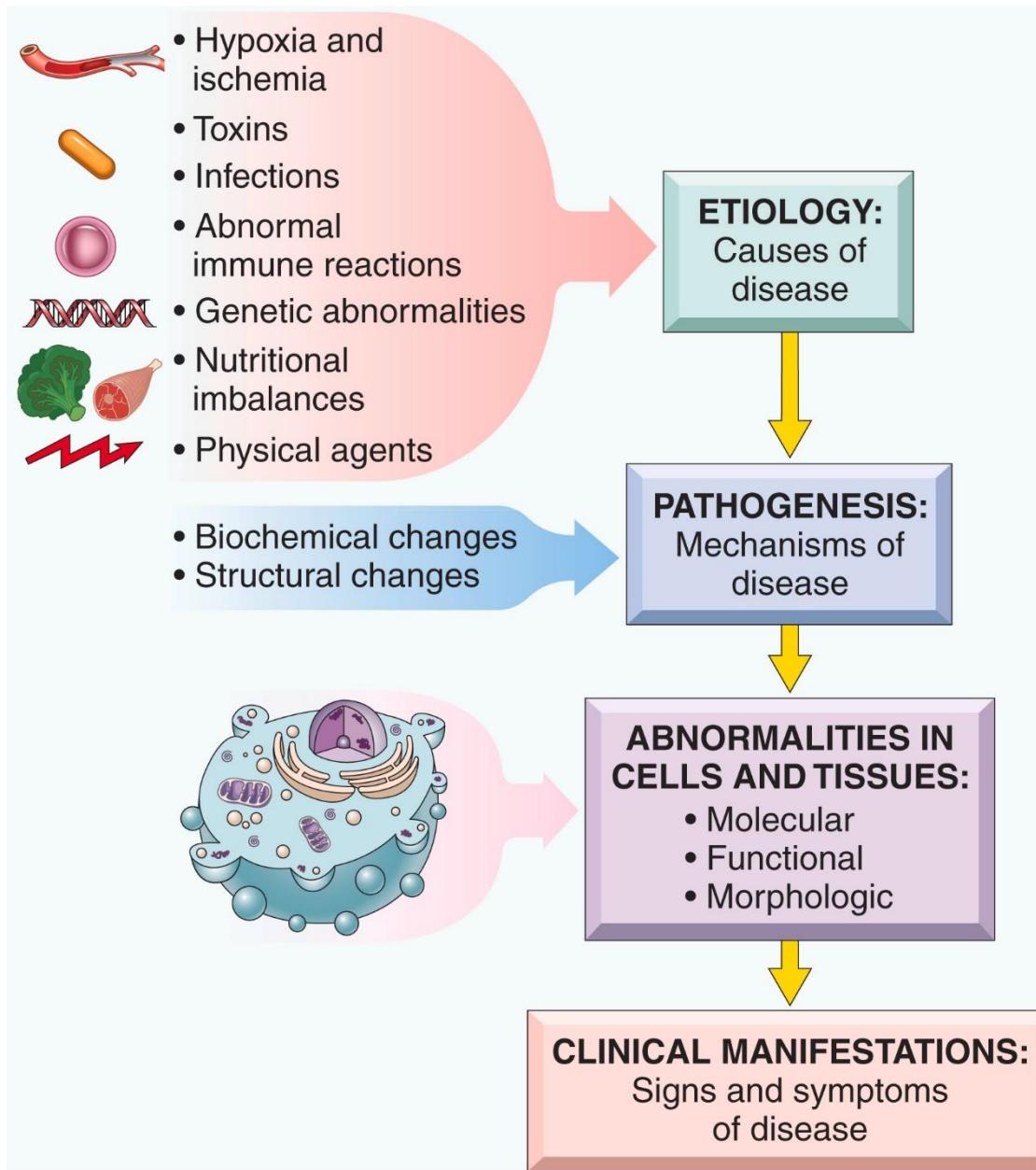


Steps in the Development of Disease



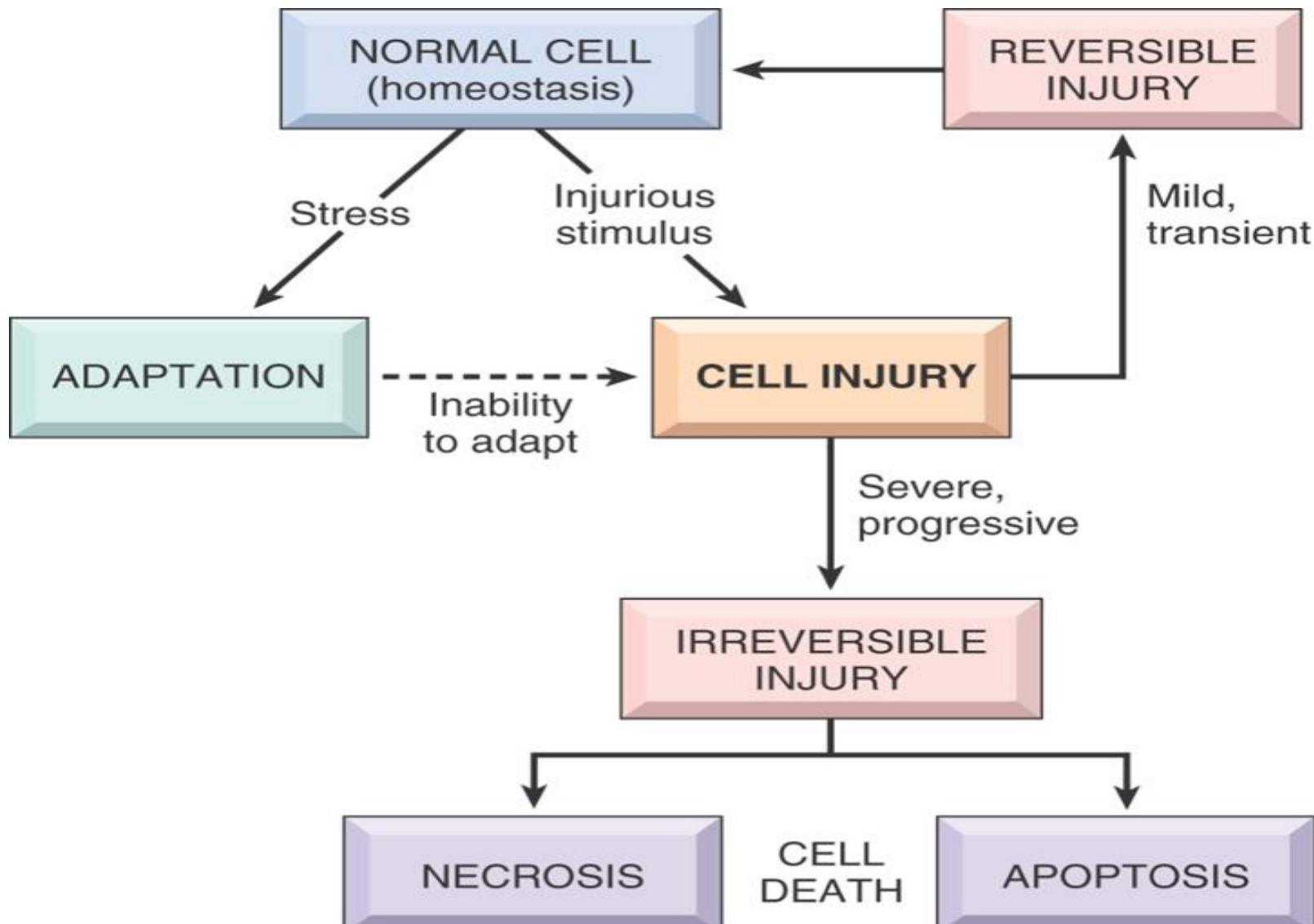
Outlines

- 1. Overview of Cellular Responses to Stress and Noxious Stimuli**
- 2. Reversible Cell Injury**
- 3. Cell Death**
- 4. Mechanisms of Cell Injury**
- 5. Cellular Adaptations to Stress**
- 6. Intracellular Accumulations**
- 7. Pathologic Calcification**
- 8. Cellular Aging**

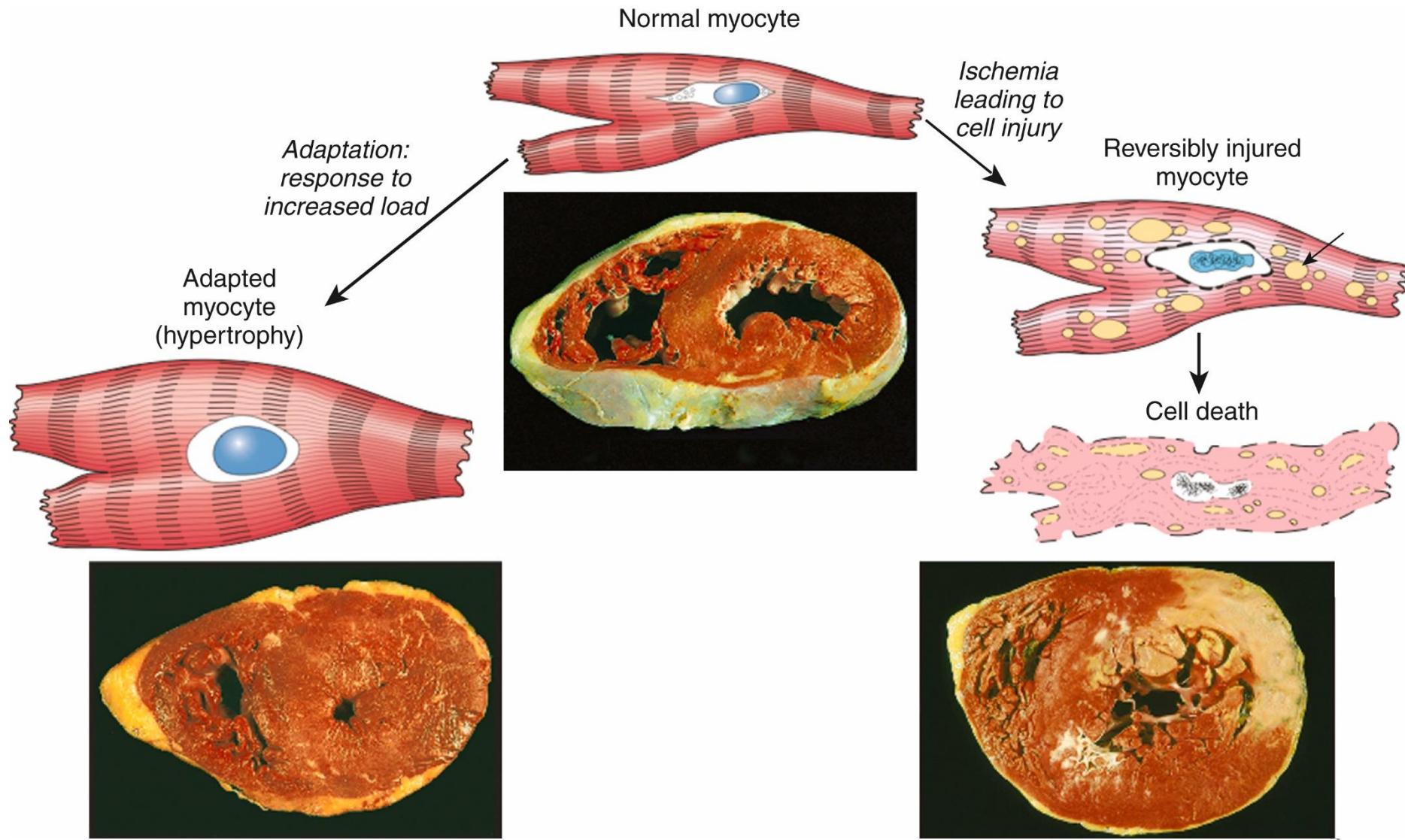
Reference:

Robbins & Kumar Basic Pathology 2023 Chap. 1 Cell injury, Cell death, and Adaptations

Overview of Cellular Responses to Stress and Noxious Stimuli



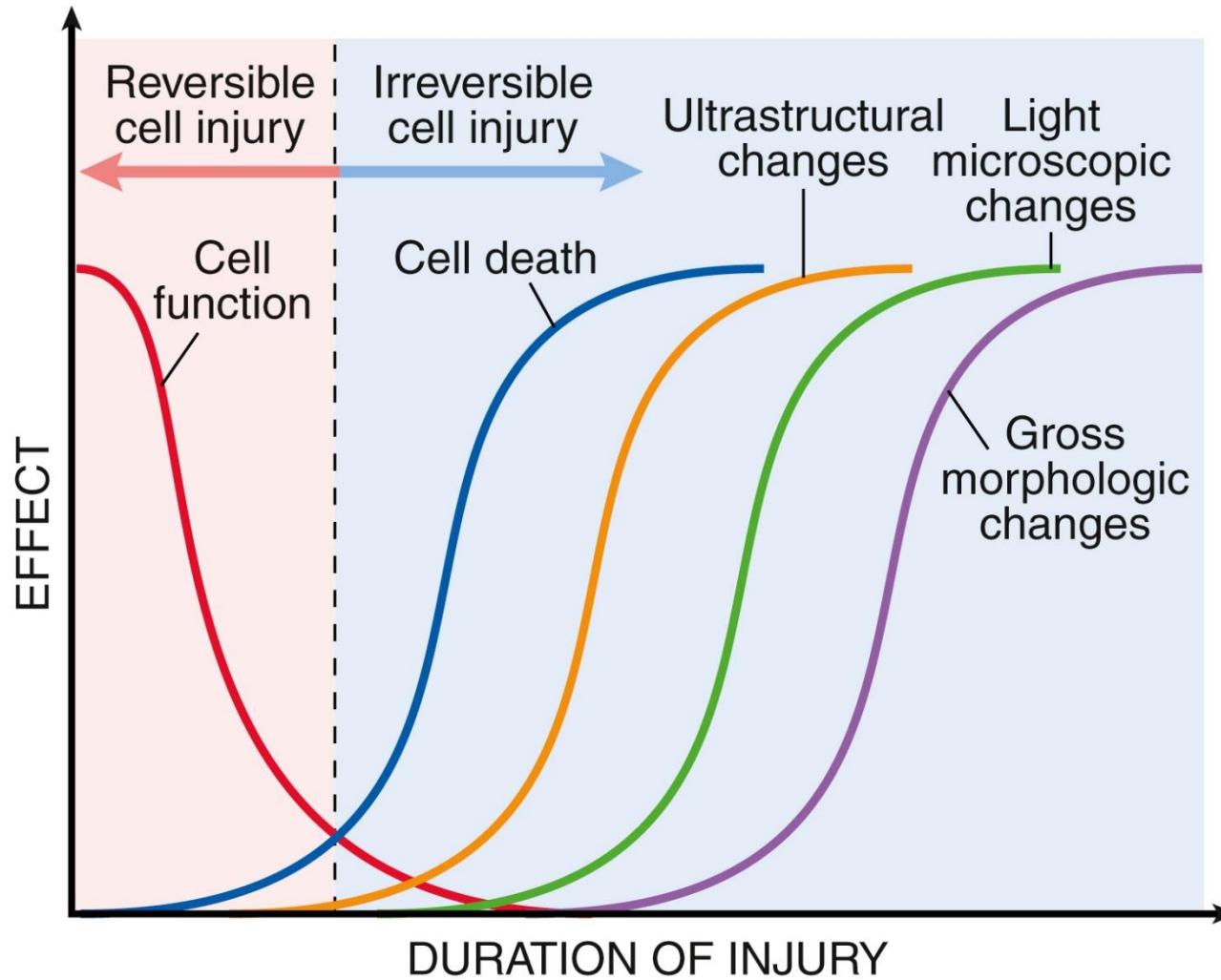
The relationship among normal, adapted, reversibly injured, and dead myocardial cells



Causes of Cell Injury

- **Oxygen deprivation: Hypoxia, common cause, Ischemia: most common cause of hypoxia**
- **Toxins:** air pollutants, poisons, insecticides, CO, etc.
- **Infectious agents**
- **Immunologic reactions:** hypersensitivity, autoimmune disease
- **Genetic abnormalities:** chromosome or gene defect
- **Nutritional imbalances:** protein-calorie insufficiency, vitamin deficiency
- **Physical agents:** trauma, temperatures, radiation, etc.

The Progression of Cell Injury and Death



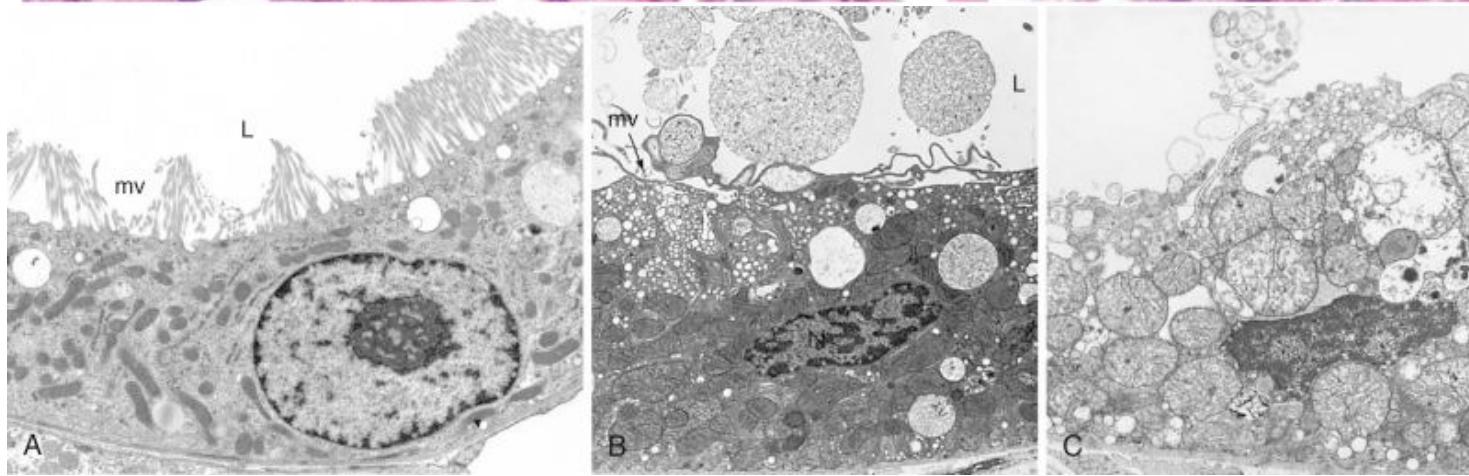
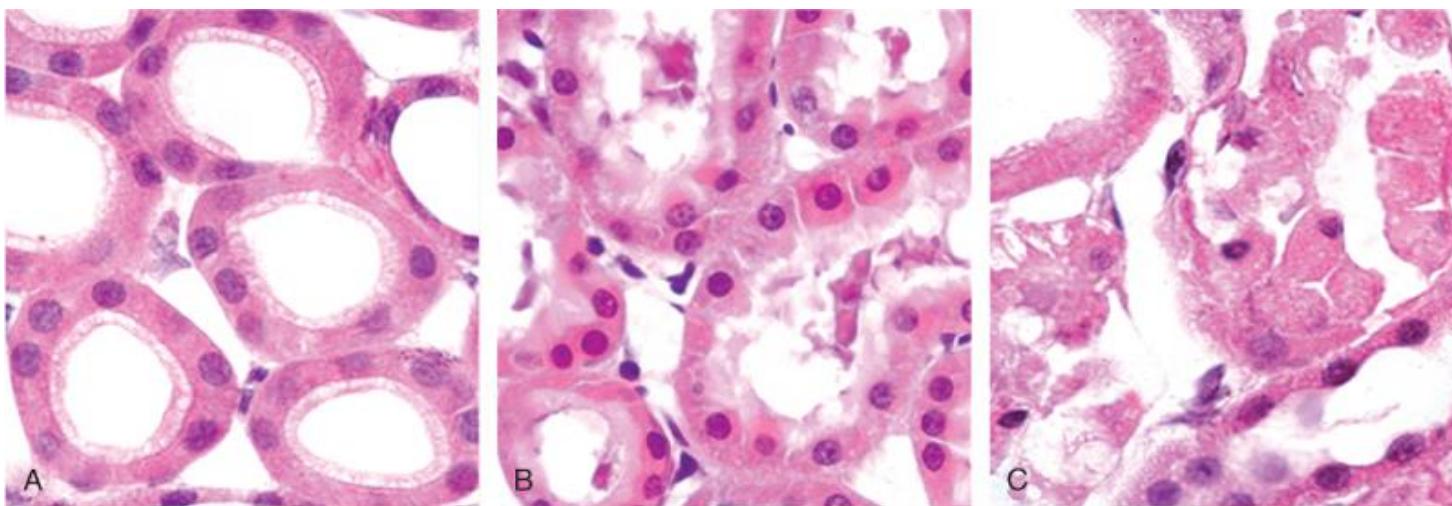
Two phenomena characterize irreversibility:

1. Inability to reverse **mitochondrial dysfunction**
2. Profound disturbances in **membrane** function

Reversible Cell Injury

The stage of cell injury at which the deranged function and morphology of the injured cells can **return to normal** if the damaging stimulus is removed

- 1. Cellular swelling** (hydropic change or vacuolar degeneration)
- 2. Fatty change**: accumulation of lipid droplets



Reversible Cell Injury and Necrosis

(1) Plasma membrane alterations:

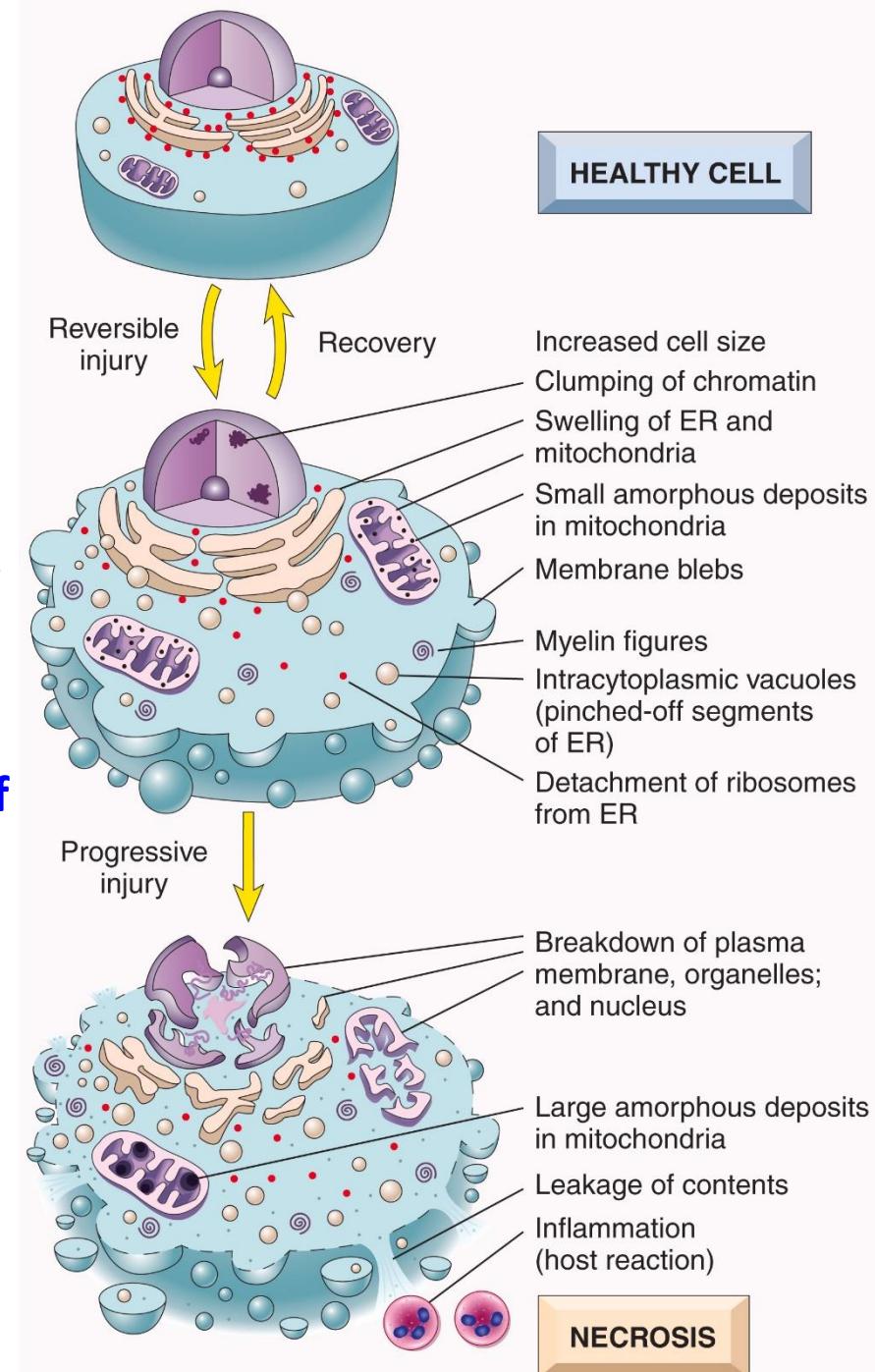
blebbing, blunting, distortion of microvilli, etc.

(2) Mitochondrial changes: swelling & the appearance of phospholipid-rich amorphous densities

(3) Dilation of the ER with detachment of polysomes

(4) Nuclear alterations: clumping of chromatin

(5) Myelin figures: collections of phospholipids derived from damaged cellular membranes



Cell Death

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis, karyorrhexis, karyolysis	Fragmentation
Plasma membrane	Disrupted	Intact
Cellular contents	Enzymatic digestion	Intact
Inflammation	Frequent	No
Role	Pathologic	Physiologic or pathologic

Necrosis

- Consequence of severe injury
- Characterized by denaturation of cellular proteins, leakage of cellular contents through damaged membranes, local inflammation, and enzymatic digestion of the lethally injured cell.
- Leakage of intracellular proteins is the basis for blood tests that detect tissue-specific cellular injury

Necrotic cell

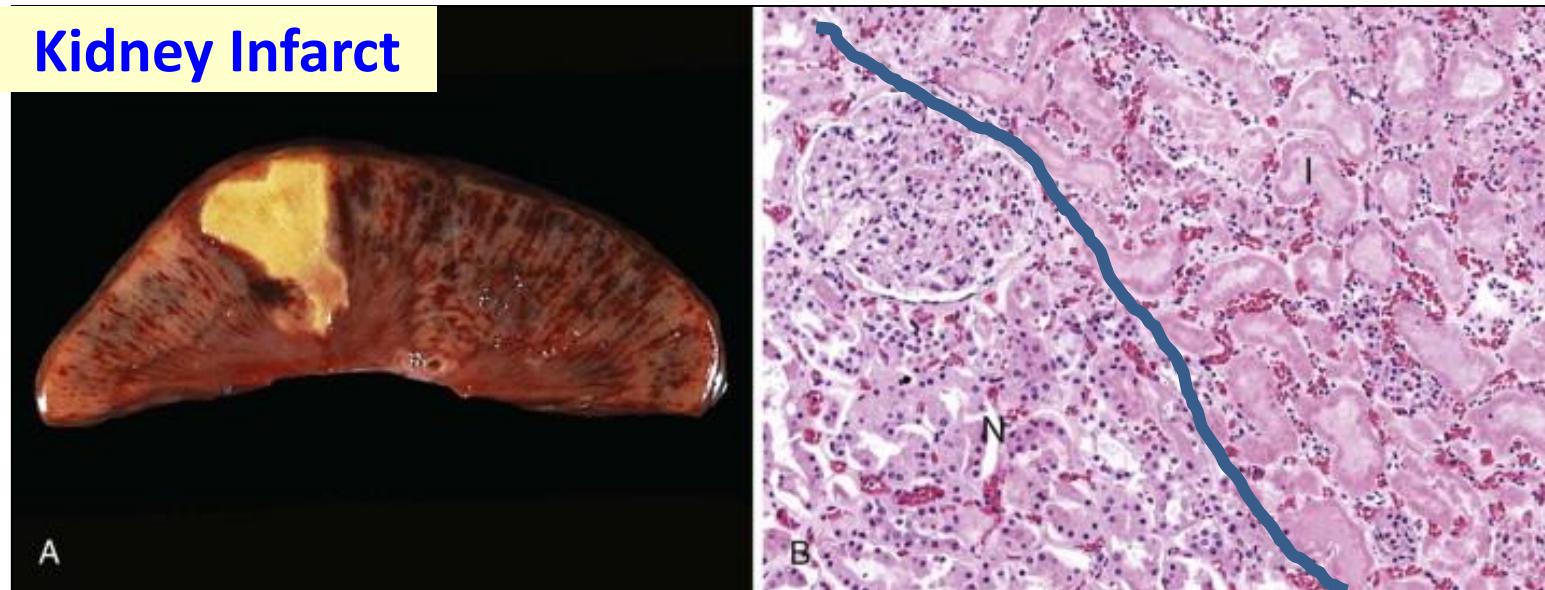
- **Increased eosinophilia:** loss of RNA
- **Karyolysis:** basophilia of chromatin fade
- **Pyknosis:** nuclear shrinkage and increased basophilia
- **Karyorrhexis:** pyknotic nucleus fragments

Fates of necrotic cells: persist for some time or be digested

Patterns of Tissue Necrosis: morphologically distinct, underlying cause

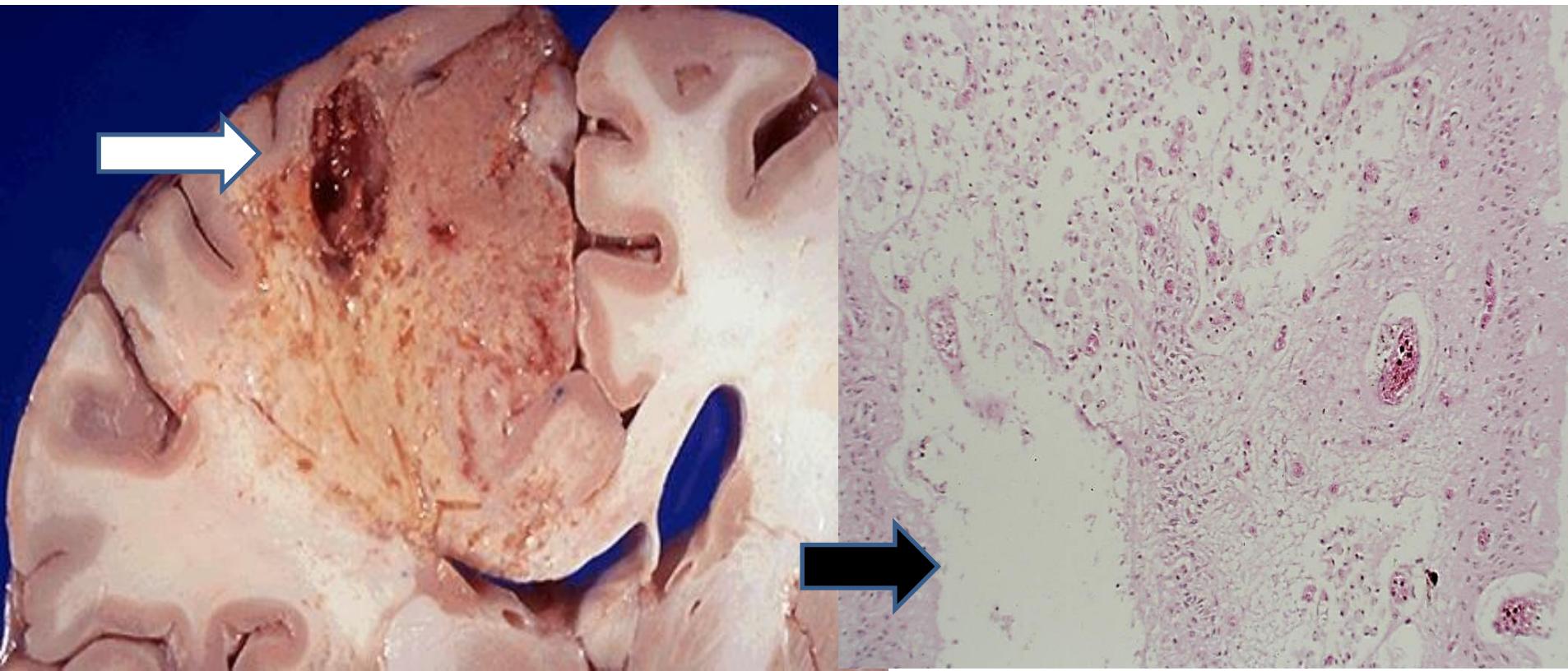
Coagulative Necrosis

- Most common
- Denaturation is the primary pattern
- Preservation of basic structural outline of the coagulated cell or tissue for days or weeks
- Ischemia caused by obstruction in a vessel may lead to coagulative necrosis of the supplied tissue in all organ except the brain
- A localized area of coagulative necrosis is called an infarct



Liquefactive Necrosis

- Dominant enzyme digestion
- Characteristic of focal bacterial or sometimes fungal infections
- Hypoxic death in the **brain (brain infarct)**

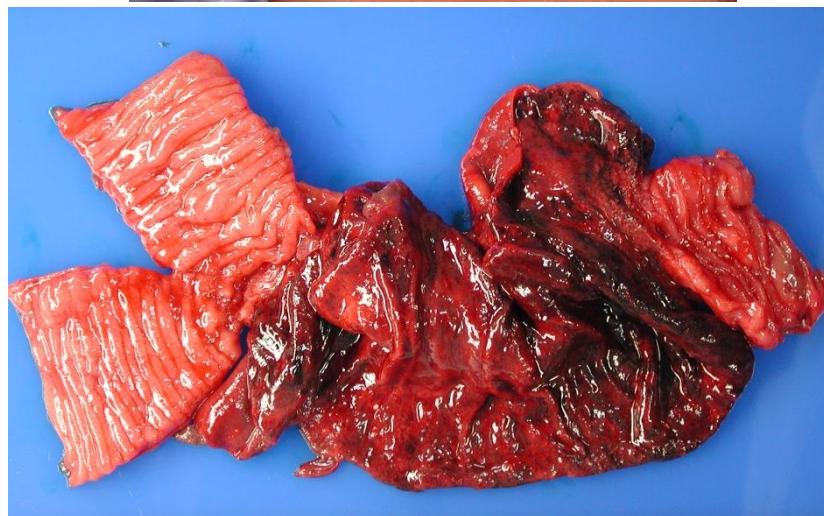


Gangrenous Necrosis

Not a distinctive pattern, ischemic coagulative necrosis,
frequently of a limb, especially common in **diabetes**



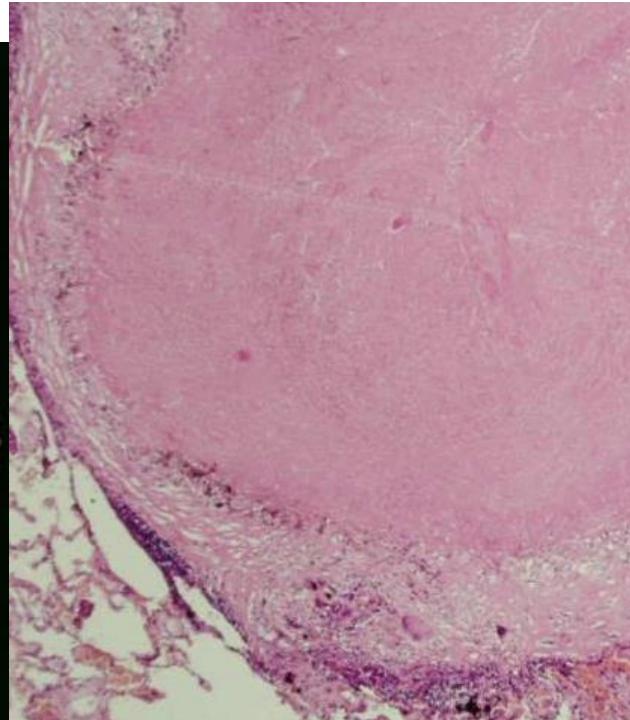
Wet gangrene: bacterial infection



Caseous Necrosis

- A special form of coagulative necrosis with limited liquefaction
- Encountered most often in foci of **tuberculous** infection
- Cheesy, white gross appearance, **structureless** amorphous granular debris
- **Granuloma:** enclosed within a distinctive inflammatory border

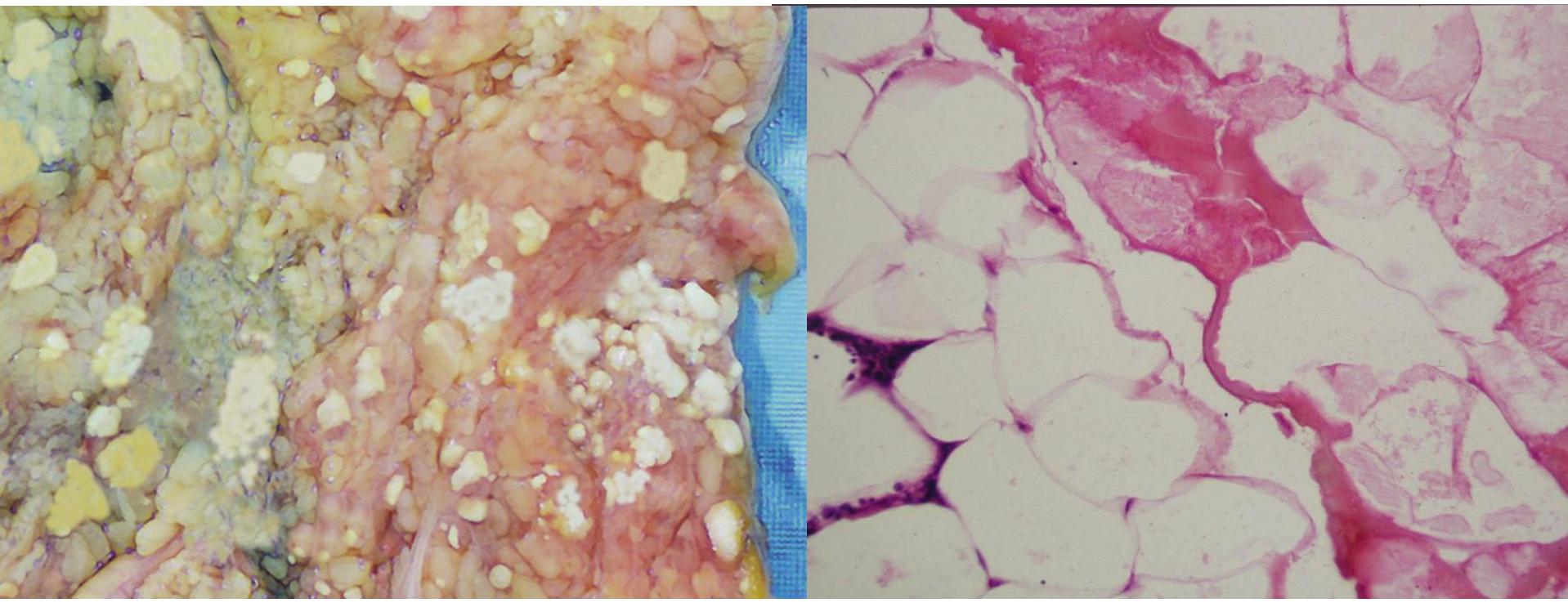
Tuberculosis of Lung



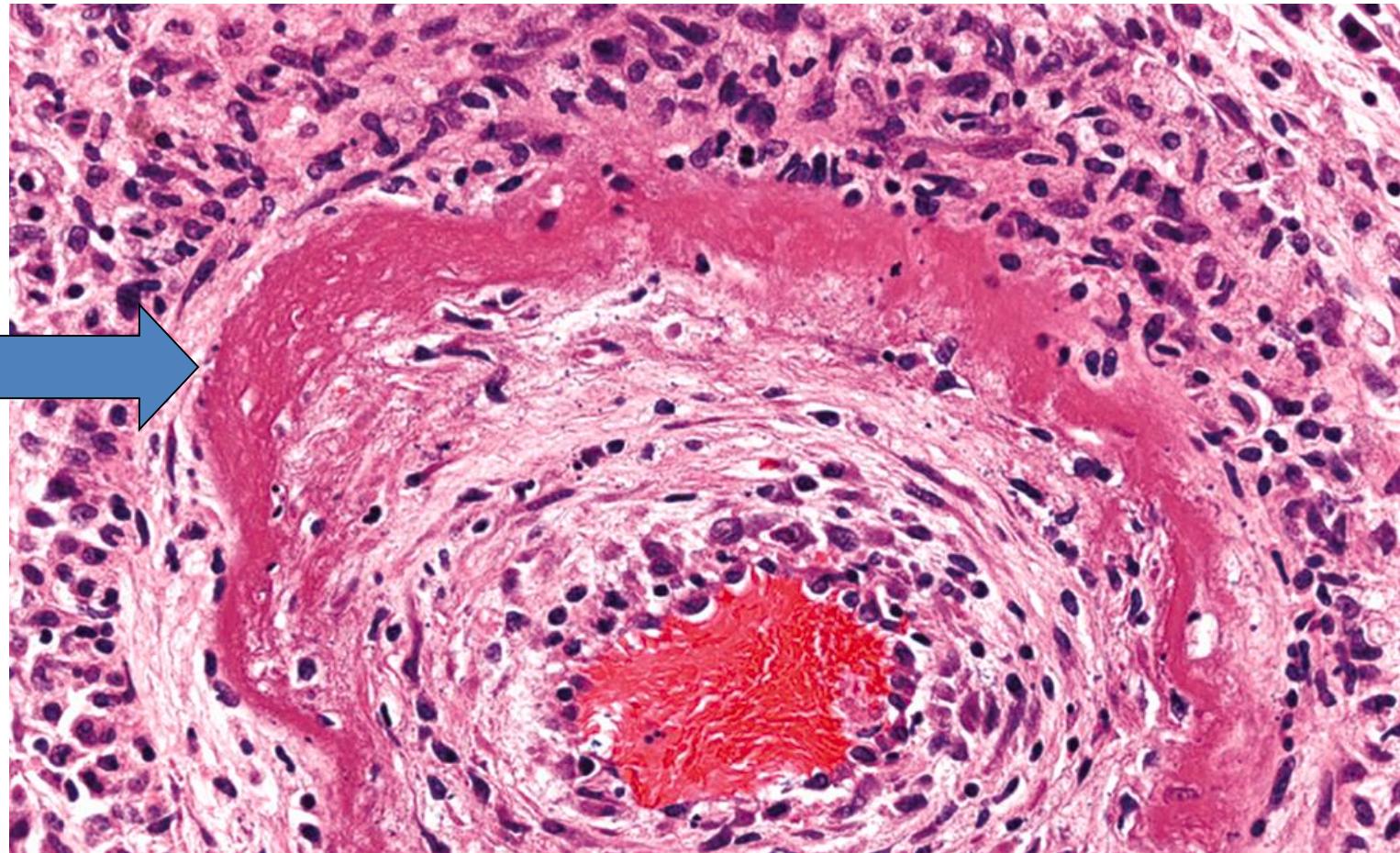
Completely obliterated
tissue architecture

Fat Necrosis

- Focal areas of fat destruction
- Typically resulting from release of activated pancreatic lipases due to **acute pancreatitis**
- Fat degrade to glycerol and free fatty acids. Free fatty acids bind to calcium (**fat saponification**)



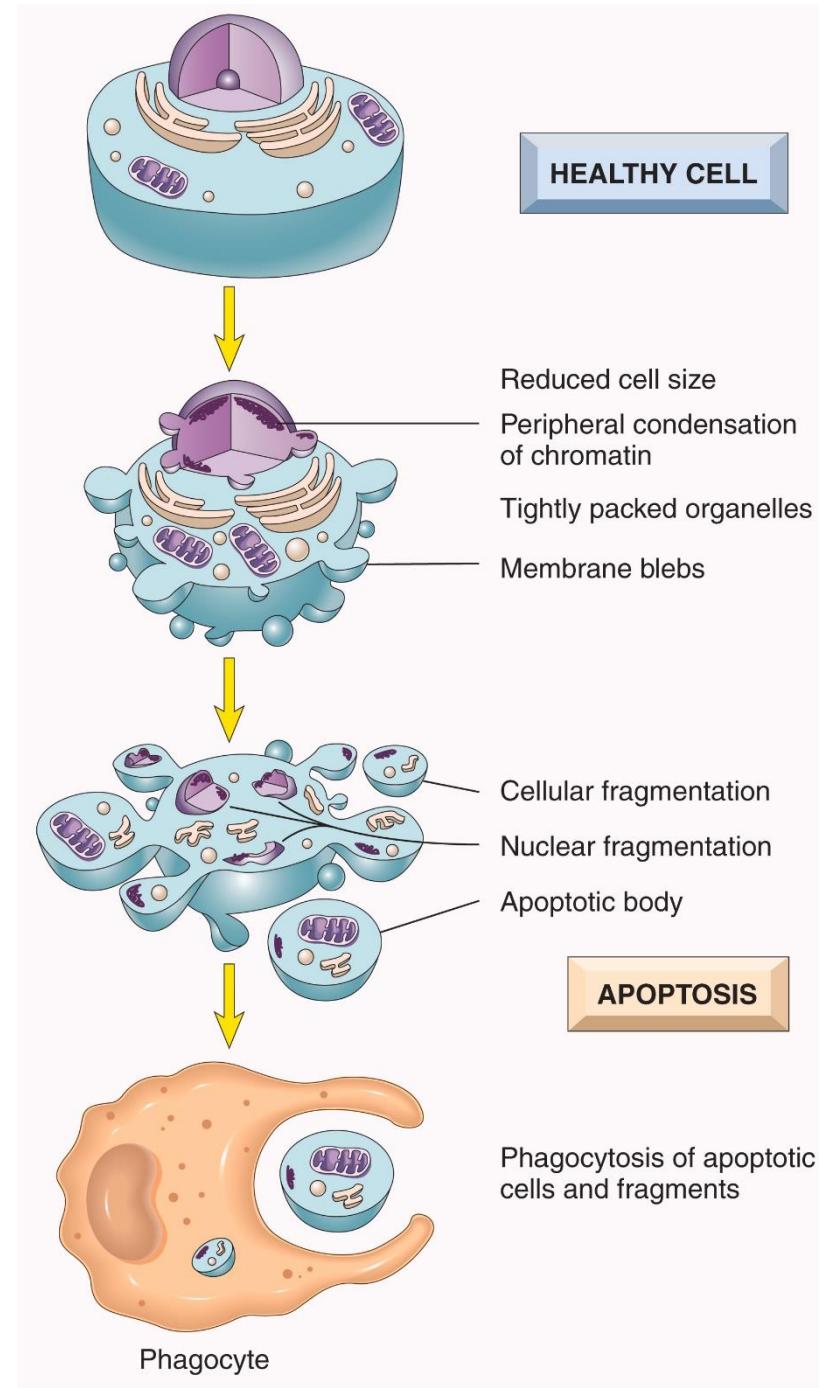
Fibrinoid Necrosis



Usually seen in immune reactions involving blood vessels

Apoptosis

A pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins

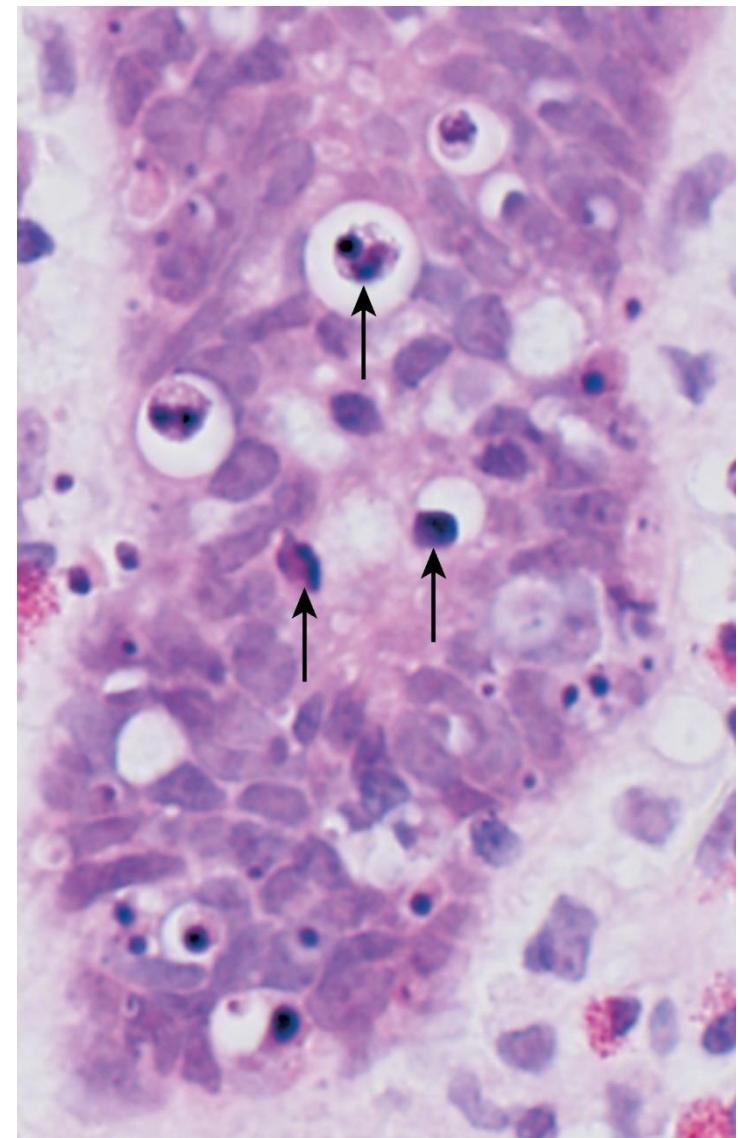


Causes of Apoptosis

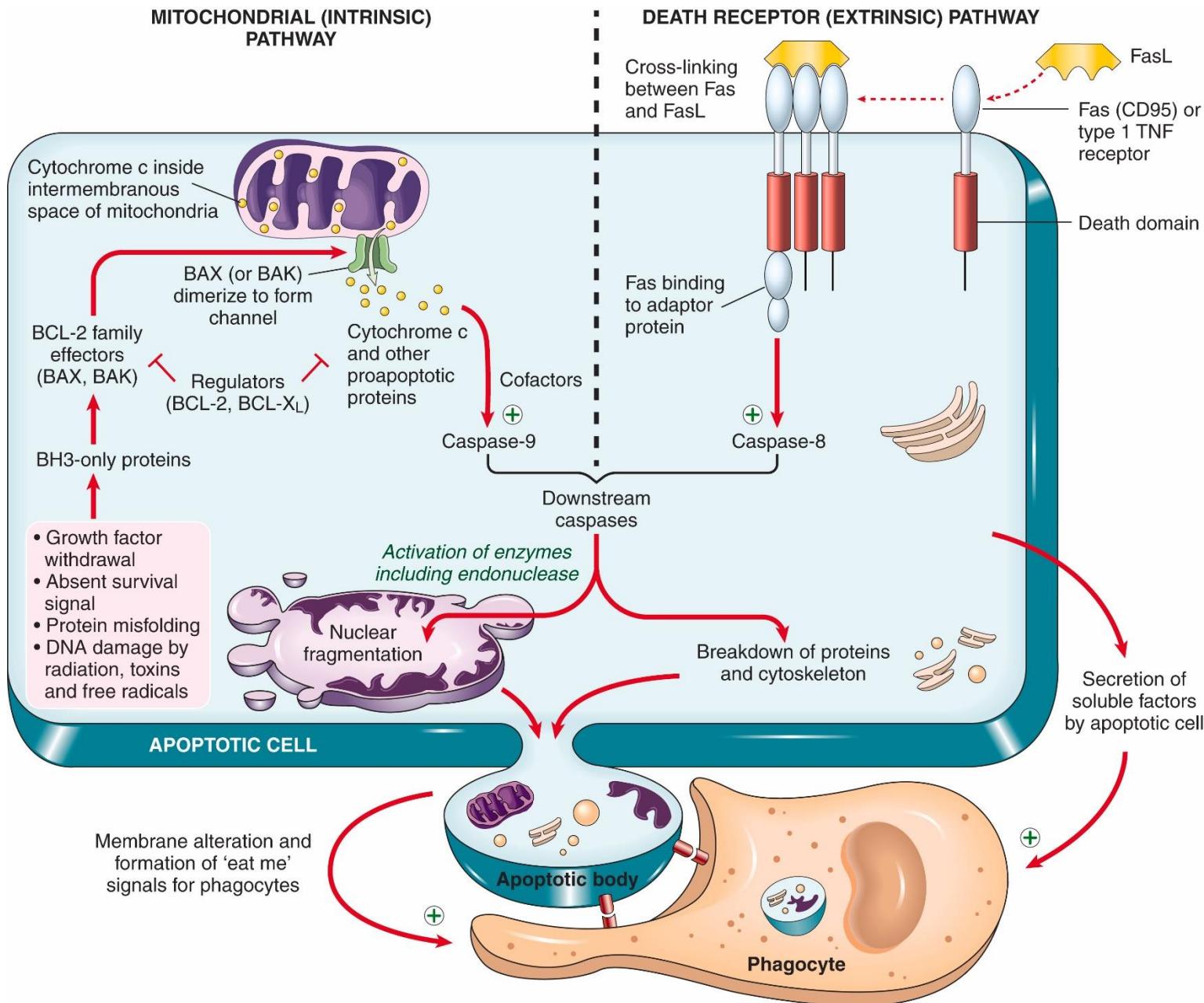
Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling
Turnover of proliferative tissues	Loss of growth factor signaling
Involution of hormone-dependent tissues	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial & death receptor pathways
Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

Morphology of Apoptosis

- HE:
 - Cell shrinkage
 - Chromatin condensation
 - Karyorrhexis
- Molecular level:
 - Fragmentation of DNA
 - Form cytoplasmic buds and fragment in to membrane-bound **apoptotic bodies**
 - Phagocytosed



Mechanisms of Apoptosis

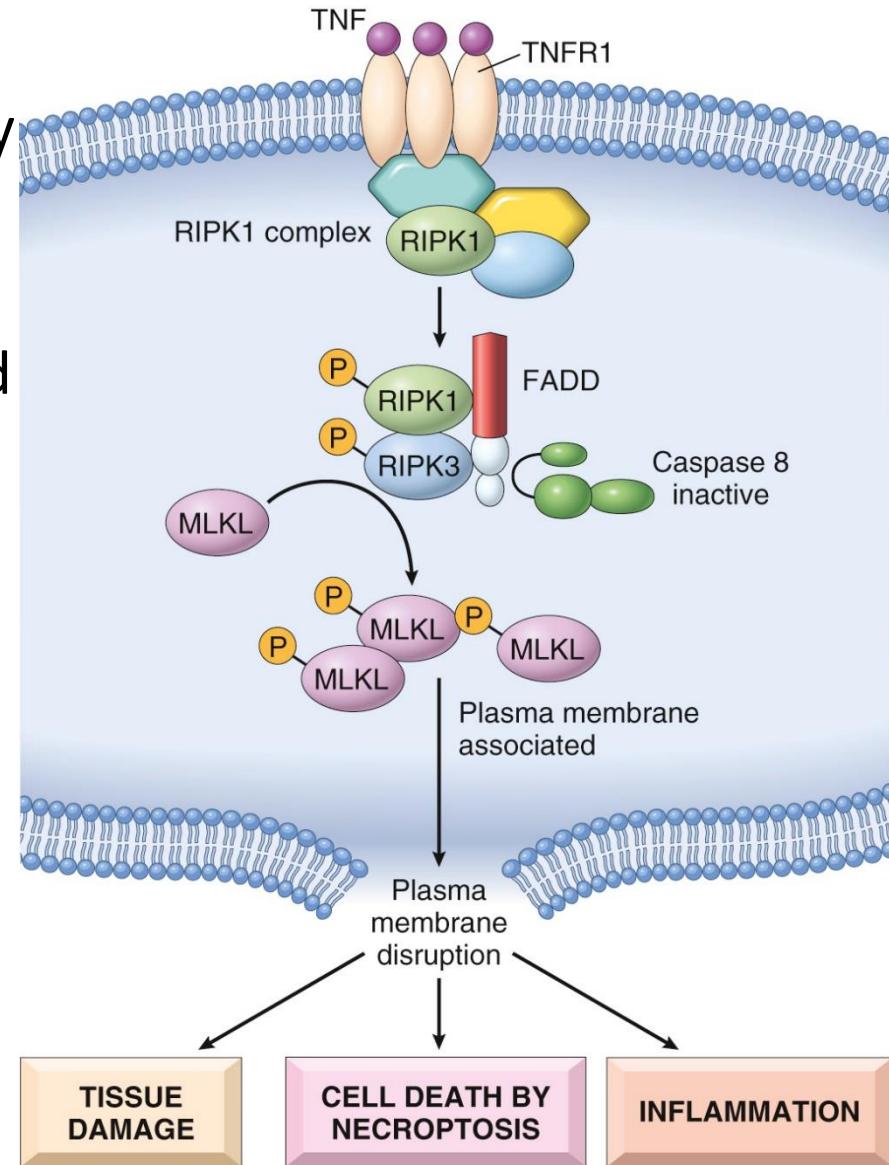


Other Mechanisms of Cell Death

Necroptosis

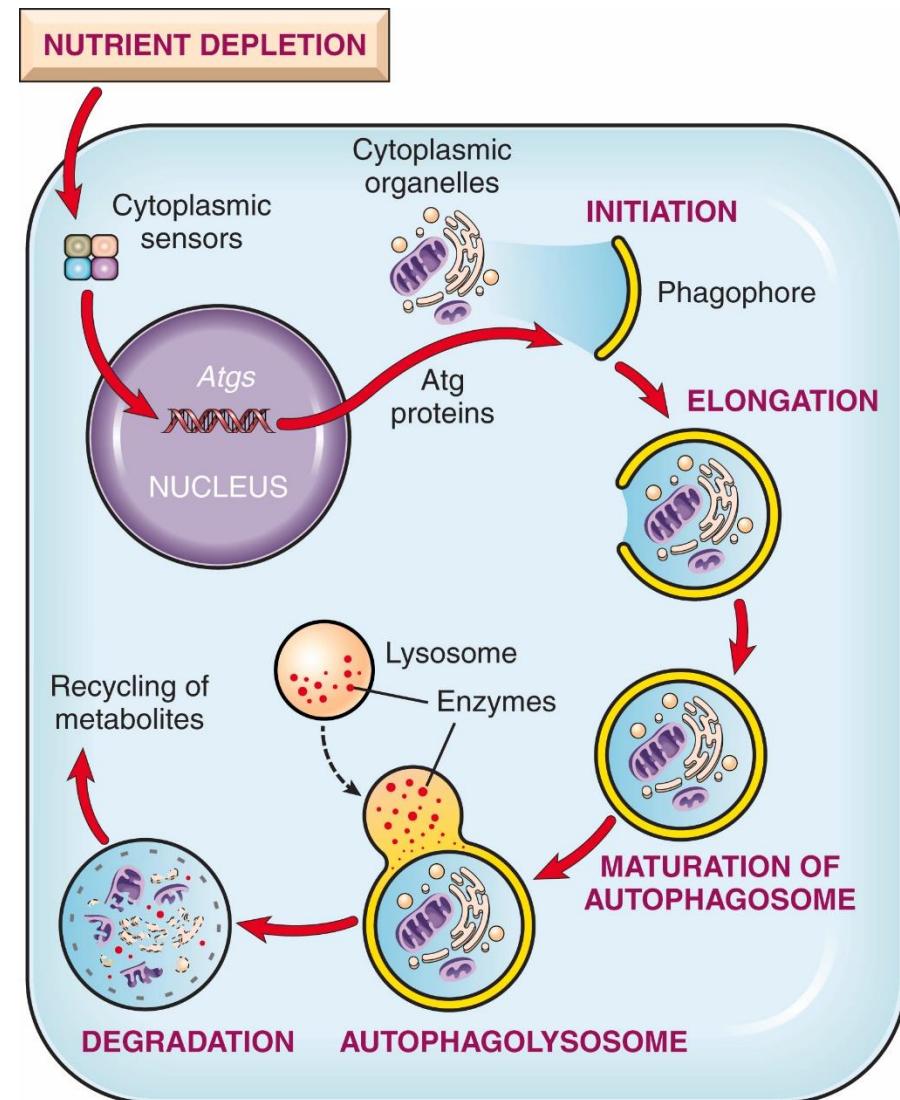
- Resemble necrosis morphologically and apoptosis mechanistically as a form of programmed cell death
- Triggered by ligation of **TNFR1**, and viral proteins of RNA and DNA viruses
- Caspase-independent but dependent on signaling by the **RIPK1 and RIPK3** complex
- Both in physiologic and pathologic conditions

Pyroptosis *Ferroptosis*



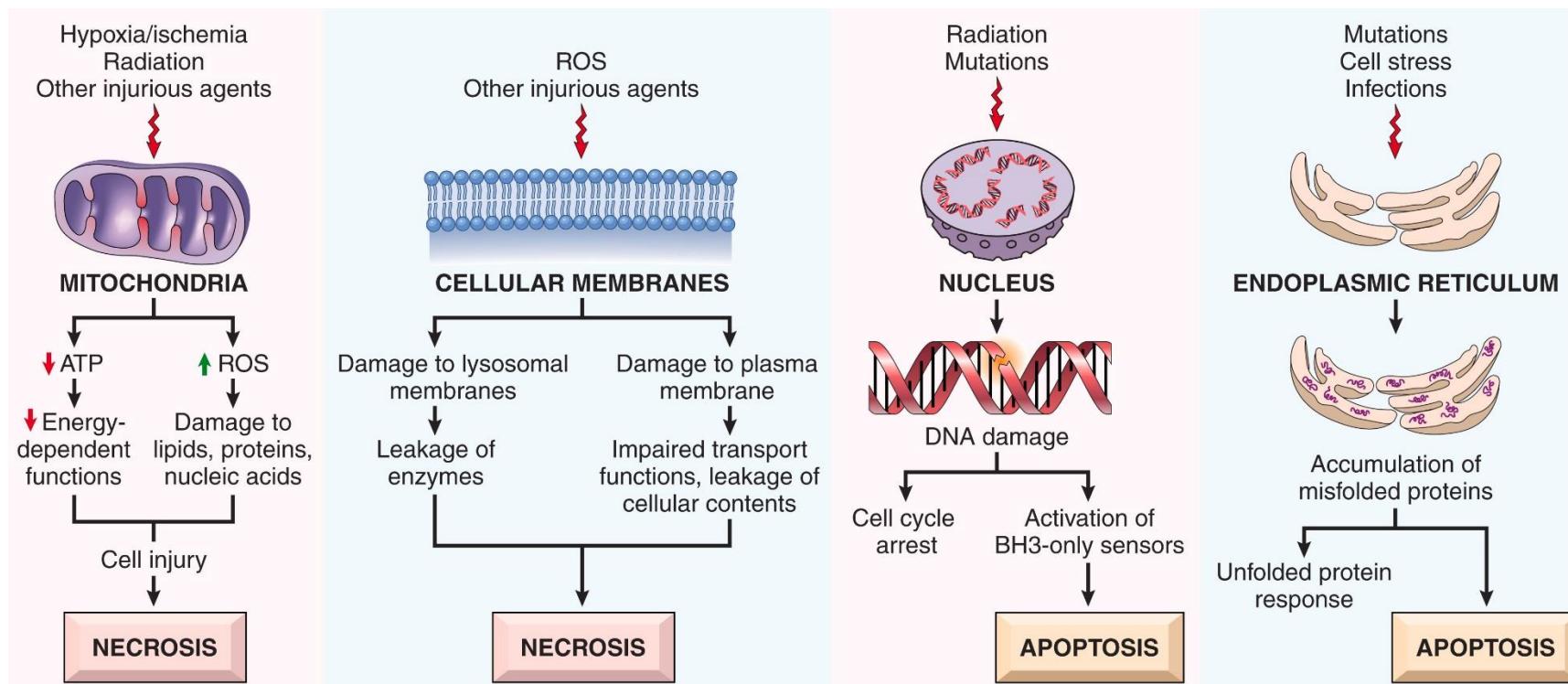
Autophagy

- Lysosomal digestion of the cell's own components, a survival mechanism initiated by proteins that sense nutrient deprivation
- Phagophore → Autophagosome → fuses with lysosomes → autophagolysosome
- May play a role in cancer, neurodegenerative disorders, infectious disease, inflammatory bowel disease

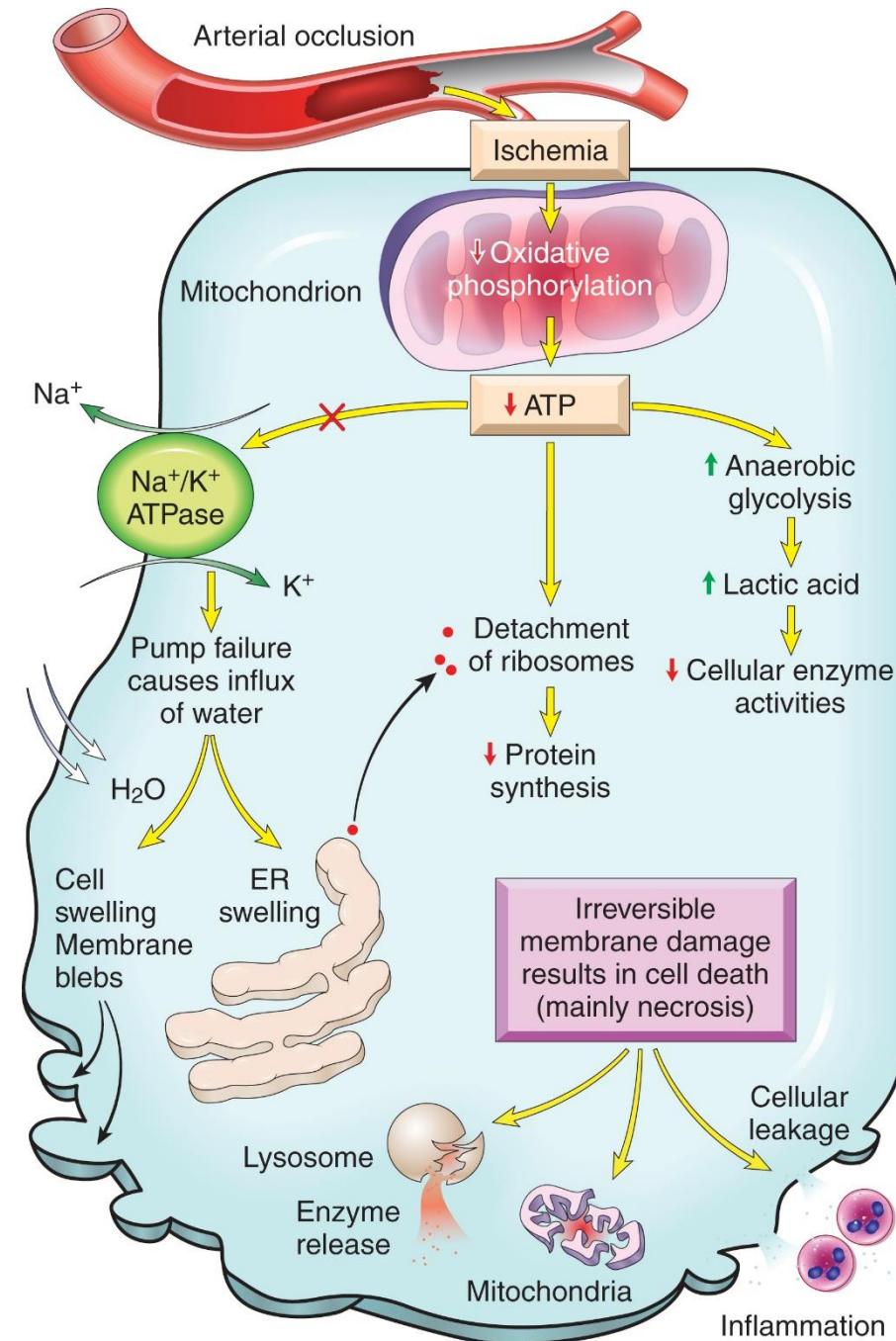


Mechanisms of Cell Injury and Cell Death

- The cellular response to injurious stimuli depends on the **type of injury** and its **duration** and **severity**.
- The consequences of an injurious stimulus depend on the **type of cell** and its **metabolic state, adaptability, and genetic makeup**.
- Cell injury results from functional & biochemical abnormalities in one or more of several **essential cellular components**



Hypoxia and Ischemia

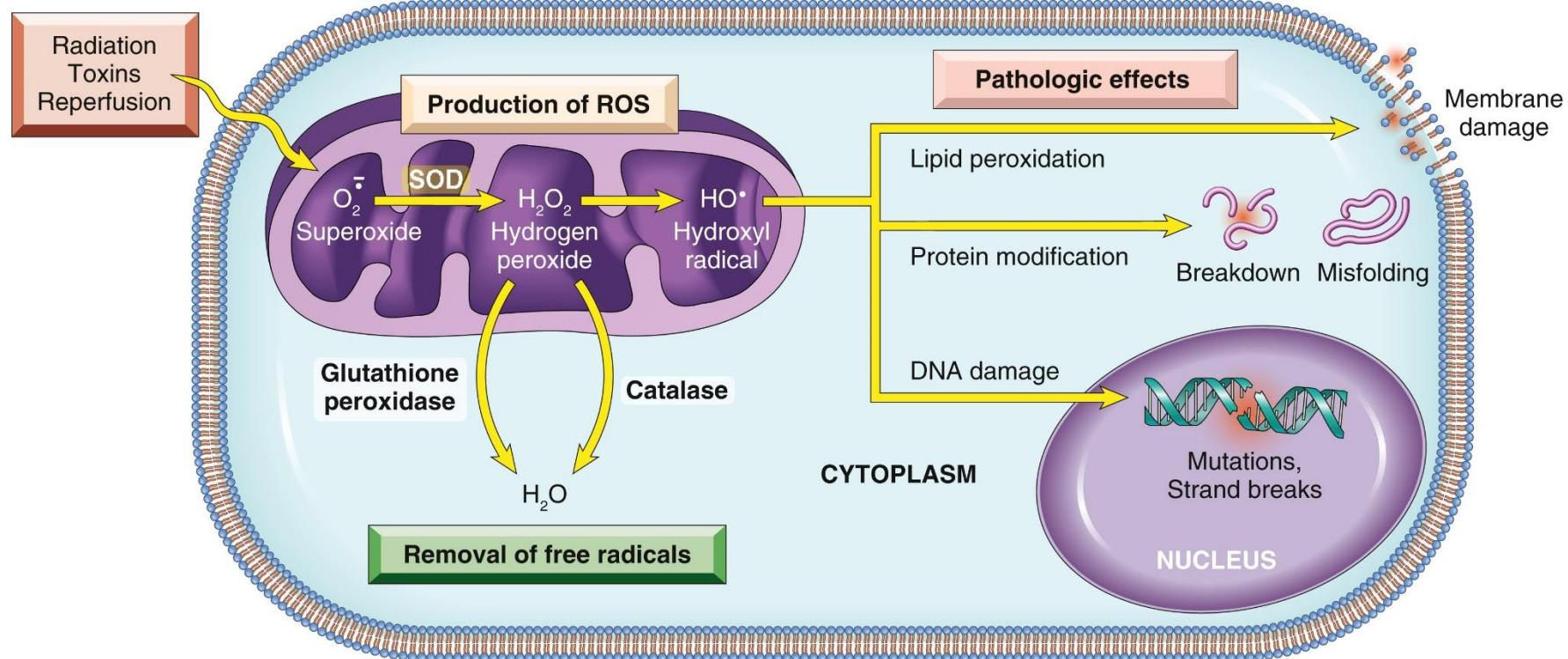


Ischemia-Reperfusion Injury

- Under certain circumstances, the restoration of blood flow to ischemic but viable tissues results, paradoxically, in **increased** cell injury.
- Mechanisms
 - New damage may be initiated during reoxygenation by **increased generation of ROS**
 - The **inflammation** induced by ischemic injury may increase
 - Influx of leukocytes and plasma proteins
 - Activation of the complement system

Oxidative Stress

- cellular damage induced by the accumulation of ROS
- **Free radicals:** extremely unstable, readily react with inorganic and organic compounds
- **Reactive oxygen species (ROS):** oxygen-derived free radical
- **The generation, removal, and role of ROS in cell injury**

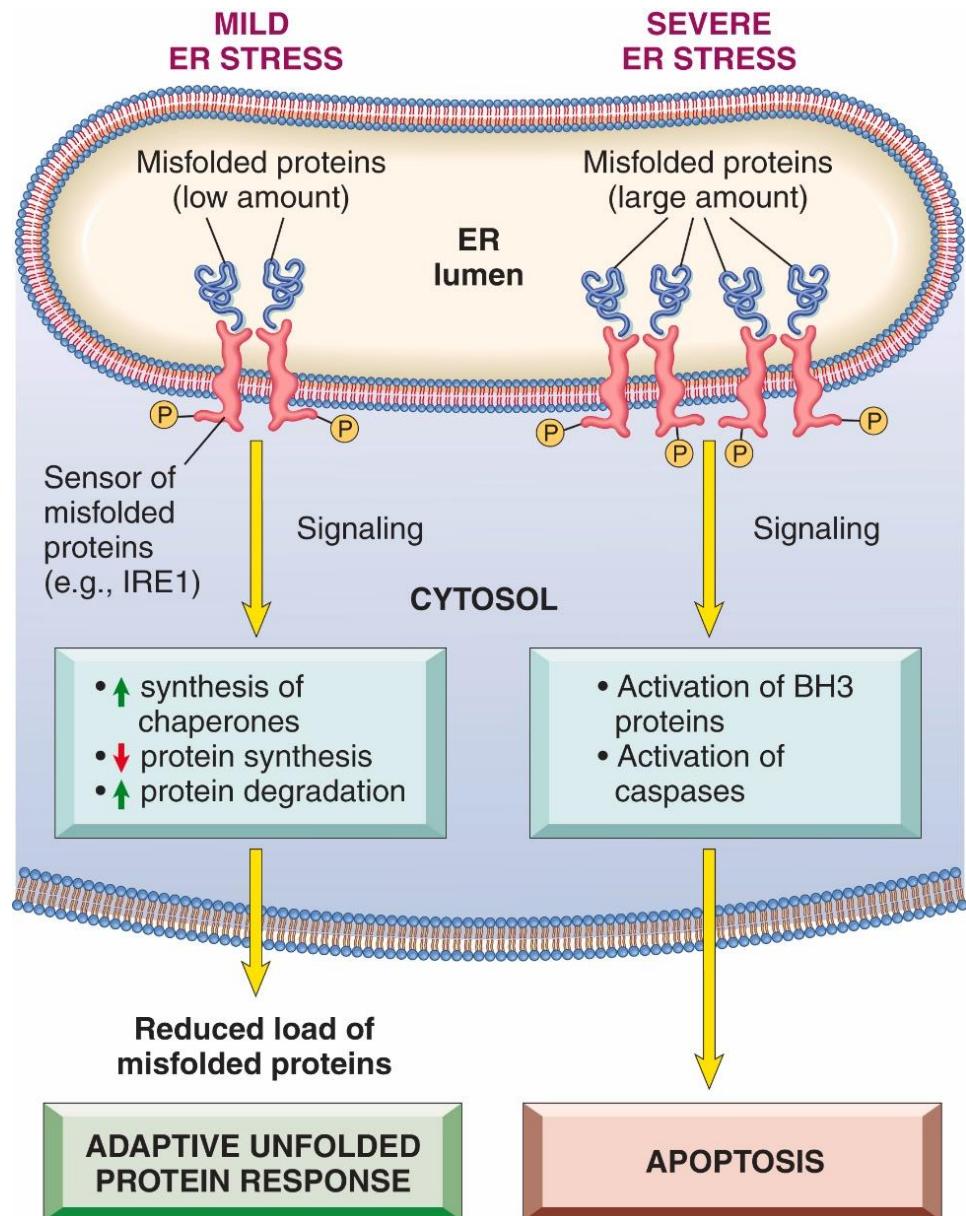


Cell Injury Caused by Toxins

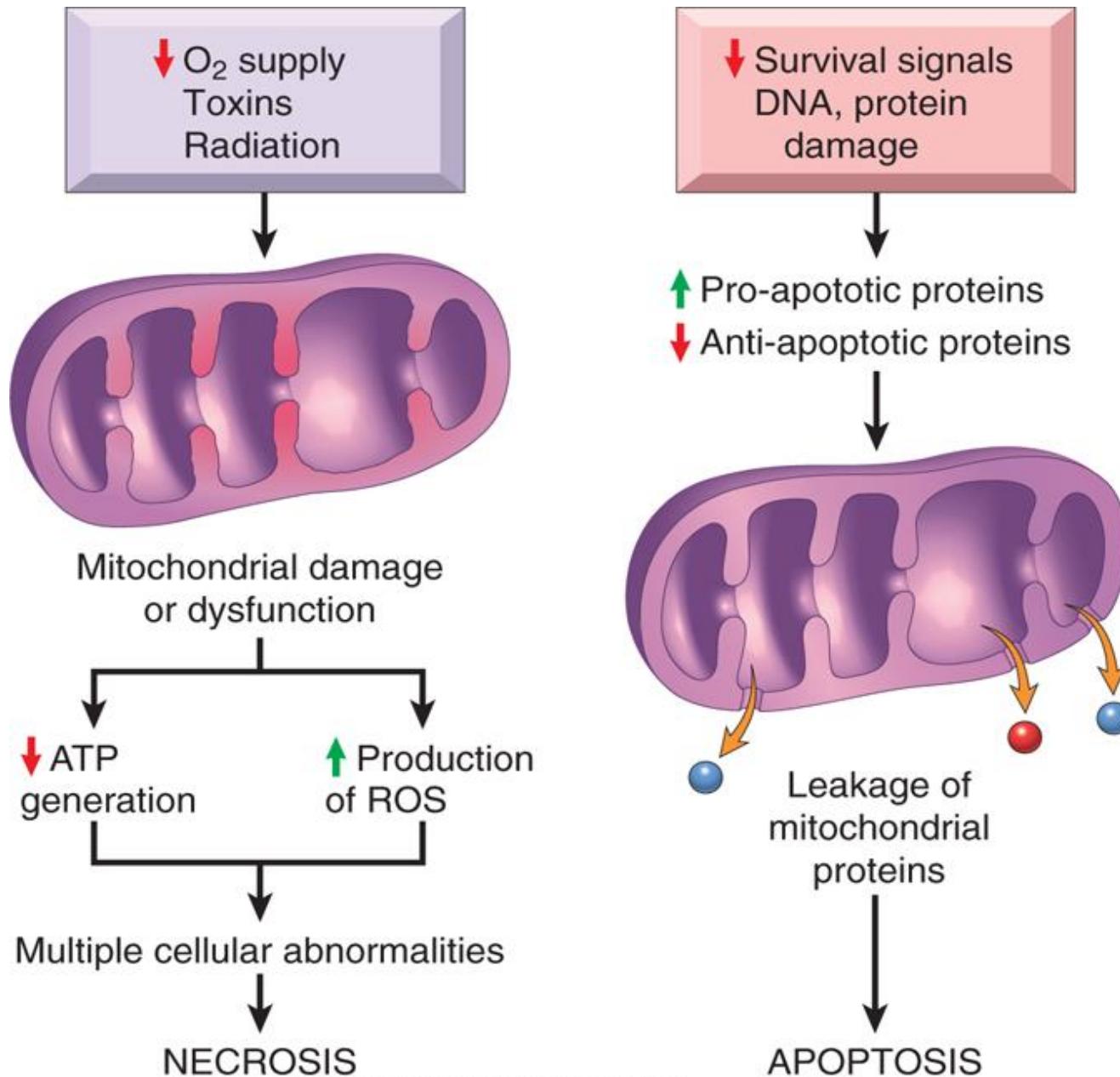
- Toxins, including environmental chemicals and substances produced by infectious pathogens, induce cell injury that culminates primarily in necrotic cell death.
- Two general mechanism:
 - ***Direct-acting toxins:*** anti-neoplastic chemotherapeutic agents, toxins made by microorganisms
 - ***Latent toxins:*** Carbon tetrachloride (CCl_4), acetaminophen

ER Stress: the Unfolded Protein Response

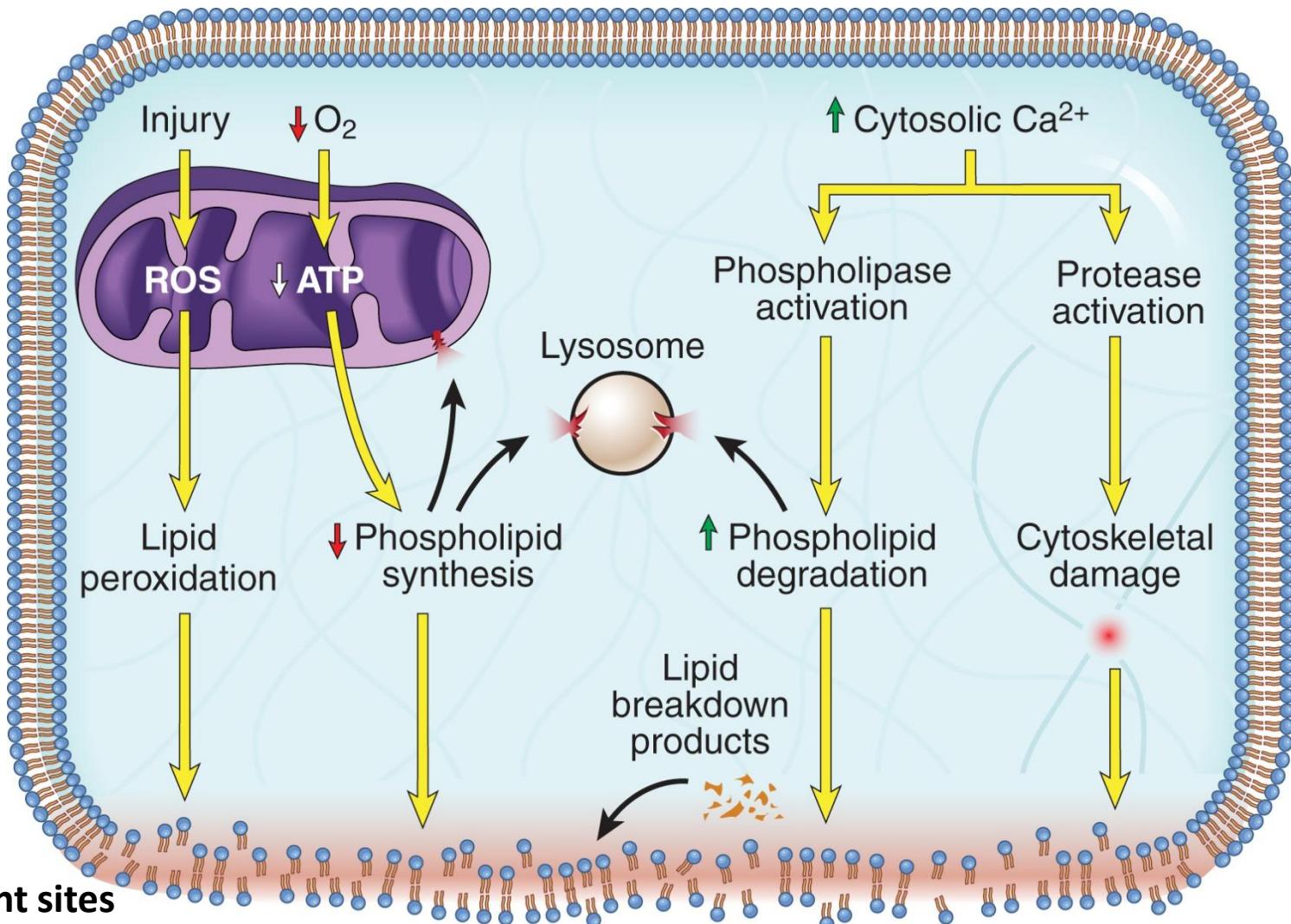
- Accumulation of misfolded proteins in a cell can stress compensatory pathways in the ER and lead to cell death by apoptosis.
- caused by abnormalities that increase the production of misfolded proteins or reduce the ability to eliminate them
- Protein misfolding within cells may cause diseases by creating a deficiency of an essential protein or by inducing apoptosis



Mitochondrial Dysfunction



Membrane Damage

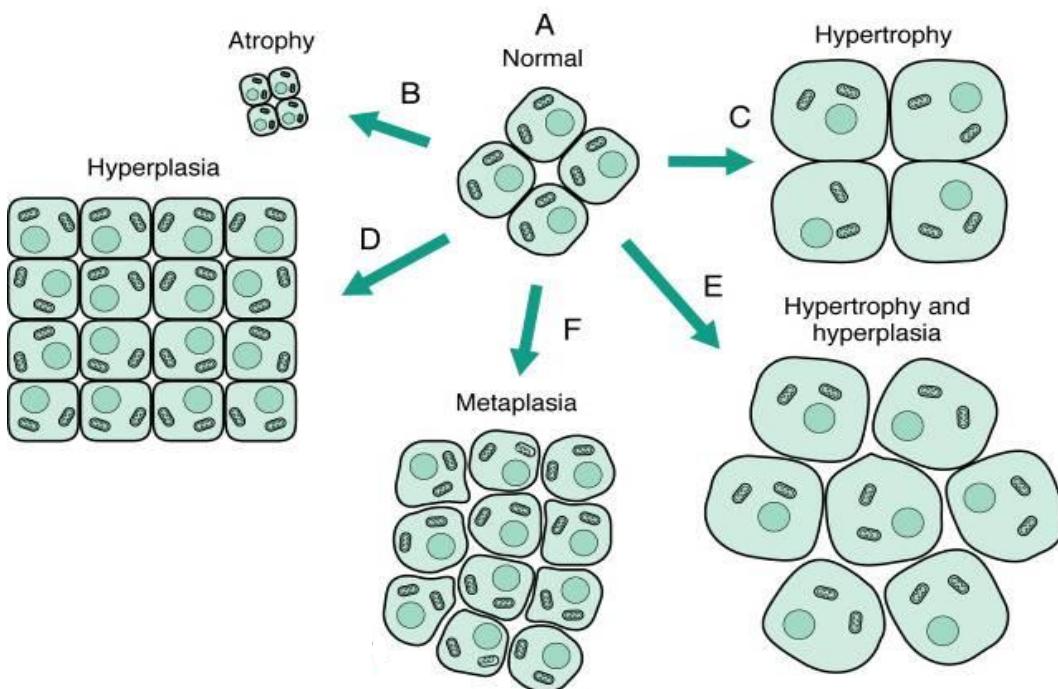


Most important sites

1. Mitochondrial membrane
2. Plasma membrane
3. Lysosomal membrane

Cellular Adaptations to Stress

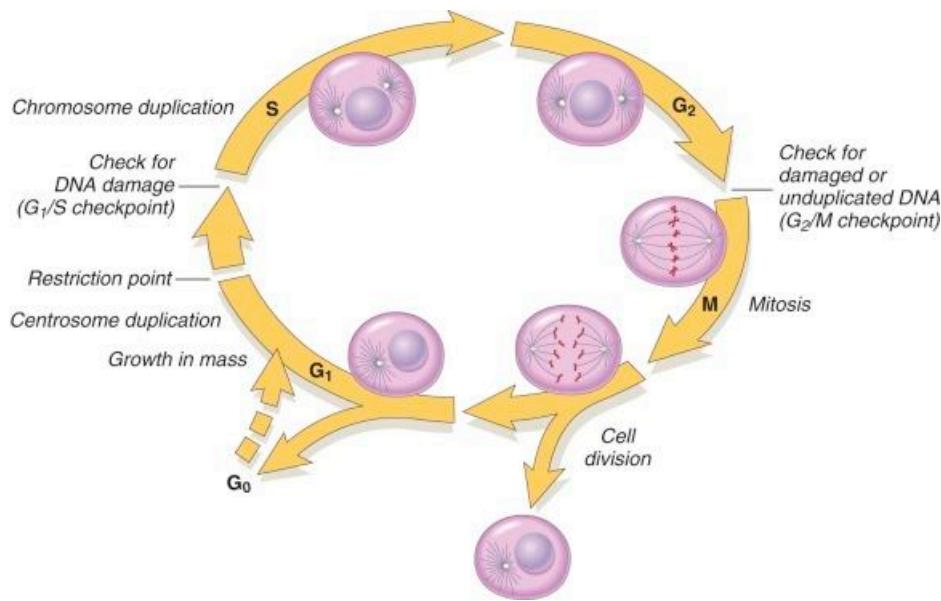
Adaptations are **reversible** changes in the **number, size, phenotype, metabolic activity, or functions** of cells in response to changes in their environment.



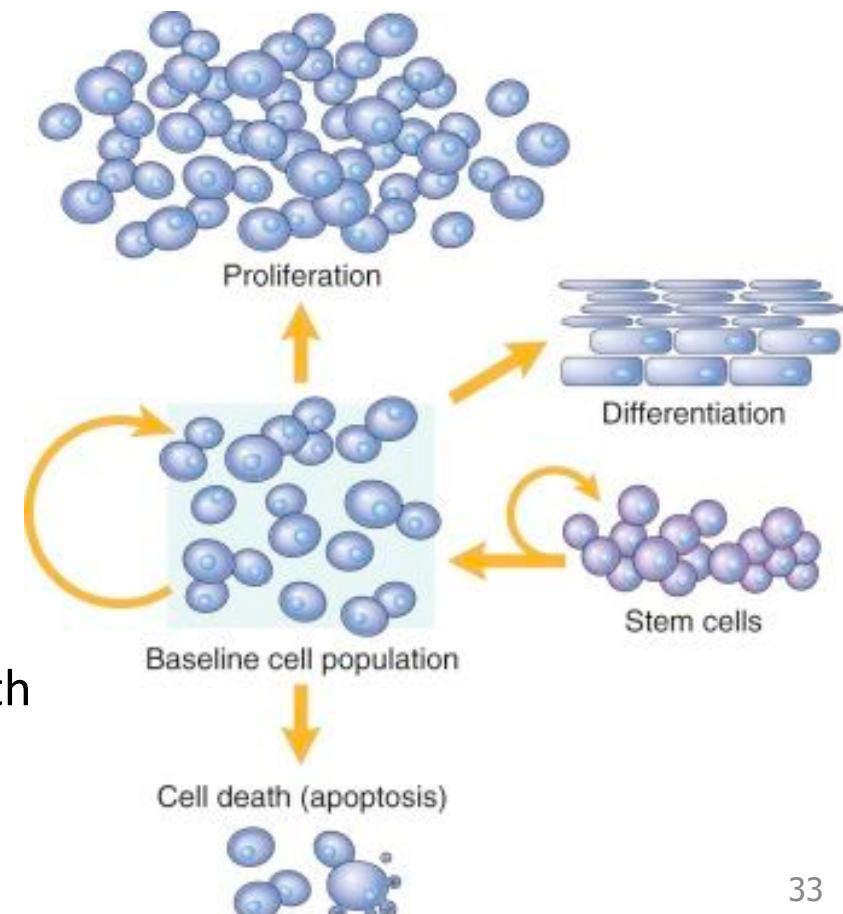
- **Hypertrophy (肥大)**
- **Hyperplasia (增生)**
- **Atrophy (萎縮)**
- **Metaplasia (化生)**

Maintaining Cell Populations

Cell cycle landmarks



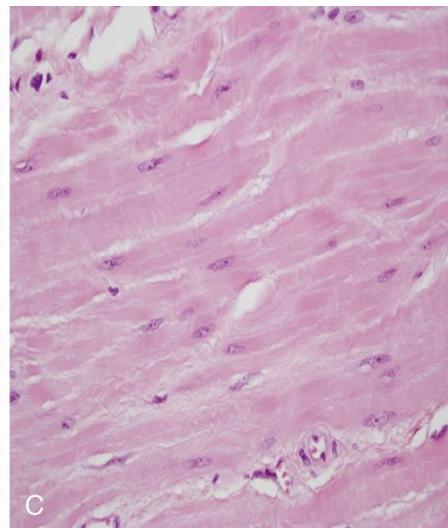
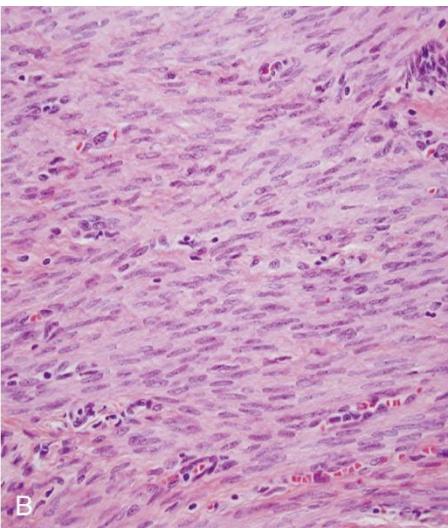
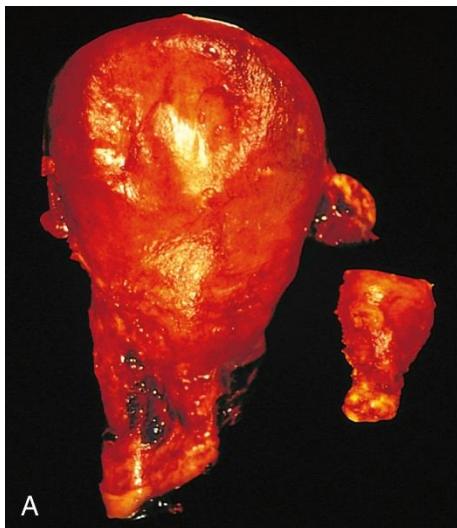
Mechanisms regulating cell population



Adult stem cells can maintain tissues with high (e.g. skin and GI tract) or low (e.g. heart and brain) cell turnover.

Hypertrophy

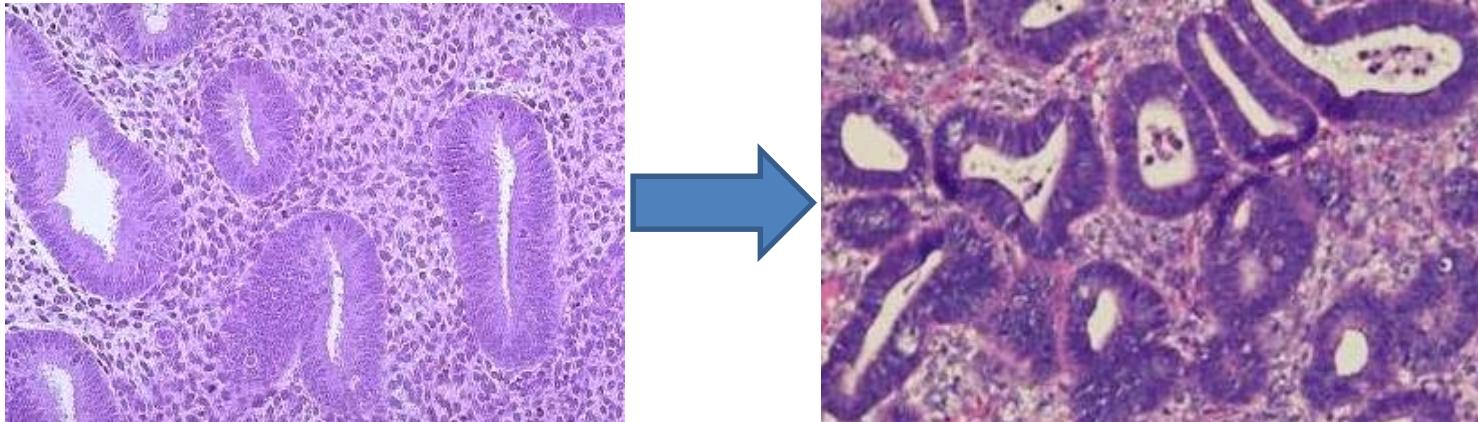
- Increase in the size of a cell
- **Hypertrophy:** nondividing cells (heart, skeletal muscle)
- **Physiologic:** uterus during pregnancy, bodybuilders



- **Pathologic:** myocardial hypertrophy, chronic hemodynamic overload resulting from either hypertension or faulty valve

Hyperplasia

- **Hyperplasia:** increased in number of cells in an organ or tissue in response to a stimulus
- **Physiologic hyperplasia**
 - (1) **hormonal:** breast at puberty & pregnancy
 - (2) **compensatory:** liver partial resected
- **Pathologic hyperplasia:** excessive hormonal or growth factor stimulation, e.g. endometrial hyperplasia



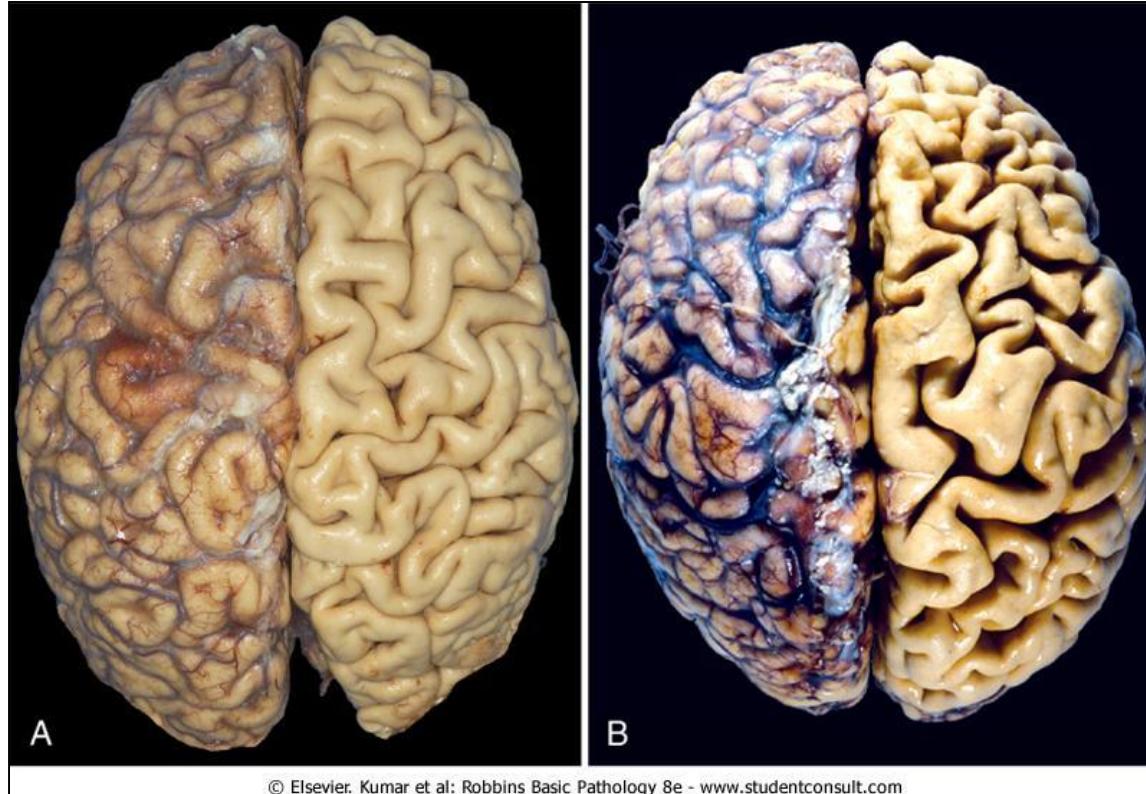
- **Mechanisms:** result of growth factor-driven proliferation of mature cells, by increased output of new cells from tissue stem cells

Atrophy

- Shrinkage in the size of a cell by the loss of cell substance
- **Physiologic atrophy**: aging (breast, uterus)
- **Pathologic atrophy**: common causes
 - Decreased workload (**disuse atrophy**) (e.g. immobilization of a limb)
 - Loss of innervation (**denervation atrophy**)
 - Diminished blood supply (**ischemia**)
 - Inadequate nutrition
 - Loss of endocrine stimulation
 - Pressure

Atrophy

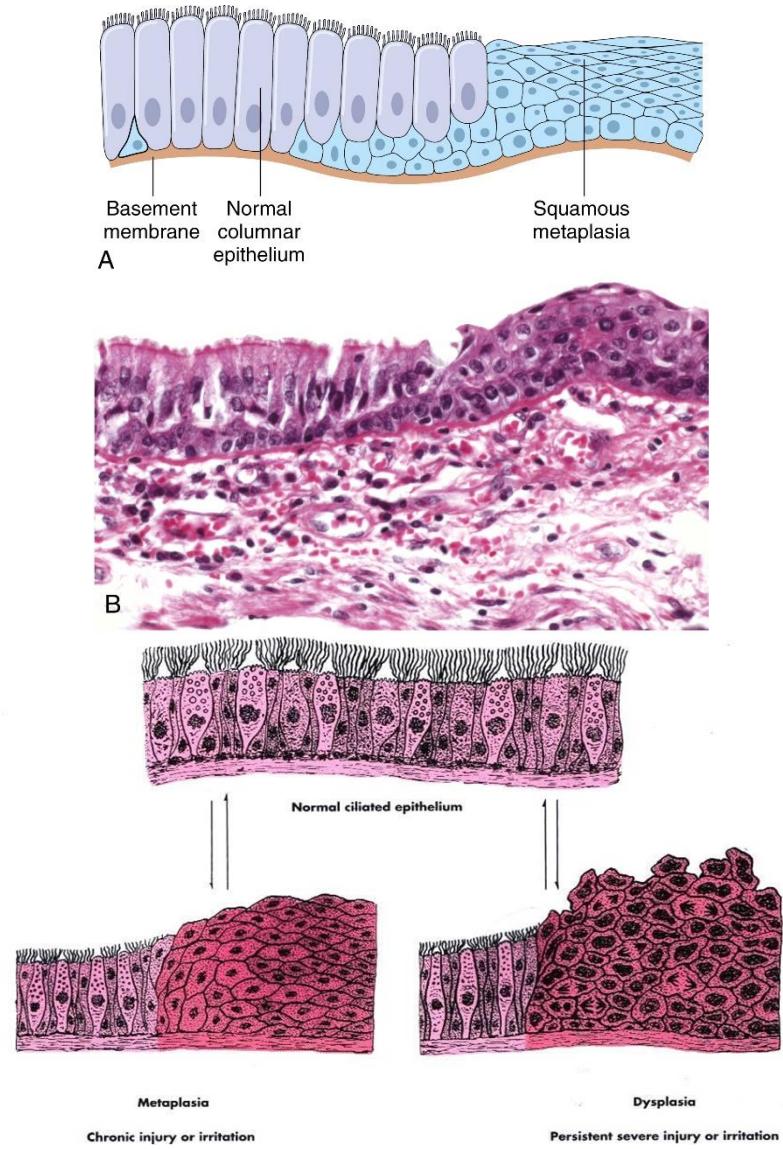
Senile atrophy



- **Mechanisms**
 - Decreased protein synthesis (Reduced metabolic activity)
 - Increased protein degradation in cells (Ubiquitin-proteasome pathway)
 - Accompanied by increased autophagy

Metaplasia

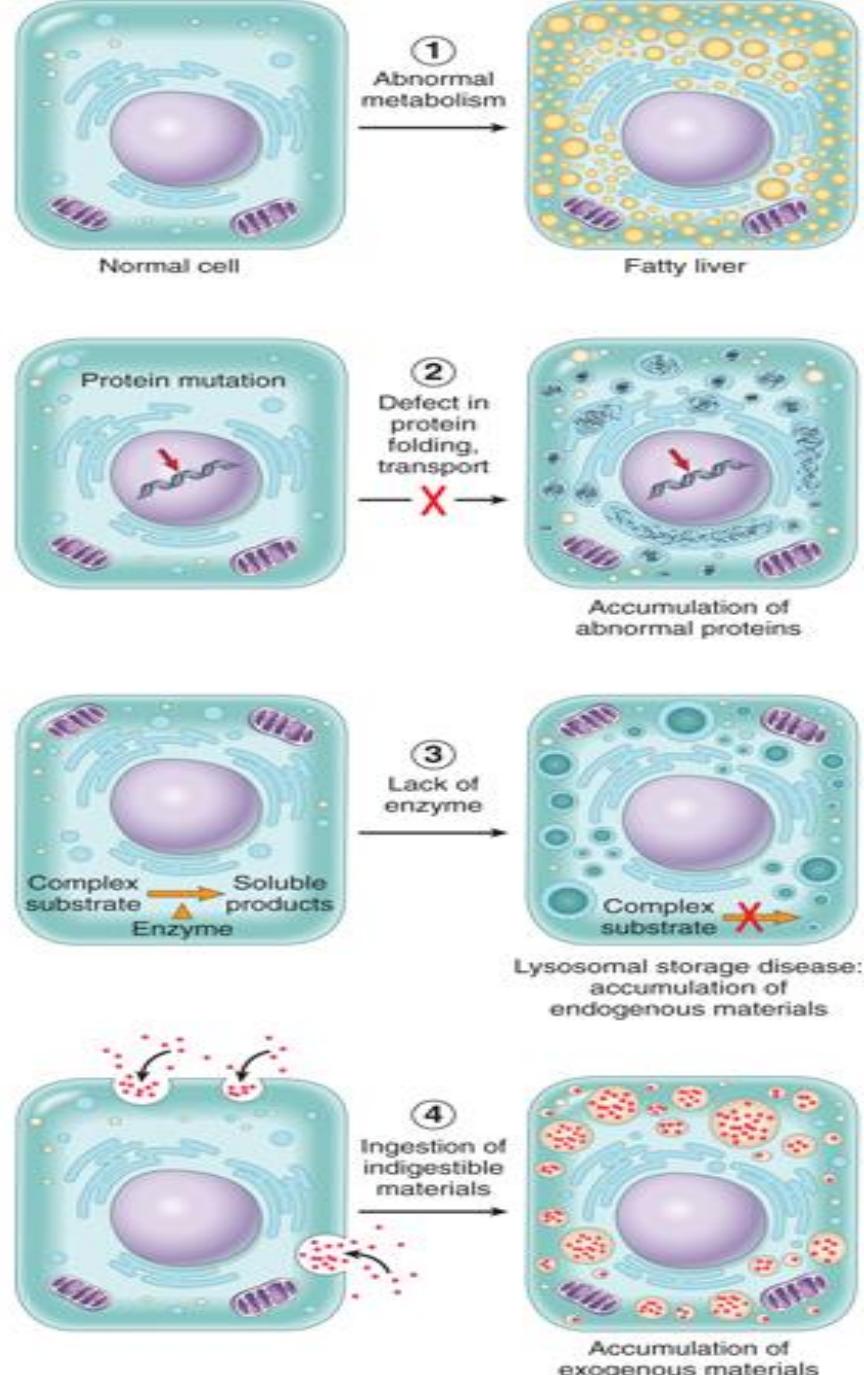
- Reversible change
- One differentiated cell type (epithelial or mesenchymal) replaced by another cell type
- Most common: columnar to squamous (**Squamous metaplasia**)
If persistent, may initiate **malignant transformation** in metaplastic epithelium
- Mechanism: reprogramming of stem cells that are known to exist in normal tissue, or of undifferentiated mesenchymal cells present in connective tissue



Intracellular Accumulation

- One of the manifestations of metabolic derangements in cells

- **Lipids**
 - Steatosis (Fatty change)
 - Cholesterol and cholesterol esters
- **Proteins**
- **Hyaline change**
- **Glycogen**
- **Pigments**
 - Exogenous
 - Endogenous

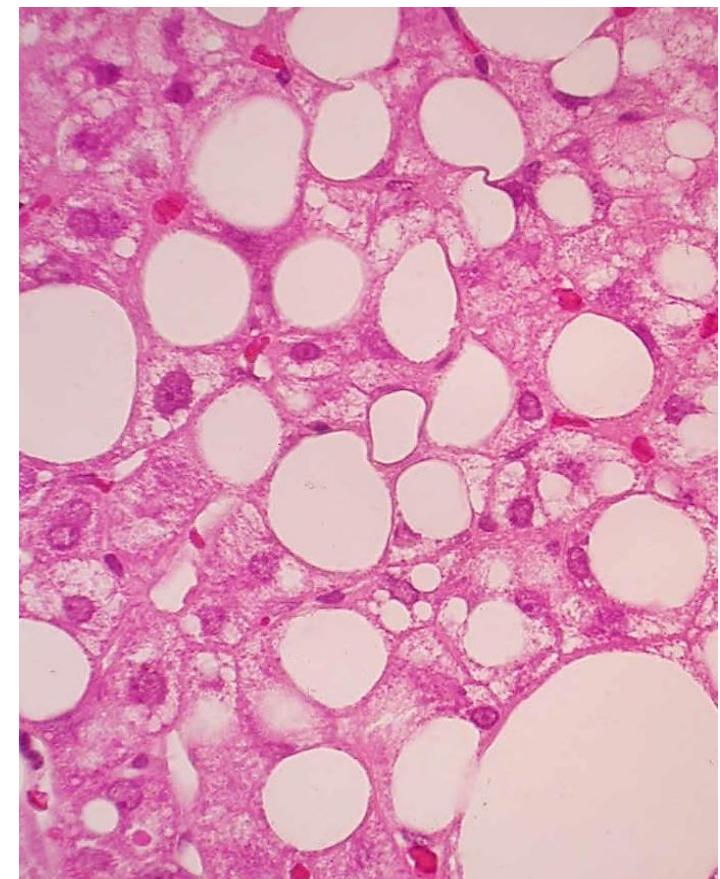


Lipids

All major classes of lipids can accumulate in cells: triglyceride, cholesterol/cholesterol esters, and phospholipids

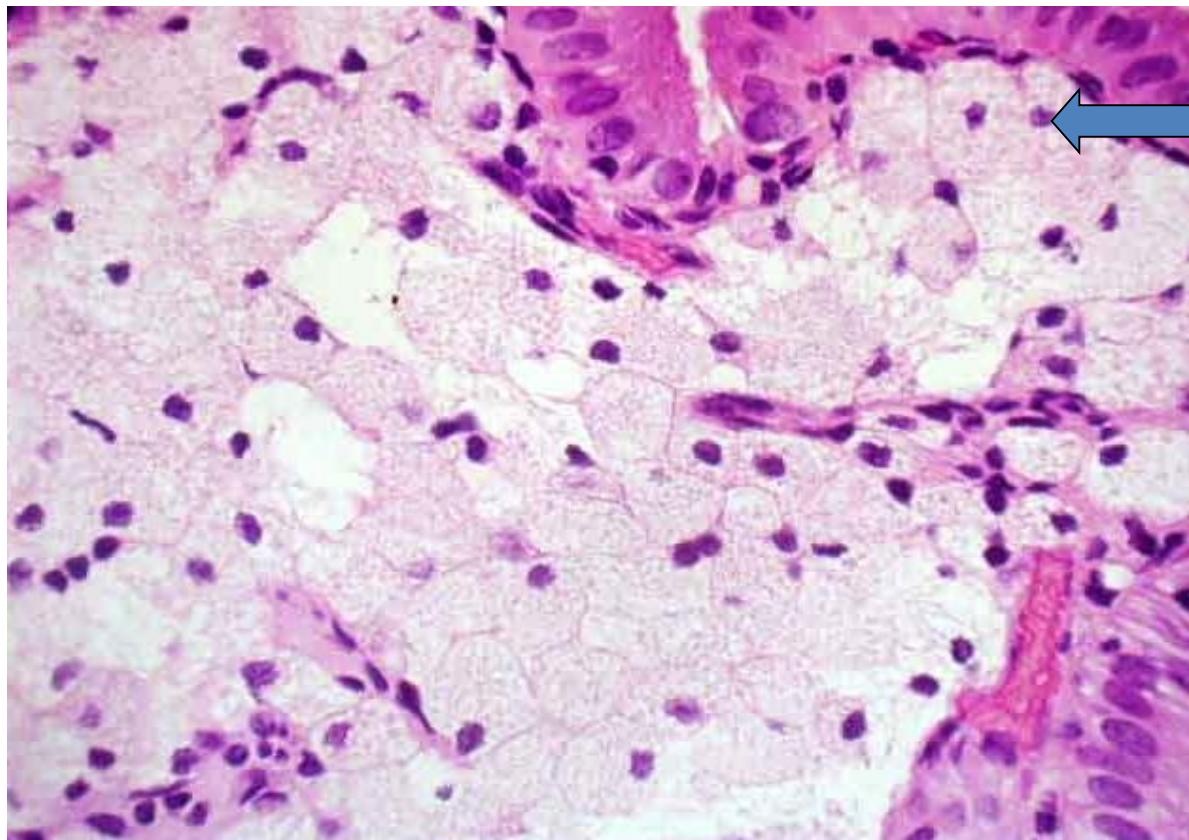
Steatosis (fatty change): abnormal accumulation of triglycerides within parenchymal cells

- Most often seen in **liver**
- May also occur in heart, skeletal muscle, kidney, etc.
- Causes
 - Toxins
 - Protein malnutrition
 - Diabetes mellitus
 - Obesity
 - Anoxia
 - Alcoholic abuse and nonalcoholic fatty liver disease



Cholesterol and cholesterol esters

- **Atherosclerosis** - in the intimal layer of aorta and large arteries
- **Xanthomas** - in the subepithelial connective tissue of skin
- **Cholesterolosis** - in the lamina propria of the gallbladder
- **Niemann-Pick disease, type C**- lysosomal storage disease

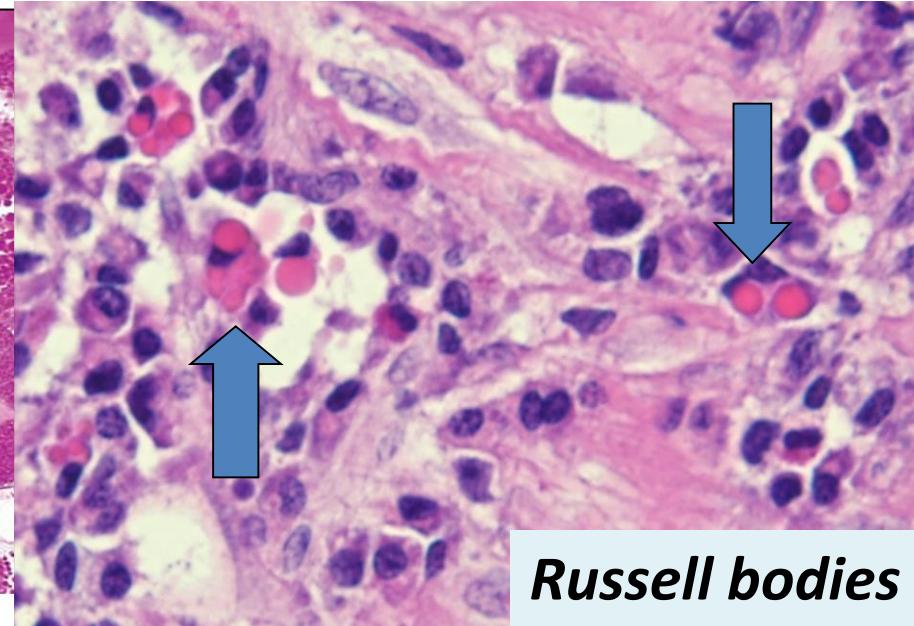
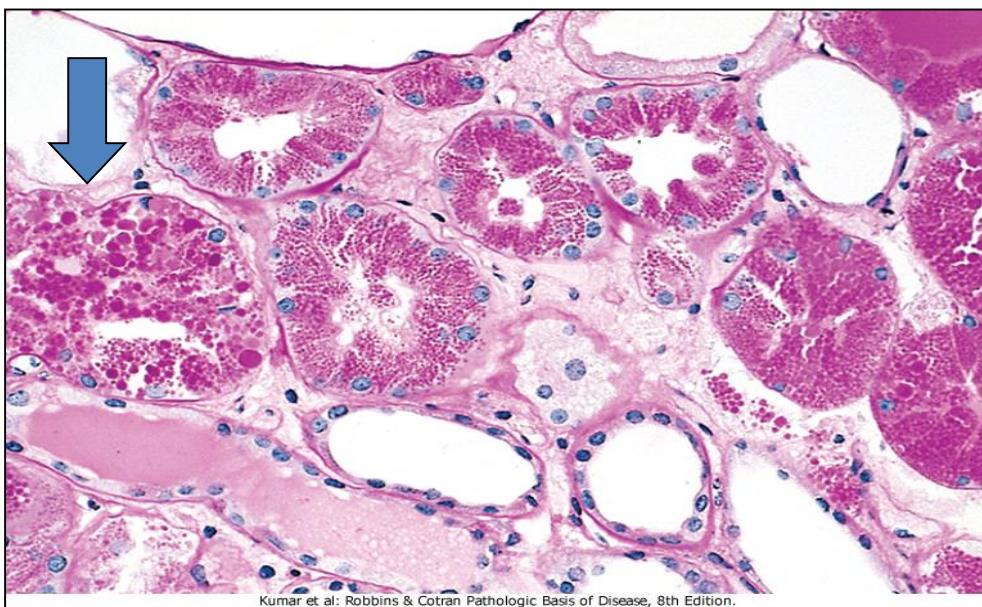


←
**Foam cells
(foamy
macrophages)**

Cholesterolosis

Proteins

- Reabsorption droplets in proximal renal tubules
- Synthesis of excessive amounts of normal secretory protein: *Russell bodies* in plasma cells
- Defective intracellular transport & secretion of critical proteins
- Accumulation of cytoskeletal proteins: alcoholic hyaline (keratin), neurofibrillary tangle in Alzheimer disease (neurofilament)
- Aggregation of abnormal folded proteins: amyloidosis

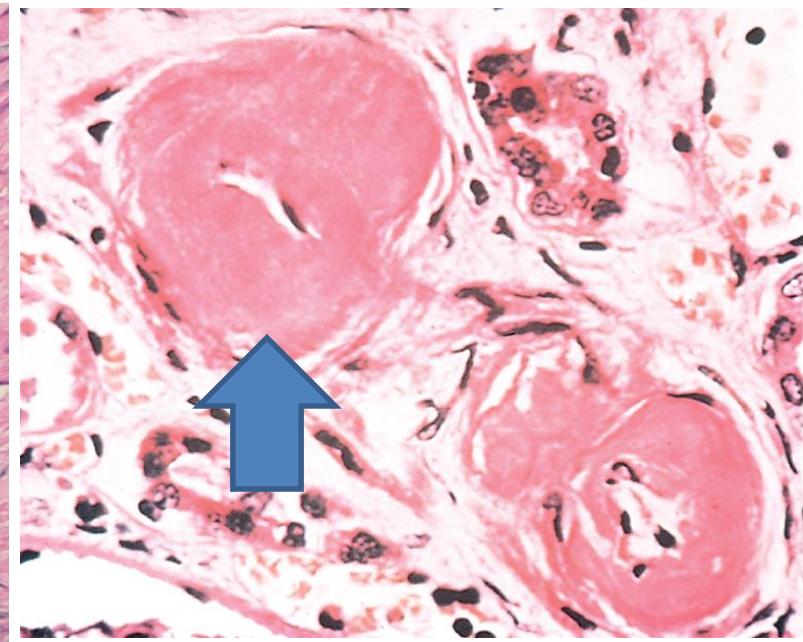
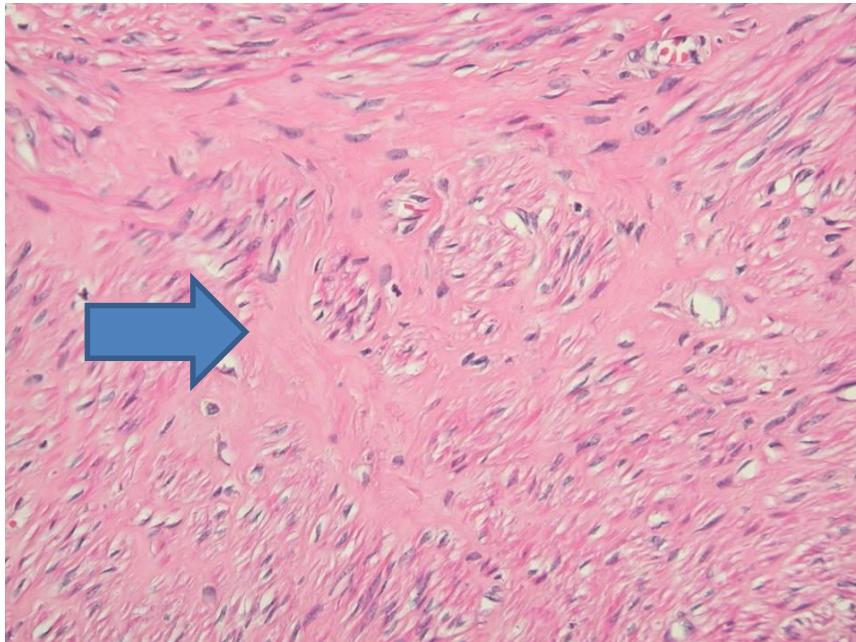


Russell bodies

Hyaline change

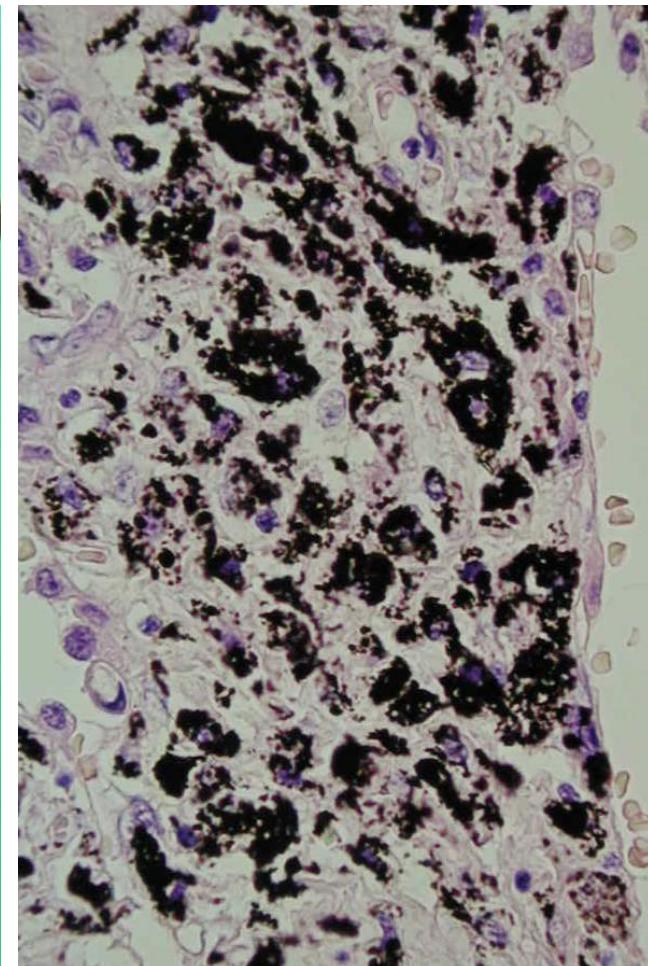
An alteration within cells or in the extracellular space that gives a homogeneous, glassy, pink appearance

- **Intracellular** -Protein accumulation
- **Extracellular**
 - Collagenous fibrous tissue
 - Wall of arterioles in hypertension and DM



Pigments

Exogenous: carbon (coal dust), anthracosis, tattooing

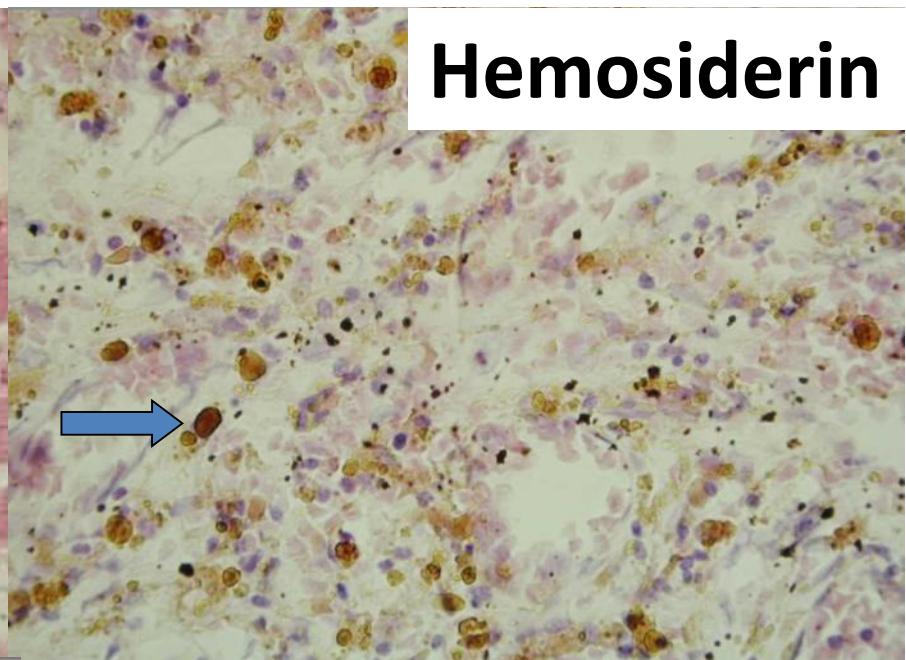


Endogenous Pigments

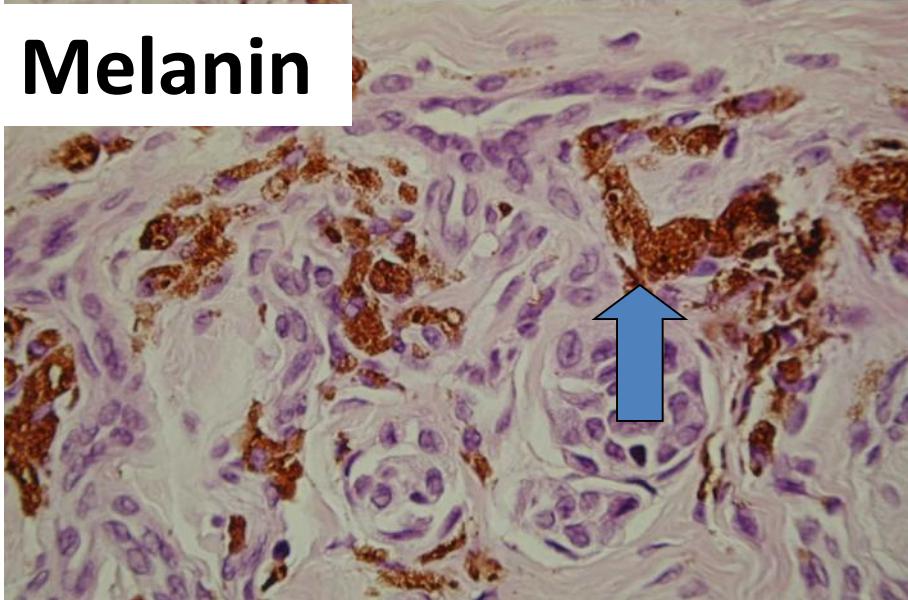
Lipofuscin



Hemosiderin



Melanin



Lipofuscin (wear-and-tear or aging pigment), brown atrophy

Melanin

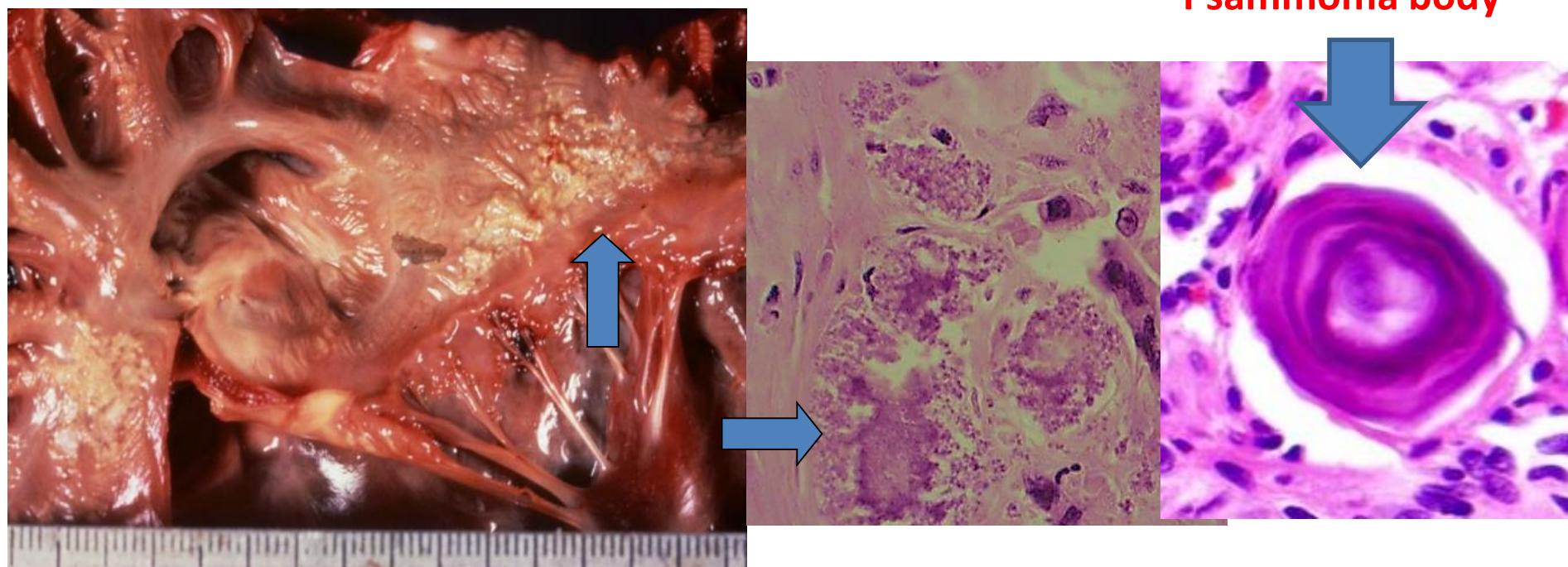
Hemosiderin, hemosiderosis

Pathologic Calcification -1

- Abnormal tissue deposition of calcium salts

1. Dystrophic calcification

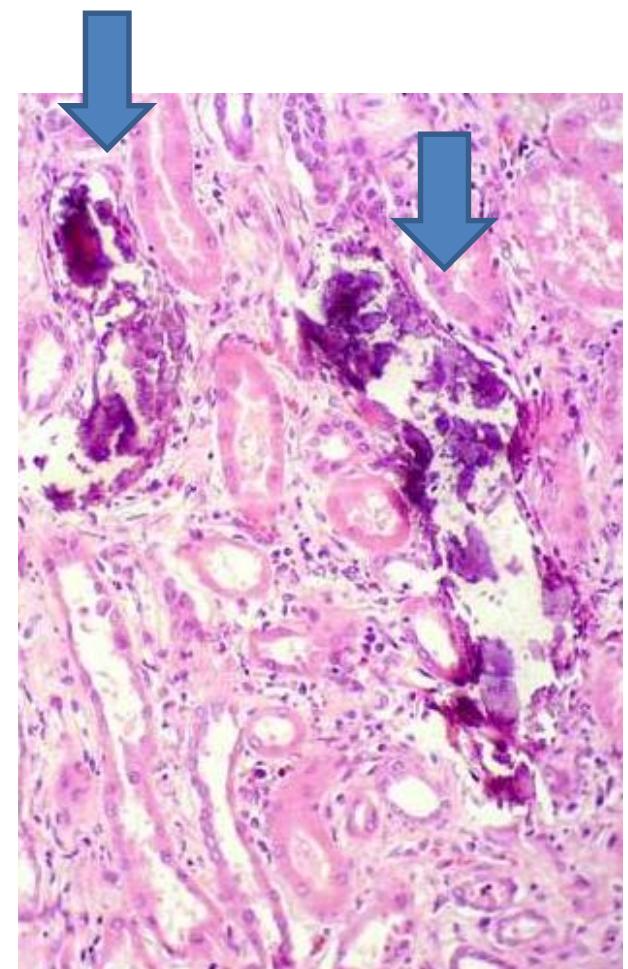
- Area of necrosis
- Atherosclerotic arteries, damaged heart valves, necrotic tumor, etc



Pathologic Calcification -2

2. Metastatic calcification

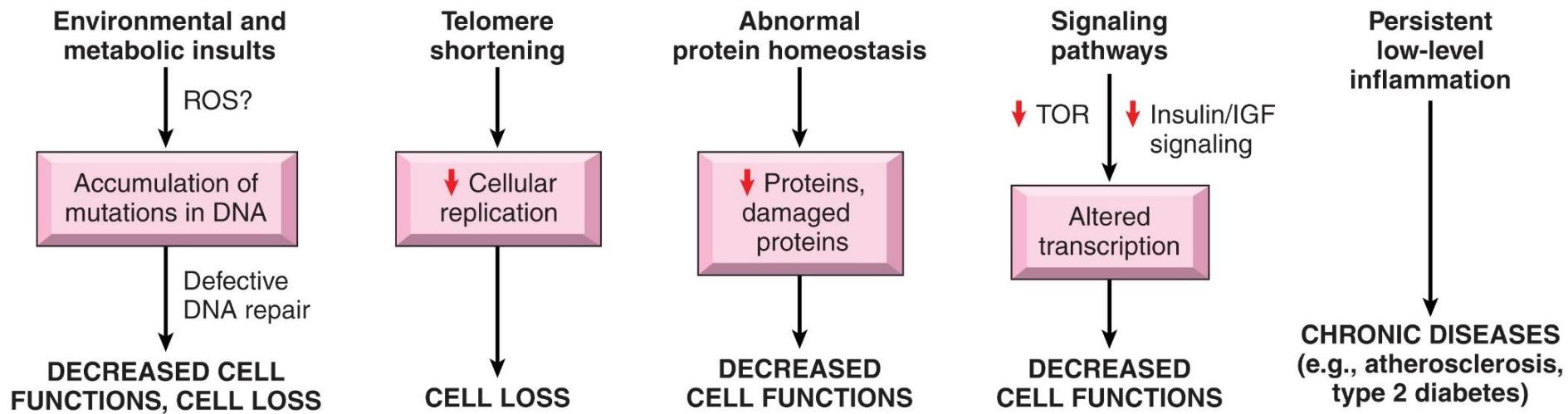
- May occur in **normal tissues** whenever there is **hypercalcemia**
- **Causes:** ↑parathyroid hormone, destruction of bone tissue, vitamin D-related disorders, renal failure
- **Widely throughout the body**
 - interstitial tissues of the gastric mucosa, kidneys, lungs, systemic arteries, and pulmonary vein



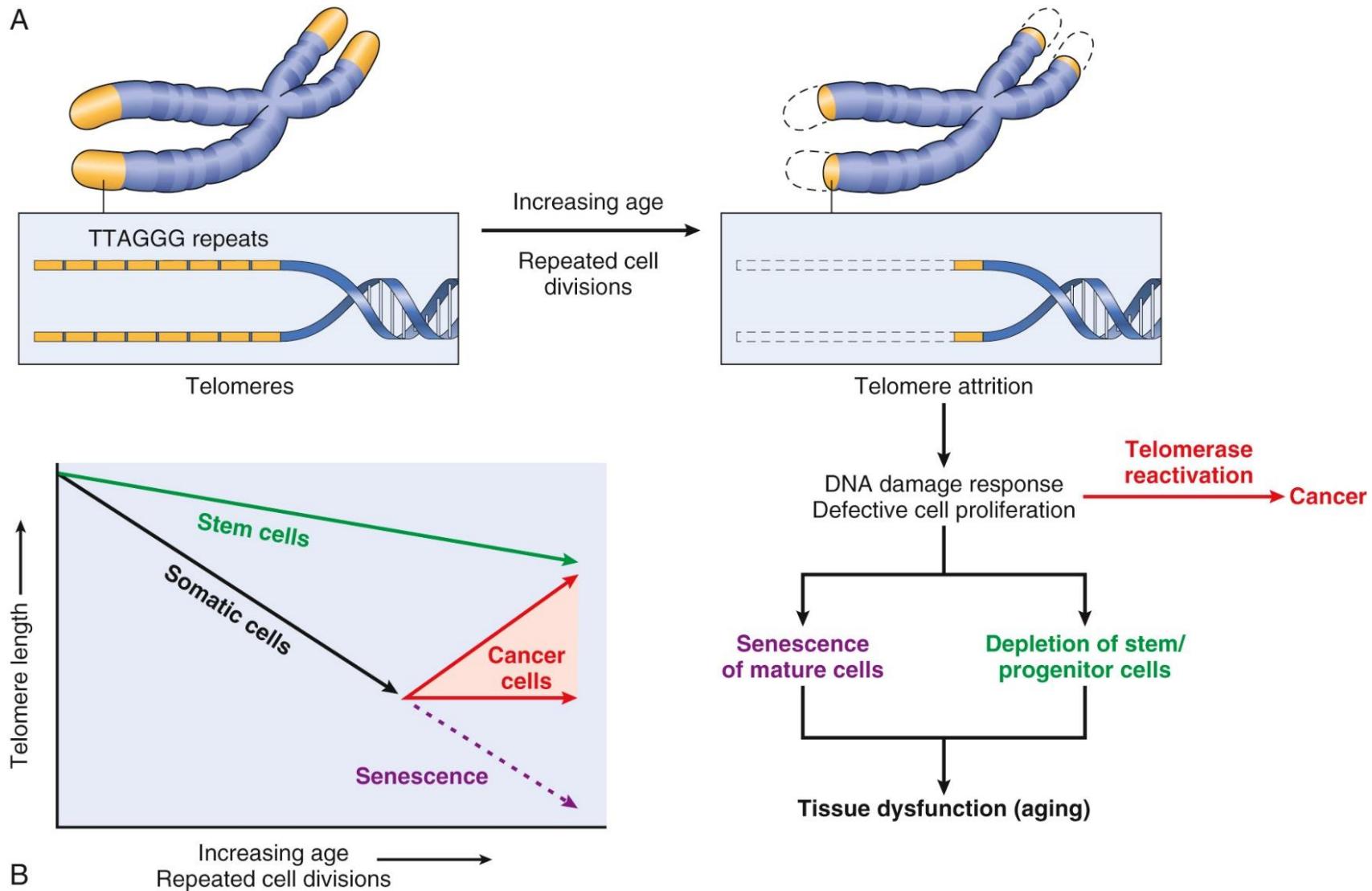
kidneys (**nephrocalcinosis**)

Cellular Aging

- a progressive decline in cellular function and viability caused by **genetic abnormalities** and the **accumulation of cellular and molecular damage** due to the effects of exposure to exogenous influences



The Role of telomeres and telomerase in replicative senescence of cells



Summary (1)

- **Cell injury** (**reversible or irreversible**) develops when cells are stressed beyond that they can tolerate.
- **Necrosis** is death of tissue following irreversible injury. Specific patterns: coagulative, liquefactive, gangrenous, caseous, fat, and fibrinoid.
- **Apoptosis** is individual cell death; may be physiological or pathological cell turnover. Characterized by **enzymatic degradation** of proteins and DNA, initiated by **caspases**; and by the recognition and removal of dead cells by **phagocytes**.
- **Mechanisms of cell injury** include hypoxia and ischemia lead to ATP depletion , ischemia-reperfusion injury, oxidative stress, protein misfolding, DNA damage, mitochondrial dysfunction, membrane damage.

Summary (2)

- **Adaptations** (**hypertrophy, hyperplasia, atrophy, and metaplasia**) are reversible changes in the size, number, phenotype, or functions of cell in response to changes in their environment.
- **Abnormal deposits** of materials in cells and tissues are the result of excessive intake or defective transport or catabolism.
- **Pathologic calcification** is the abnormal tissue deposition of calcium salts.
- **Cellular aging** results from combination of accumulating cellular damage, reduced capacity to divide, and reduced ability to repair damaged DNA.