Cell Injury and cell death lecture 2

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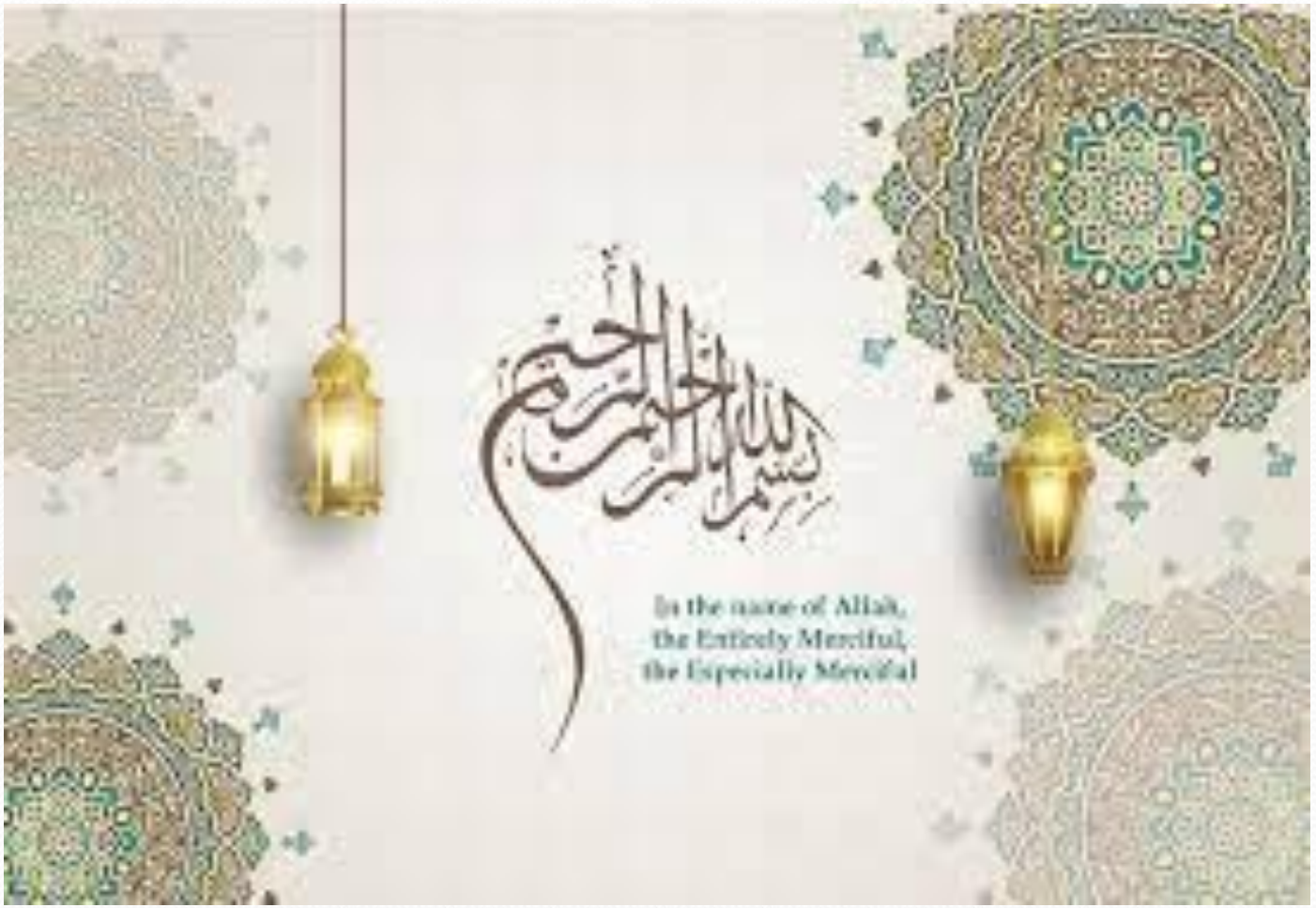

بسم الله الرحمن الرحيم
In the name of Allah,
the Entirely Merciful,
the Especially Merciful


وَٱذۡكُرِ ٱسۡمَ رَبِّكَ بُكۡرَةً وَأَصِيلًا ٢٥
AND MENTION THE NAME OF YOUR LORD
[IN PRAYER] MORNING AND EVENING
SURAH AL-INSAN | AYAH 25

Learning Objectives:

- At the end of this lecture student should be able to;
- Describe changes in reversible cell injury.
- Understand the importance of ischemic and hypoxic injury
- Understand the pathogenesis of ischemic reperfusion injury.
- Understand the pathogenesis of chemical injury .

CAUSES OF CELL INJURY:

- Oxygen Deprivation:
- Physical agents:
- Chemical Agents:
- Infectious Agents.
- Immunologic Reactions.
- Genetic Defects:
- Nutritional Imbalances.
- Ageing

Oxygen Deprivation:

- Oxygen deficiency (hypoxia) disturbs cell's oxidative respiration and is an extremely important and common cause of cell injury and death.
- Oxygen deficiency may be due to
- Ischemia (loss of blood supply) due to arterial or venous blockade.
- Loss of oxygen carrying capacity as in anemia (especially blood loss anemia) or CO poisoning.
- Improper oxygenation of blood due to pulmonary disease.
- Decreased blood supply to tissues as seen in shock.

Physical agents: These include.

- Trauma.
- Extremes of temperatures.
- Radiation.
- Electric shock.
- Sudden changes in atmospheric pressure.

Chemical Agents:

- Any chemical substance can cause injury.
- Even substances like glucose or salt disturb the osmotic environment and cause injury or cell death.
- Oxygen at sufficiently high pressures is also toxic.
- Poisons cause severe damage altering cell membrane permeability or damage the enzyme systems of cells.

- Examples include arsenic, cyanide or mercuric salts (within minutes to hours).
- Insecticides, carbon monoxide, alcohol also cause injury.
- Therapeutic drugs are important chemical agents in causing cell injury .
- Infectious Agents. These range from submicroscopic viruses to meter-long tapeworms; in between are bacteria, fungi, and protozoa.

Ageing:

- Individuals age because their cells age.
- Cellular aging is the result of a decline in the proliferative capacity and life span of cells.
- It is also the result of effects of continuous exposure to external factors that cause cellular and molecular damage.
- The process of aging is regulated by genes.

Immunologic Reactions.

- Although immune system defends the body yet it can also cause damage to the body. Examples include
- Allergic reactions against environmental substances
- Autoimmune diseases.
- Genetic Defects:
- Single base substitution, addition of a chromosome or deletion of a part of chromosome can lead to enormous derangements
- Sickle cell anemia (Base substitution)
- Several inherited metabolic disorders.
- Down syndrome (trisomy 21, extra chromosome addition)
- 5p-Deletion syndrome (cri du chat syndrome)

Nutritional Imbalances.

- Nutritional deficiencies remain a major cause of cell injury specially in developing countries.
- Examples include.
- Protein calorie malnutrition
- Kwashiorkor and marasmus
- Vitamin deficiencies found throughout the world.
- On other hand excess nutrition is also a cause of injury obesity leads to diabetes mellitus and cancer.
- Diets rich in animal fat can be a cause of atherosclerosis.

Reversible injury

- Reversible injury is 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
- In reversible injury, cells and intracellular organelles typically become swollen because they take in water as a result of the failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.
- In some forms of injury, degenerated organelles and lipids may accumulate inside the injured cells.

MORPHOLOGY

- Cellular swelling is commonly seen in cell injury associated with increased permeability of the plasma membrane.
- It may be difficult to appreciate with the light microscope, but it is often apparent at the level of the whole organ.
- When it affects many cells in an organ, it causes pallor (as a result of compression of capillaries), increased turgor, and an increase in organ weight.
- Microscopic examination may show small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum.

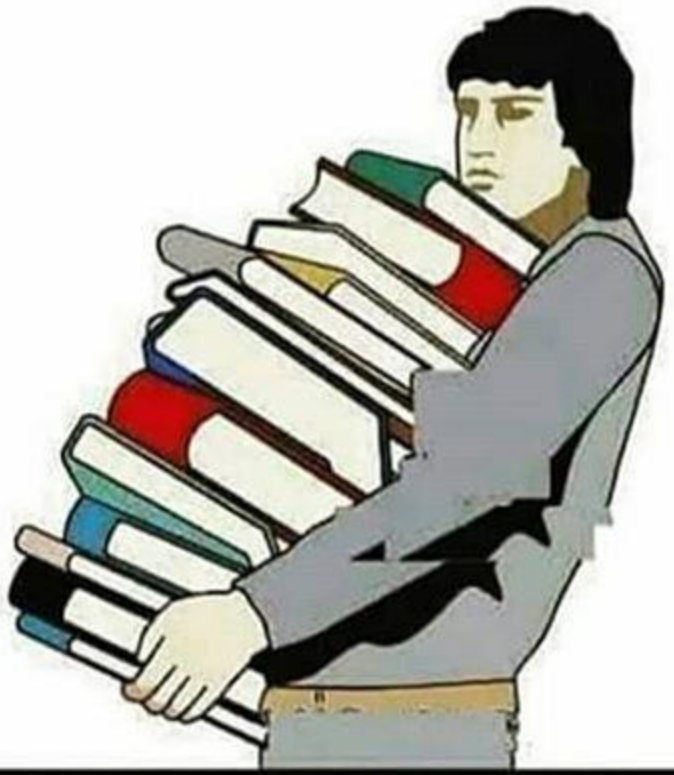
- Fatty change is manifested by the appearance of triglyceride containing lipid vacuoles in the cytoplasm.

- It is principally encountered in organs that are involved in lipid metabolism, such as the liver

- The cytoplasm of injured cells also may become redder(eosinophilic).
- Other intracellular changes associated with cell injury include
- (1)plasma membrane alterations such as blebbing, blunting, or distortion of microvilli, and loosening of intercellular attachments;
- (2) mitochondrial changes such as swelling and the appearance of phospholipid-rich amorphous densities; (3) dilation of the ER with detachment of ribosomes and dissociation of polysomes.
- (4) nuclear alterations, such as clumping of chromatin

- In some situations, potentially injurious insults induce specific alterations in cellular organelles, such as the ER.
- The smooth ER is involved in the metabolism of various chemicals, and cells exposed to these chemicals show hypertrophy of the ER as an adaptive response that may have important functional consequences. For instance, many drugs, including barbiturates, which were commonly used as sedatives in the past and are still used as a treatment for some forms of epilepsy, are metabolized in the liver by the cytochrome P-450 mixed-function oxidase system found in the smooth ER.

When someone says
"Nothing can be
more complicated than love"



Just throw medical
books on their faces..!!

Sources of ATP

- Most cellular ATP is produced from adenosine diphosphate (ADP) by oxidative phosphorylation during reduction of oxygen in the electron transport system of mitochondria.
- In total, the cells of a healthy human burn 50 to 75 kg of ATP every day ,therefore, cells deprived of oxygen are at risk of suffering catastrophic failure of many essential functions.

Adaptive Mechanisms To Replenish ATP stores.

- Cells subjected to the stress of hypoxia that do not immediately die activate compensatory mechanisms that are induced by transcription factors of the hypoxia inducible factor 1 (HIF-1) family. HIF-1 simulates the synthesis of several proteins that help the cell to survive in the face of low oxygen.
- Some of these proteins, such as vascular endothelial growth factor (VEGF), stimulate the growth of new vessels and thus attempt to increase blood flow and the supply of oxygen

- Other proteins induced by HIF-1 cause adaptive changes in cellular metabolism by stimulating the uptake of glucose and glycolysis and reducing mitochondrial oxidative phosphorylation.
- Anaerobic glycolysis can generate ATP in the absence of oxygen using glucose derived either from the circulation or from the hydrolysis of intracellular glycogen.
- normal tissues with a greater glycolytic capacity because of the presence of glycogen (e.g., the liver and striated muscle) are more likely to survive hypoxia and decreased oxidative phosphorylation than tissues with limited glucose stores (e.g., the brain)

Mechanism of cell injury

- The cellular response to injurious stimuli depends on the type of injury, its duration, and its severity.

- Thus, low doses of toxins or a brief period of ischemia may lead to reversible cell injury, whereas larger toxin doses or longer ischemic times may result in irreversible injury and cell death.

continue

- The consequences of an injurious stimulus also depend on the type, status, adaptability, and genetic makeup of the injured cell.
- The same injury has vastly different outcomes depending on the cell type.
- For instance, striated skeletal muscle in the leg tolerates complete ischemia for 2 to 3 hours without irreversible injury, whereas cardiac muscle dies after only 20 to 30 minutes of ischemia.

- The nutritional (or hormonal) status also can be important.
- A glycogen-replete hepatocyte will survive ischemia better than one that has just burned its last glucose molecule.
- Genetically determined diversity in metabolic pathways can contribute to differences in responses to injurious stimuli. For instance, when exposed to the same dose of a toxin, individuals who inherit variants in genes encoding cytochrome P-450 may catabolize the toxin at different rates, leading to different outcomes.

- Cell injury usually results from functional and biochemical abnormalities in one or more of a limited number of essential cellular components.
- different external insults and endogenous derrangements typically affect different cellular organelles and biochemical pathways.
- For instance, deprivation of oxygen and nutrients in hypoxia and ischemia) primarily impairs energy dependent cellular functions, culminating in necrosis, whereas damage to proteins and DNA triggers apoptosis

When I meet friends from high school

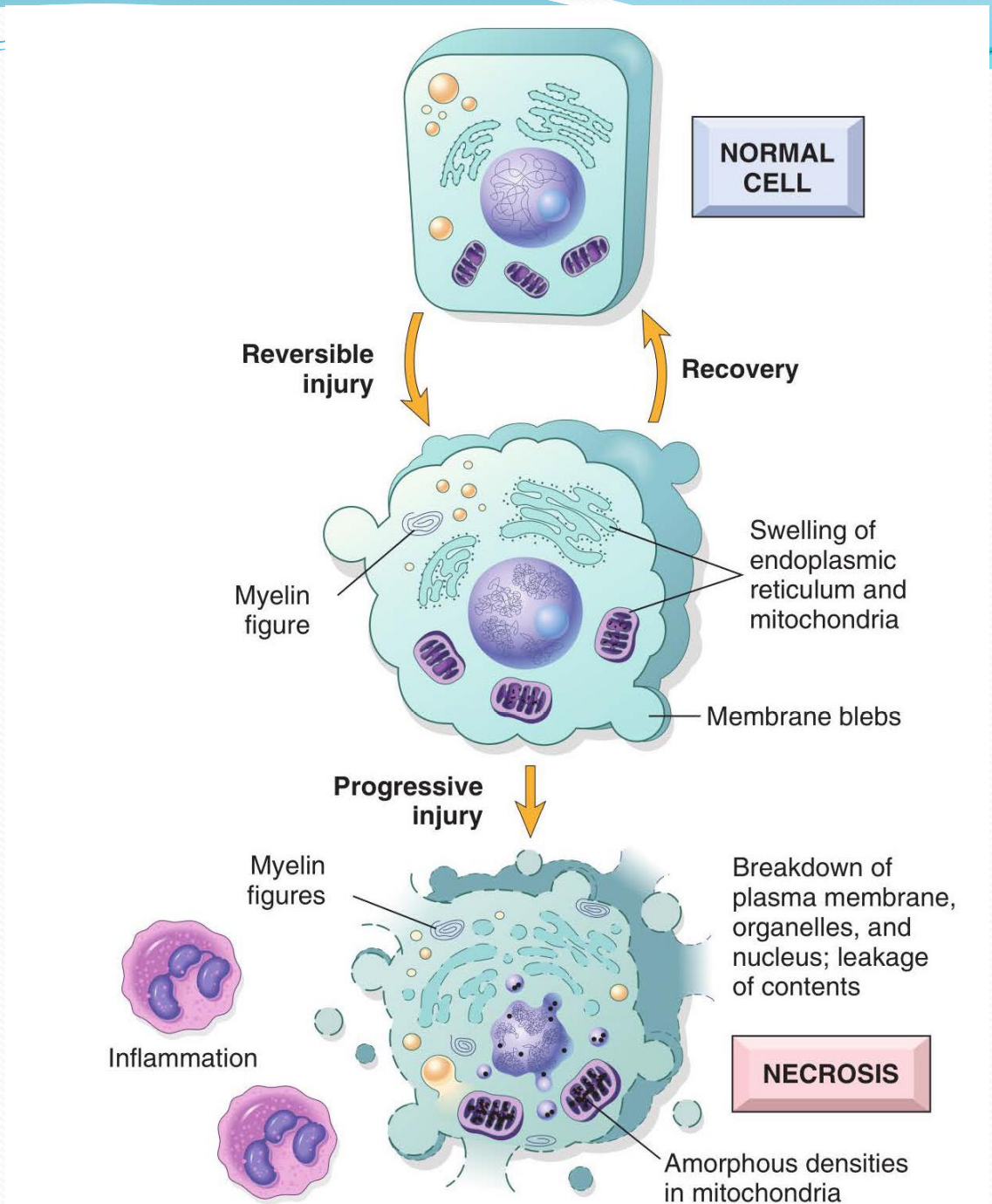
Me: **They:**

- **Ischemic and Hypoxic Injury :**
- Ischemia, or diminished blood flow is the most common cause of cell injury in clinical practice.
- In hypoxia energy generation by anaerobic glycolysis can continue.
- Ischemia in addition also compromises the delivery of nutrients.

- Therefore, ischemia injures tissues faster than does hypoxia.
- Hypoxia causes reduced generation of ATP.
- Loss of ATP leads to failure of ion pumps (leading to cell swelling, and influx of Ca^{2+}).
- Ischemia also causes reduction in protein synthesis and depletion of glycogen stores.

- At this stage cell functions are greatly affected e.g. heart muscle stops to contract within 60 seconds of coronary artery occlusion.
- However loss of contractility does not mean cell death (Injury still reversible)

- If hypoxia continues, increasing ATP depletion causes cytoskeletal protein damage, with loss of microvilli and formation of "blebs“.
- Myelin figures, derived from degenerating cellular membranes, may be seen.


NORMAL CELL
Reversible injury
Recovery
Myelin figure
Swelling of endoplasmic reticulum and mitochondria
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles, and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria

- Entire cell and its organelles (mitochondria, ER) are markedly swollen.
- There are increased concentrations of water, sodium, and chloride and a decreased concentration of potassium.
- If oxygen is restored, all of these disturbances are reversible.

- If ischemia persists, irreversible injury and death occurs.
- Irreversible injury is associated with severe swelling of mitochondria, extensive damage to plasma membranes (myelin figures), and swelling of lysosomes.
- Massive influx of calcium into the cell.

- Death is mainly by necrosis, but apoptosis also occurs (release of pro-apoptotic molecules from leaky mitochondria).
- The cell's components are progressively degraded, and there is widespread leakage of cellular contents and enzymes into the extracellular space and entry of extracellular molecules.

- Finally, the dead cells may become replaced by myelin figures.
- These are then either phagocytosed by leukocytes or degraded further into fatty acids.
- Leakage of intracellular enzymes and other proteins extracellularly and then into the blood provides important clinical indicators of cell death e.g. elevated serum levels of cardiac muscle CKMB and Troponin are early signs of myocardial infarction

- **Ischemia-Reperfusion Injury :**
- If cells are reversibly injured, the restoration of blood flow can result in cell recovery.
- However, under certain circumstances, the restoration of blood flow to ischemic tissues results in accelerated injury.
- This is called ischemia-reperfusion injury.

- This may contribute significantly to tissue damage in myocardial and cerebral infarctions.
- Several mechanisms may be responsible for this.

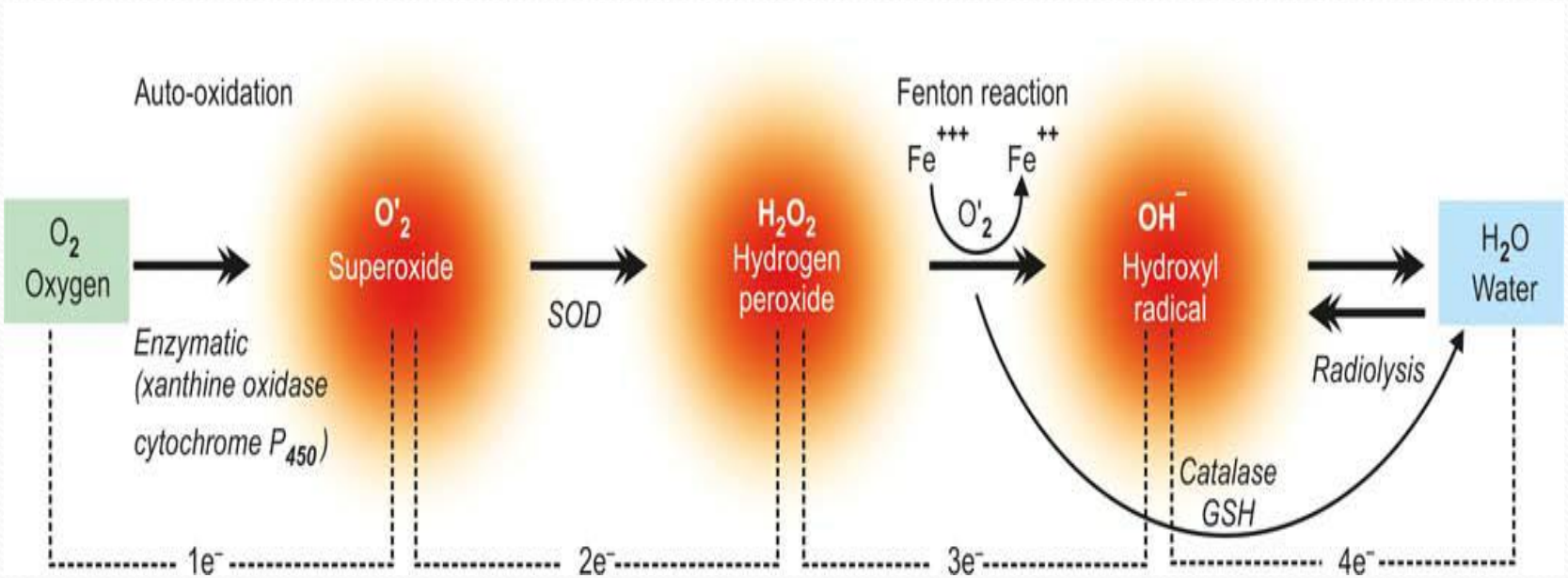
1. **Oxidative stress:**

a. When the supply of oxygen is increased, there may be a corresponding increase in the production of ROS.

b. Cellular antioxidant defense mechanisms might also have been compromised by ischemia, favoring the accumulation of free radicals.

2. **Ischemic injury** is associated with inflammation, which may increase with reperfusion because of increased influx of leukocytes and plasma proteins.

- Leukocytes utilize oxygen quickly (oxygen burst) and release large excess of ROS.



3. Activation of the complement system may contribute to ischemic-reperfusion injury.

- The complement system is involved in host defense and is an important mechanism of immune injury as well.

- Some IgM antibodies have tendency to deposit in ischemic tissues (unknown reasons), and when blood flow is resumed, complement proteins bind to these antibodies, are activated, and cause more cell injury and inflammation (classical pathway).

4. Calcium overload

- Upon restoration of blood supply, the ischemic cell is further flushed by the fluid that has more calcium ions.
- The ATP stores of the cell are low.
- This results in further calcium overload on the already injured cells, triggering lipid peroxidation.

When it occurs?

- With short periods of ischemia, reperfusion (and, thus, the resupply of oxygen) completely restores the cell's structural and functional integrity.
- Cell injury in this case is completely reversible.

- With longer periods of ischemia, reperfusion is associated with cell deterioration and death.
- In this case, lethal cell injury occurs during the period of reperfusion.

Chemical (Toxic) Injury :

- Chemical injury remains a frequent problem in clinical medicine.
- Major limitation to drug therapy.
- Many drugs are metabolized in the liver, so liver is a frequent target of drug injury.

- Chemicals induce cell injury by two general mechanisms.

1. Chemicals can injure cells directly by combining with their molecular components.

   e.g. in mercuric chloride poisoning, mercury binds to the sulfhydryl groups of cell membrane proteins (GIT, kidney), causing increased membrane permeability and disturbance in ion transport.

* Cyanide inhibits the mitochondrial cytochrome oxidase and thus inhibits oxidative phosphorylation.

- Other examples of directly cytotoxic chemicals include chemo therapeutic agents used in treatment of cancer, toxic heavy metals such as lead and iron.

2. Most of the toxic chemicals are not biologically active in their original form.

- They must be first converted to active (toxic) metabolites, which then act on target molecules.

- This conversion usually takes place by the cytochrome P-450 oxidases in the smooth ER of the liver and other organs.
- During this conversion the active toxic metabolite causes cell injury by production of ROS.

- For example CCl_4, (dyeing and dry cleaning industry) is converted by cytochrome P-450 to the highly reactive free radical $^{\cdot}CCl_3$ (active metabolite), which causes lipid peroxidation and damages many cellular structures.

- Acetaminophen (Paracetamol) an analgesic, also converted to a toxic product during detoxification in the liver, leading to cell injury if ingested in heavy doses.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