

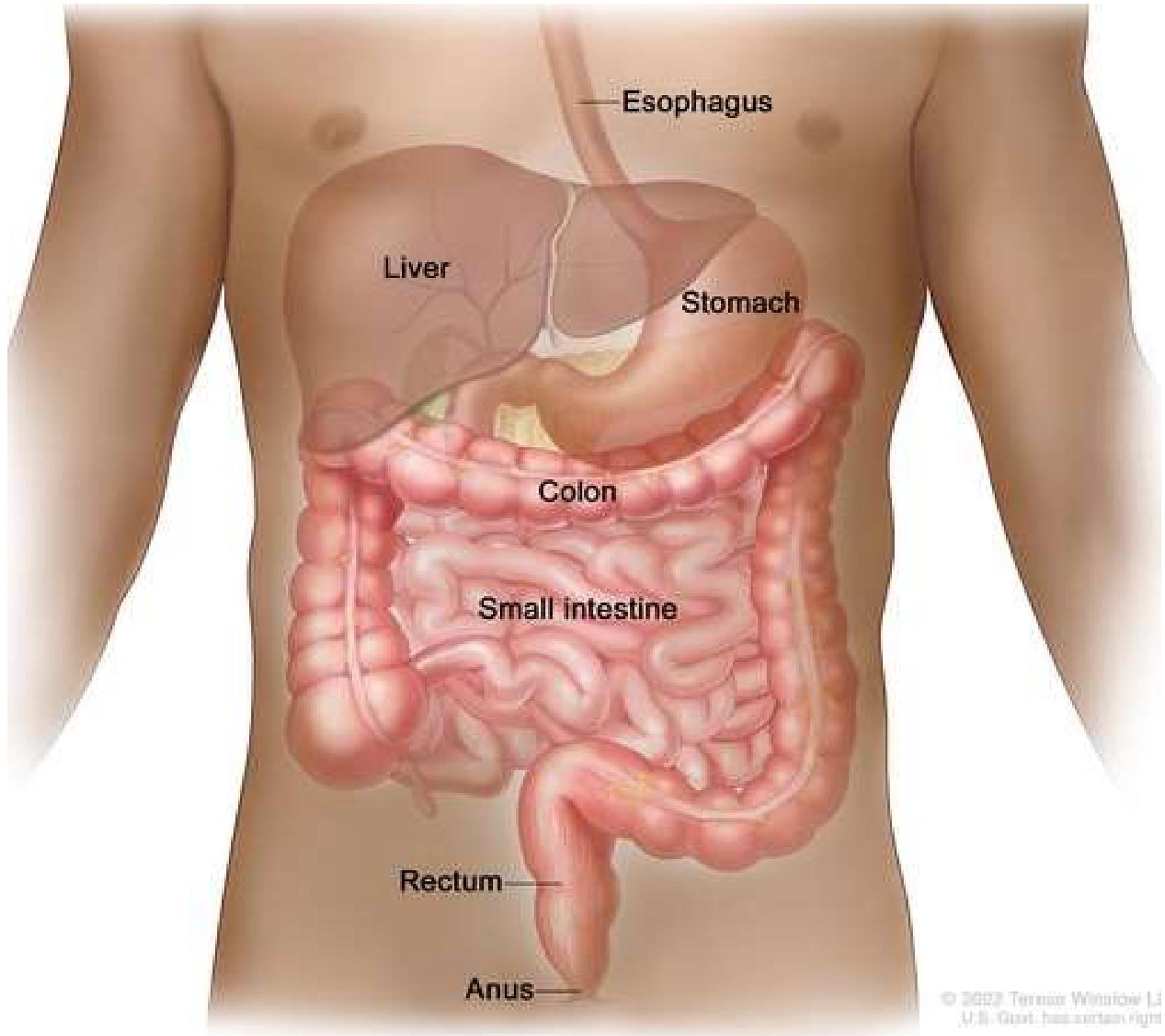
Colorectal Cancer

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Tumors of the Colon

Neoplastic

A. Benign (potential precursor to carcinoma)
adenomas (tubular, villous, tubulovillous)

B. Malignant = adenocarcinoma

Avoid use of the generic term “polyp” – it is vague and can cause confusion.

Colon Cancer Epidemiology

What Causes Colon Cancer

Sporadic – “Western” diet (low fiber, high fat, high refined carbohydrates); peak incidence 70+ years of age

Inflammatory bowel disease (especially ulcerative colitis) – younger age of onset; related to severity of inflammation

Familial (hereditary) syndromes – Lynch Syndrome (HNPCC) and FAP; younger age of onset

FAP – Familial Adenomatous Polyposis

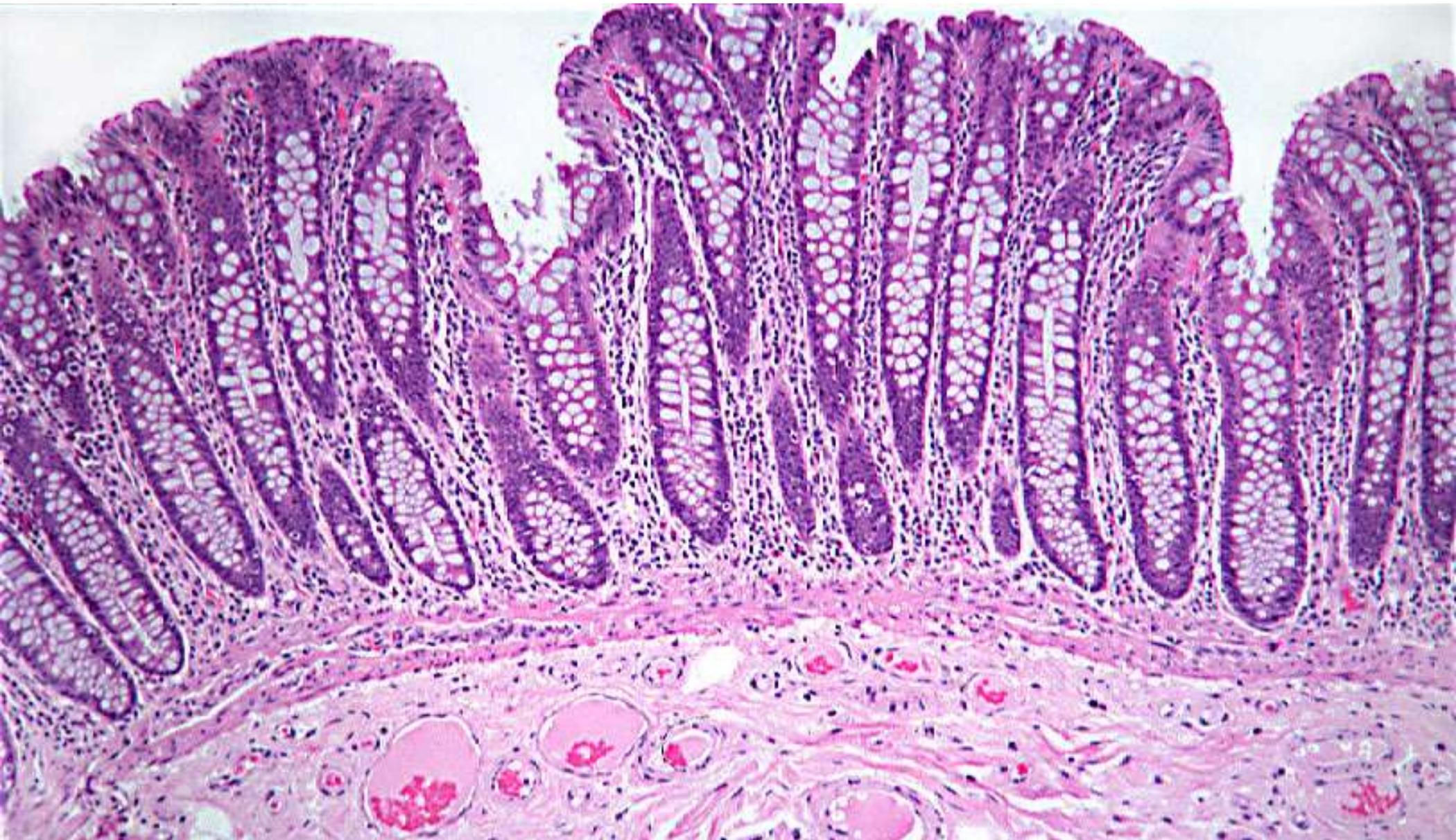
HNPCC – Hereditary Non-Polyposis Colorectal Cancer

Normal Colon with Small Adenoma

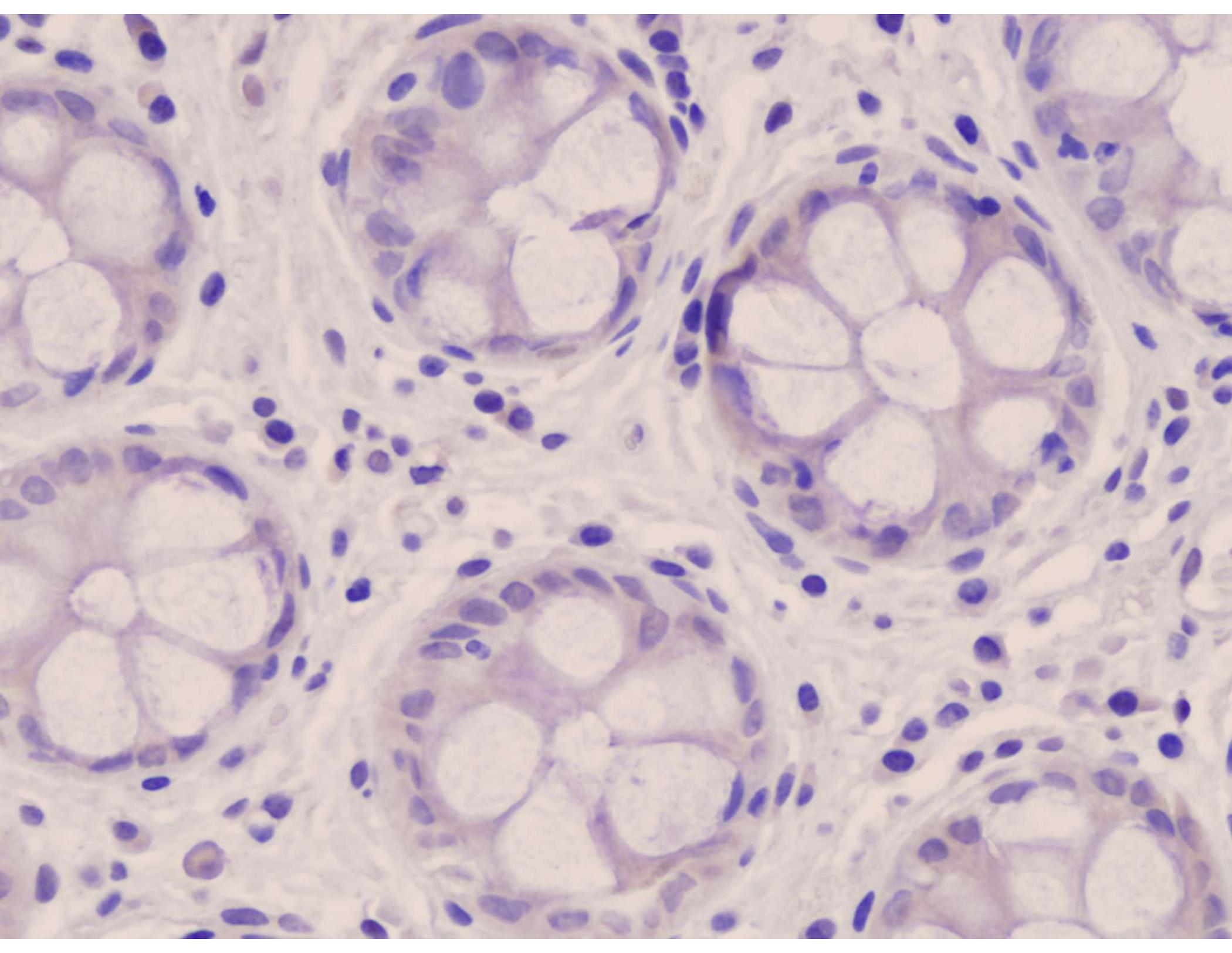




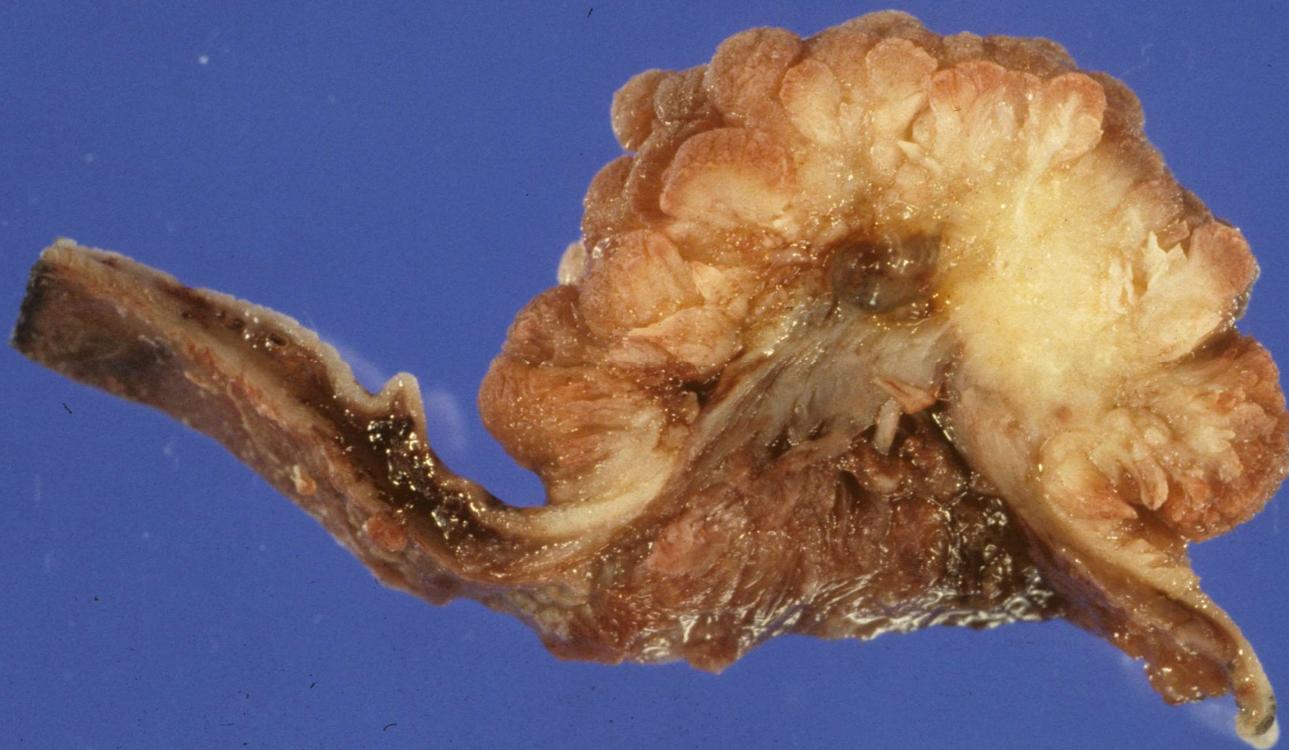
Normal Colon Histology



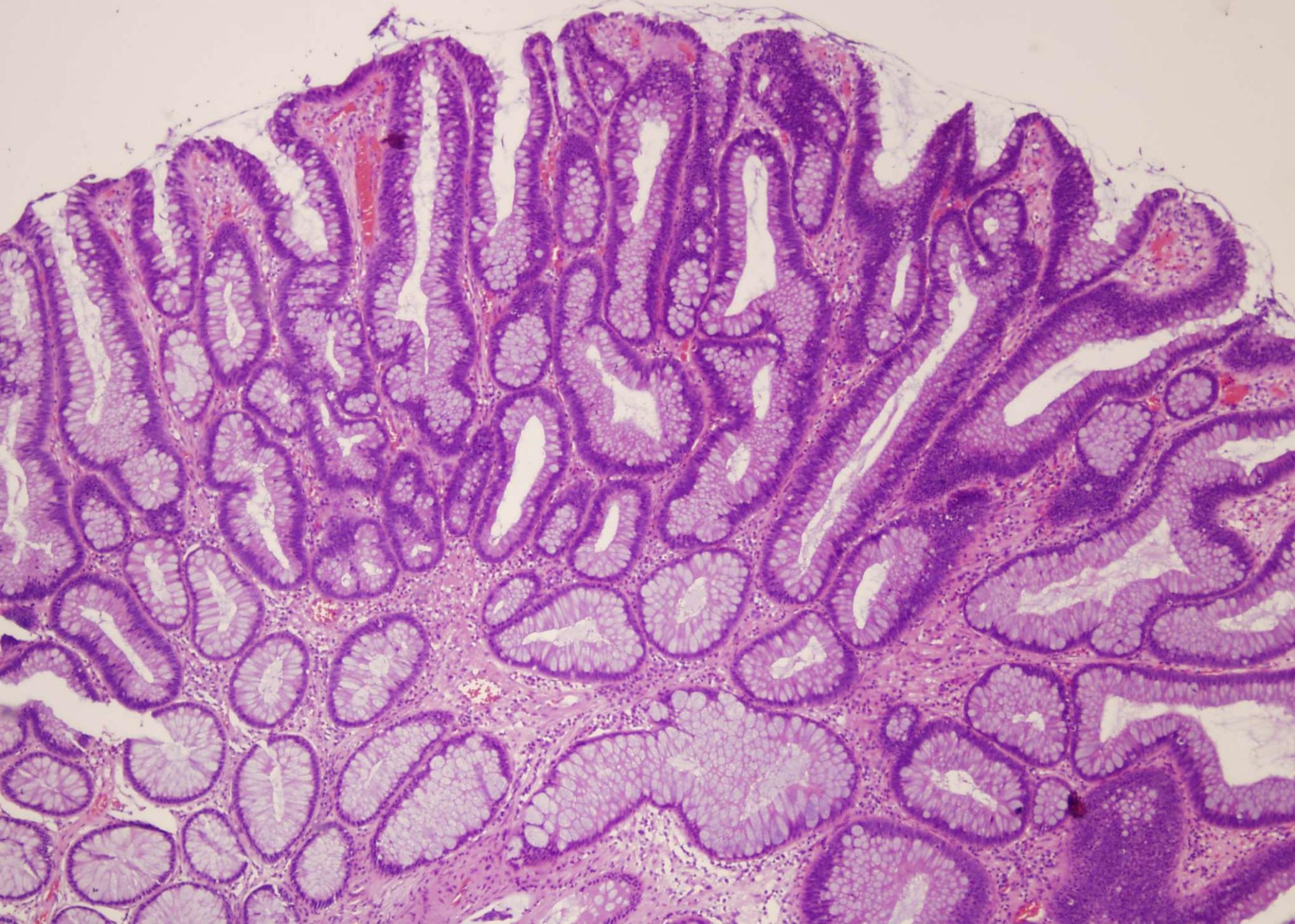




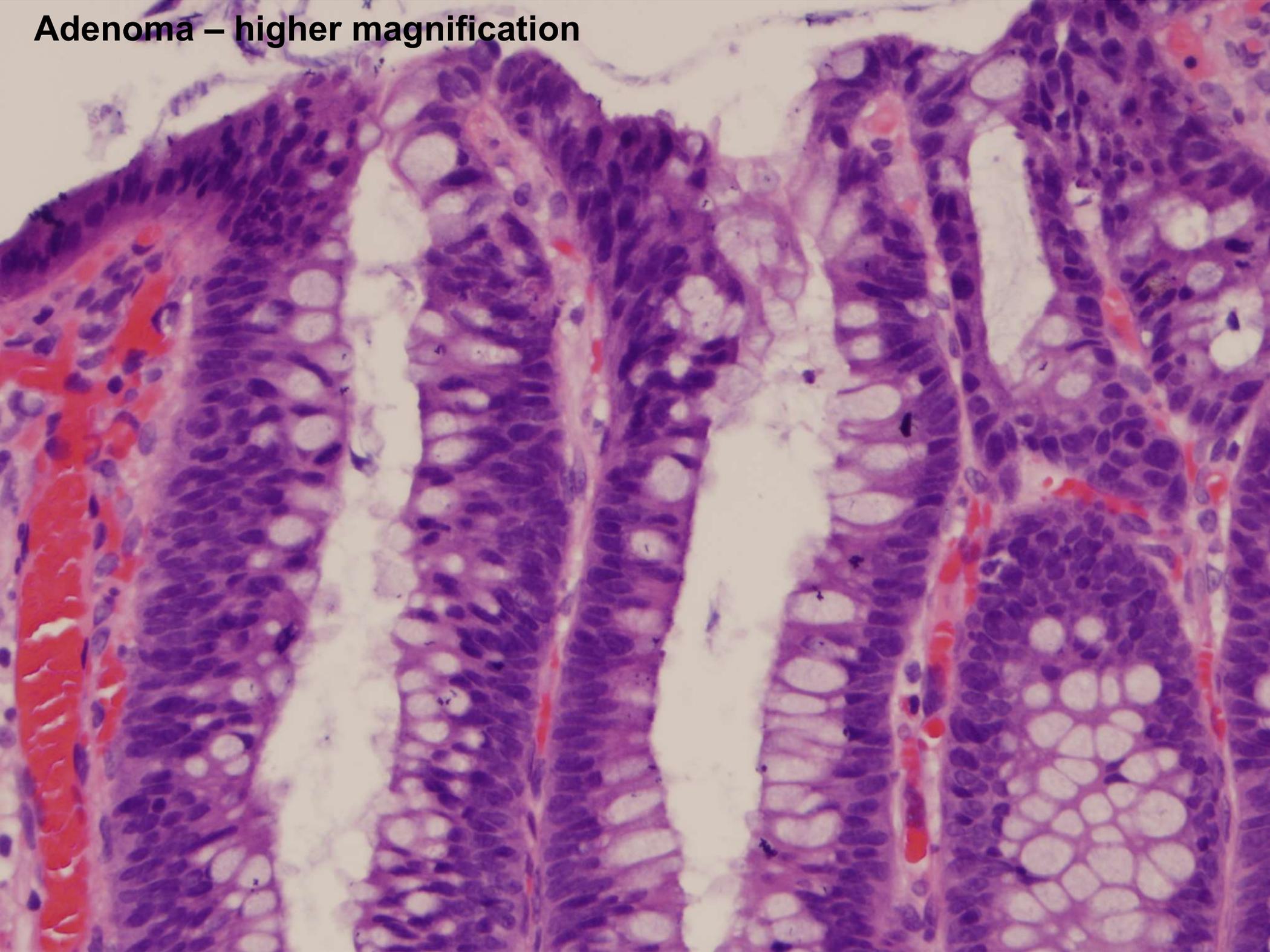
Colon - Adenoma

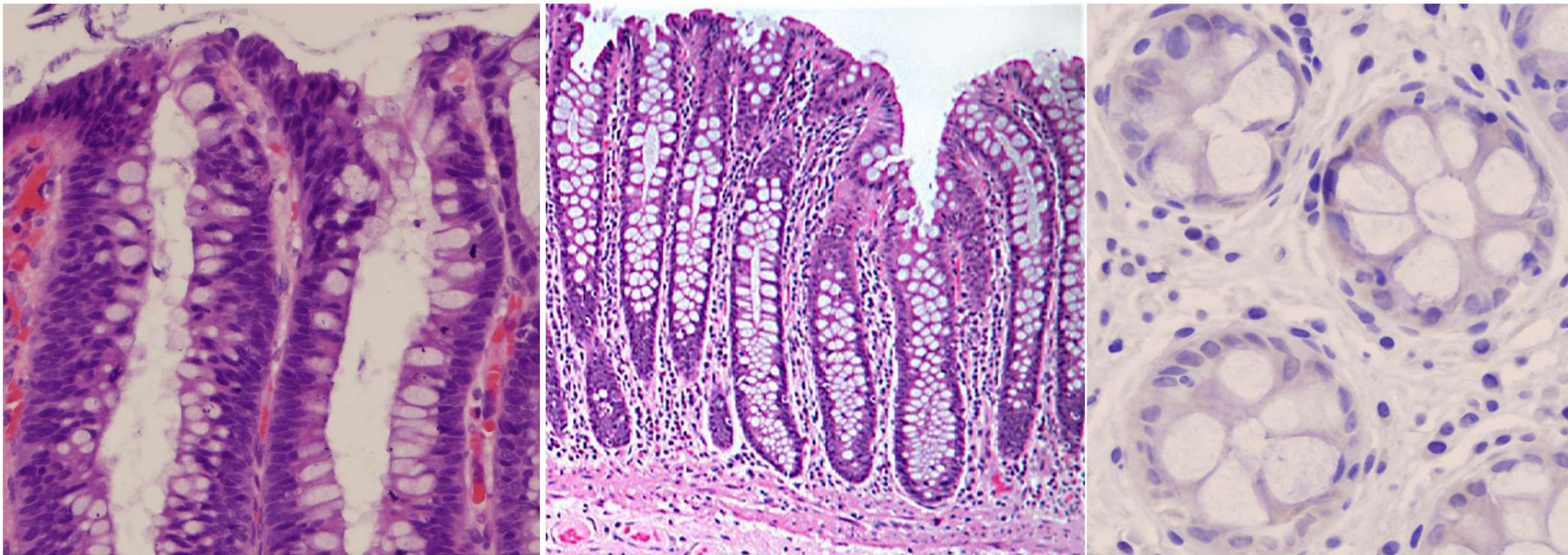


Tubular Adenoma



Adenoma – higher magnification

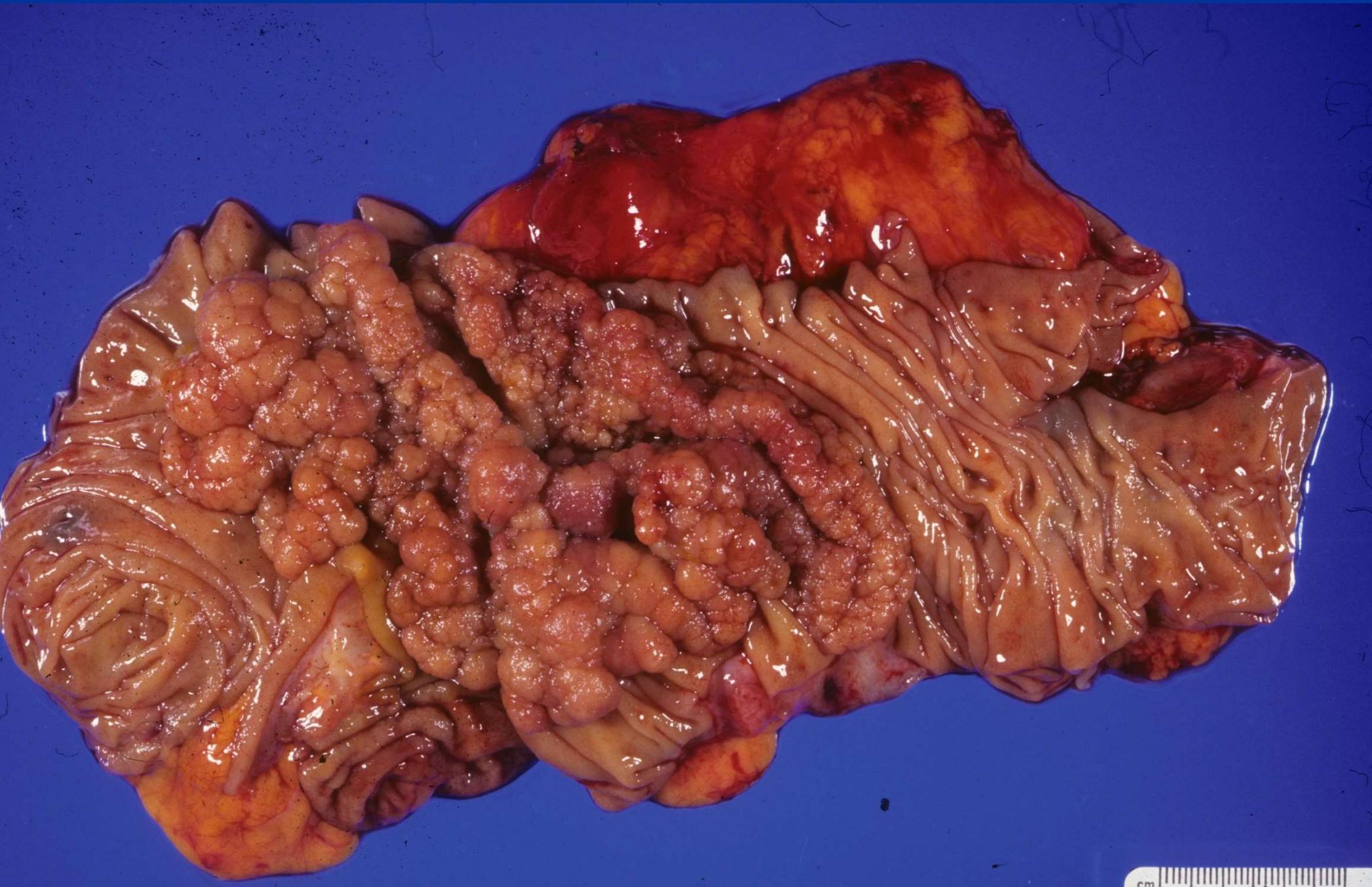


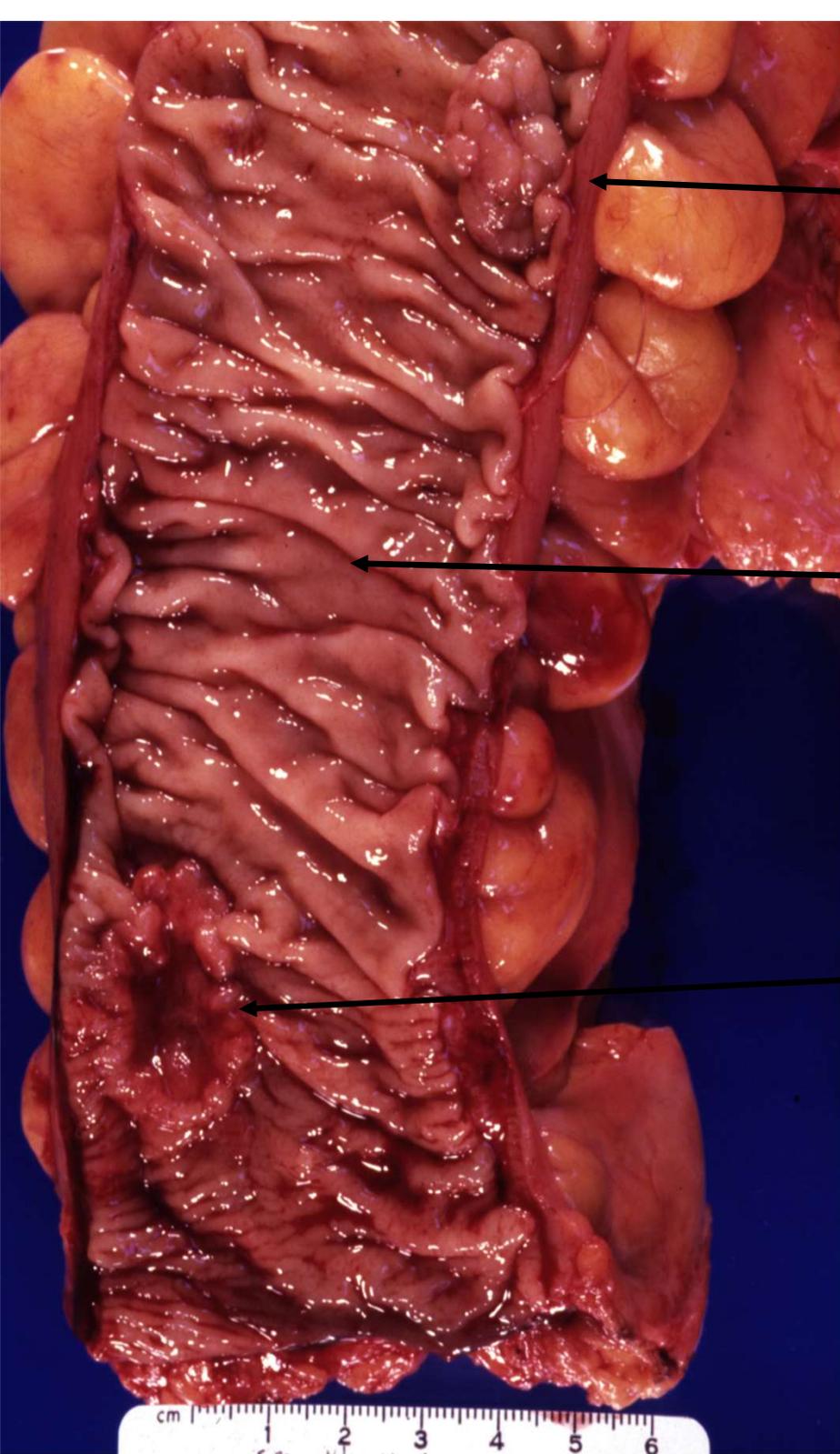


Compared to normal colon, adenomas...

1. Individual adenoma cells have higher nuclear:cytoplasmic ratio
2. Individual adenoma cells have less mucin or no mucin
3. Adenoma crypts have nuclear stratification
4. Adenoma crypts are elongated and may have branching because of increased proliferation and/or decreased apoptosis

Colon – Large Villous Adenoma



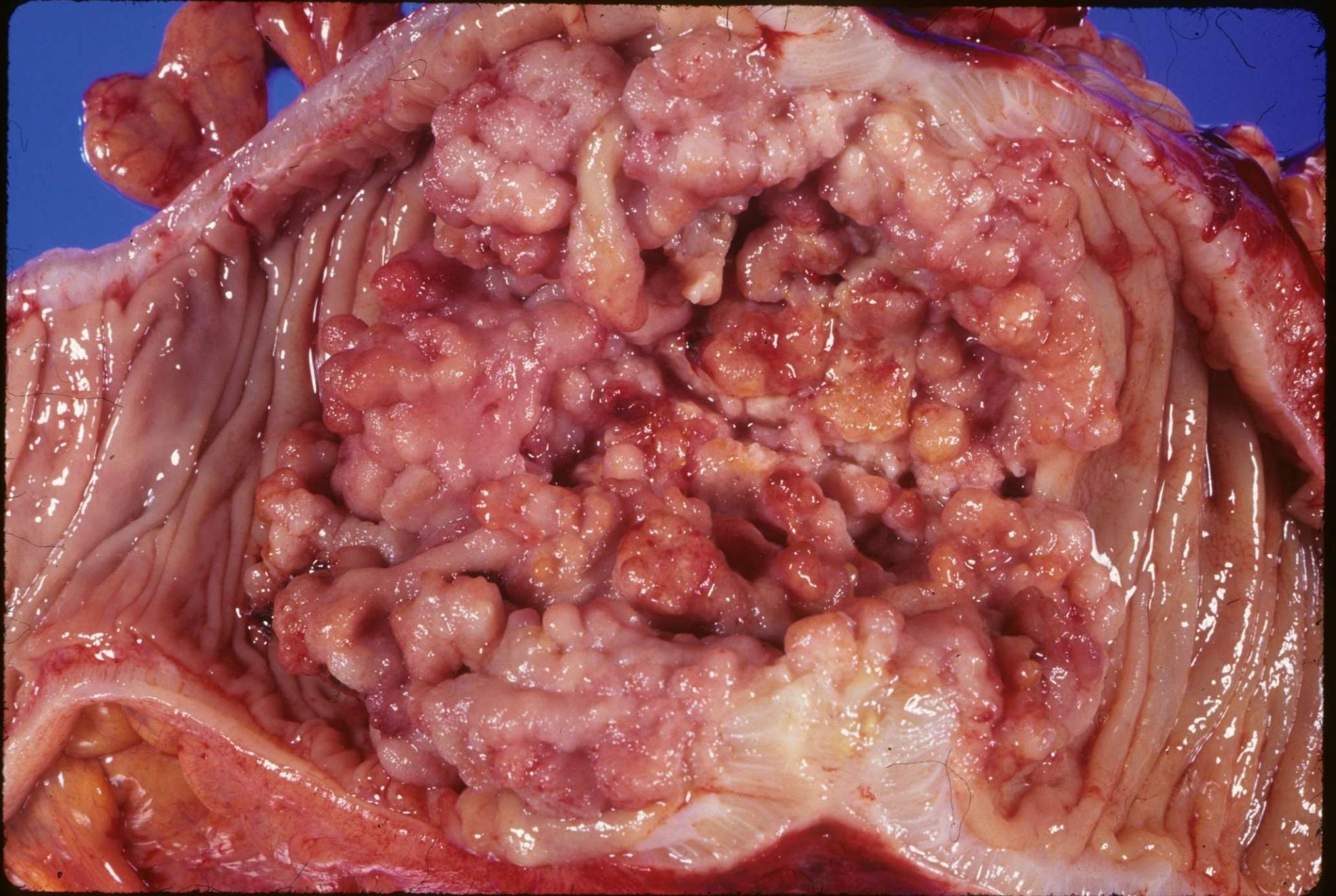


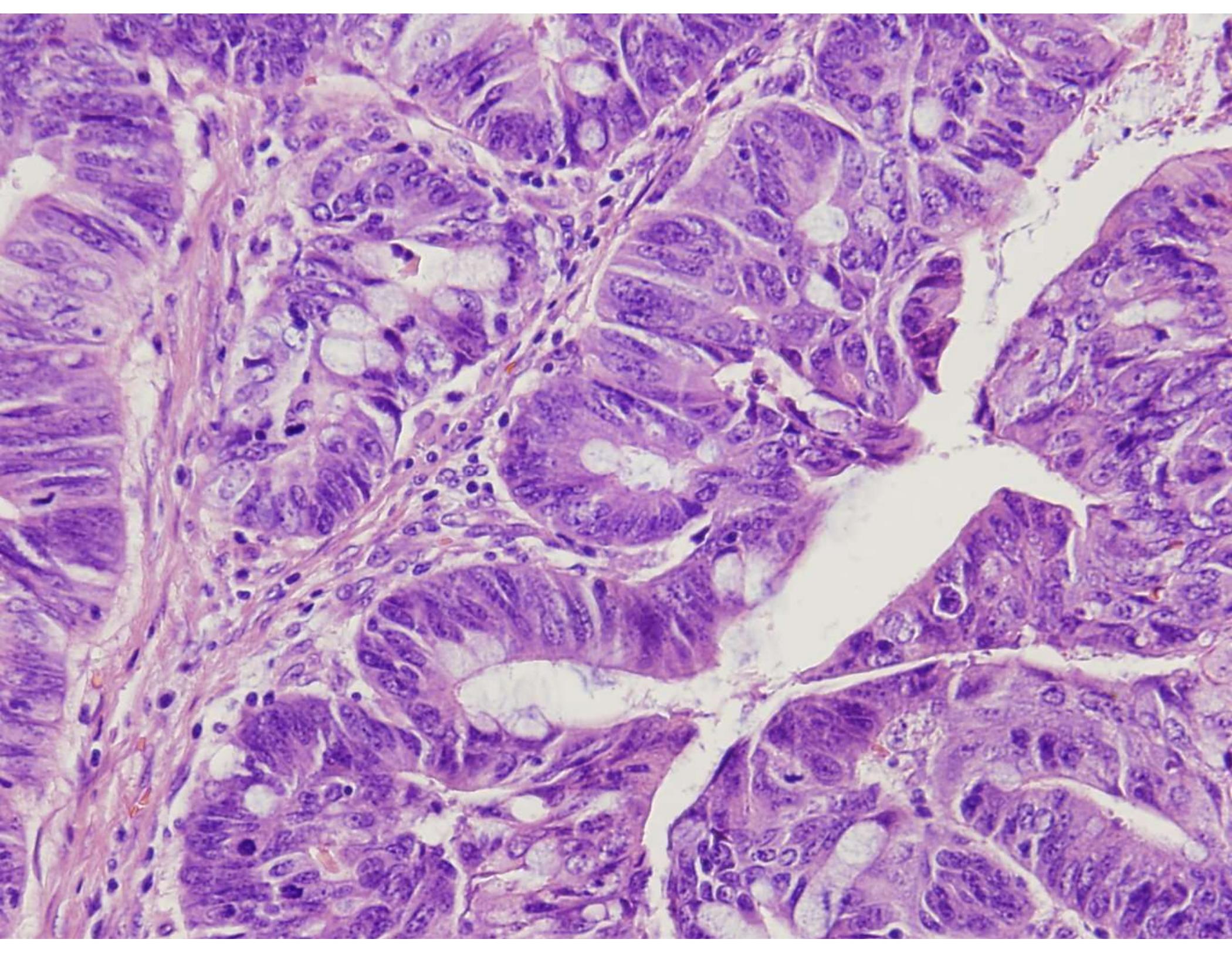
Adenoma

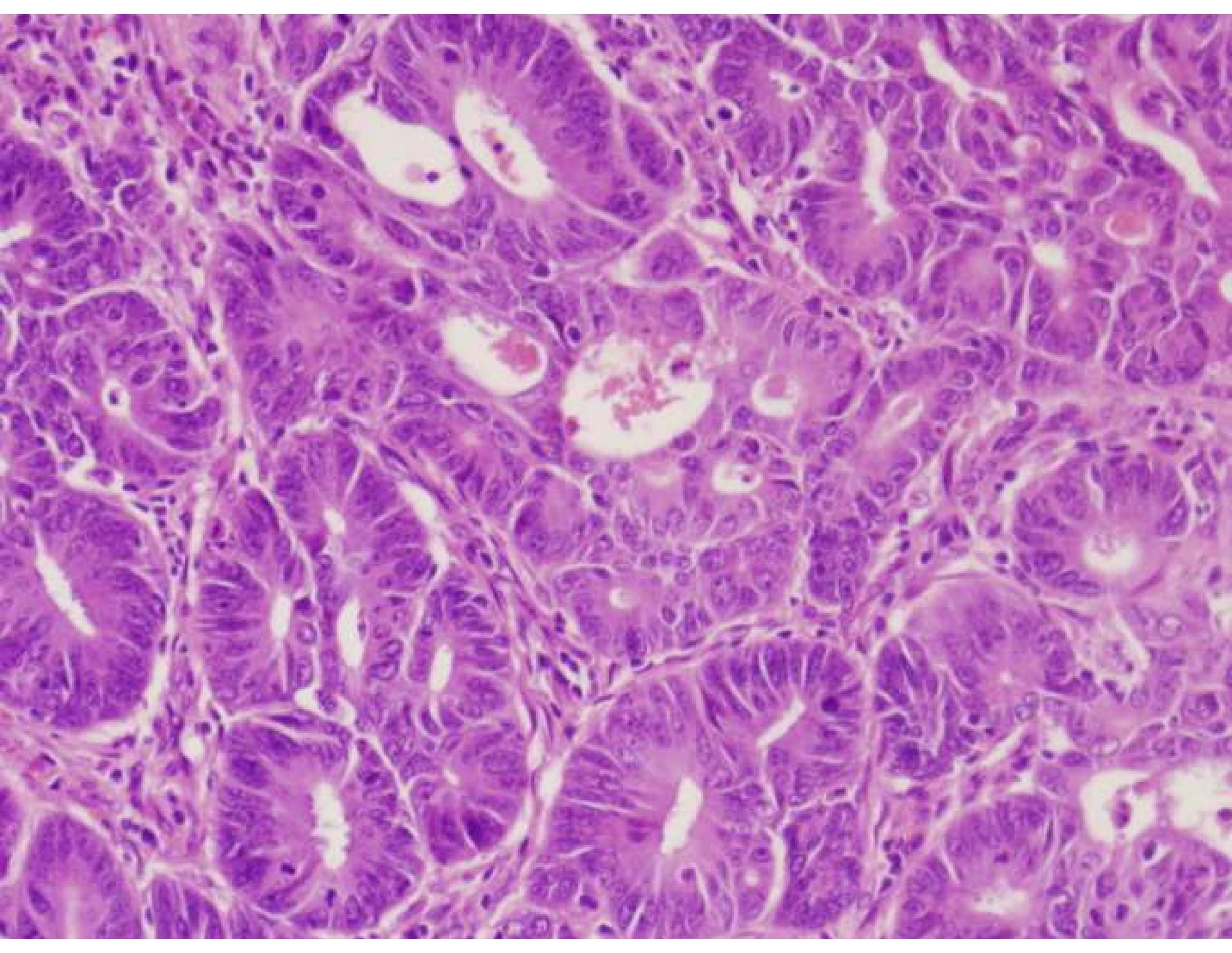
Normal colon mucosa

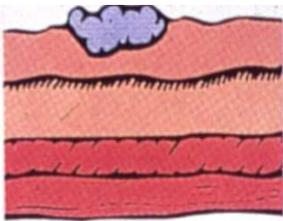
Adenocarcinoma

Colon – Adenocarcinoma with Adenoma at Periphery

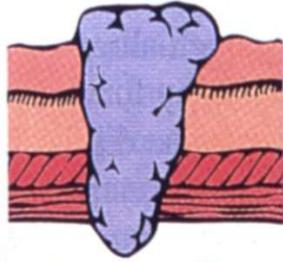
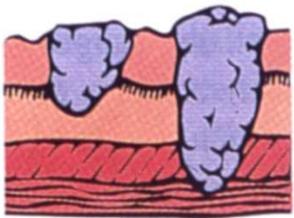




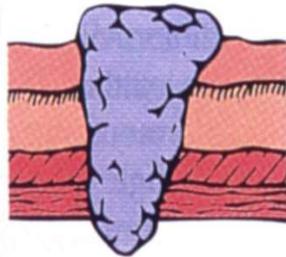
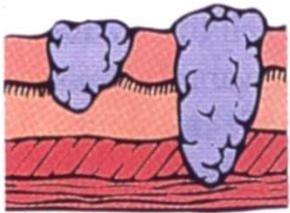




**Early stage –
confined to mucosa**



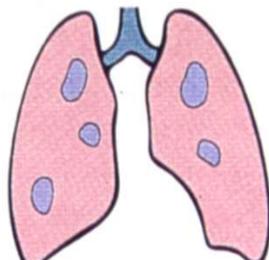
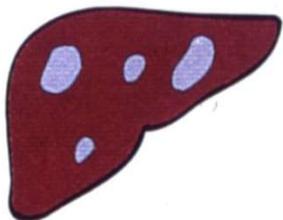
**Invading muscle
wall of colon**



**Regional lymph node
metastasis**



Distant metastasis



Colon cancer does not arise *de novo* (on its own)

Rather, colon cancer arises from a precursor adenoma

Adenoma-to-Carcinoma Sequence for Sporadic Colon Cancer

Hyperproliferative Epithelium



Early Adenoma



Intermediate Adenoma



Late Adenoma

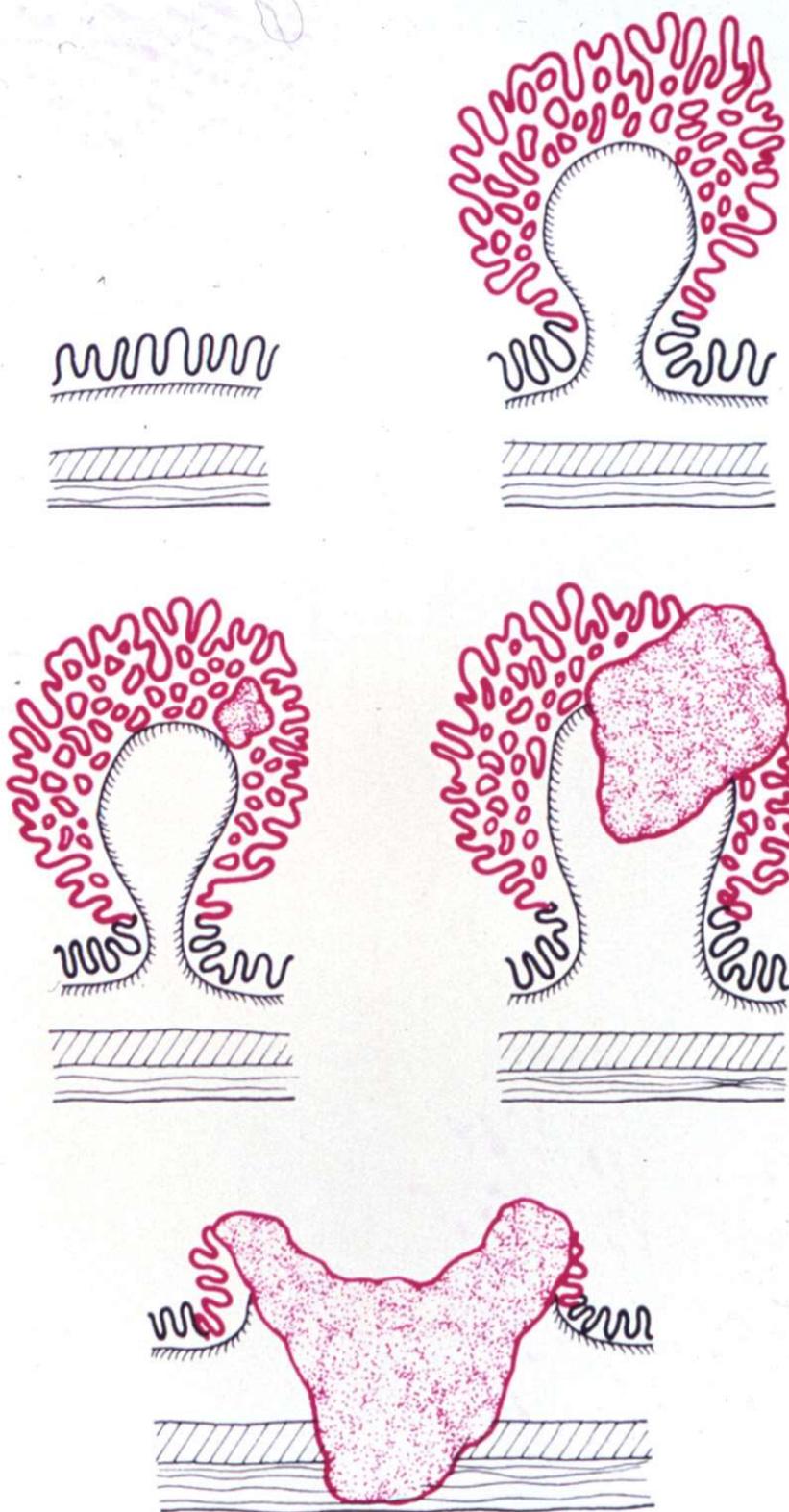


Adenocarcinoma



Metastasis

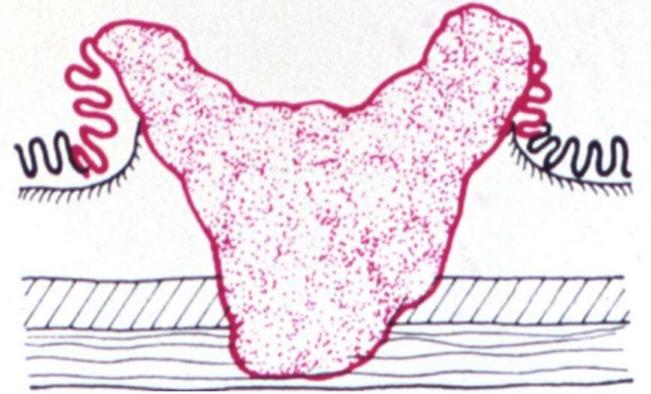
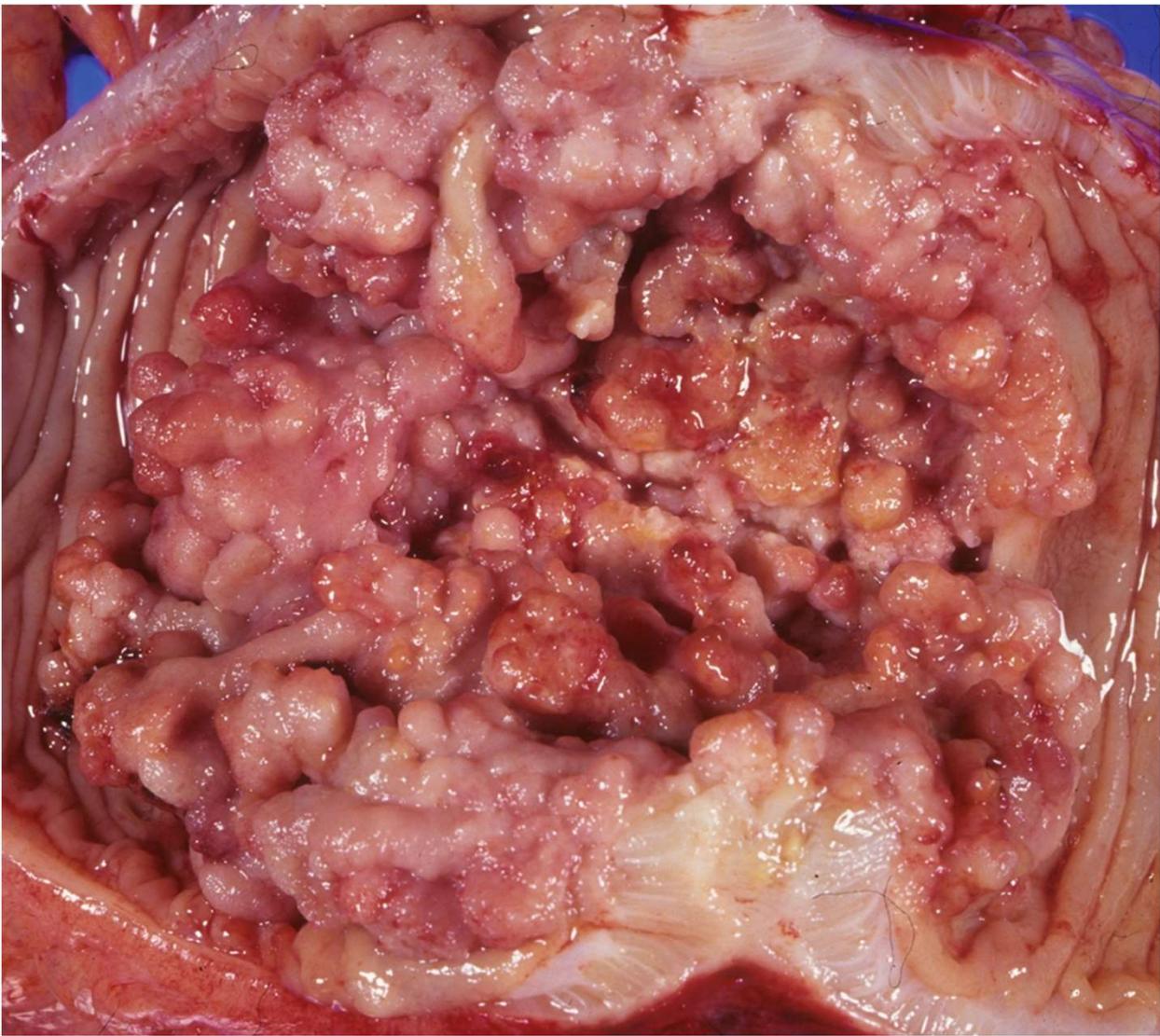
*Adapted from Fearon
and Vogelstein
Cell 1990: 61:759-767*



Diagrammatic representation of the adenoma-to-carcinoma sequence.

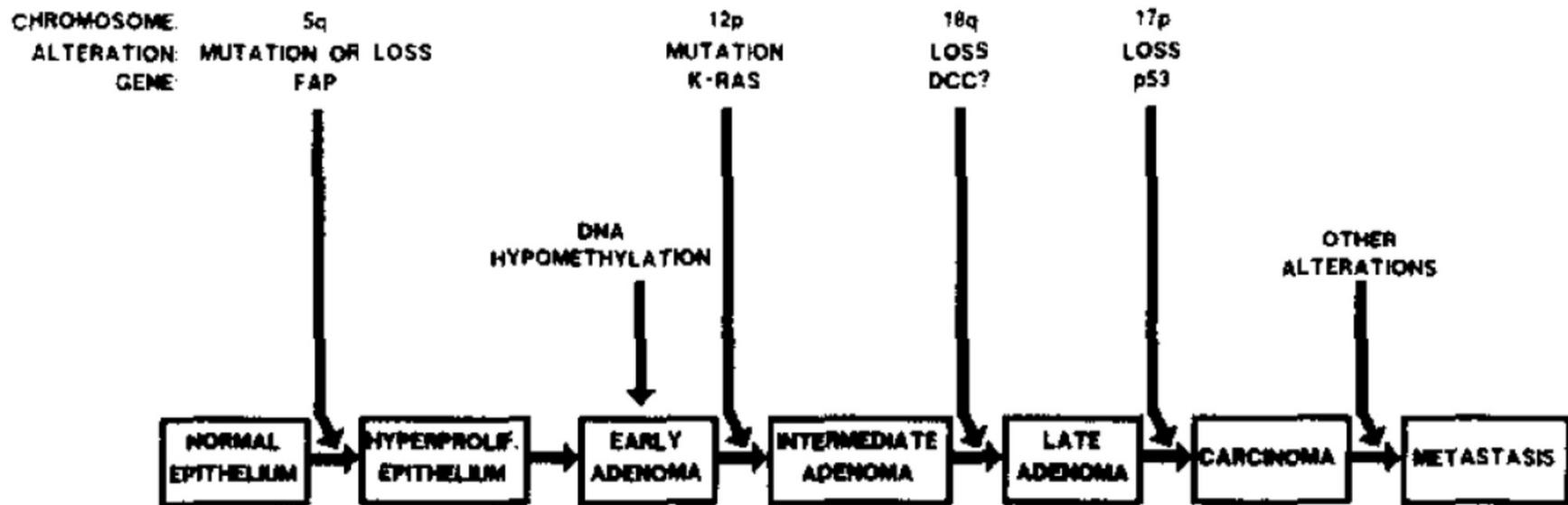
Adenoma grows outward towards the lumen.

Adenocarcinoma grows inward to invade the underlying muscle wall.



“Vogel-gram”

Adenoma-to-Carcinoma Sequence



Accumulation of molecular events rather than exact order is most important

Cell 1990; 61: 759-767

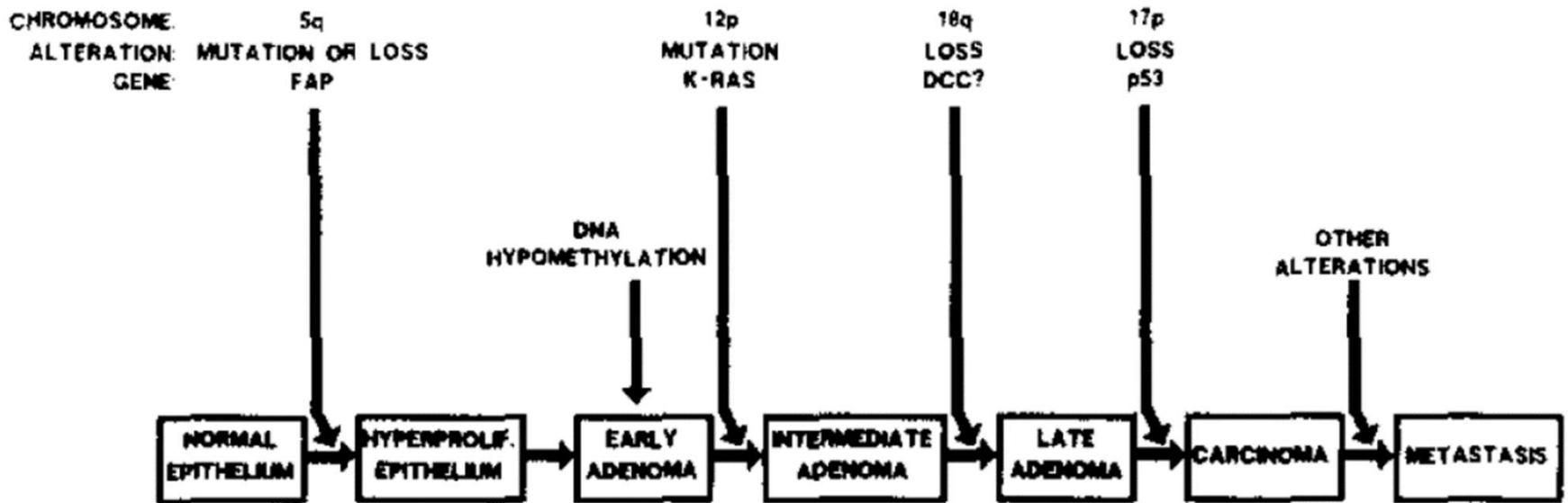
Importance of Adenoma Size

- <1cm 1.3% are malignant
- 1-2 cm 9.5% are malignant
- >2cm 46% are malignant

- This implies that as an adenoma grows, it acquires characteristics of malignancy.

Shortcomings of Molecular Model

- Does not explain cancers arising in inflammatory bowel disease or small, flat, sporadic cancers
- Does not explain mechanisms of metastasis
- Does not explain how an exophytic adenoma becomes a deeply invasive, ulcerative cancer
- Does not explain the well-documented role of diet in colon cancer
- Does not explain racial disparities in colon cancer

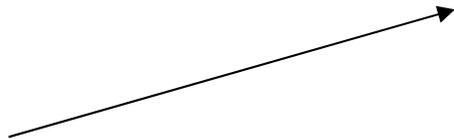


Microbiome

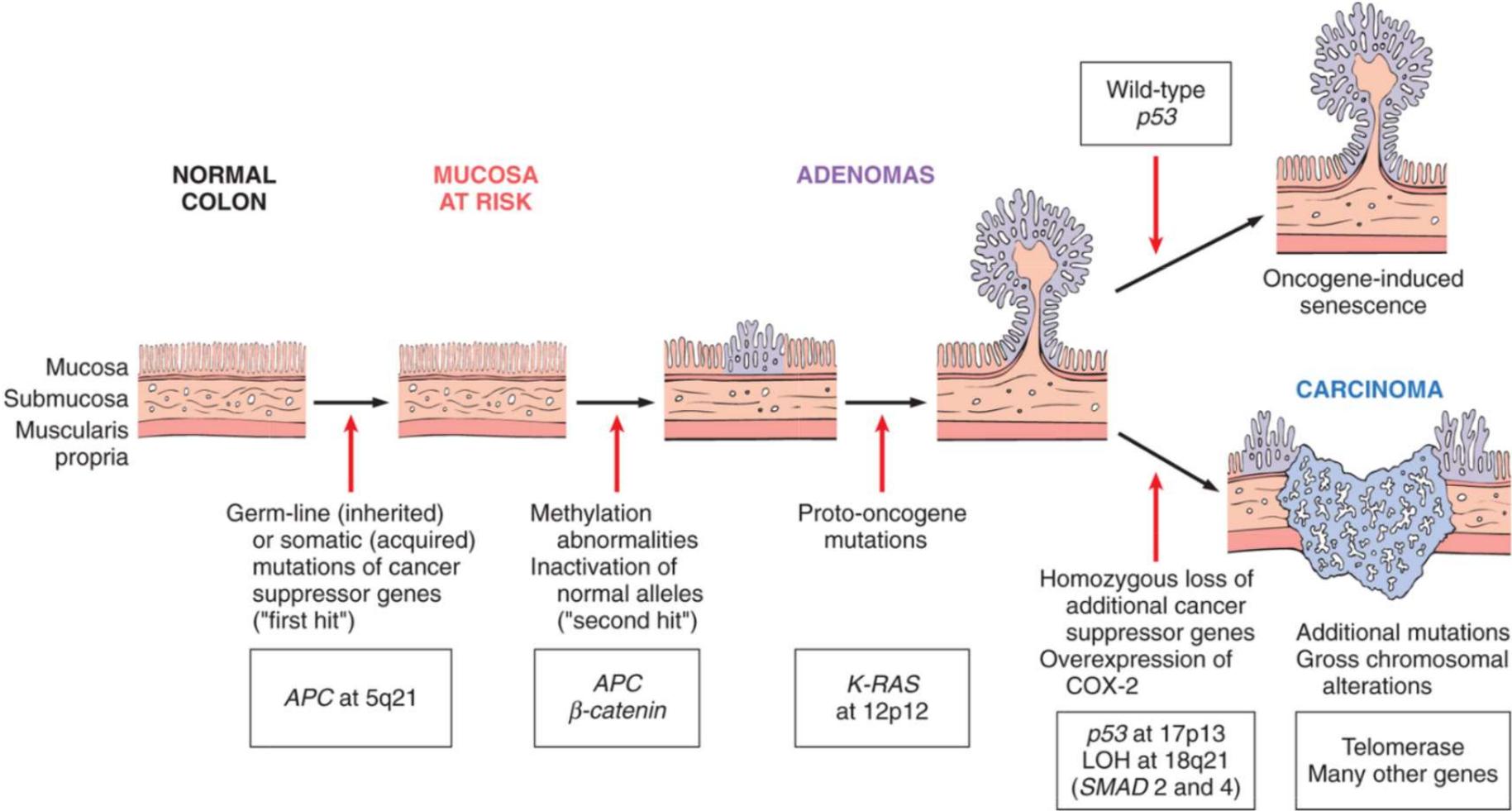
Diet

Inflammation and injury

Immune microenvironment



More Modern Adenoma-to-Carcinoma Sequence



Robbins and Cotran's Pathologic Basis of Disease

Key Point

- In the setting of sporadic colon cancer, the adenoma-to-carcinoma sequence is NOT inevitable.

Most adenomas never grow larger than 2 cm.

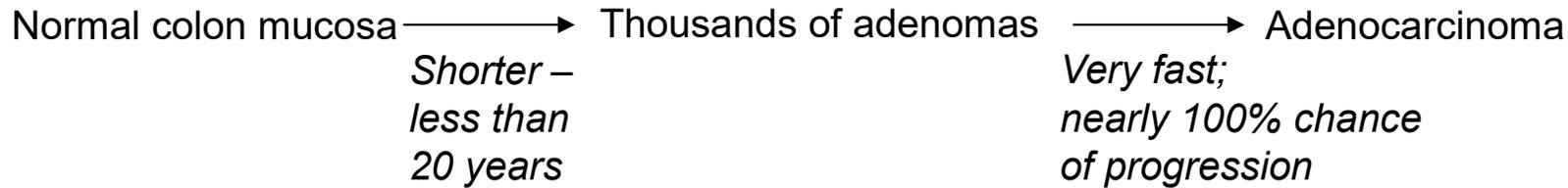
Big Question

- How do you predict which adenomas convey the most risk for subsequent development of colon cancer?
- If such a prediction can be made, can medicine intervene to prevent progression of the adenoma-to-carcinoma sequence?

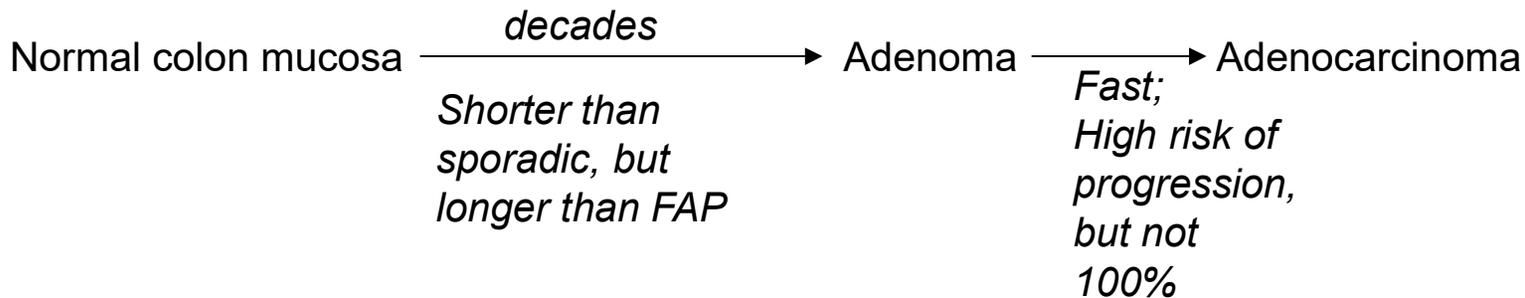
Sporadic



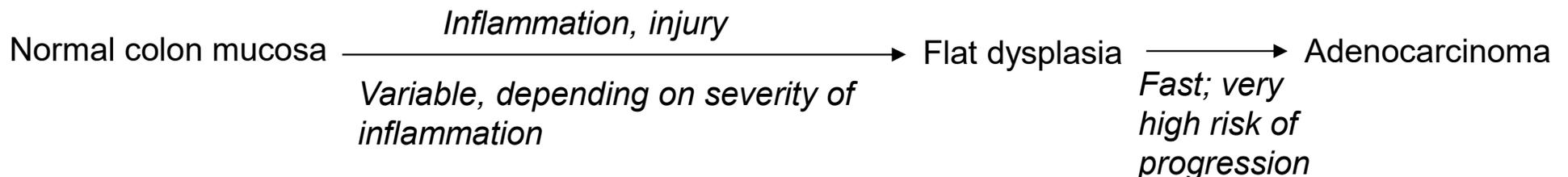
FAP – APC germline mutation



Lynch Syndrome – germline mutation of MLH1, MSH2, MSH6, or PMS2



Ulcerative colitis



Colorectal Cancer Health Disparity

- African Americans more often diagnosed at a younger age (but likely no increased incidence of Lynch or FAP)
- African Americans more often diagnosed with advanced disease (higher stage)
- African Americans have a greater proportion of cancers in the proximal colon
- African Americans - incidence 60/100,000
South African Blacks – incidence 5/100,000

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