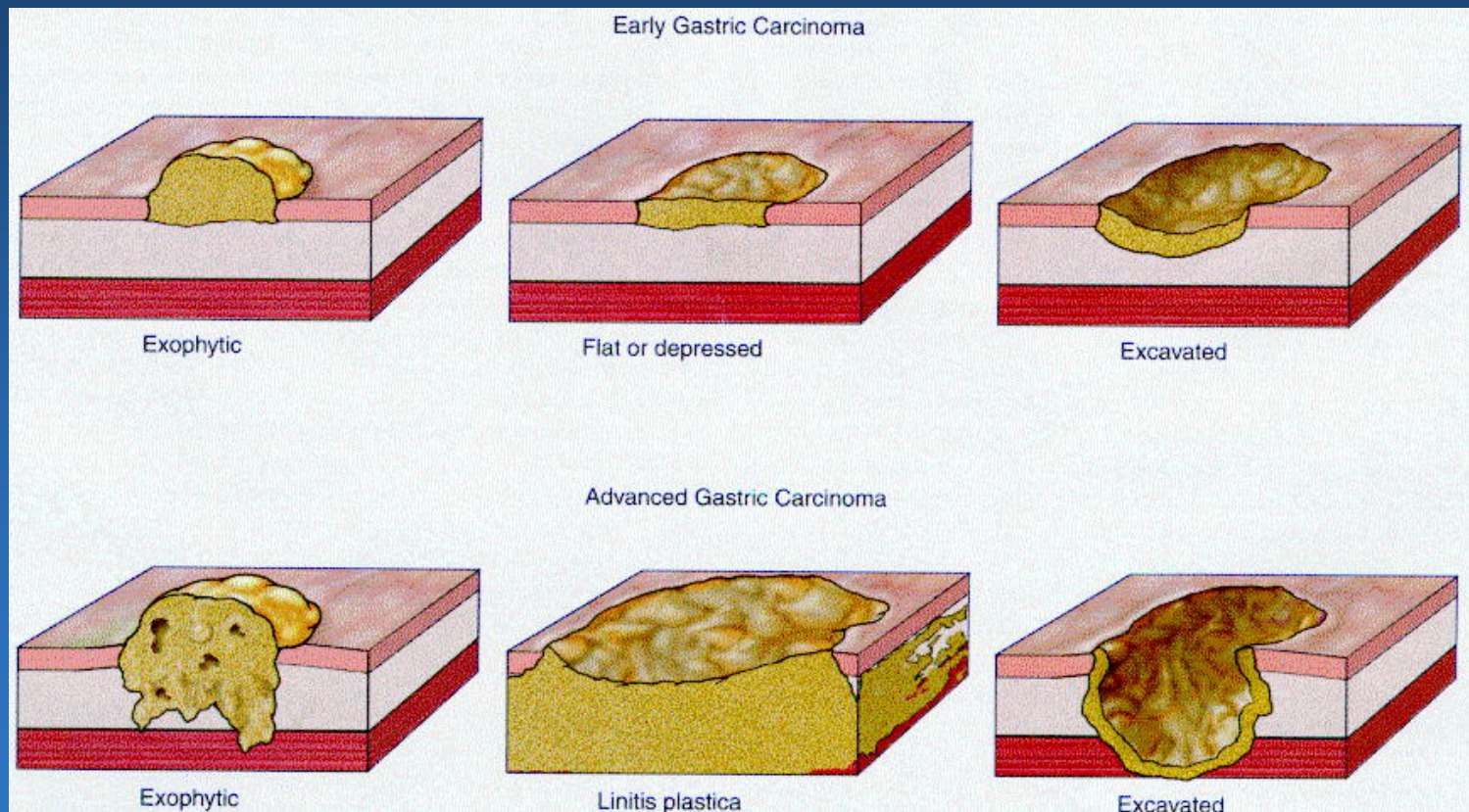
- C-met/HGF amplification/
overexpression
- 9p21 deletion/p16 inactivation
- 19q12 amplification/Cyclin E
overexpression
- 18q deletion
- 16q22 deletion/E-cadherin loss
- chromosomal deletions (1p, 1q,
7q, 13q)



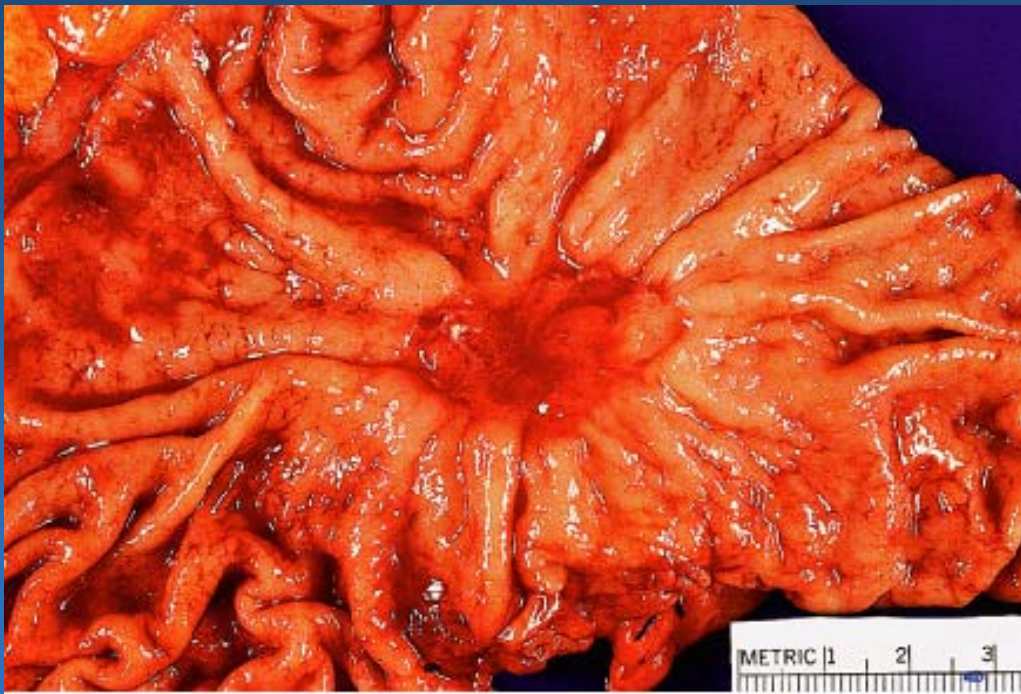
Gastric carcinoma- pathology

- **Location:** antrum (70%)>lesser curvature, cardia (25%)>diffuse (5%)
- **Gross configuration:** polypoid, ulcerating, or infiltrating
- **Intestinal type:** gland formation, associated with intestinal metaplasia, dysplasia
- **Diffuse type:** signet ring cells, arises directly from surface foveolar cells, not associated with environmental factors

Gastric carcinoma



Intestinal-type gastric carcinoma- gross

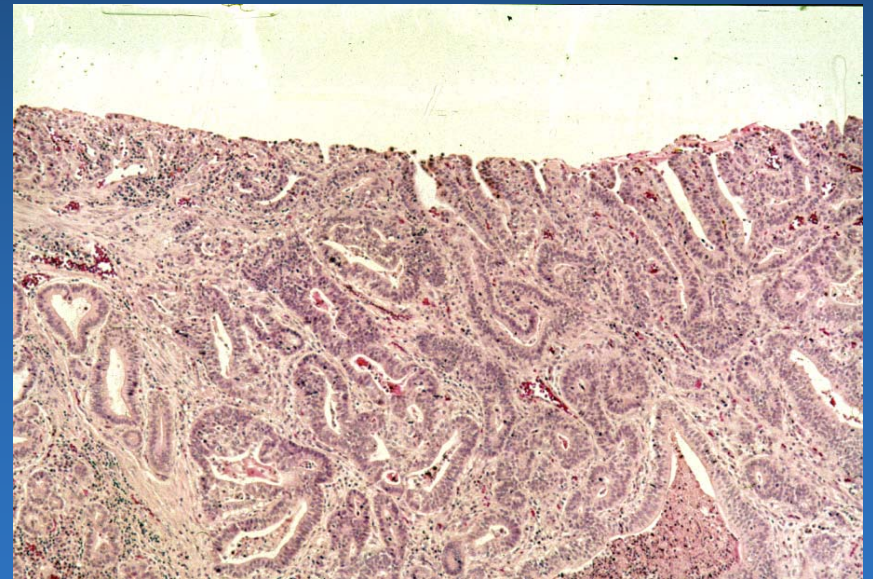


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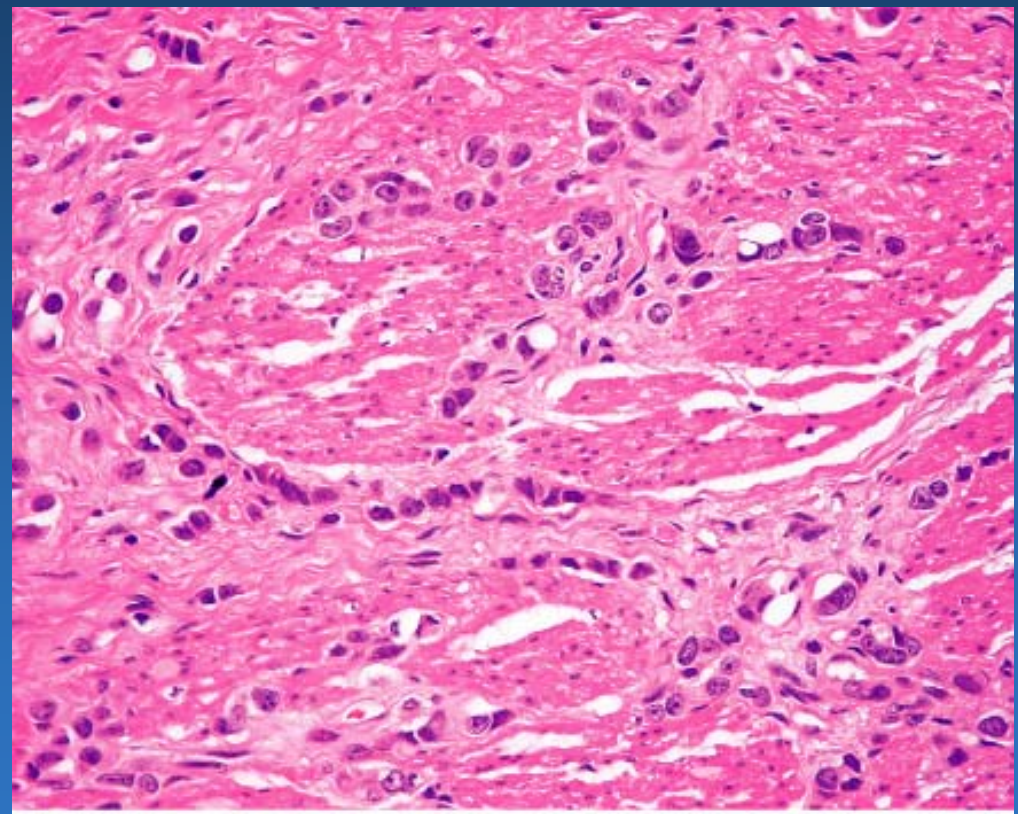
Gastric carcinoma



Diffuse type gastric carcinoma



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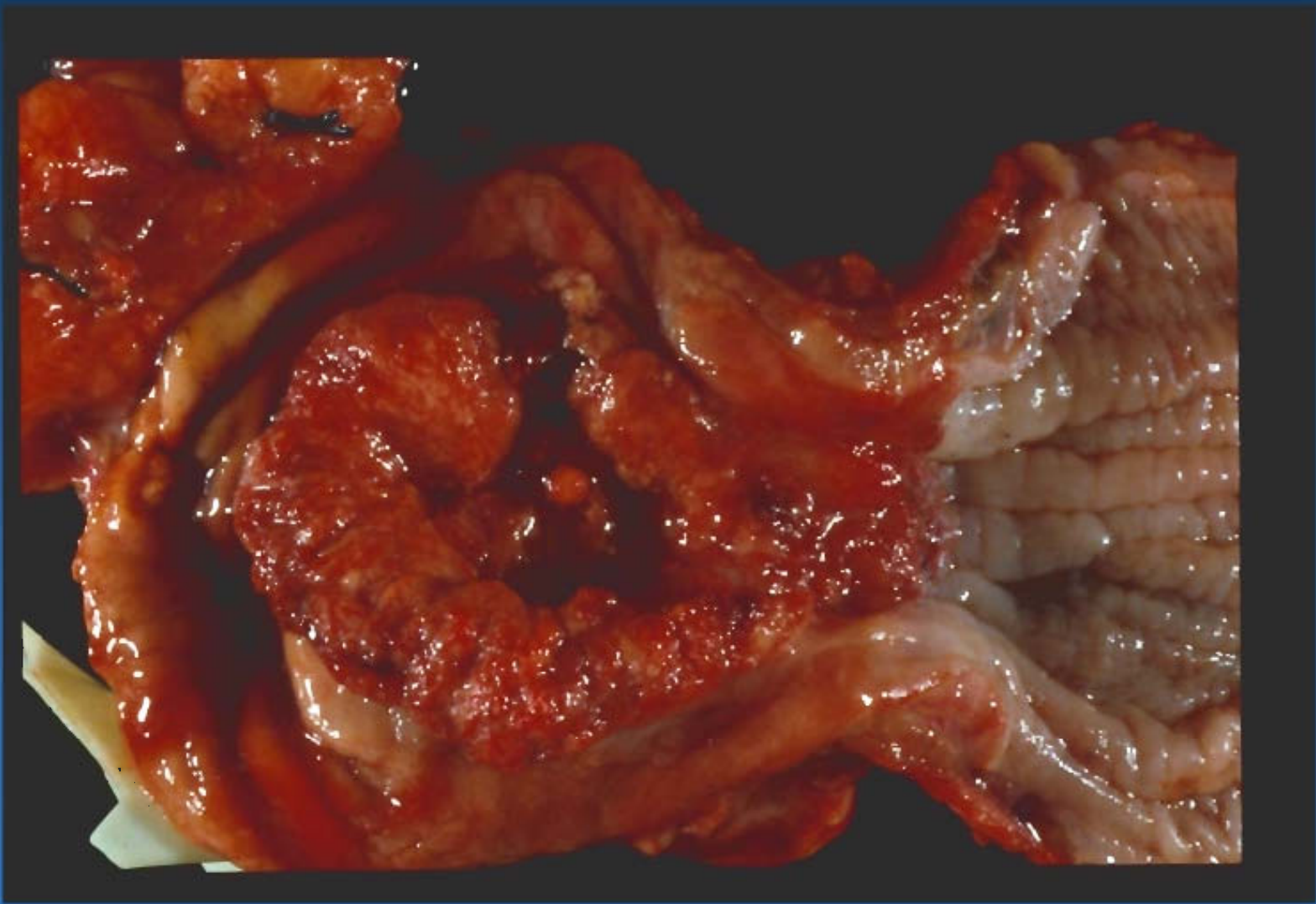
Esophageal carcinomas

- Two major types
 - Squamous cell carcinoma
 - Adenocarcinoma
- Squamous cell carcinoma more common worldwide
- Incidence of adenocarcinomas rising in U.S., Western Europe, now accounts for 50% of esophageal malignancies in those regions

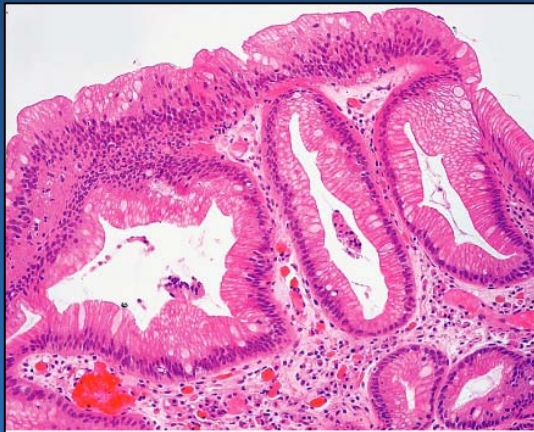
Esophageal adenocarcinoma

- **Peak age 60-70 years, M>>F**
- **Symptoms: dysphagia, weight loss**
- **Arises in setting of Barrett's esophagus (columnar metaplasia with goblet cells) in distal esophagus**
- **Proceeds through dysplasia-carcinoma sequence**
- **Microscopically similar to adenocarcinomas elsewhere in GI tract**
- **Aggressive tumors; key to survival is early detection**



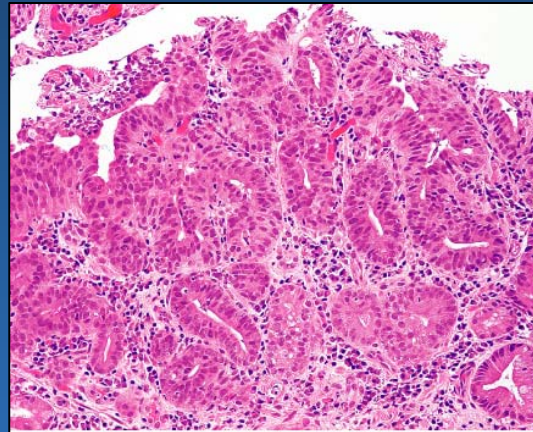


Esophageal adenocarcinoma- precursors



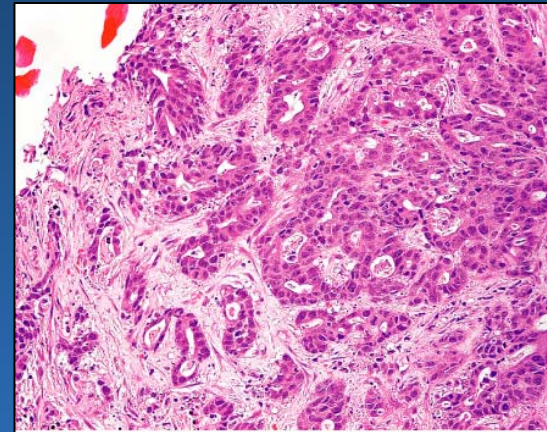
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Barrett's esophagus



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Dysplasia



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Adenocarcinoma

Esophageal squamous cell carcinoma

- Incidence highest in Africa, Iran, China
- Peak age: 55-65 years, M>F
- Causative factors
 - Alcohol, tobacco
 - Corrosive esophagitis
 - Achalasia
 - ?HPV
- Symptoms: dysphagia, weight loss
- Aggressive tumors (10% 5 year survival)

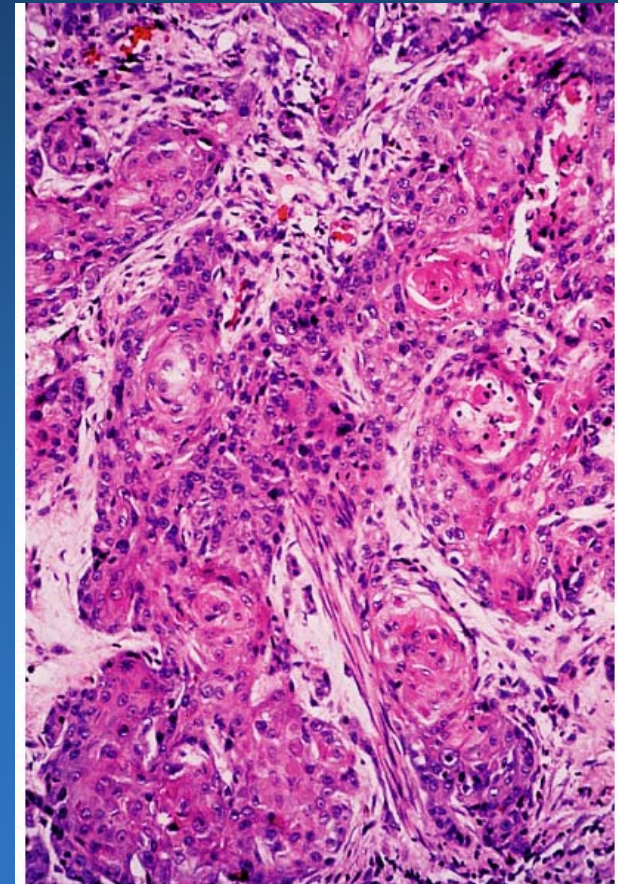
Esophageal squamous cell carcinoma



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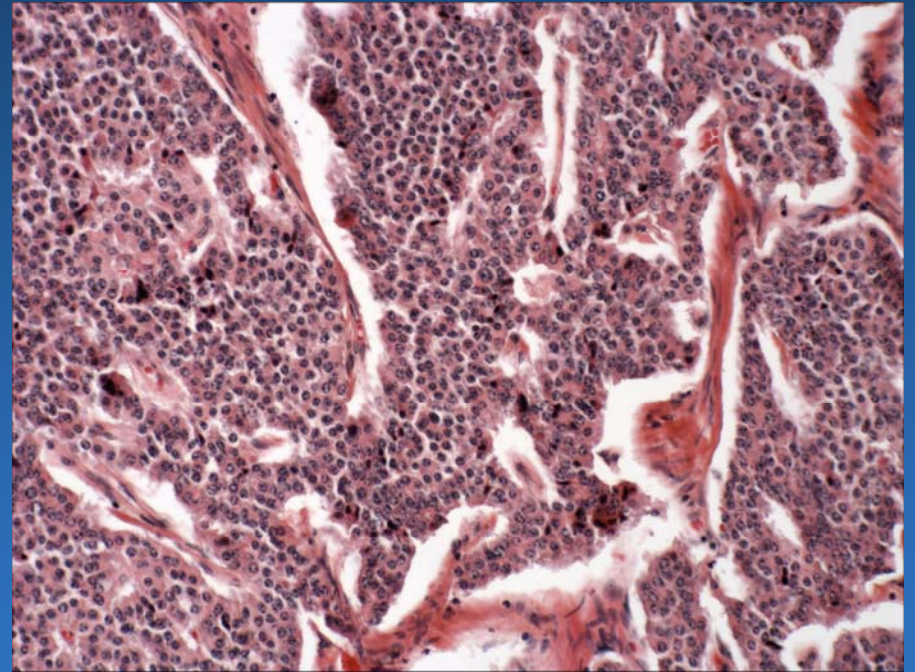
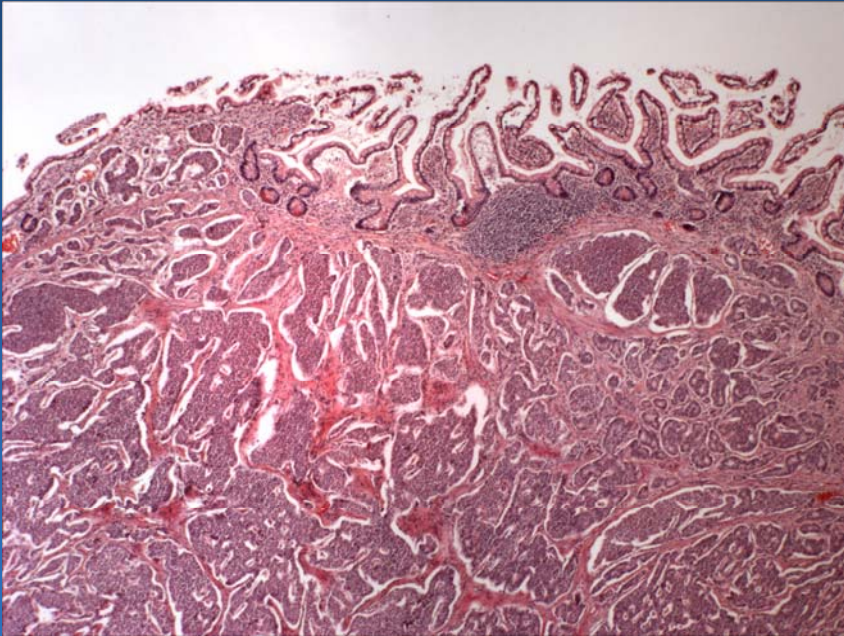


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Neuroendocrine (carcinoid) tumors

- Arise from neuroendocrine cells of gastrointestinal mucosa and its derivatives (e.g. lung, pancreas)
- Variable clinical behavior but often slow-growing
- Appendix most common site (35%) followed by ileum (20%)
- Pathology: uniform cells with round nuclei, “salt and pepper” chromatin
- Extra-appendiceal carcinoids frequently invade wall, metastasize

Carcinoid tumor



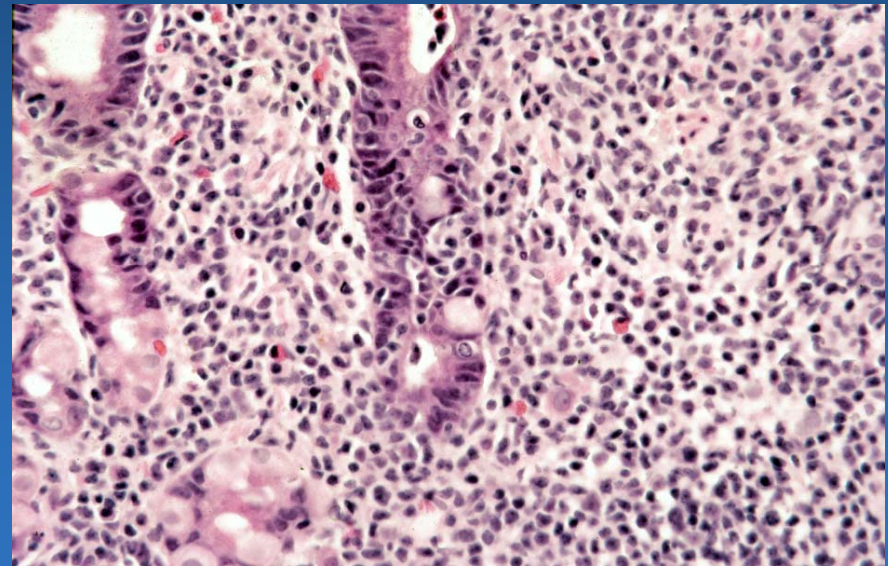
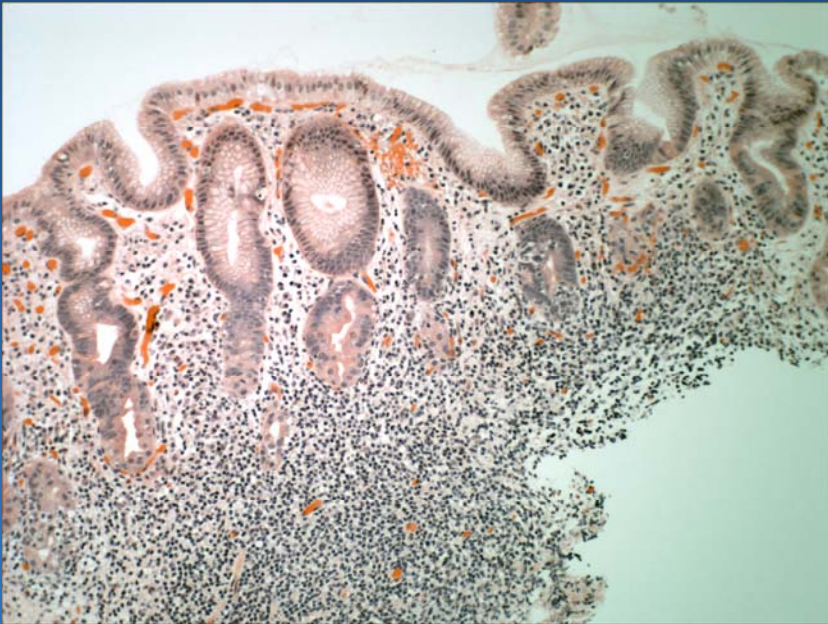
Carcinoid syndrome

- **Only develops in patients with liver metastases**
- **Tumors elaborate serotonin, plus histamine, others**
- **Flushing, diarrhea, bronchoconstriction, valvular changes in right heart**
- **Treatment: removal or ablation of metastasis or antagonism/suppression of circulating serotonin**

GI tract lymphomas

- Nearly all non-Hodgkin's lymphomas (NHL)
- GI tract involved in 70% of patients with NHL
- Stomach most common site, followed by intestine and colon
- Nearly all B cell type, except for enteropathy associated T cell lymphoma (a/w celiac disease)
- **MALT lymphoma:** gastric lymphomas develop in setting of H. pylori infection (potentially treatable by H. pylori eradication)

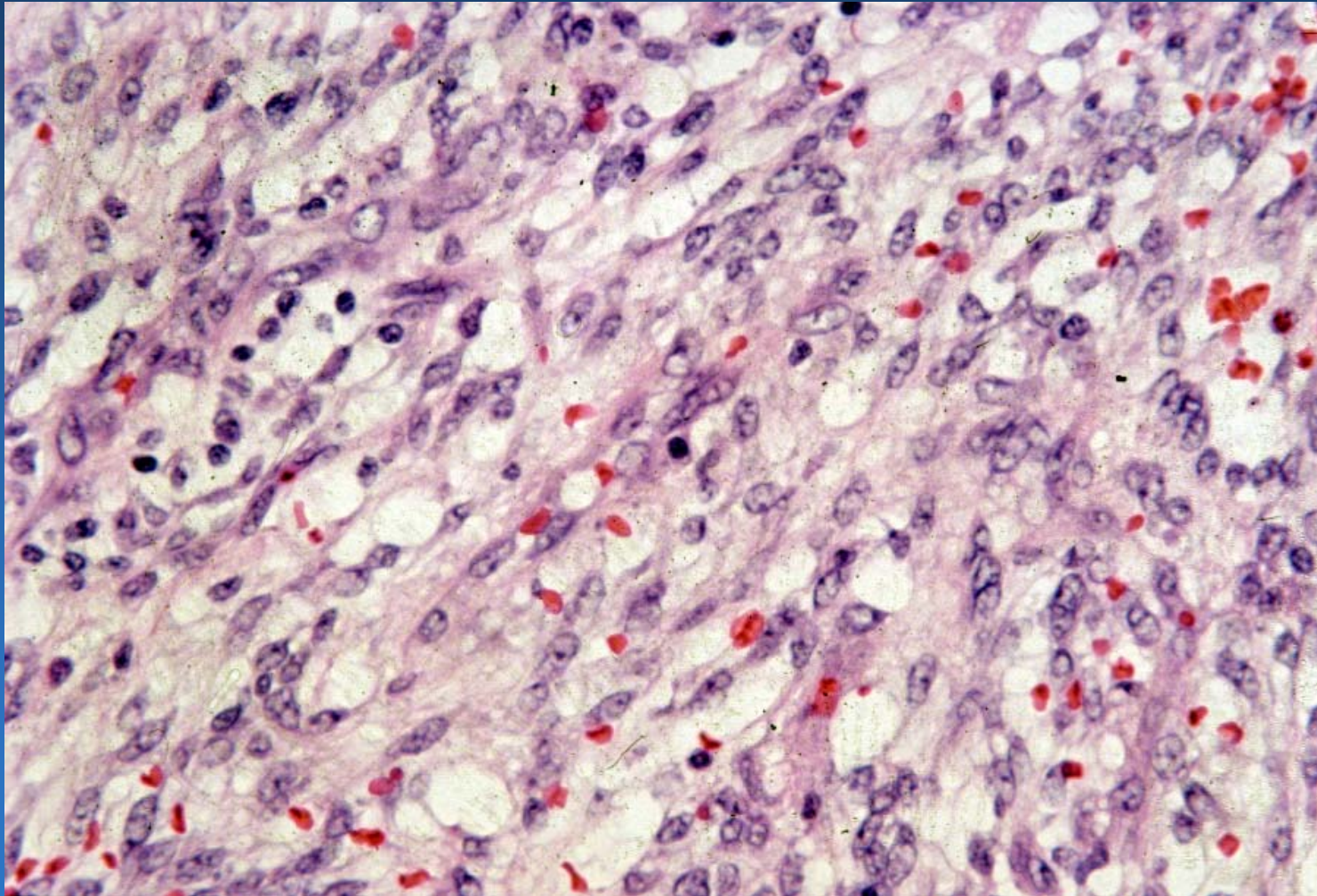
Gastric MALT lymphoma



Gastrointestinal stromal tumors (GISTs)

- Spindle cell neoplasms arising from interstitial cells of Cajal (pacemaker cells)
- Most associated with activating mutations in c-kit tyrosine kinase; sensitive to treatment with inhibitor (Gleevec)
- Variable aggressiveness
- Prognostic factors: size, location, histologic grade
- Distinguish leiomyomas (true neoplasms of smooth muscle)

GI stromal tumor



Other tumors

- **Adenocarcinoma of small intestine, appendix**
- **Anal squamous cell carcinoma**
- **Mesotheliomas of peritoneum**
- **Melanoma (rectum, anus, esophagus)**
- **Lipoma (colon, stomach)**
- **Kaposi's sarcoma**

