CELL DAMAGE, INJURY, DEATH, AND ADAPTATION

I. Cell damage, adaptation and cellular response to injury
II. Reversible and Irreversible cell injury

CELL DAMAGE, ADAPTATION AND CELLULAR RESPONSE TO INJURY

Cells, as active biological and physiological units, operate to achieve different functions on all levels. These activities are continuously controlled and coordinated to maintain the "constant or balanced" body state, i.e. *homeostasis* (homo-= similar & -stasis=steady).
Therefore, cells require continual supply of energy, an intact plasma membrane, proper cellular activities, genomic integrity and controlled cell division.

Once cells are exposed to a "stressor" or "pathological" factor in their internal or external environment, they respond; adjust their size, number, metabolic activities, morphology or operations to maintain the stable internal homeostatic state. These responses are termed: **physiological ADAPTATION**
Adaptation is a temporary state; cells retain their "normal" state once the stressor effect is removed or cease.

When the stressor effect exceeds cells adaptive capacities; CELL INJURY takes place.

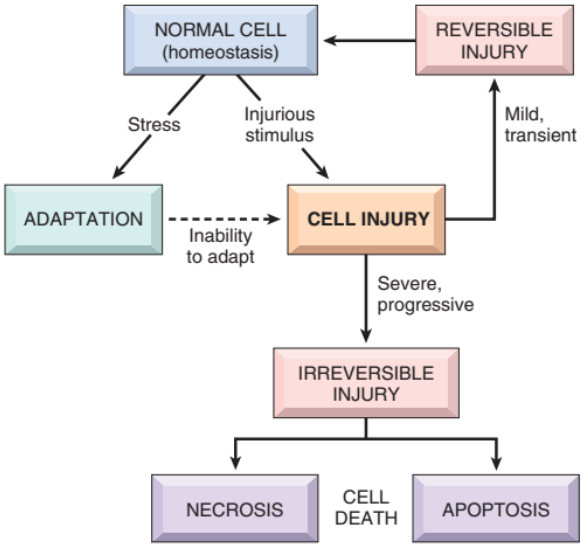
Cellular response may be:

- Cellular adaptations: *Hypertrophy*, *Hyperplasia*, *Atrophy* and *Metaplasia*
- Reversible cell injury: injury is mild to moderate
- Irreversible cell injury (cell death or *necrosis*)
- Intracellular accumulations

Cellular adaptations
Cellular adaptation may be either: *physiologic* (normal) or *pathologic* (abnormal).

Physiological adaptations represent tissue responses to normal stimulation, which may be initiated by hormones or endogenous chemical mediators (hormone-induced breast enlargement); or due to increased mechanical stress on muscles or bones for example.

Pathological adaptations when cells and tissues modulate their size, structure, and function to avoid or minimize further or permanent damage or injury.



Morphological adaptations may be:

Hypertrophy

Increase in the **SIZE** of non-dividing cells, where increased demand or stimulation leads to increase in protein synthesis, size, and the number of intracellular organelles; thereby, the whole tissue or organ. It doesn't involve increase in cells number.

As an adaptive response, hypertrophy may be physiologic; as in hypertrophy is muscular hypertrophy in response to exercise where muscle fibers increase their diameter and accumulate extra structural contractile proteins. Pathologic hypertrophy occurs as a response to an abnormal stressor as seen in an increase in cardiac hypertrophy, when the size of the cardiac muscles and thereby the heart enlarge significantly due to hypertension or a diseased valve that increase resistance as in aortic stenosis.

Hyperplasia

Hyperplasia describes an increase in the **NUMBER** of cells, which gradually increases the organ's size as more **NEW** cells are produced.

Hyperplasia is seen in tissue cells that can divide (mitosis); also called labile cells. Commonly in response to hormonal stimulation, inflammation, or physical trauma. Examples of these cells are epithelial cells of the skin, the mouth, intestine, genito-urinary tract, and also epithelial cells of the duct of exocrine and salivary glands as well as hematopoietic cells of the bone marrow.

Unlike neoplastic cellular proliferation; hyperplasia is generally stimulus-controlled cells overgrowth: i.e. one the causative stimulus is removed it subsides, whereas, in neoplasia, cell proliferation continues even after the removal of the stimulus.

Hyperplasia may also be physiologic or pathologic:

Physiologic hyperplasia

Hormonal hyperplasia: as seen in epithelial cells proliferation of the glandular ducts of the female breast during puberty and pregnancy.

Compensatory hyperplasia: when a residual portion the tissue initiates regeneration by restoring mitotic activity in its cell in order to replace or restore a diseased or resected part of the tissue or organ as seen in the liver, where hyperplasia and regeneration start as early as 12 hours after resection.

Pathologic hyperplasia may be caused by internal factor such as excessive hormonal or growth factor stimulation as seen in endometrial hyperplasia due to excess estrogen hormones and in benign prostatic hyperplasia (BPH) due to excess androgens.
Additionally, it may be caused by exogenous factors as in certain viral infections; f. ex., skin or genital warts caused by papillomaviruses and hyperplastic candidiasis caused by Candida albicans infection.

Pathologic hyperplastic lesions in the oral cavity, are commonly reactive lesions in response to a low-grade irritation or injury. These include hyperplastic pulpitis resulting from chronic pulpal inflammation due to open carious defect and mucosal lesions such as irritation fibroma, pyogenic granuloma, peripheral giant cell granuloma, inflammatory papillary hyperplasia and drug-induced gingival overgrowth (DIGO), as in Anticonvulsants (Phenytoin), Calcium Channel Blocker (CCB) and Immunosuppressants (Cyclosporin).
đ - All oral hypertrophic and hyperplastic lesions clinically present as tissue enlargements. The distinction between the two is confirmed by histopathology.

Atrophy

Shrink in the **SIZE** of cells due to the loss of cell substance. The atrophied cells are alive and not dead but their reserved function is largely reduced. This may result from reduced workload (limb immobilization after fractures), nerve damage, reduced blood supply, inadequate or lack of nutrition, loss of endocrine stimulation, and aging (senile atrophy).

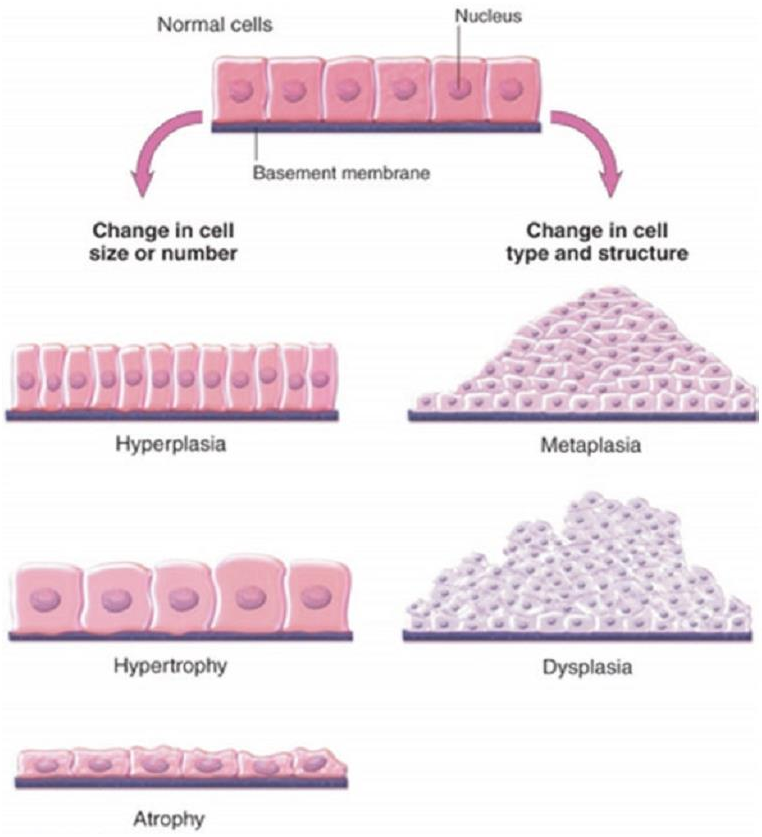
Metaplasia

Metaplasia is a REVERSIBLE CHANGE of one adult epithelial or mesenchymal *cell type* to another adult epithelial or mesenchymal cell type in the same tissue. Generally, its considered as a protective mechanism to compensate the effect of persistent cellular trauma.
The classical examples are seen in smokers, where the normal ciliated columnar epithelial cells of the respiratory epithelium is replaced by stratified squamous epithelial cells (flattening) and the change of stratified squamous epithelial cells into goblet cells in the esophagus due

to continued acid reflux (Barrett's esophagus). However, metaplasia may also result from a change in the pH, excessive hormones stimulation, or alcohol. Metaplasia can occur in salivary gland tumors.

The term **Dysplasia**, sometimes called "atypical hyperplasia" is not a true type of adaptation, rather it refers to a state of *disturbed cellular development*. Commonly this type of cellular change takes place prior to or with metaplasia. It involves reversible changes in cellular shape, size, and organization.

Although dysplasia is reversible, if causes persist, then dysplasia progresses to carcinoma in situ or invasive carcinoma.
The cervical and respiratory epithelium are dysplasia-prone tissues and these lesions are strongly associated with cancerous diseases.
Similarly, dysplasia of oral mucosal may potentially produce malignant lesions and lead to the development of oral cancer.



CELLULAR INJURY AND CELLULAR DEATH

Human cells vary in their ability to withstand injury as well as in their ability to regenerate. When the stressors agents induce severe and/or persistent damaging effect on the cell to the limit where these cells cannot adapt and tolerate, cell injury occurs. This results in intrinsic changes and abnormalities, which may be a reversible stage but may end up in cell death.

Etiology of cell injury:

Genetic / congenital causes (Heritable and non-heritable factors)

Acquired causes:

Hypoxia and ischemia.

Hypoxia: partial reduction in O_2 levels in tissues.

Anoxia: complete lack of oxygen in tissues.

Hypoxemia: low levels of O_2 in blood.

Ischemia: reduced blood flow to an organ, which affects both oxygen and substrate delivered to the tissue.

Physical agents (trauma, heat, irradiation)

Chemical agents and drugs (air pollutants, insecticides, CO, asbestos, alcohol)

Microbial agents (Viruses, rickettsia, bacteria, fungi, protozoans and tapeworms).

Immunologic agents (autoimmune reactions tissues and allergic reactions)

Nutritional causes (protein–calorie insufficiency, deficiencies and excess).

Psychogenic diseases.

Ageing

Iatrogenic factors.

Idiopathic diseases

The extent and response to cell injury vary widely depending on:

Type and characteristics of causative factor

Status of the host and tissues involved in the injury.

Mechanisms of cell injury

- **Adenosine Triphosphate (ATP) depletion**

ATP is essential energy source to fuel different cell processes and functions. Reduction in ATP levels affects the normal functions including the plasma membrane Na^+-K^+ pump system and Na^+-Ca^{++} exchange. Failure of this pumping and exchange processes leads to accumulation of Na^+ and Ca^{++} in intracellular compartment and diffusion of K^+ to ECF.

This increases Na+ and water influx into the cell freely causing cellular swelling (Hydropic swelling), dilation of the endoplasmic reticulum, detachment of ribosomes and reducing protein synthesis.
This distortion of normal status is reversible once O2 is restored and the cell resumes its normal pump and exchange system. If O2 is not restored, continuous accumulation of water and Ca++ causes swelling of lysosomes and mitochondria, leading to membrane damage, cytoskeleton disruption, activation of inflammation, DNA degradation and cell death.

- **Loss of Ca++ homeostasis**

The concentration of Ca++ in normal state is higher in ECF than the cytosolic free Ca++ in the cell. Ca normally is stored intracellular in the mitochondria and endoplasmic reticulum. Ca++ influx and leakage from damaged mitochondria and ER, cause cytosolic Ca to mediate cell injury by activation of many enzymes which include: Phospholipases: cause cell membrane damage; Proteases: catabolizing the structural & membrane proteins; ATPase: accelerates ATP depletion; Endonuclease: fragmented the genetic material.

- **Defect in plasma membrane permeability.**

Defective plasma membrane permeability leads to changes in the concentrations of different metabolites across the cell membrane.

- **Free Radicals Production**

Cellular metabolism produces many free radicals derived from O2 called reactive oxygen species ROS which includes: superoxide anion (O2-), hydroxyl radical (OH-), Hydrogen peroxide (H2 O2). During cell injury, as in ischemia, ROS accumulated in cell and react with protein, lipids, and carbohydrates, causing plasma membrane damage, enzymes inactivating, and DNA nucleic acid damage. Restoration of oxygen may add additional injury called reperfusion injury or oxidative stress.

- **Mitochondrial damage.**

This is an important cause of irreversible cell injury. In which Oxidative stress and increase in cytoplasmic Ca++ concentration may lead to mitochondria and breakdown of mitochondrial membrane phospholipid by activated phospholipases.

- **Intracellular lactic acidosis**

Intracellular lactic acidosis (low intracellular PH) may be caused by anaerobic glycolytic pathway, which leads to lactic acid accumulation and clumping of nuclear chromatin.

- **Reduced protein synthesis**

Prolonged hypoxia affects the membranes of ER and GA leading to their swelling and detachment of ribosomes from rER. Ribosomes then become dispersed in the cytoplasm and inactivated. This disrupt their normal function leading to reduced protein synthesis in GA.

REVERSIBLE CELL INJURY

When cellular injury occurs for a short period of time as in hypoxia and ischemia, the resulting injurious effects may be reversible once the cell rapidly restores normal circulation.

At earlier stages, the cellular injury is mild, and the alterations in cellular *function* and *morphology* are reversible. The injury at this stage didn't cause plasma membrane damage or affect nuclear integrity severely.

Morphologic changes of reversible cell injury

- **Cellular swelling**

When the cell is shortly injured, plasma membrane changes (such as blebbing) occur with increased permeability causing loss of intercellular attachments.

- **Hydropic change (cloudy swelling or cytoplasmic vacuolation)**

Reversible water accumulation in the cytoplasm of the cell.

- **Mucoid change**

Excessive deposition of mucinous material in epithelial and connective tissues.

- **Fatty change (steatosis)**

Neutral fat accumulation within the cytoplasm of parenchymal cells (fatty metamorphosis). Commonly in the liver, possibly in other organs such as heart, skeletal muscles and kidneys.

- **Hyaline change**

Glassy, homogeneous, eosinophilic appearance of protein material using H&E stain.

- **Mitochondrial changes**

Swelling and appearance of phospholipid-rich amorphous densities

- **Dilation of the ER with detachment of ribosomes**
- **Nuclear alterations**

clumping of chromatin.

- **Myelin figures**

Collections of phospholipids in the cytoplasm similar to myelin sheaths