Welcome to Pathology135

Pathology: Cell Injury and Cellular Adaptations

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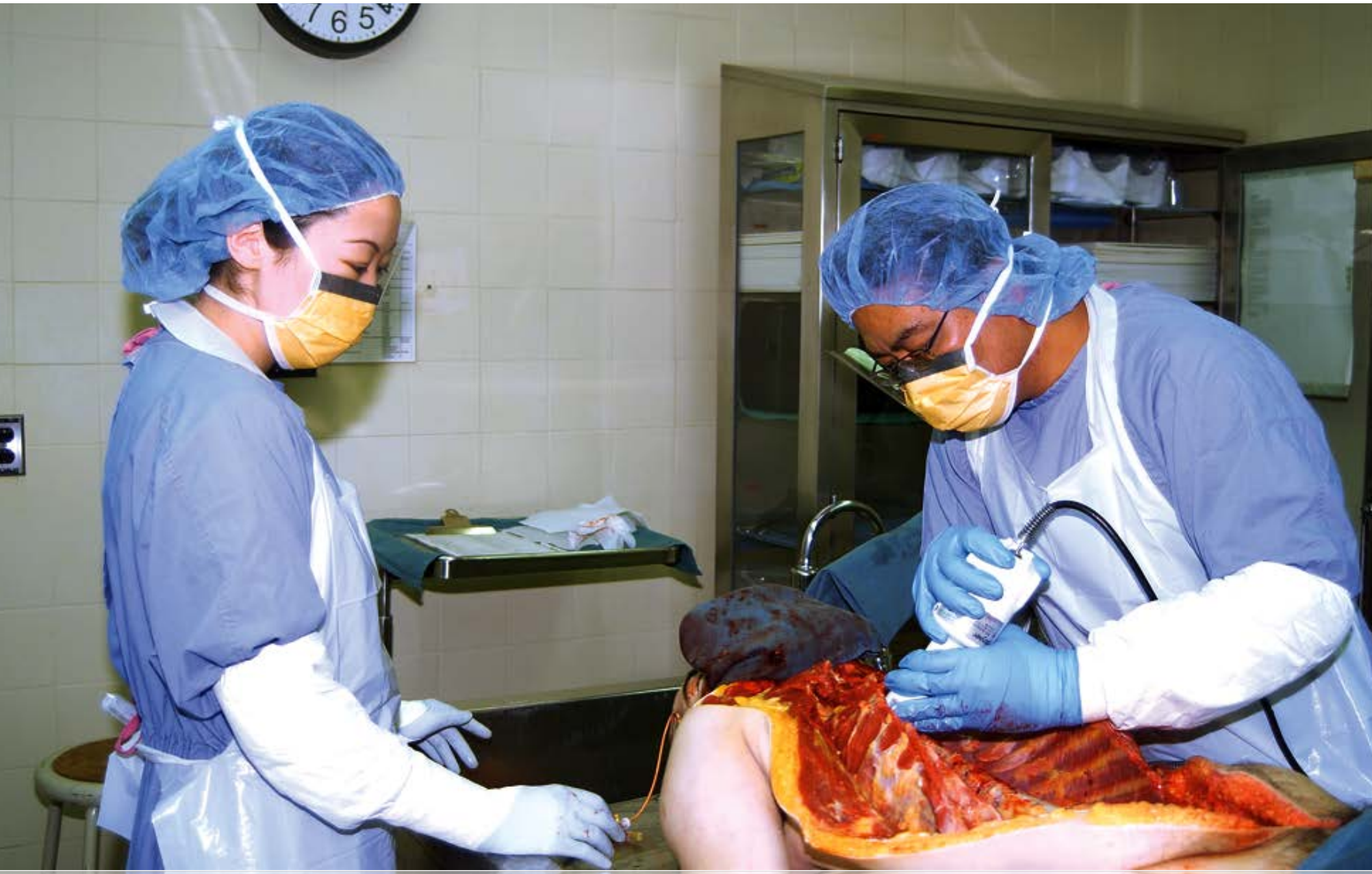
Fiction: CSI “Toe Tags”



Fact: Actual Autopsy

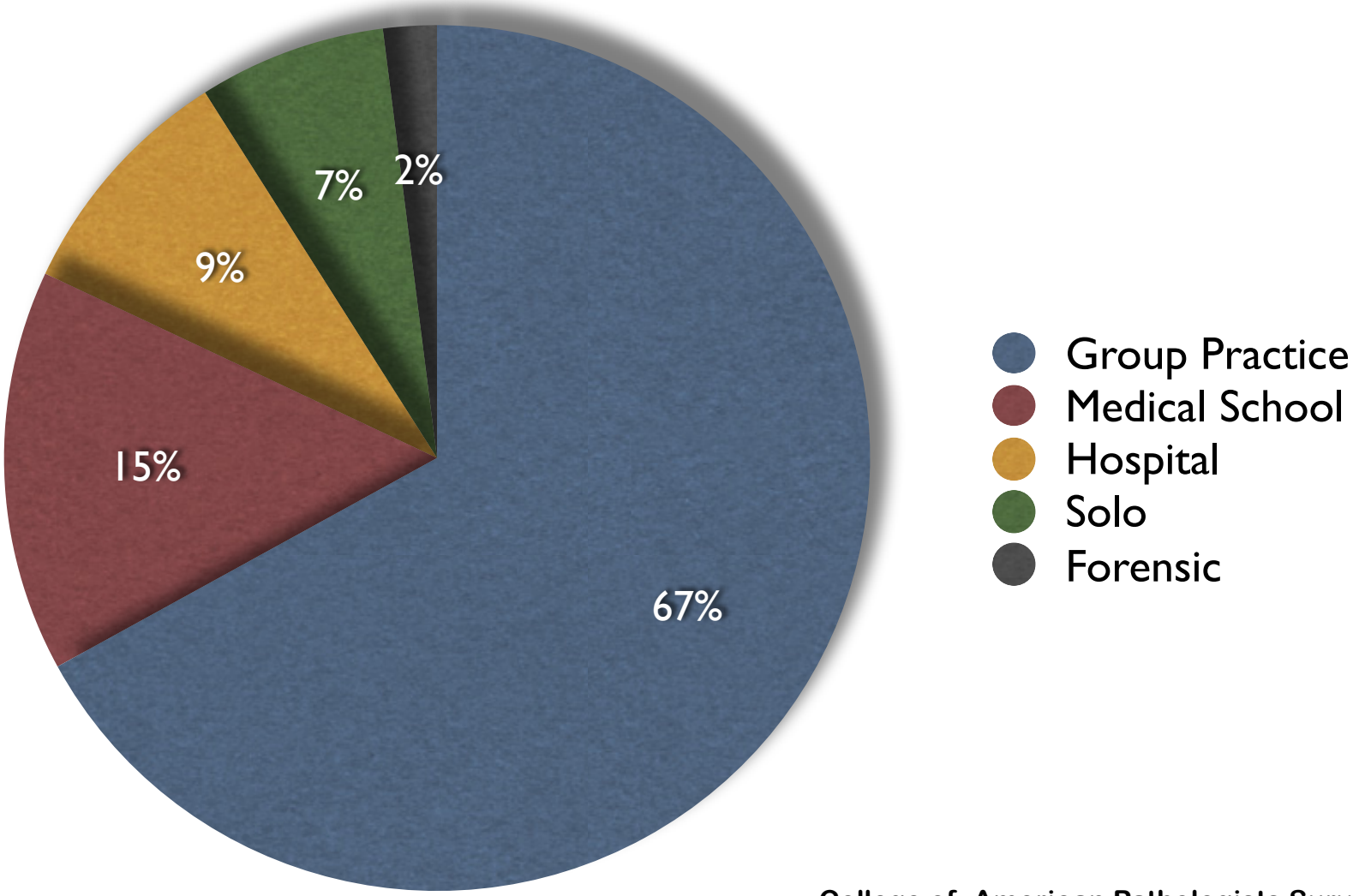
Pathology 135

- Course is divided into two components:
  - Mechanisms of Disease
  - Systemic Pathology
- Textbooks
- Exams - Midterm (11/3/15) and Final Exam (12/9/15)
  - Weekly Online Quiz: Starting 9/25/15
- Grading

The Roles of the Pathologist

- The study of disease
  - Morphologic description of disease
  - Experimental studies
  - Molecular analyses (studying expression of genes and molecules in diseased tissue)
- The diagnosis of disease
  - The clinical discipline of Pathology
  - Anatomic (surgical pathologist, cytopathologist and autopsy pathologist) and clinical pathology (laboratory medicine)

US Pathology Practice Demographics



College of American Pathologists Survey &
The Intersociety Council for Pathology Information, Inc

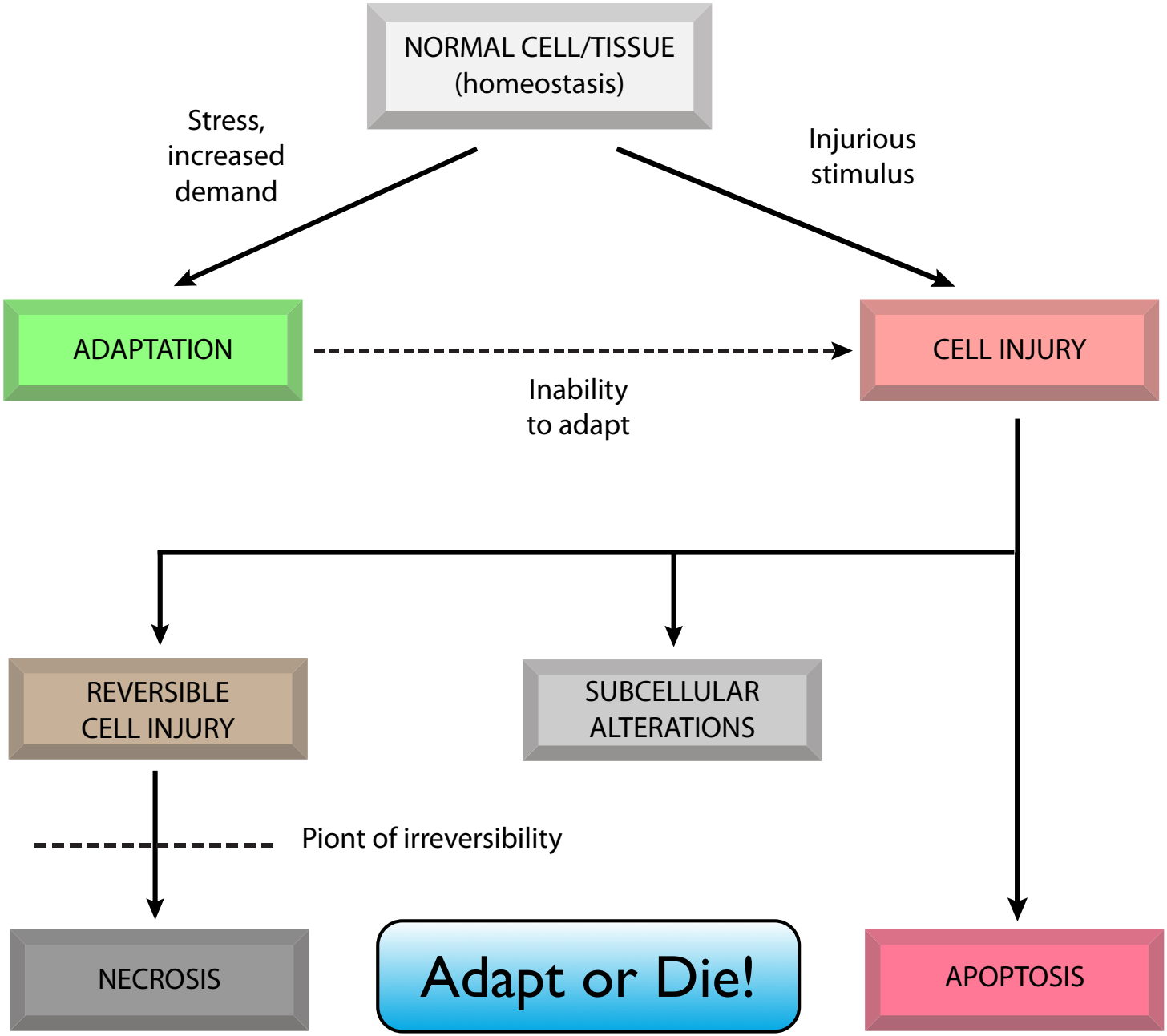
Cell Injury: Mechanisms & Adaptations

Introduction to Pathology

- Definition: study of disease ("suffering")
  - Pathology is the convergence of basic science and clinical medicine
  - Study of structural and functional changes in cells, tissues and organs that underlie disease
  - Fundamental knowledge that is relevant to all other medical disciplines

Overview of Pathology

- Etiology or cause
- Pathogenesis
- Morphologic changes
- Functional derangements and clinical significance


NORMAL CELL/TISSUE
(homeostasis)
Stress,
increased
demand
Injurious
stimulus
ADAPTATION
CELL INJURY
Inability
to adapt
REVERSIBLE
CELL INJURY
SUBCELLULAR
ALTERATIONS
Piont of irreversibility
NECROSIS
Adapt or Die!
APOPTOSIS

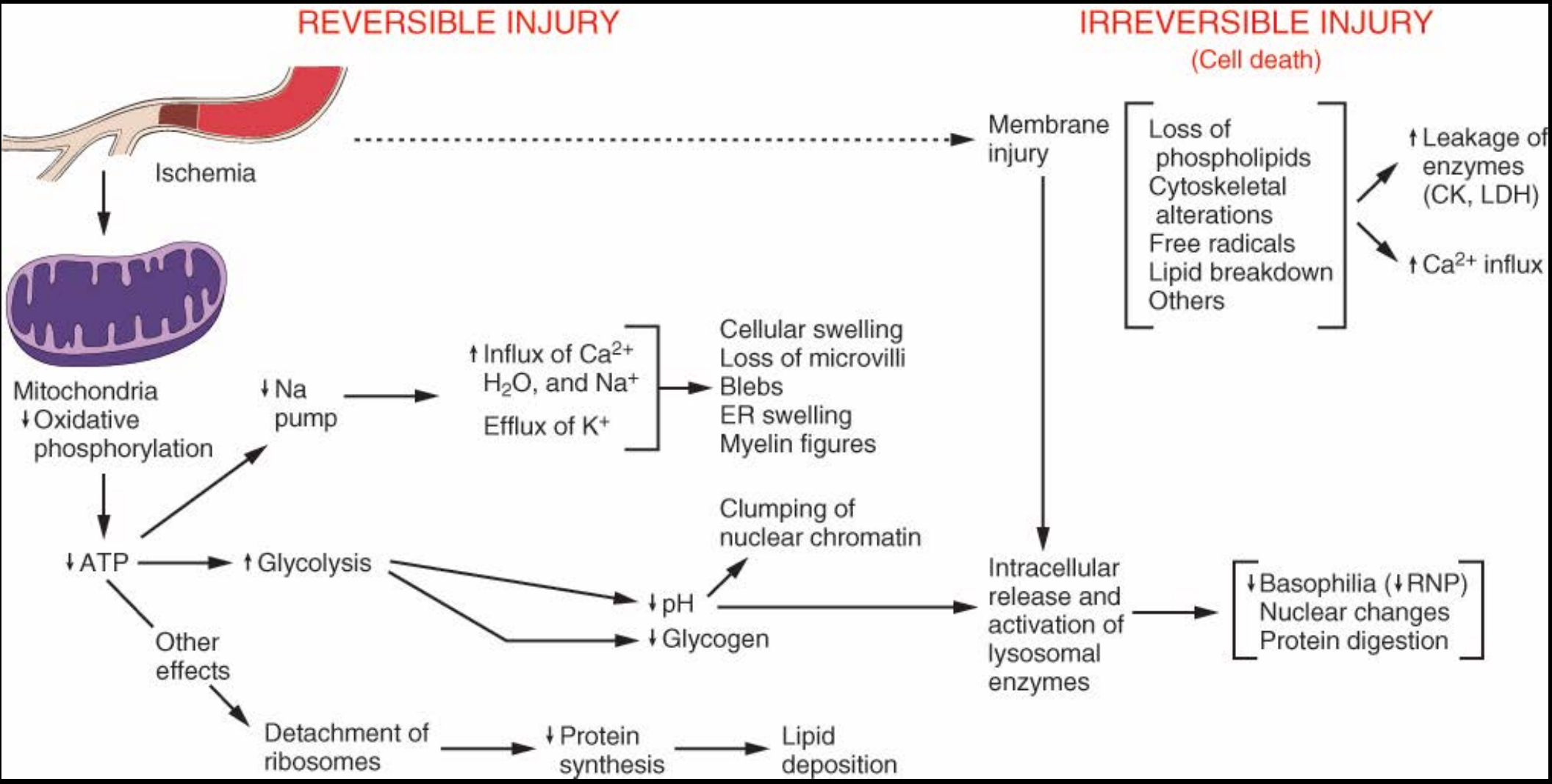
Mechanisms of Cell Injury

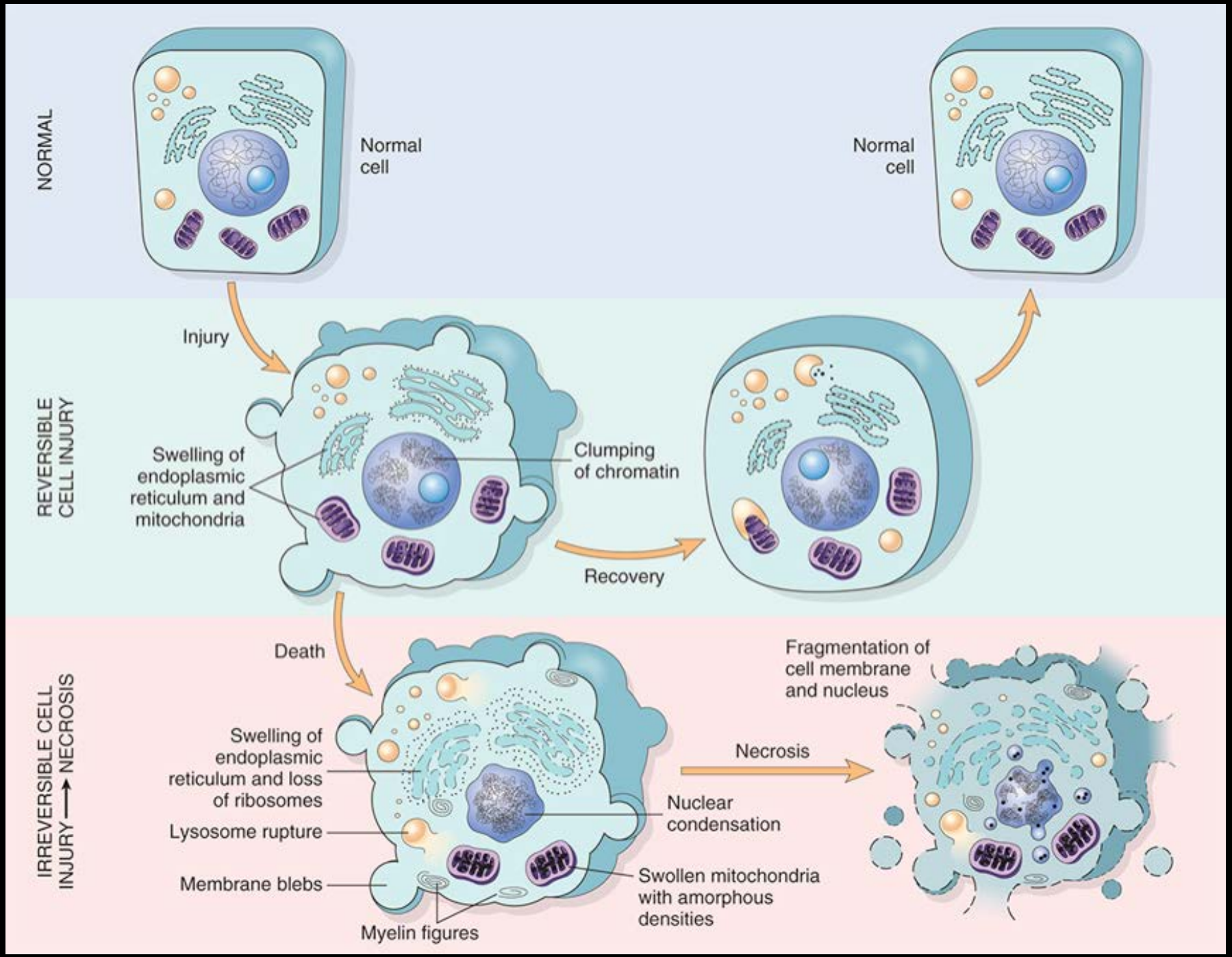
Four cellular systems susceptible to cell injury

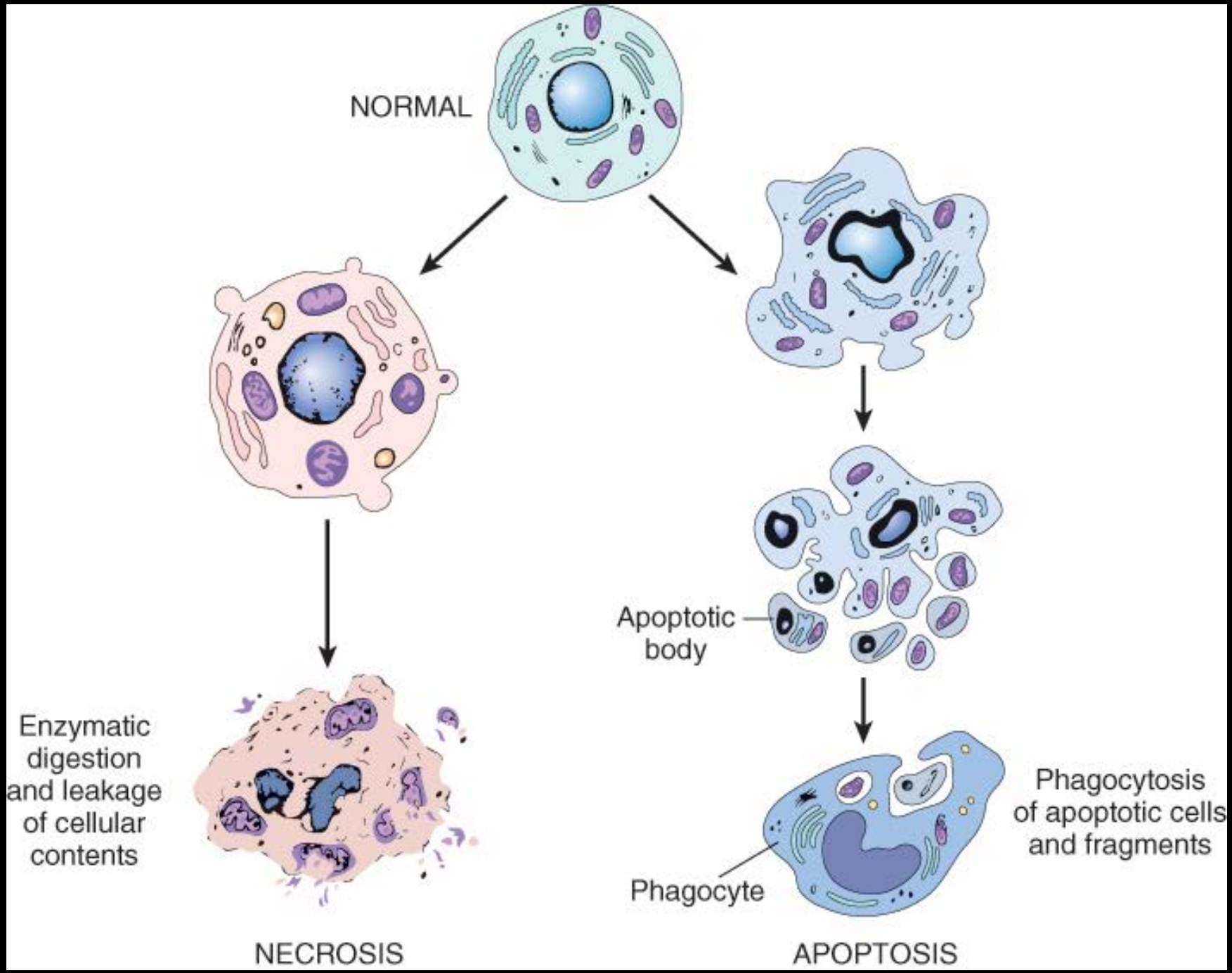
1. Integrity of cell membranes
2. Aerobic respiration
3. Synthesis of enzymes and structural proteins
4. Preservation of genetic apparatus of the cell

Cell Injury

- Disruption to cellular metabolism
- Morphologic changes are preceded by some critical biochemical alteration(s)
- Morphologic reactions are dependent upon the type of injury, its duration and severity
- Intrinsic characteristics of each cell will dictate the type of morphologic changes seen due to cell injury
- Cell's ability to adapt


REVERSIBLE INJURY
IRREVERSIBLE INJURY
(Cell death)
Ischemia
Membrane injury
Loss of phospholipids
Cytoskeletal alterations
Free radicals
Lipid breakdown
Others
↑ Leakage of enzymes (CK, LDH)
↑ Ca2+ influx
Mitochondria
↓ Oxidative phosphorylation
↓ Na pump
↑ Influx of Ca2+ H2O, and Na+
Efflux of K+
Cellular swelling
Loss of microvilli
Blebs
ER swelling
Myelin figures
Clumping of nuclear chromatin
↓ ATP
↑ Glycolysis
↓ pH
↓ Glycogen
Intracellular release and activation of lysosomal enzymes
↓ Basophilia (↓ RNP)
Nuclear changes
Protein digestion
Other effects
Detachment of ribosomes
↓ Protein synthesis
Lipid deposition


NORMAL
Normal cell
Normal cell
REVERSIBLE CELL INJURY
Injury
Swelling of endoplasmic reticulum and mitochondria
Clumping of chromatin
Recovery
IRREVERSIBLE CELL INJURY → NECROSIS
Death
Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture
Membrane blebs
Myelin figures
Nuclear condensation
Swollen mitochondria with amorphous densities
Necrosis
Fragmentation of cell membrane and nucleus


NORMAL
Enzymatic digestion and leakage of cellular contents
NECROSIS
Apoptotic body
Phagocyte
Phagocytosis of apoptotic cells and fragments
APOPTOSIS

Apoptosis

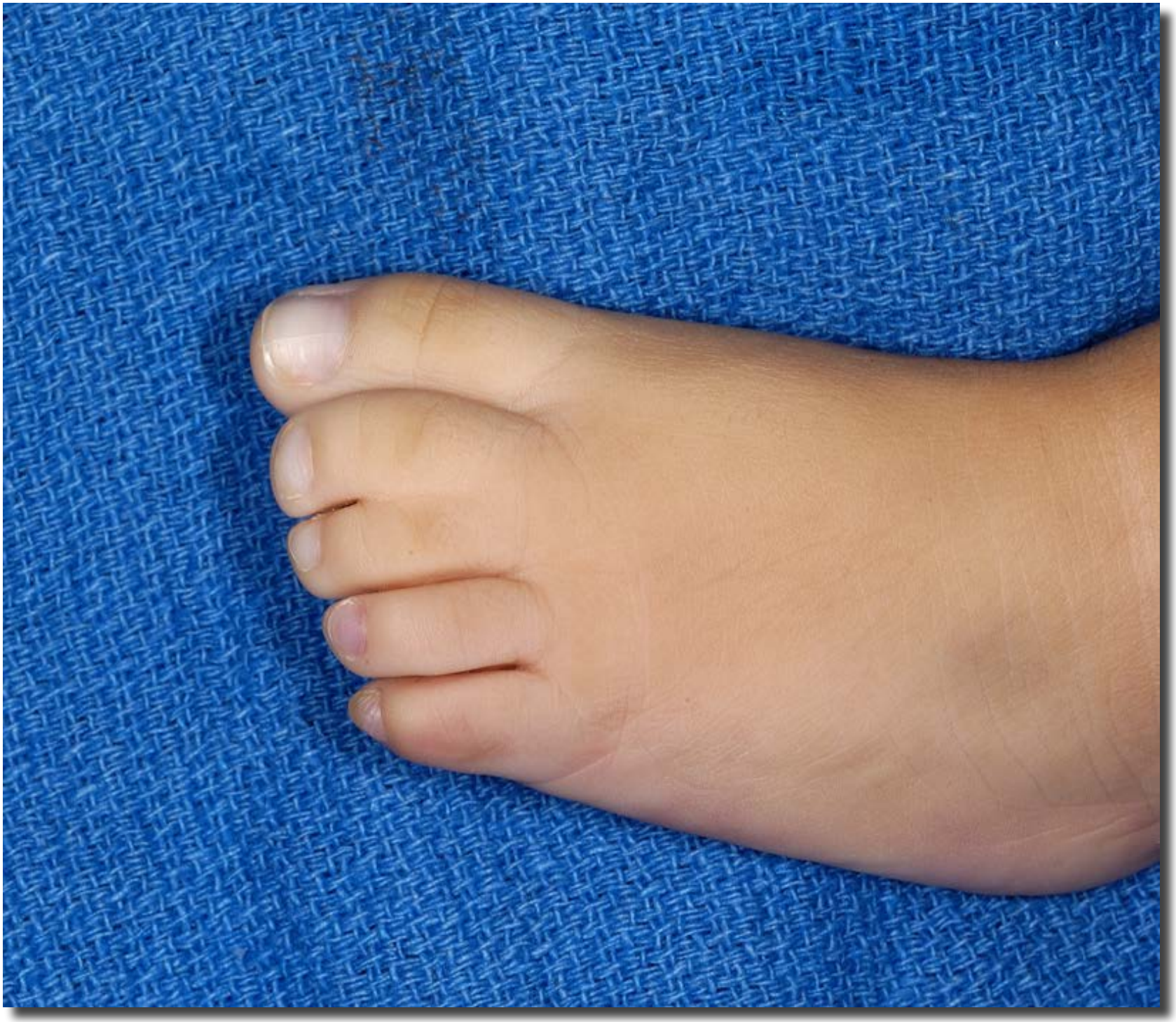
Light microscopy

Definition - programmed cell destruction or death without an inflammatory response

Physiologic

- Embryogenesis
- Hormone-dependent involution (e.g., endometrium, ovarian follicular atresia, decreased breast size following the cessation of breast feeding)
- Deletion of a portion of proliferating cells
- Selective death of immunocytes (T- and B-cells)

Syndactyly (fusion of digits)



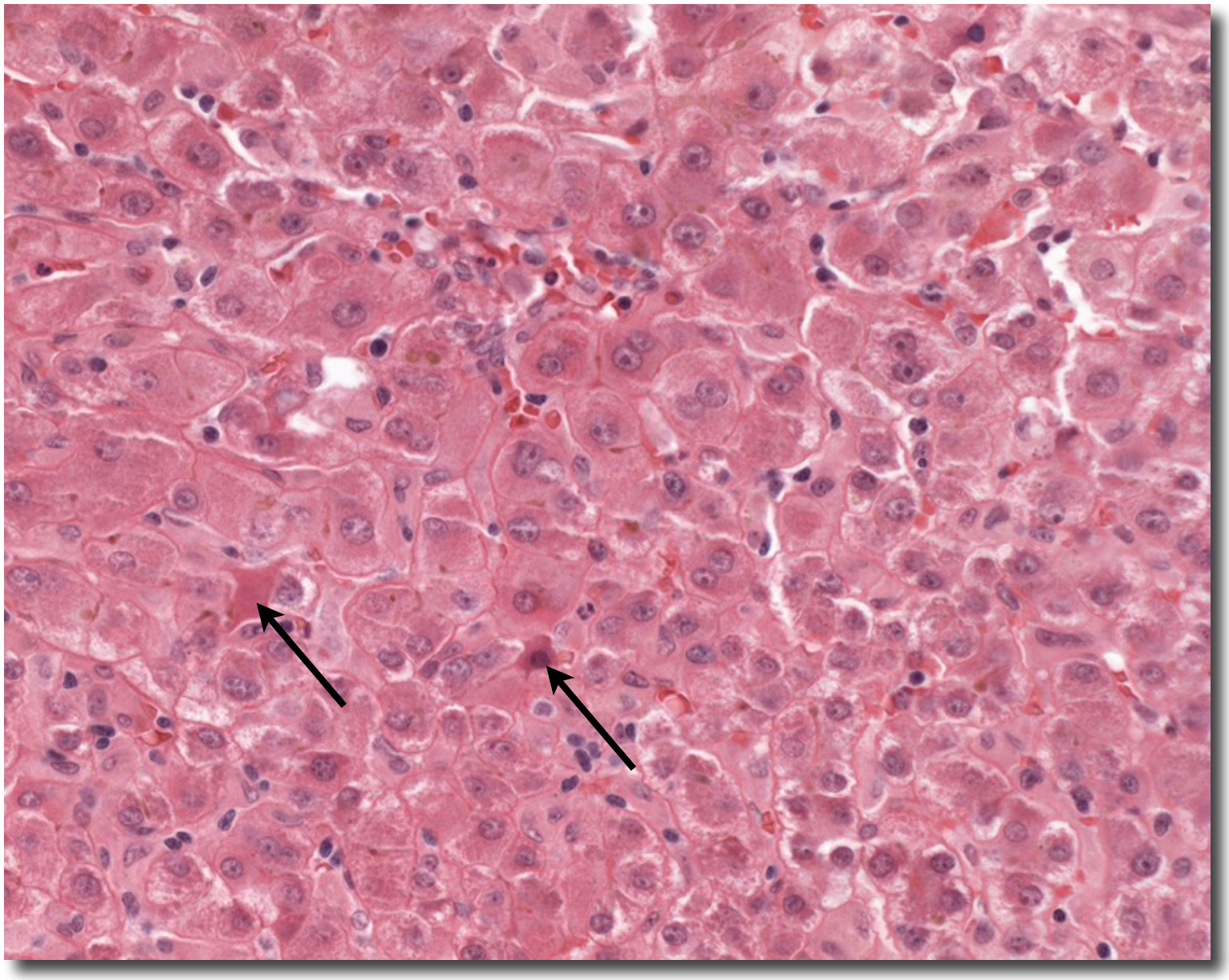
Morphology of Injured Cells

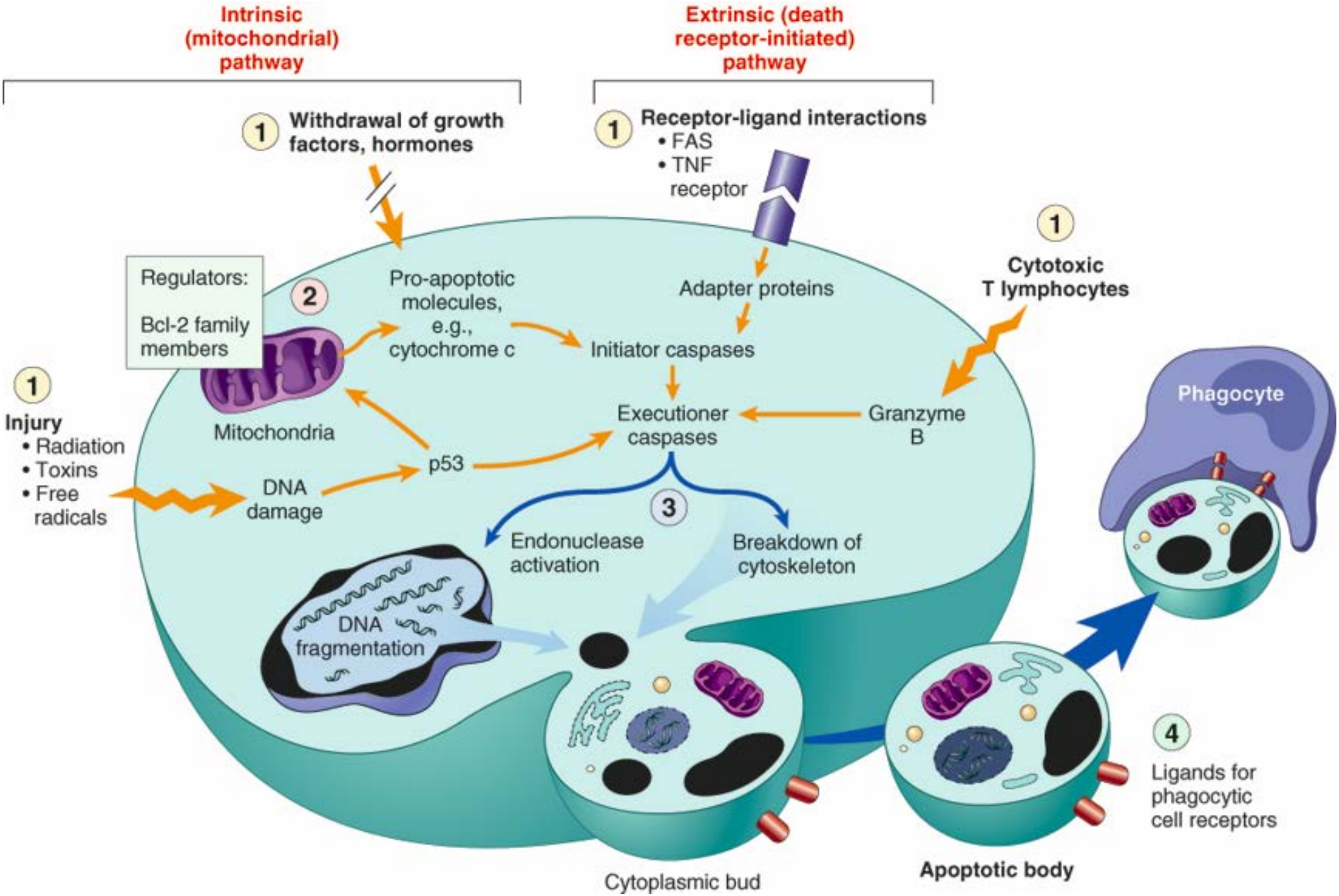
Light microscopy

Pathologic

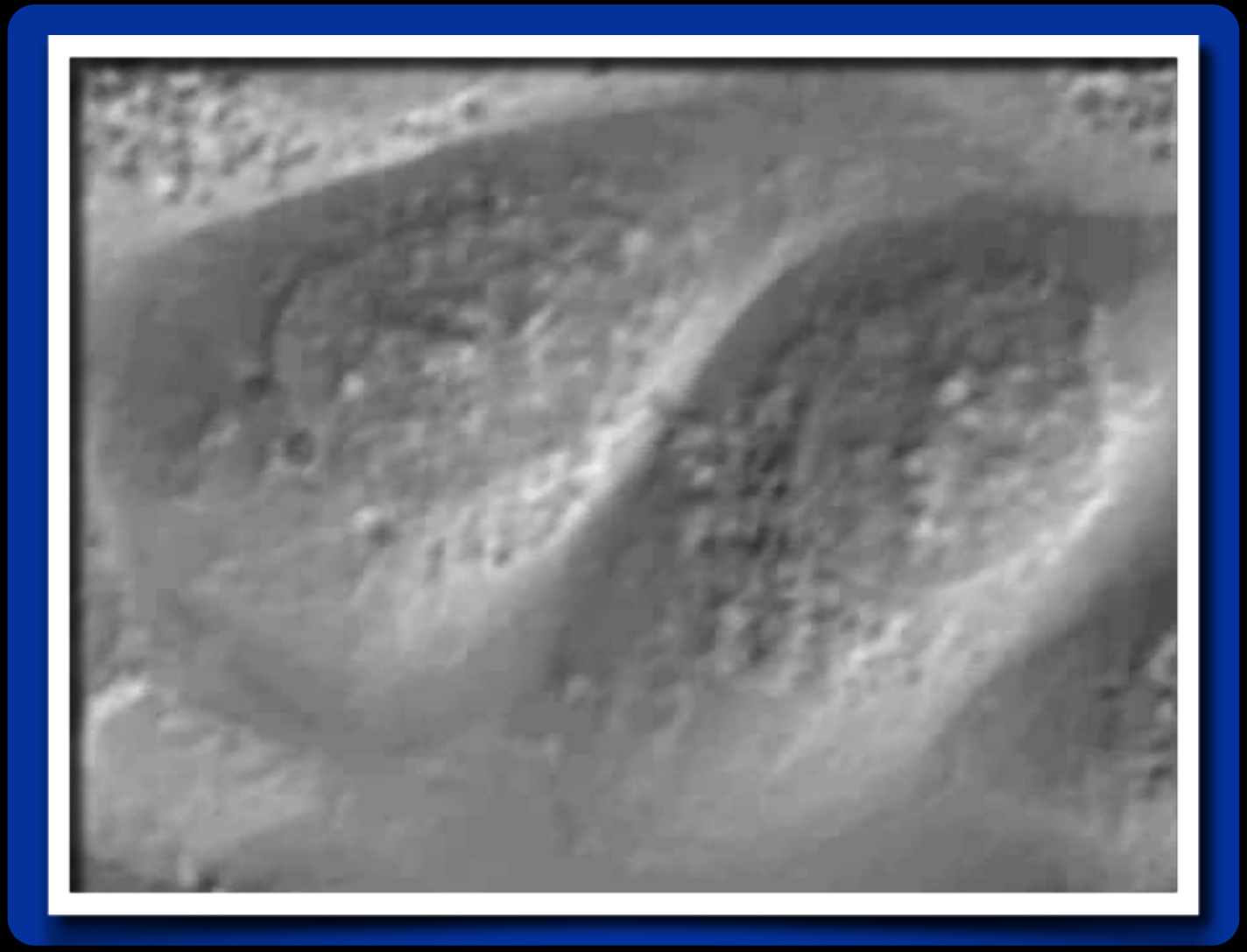
- Viral diseases leading to cell death (Councilman bodies in toxic or viral hepatitis)
- Atrophy (prostatic atrophy after castration)
- Duct obstruction (kidney, pancreas and parotid)
- Cell death induced by T8 lymphocytes (GHD)
- Injurious agents (cytotoxic anticancer drugs)

Acute Viral Hepatitis: Apoptosis

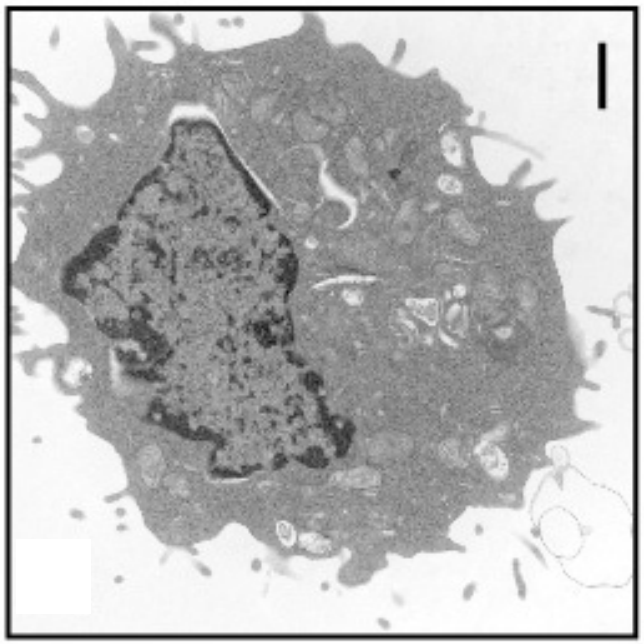



Intrinsic (mitochondrial) pathway
Extrinsic (death receptor-initiated) pathway
1 Withdrawal of growth factors, hormones
1 Receptor-ligand interactions
• FAS
• TNF receptor
1 Cytotoxic T lymphocytes
Regulators:
Bcl-2 family members
2
Pro-apoptotic molecules, e.g., cytochrome c
Adapter proteins
Initiator caspases
1 Injury
• Radiation
• Toxins
• Free radicals
Mitochondria
Executioner caspases
Granzyme B
p53
DNA damage
3
Endonuclease activation
Breakdown of cytoskeleton
DNA fragmentation
Phagocyte
4 Ligands for phagocytic cell receptors
Cytoplasmic bud
Apoptotic body

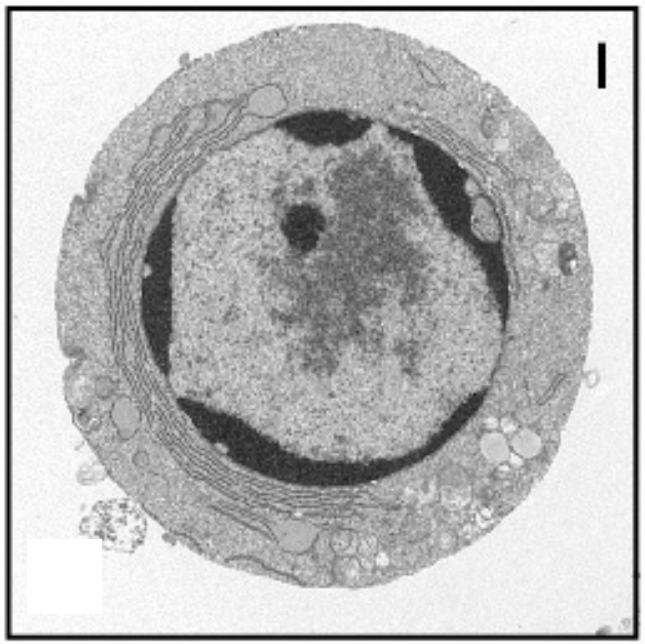
Apoptosis



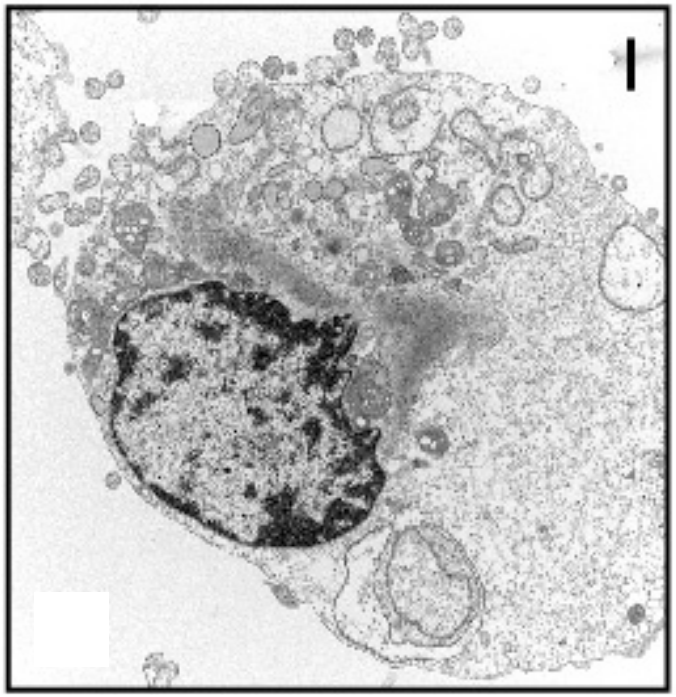
Normal

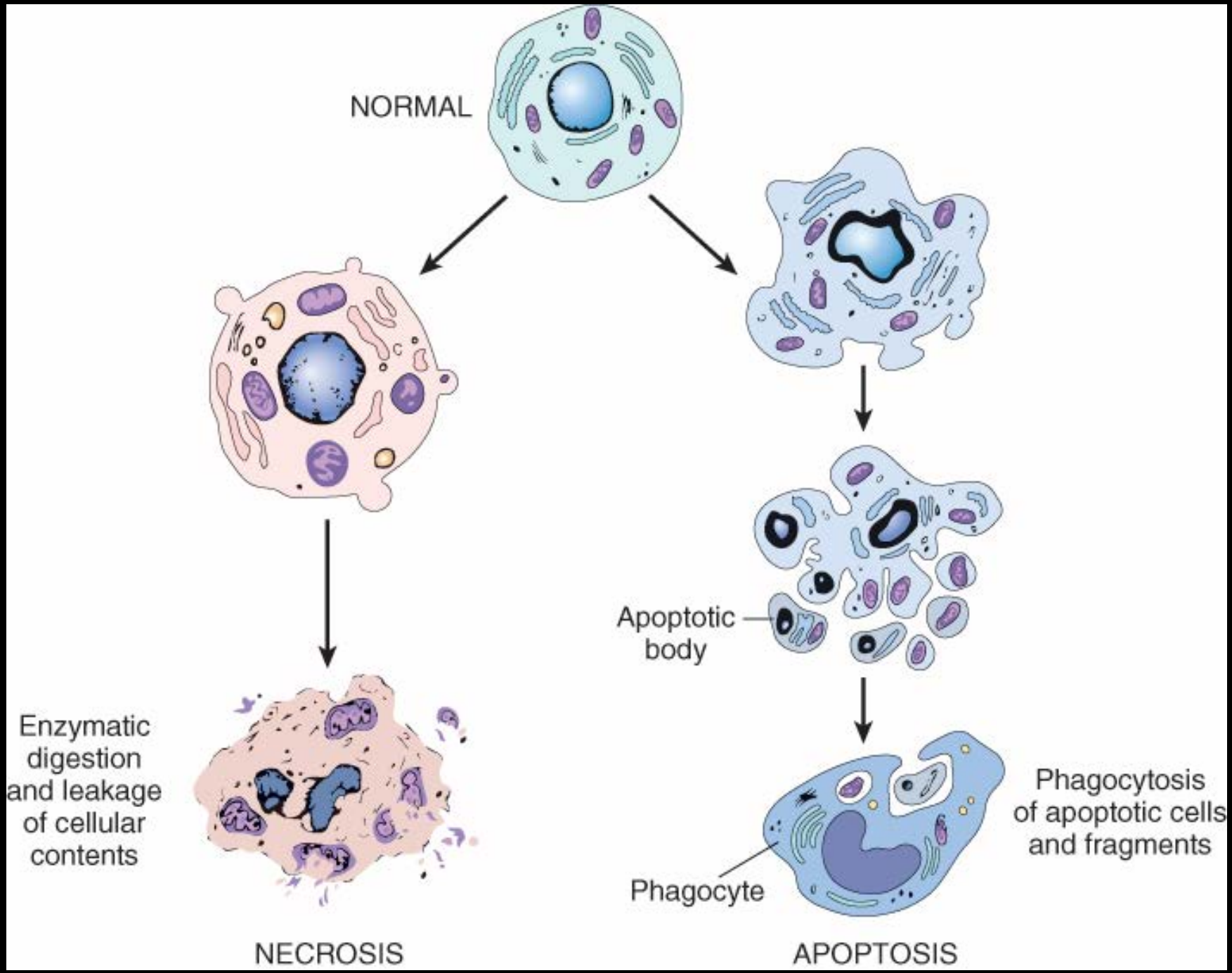


Apoptosis



Necrosis

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Enzymatic digestion and leakage of cellular contents
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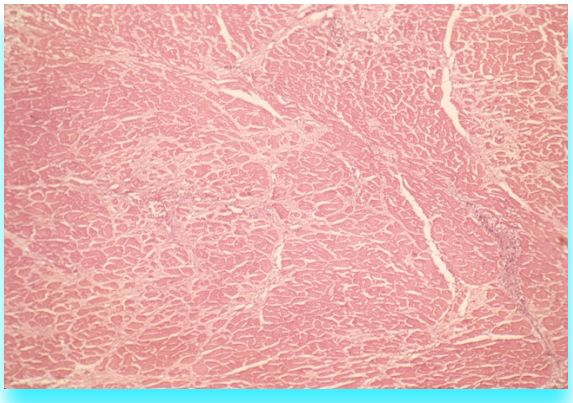
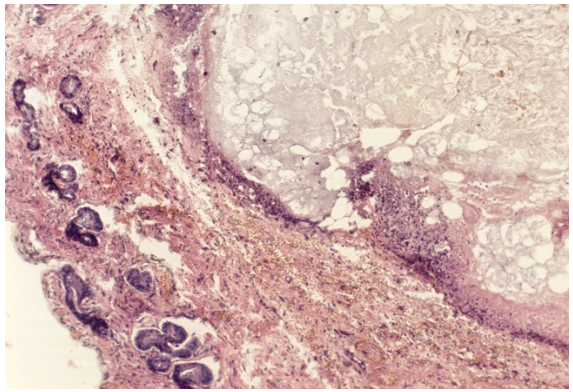
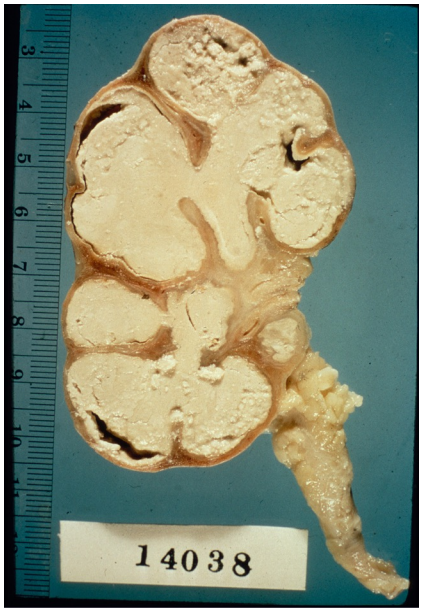
Types of Necrosis



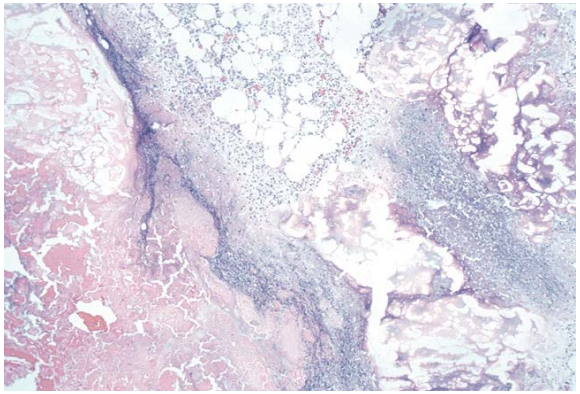
Coagulative Necrosis



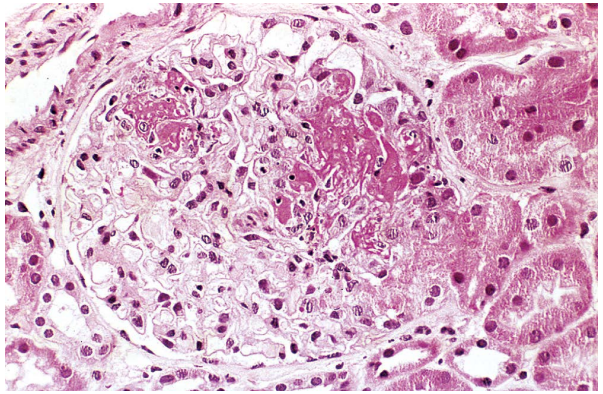
Liquifactive Necrosis



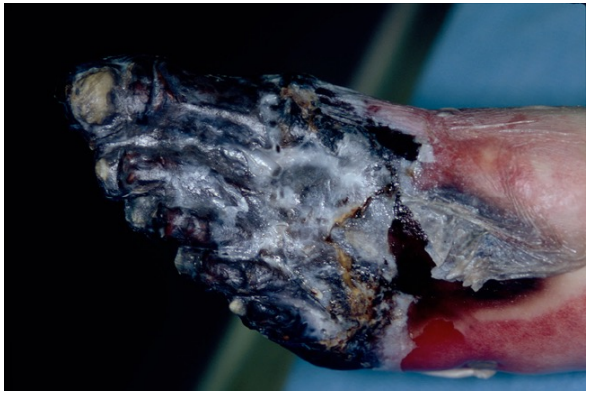
Caseous Necrosis



Fat Necrosis



Fibrinoid Necrosis

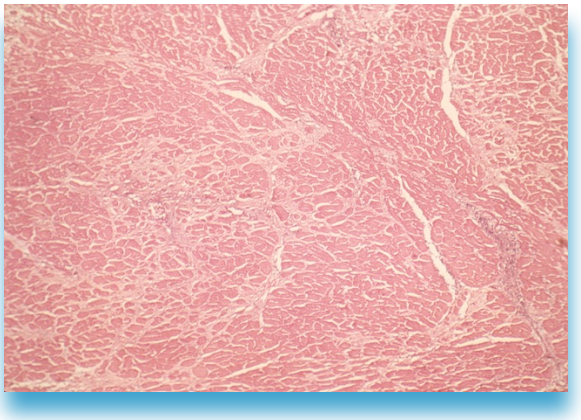


Gangrenous Necrosis

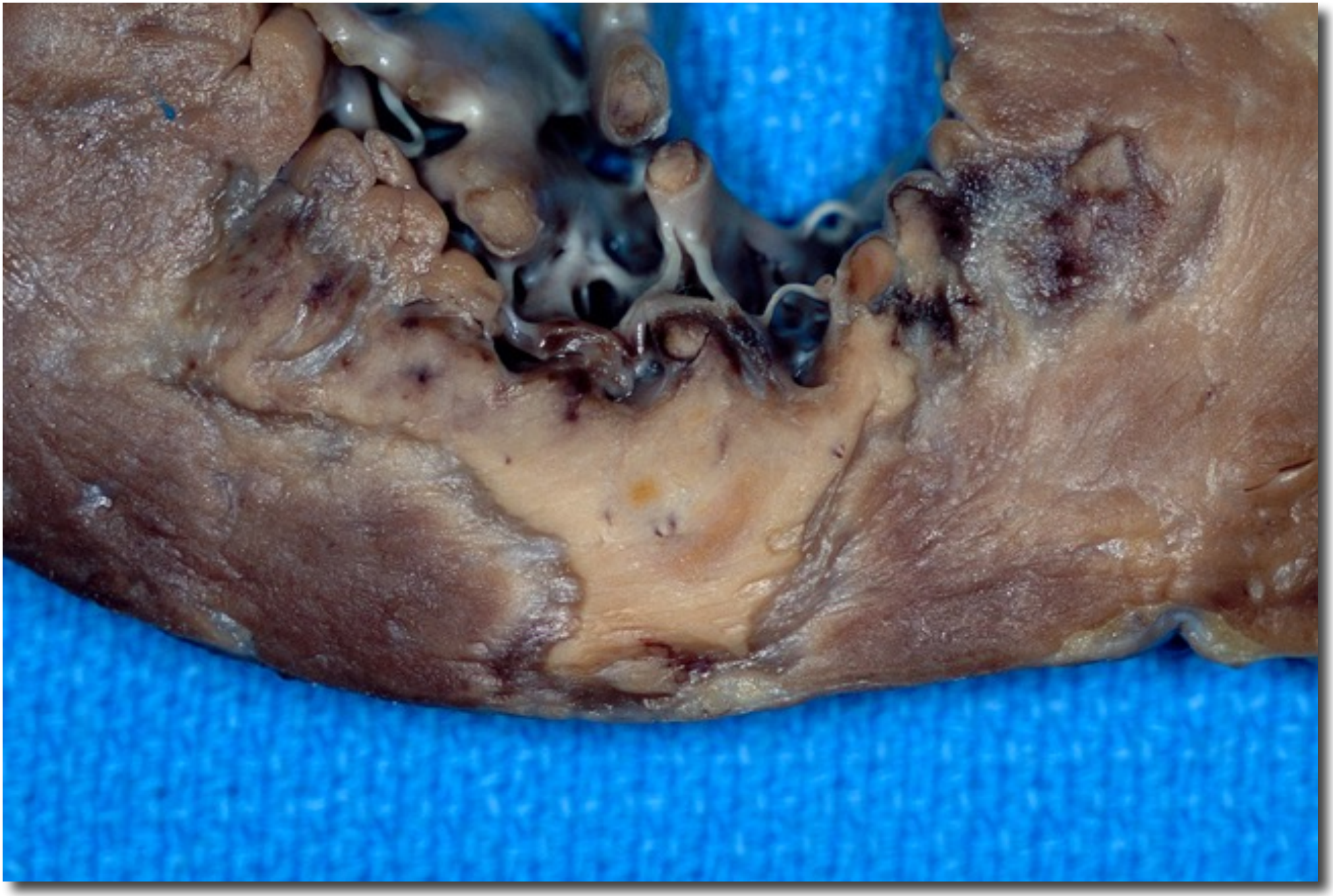
Types of Necrosis

Coagulative necrosis

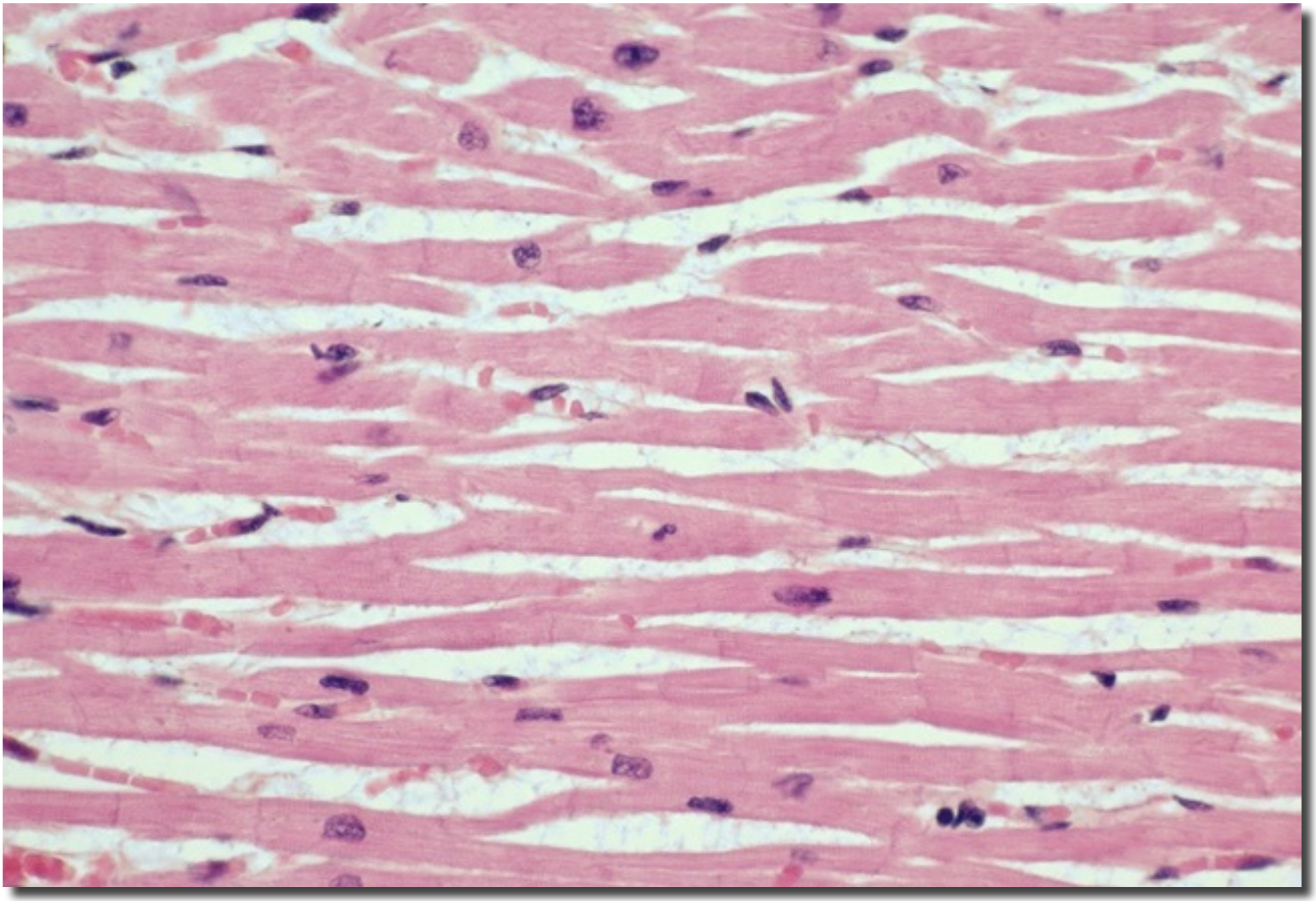
- Dissolution of nucleus with preservation of the basic cellular shape and tissue architecture
- Most common pattern of necrosis
- Mechanism: Ischemia leading to infarction



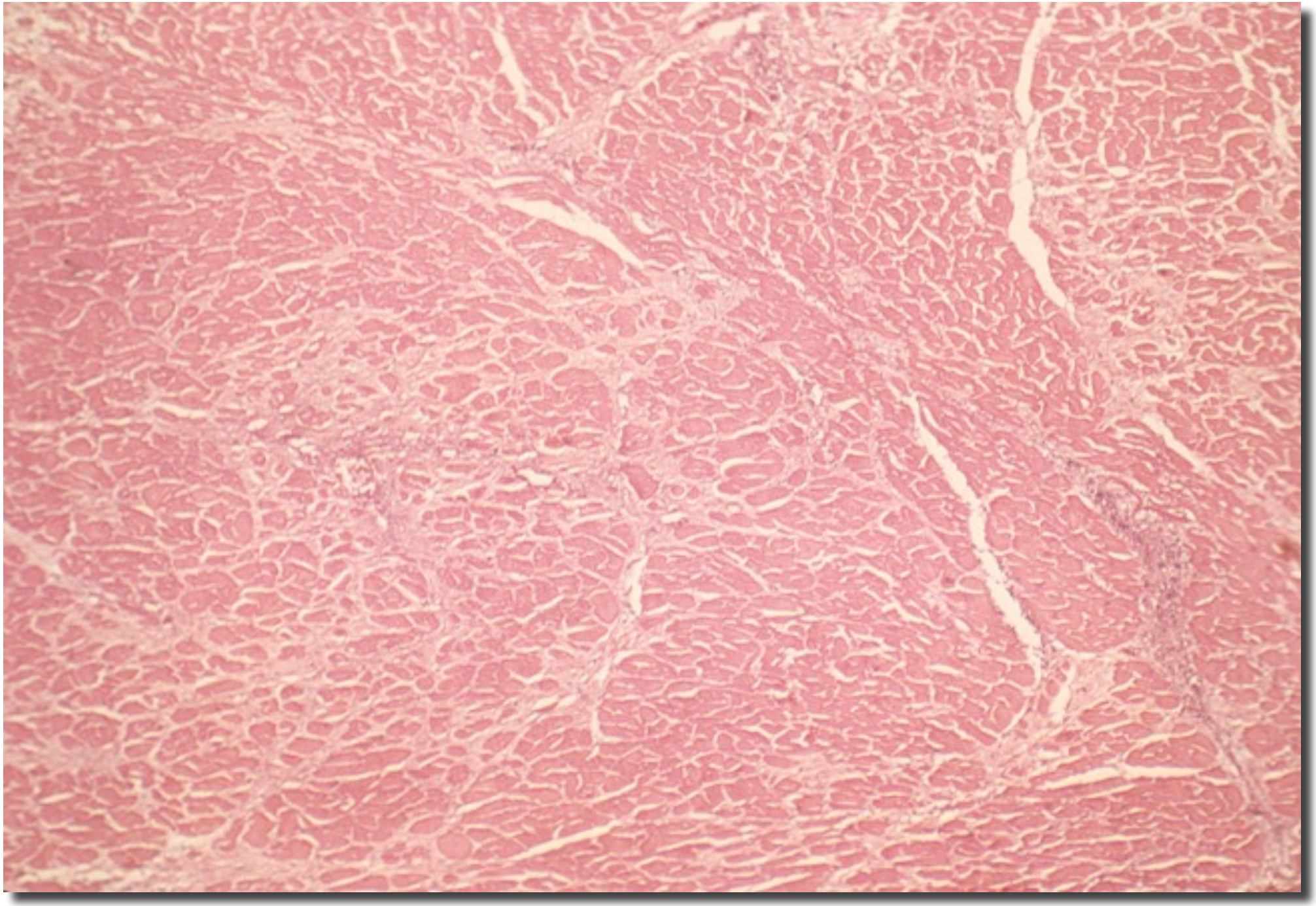
Acute Transmural Myocardial Infarct: Coagulative Necrosis



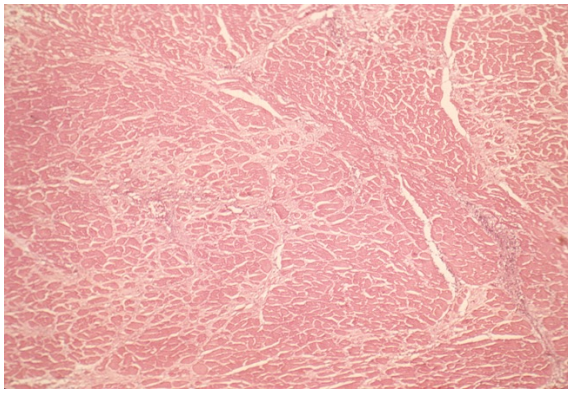
Normal Myocardium



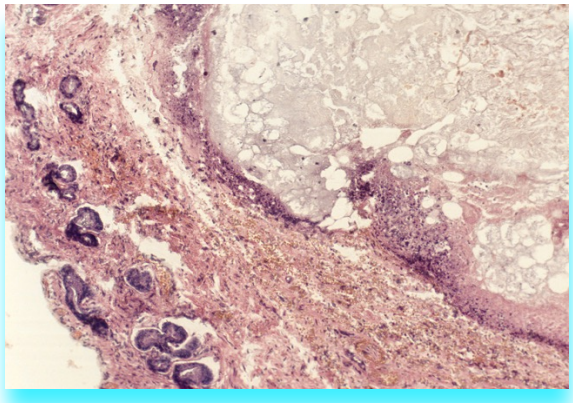
Acute Myocardial Infarct: Coagulative Necrosis



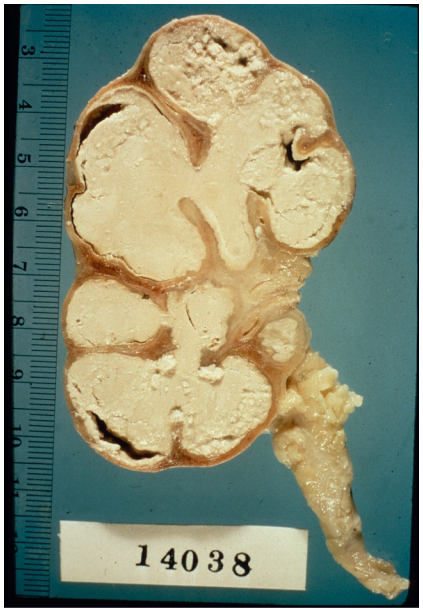
Types of Necrosis



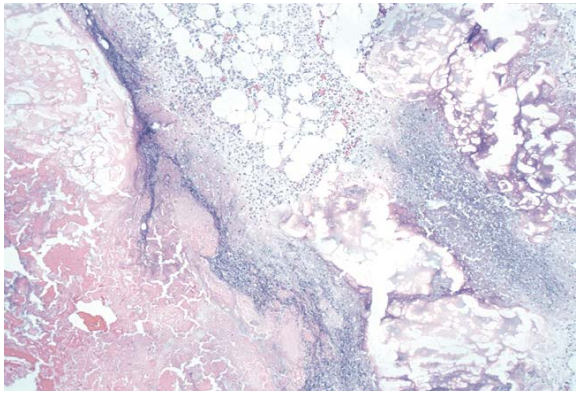
Coagulative Necrosis



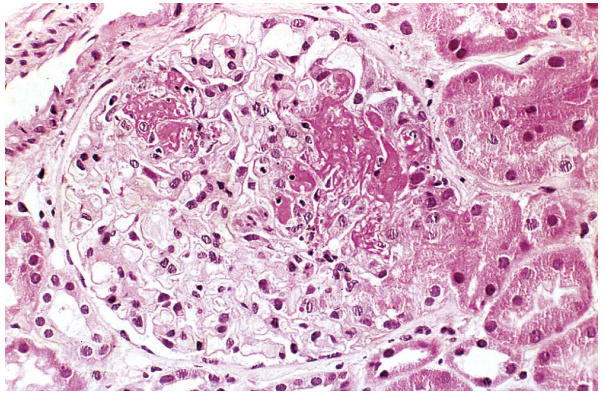
Liquifactive Necrosis



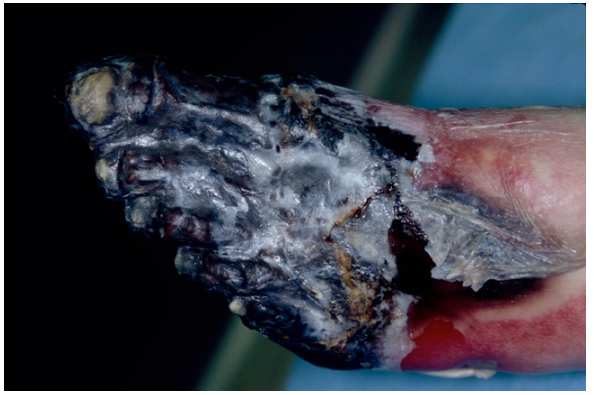
Caseous Necrosis



Fat Necrosis



Fibrinoid Necrosis

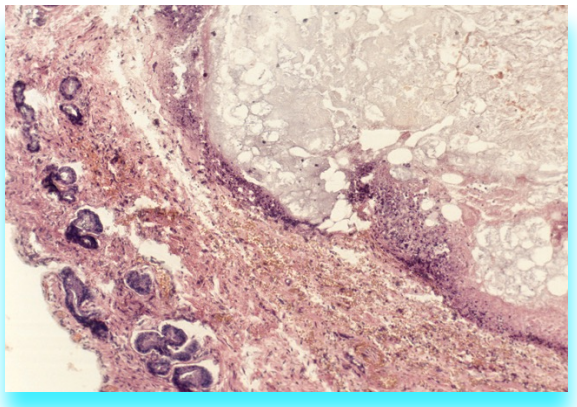


Gangrenous Necrosis

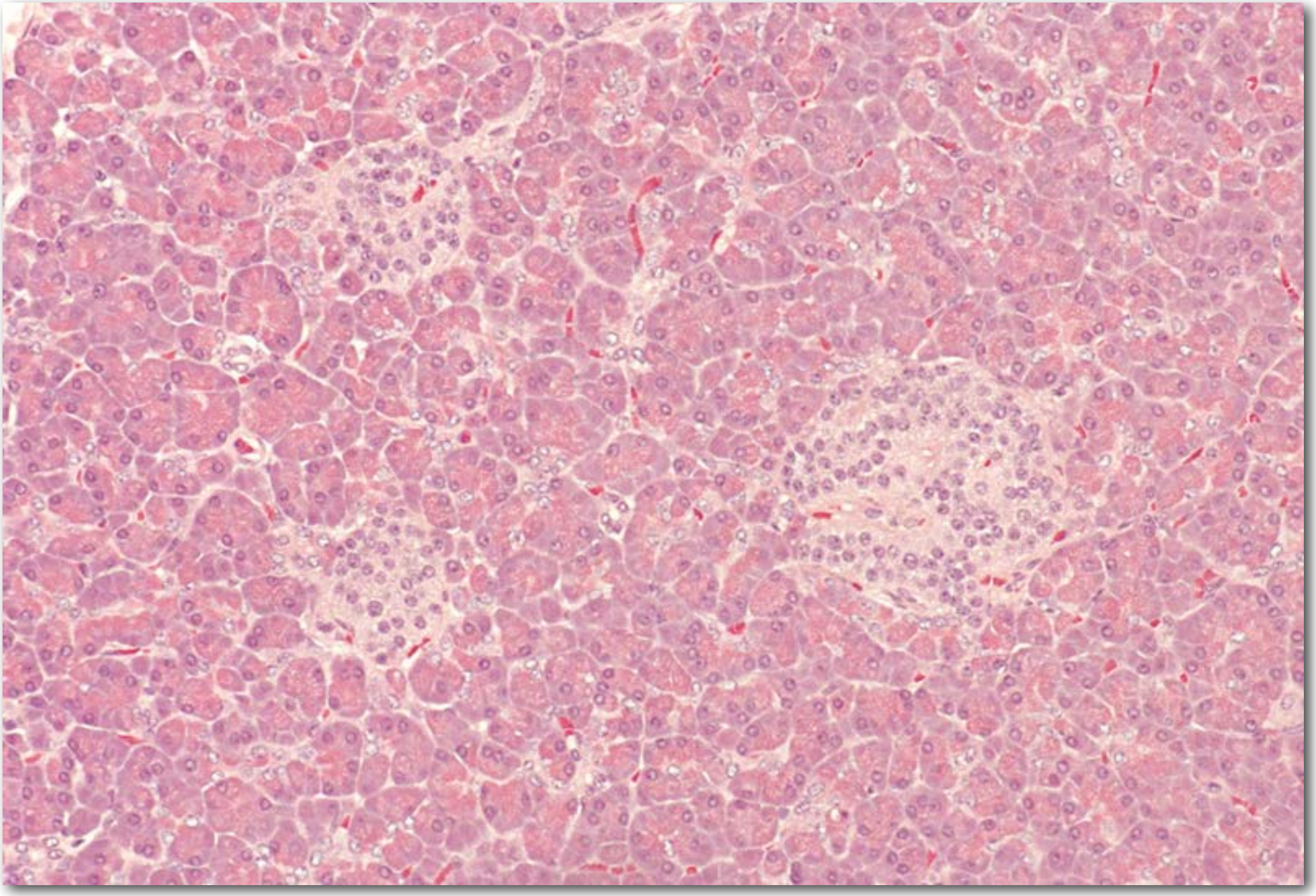
Types of Necrosis

Liquefactive necrosis

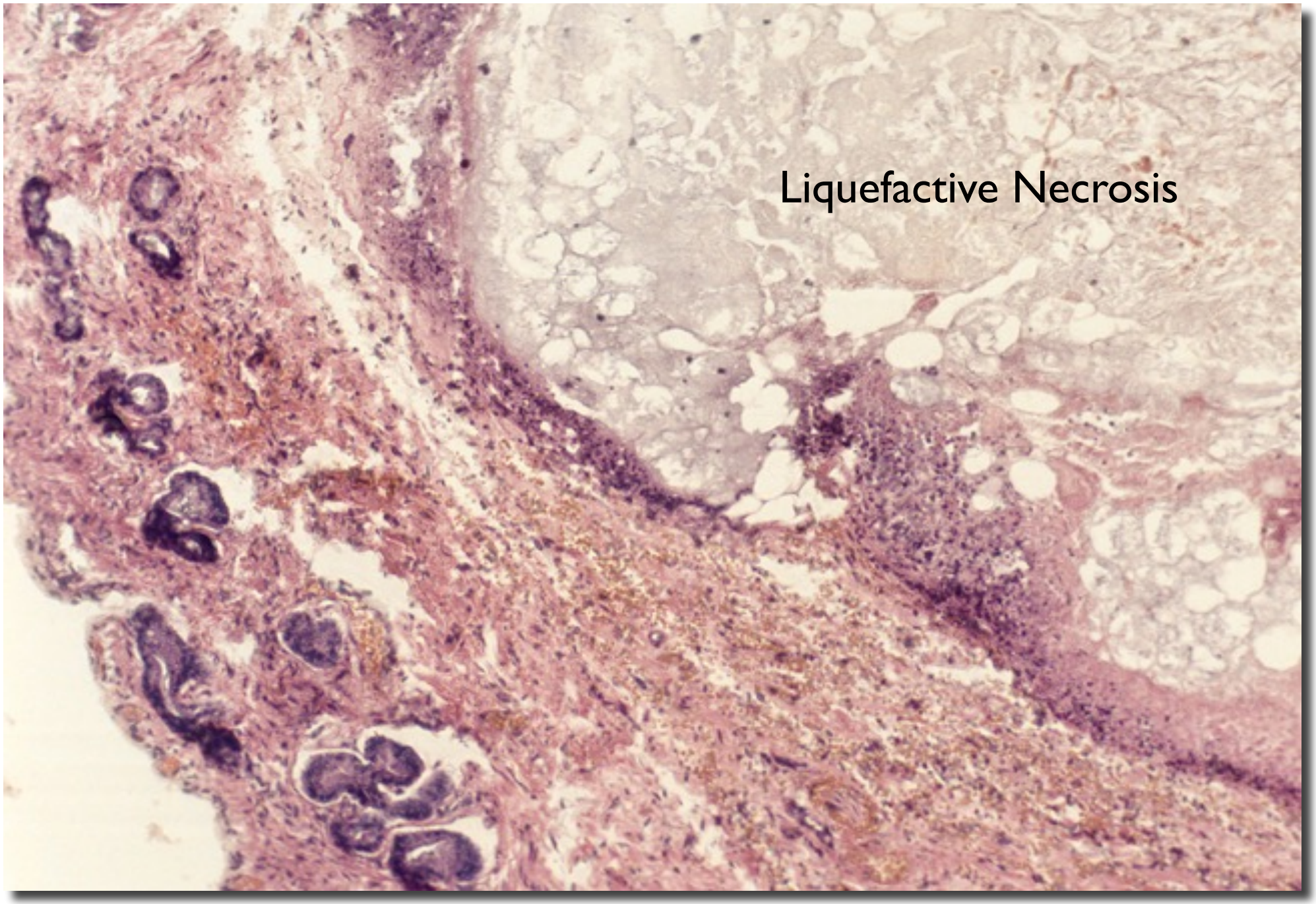
- Action of hydrolytic enzymes including autolysis and heterolysis
- Mechanism: Extensive release of enzymes - abscess formation, pancreatic pseudocyst in acute and chronic pancreatitis



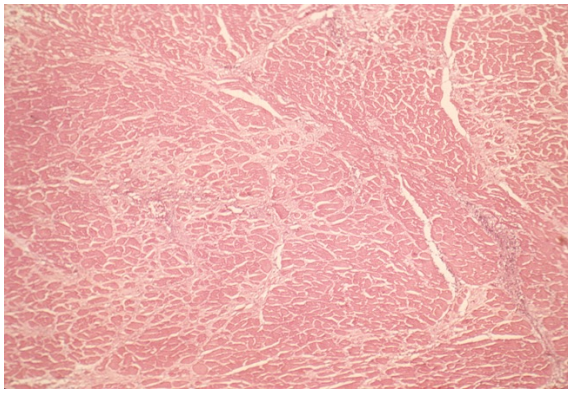
Normal Pancreas



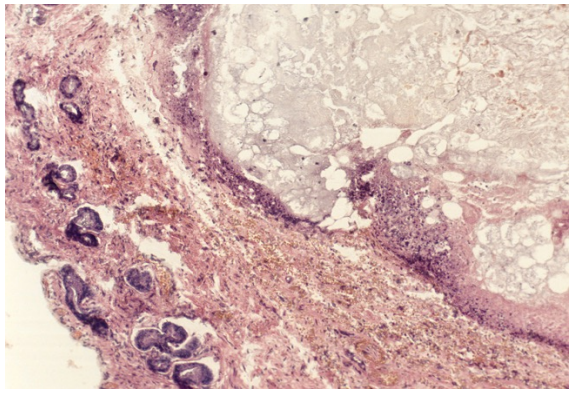
Acute Pancreatitis: Liquefative Necrosis



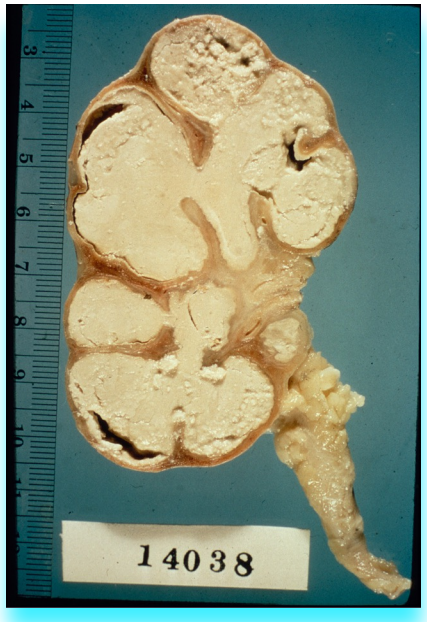
Types of Necrosis



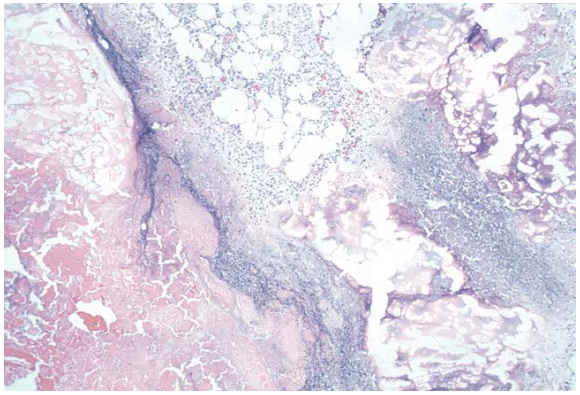
Coagulative Necrosis



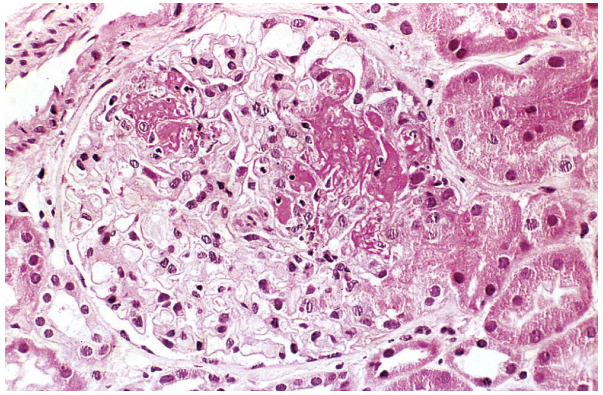
Liquifactive Necrosis



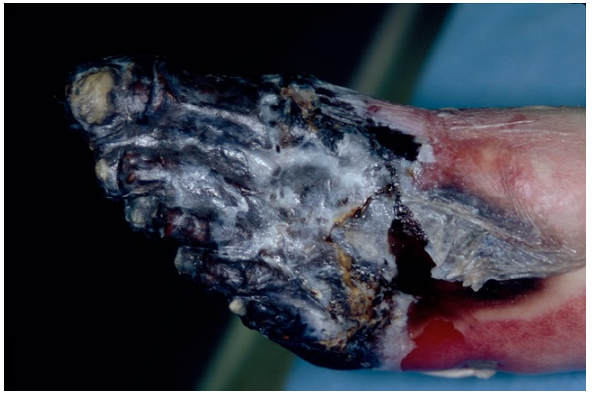
Caseous Necrosis



Fat Necrosis



Fibrinoid Necrosis



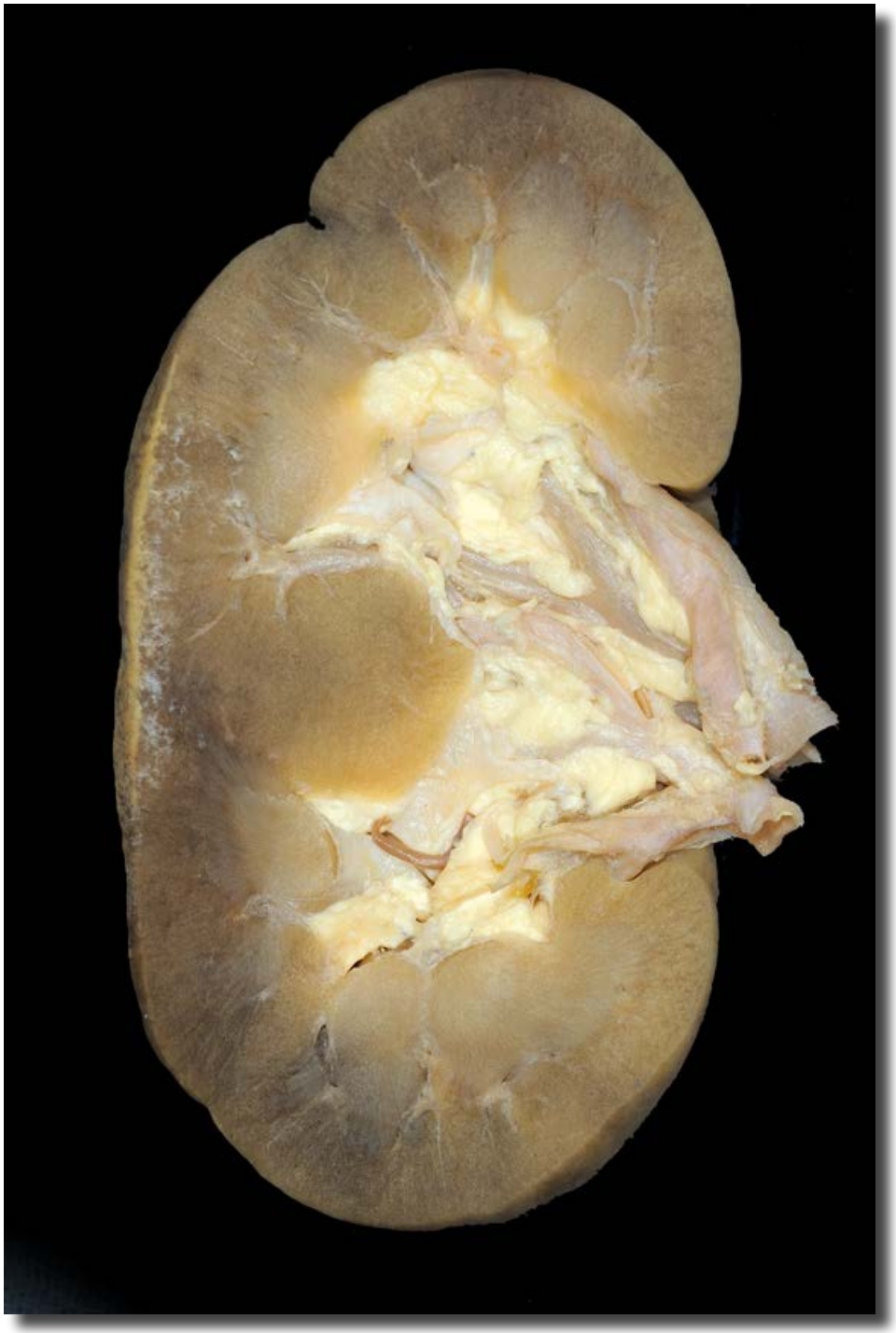
Gangrenous Necrosis

Types of Necrosis

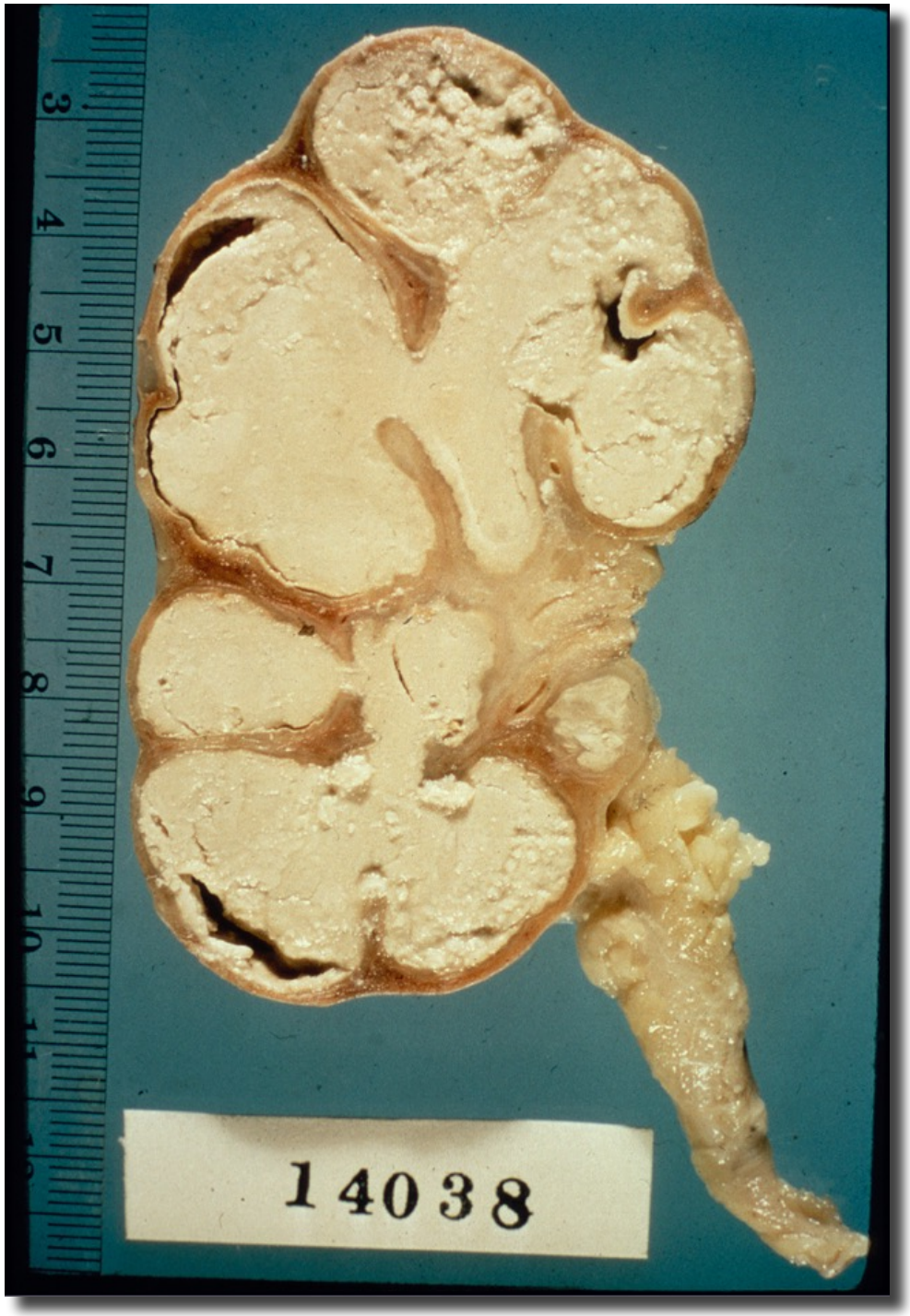
Caseous (cheesy) necrosis

- Combination of coagulative and liquefaction necrosis
- Mechanism: Granulomatous inflammation

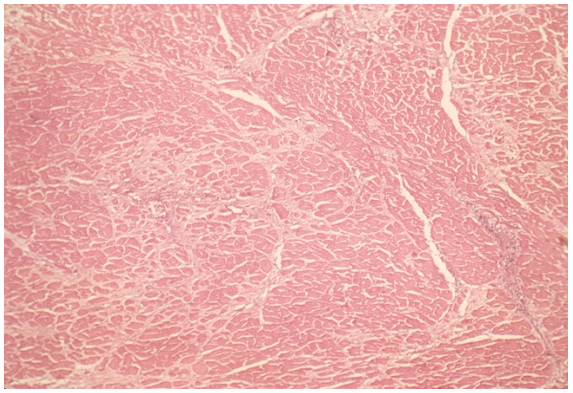
Normal Kidney



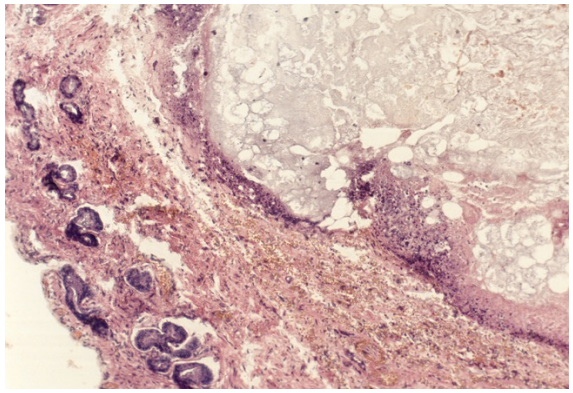
Renal Tuberculosis: Caseous Necrosis



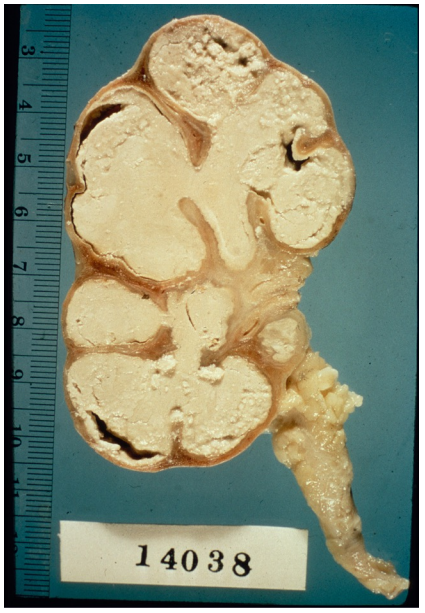
Types of Necrosis



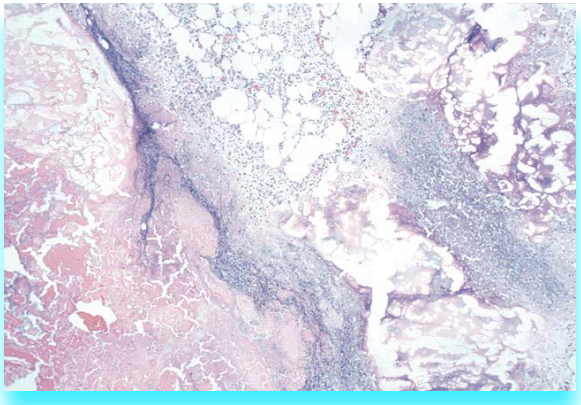
Coagulative Necrosis



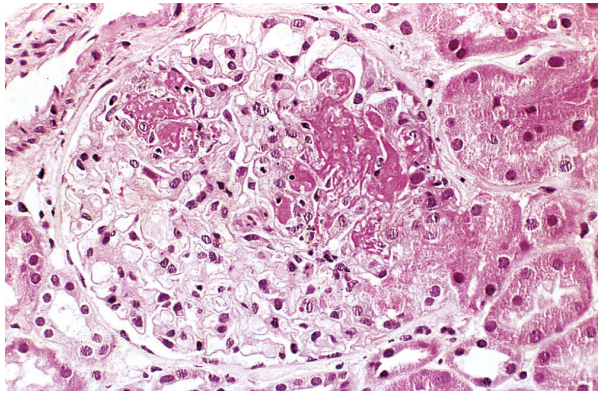
Liquifactive Necrosis



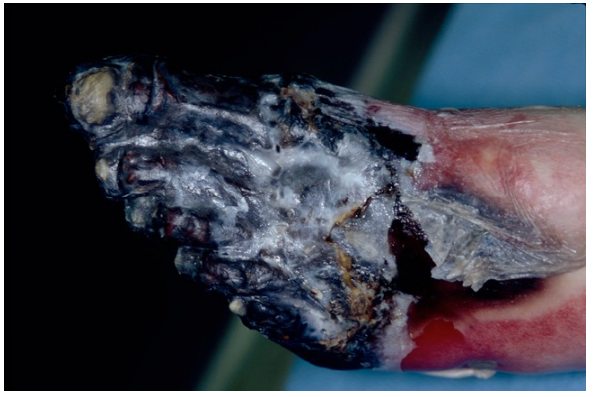
Caseous Necrosis



Fat Necrosis



Fibrinoid Necrosis

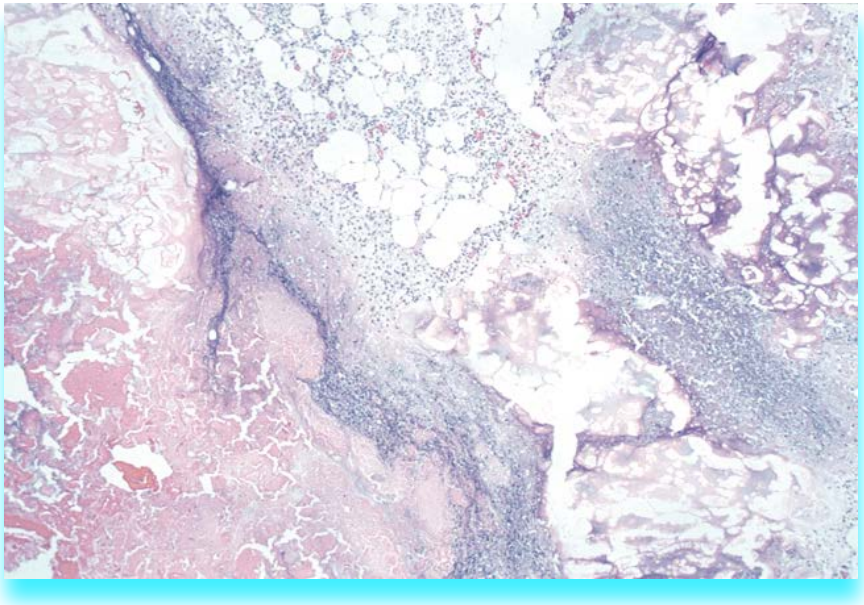


Gangrenous Necrosis

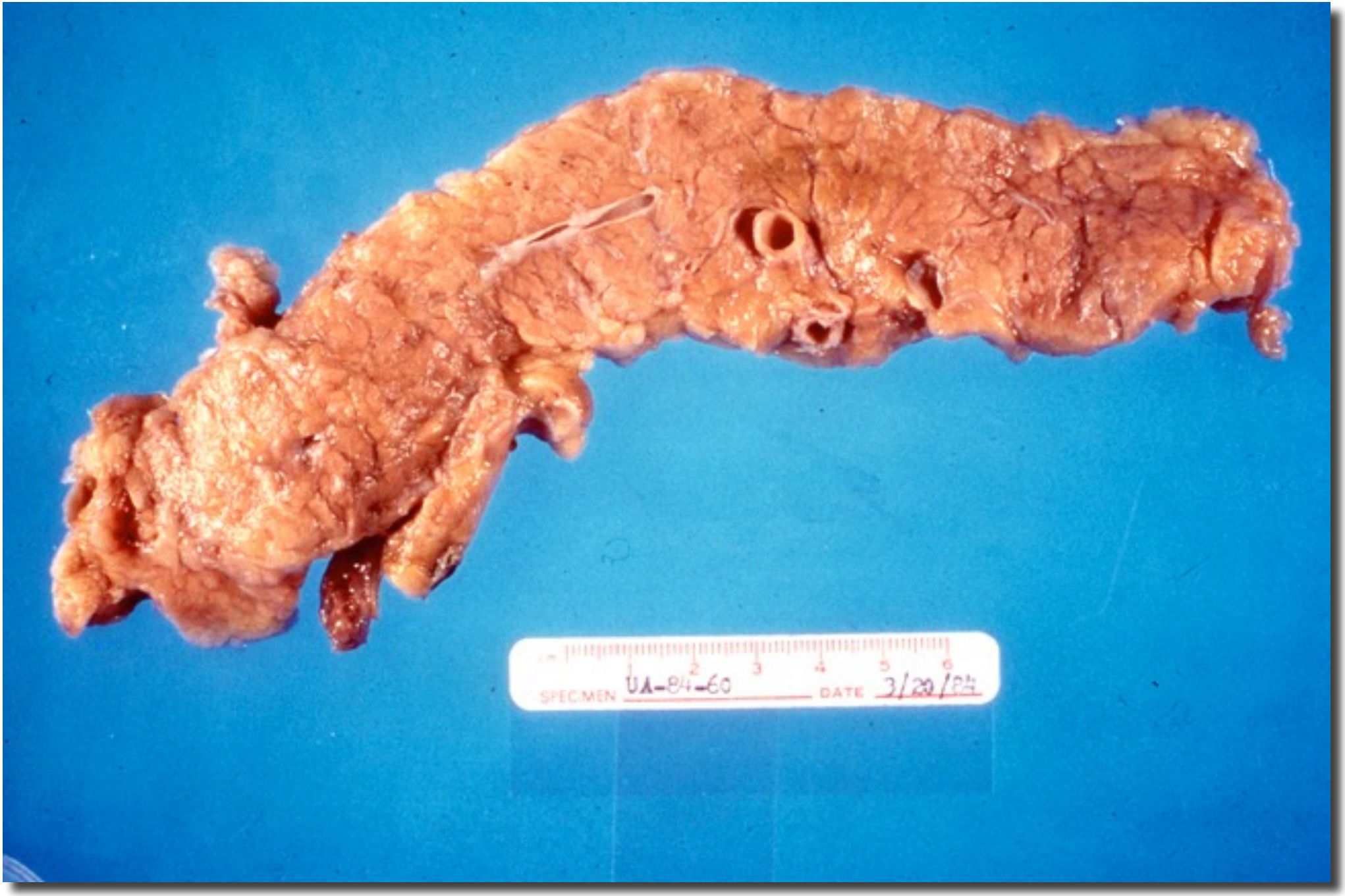
Types of Necrosis

Fat necrosis

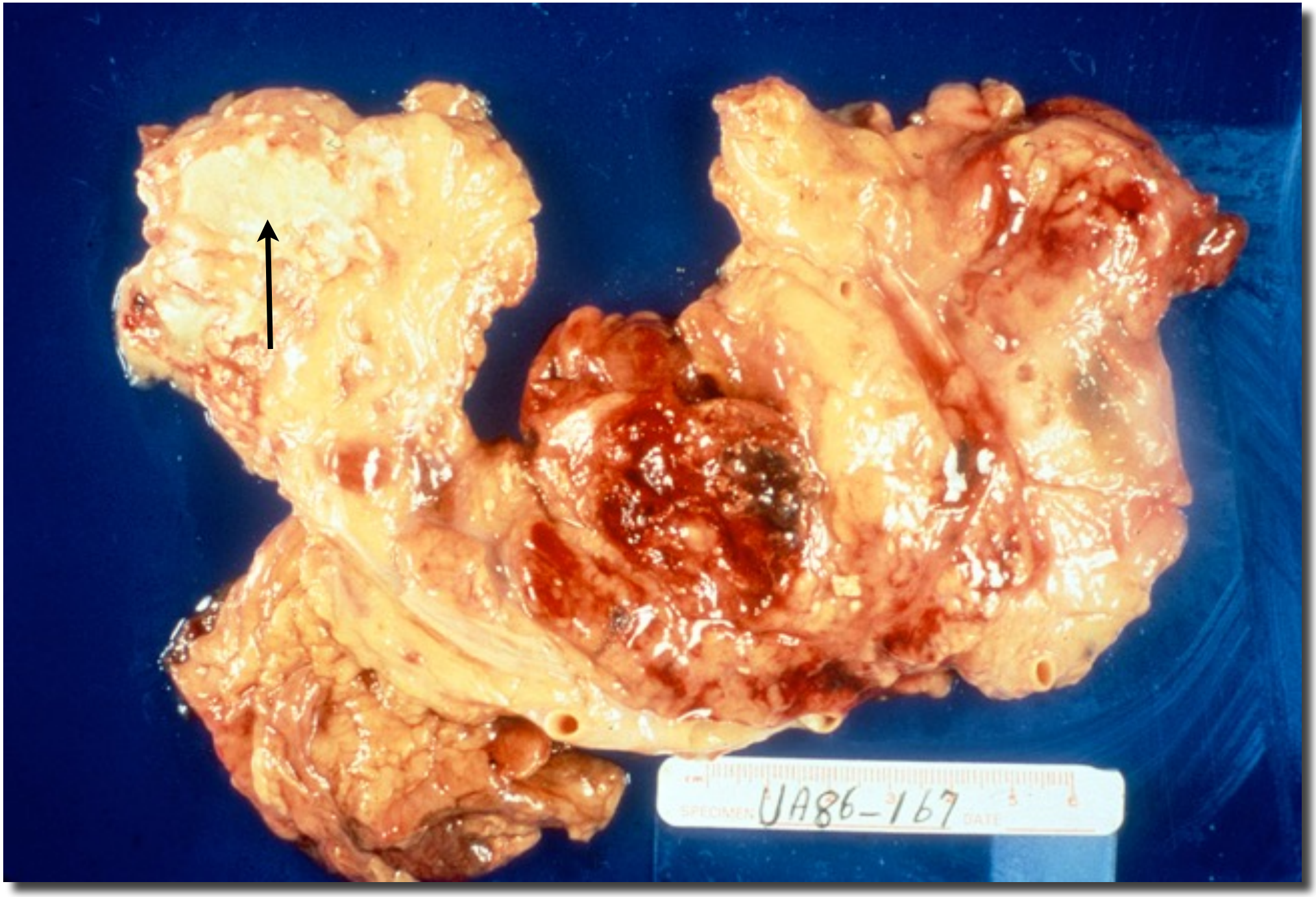
- Mechanism: Destruction of adipose tissue due to the action of lipases



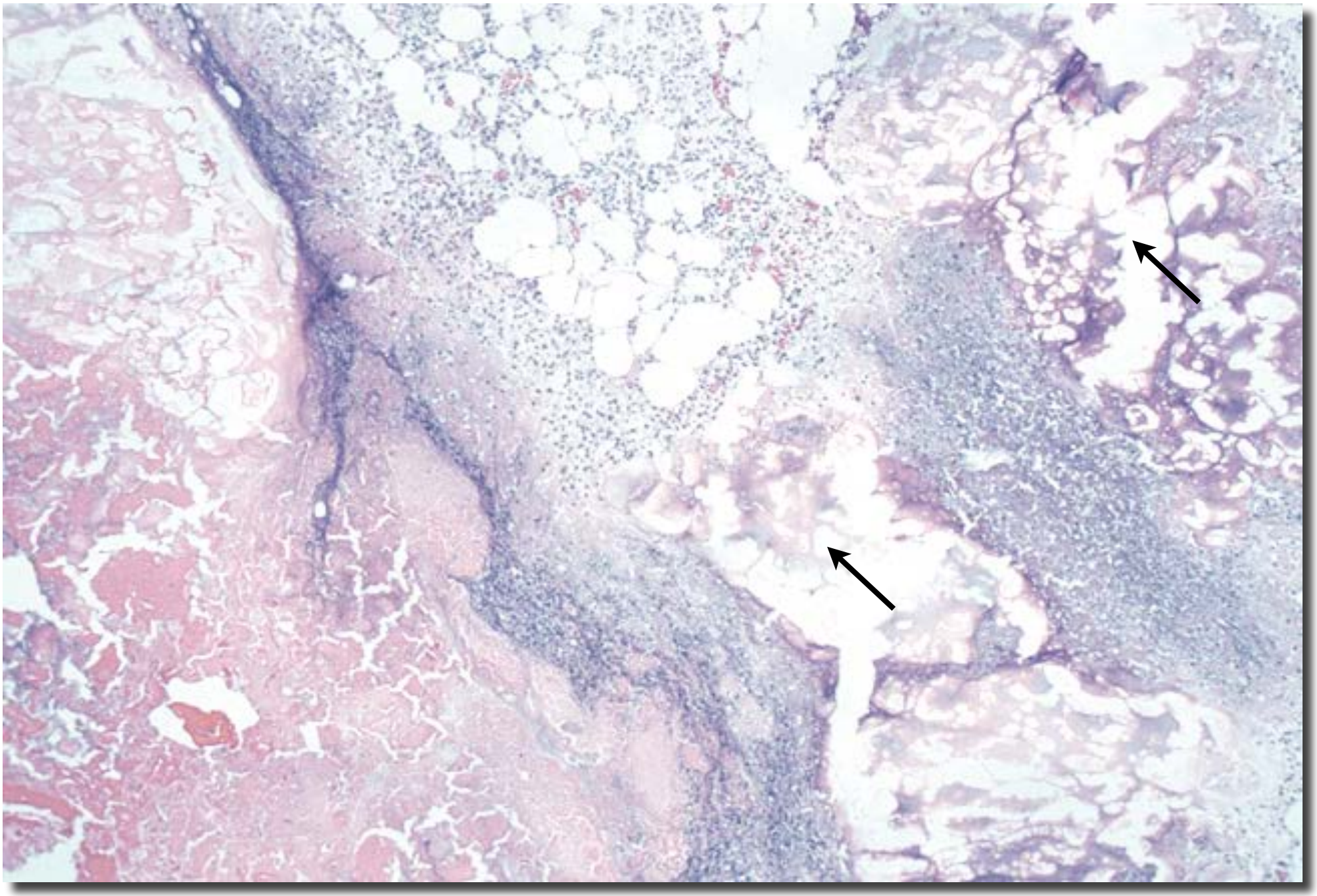
Normal Pancreas



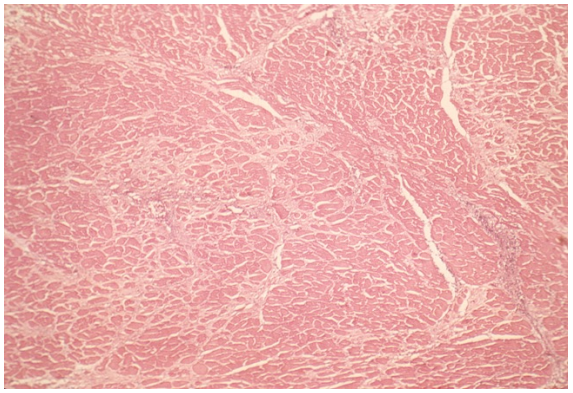
Acute Hemorrhagic Pancreatitis: Fat Necrosis



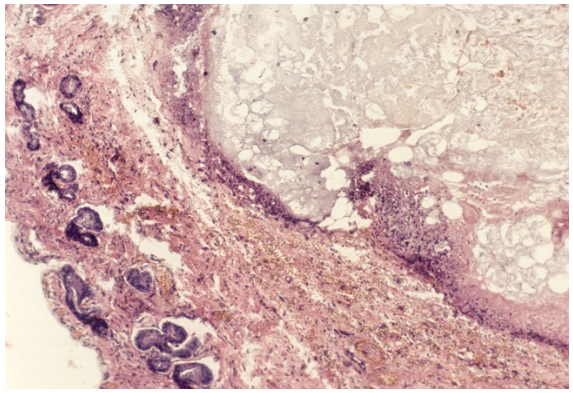
Acute Pancreatitis: Fat Necrosis



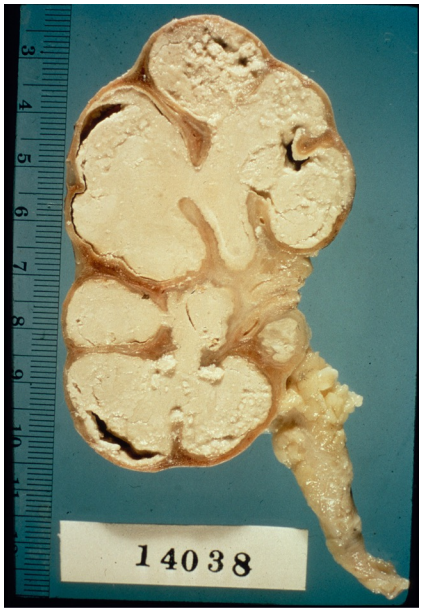
Types of Necrosis



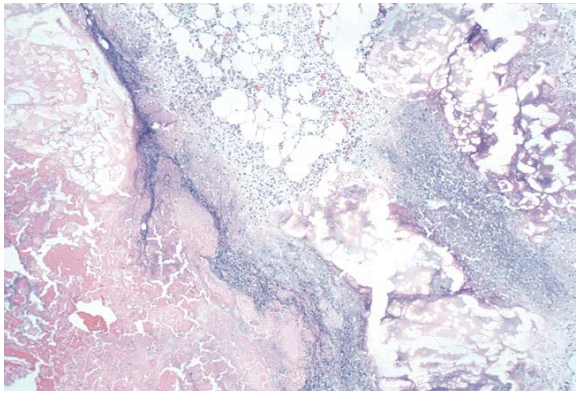
Coagulative Necrosis



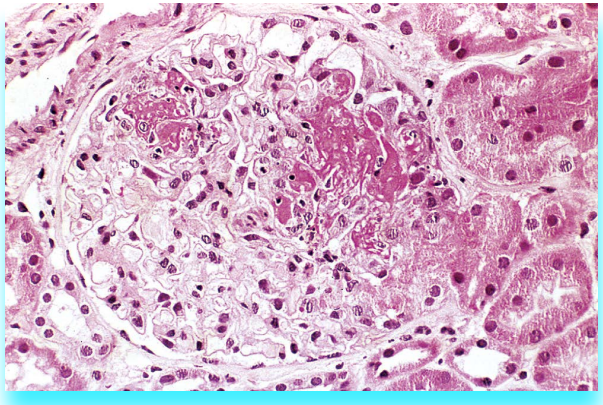
Liquifactive Necrosis



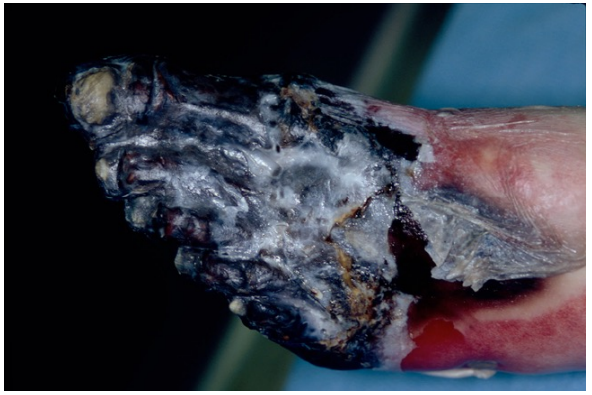
Caseous Necrosis



Fat Necrosis



Fibrinoid Necrosis

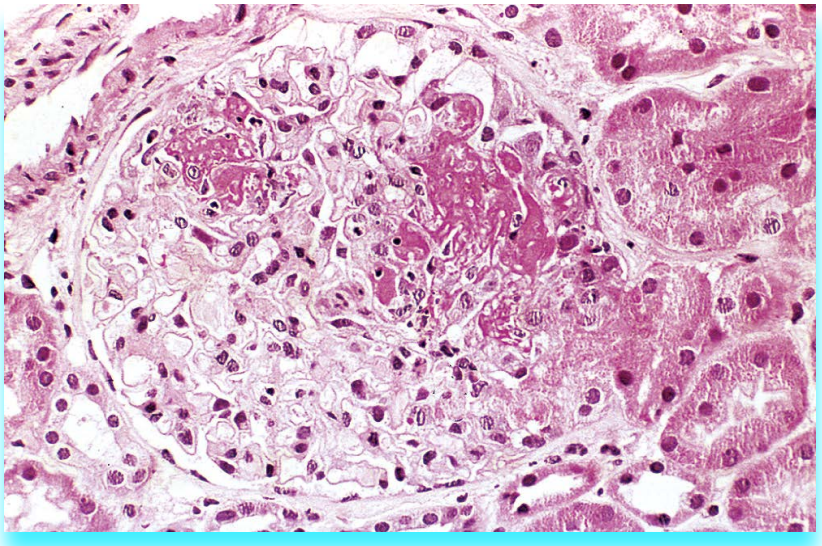


Gangrenous Necrosis

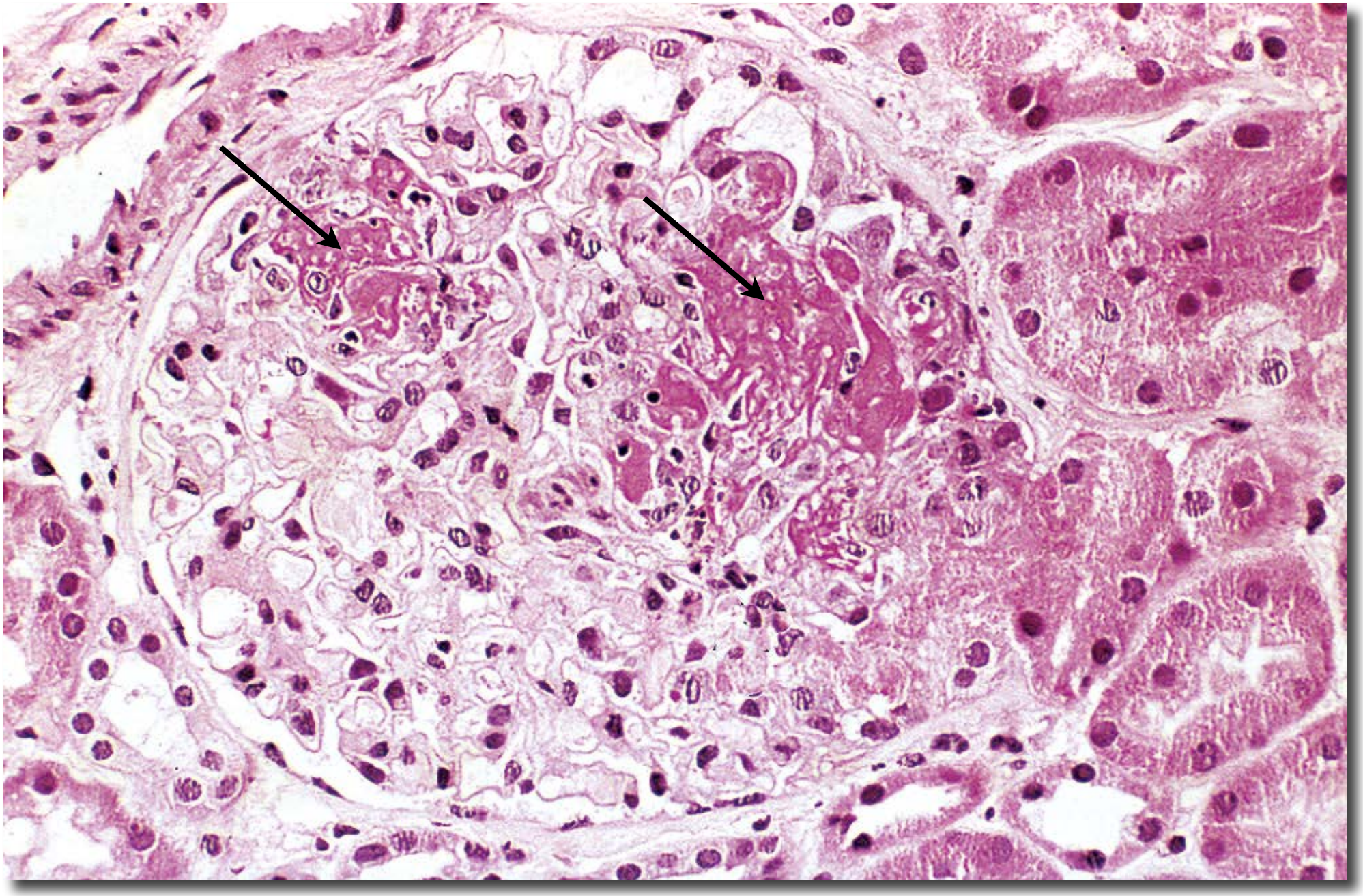
Types of Necrosis

Fibrinoid necrosis

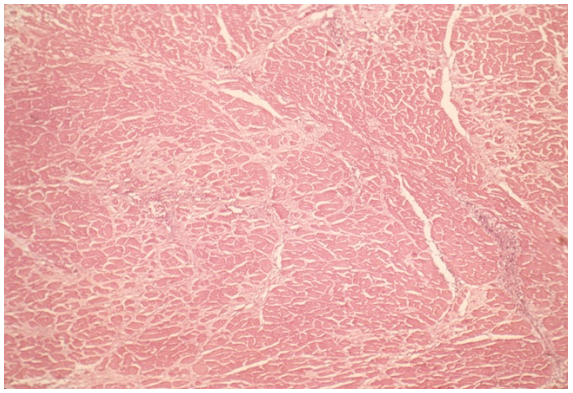
- Necrotic tissue that has some staining characteristics resembling fibrin (deeply eosinophilic, homogenous and refractile)
- Mechanism: Acute immunologic injury, or vasculitis



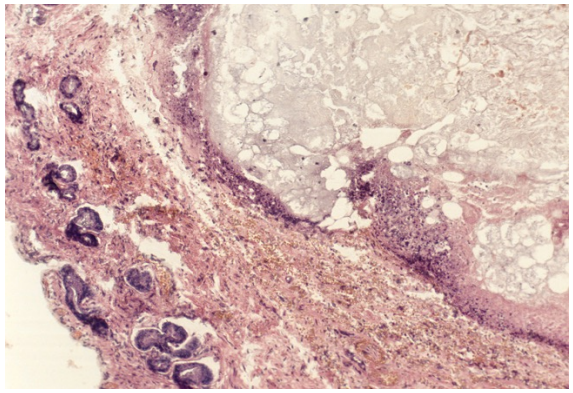
Acute Immune Complex Glomerulonephritis: Fibrinoid Necrosis



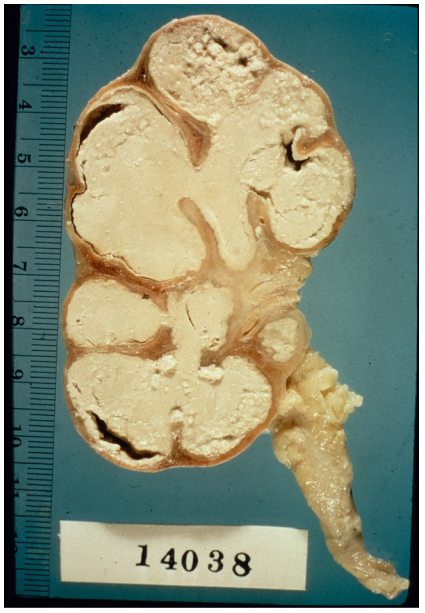
Types of Necrosis



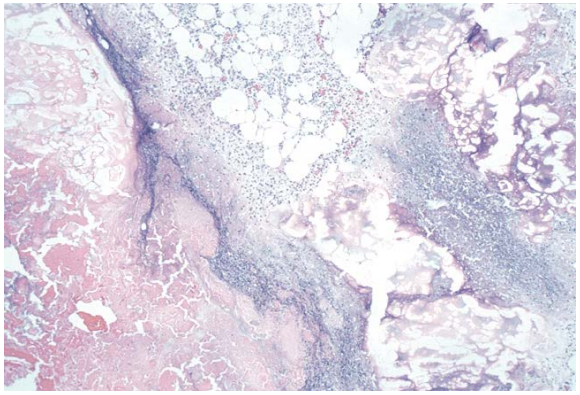
Coagulative Necrosis



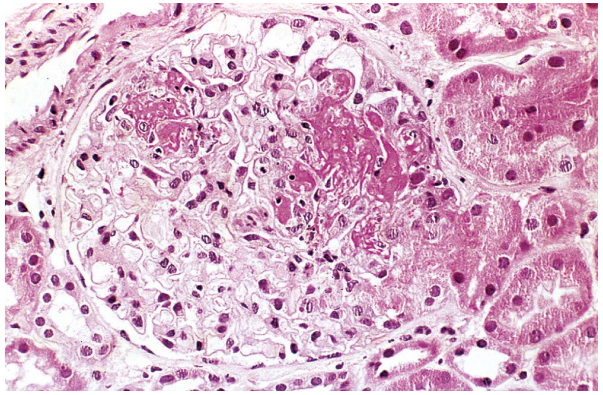
Liquifactive Necrosis



Caseous Necrosis



Fat Necrosis



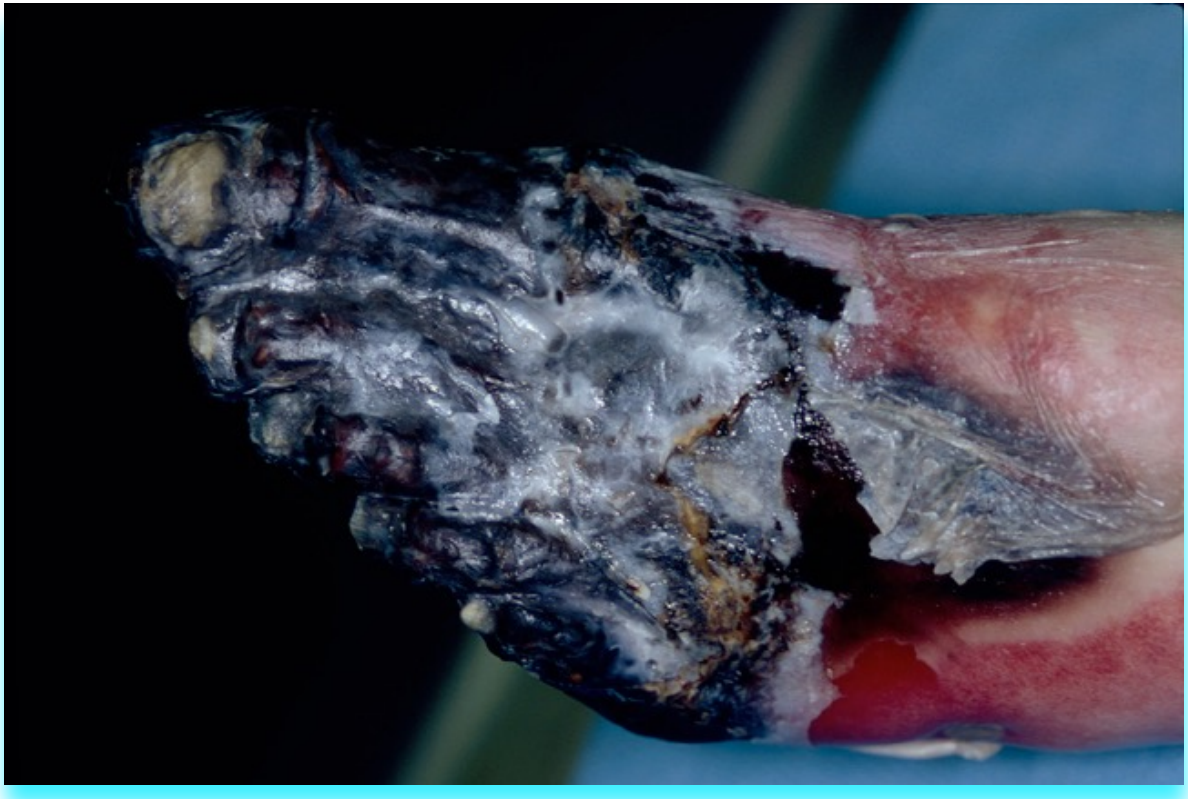
Fibrinoid Necrosis

Gangrenous Necrosis

Types of Necrosis

Gangrenous necrosis

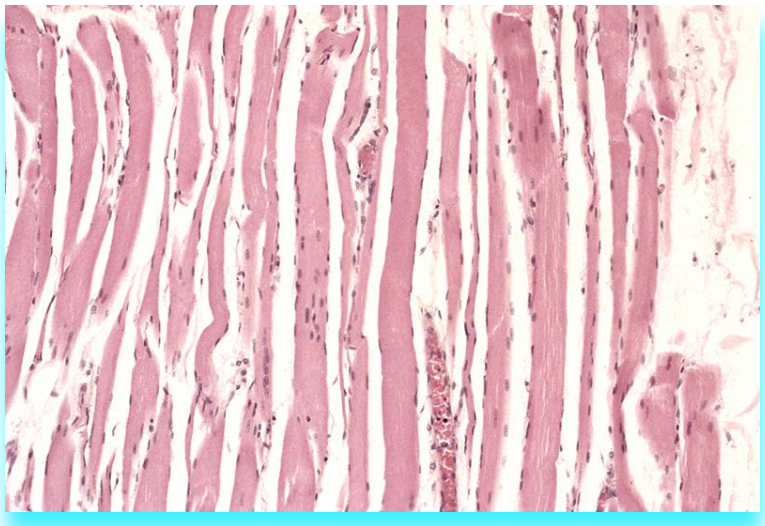
- Dry gangrene - coagulative necrosis is the predominant pattern
- Wet gangrene - liquefactive necrosis is the dominant pattern



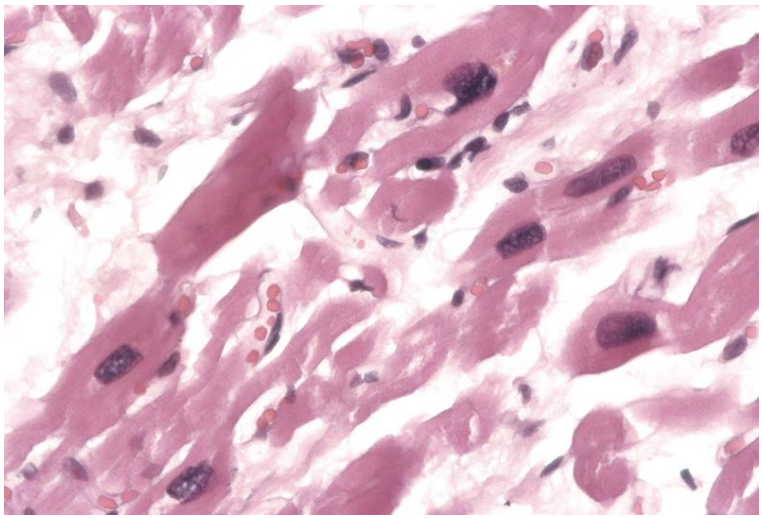
Foot: Dry Gangrene

Cellular Adaptations

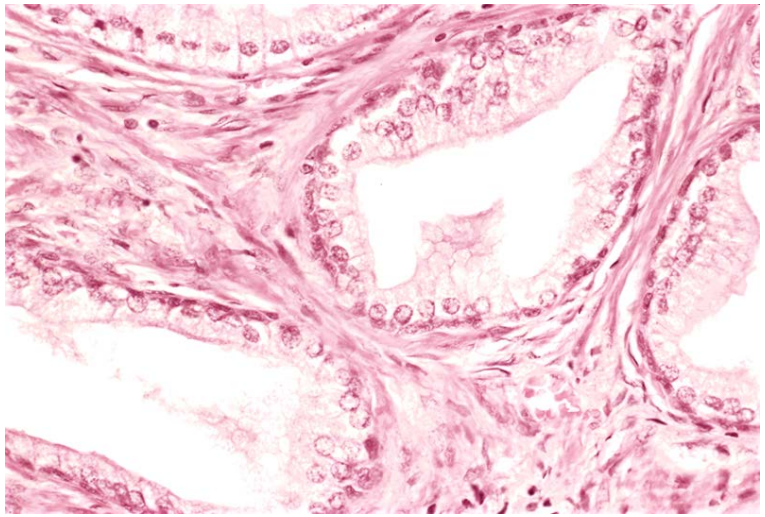
Cellular Adaptations



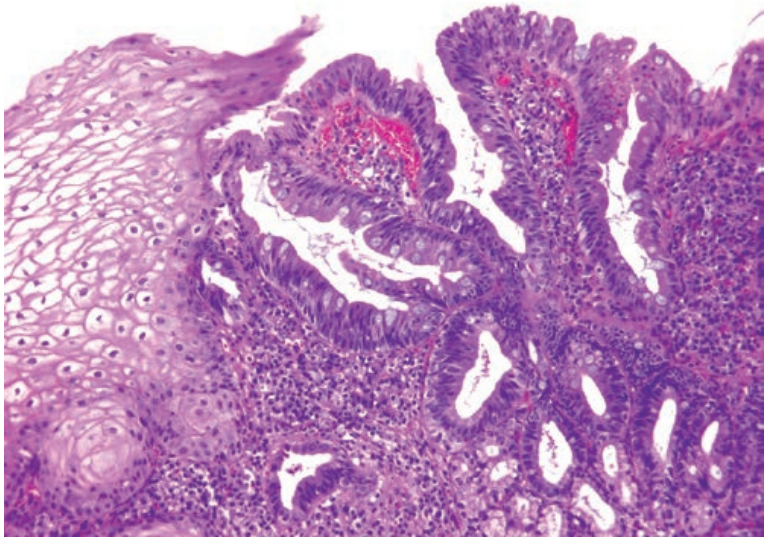
Atrophy



Hypertrophy



Hyperplasia



Metaplasia

Cellular Adaptations: Overview

- Potentially reversible once the stimulus is removed
- Adaptations involving growth (-plasis) can in crease the risk for neoplasia

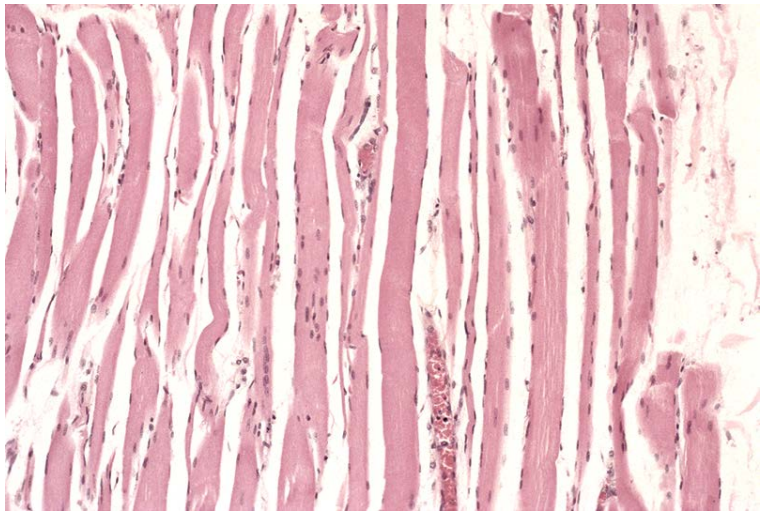
Atrophy

Definition

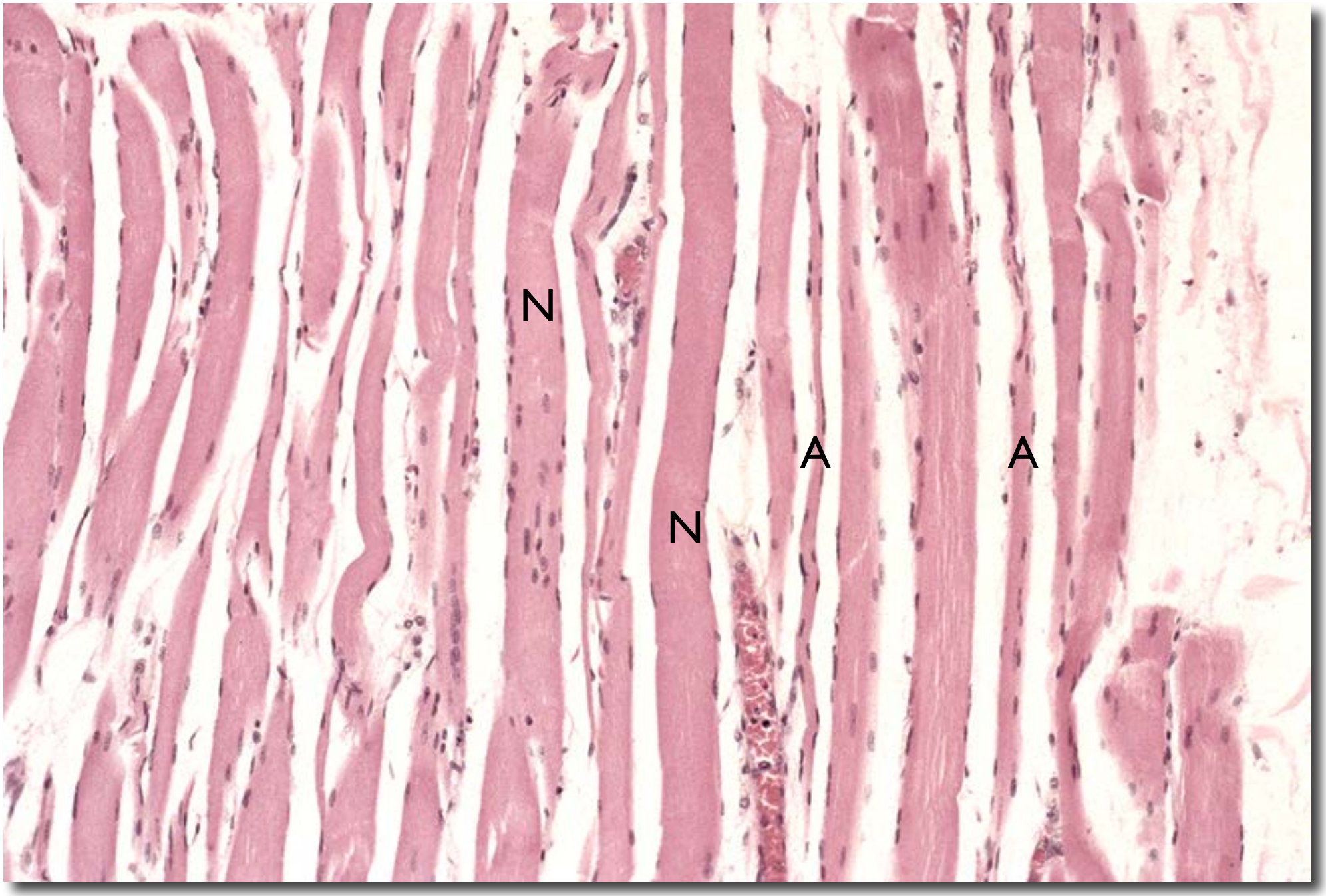
- Shrinkage in the size of the cell by loss of structural components

Causes

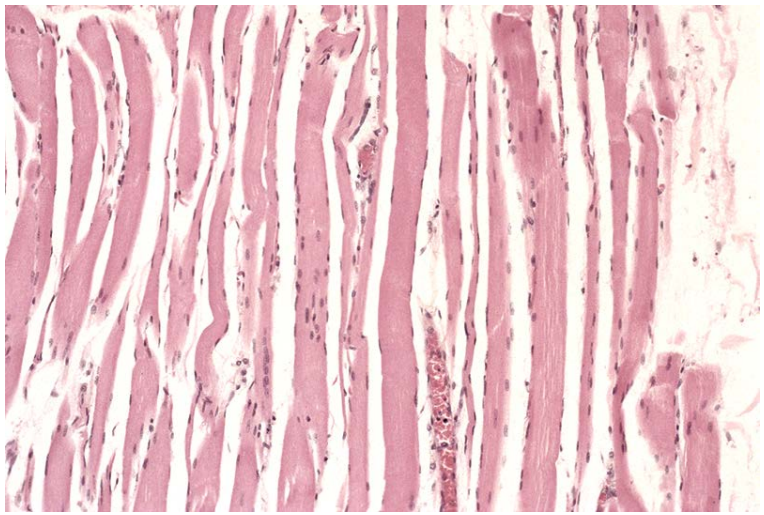
- Decreased work load
- Loss of innervation
- Diminished blood supply
- Inadequate nutrition
- Loss of endocrine stimulation
- Aging (most common cause)



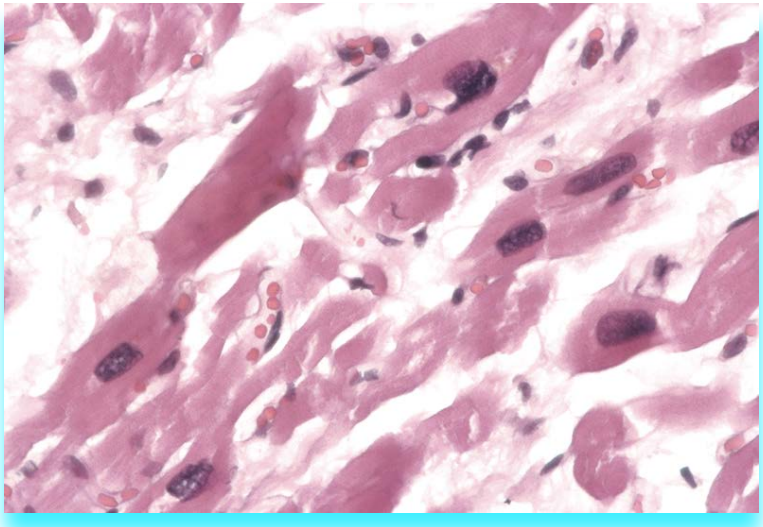
Skeletal Muscle: Disuse Atrophy



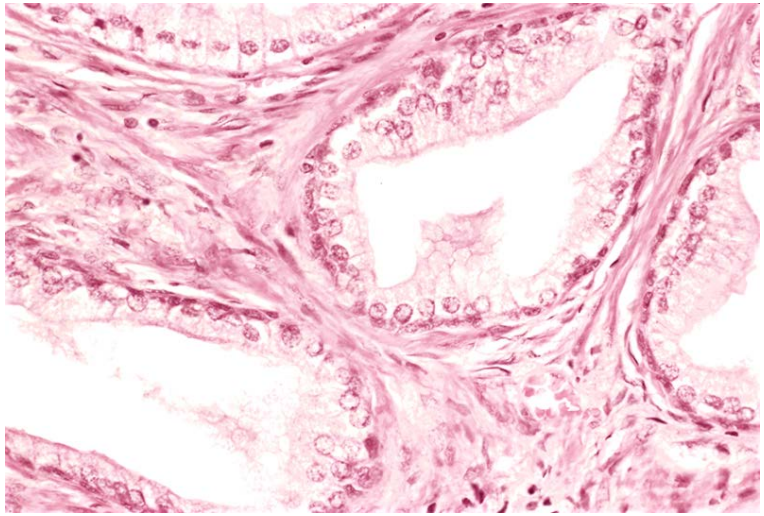
Cellular Adaptations



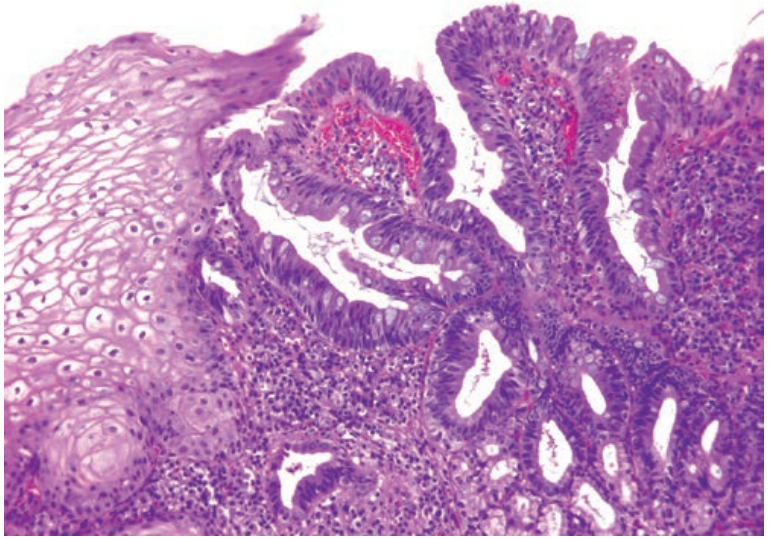
Atrophy



Hypertrophy



Hyperplasia



Metaplasia

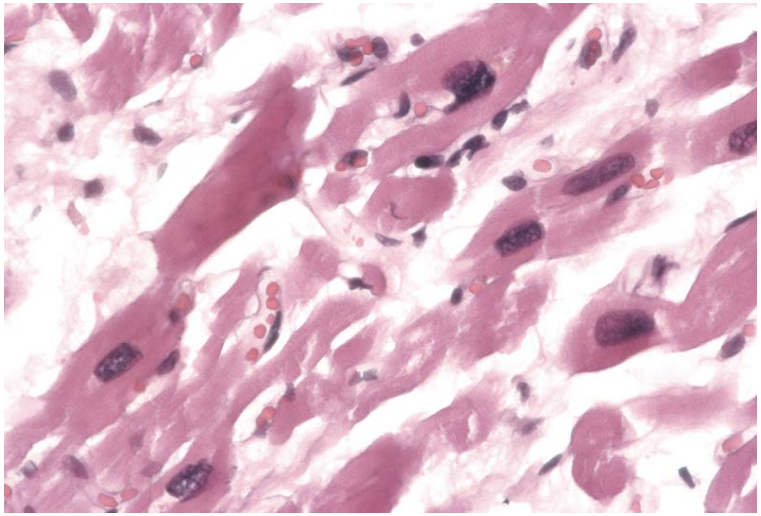
Hypertrophy

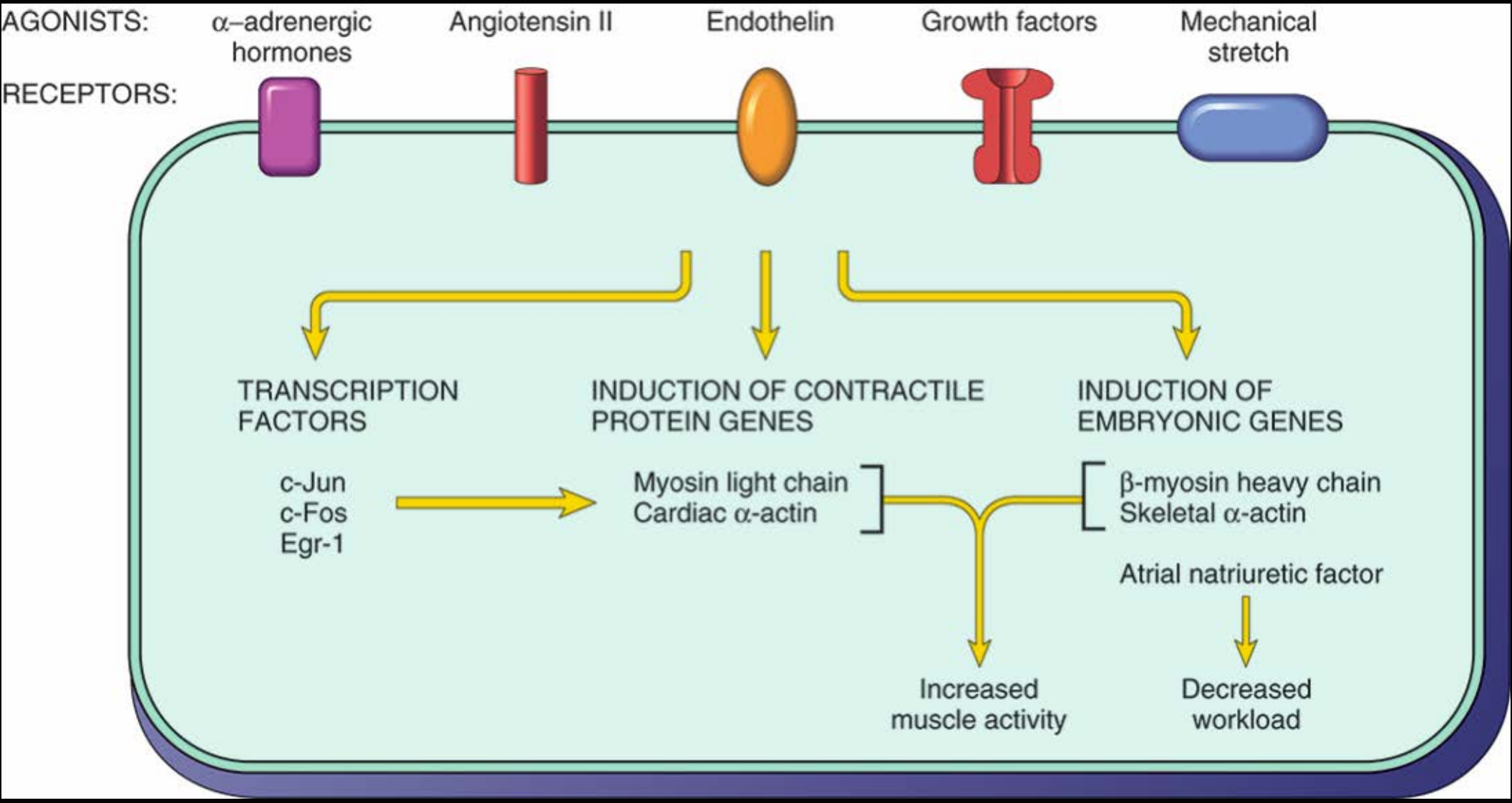
Definition

- Increase in cell size due to the synthesis of more structural components

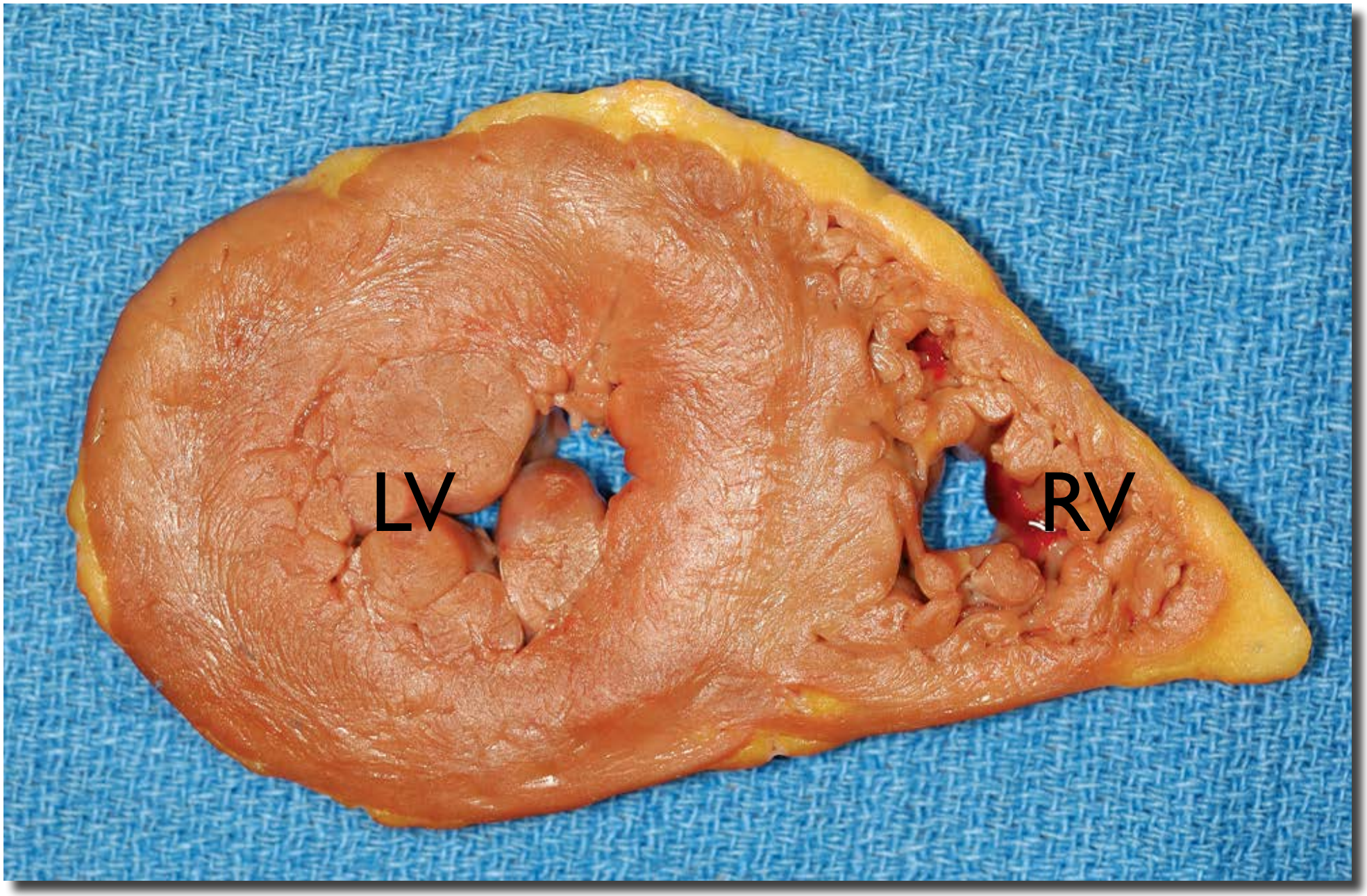
Physiologic - growth of uterus during pregnancy

Pathologic - left ventricular hypertrophy due to hypertension

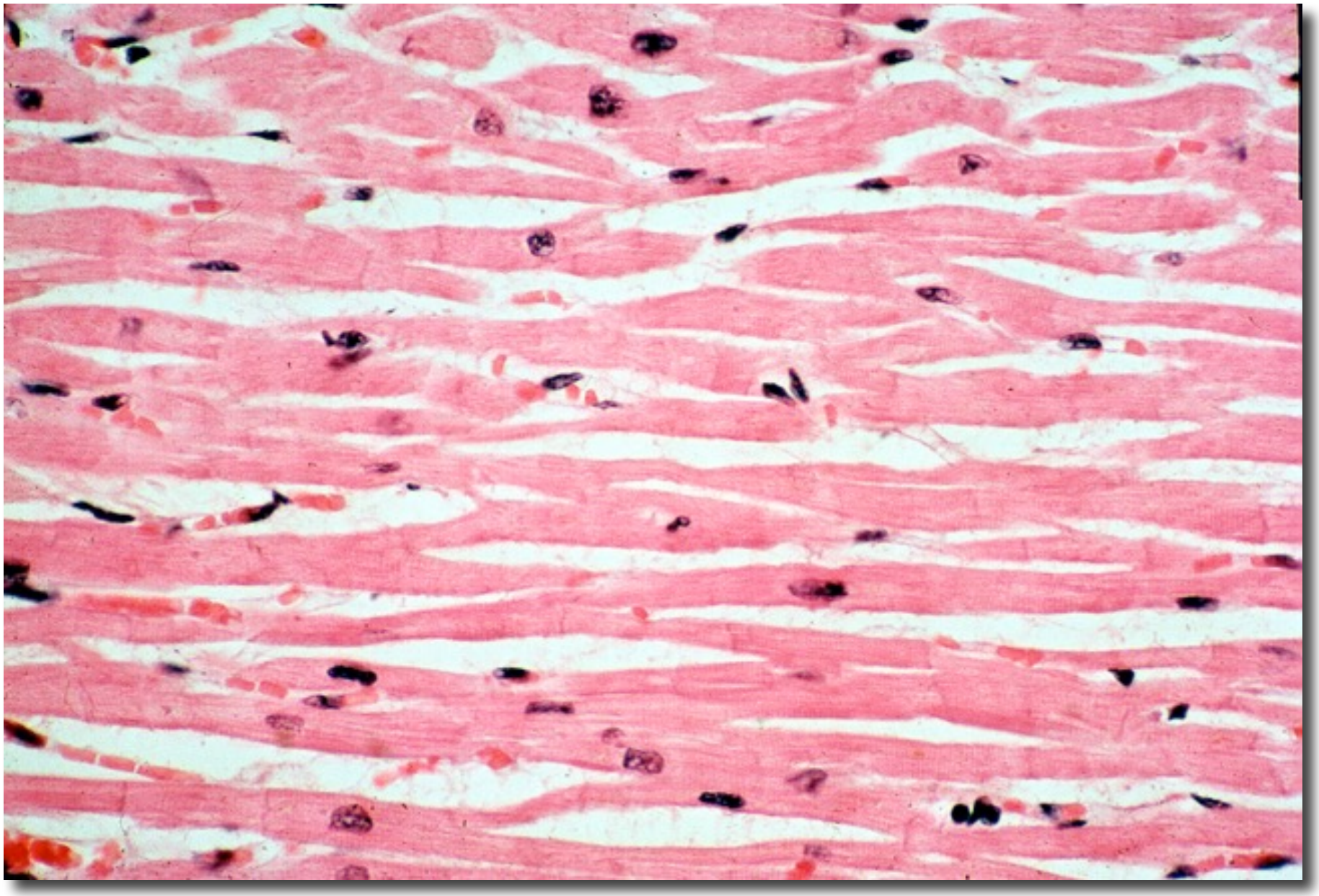



AGONISTS:
α–adrenergic hormones
Angiotensin II
Endothelin
Growth factors
Mechanical stretch
RECEPTORS:
TRANSCRIPTION FACTORS
INDUCTION OF CONTRACTILE PROTEIN GENES
INDUCTION OF EMBRYONIC GENES
c-Jun
c-Fos
Egr-1
Myosin light chain
Cardiac α-actin
β-myosin heavy chain
Skeletal α-actin
Atrial natriuretic factor
Increased muscle activity
Decreased workload

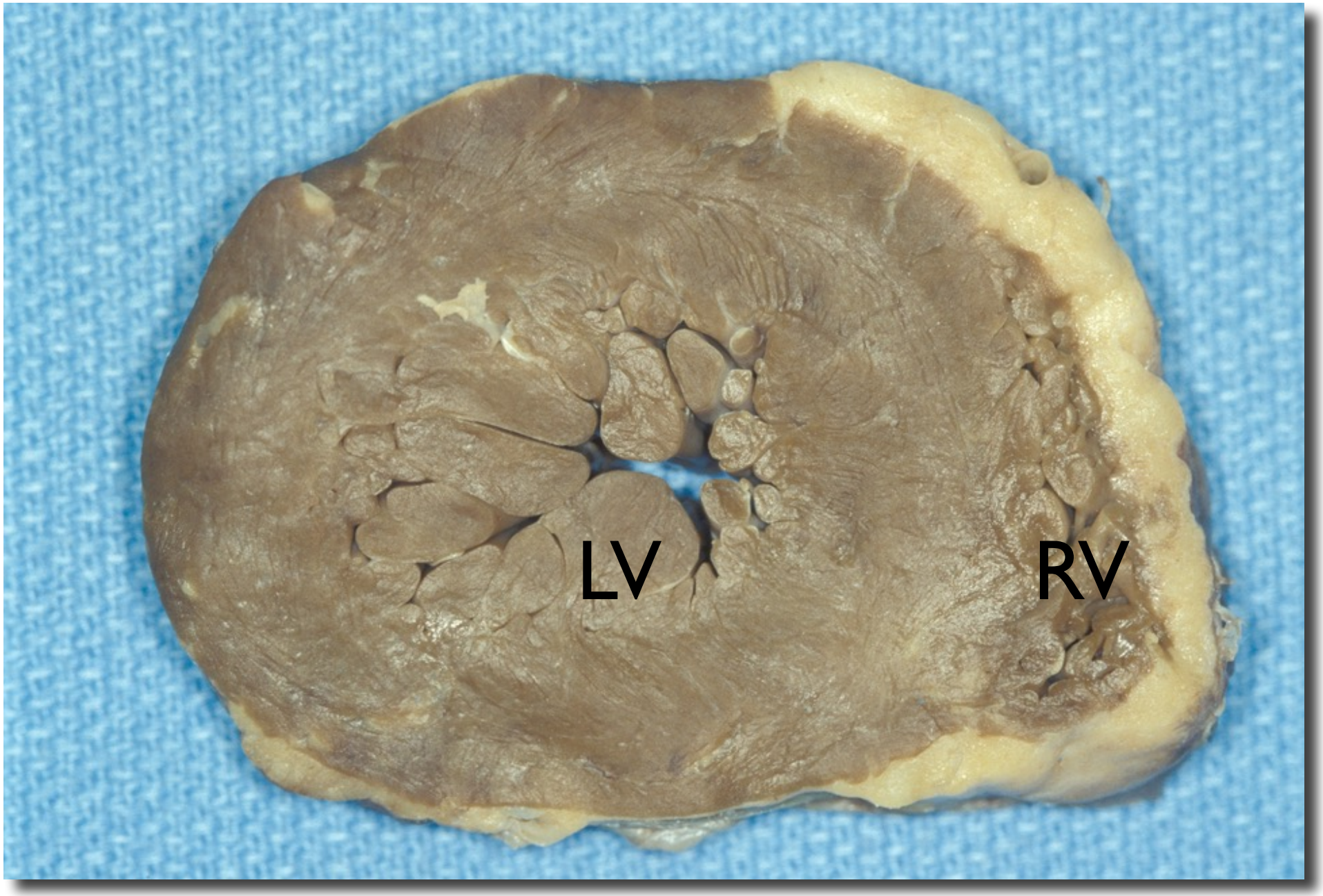
Normal Heart



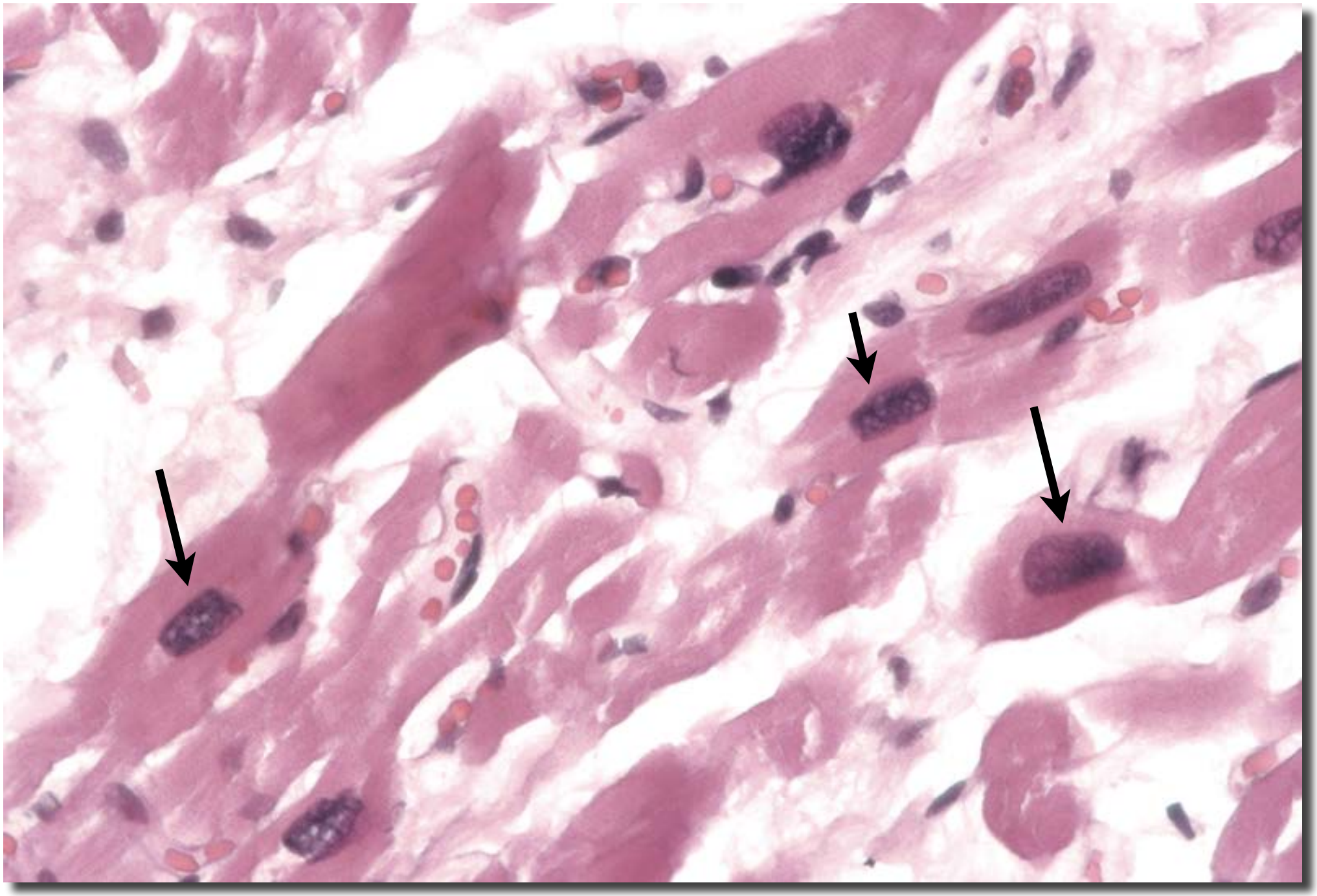
Normal Myocardium



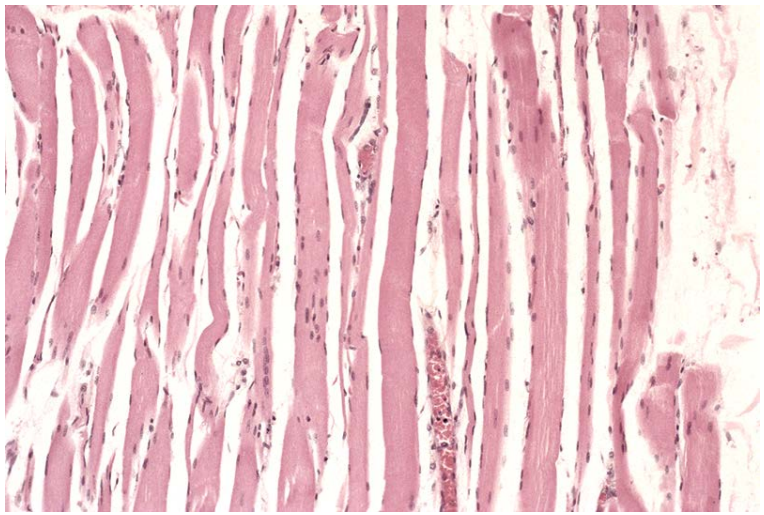
Hypertensive Heart Disease



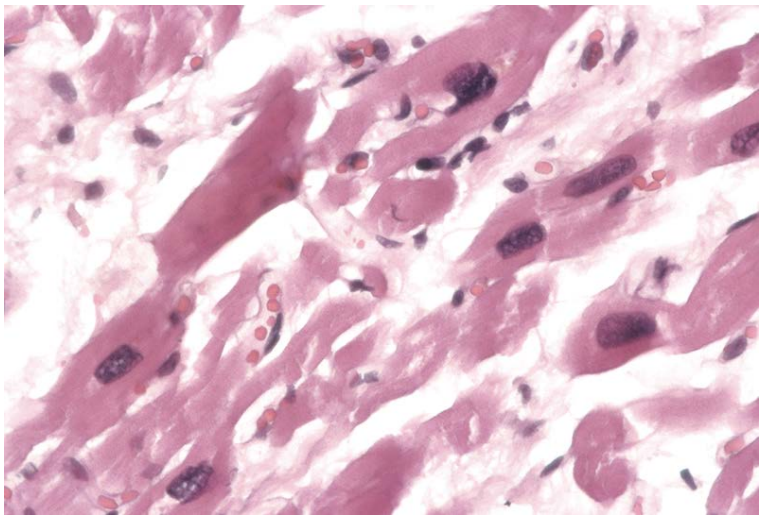
Cardiac Myocyte Hyertrophy



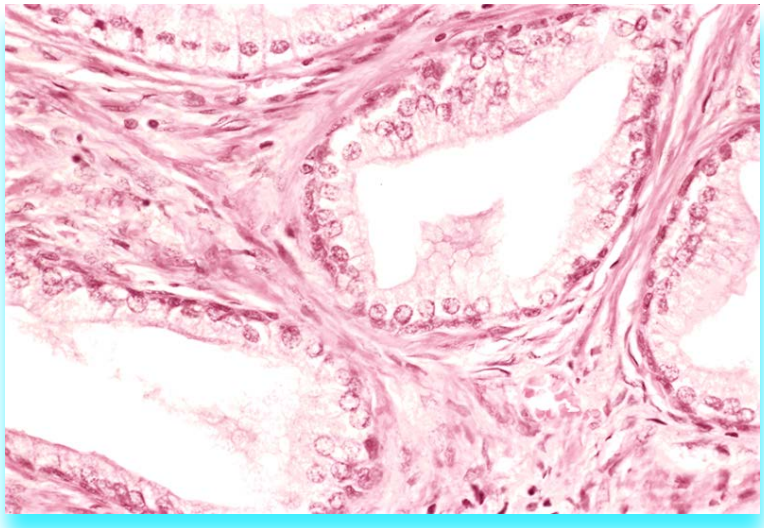
Cellular Adaptations



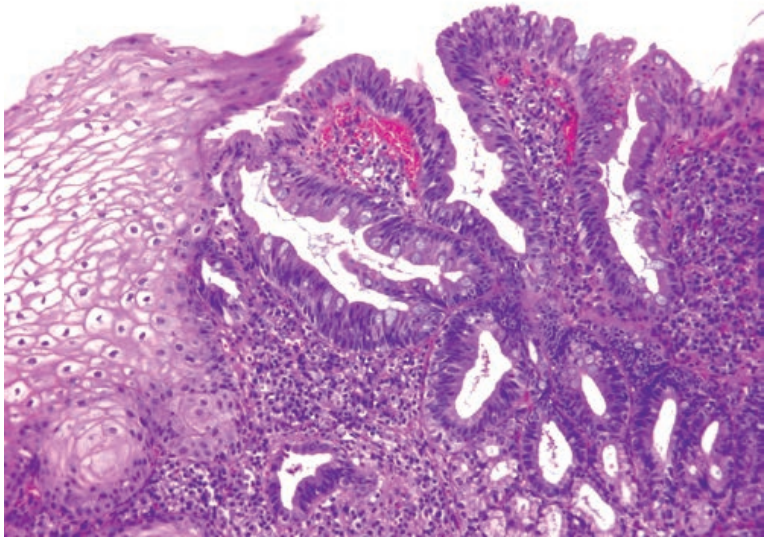
Atrophy



Hypertrophy



Hyperplasia



Metaplasia

Hyperplasia

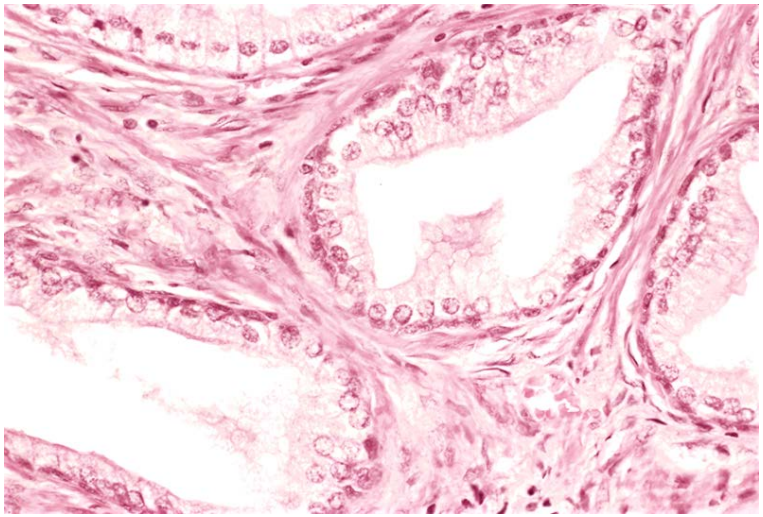
Definition

- Increase in the number of cells

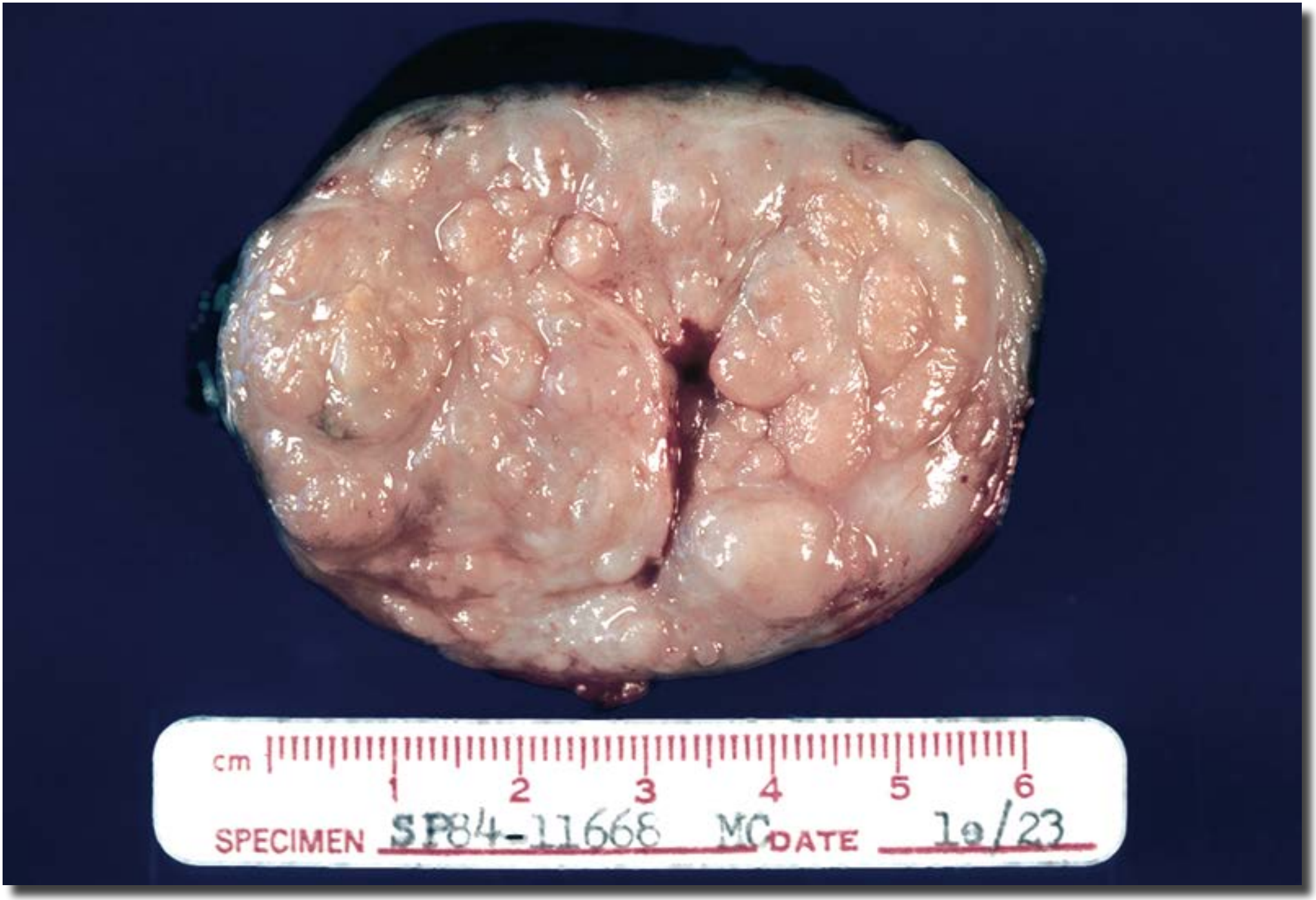
Hormonal hyperplasia - breast at puberty, or during pregnancy

Compensatory hyperplasia - regeneration of an organ or tissue

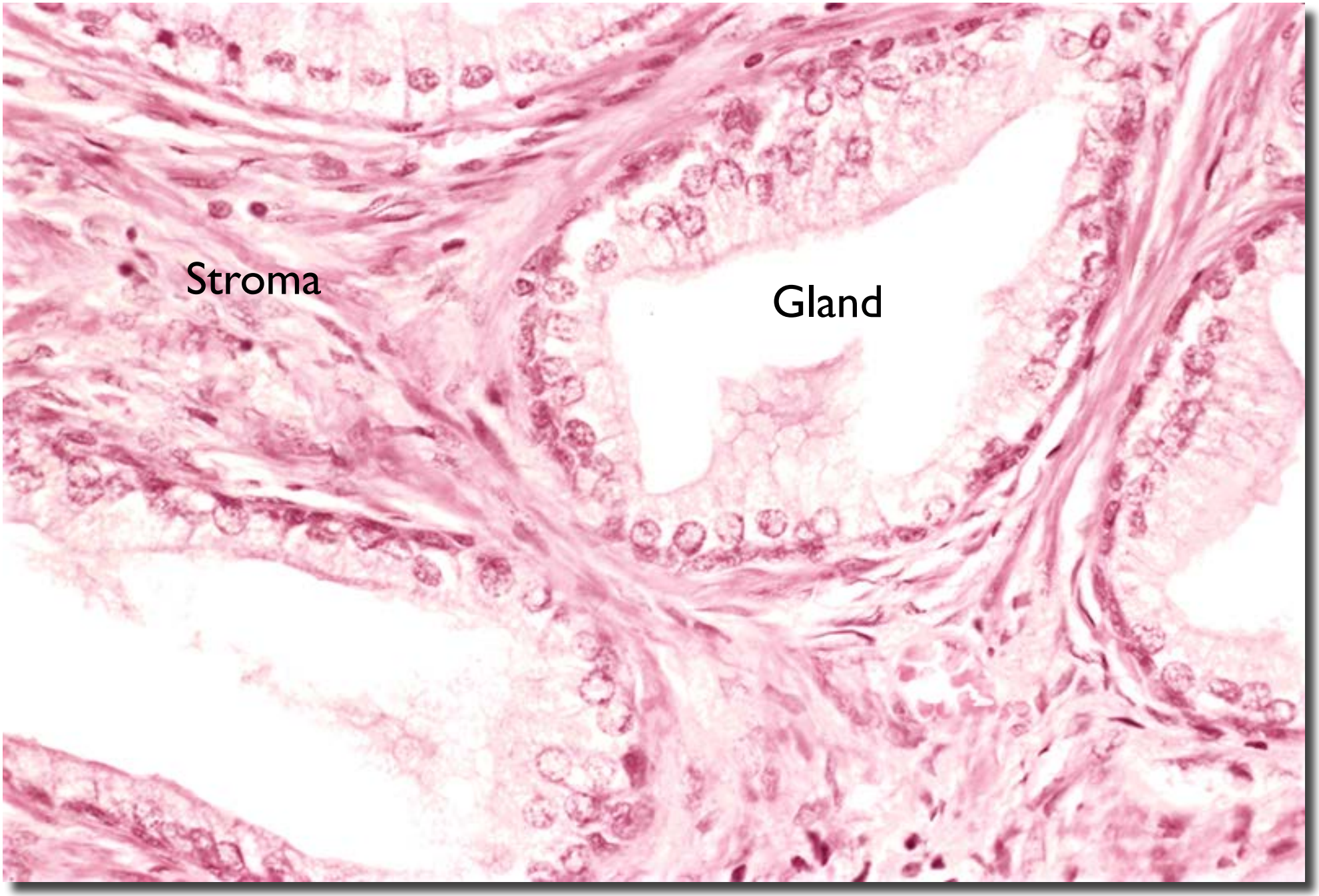
Pathologic - majority of pathologic hyperplasias are due to excessive hormonal stimulation, or the effects of growth factors on target cells (e.g., endometrial hyperplasia in a post-menopausal woman)



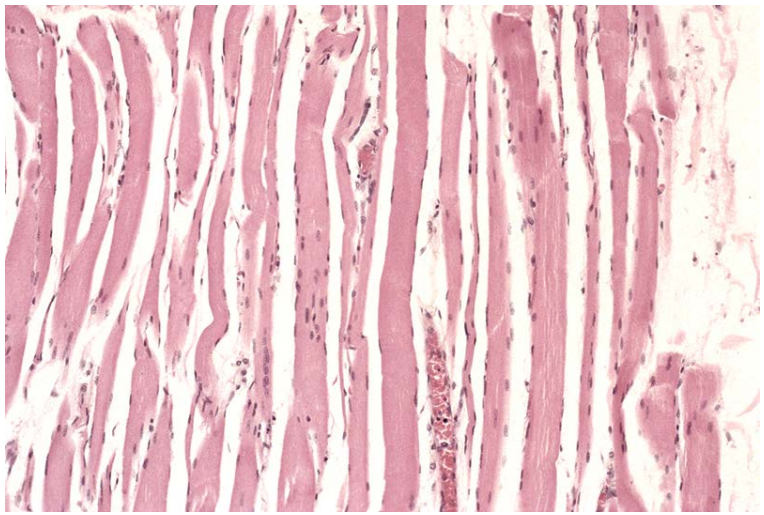
Prostatic Nodular Hyperplasia



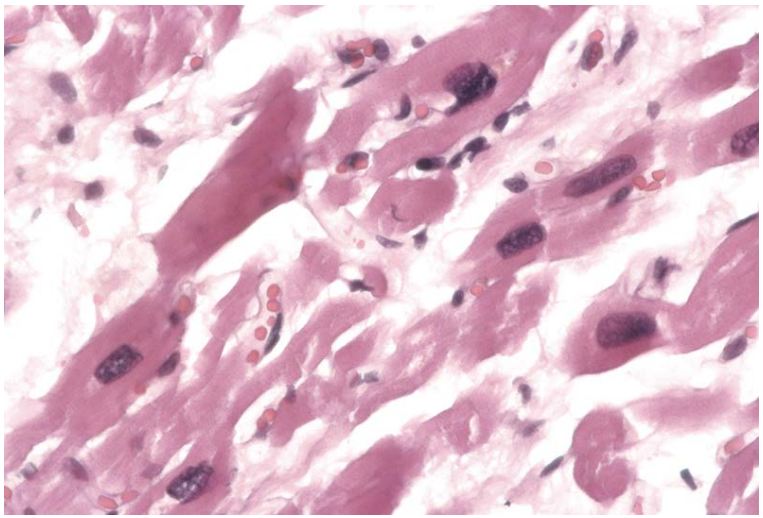
Prostatic Nodular Hyperplasia



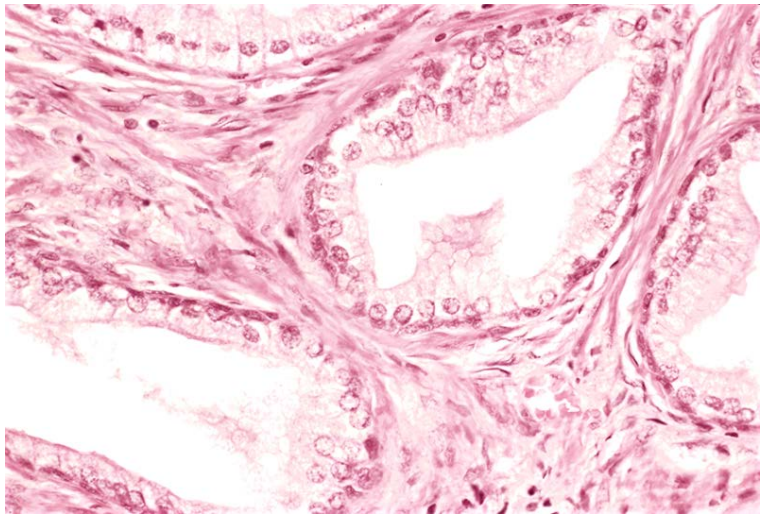
Cellular Adaptations



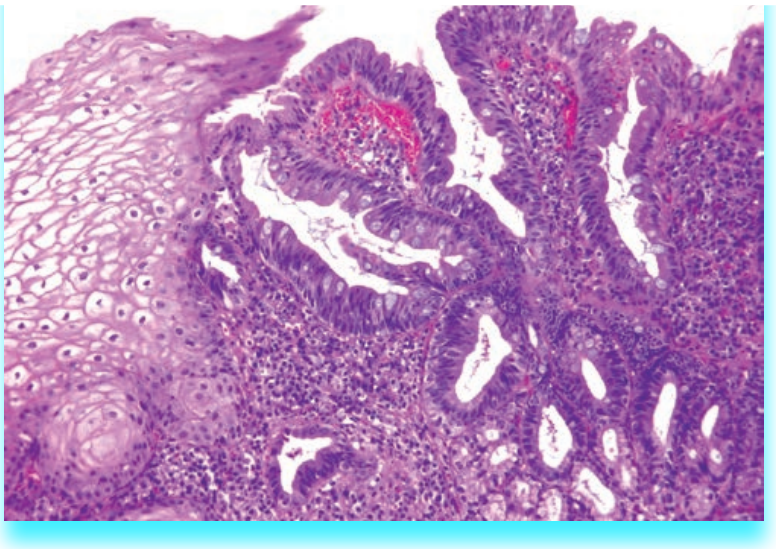
Atrophy



Hypertrophy



Hyperplasia



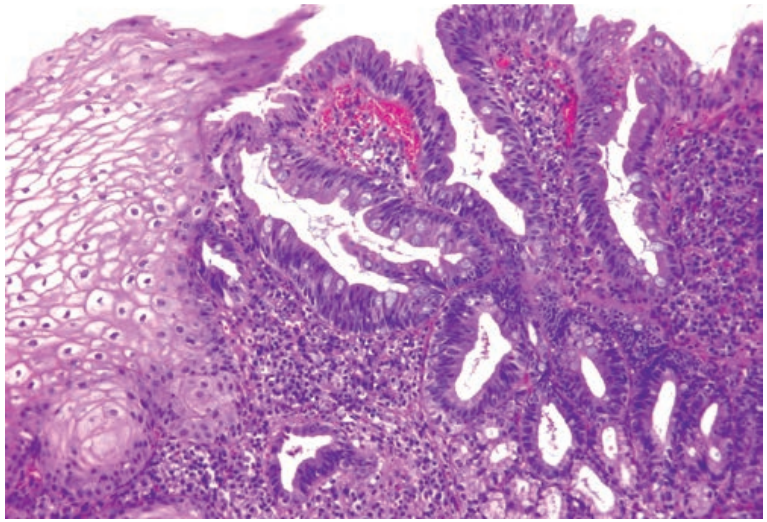
Metaplasia

Metaplasia

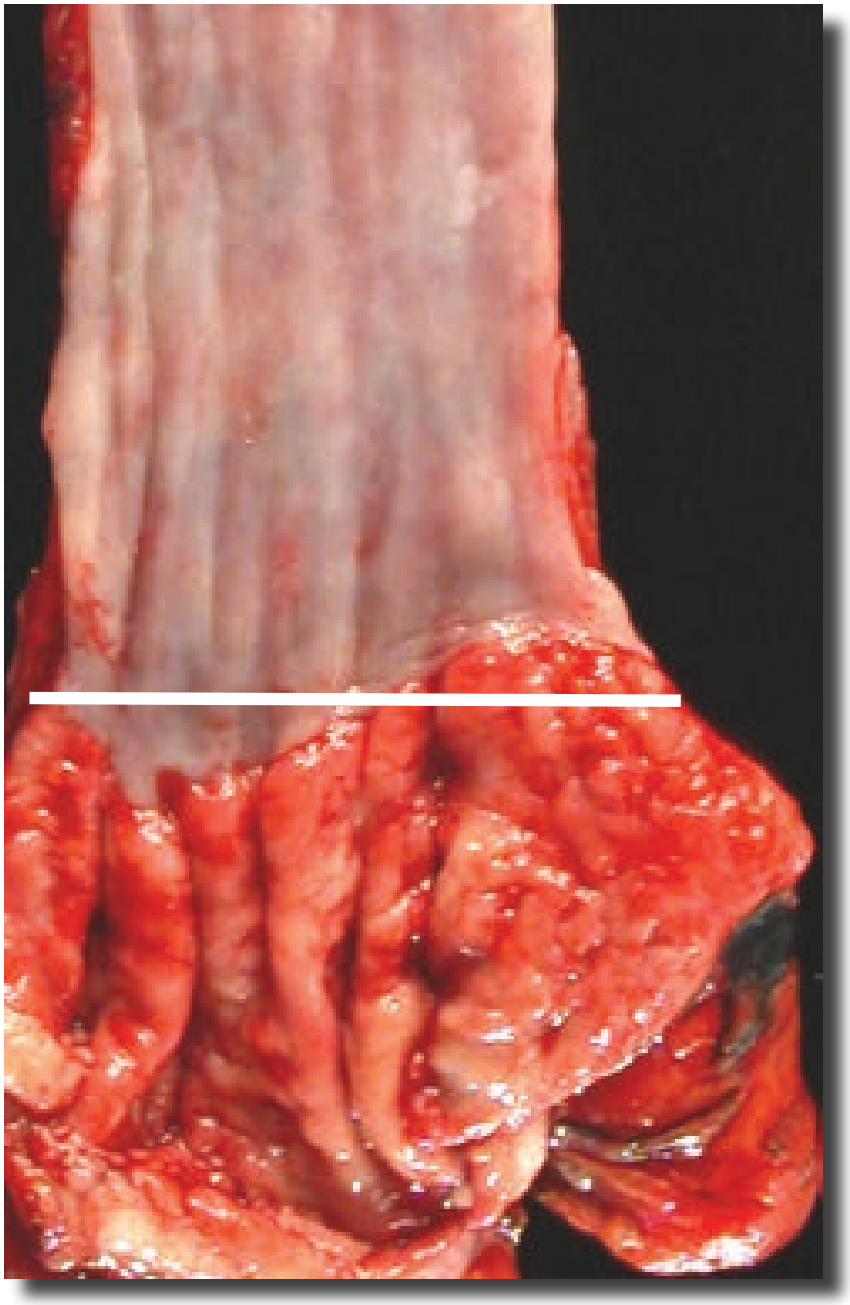
Definition

- Reversible change in which an adult cell type is replaced by another adult cell type

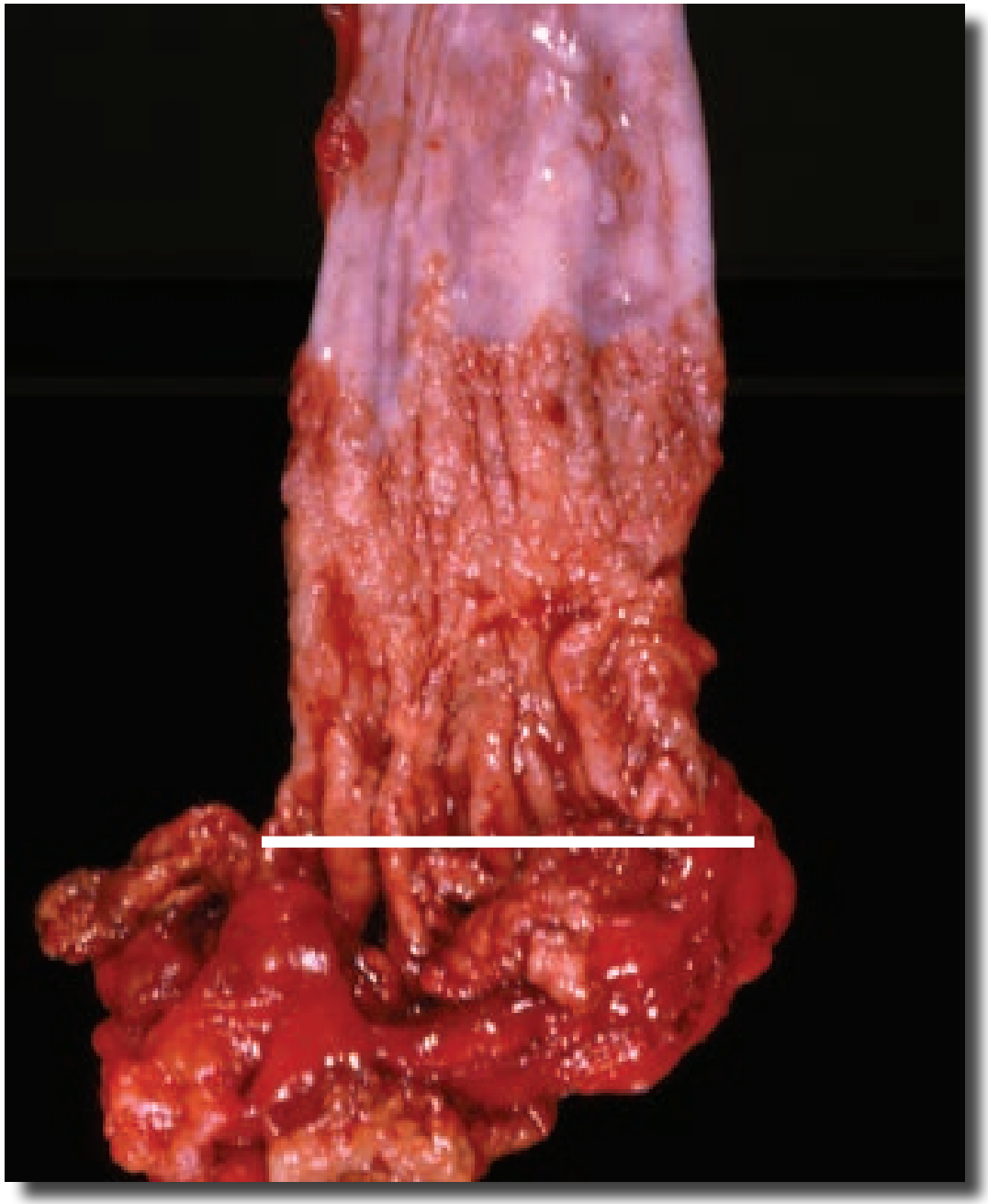
Examples: Barrett esophagus, squamous metaplasia in chronic bronchitis



Normal Esophagus



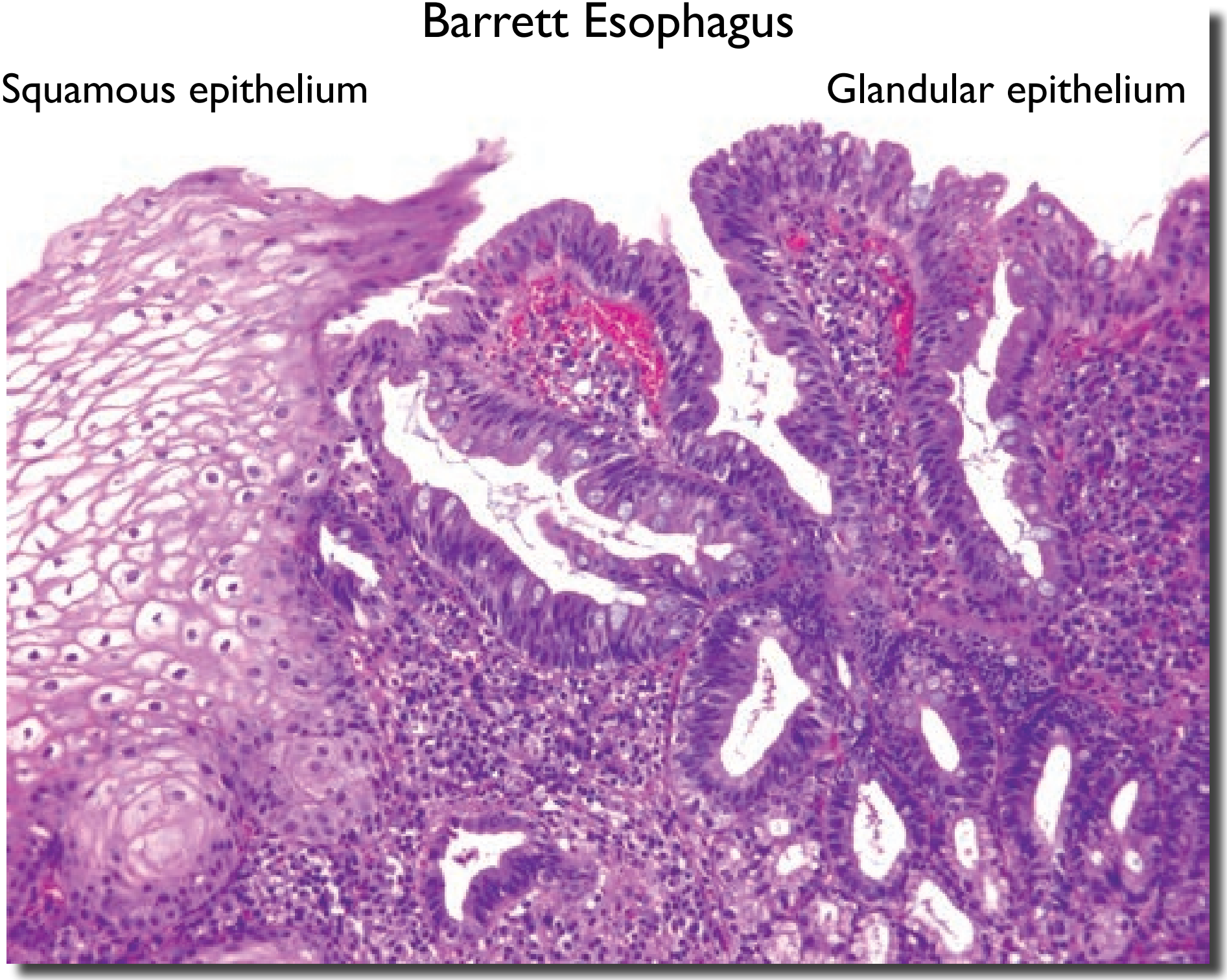
Barrett Esophagus



Barrett Esophagus

Squamous epithelium

Glandular epithelium

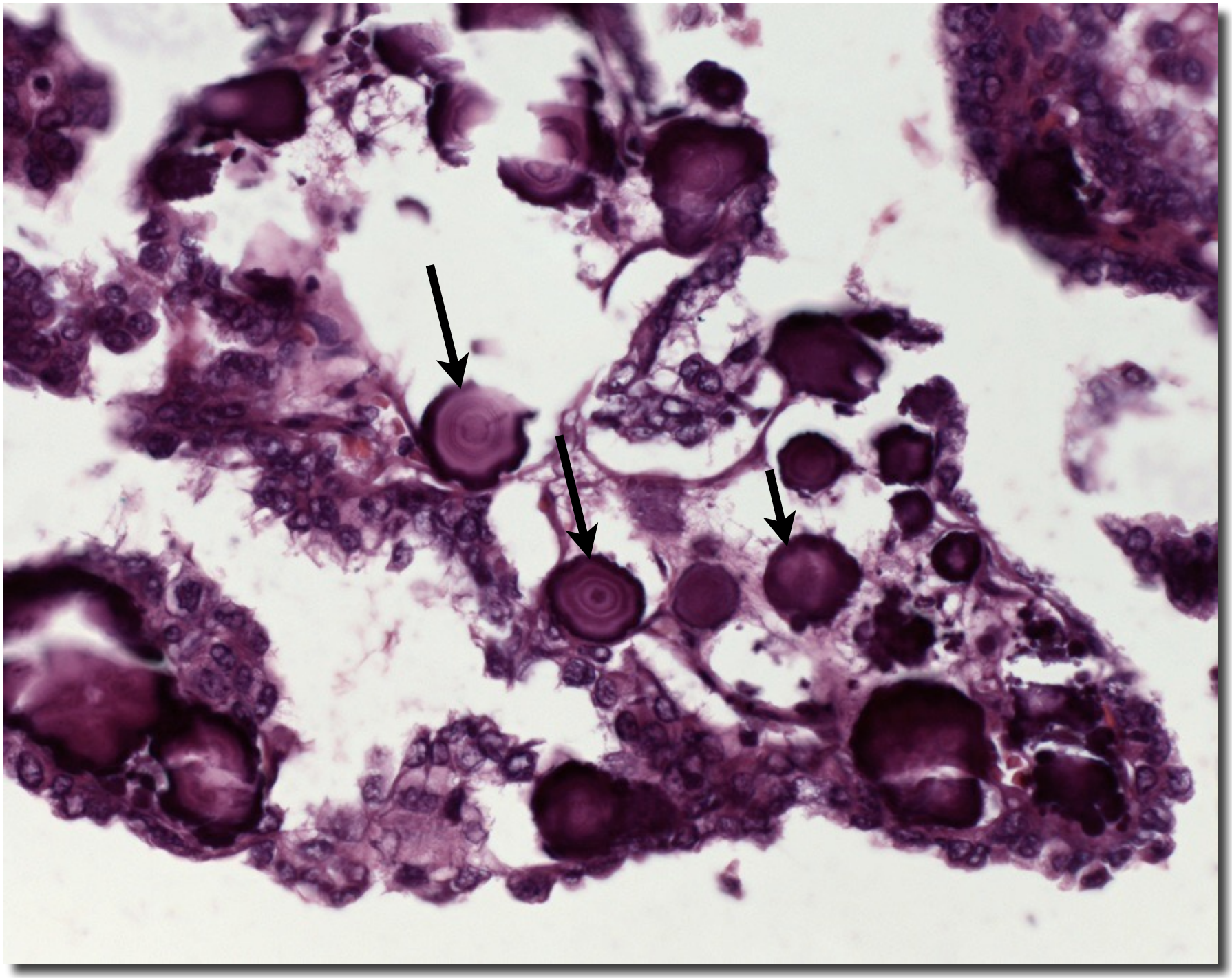


Calcification

Dystrophic calcification

- Deposition of calcium salts in nonviable or dying tissues
- Deposition can be intracellular, extracellular, or both
- Examples: Atherosclerosis, psammoma bodies (e.g., papillary carcinoma of the thyroid)

Papillary Carcinoma of the Thyroid: Dystrophic Calcification

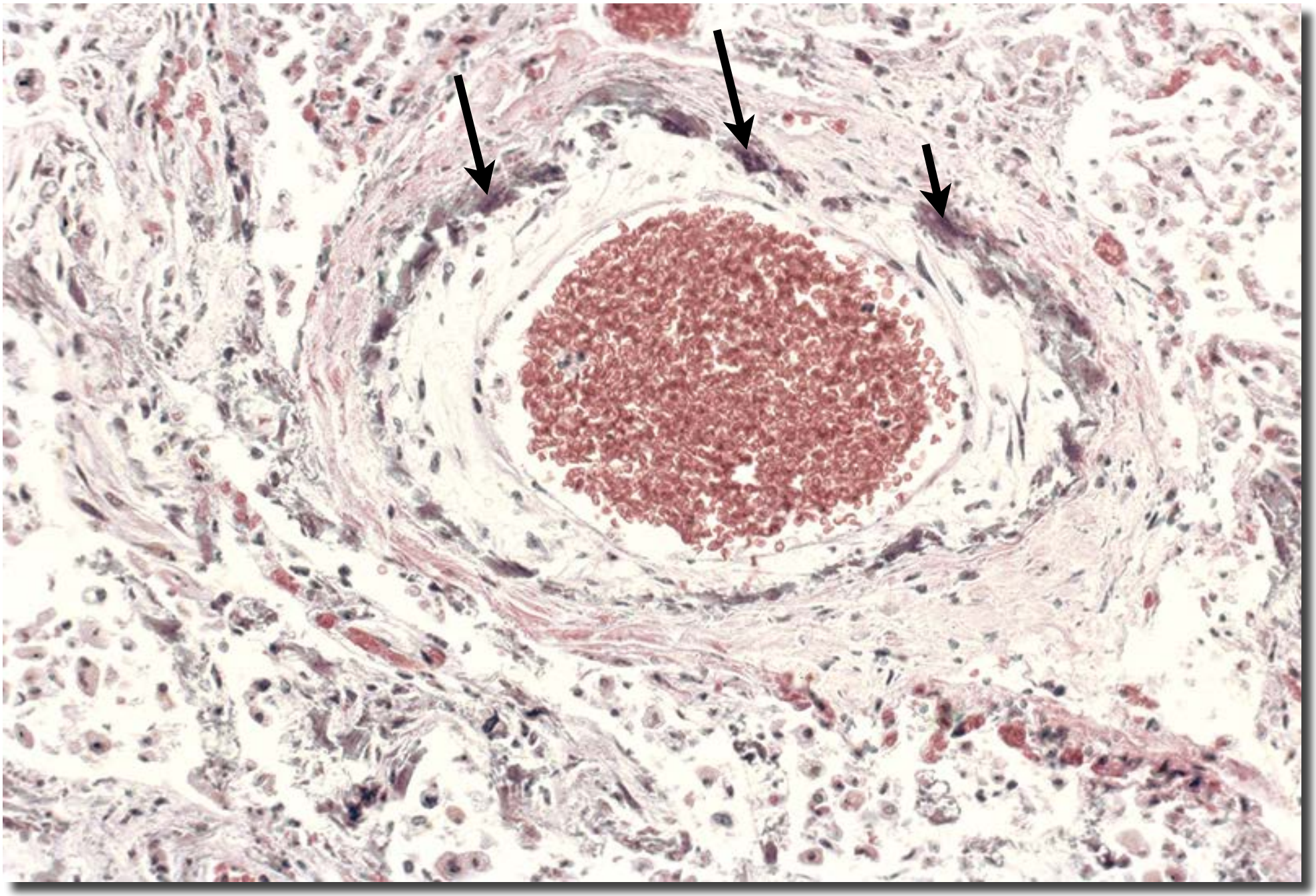


Calcification

Metastatic calcification

- Deposition of calcium in normal tissues due to hypercalcemia
- Causes: hyperparathyroidism, systemic sarcoidosis, etc.
- Primarily affects the interstitial tissues of blood vessels, kidneys, lungs and gastric mucosa

Lung: Metastatic Calcification



Hyaline Change

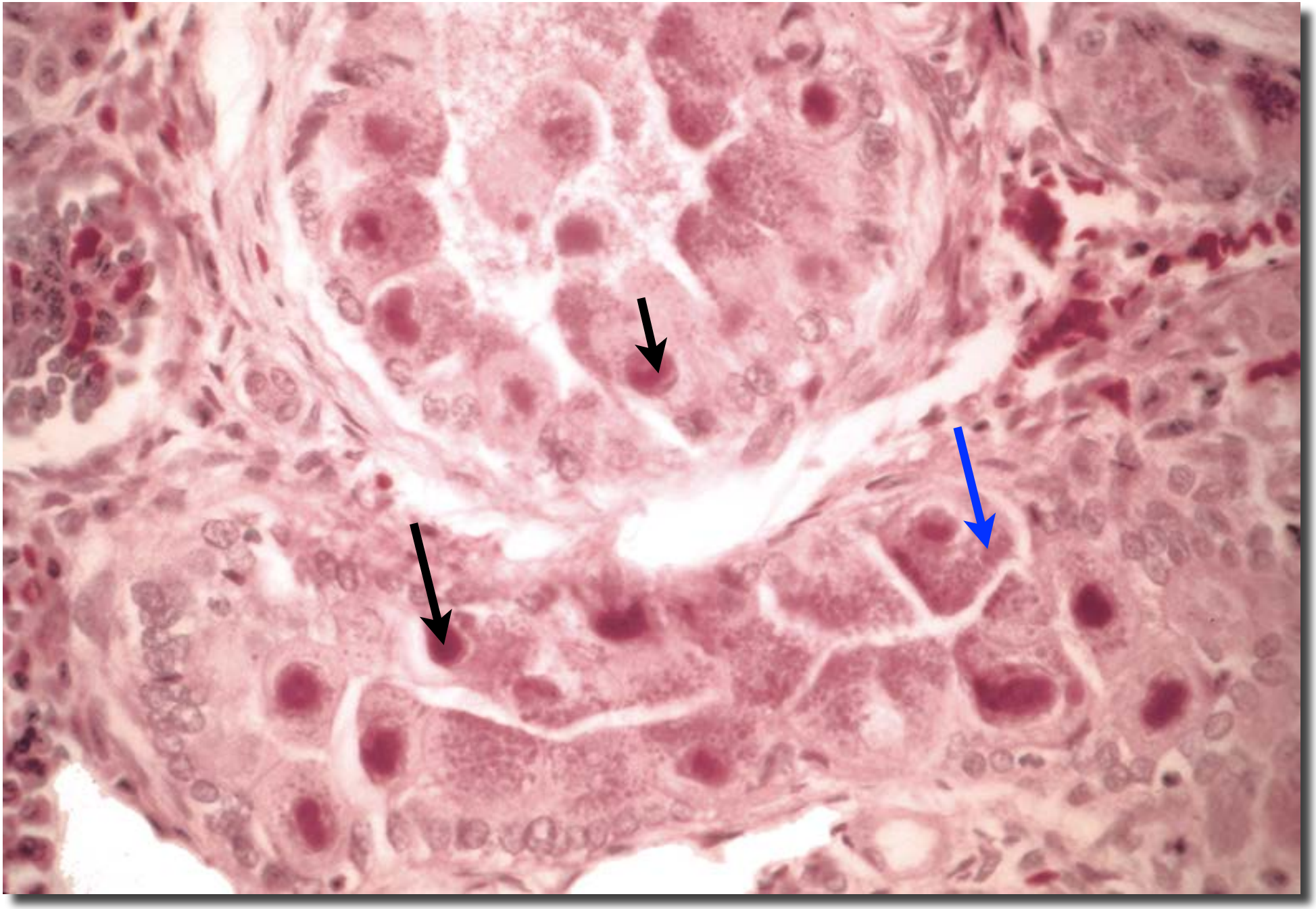
Definition

Any alteration within cells, or in the extracellular space which gives a homogenous glassy, pink appearance in routine histologic sections stained with H&E

Intracellular hyaline

- Hyaline droplets in proximal tubular epithelial cells
- Russell bodies in plasma cells
- Viral inclusions
- Alcoholic hyaline in hepatocytes

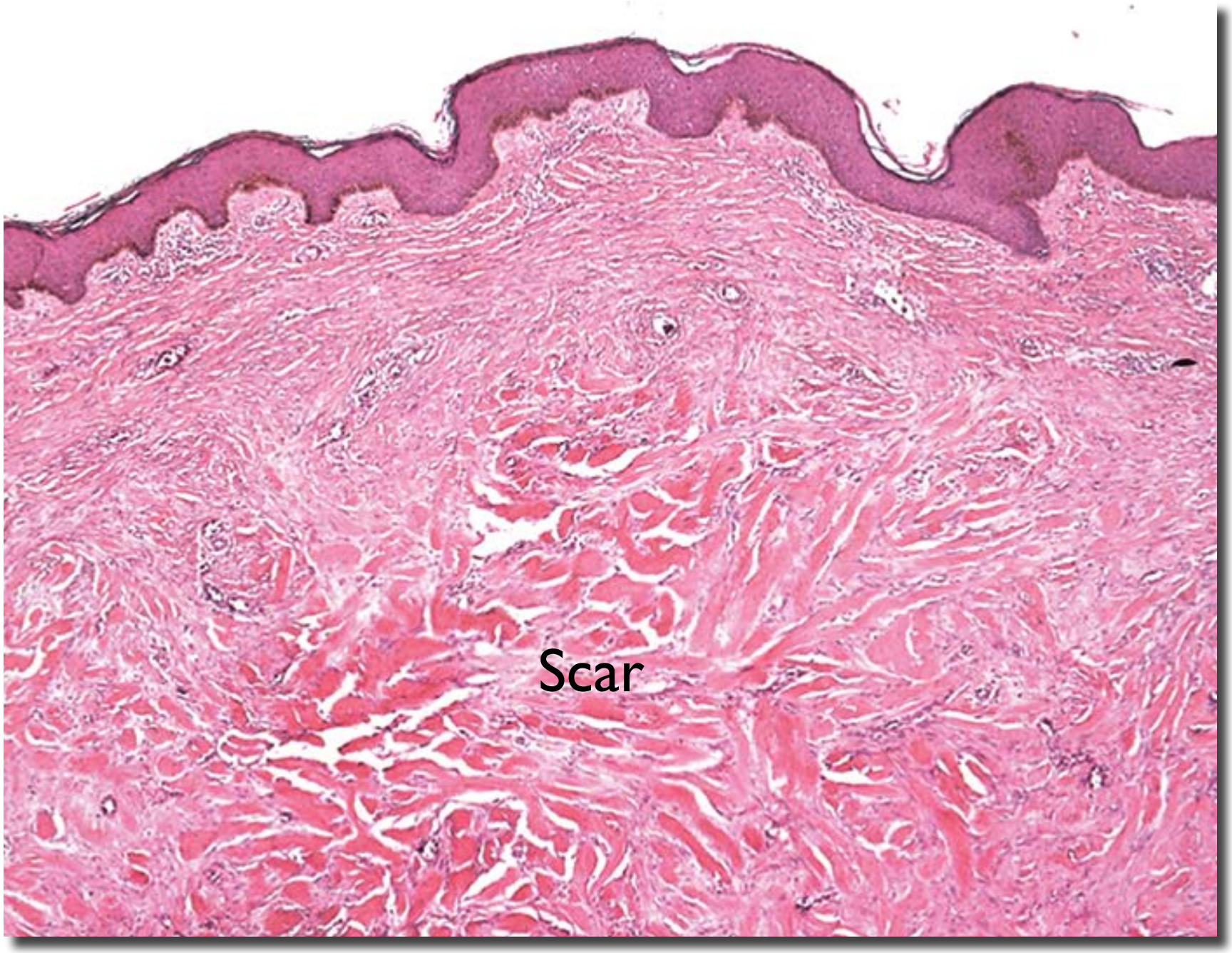
Pediatric Kidney: Cytomegaloviral Inclusion Disease



Extracellular hyaline

- Amyloidosis
- Arteriolosclerosis in hypertension, diabetes and aging
- Hyalinization of glomeruli with chronic damage

Skin with Scar



Summary

- Increased demand, stress or injurious stimulus can lead to individual cell death (apoptosis), tissue death (necrosis) and/or cellular adaptations
- Other cellular and tissue changes includes calcifications and hyaline changes