
**كلية : التربية للعلوم الصرفة**

**القسم او الفرع : علوم الحياة**

**المرحلة: دكتوراه**

**أستاذ المادة : ا.م. د.لؤي حاتم علي**

**اسم المادة باللغة العربية : علم النسج المرضية**

**اسم المادة باللغة الإنكليزية : histopathology**

**اسم المحاضرة الأولى باللغة العربية: الضرر الخلوي**

**اسم المحاضرة الأولى باللغة الإنكليزية : Cell Injury**

**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.**

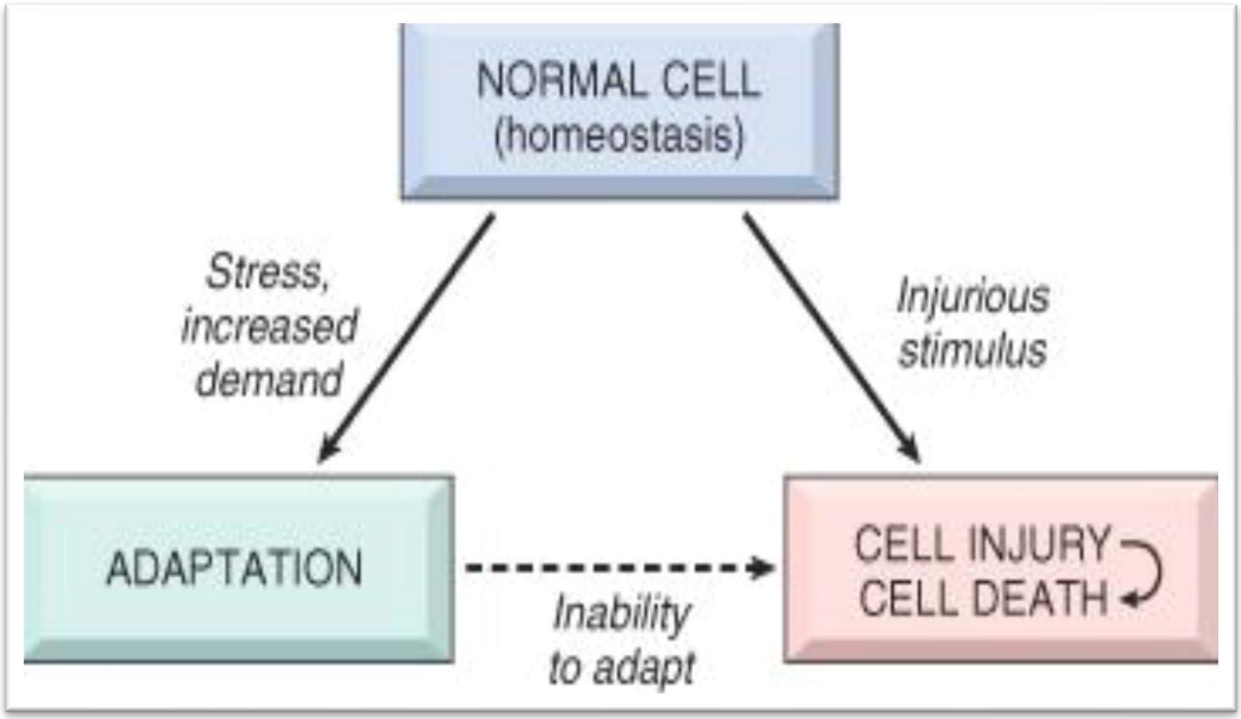
**If the injury is too severe ("irreversible injury"), the affected cells die.**

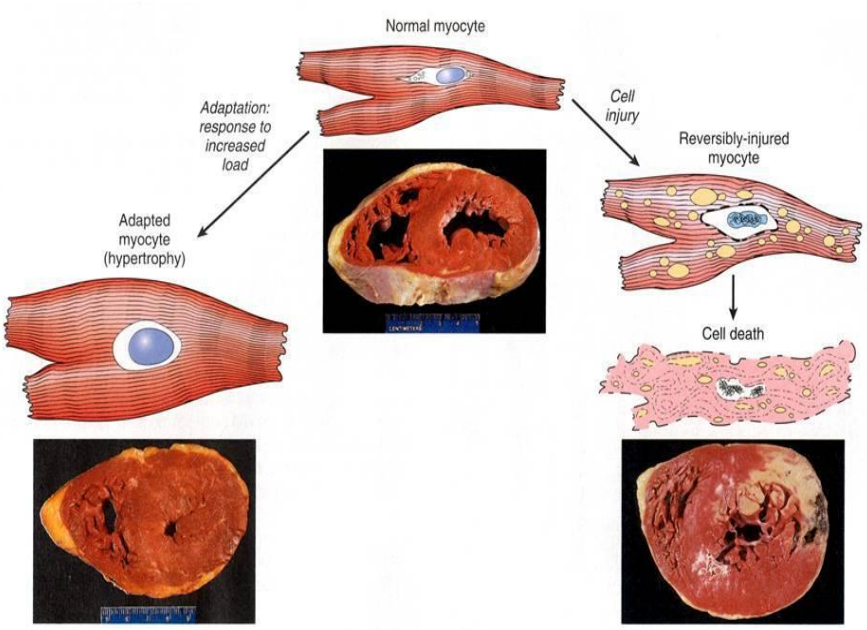
**Damage or alteration of one or more cellular components**

**1 .Many types of injury are tissue-specific because of anatomic relationships and tissue response to chemical and infectious agents.**

**2. Cell injury disrupt cell physiology; so the cell does not function at full capacity**

**Stages in the cellular response to stress and injurious stimuli:**






**Principles:**

**.Human disease occurs because of injury to cells/tissue**

**.Most human disease results from injury to epithelium**

**Injury to one tissue usually affects the adjacent or underlying tissue as .well**

**Cell injury produces morphologic changes.**

**Causes of Cell Injury:**

**1-Hypoxia and ischemia**

**2-Chemical agents**

**3-Physical agents**

**4-Infections**

**5-Immunological reactions**

**6-Genetic defects**

**7-Nutritional defects**

**8-Aging**

**9-Free radical injury**

**General Biochemical Mechanisms:**

**1. Loss of energy (ATP depletion, O2depletion)**

**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).***

**HYPOXIC CELL INJURY:**

**A. Causes.** Hypoxic cell injury results from cellular **anoxia** or **hypoxia,** which in turn results from various mechanisms, including:

**1. Ischemia** (obstruction of arterial blood flow), which is the most common cause.

**2. Anemia,** which is a reduction in the number of oxygen-carrying red blood cells.

**3. Carbon monoxide poisoning,** which results in diminution in the oxygen-carrying capacity of red blood cells by chemical alteration of hemoglobin.

**4. Decreased perfusion of tissues by oxygen-carrying blood,** which occurs in cardiac failure, hypotension, and shock.

**5. Poor oxygenation of blood** secondary to pulmonary disease.

**B. Early stage.** Hypoxic cell injury first affects the mitochondria, with resultant decreased **oxidative phosphorylation** and ***adenosine triphosphate (ATP) synthesis***. Consequences of **decreased ATP availability** include:

**1. Failure of the cell membrane pump**

**a. Cellular swelling,** or **hydropic change,** is characterized by the presence of large vacuoles in the cytoplasm.

**b. Swelling of the endoplasmic reticulum is one of the first ultrastructural changes evident in reversible injury.**

**c. Swelling of the mitochondria** progresses from reversible, low-amplitude swelling to irreversible, high-amplitude swelling, which is characterized by marked dilation of the inner mitochondrial space.

**2. Disaggregation of ribosomes leads to failure of protein synthesis.** Ribosomal disaggregation is also promoted by membrane damage.

**3. Stimulation of phosphofructokinase activity** results in increased glycolysis, accumulation of lactate, and **decreased intracellular pH. Acidification causes reversible clumping of nuclear chromatin.**

**C. Late stage**

**1.** Hypoxic cell injury eventually results in **membrane damage** to plasma and to lysosomal and other organelle membranes, with loss of membrane phospholipids.

**2.** Reversible morphologic signs of damage include the formation of:

**a. Myelin figures,** whorl-like structures probably originating from damaged membranes.

**b. Cell blebs,** a cell surface deformity most likely caused by disorderly function of the cellular cytoskeleton.

**D. Cell death.** Finally, **cell death** is caused by severe or prolonged injury.

**1.** The **point of no return** is marked by **irreversible damage to cell membranes,** leading to **massive calcium influx, extensive calcification of the mitochondria,** and **cell death.**

**2. Intracellular enzymes and various other proteins are released** from necrotic cells into the circulation as a consequence of the loss of integrity of cell membranes. This phenomenon is the basis of a number of useful laboratory determinations as indicators of necrosis.

**a. Myocardial enzymes in serum.** .

**(1)** Enzymes that have been useful in the diagnosis of myocardial infarction **("heart attack)** include the following:

**(a) Aspartate aminotransferase (AST,** previously known as **SGOT)**

**(b) Lactate dehydrogenase (LDH)**
**(c) Creatine kinase (CK,** also known as **CPK)**

**b. Liver enzymes in serum.** Enzymes of special interest include the transaminases **(AST** and **alanine aminotransferase [ALT]), alkaline phosphatase,** and γ**-glutamyltransferase (GGT).**

**3.** The **vulnerability of cells to hypoxic injury varies** with the tissue or cell type. Hypoxic injury becomes irreversible after:

**a. 3–5 minutes for neurons.** Purkinje cells of the cerebellum and neurons of the hippocampus are more susceptible to hypoxic injury than are other neurons.

**b. 1–2 hours for myocardial cells and hepatocytes**
**c. Many hours for skeletal muscle cells**

## FREE RADICAL INJURY

**A. Free radicals**

**1.** These molecules have a **single unpaired** electron in the outer orbital.
**2.** Examples include the activated products of oxygen reduction, such as the superoxide **(O2· )** and the hydroxyl **(OH·)** radicals

**B. Mechanisms that generate free radicals**

**1. Normal metabolism**

**2. Oxygen toxicity,** such as in the alveolar damage that can cause adult respiratory distress syndrome or as in retrolental fibroplasia (retinopathy of prematurity), an ocular disorder of premature infants that leads to blindness

**3. Ionizing radiation**

**4. Ultraviolet light**

**5. Drugs and chemicals,** many of which promote both proliferation of the smooth endoplasmic reticulum (SER) and induction of the P-450 system of mixed function oxidases of the SER. Proliferation and hypertrophy of the SER of the hepatocyte are classic ultrastructural markers of barbiturate intoxication.

**6. Reperfusion after ischemic injury**.

**C. Mechanisms that degrade free radicals**

**1. Intracellular enzymes,** such as glutathione peroxidase, catalase, or superoxide dismutase

**2. Exogenous and endogenous antioxidants,** such as **vitamin A, vitamin C, vitamin E,** cysteine, glutathione, selenium, ceruloplasmin, or transferrin.

**3. Spontaneous decay**.

## CHEMICAL CELL INJURY:

Chemical cell injury is illustrated by **the model of liver cell membrane damage induced by carbon tetrachloride** ($CCl_4$).

**A.** In this model, **CCl4** is processed by the P-450 system of mixed function oxidases within the SER, producing the **highly reactive free radical CCl3·.**

**B.** CCl3- diffuses throughout the cell, initiating **lipid peroxidation of intracellular membranes.**Widespread injury results, including:

**1. Disaggregation of ribosomes,** resulting in **decreased protein synthesis.** Failure of the cell to synthesize the apoprotein moiety of lipoproteins causes an accumulation of intracellular lipids **(fatty change).**

**2. Plasma membrane damage,** caused by products of lipid peroxidation in the smooth endoplasmic reticulum, resulting in **cellular swelling** and **massive influx of calcium,** with resultant mitochondrial damage, denaturation of cell proteins, and cell death

## NECROSIS:

### A. General considerations

**1. Necrosis** is one of two contrasting morphologic patterns of tissue death. The other is apoptosis.

**2. Necrosis** is the sum of the ***degradative and inflammatory reactions*** occurring after tissue death caused by injury (e.g., hypoxia, exposure to toxic chemicals); it **occurs within living organisms.** In pathologic specimens, fixed cells with well-preserved morphology are **dead** but not **necrotic.**

**3. Autolysis** refers to degradative reactions in cells caused by intracellular enzymes indigenous to the cell. **Postmortem autolysis** occurs after the death of the entire organism and is not necrosis.

**4. Heterolysis** refers to cellular degradation by enzymes derived from sources extrinsic to the cell (e.g., bacteria, leukocytes).

## Autophagy:

- Autophagy is an intracellular **lysosomal (vacuolar) degradation** process characterized by the formation of double-membrane vesicles, autophagosomes, which sequester cytoplasm.
- It is involved in **growth, survival, development** and **death** of cells.

## REVERSIBLE CELLULAR CHANGES AND ACCUMULATIONS

### Fatty change (fatty metamorphosis, steatosis)

**a.** Fatty change is the **accumulation of intracellular parenchymal triglycerides** and is observed most frequently in the **liver, heart,** and **kidney.** For example, in the liver, fatty change may be secondary to alcoholism, diabetes mellitus, malnutrition, obesity, or poisonings.

**2. Imbalance among the uptake, utilization, and secretion of fat** is the cause of fatty change, and this can result from any of the following mechanisms.

**a. Increased transport of Tg or fatty acids** to affected cells

**b. Decreased mobilization of fat from cells,** most often mediated by decreased production of **apoproteins** required for fat transport.

**c. Decreased use of fat by cells.**

**d. Overproduction of fat in cells.**

### B. Hyaline change:

**1.** This term denotes a characteristic ***(homogeneous, glassy, eosinophilic)*** appearance in hematoxylin and eosin sections.

**2.** It is caused most often by nonspecific accumulations of ***proteinaceous*** material

### C. Accumulations of exogenous pigments

**1. Pulmonary accumulations of carbon (anthracotic pigment), silica, and iron dust**

**2. Plumbism** (lead poisoning)

**3. Argyria** (silver poisoning), which may cause a permanent gray discoloration of the skin and conjunctivae.

## D. Accumulations of endogenous pigments

1. **Melanin**
   a. **Increased melanin pigmentation-** suntanning and variety of diseases.
   b. **Decreased melanin pigmentation** is observed in albinism and vitiligo.

**2. Bilirubin-** causes yellowish discoloration called jaundice.

**3. Hemosiderin-** iron-containing pigment consists of aggregates of ferritin.

***Hemosiderosis*** is accumulation of hemosiderin, primarily within tissue macrophages, **without** associated tissue or organ damage.

***Hemochromatosis*** is ***more extensive*** accumulation of hemosiderin, often within parenchymal cells, with accompanying ***tissue damage***, scarring, and organ dysfunction. This condition occurs in both **hereditary (primary)** and **secondary** forms.

## Con'd

-Hereditary hemochromatosis is most often caused by a mutation in the Hfe **gene on chromosome 6.**

**(i)** Hemosiderin deposition and organ damage in the liver, pancreas, myocardium, and multiple endocrine glands is characteristic, as well as melanin deposition in the skin.

**(ii)** This results in the triad of **micronodular cirrhosis, diabetes mellitus,** and

**skin pigmentation.** This set of findings is referred to as **"bronze diabetes."**

Laboratory abnormalities of note include marked elevation of the serum

transferrin saturation because of the combination of **increased serum iron** and **decreased total iron-binding capacity (TIBC).**

**-Secondary hemochromatosis** is most often caused by **multiple blood transfusions** administered to subjects with hereditary hemolytic anemias such as thalassemia major.

## 4. Lipofuscin/end product

**a.** This yellowish, fat-soluble pigment is an **end product of membrane lipid peroxidation.**

**b.** It is sometimes referred to as **"wear-and-tear"** pigment.

**c.** It commonly accumulates in elderly patients, in whom the pigment is found most often within hepatocytes and at the poles of nuclei of myocardial cells. The combination of lipofuscin accumulation and atrophy of organs is referred to as **brown atrophy**

## E. Pathologic calcifications

### 1. Metastatic calcification

**a. The cause of metastatic calcification is hypercalcemia.**

**b.** Hypercalcemia most often results from any of the following causes:

**(a)** Hyperparathyroidism.

**(b)** Osteolytic tumors with resultant mobilization of calcium and phosphorus.

**(c)** Hypervitaminosis D

**(d)** Excess calcium intake, such as in the milk-alkali syndrome (nephrocalcinosis and renal stones caused by milk and antacid self-therapy).

## 2. Dystrophic calcification

**a.** Dystrophic calcification is defined as **calcification in previously damaged tissue,** such as areas of ***old trauma, tuberculosis lesions, scarred heart valves, and atherosclerotic lesions*****.**

**b.** The cause is **not** hypercalcemia; typically, the serum calcium concentration is normal.

**DISORDERS CHARACTERIZED BY ABNORMALITIES OF PROTEIN FOLDING.**

- These disorders involve ***failure of protein*** structural stabilization or degradation by specialized proteins known as **chaperones.** Important chaperones include **heat shock proteins/HSP/** induced by stress, one of which is **ubiquitin**, which ***marks*** abnormal proteins for degradation.

**B. Two known pathogenetic mechanisms include:**

**1. Abnormal protein aggregation,** which is characteristic of ***amyloidosis***; a number of neurodegenerative diseases, such as ***Alzheimer disease, Huntington disease,*** and ***Parkinson disease;*** and perhaps ***prion diseases***, such as **"mad cow"** disease.

**2. Abnormal protein transport and secretion,** which is characteristic of ***cystic fibrosis*** and ***1-antitrypsin deficiency.***