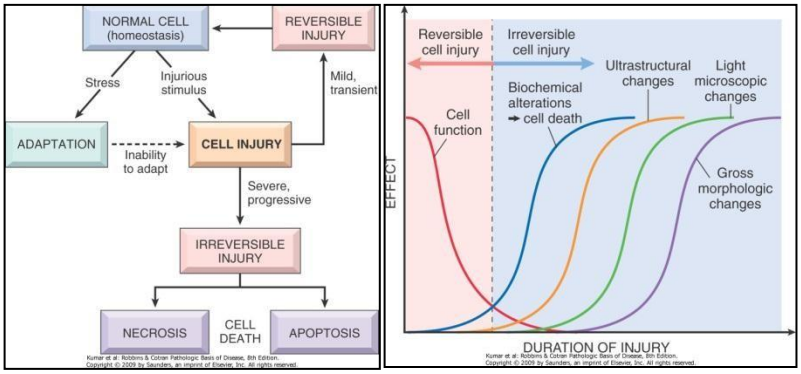
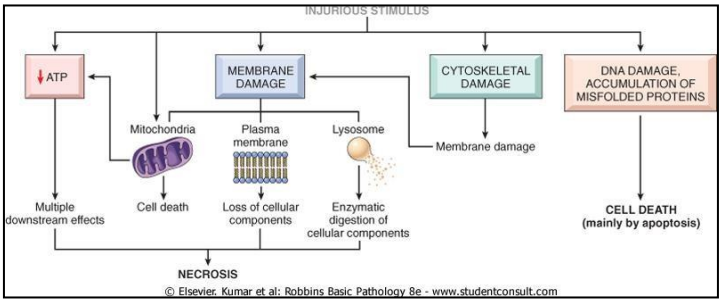
Cell Injury



- 4 interrelated cell systems especially susceptible to injury
    - Membranes (cellular and organellar)
    - Aerobic system
    - Protein synthesis (enzymes, structural proteins, etc)
    - Genetic apparatus (DNA, RNA, etc)

Mechanisms for cell injury

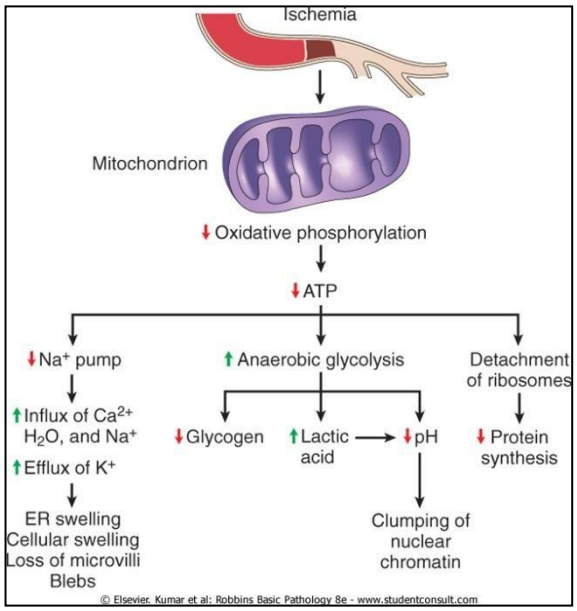
- Loss of Ca^{++} homeostasis
- Membrane permeability defects
- ATP depletion
- O_2 and O_2 derived free radicals



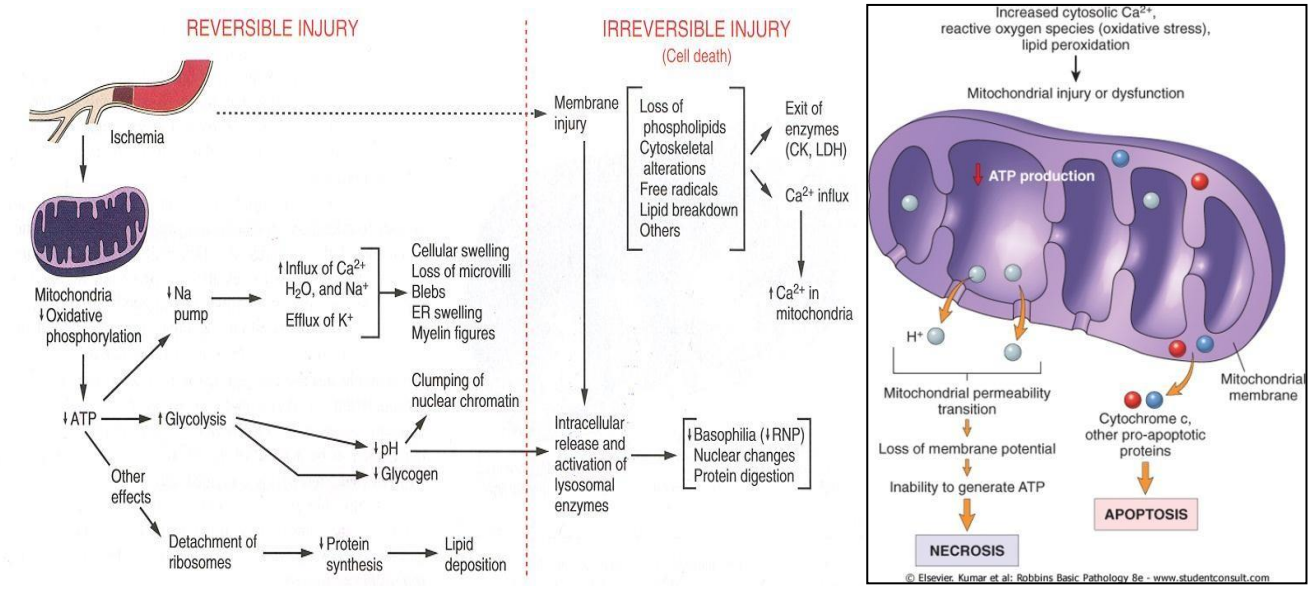
Causes of Cell Injury

- Hypoxia (ischemia – block in blood flow, hypoxemia – decreased partial pressure of oxygen in blood,anemia – decreased oxygen carrying capacity)
    - Block in ventilation(foreign body), oxygen diffusion (pneumonia, pulmonary edema), perfusion(pulmonary embolus), decreased cardiac output
- Free radical damage
- Chemicals, drugs, toxins
- Infections
- Physical agents

- Immunologic reactions
- Genetics
- Nutritional imbalance

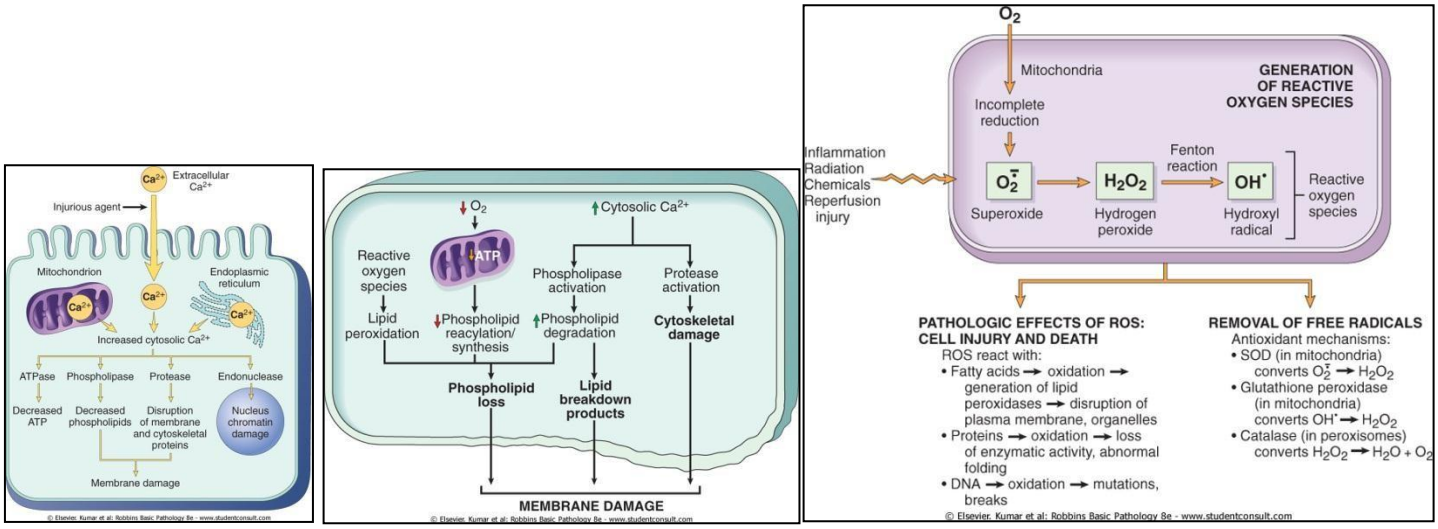


- Oxygen tension falls disrupts oxidative phosphorylation decreased ATP
  - ↓ Na^+/K^+ ATPase increased intracellular Na^+ swelling
  - ↓ ATP-dependent Ca^{++} pumps increased cytosolic Ca^{++}
  - Depletion of glycogen from altered metabolism
  - Decreased pH from lactic acid accumulation
  - Decreased protein synthesis from ribosome detachmentfrom RER
- End result – cytoskeletal disruption with loss of microvilli, blebformation, etc



Excess cytoplasmic Ca^{++} □ denatures proteins, poisons mitochondria, inhibits cellular enzymes

- Therefore, membrane damage and Ca^{++} homeostasis is critical



- Injured membranes allow intracellular components to enter the serum and can be measured

Free radical injury (acetaminophen – Tylenol overdose)

- Lipid peroxidation – damage to cellular and organellar membranes
- Protein crosslinking/fragmentation from oxidative modification of amino acids and proteins
- DNA damage from free radical reaction with thymine

Types

- Chemical
- Inflammation/microbial killing
- Irradiation
- Oxygen
- Age-related

Free Radical Derivations

- Superoxide – $O_2^{\bullet -}$ – produced by cellular oxidases
- H_2O_2 – produced by superoxide mutase or catalase
- $OH^{\bullet -}$ – produced by ionizing radiation, H_2O_2 and $O_2^{\bullet -}$, and fenton reaction

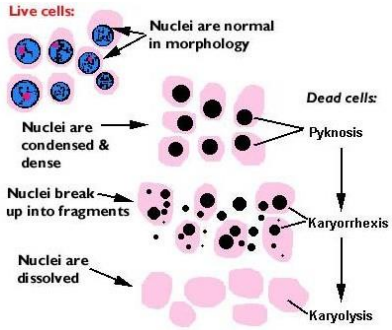
- Morphological changes follow functional changes

Reversible injury

- Light microscope – cell swelling, fatty change
- Ultrastructural changes – cell membrane alterations, swelling and small deposits ofmitochondria, RER and attached ribosome swelling

Irreversible injury

- Light microscope
- Loss of RNA (which is basophilic) – increased cytoplasmic eosinophilia (pink colour)
- Cytoplasmic vacuolization
- Nuclear chromatin clumping
- Ultrastructural
- Membrane breakage
- Large amorphous densities in mitochondria
- Nuclear changes
- Pyknosis – nuclear shrinkage, increased basophilia (blue colour)
- Karyorrhexis – fragmentation of pyknotic nucleus
- Karyolysis – fading of basophilia of chromatin



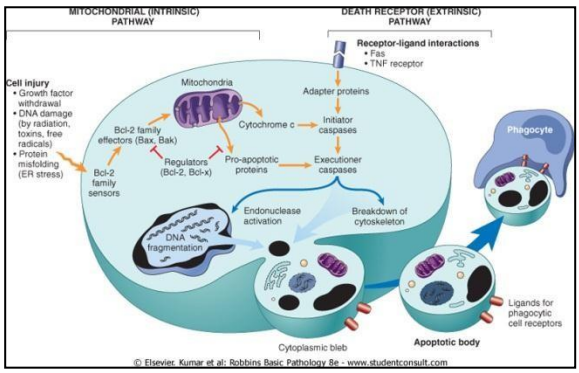
Types of Cell Death

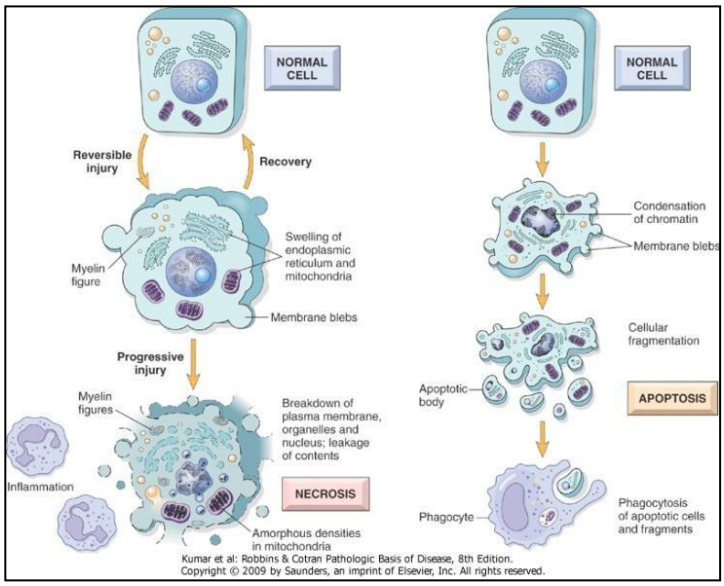
- Apoptosis – usually regulated, may be pathogenic, has a role in embryogenesis
- Necrosis – always pathologic, many causes

Apoptosis

- Programmed cell death in embryogenesis
- Hormone dependent involution of adult organs(thymus)

- Cell deletion in proliferative populations
- Cell death in tumors
- Cell injury in some viral diseases (hepatitis)





Necrosis

- Causes
  - Coagulative (most common)
    - Cells basic outlines are preserved
    - Homogenous, glassy eosinophilic appearance due to loss of cytoplasmic RNA(basophilic) and glycogen (granular)
    - Nucleus may show any of pyknosis, karyorrhexis, or karyolysis
  - Liquefactive – most often in CNS and abscess – usually from enzymatic dissolution of necrotic cells (usually due to release of proteolytic enzymes from neutrophils)
  - Caseous
    - Gross form – resembles cheese
    - Micro form – amorphous, granular eosinophilic material surrounded by rim of inflammatory cells (no visible cell outlines, tissue architecture is obliterated)
    - Usually seen in infections (mycobacterial and fungal)
  - Enzymatic fat necrosis
    - Hydrolytic action of lipases on fat, most often in and

around pancreas, can also be seenin other fatty body areas (usually via trauma)
    - Fatty acids released via hydrolysis react with Ca^{++} to form chalky white areas –"saponification"
- Gangrenous necrosis
    - Most often in extremities via trauma/physical injury
    - Dry gangrene – no bacterial superinfection, looks dry
    - Wet gangrene – has bacterial superinfection, looks wet and liquefactive
- Fibrinoid necrosis
    - Usually seen in walls of vessels (vasculitides)
    - Glassy, eosinophilic fibrin-like material deposited within vascular walls
    - Immune disorders