Cells, Tissues and Organs: Basic Principles of Functional Histology and Pathology

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The Problem: Blood In The Stool, Ulcer In The Rectum

- 50-year old mother of 3 returns from vacation in Mexico

- Diarrhea & constipation with blood in stool

- Family history of colon cancer

- Age 25: similar episode - diagnosis ulcerative colitis

  - Life-long (chronic) form of inflammation of the colon

  - Cause unknown but related to immune system dysfunction

  - Typically waxes and wanes periodically

Investigating the Problem

- A gastroenterologist performs a colonoscopy

Findings

- An ulcer is seen the middle of the rectum

- Possible causes are multiple and diverse

Possibility One: Infection

- **Cause:** Infection from an invasive organism

  - Parasite

  - Bacterium

- **Treatment:** Antibiotic drugs

- **Prognosis:** Cure

Possibility Two: Inflammation

- **Cause:** Ulcerative colitis [UC] relapse

- **Treatment**: Anti-inflammatory drugs

- **Prognosis**: Suppression of inflammatory flare-up but life-long follow-up for other flare-ups or complications

Possibility Three: Cancer

- **Cause:** Rectal cancer

  - UC is a risk factor for colorectal cancer

- **Treatment**: Surgery (rectum removed)

  - Possible chemotherapy and/or radiation as well

- **Prognosis**: Probability of cure depends on extent of tumor spread (stage) at the time of discovery

Possibility Four: Ischemia

- **Cause:** Rectal prolapse (collapse)
  - Rectal supporting tissues weakened (childbirth)
  - Straining at stool $\Rightarrow$ buckling of rectal wall
  - Blood vessel compression
  - Reduced blood (oxygen) to rectal tissues
  - Necrosis of oxygen-starved tissue (ulcer forms)
- **Treatment:** Stool softeners
- **Prognosis:** Recurrence possible

Challenge: Diagnosis

- Many diseases and disorders "look alike" clinically

- **Differential diagnosis (DDx)** - the list of all conditions capable of producing the same findings and symptoms

- **Case in point:** Range of possible causes, treatments, and implications for outcome may be wide

The First Principle of Medicine

Correct treatment and accurate prognosis depend upon correct diagnosis

The Diagnostic Biopsy

- Gastroenterologist takes samples of tissue from the ulcer

- The biopsies are sent for pathologic examination

- The correct diagnosis is………..

Pathology: Footprints of Disease - Keys to Diagnosis

- The morphologic changes in tissues affected by disease are often distinctive and sometimes unique

- These pathologic features permit distinction among classes of disease and often permit precise diagnosis

- For many diseases, morphologic analysis is the "gold standard" of diagnosis

  - Can be expanded by molecular localization techniques (eg, IHC, ISH, *multiplex techniques using nano-particles*, etc.)

  - Preferable to techniques that destroy architecture

Gold Goes Platinum: An Eye to the Future

- Pathologist's role: to derive data from human biospecimens and interpret that data in the context of their medical training to provide useful information for patient management to treating clinicians

  - Morphologic (phenotype)

  - Molecular (genotype, etc.)

- Tools to derive data from specimens are ever increasing in specificity and sensitivity: data tsunami

- The bar for preservation of molecular integrity is increasing

The Classes of Human Disease

- **Three major classes of disease**
  - Inflammatory / immunologic:
    - Infectious diseases
    - Non-infectious
  - Ischemic
  - Neoplastic
    - Benign tumors
    - Malignant tumors
- **All represent essential functions gone awry**

Inflammatory Disease

- **Principle:** Inflammation is a protective response, the goal of which is three-fold:
  - Get rid of the agent causing the injury
  - Get rid of the debris resulting from the injury
  - Repair the injured tissue

- **Inflammation is essential to life:** without inflammation, infections would go unchecked and wounds would never heal

- **Control is key:** Turn on when needed and turn off when mission completed

Inflammatory Disease

- **Disease results when inflammatory process is:**
  - Great in amount
  - Of long duration
  - Triggered inappropriately
  - Cannot be turned off

- Terminology: affected organ or tissue + suffix "itis" ("inflammation")
  - Colitis = inflammation of the colon
  - Dermatitis = inflammation of the skin
  - Bronchitis = inflammation of the bronchi (airways)

Inflammatory Disease

- Two basic types: acute and chronic

    - Acute: recent onset

    - Chronic: long duration with continuing (repeated) injury and tissue repair (regeneration or scarring)

- Variations in intensity: mild, moderate, severe

- Type + intensity $\Rightarrow$ prognosis

Inflammatory Disease: General Characteristics

- Acute
  - White blood cells
    - Neutrophils
    - Macrophages
   - Lymphocytes and plasma cells (immune cells)
  - Injury of normal cells
- Chronic
  - Continued "acute" inflammation
  - Scarring of injured tissue that cannot regenerate
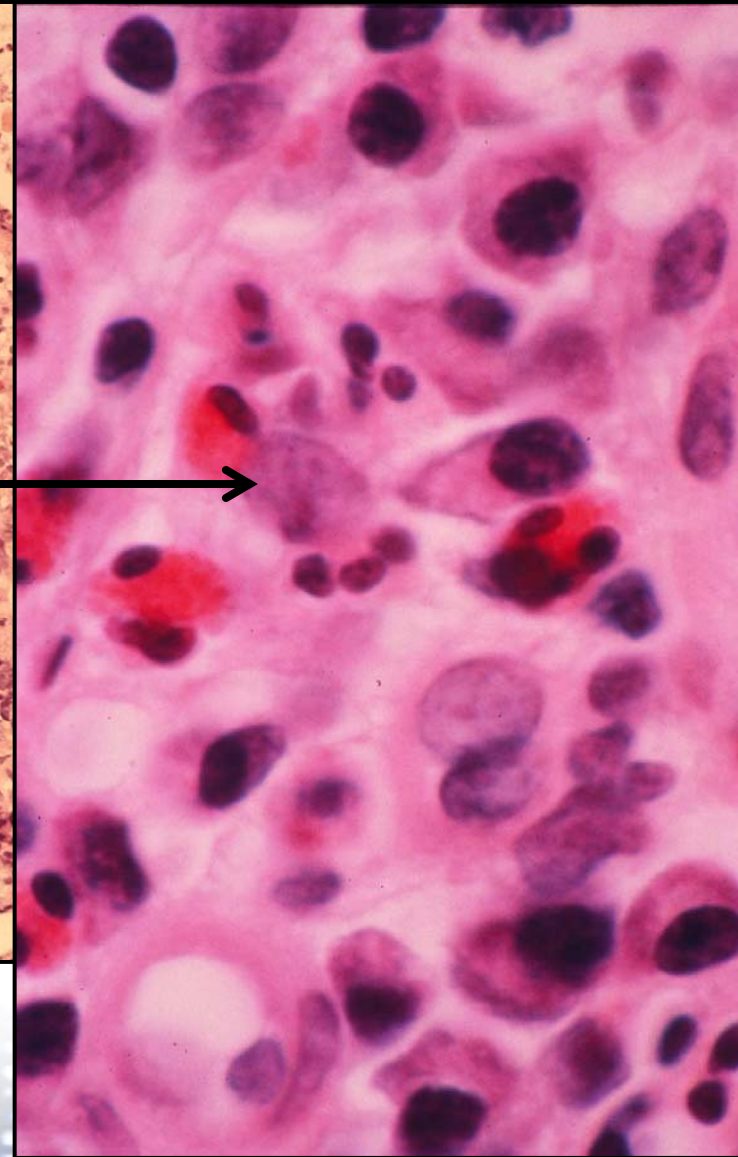 - Regeneration of tissue - partial, or complete

Inflammatory Disease: Specific Characteristics

- Depend on:
  - Cause
  - Tissue involved
  - Severity
  - Complications

- Common examples:
  - Acute:
    - Appendicitis: obstruction, bacterial overgrowth
  - Chronic:
    - Gastritis: infection
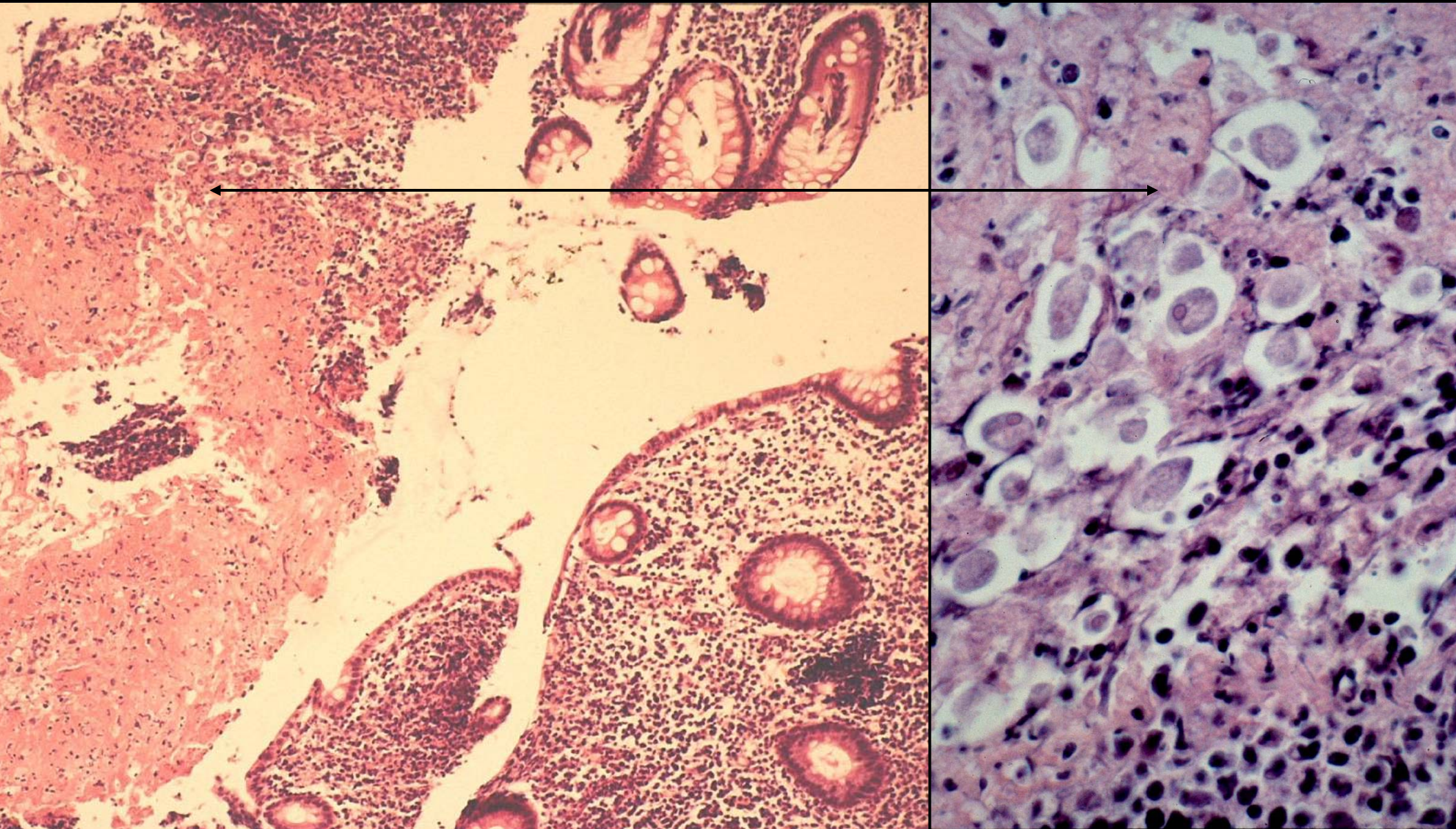   - Esophagitis: backwash of stomach acid
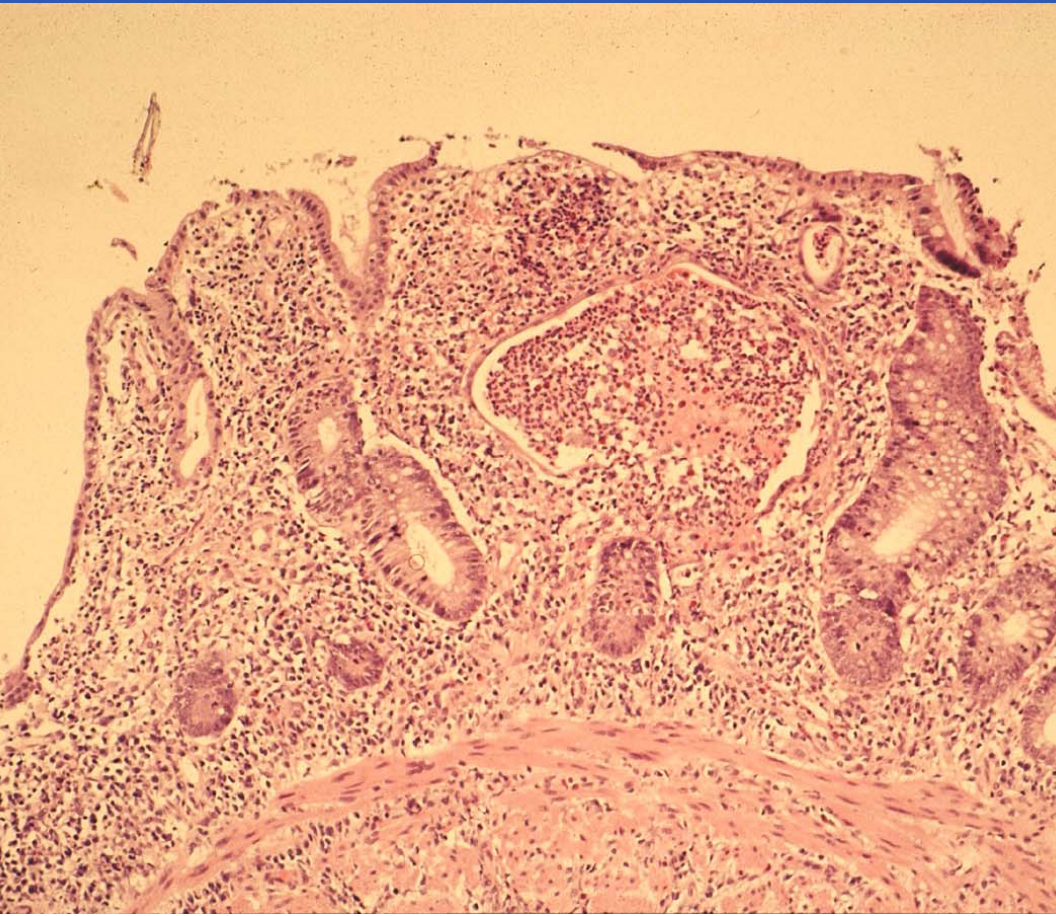
Normal Human Colonic Mucosa
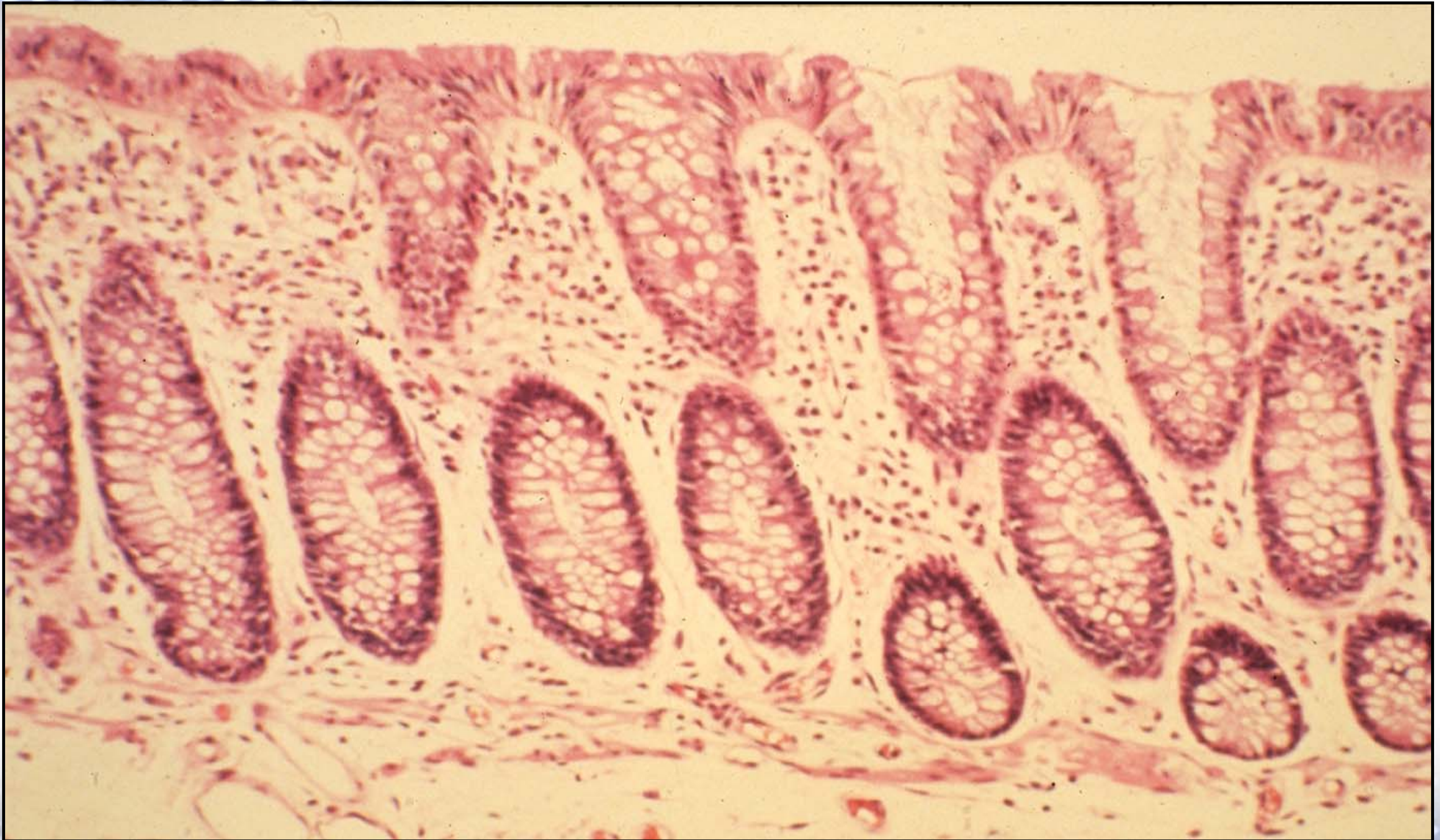
Acute Colitis

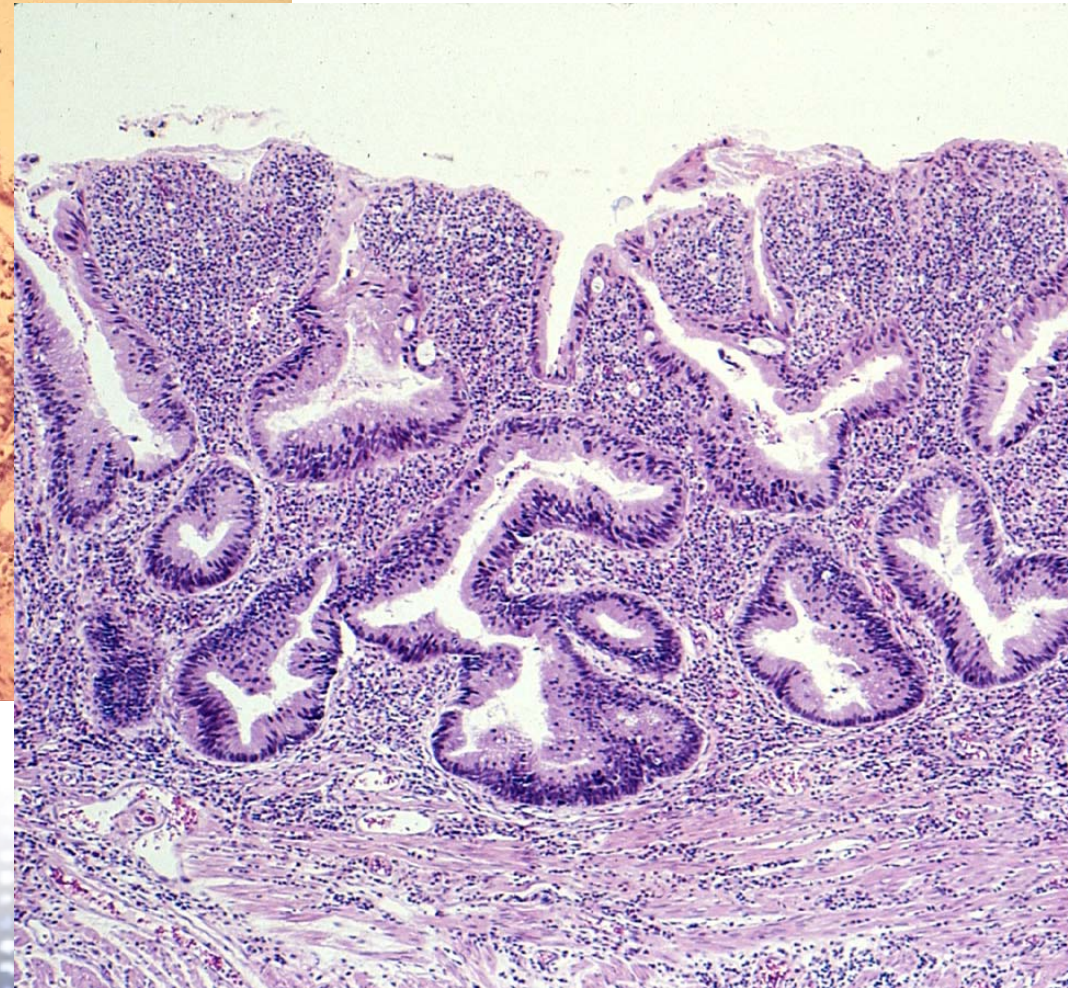- Inflammatory and immune cell infiltrates

Infectious Colitis: Amebic Colitis

Chronic Colitis and Progression to Cancer: FLCs

- Architecture altered

- Dysplasia

Ischemic Disease

- **Principle:** Changes in blood flow occur normally as an adaptive mechanism for providing more or less oxygen as required by the metabolic state of a tissue

- **Control is key:** Provide more blood when needed and less when not needed

- For normal function, blood vessels must be:
  - Normal in structure
  - Normally responsive to physiologic stimuli
  - Unblocked

- A problem with *any* of the above may cause ischemia

Ischemic Disease

- Disease results when:

  - Too little blood (oxygen) reaches the tissue in need and injury occurs (ischemia)

  - Tissues die when deprived of oxygen for too long (infarction)

- Terminology: involved organ + ischemia/infarction

  - Example: Myocardial (heart muscle) infarction

Ischemic Disease

- Common causes include:

  - Disease in vessels that carry the blood

    - Atherosclerosis ("hardening of the arteries"): the build-up of brittle plaques of cholesterol and scar tissue in vessel walls

    - Vasculitis: inflammation of vessels

  - Plugging of a vessel by a circulating mass (embolus)

    - Clotted blood: developed within the vessel

    - Air, fat, foreign particles: introduced into the vessel

  - Compression of vessels by external pressure

Ischemic Disease

- **General tissue characteristics:**
  - Tissue hemorrhage (blood outside of vessels)
  - Cell injury or death (necrosis) without inflammation

- **Specific characteristics - depend on tissue:**
  - Tissues without digestive enzymes become mummified (coagulative necrosis)
    - Example: Heart muscle
  - Tissues without digestive enzymes auto-digest (liquefactive necrosis)
    - Example: Pancreas

Ischemic Colitis: More FLCs

- Acute →

- Chronic
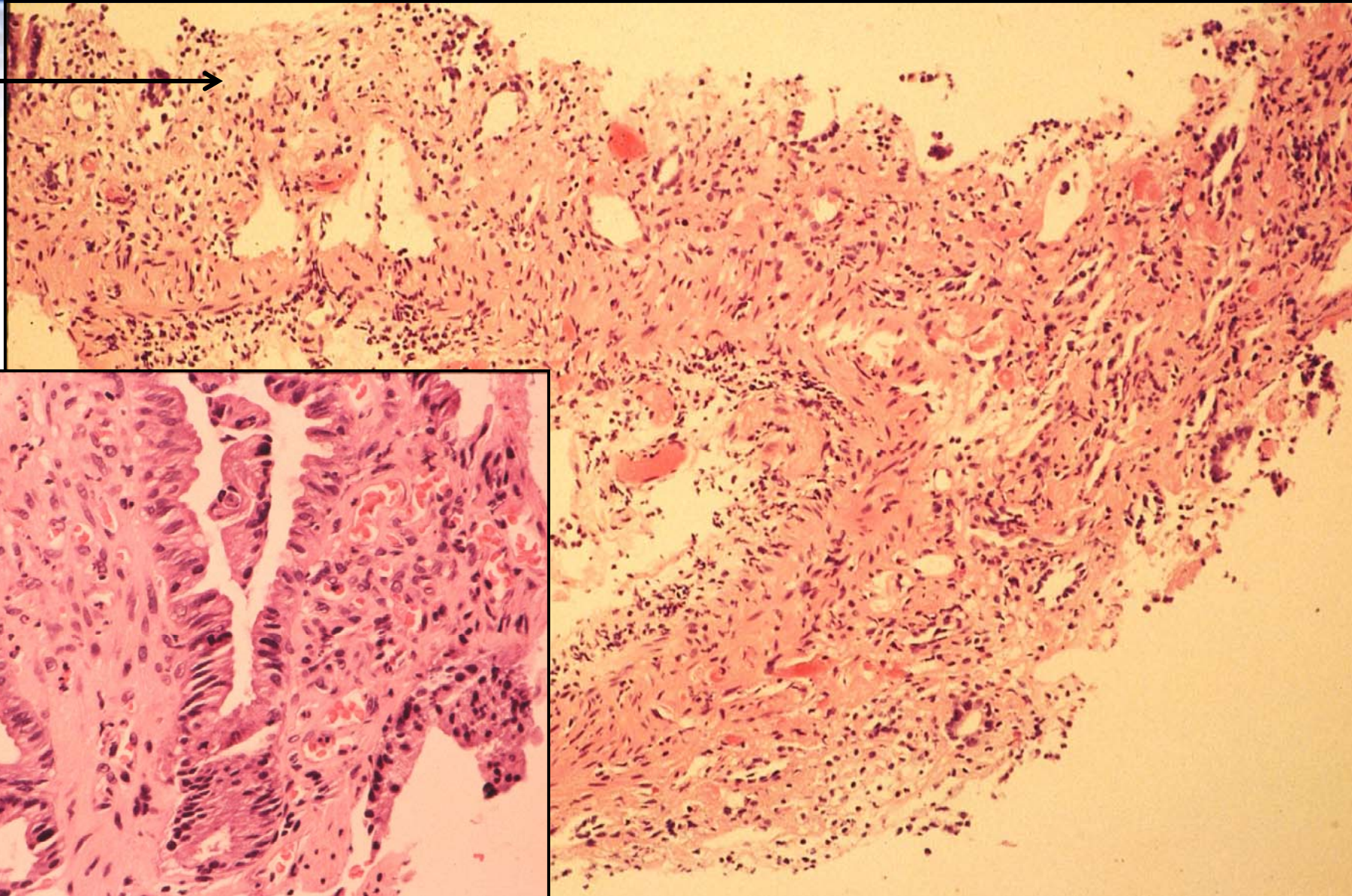
Neoplastic Disease

- **Principle:** Cell growth (division) is necessary for normal function of tissues
  - Continual cell renewal throughout life: blood cells, intestinal lining cells, skin cells
  - Cell renewal on demand: repair of tissue after injury

- **Control is key:** The controls are complex
  - Numerous checks and balances
  - Balance between "on" and "off" control signals for growth

- **Control signals** = proteins that interact in series (domino effect) to stimulate or suppress cell division

Neoplastic Disease

- **Tumors (neoplasms):** abnormal masses that develop because growth control and architectural order within a normal tissue are lost

- **Loss of growth control:** genes that encode signals of growth activation and suppression malfunction or are dysregulated

- Tumor formation requires malfunction of numerous growth-controlling and architecture-controlling genes

  – Usually the result of *sporadic* events that mutate such genes

  – Uncommonly, a mutated growth-controlling gene is *inherited*

Neoplastic Disease

Two broad classes of tumors correspond to increasing loss of growth control:

- Benign tumors
  - Curable with ablation
  - Expansile growth
  - Slower growth
  - Never metastasize

- Malignant tumors
  - May or may not be curable
  - Invasive growth
  - Rapid growth
  - Ability to metastasize

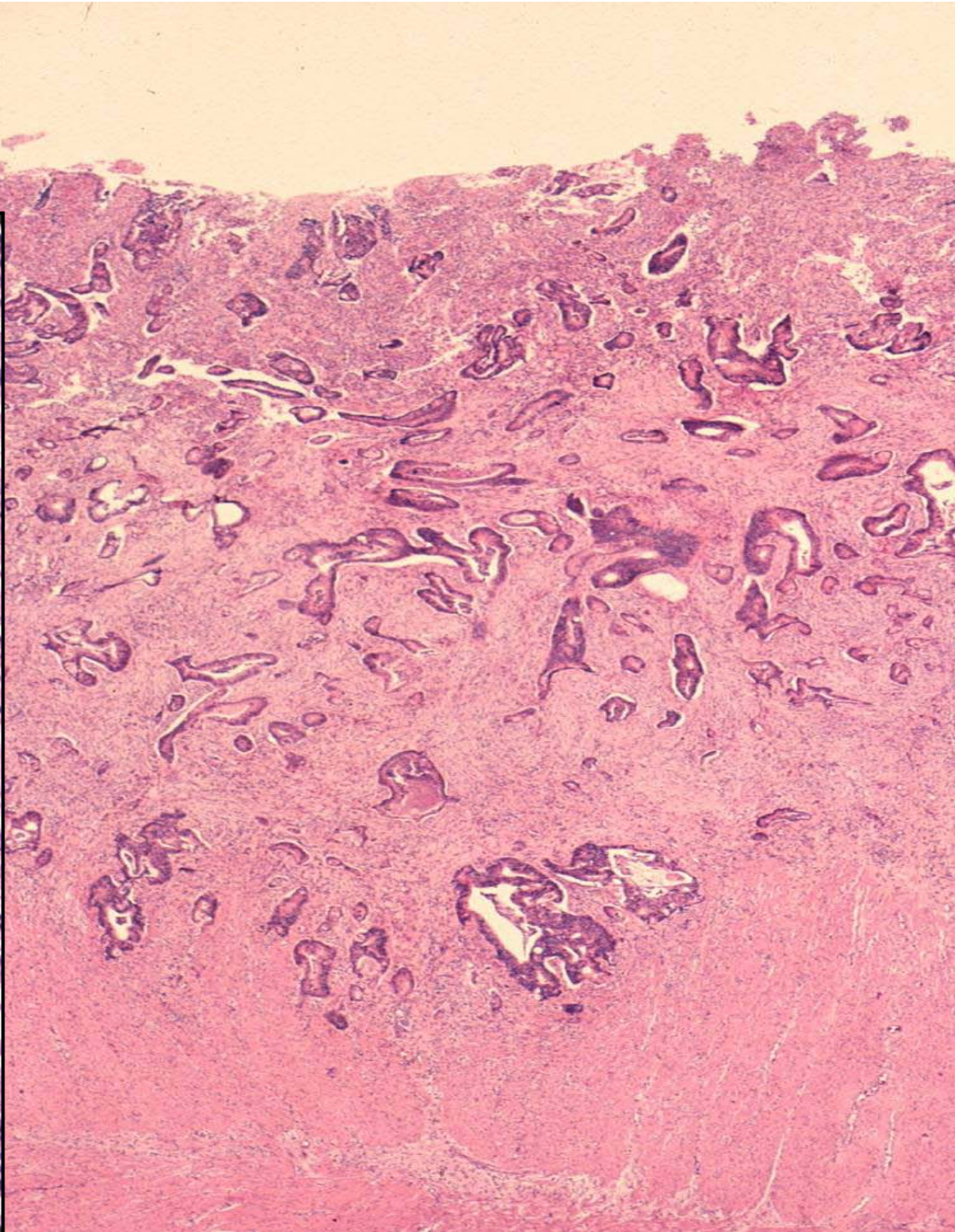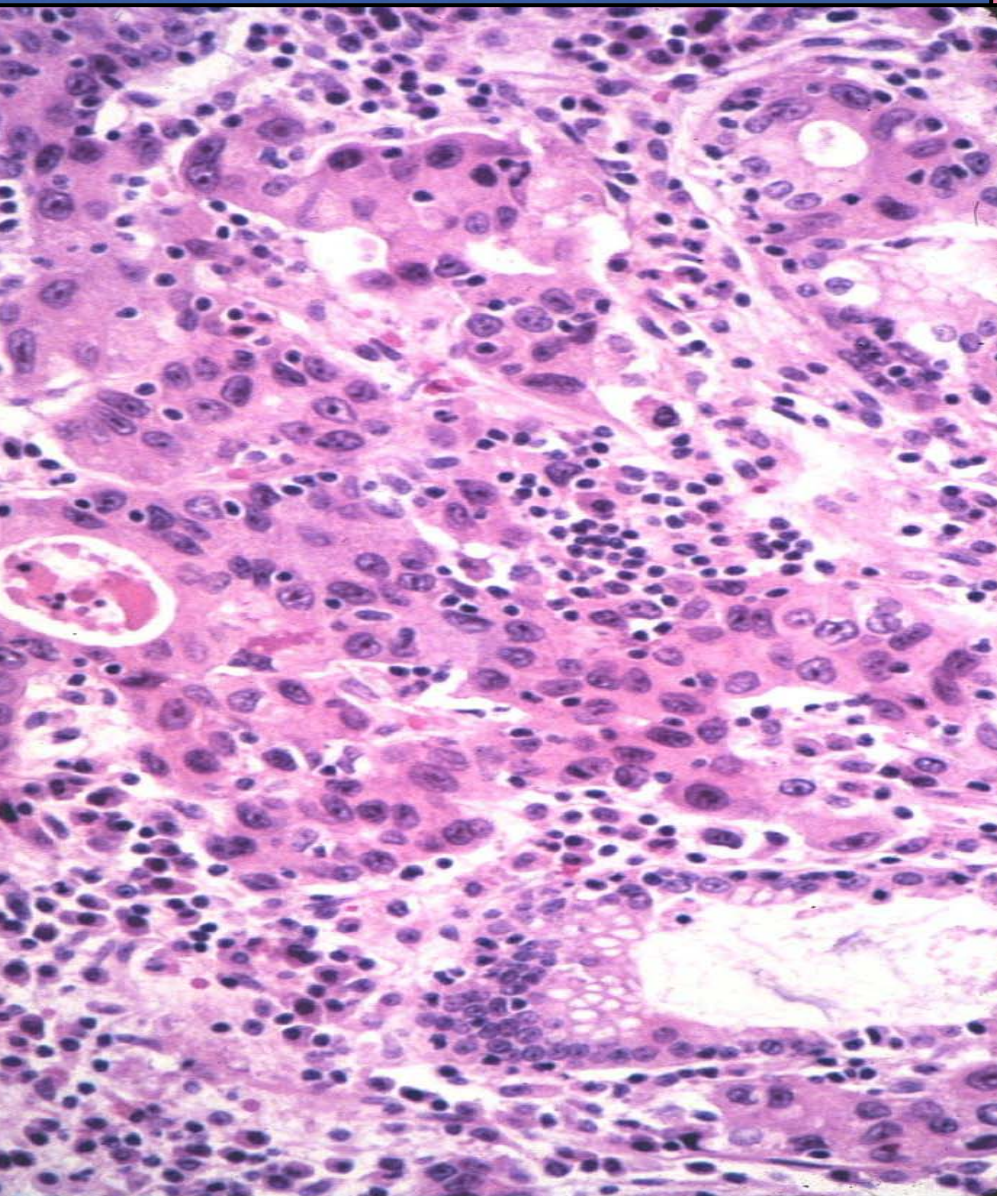# Neoplastic Disease

- **General characteristics:**

    - Disorganized, abnormal masses of tissue

    - Individual cells large and oddly shaped

    - Growth that does not respect normal tissue architecture

- **Specific characteristics:**

    - Dependent on tissue of origin

    - Usually bear some resemblance to the tissue of origin

Colon Cancer

Neoplastic Disease

- Terminology related to cells of origin:

    - Carcinoma – epithelial cells

    - Sarcoma – connective tissue cells

    - Lymphoma - lymphocytes

    - Leukemia - bone marrow-derived blood cells

    - Melanoma - melanocytes (pigment-forming cells)

Neoplastic Disease

- Most malignant tumors are carcinomas

- Examples:

  - Squamous cell carcinoma - from squamous epithelium:

    - Skin

    - Esophagus

  - Adenocarcinoma - from gland-forming epithelium (adeno = gland)

    - Colon or rectum

    - Bronchi (lungs)
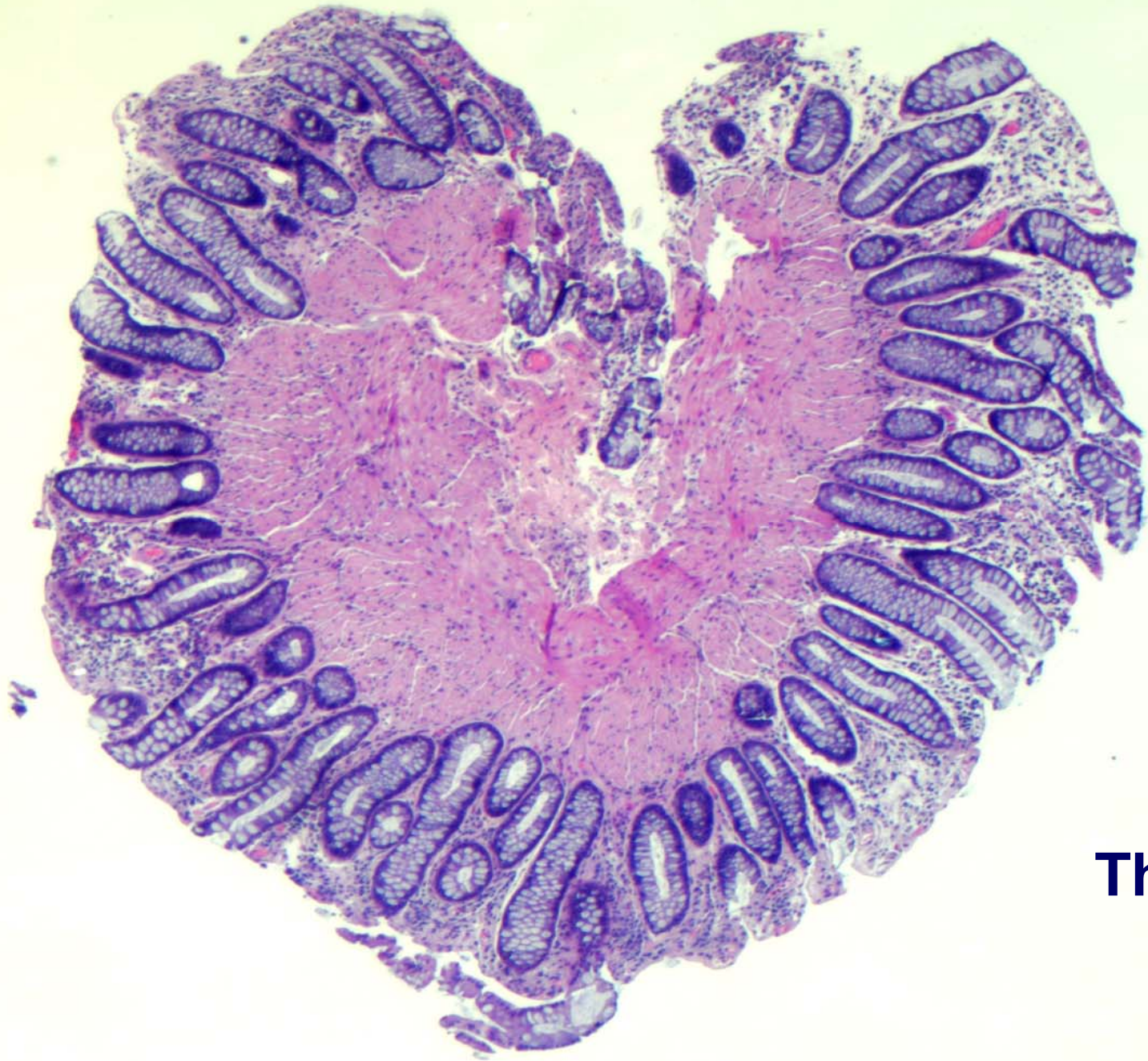
    - Pancreas

    - Stomach

Neoplastic Disease

- **<u>Principle</u>:** Pathologic diagnosis is essential to –

  - Differentiate inflammatory from neoplastic masses

  - Differentiate benign from malignant tumors

  - Determine the type of malignant tumor, which, in turn, determines:

    - Appropriate treatment

    - Likely outcome for the patient (prognosis)

And The Answer Is ……..

- **The biopsy from our patient showed:**

  - Severe inflammation

  - Signs of chronicity

    - Disarray of glandular architecture with scarring from repeated injury and repair

  - No parasites

  - No ischemia

  - No tumor

And The Answer Is ……..

- **Pathologic diagnosis: Ulcerative colitis**

- The patient was successfully treated with anti-inflammatory drugs and scheduled for regular follow-up for monitoring of:

    - efficacy of treatment for disease activity

    - possible complications of disease or therapy

    - risk of colorectal cancer

The End