Kazan (Volga region) Federal University
Institute of Fundamental Medicine and Biology
Department of Morphology and General Pathology

Cellular injury. Mechanisms.

Lecture 1

Lecturer
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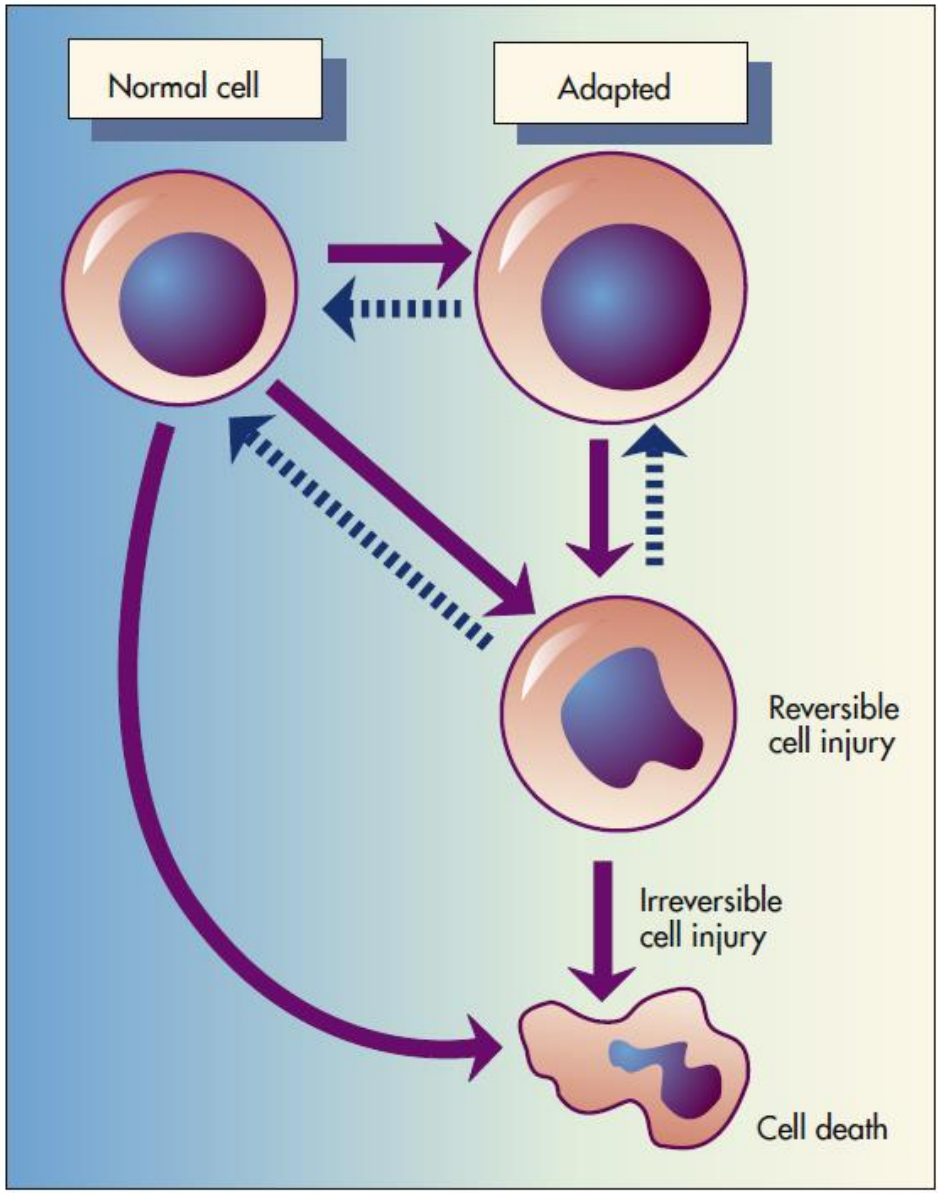
Cellular injury and responses



Causes of cell injury

- Oxygen deprivation
- Chemical agents
- Infectious agents
- Immunologic reactions
- Genetic factors
- Nutritional imbalances
- Physical agents
- Aging

Oxygen deprivation

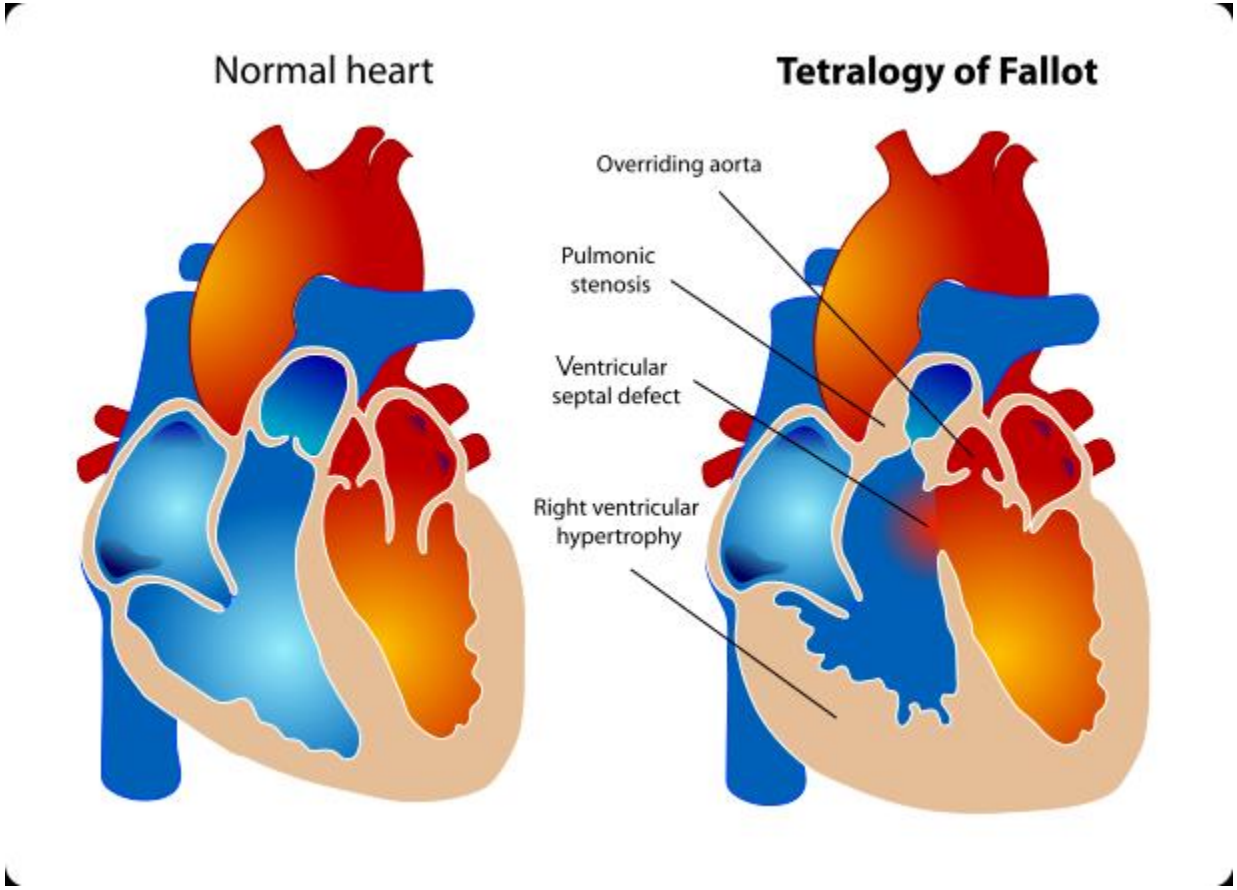
- Hypoxia – most common cause of cell injury

Hypoxia causes a loss of ATP production secondary to oxygen deficiency and can

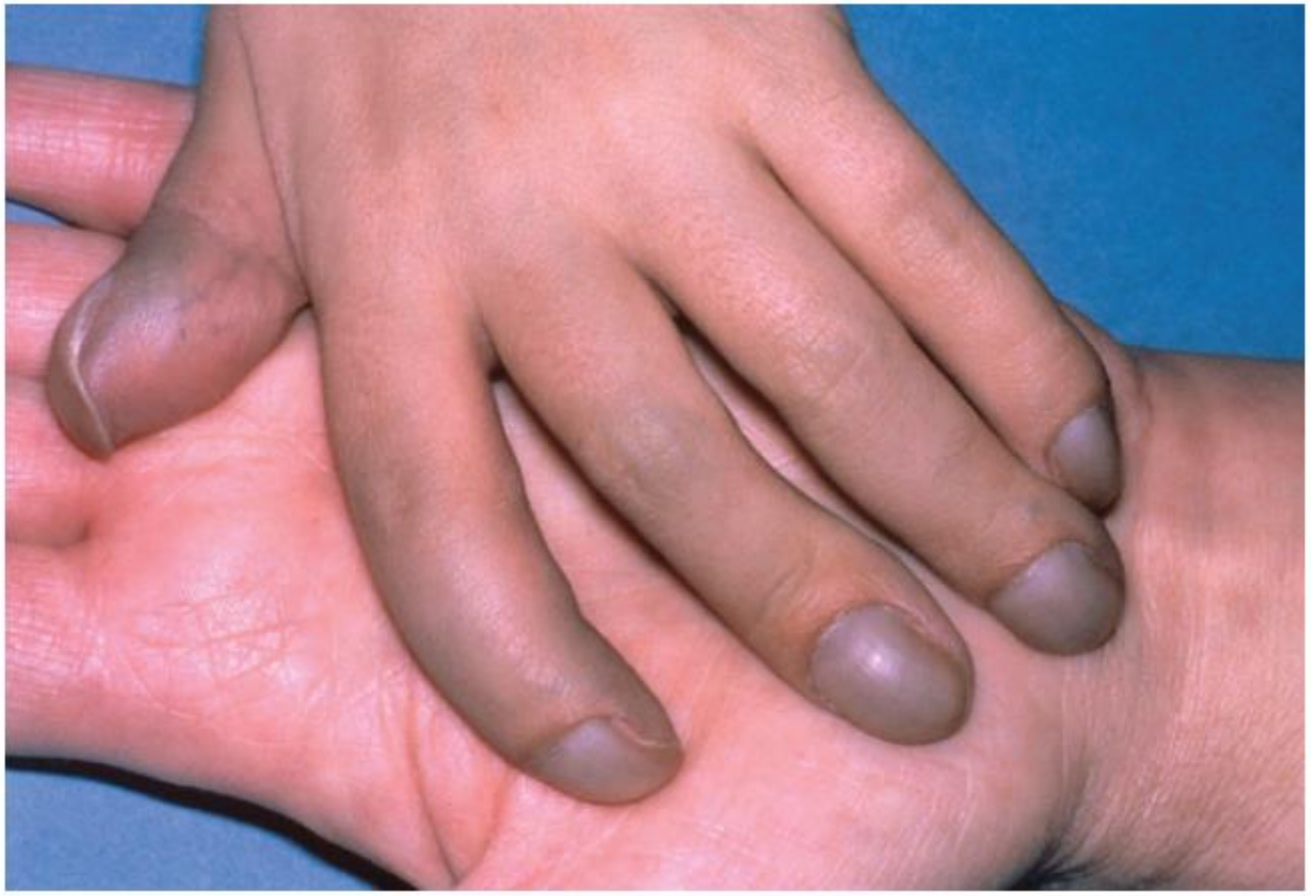
be caused by ischemia, cardiopulmonary failure, or decreased oxygen-carrying

capacity of the blood.

Oxygen deprivation in tetralogy of Fallot



Oxygen deprivation in tetralogy of Fallot



Chemical agents

- Hypertonic concentration of salt – deranging electrolyte homeostasis
- Poisons – arsenic, cyanide, or mercuric salts
- Insecticides and Herbicides
- Air pollutant – carbon monoxide
- Occupational hazard – asbestos
- Alcohol and Narcotic drugs

Infectious agents

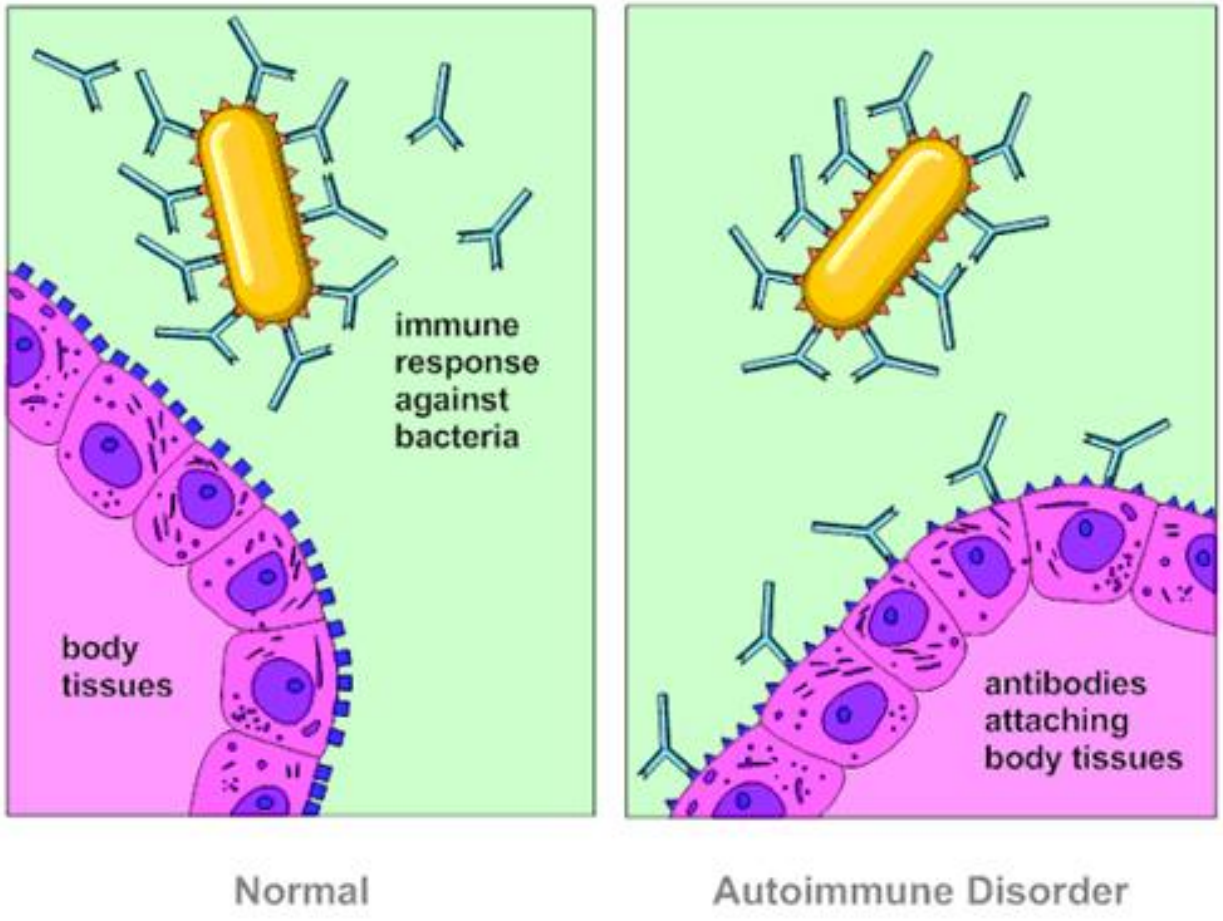
can injure cells directly, or indirectly, via toxin production or host inflammatory response

- Parasites
- Fungi
- Bacteria
- Rickettsiae
- Viruses

Immunologic reactions

- Anaphylactic reaction to foreign protein or drug
- Reactions to endogenous self-antigens – autoimmune diseases

Immunologic reactions

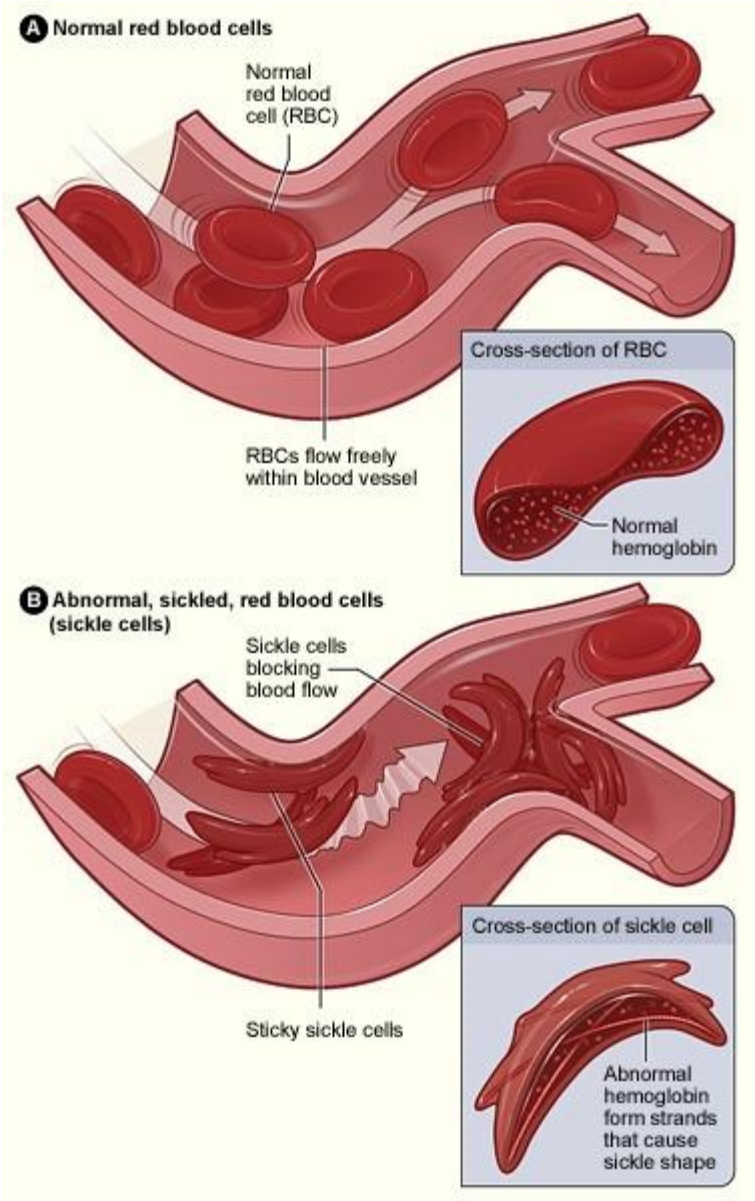


Genetic factors

- Congenital malformation – Down syndrome
- Decreased life of red blood cell – Thalassemia, Sickle cell anemia
- Inborn errors of metabolism

Causes of cell injury

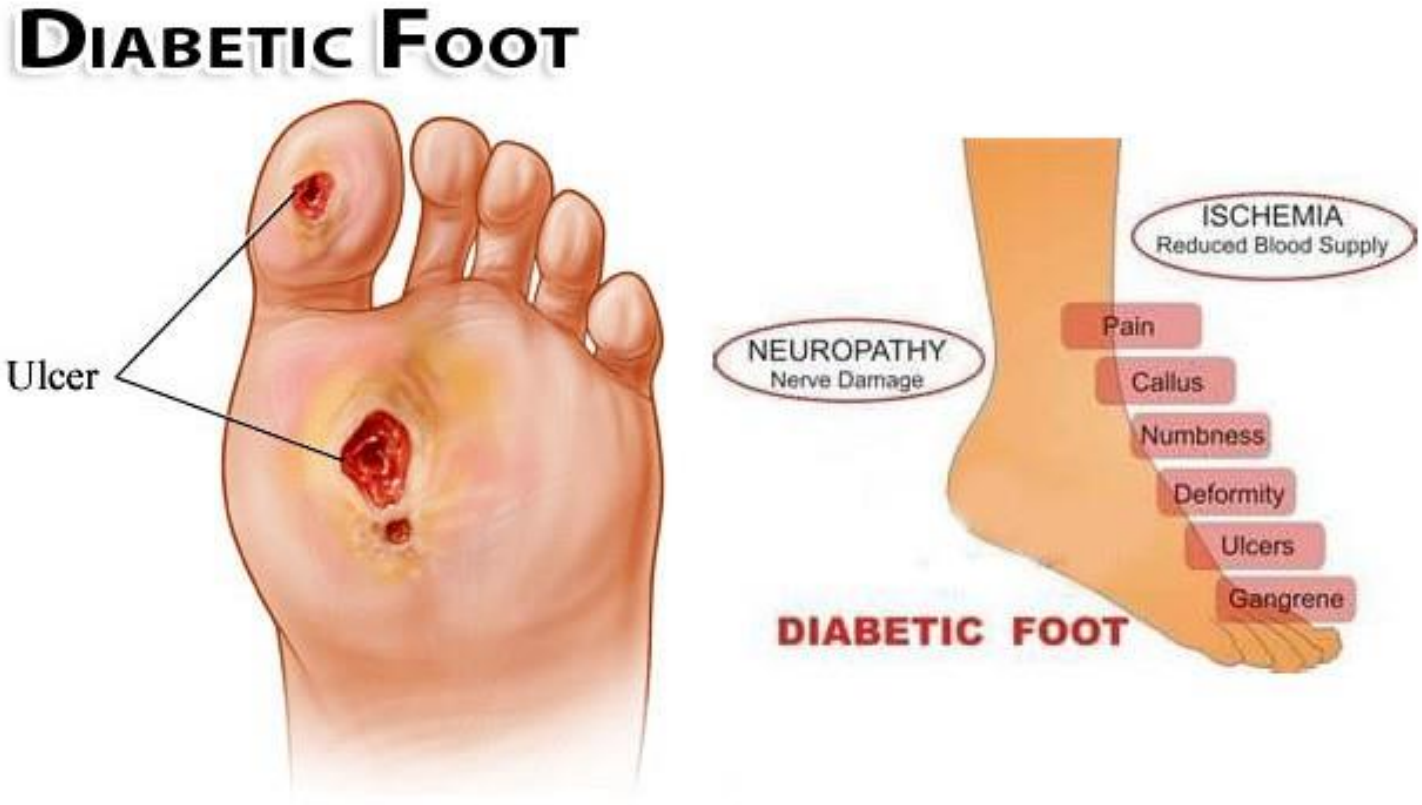
Genetic factors



Nutritional imbalances

- Protein-calorie deficiencies
- Vitamin deficiencies
- Anorexia nervosa
- Excesses of lipids – Obesity, Atherosclerosis
- Metabolic diseases – Diabetes

Nutritional imbalances



Physical agents

- Mechanical trauma
- Extremes of temperature – burns, deep cold
- Radiation
- Electric shock

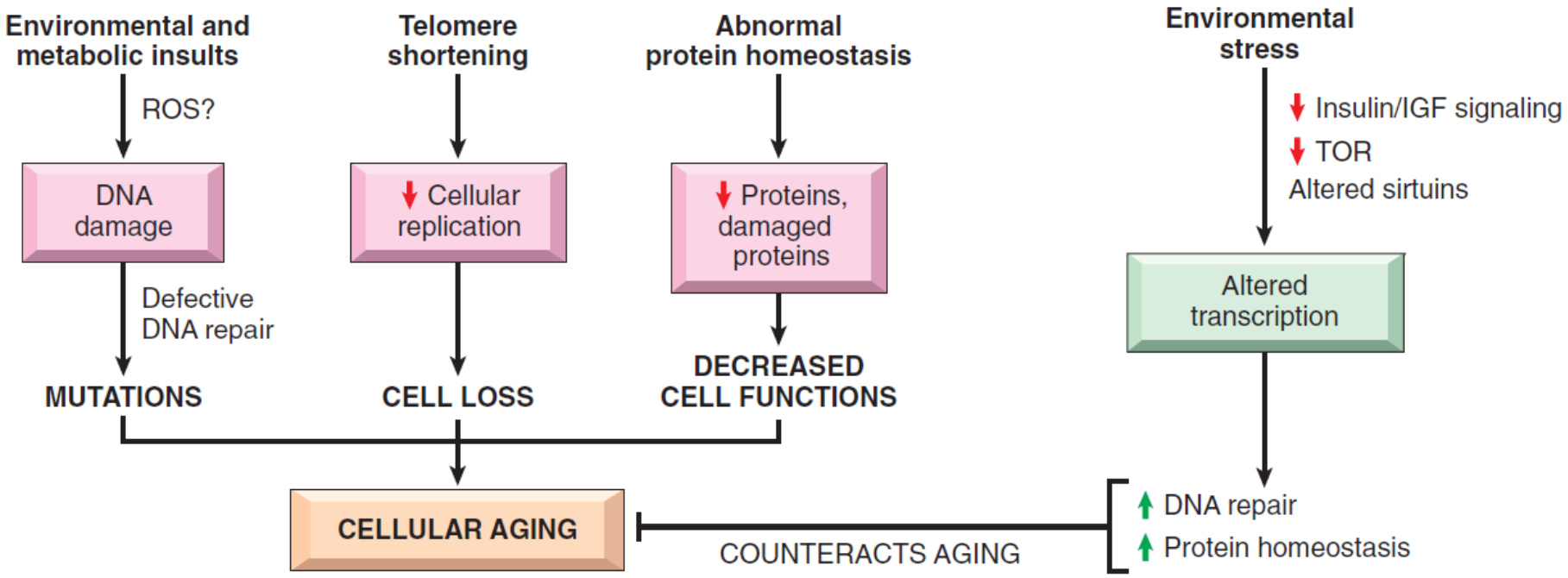
Physical agents

Electrical burn of the skin

Causes of cell injury

Aging

"Individuals age because their cells age"



Factors that affect cell injury

1. Type, duration and severity of injury.

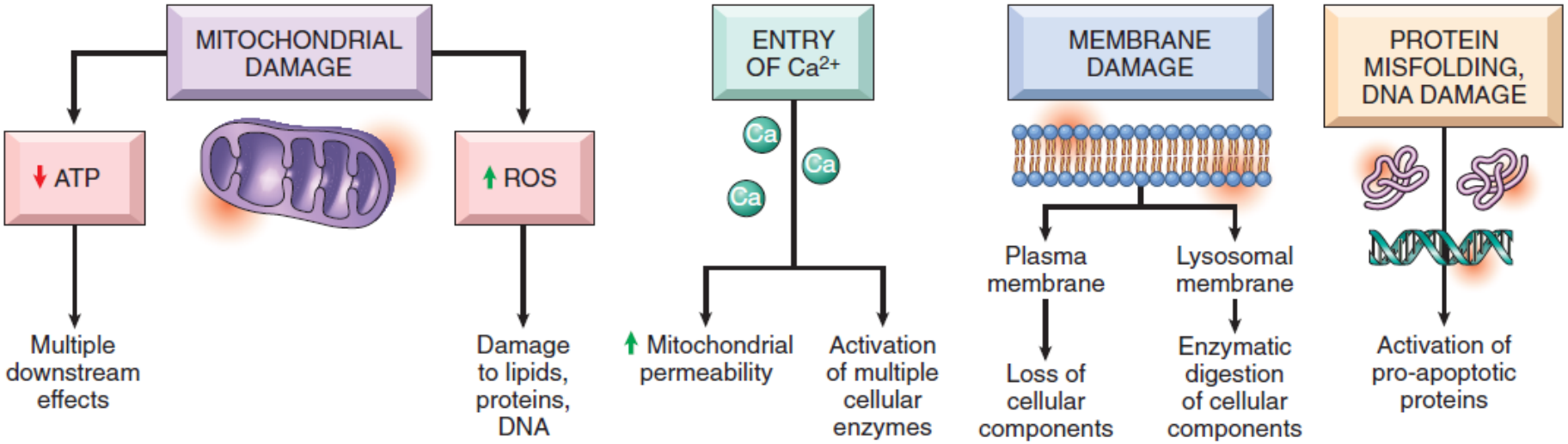
2. Type of injured tissue, its adaptability and genetic makeup e.g.:

- Brain tissue is very sensitive to hypoxia (2-5 min.)
- Myocardium 1-2 hours
- Skeletal muscles can adapt hypoxia for 2-6 hours
- Fibroblasts – hours

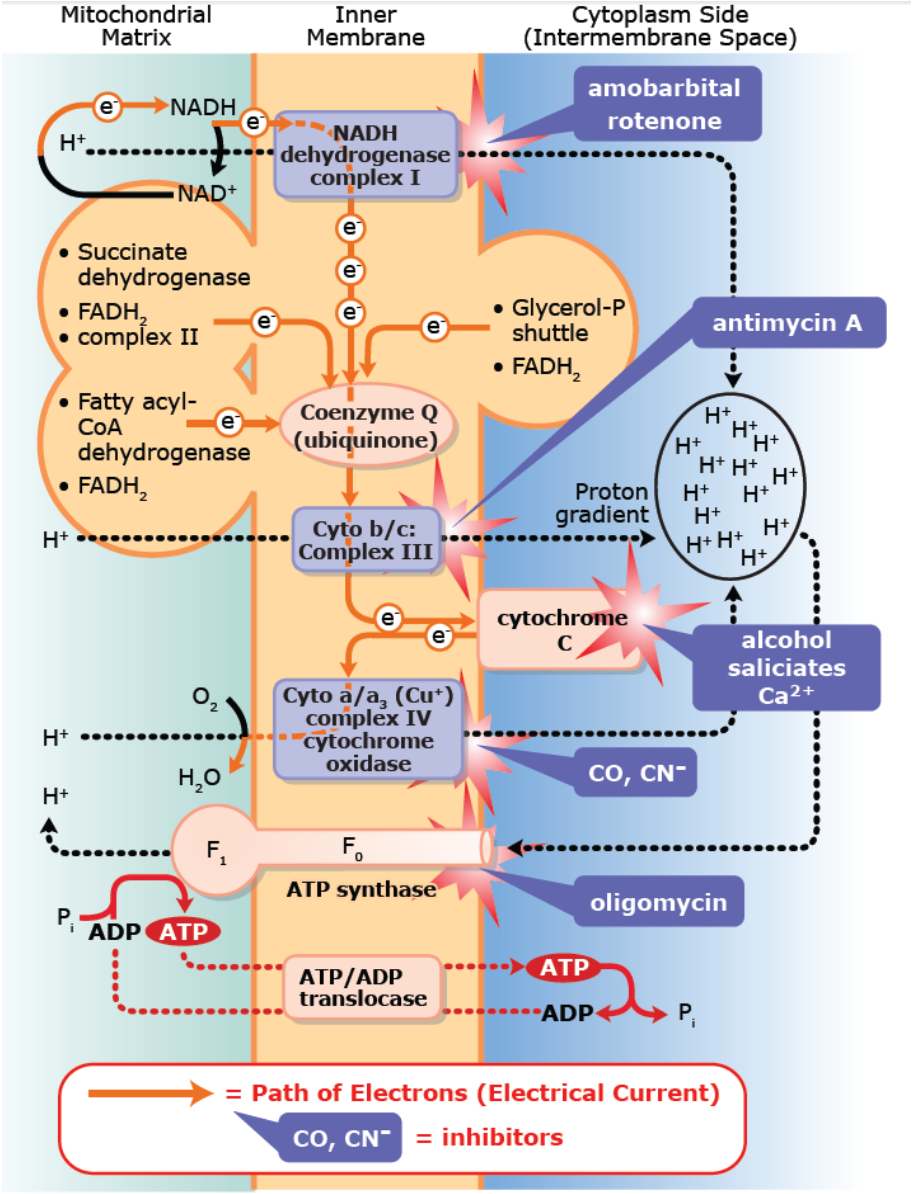
Important targets of cell injury

- Aerobic respiration –
  - ATP depletion or decreased synthesis.
- Cell membranes - plasma membranes, mitochondrial, lysosomal and other organelle membranes.
- Protein synthesis.
- Cytoskeleton.
- Genetic apparatus.

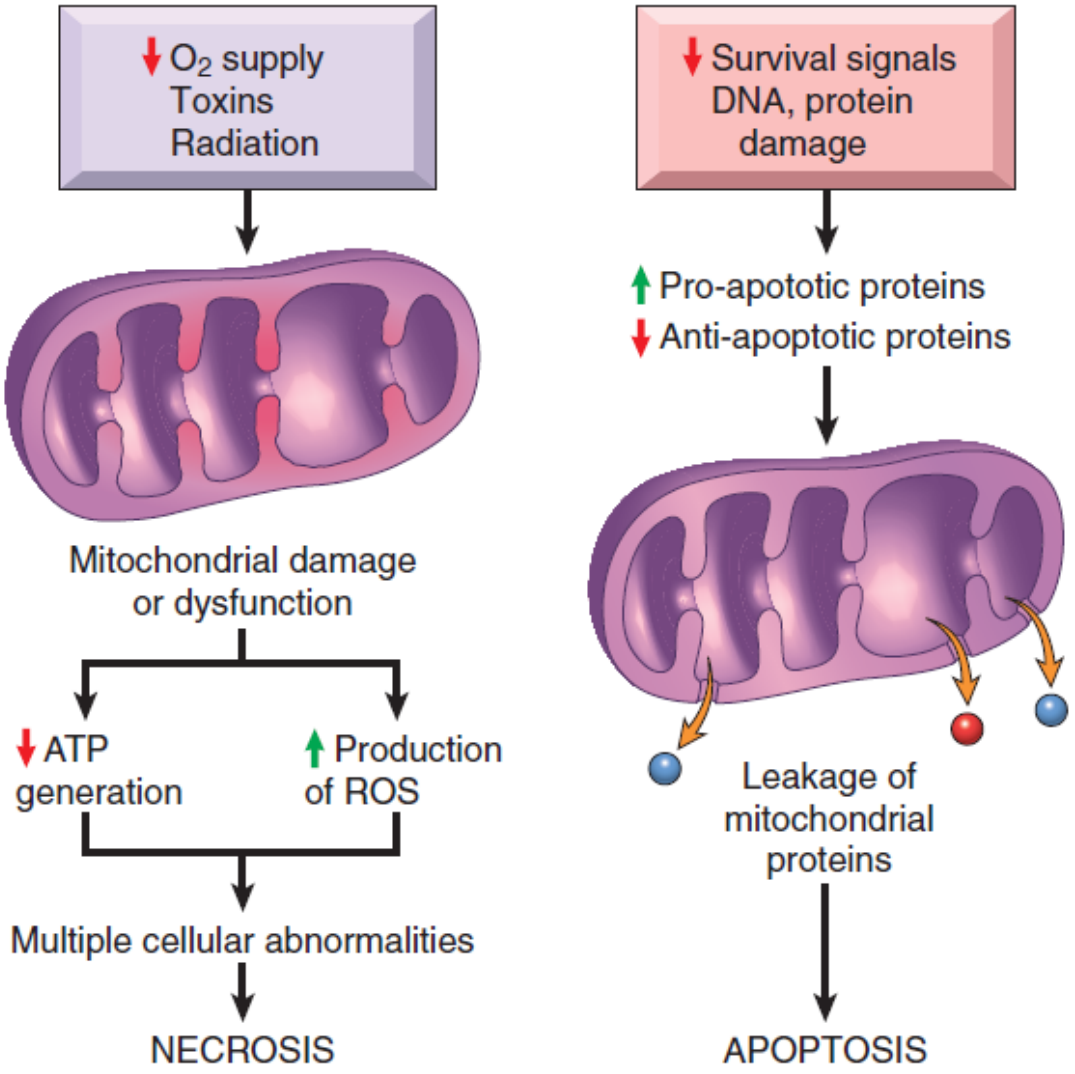
Mechanisms of cell injury



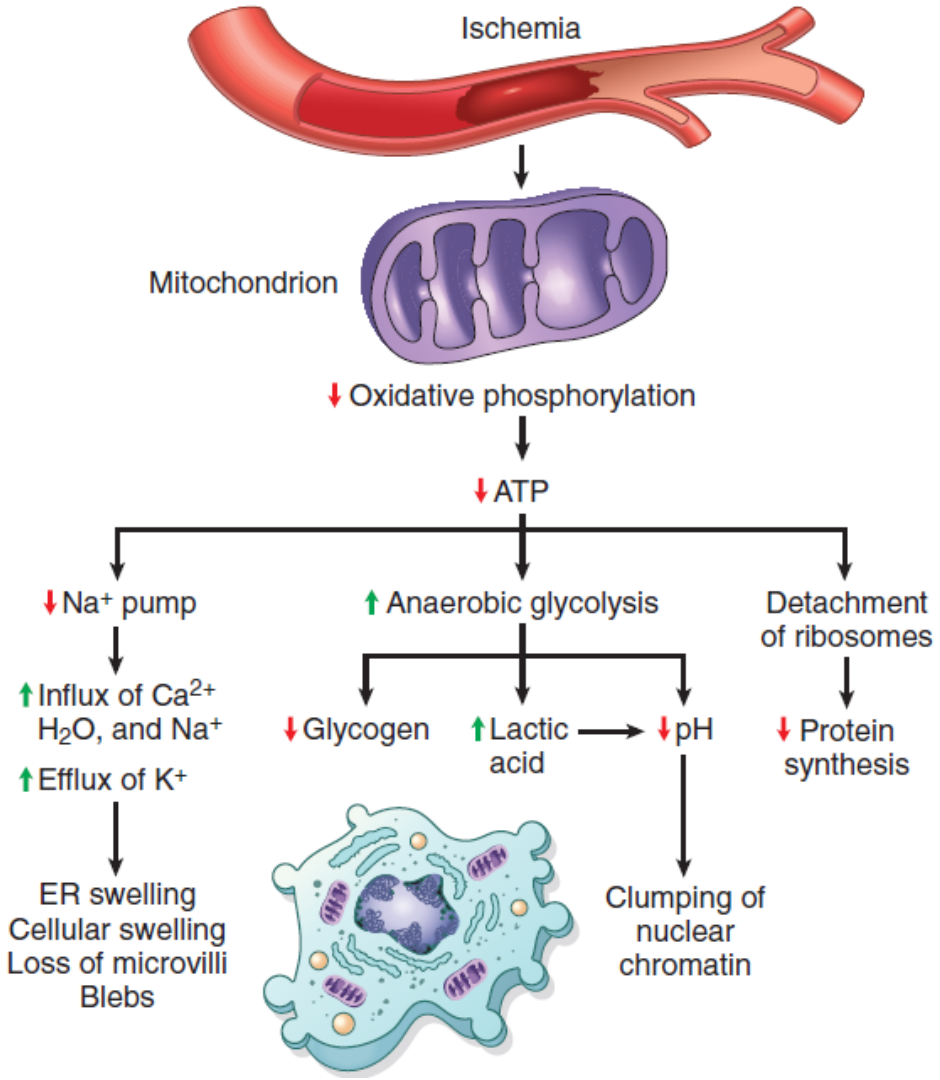
Oxidative phosphorylation



Mitochondrial damage



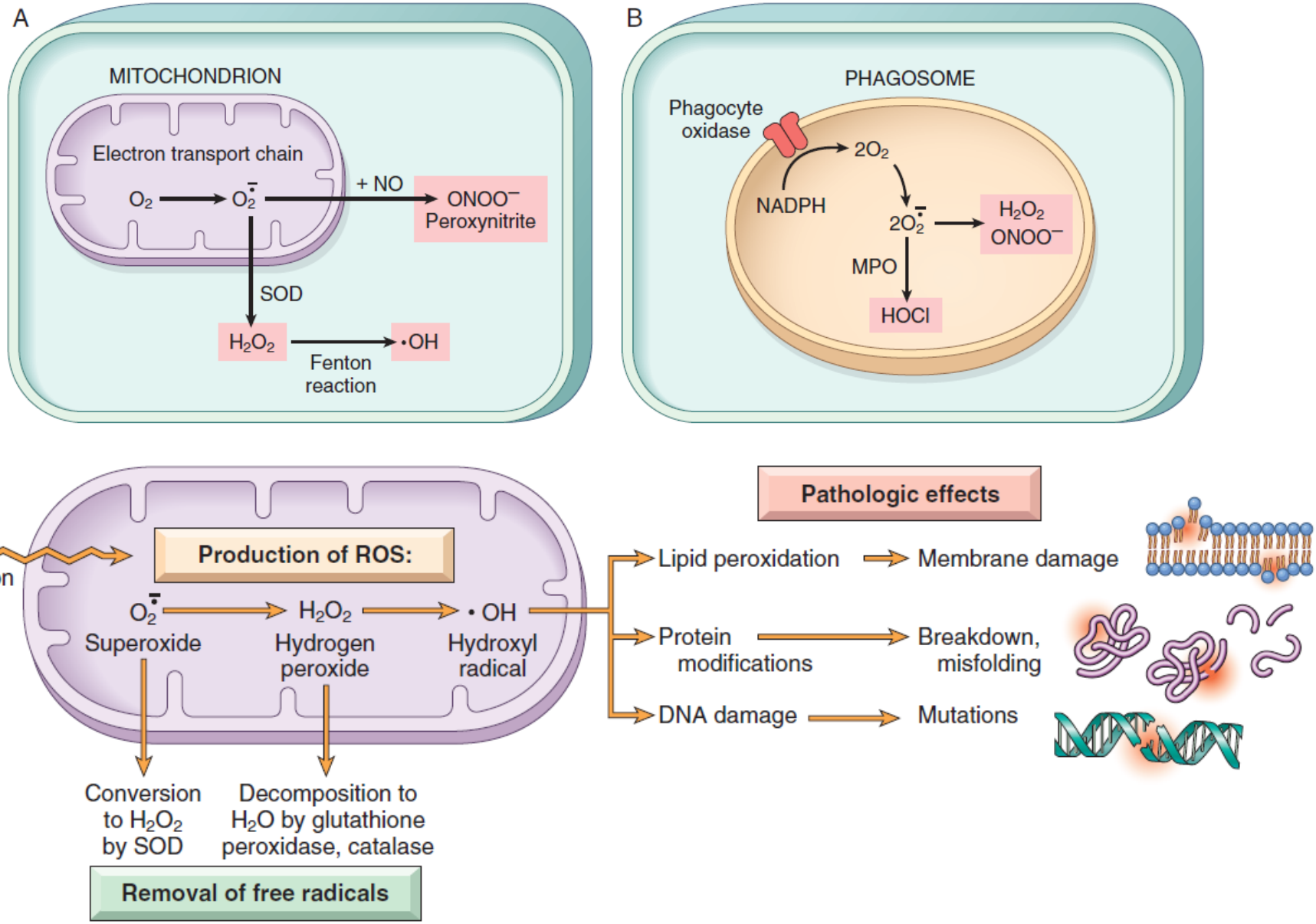
Mitochondrial damage: depletion of ATP



Mitochondrial damage: depletion of ATP

- **Mitochondria** - reduced oxidative phosphorylation.
- **Cell membrane** - reduced sodium pump.
- Sodium and water enter the cell; potassium exits.
- **Endoplasmic reticulum** dilates, the cell swells, blebs appear.
- Anaerobic glycolysis occurs with loss of glycogen, accumulation of lactic acid, acid pH which interferes with enzymes.
- Failure of the calcium pump leads to influx of Ca++ into the cell, activate various enzymes to the detriment of the cell.
- **ER** loses ribosomes and protein synthesis falls - structural proteins (membranes, cytoskeleton) and enzymes.
- Misfolded proteins lead to the unfolded protein response which may further injure the cell.

Mitochondrial damage: oxidative stress



Mitochondrial damage: oxidative stress

- Free radicals have a **single unpaired electron** in the outer orbit. They are **highly reactive** with adjacent molecules.
- Are usually derived from oxygen to produce reactive oxygen species, superoxide, hydroxyl radicals, H2O2, etc.
- Are normally produced during cellular respiration. Protective molecules include superoxide dismutase, glutathione peroxidase, vitamin E, vitamin C, catalase.
- Produced in excess, they react with, and damage proteins, lipids, carbohydrates, nucleic acids.
- These damaged molecules may themselves be reactive species with a chain reaction being set up with widespread damage.

Mitochondrial damage: oxidative stress

- In addition to oxygen-derived free radicals, nitric oxide (NO) can act as a free radical and be converted to an even more reactive anion.
- Iron and copper catalyze free radical formation and are thus important in the generation of reactive oxygen species.

Fenton reaction

- Binding to molecules such as transferrin, ferritin and ceruloplasmin is protective.
- Free radicals cause lipid peroxidation in cell membranes, oxidation of amino acids and proteins resulting in fragmentation, and protein-protein cross linkages. Altered proteins are acted on by the proteosomes with further cell damage.

Mitochondrial damage: oxidative stress

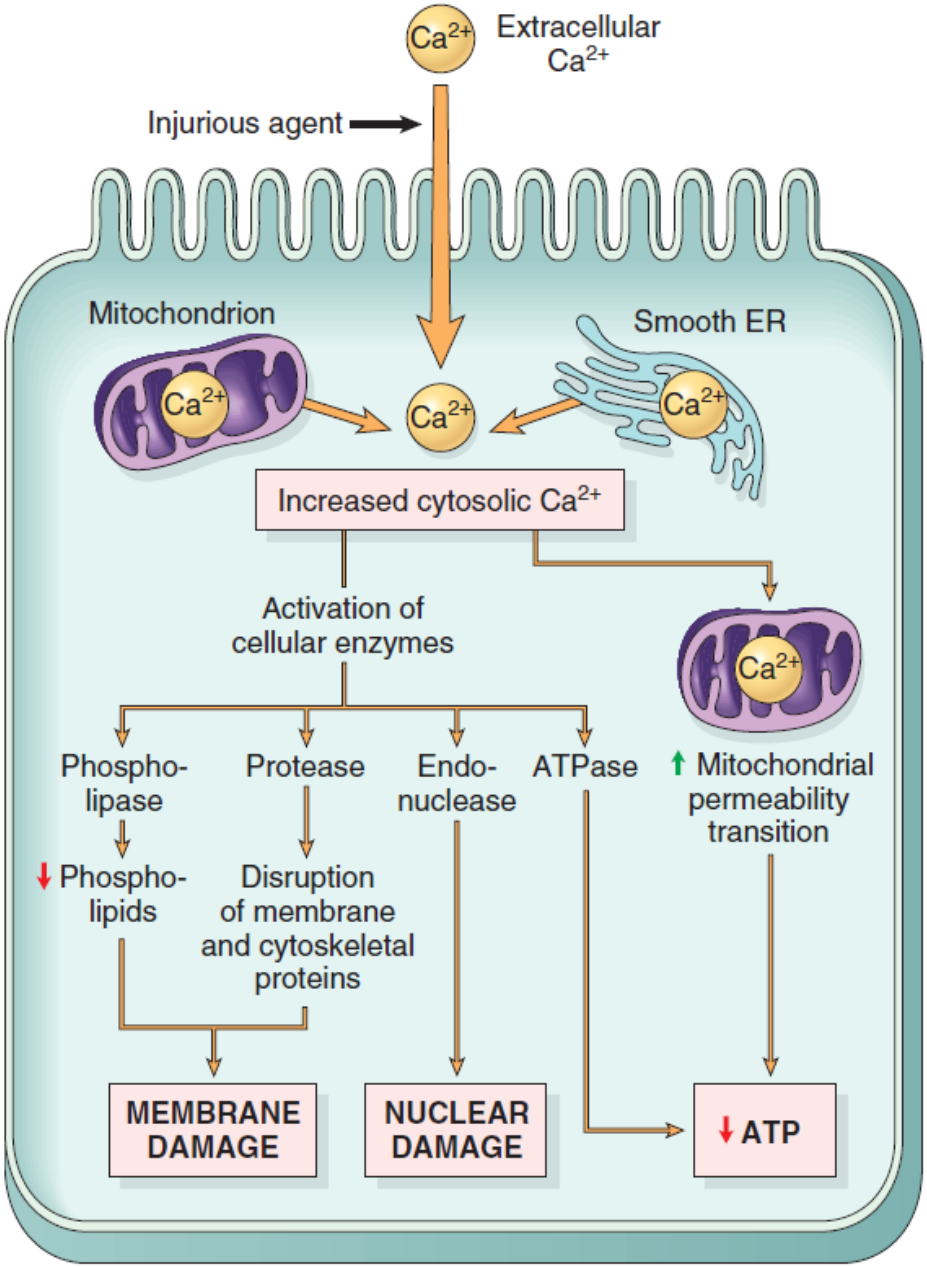
- Free radicals may be a common pathway for most types of cell damage, particularly oxygen-derived free radicals (oxidative stress).

Some examples are:

- oxygen toxicity, ischaemia/reperfusion injury, radiation injury (hydrolyses H2O to OH & H), metabolism of drugs, toxins, pollutants (eg Paracetamol to reactive metabolite; CCl4 to CCl3, cigarette smoke);
- leukocyte killing of bacteria or in non-bacterial inflammations, release of iron in haemorrhages enhances oxidative stress (important in CNS),
- lipid peroxidation of low-density lipoproteins in atherosclerosis, cancer production (damage to DNA), ageing.

Therapies for combating oxidative stress are available for prevention or treatment with antioxidants and/or free-radical scavengers.

Entry of Ca^{2+}


Ca2+
Extracellular Ca2+
Injurious agent
Mitochondrion
Smooth ER
Ca2+
Ca2+
Ca2+
Increased cytosolic Ca2+
Activation of cellular enzymes
Ca2+
Phospho-lipase
Protease
Endo-nuclease
ATPase
↑ Mitochondrial permeability transition
↓ Phospho-lipids
Disruption of membrane and cytoskeletal proteins
MEMBRANE DAMAGE
NUCLEAR DAMAGE
↓ ATP

Entry of Ca^{2+}

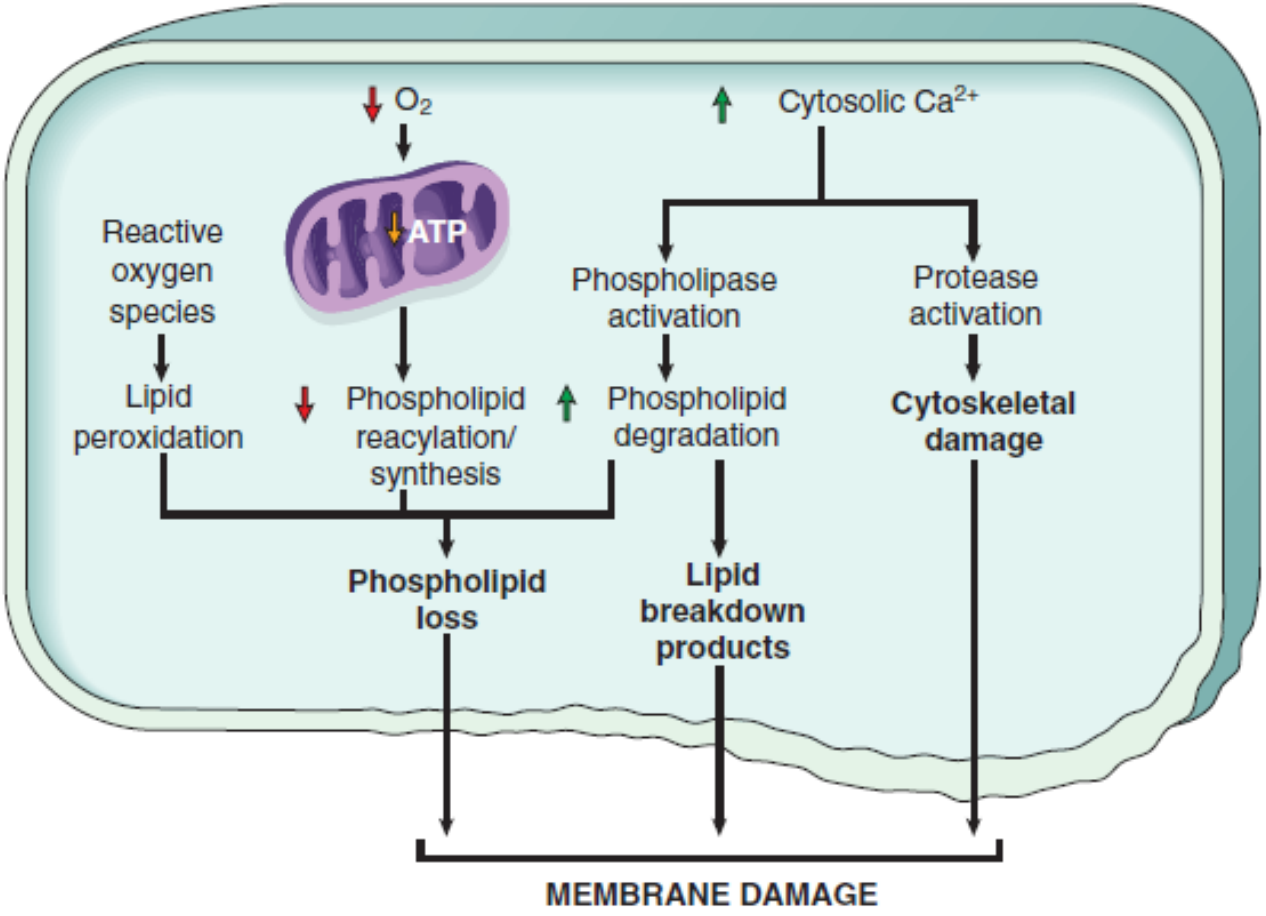
Influx of calcium to the cytosol comes from the extracellular fluid and stores in mitochondria and endoplasmic reticulum.

Ca++ activates phospholipases (damages cell membranes),proteases (damages cell membranes and cytoskeleton) and endonucleases (damages DNA).

This is one of the main mechanisms of cell death, either through severe damage to membranes of lysosomes and leakage of lysosomal enzymes or triggering apoptosis.

Occurs particularly in hypoxia and ischaemia and with certain toxins. Preventing the rise in Ca++ or restoring to normal levels prevents cell death.

Membrane damage



Membrane damage

- **Mitochondria –**
  - mitochondrial permeability transition;
  - this non-selective pore may be reversible or become permanent leading to cell death.
  - Leakage of cytochrome c can trigger apoptosis.
- **Plasma membrane –**
  - mechanisms include those occuring with hypoxia/ischaemia and free radicals, but also
  - immune mechanisms as with complement activation and
  - perforin from lymphocyte attack on cells infected with a virus.
- **All membranes may be damaged and ruptured by**
  - mechanical force as in trauma, or by
  - ice crystals as in extreme cold.

Damage to lysosomal membranes can lead to cell death by necrosis.

Protein misfolding, DNA damage

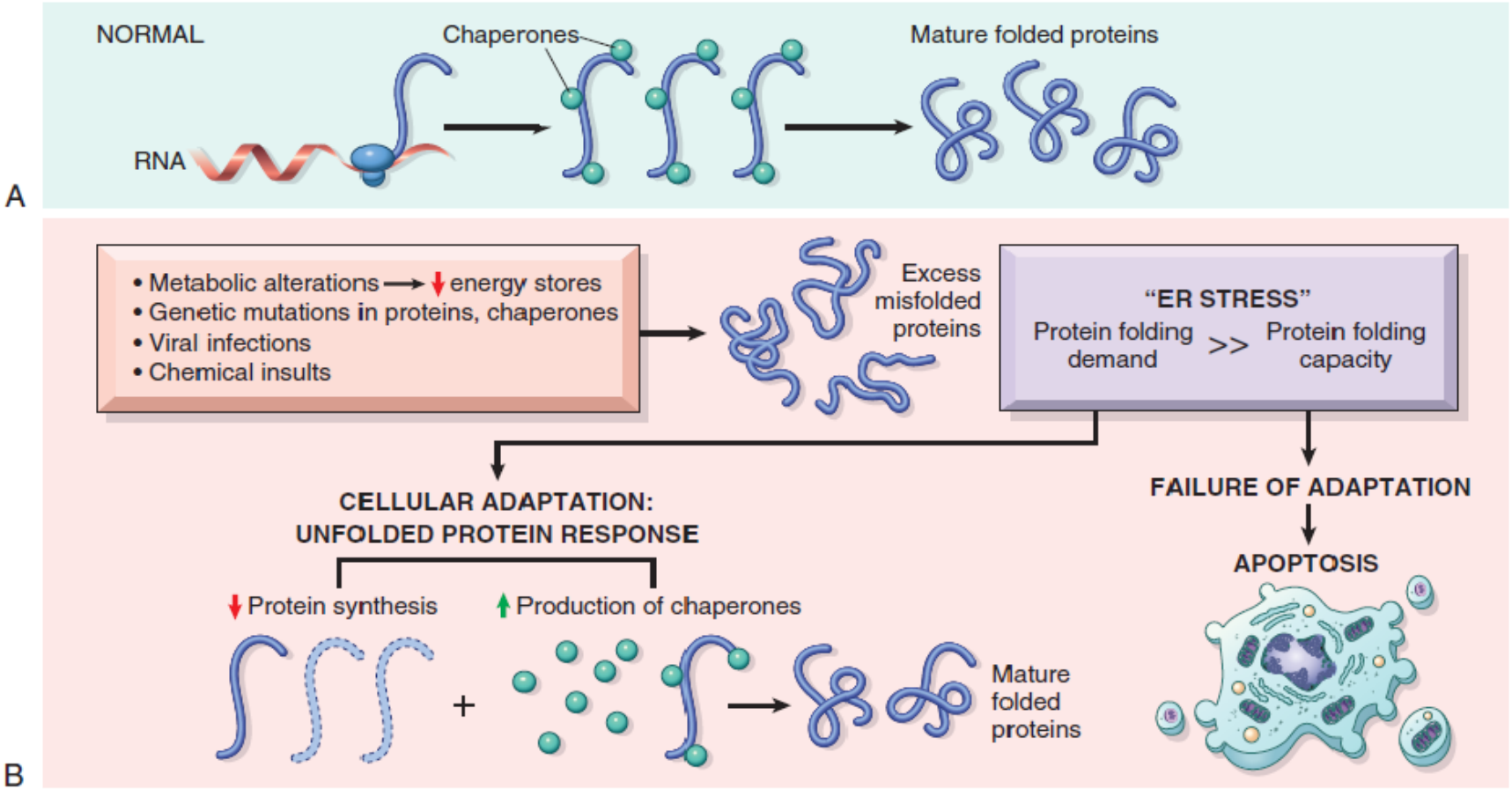


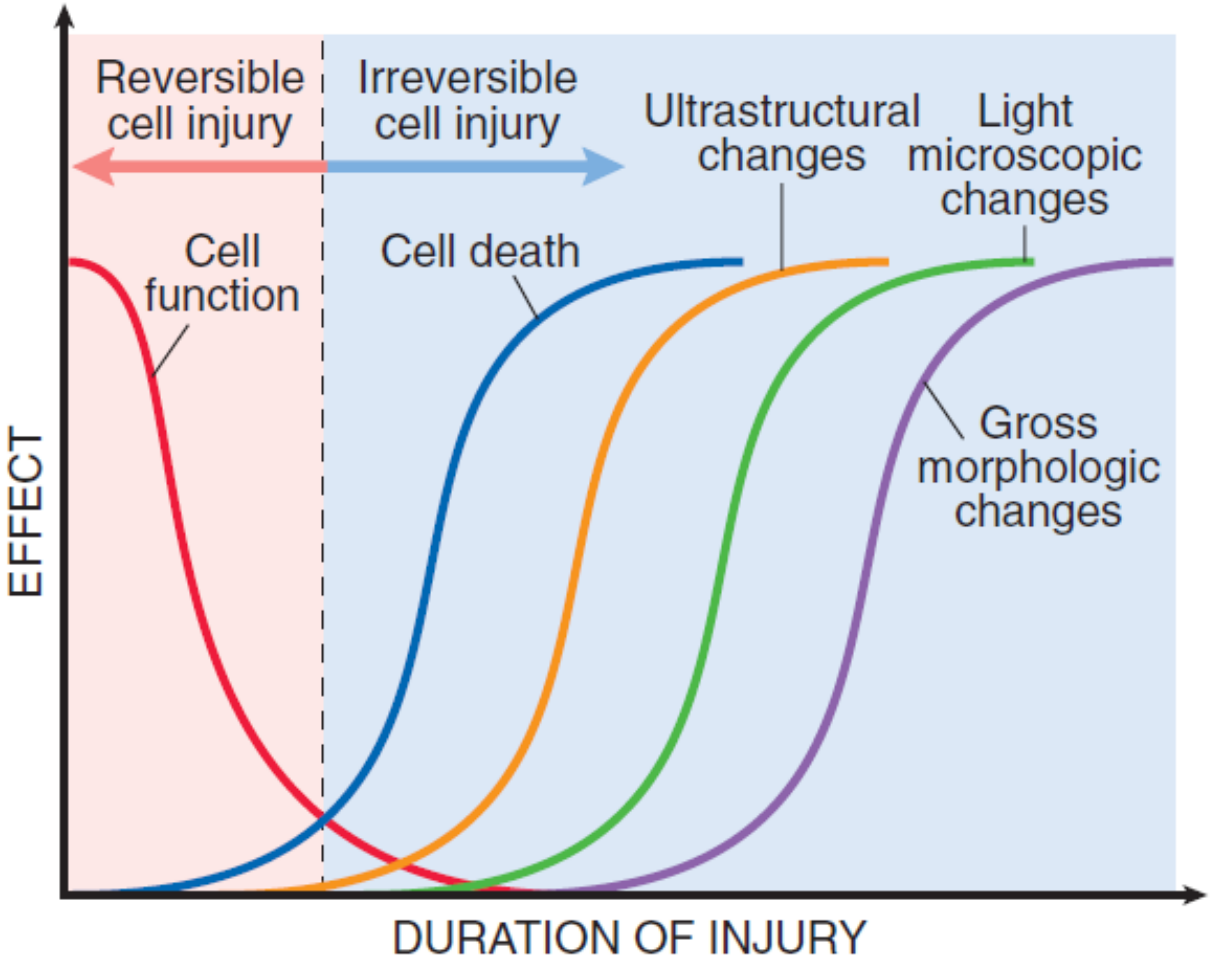
Figure 1–24 The unfolded protein response and ER stress. **A,** In healthy cells, newly synthesized proteins are folded with the help of chaperones and are then incorporated into the cell or secreted. **B,** Various external stresses or mutations induce a state called ER stress, in which the cell is unable to cope with the load of misfolded proteins. Accumulation of these proteins in the ER triggers the unfolded protein response, which tries to restore protein homeostasis; if this response is inadequate, the cell dies by apoptosis.

Characteristics of reversible cell injury

- Decreased synthesis of ATP by oxidative phosphorylation.
- Decreased function of Na+K+ ATPase membrane pumps, which in turn causes influx of Na+ and water, efflux of K+, cellular swelling (hydropic swelling), and swelling of the endoplasmic reticulum.
- The switch to glycolysis results in depletion of cytoplasmic glycogen, increased lactic acid production, and decreased intracellular pH.
- Decreased protein synthesis leads to detachment of ribosomes from the rough endoplasmic reticulum.
- Plasma-membrane blebs and myelin figures may be seen

Characteristics of irreversible cell injury

- Severe membrane damage plays a critical role in irreversible injury, allows a massive influx of calcium into the cell, and allows efflux of intracellular enzymes and proteins into the circulation.
- Marked mitochondrial dysfunction produces mitochondrial swelling, large densities seen within the mitochondrial matrix, irreparable damage of the oxidative phosphorylation pathway, and an inability to produce ATP.
- Rupture of the lysosomes causes release of lysosomal digestive enzymes into the cytosol and activation of acid hydrolases followed by autolysis.



REVERSIBLE →
IRREVERSIBLE→
DEATH→
EM→
LIGHT MICROSCOPY→
GROSS APPEARANCES