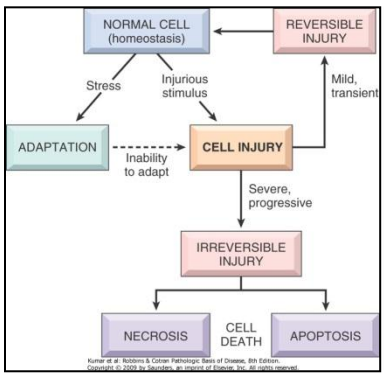
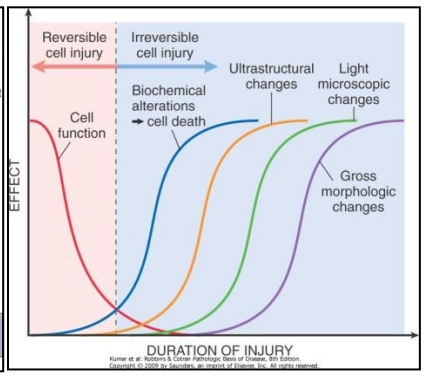
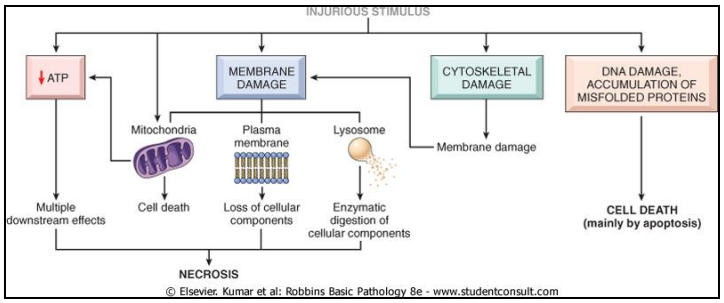
Cell Injury

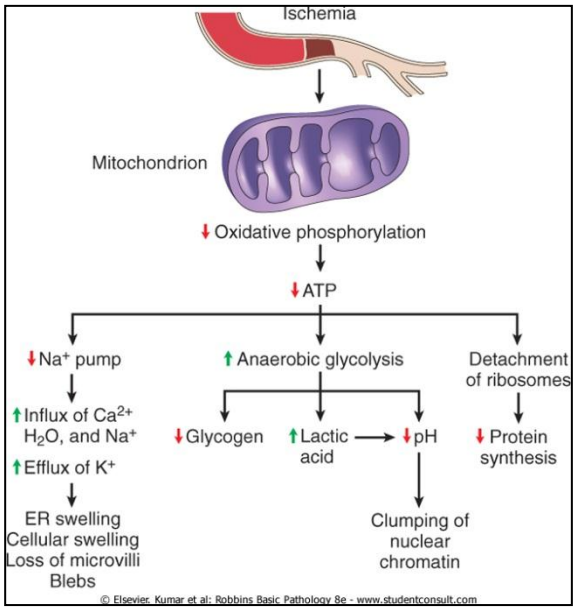


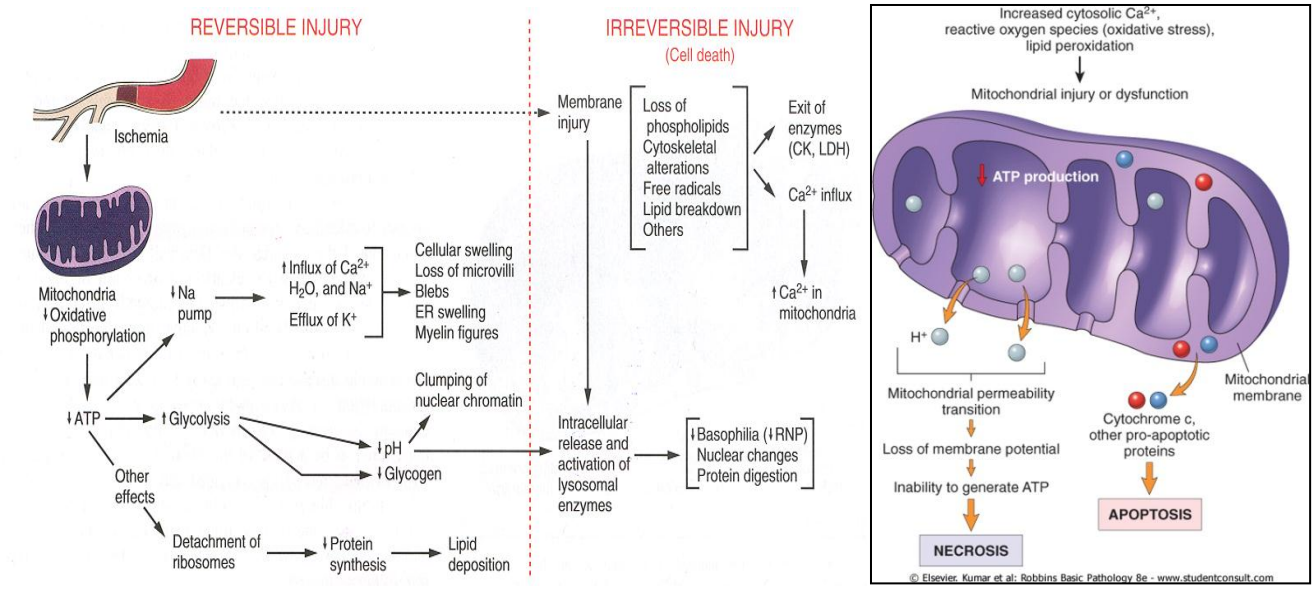


- 4 interrelated cell systems especially susceptible to injury
  - Membranes (cellular and organellar)
  - Aerobic system
  - Protein synthesis (enzymes, structural proteins, etc)
  - Genetic apparatus (DNA, RNA, etc)
- Mechanisms for cell injury
  - Loss of Ca^{++} homeostasis
  - Membrane permeability defects
  - ATP depletion
  - O_2 and O_2 derived free radicals

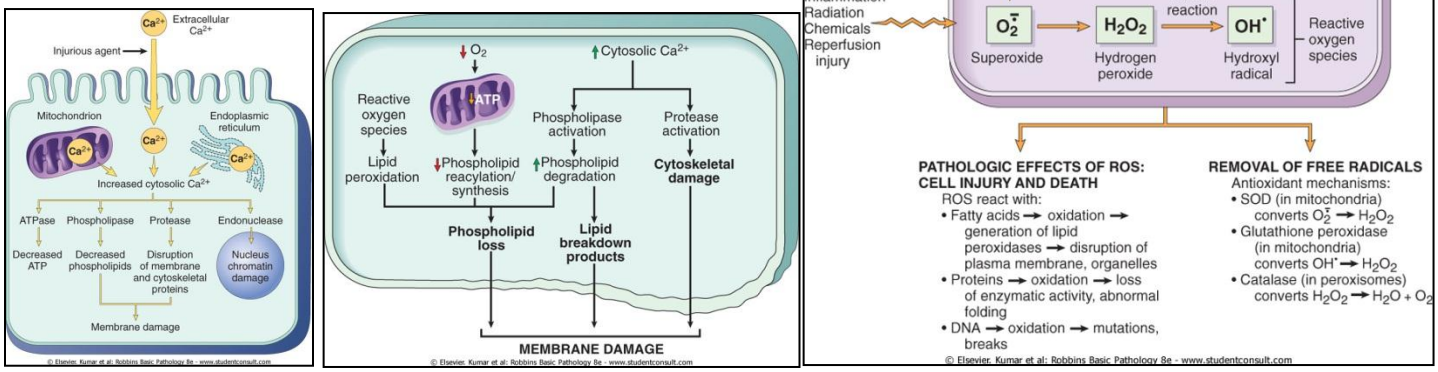


- Causes of Cell Injury
  - Hypoxia (ischemia – block in blood flow, hypoxemia – decreased partial pressure of oxygen in blood, anemia – decreased oxygen carrying capacity)
    - Block in ventilation(foreign body), oxygen diffusion (pneumonia, pulmonary edema), perfusion (pulmonary embolus), decreased 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 detachment from RER
- End result – cytoskeletal disruption with loss of microvilli, bleb formation, etc



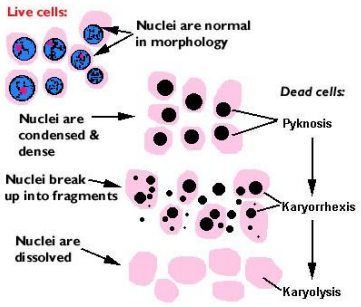


- Excess cytoplasmic Ca^{++} → denatures proteins, poisons mitochondria, inhibits cellular enzymes
    - Therefore, membrane damage and Ca^{++} homeostasis is critical

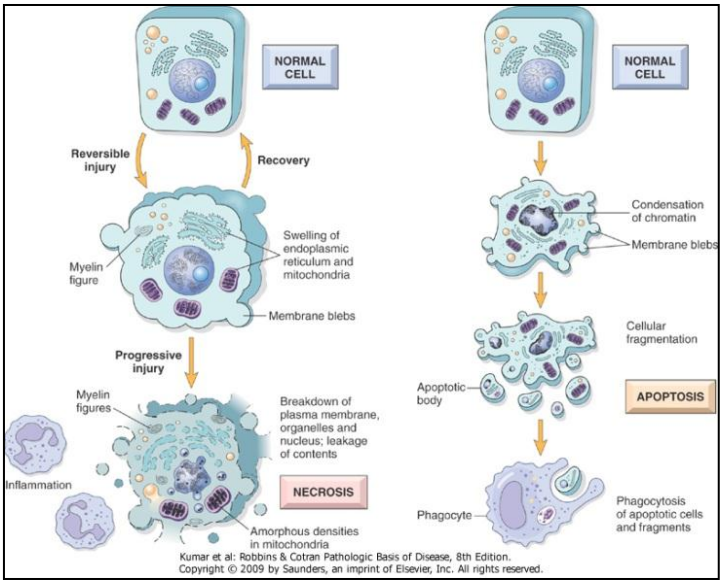


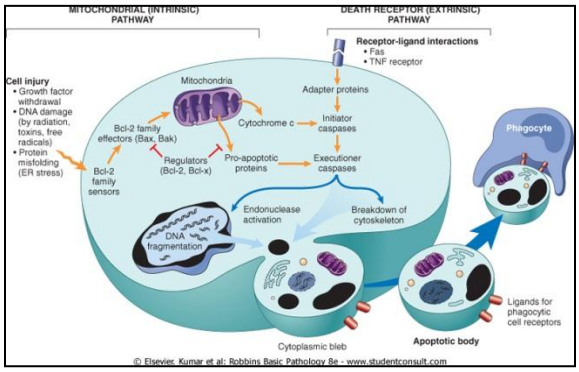
    - Injured membranes allow intracellular components to enter the serum and can be measured
- Free radical injury (acetaminophen – Tylenol overdose)
    - Lipid peroxidation – damage to cellular and organellar membranes
    - Protein crosslinking/fragmentation from oxidative modification of amino acids 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 of mitochondria, 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 seen in 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