# Growth disturbance & Cell Injury

## Cellular Responses to Harmful Stimuli:

Each cell in the body is designed to carry out a specific function or functions, which is dependent on its metabolic pathways. The ability of all parts of the cell to maintain dynamically stable state is referred to as homeostasis. If cells encounter more severe changes (physiological or pathological), they can modify the homeostatic state and achieve a new steady state to counteract the noxious effects of these changes. These changes are referred to as **adaptation. The aim behind these adaptations is to avoid cell injury and death.**

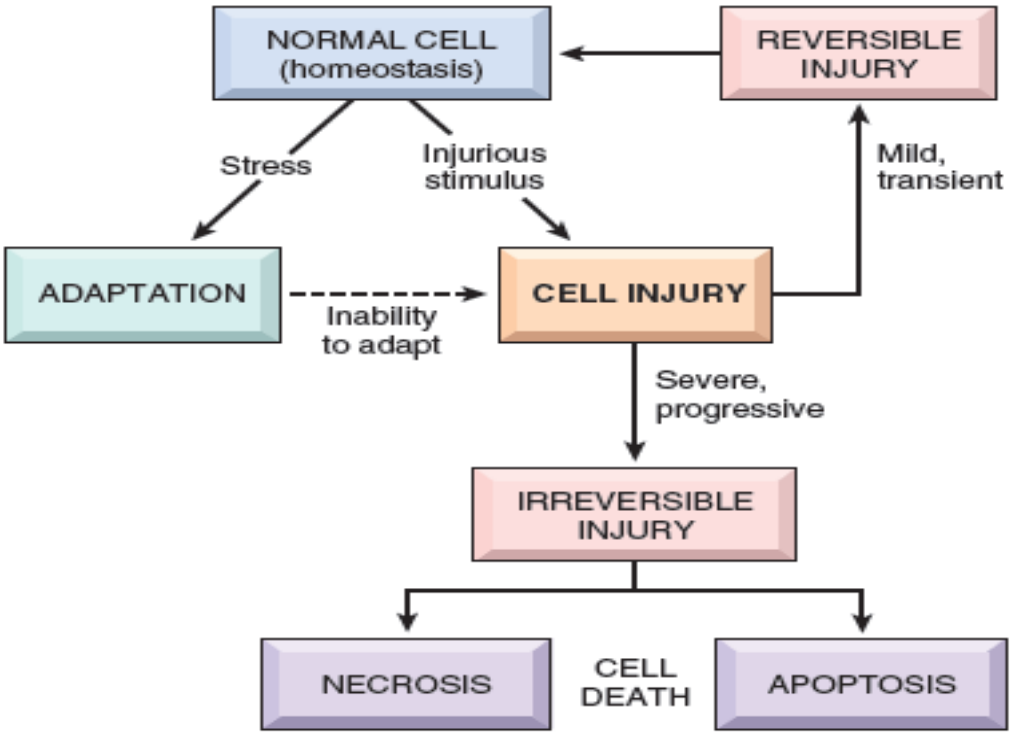



**Figure (1): stages of cellular responses to stress and harmful stimuli**

**Table (1): Cellular Responses to Injury**

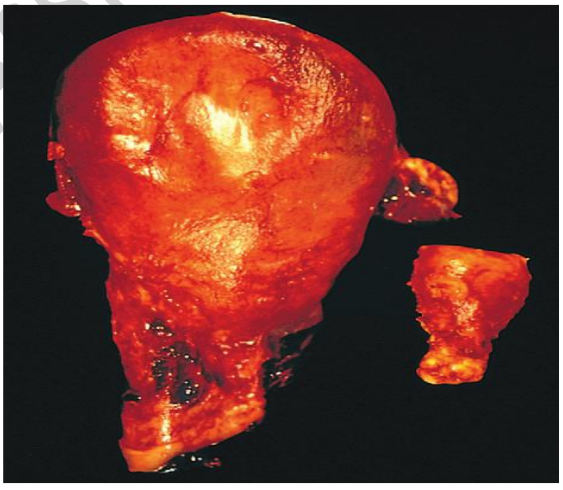
| Nature of Injurious Stimulus | Cellular Response |
|---|---|
| Altered physiologic stimuli; some nonlethal injurious stimuli | Cellular adaptations |
| Increased demand, increased stimulation (e.g., by growth factors, hormones) | Hyperplasia, hypertrophy |
| Decreased nutrients, decreased stimulation | Atrophy |
| Chronic irritation (physical or chemical) | Metaplasia |
| Reduced oxygen supply; chemical injury; microbial infection | Cell injury |
| Acute and transient | Acute reversible injury<br>Cellular swelling fatty change |
| Progressive and severe (including DNA damage) | Irreversible injury → cell death<br>Necrosis<br>Apoptosis |



## Cellular Growth Adaptation and Differentiation:

**Adaptation** means reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment. The adaptation of a certain tissue falls into several medical forms:

- **Hypertrophy:** refers to an increase in the size of cells, which result in an increase in the size of the affected organ. It occurs due to increase production of cellular proteins. It could be physiologic and pathologic.



**Physiologic hypertrophy of the uterus during pregnancy**

- **Hyperplasia:** is defined as an increase in the number of cells in an organ or tissue in response to a stimulus. It is the result of growth factor-driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells.

  **Note:** hyperplasia and hypertrophy are distinct processes, they frequently occur together, and may be triggered by the same external stimulus.
  Hyperplasia can only take place if tissue contains cells capable of dividing; thus increasing the number of cells. It can be physiological and pathological.

  1. **Physiologic Hyperplasia:**
     Is due to the action of hormones or growth factors occurs in several circumstances: when there is a need to increase functional capacity of hormone sensitive organs; when there is need for compensatory increase after damage or resection.
     (**eg:** enlargement of the uterus during pregnancy due estrogen – stimulated smooth muscle hypertrophy and hyperplasia)

  2. **Pathologic Hyperplasia:**
     Most forms of pathologic hyperplasia are caused by excessive or inappropriate actions of hormones or growth factors acting on target cells.
     (**eg: endometriosis**, an excessive estrogen stimulation of the uterine endometrium that will result with abnormal uterine bleeding. **Benign prostatic hyperplasia**, caused by excessive androgen stimulation)

- **Atrophy:** is defined as a reduction in the size of an organ or tissue due to a decrease in cell size and number. It can be either physiologic or pathologic.

1. **Physiologic Atrophy:** is common during normal development like decrease in the size of the uterus that occurs shortly after parturition.

2. **Pathologic Atrophy:** it has several causes and it can be local or generalized. The common causes of atrophy are the following:
    - **Atrophy of Disuse (decreased workload):** prolonged immobilization or decreased activity of the affected organ or tissue. (eg: wasting of the skeletal muscle after bone fracture).
    - **Denervation Atrophy (loss of nerve supply):** damage to the nerve supply (eg: poliomyelitis results from atrophy of muscle fibers due nerve damage)
    - **Ischemic Atrophy (diminished blood supply):** due to decrease in blood supply which leads to shrinkage of the affected organ. (eg: obstruction of the renal artery leads to atrophy of the kidney, and brain atrophy due to cerebrovascular disease).
    - **Starvation Atrophy (Inadequate nutrition):** a reduction in carbohydrates, fats and proteins with general weakness. (eg: cancer)
    - **Endocrine Atrophy (loss of endocrine stimulation):** loss of endocrine regulatory mechanism. (eg: loss of estrogen stimulation after menopause results in physiologic atrophy of endometrium, vaginal epithelium and breasts).
    - **Pressure Atrophy:** tissue compression for any length of time can cause atrophy. (eg: enlarged tumor can cause atrophy of the surrounding tissues).

In histopathological microscopic examination, there are 2 types of tissue atrophy:

- **Fatty Atrophy:** the atrophic parenchyma is replaced with fatty tissue (hassals corpuscles) (eg: thymus gland and salivary gland)

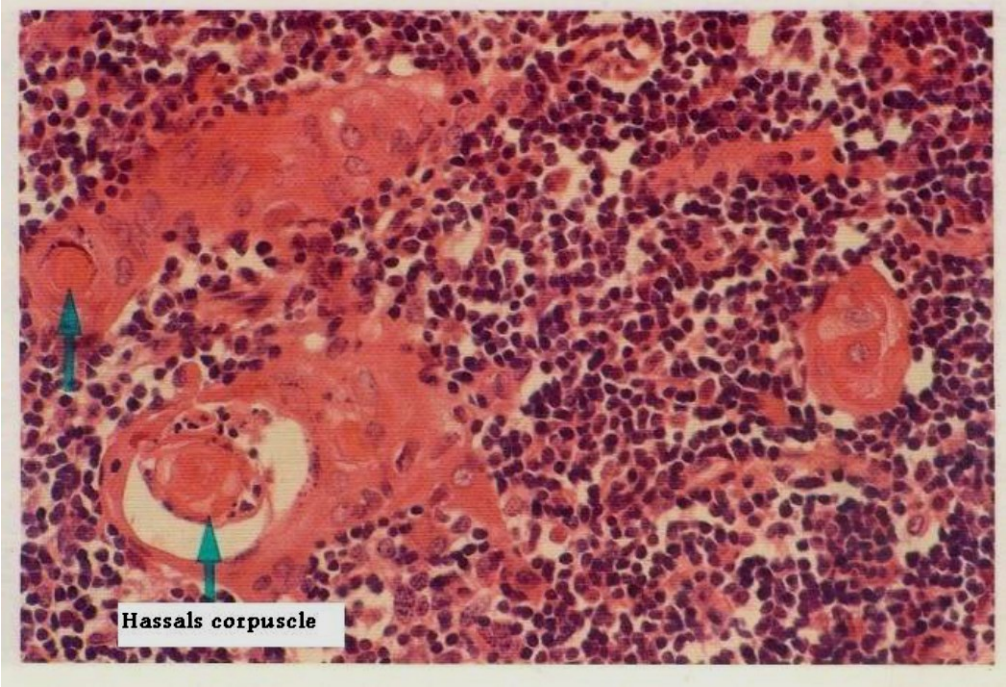



**Figure (2): a section of atrophic thymus gland with fatty tissue**

- **Brown Atrophy:** the atrophic cells accumulate brown pigment (lipofuscin) pigment, under microscope this pigment can be seen close to the nuclei. (eg: heart and liver)

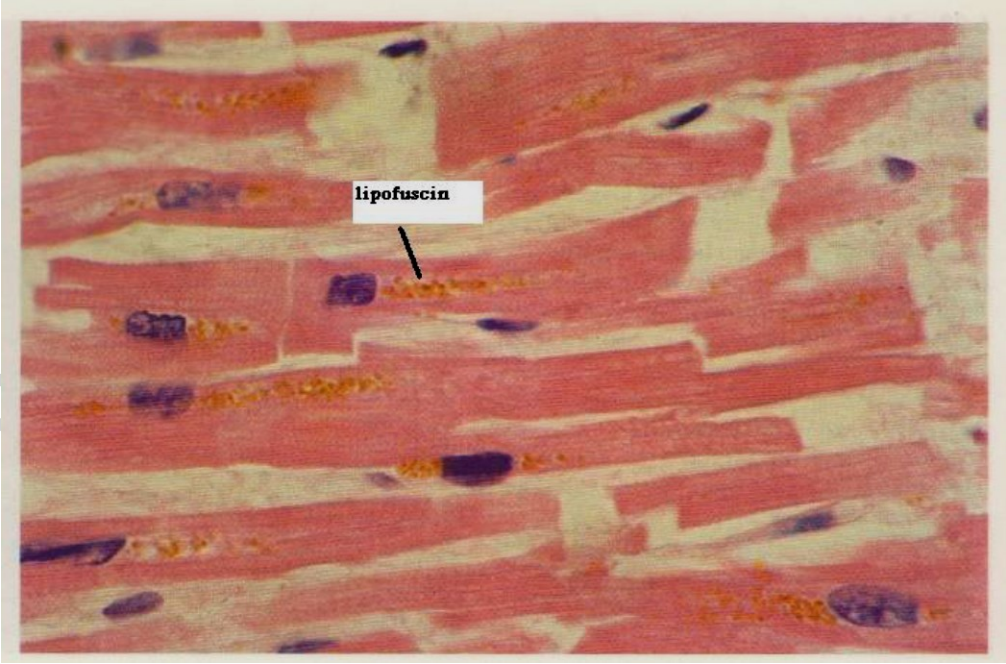
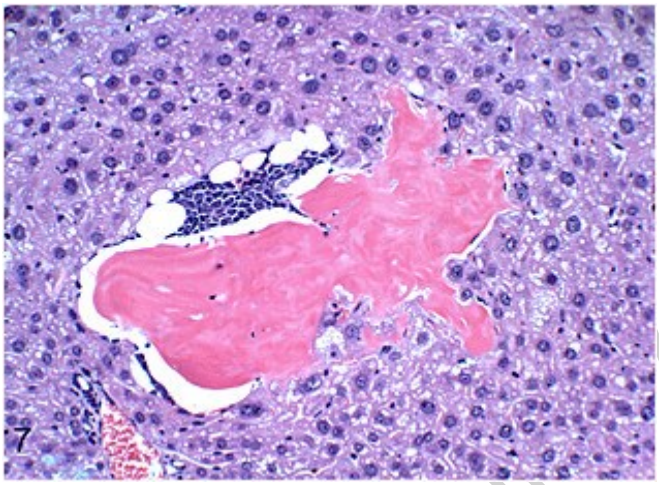
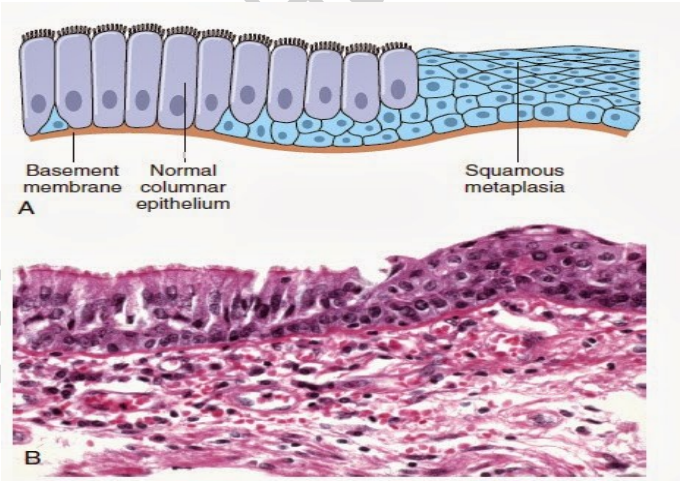



**Figure (3): a section of the myocardium with brown atrophic tissue**

- **Metaplasia:** is a reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. It is of two types:
    1. **Squamous metaplasia:** is the replacement of one type of epithelium by squamous epithelium. (eg: the columnar epithelium of the bronchus is replaced by squamous epithelium in cigarette smokers).
    2. **Osseous metaplasia:** is the replacement of connective tissue by bone. (eg: liver, testis, thyroid gland, bone marrow, … etc)



**Osseous Metaplasia of the Liver**




**Squamous Metaplasia of the Bronchus at the right side of section A & B**

## Cell Injury:

It can be defined as a sequence of events that occur if the limits of the adaptive responses are exceeded or if cells are exposed to injurious agents or stress, deprived of essential nutrients, or become compromised by mutations that affect essential cellular constituents. It could be:

- **Reversible (adaptation)**
- **Irreversible (cell death), this is done either by *Necrosis* or *Apoptosis***

**Causes of Cell Injury:**

- **Hypoxia:** oxygen deprivation, which can be caused by ischemia (reduced blood supply).
- **Physical agents:** like external trauma (burn, radiation, electrical shock)
- **Chemical agents and Drugs:** poisons (arsenic, cyanide and mercuric salt), environmental and air pollutant (CO, asbestos, insecticides, herbicides) and certain drugs
- **Infectious agents:** parasites, bacteria and fungi
- **Immunologic reactions:** immunological reaction to foreign antigen like viruses and some environmental substances
- **Genetic abnormalities:** defects in chromosomes at the level of DNA like Down syndrome
- **Nutritional imbalance:** like anorexia nervosa

**Mechanisms of Cell Injury:**

1. Depletion of ATP
2. Mitochondrial damage
3. Influx of intracellular calcium and loss of calcium homeostasis
4. Accumulation of oxygen-derived free radicals (oxidative stress)
5. Defects in membrane permeability

**Necrosis:**

It is un-programed and unregulated form of cell death where there are morphological changes in the cell membrane and intracellular components which will result in either fatty changes or cellular swelling. These morphological changes may include:

- Plasma membrane alteration
- Mitochondrial changes
- Dilation of the endoplasmic reticulum
- Nuclear alteration

**Apoptosis:**

It is also called a programed cell death. It is a regulated process characterized by nuclear dissolution, fragmentation of the cell without loss of membrane integrity and then rapid removal cellular debris by phagocytosis.

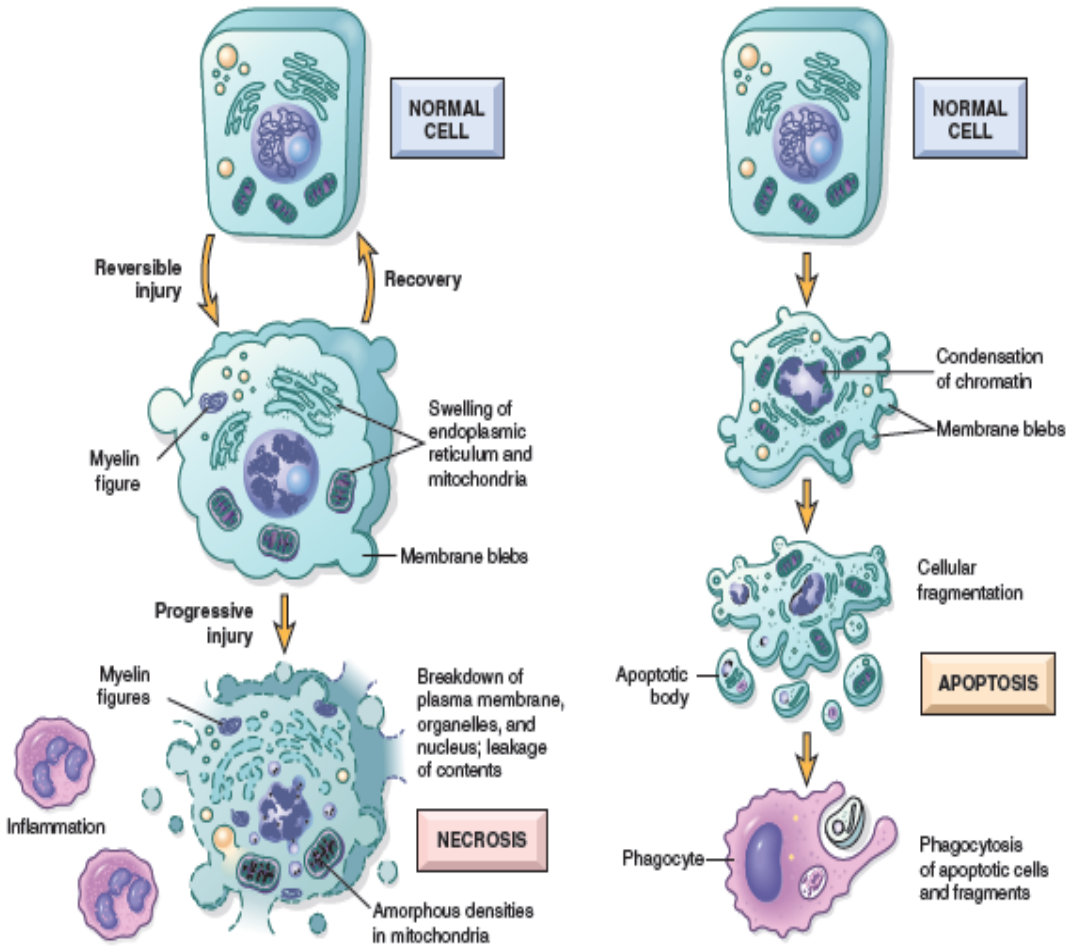



**Figure (4):** schematic illustration of the morphologic changes in cell injury resulting in necrosis or apoptosis

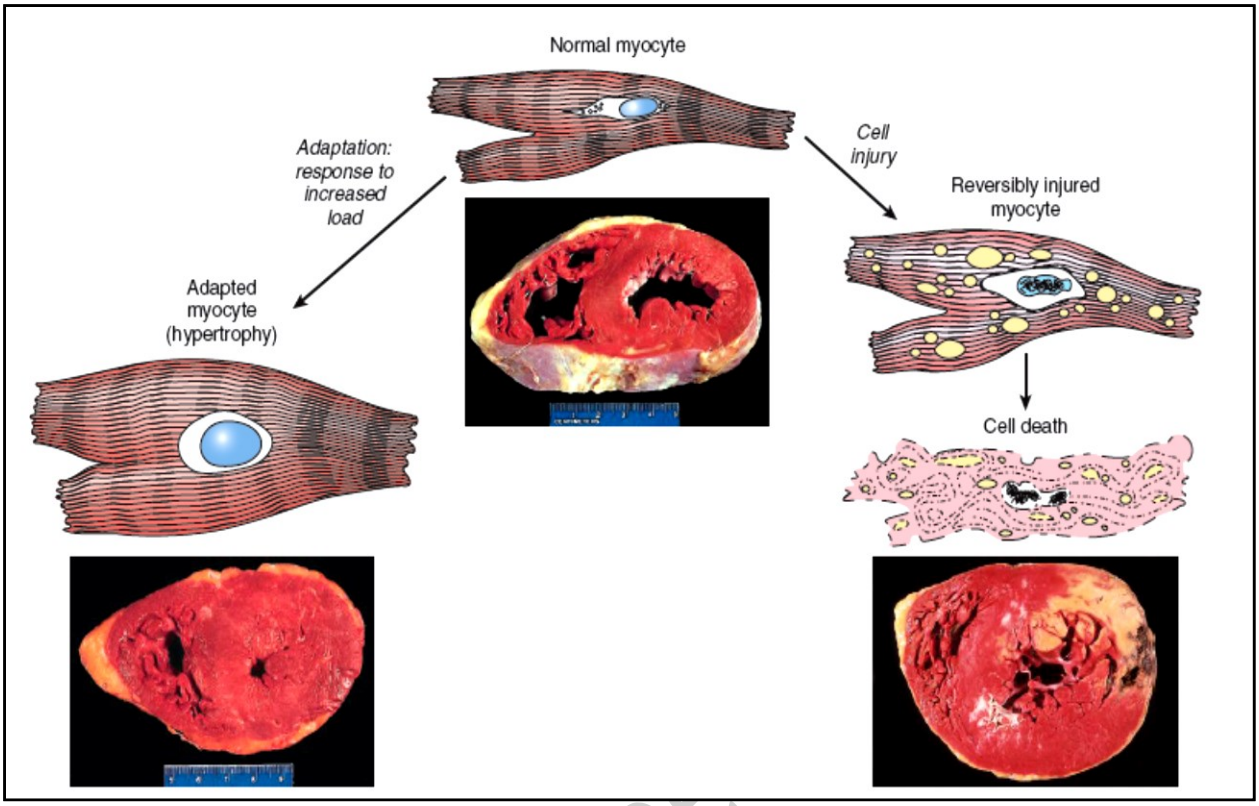



**Figure (5):** The relationship between normal, adapted, reversibly injured, and dead myocardial cells.