

Cell Injury, Adaptation and Death

HST.035

Spring 2003

Overview of Cell Injury

- Cells actively control the composition of their immediate environment and intracellular milieu within a narrow range of physiological parameters (“*homeostasis*”)
- Under physiological stresses or pathological stimuli (“*injury*”), cells can undergo adaptation to achieve a new steady state that would be compatible with their viability in the new environment.
- If the injury is too severe (“*irreversible injury*”), the affected cells die.

Causes of Cell Injury

- Hypoxia and ischemia
- “Chemical” agents
- “Physical” agents
- Infections
- Immunological reactions
- Genetic defects
- Nutritional defects
- Aging

Hypoxia (oxygen deficiency) and ischemia (blood flow deficiency)

“Chemical” agents: including drugs and alcohol

“Physical” agents: including trauma and heat

Infections

Immunological reactions: including anaphylaxis and loss of immune tolerance that results in autoimmune disease

Genetic defects: hemoglobin S in SS disease, inborn errors of metabolism

Nutritional defects: including vitamin deficiencies, obesity leading to type II DM, fat leading to atherosclerosis

Aging: including degeneration as a result of repeated trauma, and intrinsic cellular senescence

Mechanisms of Cell Injury: General Principles

- Cell response to injury is not an all-or-nothing phenomenon
- Response to a given stimulus depends on the type, status, and genetic make-up of the injured cell
- Cells are complex interconnected systems, and single local injuries can result in multiple secondary and tertiary effects
- Cell function is lost far before biochemical and subsequently morphological manifestations of injury become detectable

Cell response to injury is not an all-or-nothing phenomenon: The stronger and the longer the stimulus, the larger the damage

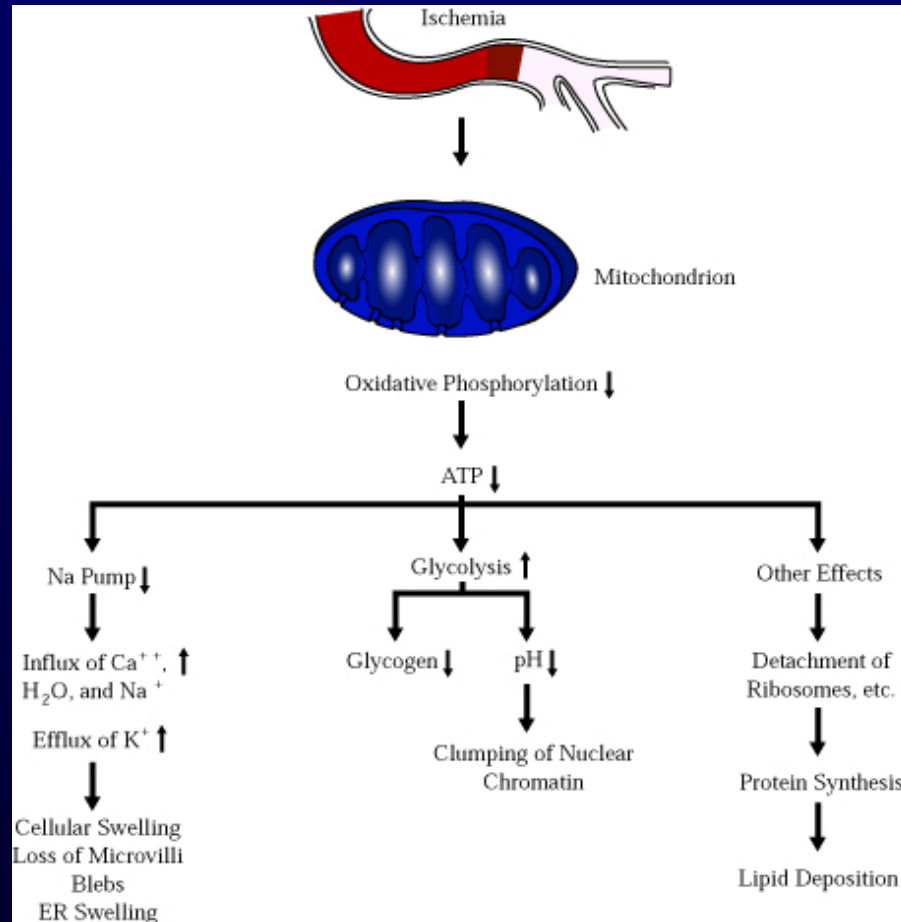
Response to a given stimulus depends on the type, status, and genetic make-up of the injured cell: Contrast ischemia in skeletal muscle (tolerates 2 hours) versus cardiac muscle (tolerate 20 minutes); contrast neurons and glia.

Cells are complex interconnected systems, and single local injuries can result in multiple secondary and tertiary effects: Cyanide indirectly affects osmotic regulation by loss of function of Na/K-ATPase

Cell function is lost far before biochemical and subsequently morphological manifestations of injury become detectable: This has big implications for the use of pathology as gold standard for evaluation of new technologies that could detect changes before they are morphologically apparent

General Biochemical Mechanisms

1. Loss of energy (ATP depletion, O₂ depletion)

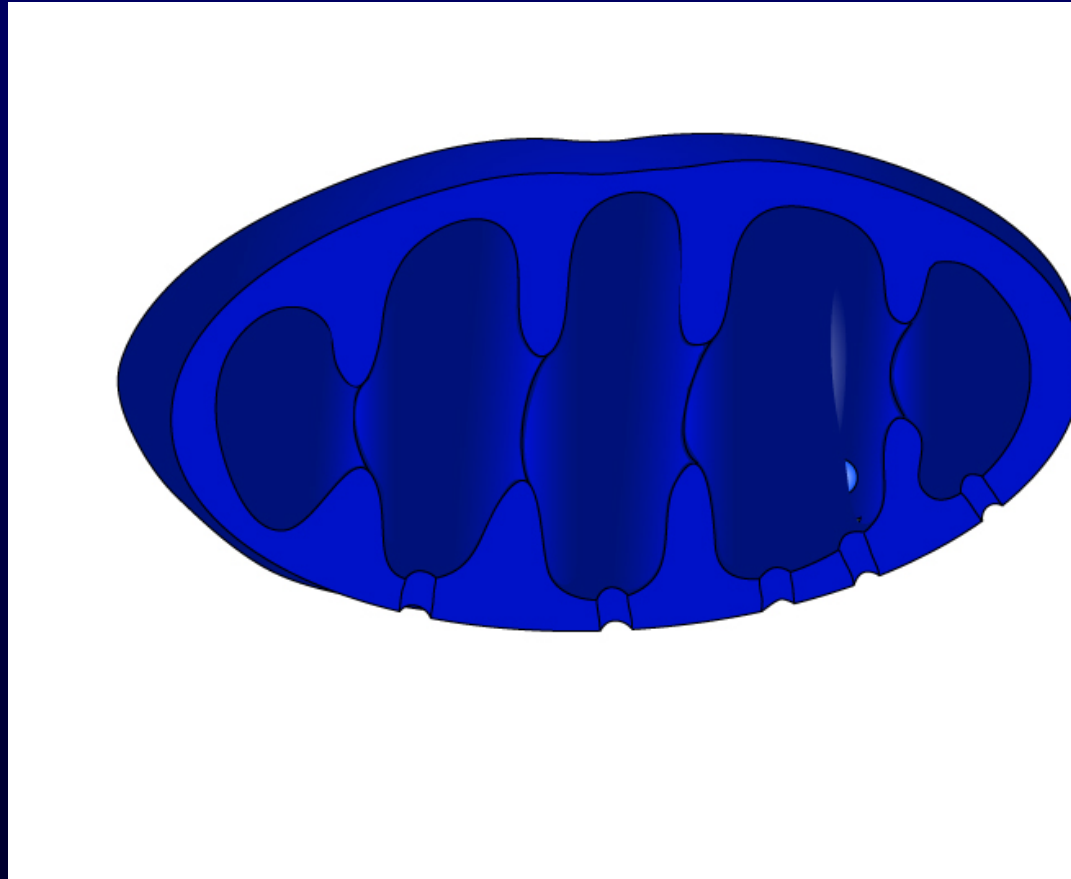


Cytosolic free calcium is 10,000 times lower than extracellular calcium or sequestered intracellular calcium. Increase in cytosolic calcium can result in activation of phospholipases (membrane damage), proteases, ATPases, and endonucleases.

Increase in cytosolic calcium, oxidative stress, and lipid breakdown products result in formation of high-conductance channels in inner mitochondrial membranes (“mitochondrial permeability transition”) that result in loss of proton gradient. Cytochrome C can also leak into the cytosol, activating apoptotic pathways.

General Biochemical Mechanisms

1. Loss of energy (ATP depletion, O₂ depletion)
2. Mitochondrial damage (“permeability transition”)

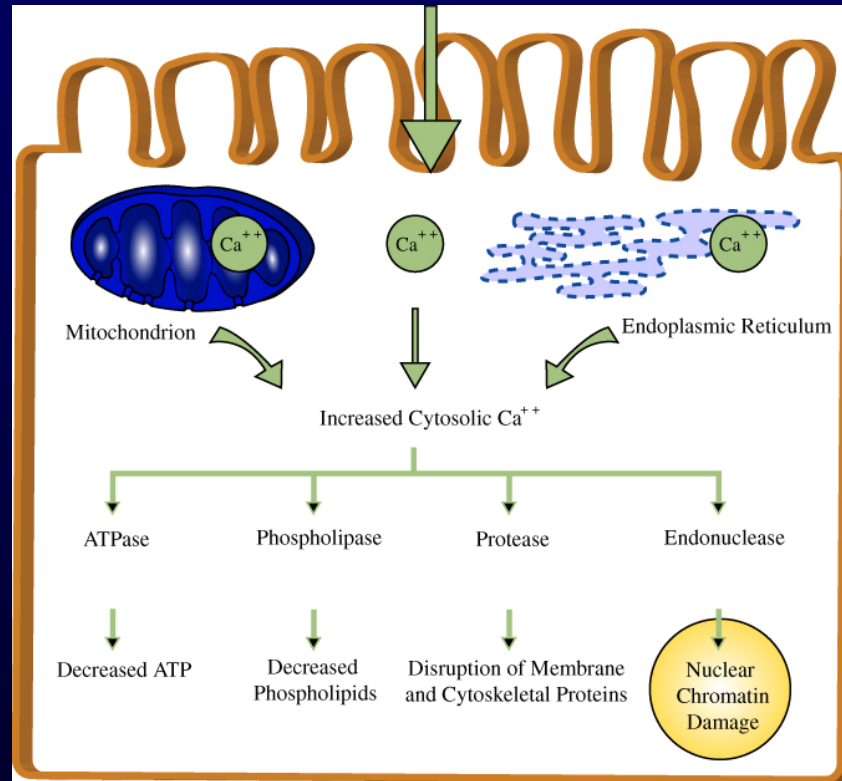


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3. Loss of calcium homeostasis



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3. Loss of calcium homeostasis
4. Defects in plasma membrane permeability

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General Biochemical Mechanisms

1. Loss of energy (ATP depletion, O₂ depletion)
2. Mitochondrial damage
3. Loss of calcium homeostasis
4. Defects in plasma membrane permeability
5. Generation of reactive oxygen species (O₂[•], H₂O₂, OH[•]) and other *free radicals*

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Free Radicals

- Free radicals are chemical species with a single unpaired electron in an outer orbital
- Free radicals are chemically unstable and therefore readily react with other molecules, resulting in chemical damage
- Free radicals initiate autocatalytic reactions; molecules that react with free radicals are in turn converted to free radicals

Intracellular Sources of Free Radicals

- Normal redox reactions generate free radicals
- Nitric oxide (NO) can act as a free radical
- Ionizing radiation (UV, X-rays) can hydrolyze water into hydroxyl (OH•) and hydrogen (H•) free radicals
- Metabolism of exogenous chemicals such as CCl₄ can generate free radicals
- Free radical generation is a “physiological” antimicrobial reaction

Neutralization of Free Radicals

1. Spontaneous decay

2. Superoxide dismutase (SOD):



3. Glutathione (GSH):



4. Catalase:



5. Endogenous and exogenous antioxidants (Vitamins E, A, C and β -carotene)

Free Radical-Induced Injury

- If not adequately neutralized, free radicals can damage cells by three basic mechanisms:
 1. **Lipid peroxidation of membranes:** double bonds in polyunsaturated membrane lipids are vulnerable to attack by oxygen free radicals
 2. **DNA fragmentation:** Free radicals react with thymine in nuclear and mitochondrial DNA to produce single strand breaks
 3. **Protein cross-linking:** Free radicals promote sulfhydryl-mediated protein cross-linking, resulting in increased degradation or loss of activity

“Reperfusion” Damage

- If cells are *reversibly* injured due to ischemia, restoration of blood flow can paradoxically result in accelerated injury.
- Reperfusion damage is a clinically important process that significantly contributes to myocardial and cerebral infarctions
- Exact mechanisms are unclear, but
 - Restoration of flow may expose compromised cells to high concentrations of calcium, and
 - Reperfusion can result in increase free radicals production from compromised mitochondria and the circulating inflammatory cells

Chemical Injury

- Direct damage such as binding of mercuric chloride to sulfhydryl groups of proteins
- Generation of toxic metabolites such as conversion of CCl_4 to $\text{CCl}_3\cdot$ free radicals in the SER of the liver

Cellular Adaptation to Injury

- Cellular adaptations can be induced and/or regulated at any of a number of regulatory steps including receptor binding, signal transduction, gene transcription or protein synthesis
- The most common morphologically apparent adaptive changes are
 - **Atrophy** (decrease in cell size)
 - **Hypertrophy** (increase in cell size)
 - **Hyperplasia** (increase in cell number)
 - **Metaplasia** (change in cell type)

Atrophy

- Atrophy is the shrinkage in cell size by *loss of cellular substance*
- With the involvement of a sufficient number of cells, an entire organ can become *atrophic*
- Causes of atrophy include decreased workload, pressure, diminished blood supply or nutrition, loss of endocrine stimulation, and aging
- Mechanisms of atrophy are not specific, but atrophic cells usually contain increased *autophagic vacuoles* with persistent residual bodies such as *lipofuscin*

Brain Atrophy

For an illustration of an atrophic and normal brain, please see figure 1-8 of Kumar et al. *Robbins Basic Pathology*. 7th edition. WB Saunders 2003. ISBN: 0721692745.

Hypertrophy

- Hypertrophy is an increase in cell size by *gain of cellular substance*
- With the involvement of a sufficient number of cells, an entire organ can become *hypertrophic*
- Hypertrophy is caused either by increased functional demand or by specific endocrine stimulations
- Not only the size, but also the phenotype of individual cells can be altered in hypertrophy
- With increasing demand, hypertrophy can reach a limit beyond which degenerative changes and organ failure can occur

Cardiac Hypertrophy

For an illustration of Hypertrophic Cardiomyopathy and a normal heart, please see figure 1.1 of Kumar et al. *Robbins Basic Pathology*. 7th edition. WB Saunders 2003. ISBN: 0721692745.

Hyperplasia

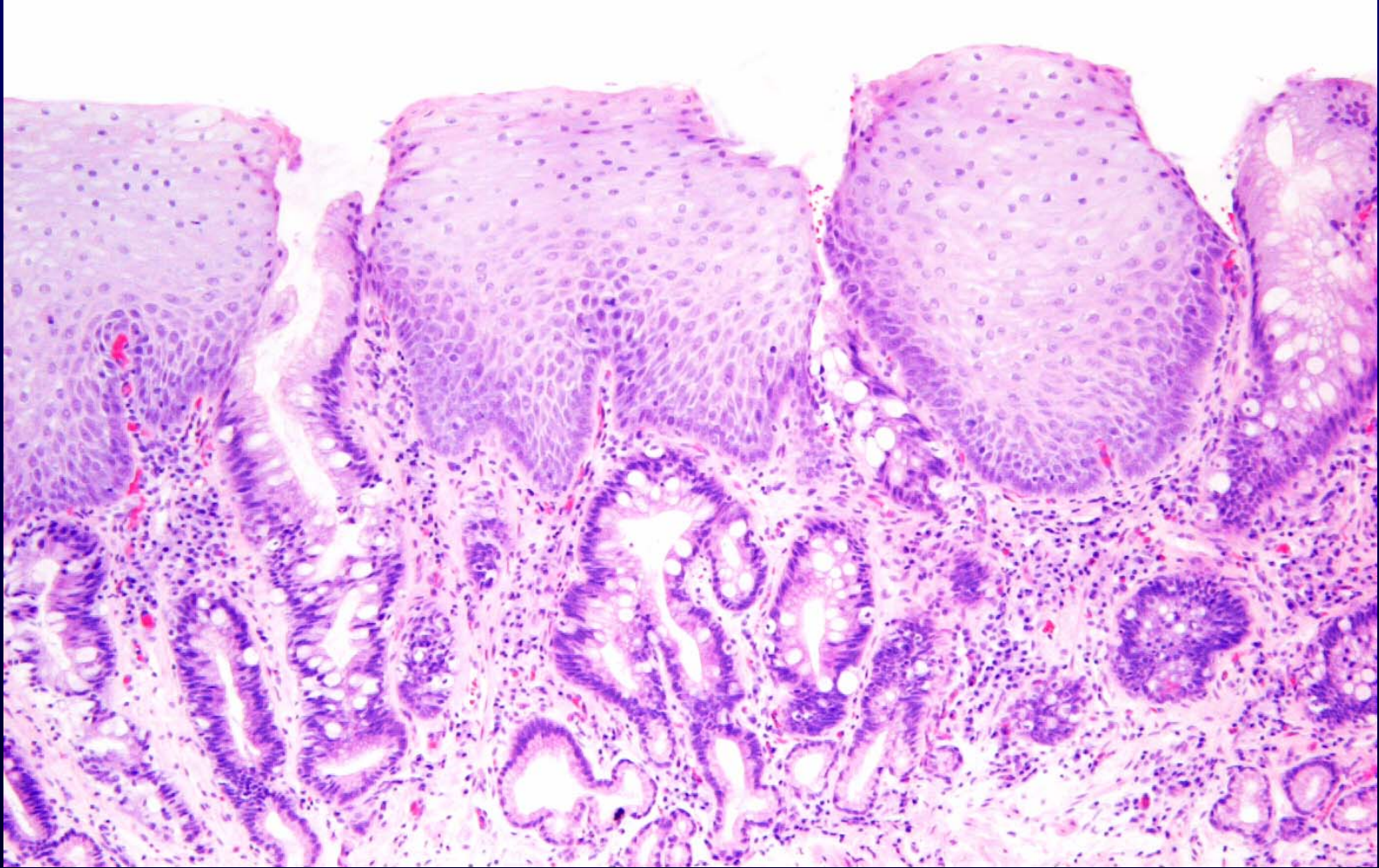
- Hyperplasia constitutes an increase in the number of indigenous cells in an organ or tissue
- Pathological hyperplasia is typically the result of excessive endocrine stimulation
- Hyperplasia is often a predisposing condition to neoplasia

Metaplasia

- Metaplasia is a “reversible” change in which one adult cell type is replaced by another adult cell type
- Metaplasia is a cellular adaptation in which indigenous cells are replaced by cells that are better suited to tolerate a specific abnormal environment
- Because of metaplasia, normal protective mechanisms may be lost
- Persistence of signals that result in metaplasia often lead to neoplasia

Barrett's Esophagus

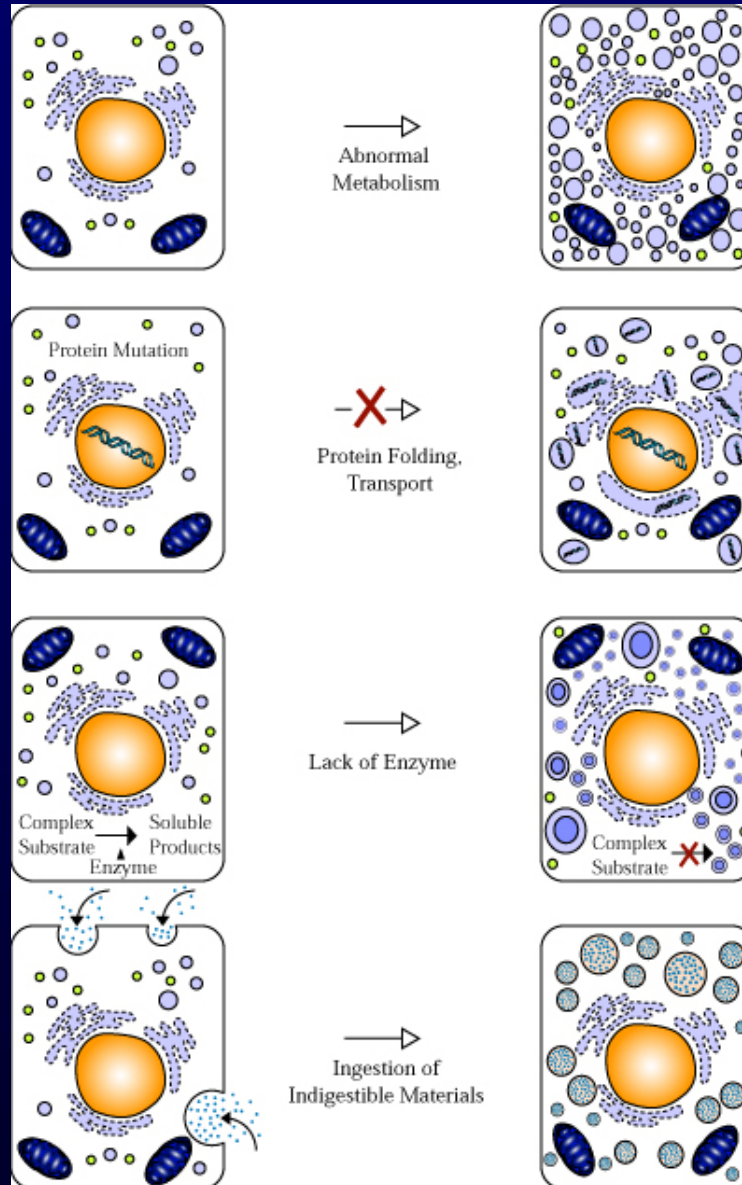
Intestinal Metaplasia of the Esophagus



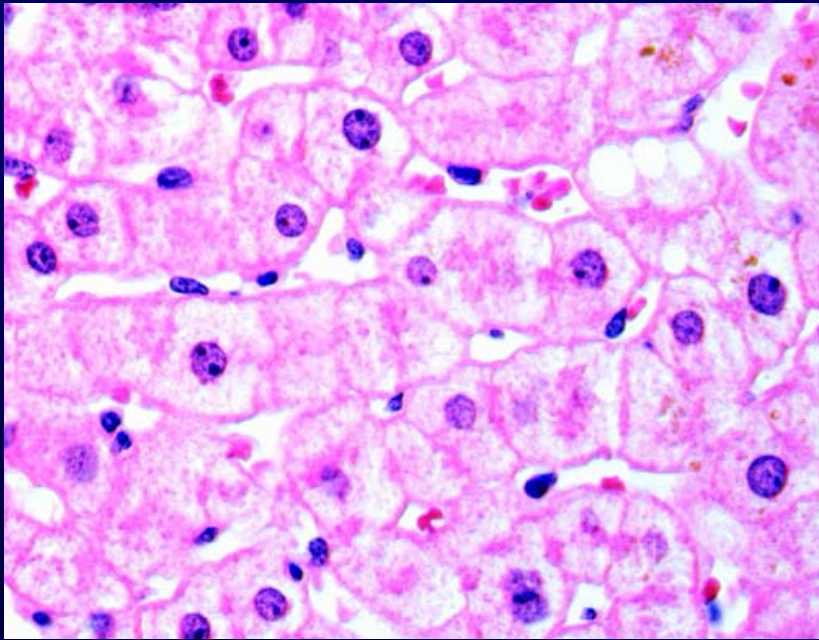
Subcellular Responses to Cell Injury

- Autophagic vacuoles
- Induction/hypertrophy of RER
- Abnormal mitochondria
- Cytoskeletal abnormalities

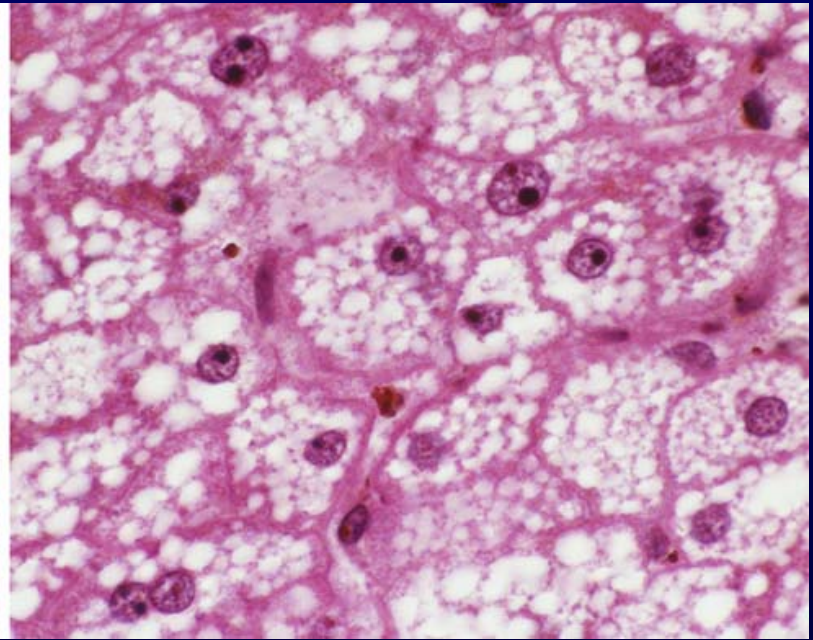
Intracellular Storage



Fatty Liver



Normal Liver

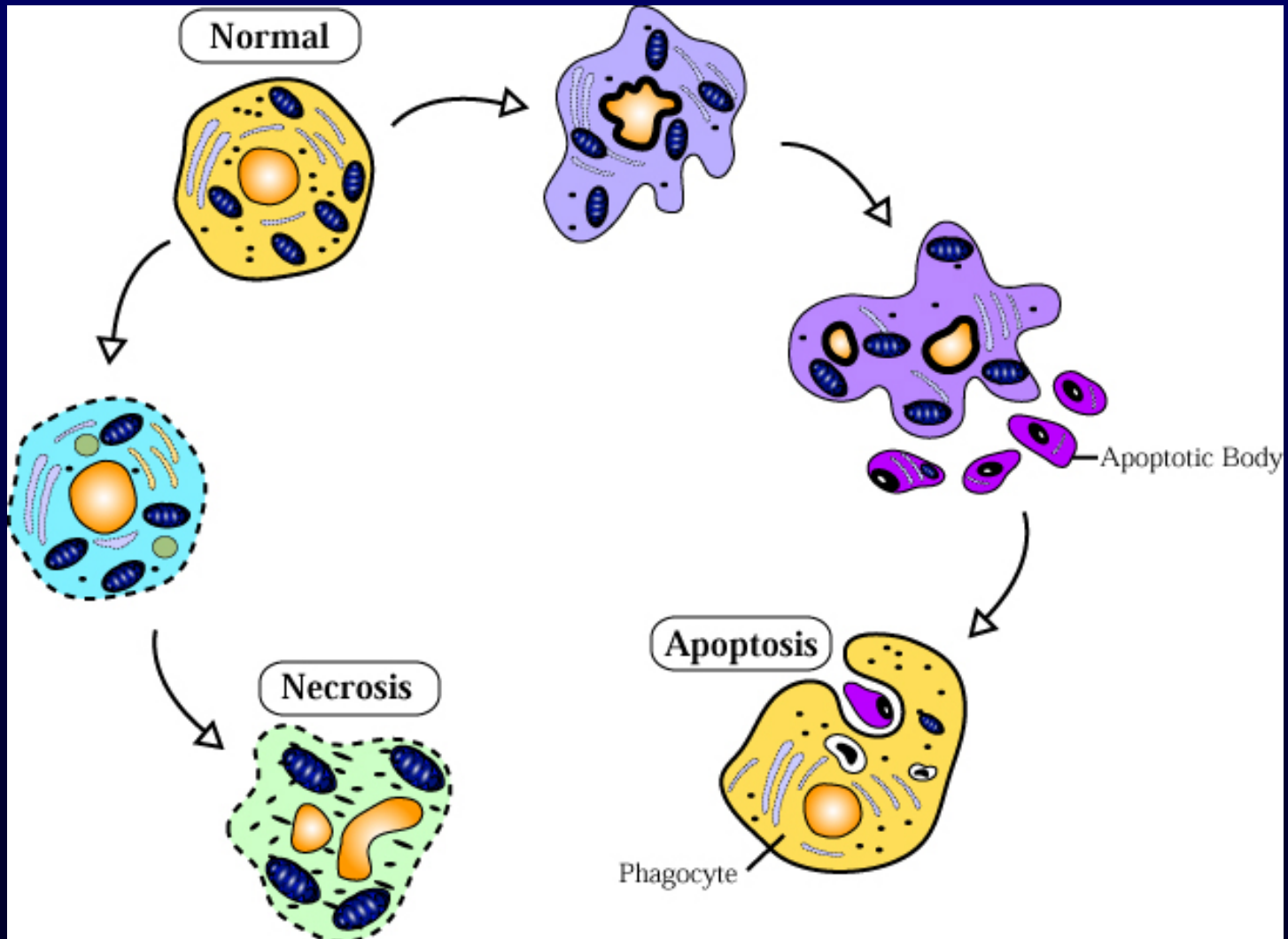


Steatosis

Pathologic Calcification

- *Dystrophic calcification* is the abnormal deposition of calcium phosphate in dead or dying tissue
- Dystrophic calcification is an important component of the pathogenesis of atherosclerotic disease and valvular heart disease
- *Metastatic calcification* is calcium deposition in normal tissues as a consequence of hypercalcemia:
 - Increased PTH with subsequent bone resorption
 - Bone destruction
 - Vitamin D disorders (intoxication, Sarcoidosis, Williams syndrome)
 - Renal failure with 2° ↑PTH

Cell Death



Coagulative Necrosis vs. Apoptosis

	Coagulation Necrosis	Apoptosis
Stimuli	Hypoxia, toxins	Physiologic and pathologic factors
Histologic appearance	Cellular swelling Coagulation necrosis Disruption of organelles	Single cells Chromatin condensation Apoptotic bodies
DNA breakdown	Random, diffuse	Internucleosomal
Mechanisms	ATP depletion Membrane injury Free radical damage	Gene activation Endonucleases Proteases
Tissue reaction	Inflammation	No inflammation Phagocytosis of apoptotic bodies

Highlight of Events in Apoptosis

