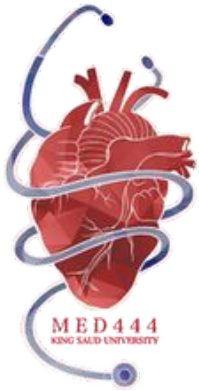


PATHOLOGY TEAMWORK

MED444

Cell Injury I

Adaptation to cell injuries

Editing File :

Color index:

Main text (Black)

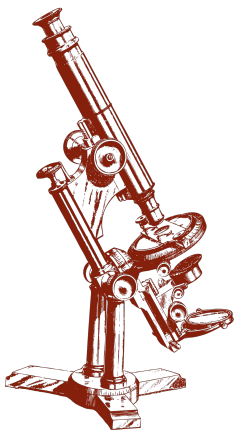
Female slides (pink)

Male slides (blue)

Important (red)

Dr's note (green)

Extra Info (grey)



Objectives

- Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
- Is aware of the concept of hypoxic cell injury and its major causes.
- Understand the definitions and mechanisms of free radical injury.

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Cellular adaptation

As cells encounter (face) **physiologic stresses** (such as increased workload in the heart)(or pathological stress), they can undergo **adaptation**, achieving a new steady state and preserving viability and function.

- **Adaptations** are reversible changes that happens in response to changes in the cell's environment.

Physiologic adaptations	**Physiologic adaptations**: usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators. Example: -The enlargement of the breast caused by hormone during pregnancy. -The demands during mechanical stress (an example is the hypertrophy of muscle cells in response to resistance such as lifting weights 💪).
Pathologic adaptations	**Pathologic adaptations**: are responses to stress that allow cells to modulate their structure and function and thus escape injury, but at the expense of normal function. Such as: squamous metaplasia of bronchial epithelium in smokers.

cont. Cellular adaptation

- **Homeostasis:** is the state in which the intracellular milieu (environment) of cells is normally regulated and remains constant.
- **Cell injury** develops if:
  A. The adaptive capability of the cell is **exhausted**.
  B. The external stress is **too harmful**
- Within certain limits injury is **reversible** and cells return to normal.
- But, in **severe** or **persistent** stress the injury becomes **irreversible** and leads to **cell death**.
- The **principal adaptive responses are**:
  a. **Hypertrophy**
  b. **Hyperplasia**
  c. **Atrophy**
  d. **Metaplasia**

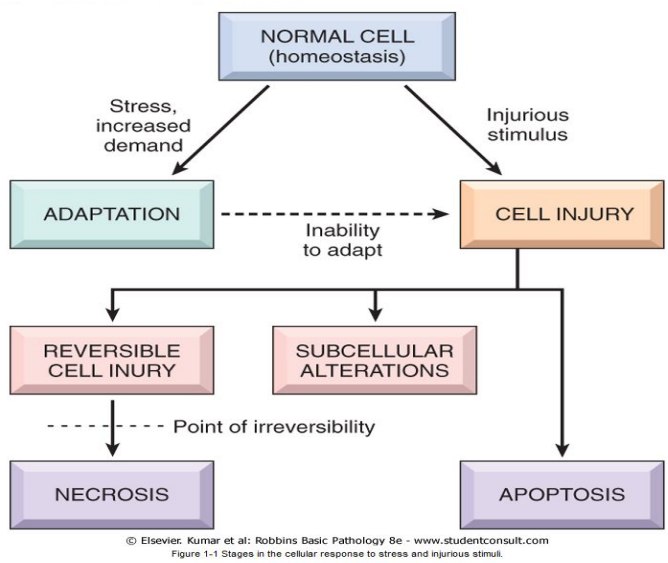

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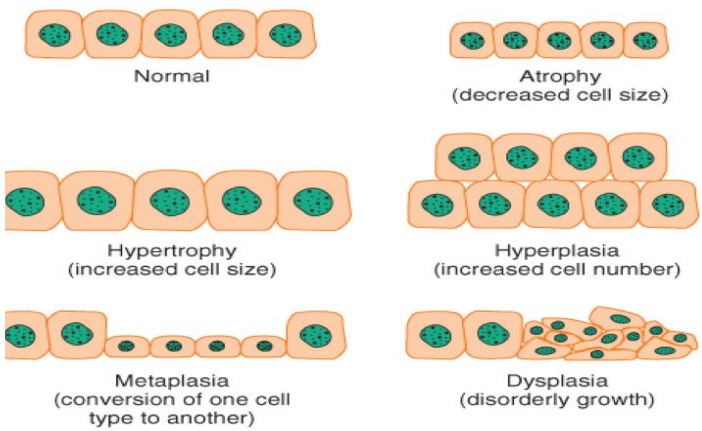
Figure 1-1 Stages in the cellular response to stress and injurious stimuli.



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Hypertrophy

DEFINITIONS

-Hypertrophy is an increase in the size of cells resulting in an increase in the size of the organ.
-There is no new cells.
-Hypertrophy occurs in cells that are incapable of dividing/replication e.g. all types of muscle

Hypertrophy is either physiological or pathological :

Physiological hypertrophy:

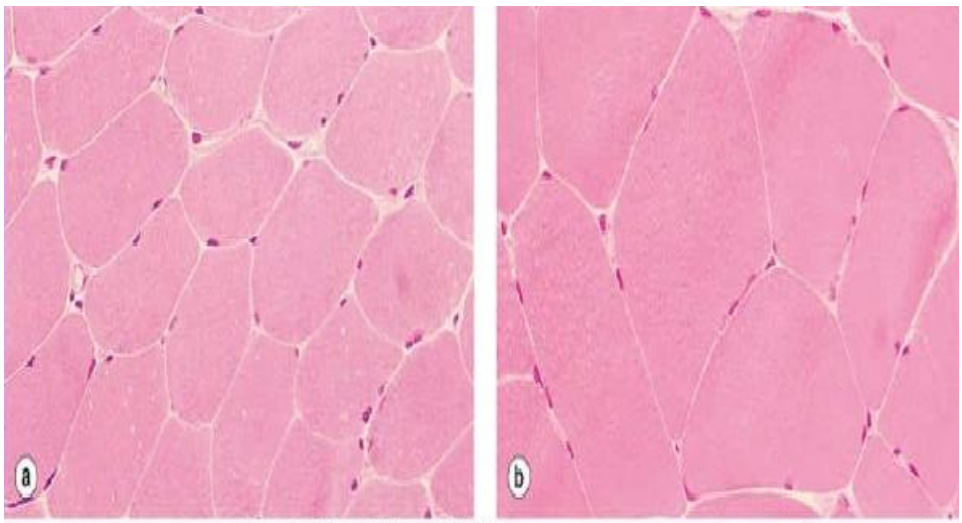
examples:

-The skeletal muscles undergo only hypertrophy in response to increased demand by exercise. (weightlifter).

-The massive enlargement of the uterus during pregnancy occurs because of estrogen which stimulates smooth muscle hypertrophy.
-Breast during lactation

Pathologic hypertrophy

- Cardiomyocytes are cells of the heart (myocardium), they undergo hypertrophy in heart failure(e.g. hypertension or aortic valve disease.)



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Hyperplasia

DEFINITIONS

-Hyperplasia is an increase in the number of cells may lead to an increase in the size of the organ.
-takes place if the tissue contains cell populations capable of replication, and it may occur concurrently (simultaneously) with hypertrophy, and often in response to the same stimulus.

Hyperplasia is either physiological or pathological :

-Physiologic hyperplasia are of two types:
-Hormonal hyperplasia e.g. the proliferation (reproduction) of the glands of the female breast at puberty and during pregnancy.
-Compensatory hyperplasia e.g. when a portion of liver is partially resected, the remaining cells multiply and restore the liver to its normal size.

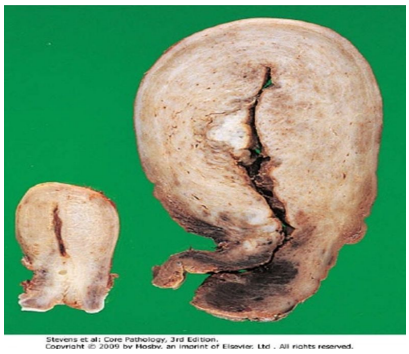
Pathologic hyperplasia is caused by abnormal excessive stimulation of cells by hormones or growth factors e.g. excess estrogen hormone leads to endometrial hyperplasia in the uterus which causes abnormal menstrual bleeding.

-An important point is that in all of these situations, the hyperplastic process remains controlled; if the signals that initiate it abate (lessen), the hyperplasia disappears.

-It is this responsiveness to normal regulatory control mechanisms that distinguishes pathologic hyperplasia from cancer, in which the growth control mechanisms become permanently dysregulated or ineffective .

-Nevertheless, in many cases, pathologic hyperplasia constitutes a fertile soil in which cancers may eventually arise. For example, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer.

Hypertrophy and Hyperplasia



Hypertrophy and Hyperplasia can occur together

1-Uterus during pregnancy: there is both Hypertrophy and Hyperplasia in the smooth muscle of the uterus

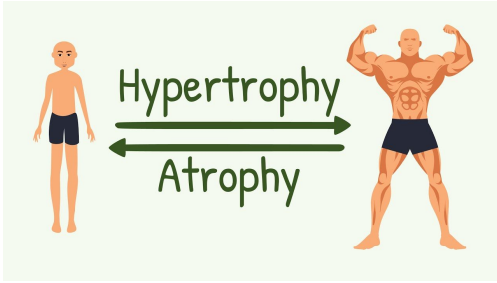
2-Prostate in elderly: there is both Hypertrophy and Hyperplasia of the prostate gland and stroma. This condition is called ''benign nodular prostatic hyperplasia'' * which means no increased risk for cancer

Atrophy

Atrophy is **shrinkage in the size of the cells, due to a reduced demand** or when a **sufficient number of cells are involved,** all of which leads to **Atrophy.**

-Atrophic cells are **not dead** but have **diminished function.**

-In atrophic cells there is **decreased** protein synthesis and increased protein degradation.



Causes	1-Decreased workload or disuse (e.g. immobilization of a limb in fracture). 2-Loss of innervation (lack of neural stimulation to the peripheral muscles - caused by injury to the supplying nerve - causes atrophy of that muscle). 3-Diminished blood supply. 4-Inadequate (insufficient) nutrition. 5-Loss of endocrine stimulation (e.g. the loss of hormone stimulation in menopause). 6-Aging: senile atrophy of brain can lead to dementia. >Some of these stimuli are physiologic (the loss of hormone stimulation in menopause) and others pathologic (denervation).

On an organ level, atrophy is a decrease in the size of the organ, it can happen via: 1) decrease in cell size. 2) decrease in cell number.

Involution: it is the reduction in the cell number.

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Metaplasia

DEFINITIONS

Certain types of cells are extra sensitive to a particular toxic agent or environment. When they get exposed to that agent or environment, they get replaced by another type of cell which is better able to tolerate that toxic agent or environment. This is known as **metaplasia.**

Metaplasia is **usually a reversible** when the causative toxic agent is removed. Examples include:

- Squamous metaplasia
- Columnar cell metaplasia
- Osseous metaplasia
- Myeloid metaplasia

They always ask questions about Squamous metaplasia And Columnar cell metaplasia **in the exams.**

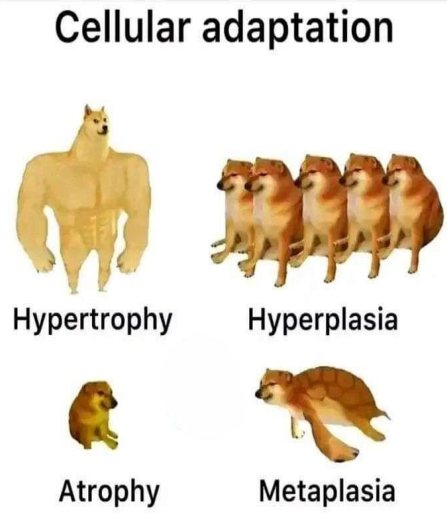
Squamous metaplasia	**The respiratory tract:** the columnar lining the bronchus are replaced by squamous cell following chronic injury in smokers. > The squamous epithelium is able to survive the toxicity of tobacco better, but the important protective functions of the columnar epithelium are lost, such as mucus secretion and ciliary function. **The cervix:** at the squamocolumnar junction: columnar cells are replaced by squamous cells following chronic irritation and inflammation if the causative agent persists, it may predispose to or provide a platform for cancer to develop
Columnar cell metaplasia **Hot question :** Columnar cell metaplasia is called (barrett's esophagus) and lead to adenocarcinoma	-**replacement of squamous cells by columnar cells.** Seen in the esophagus in chronic gastroesophageal acid reflux disease. because the normal stratified squamous epithelium of the lower esophagus cannot handle the acidity and undergoes **metaplastic transformation to columnar epithelium**, this change is **barrett's oesophagus** and it can **precancerous** and lead to development of adenocarcinoma of esophagus.

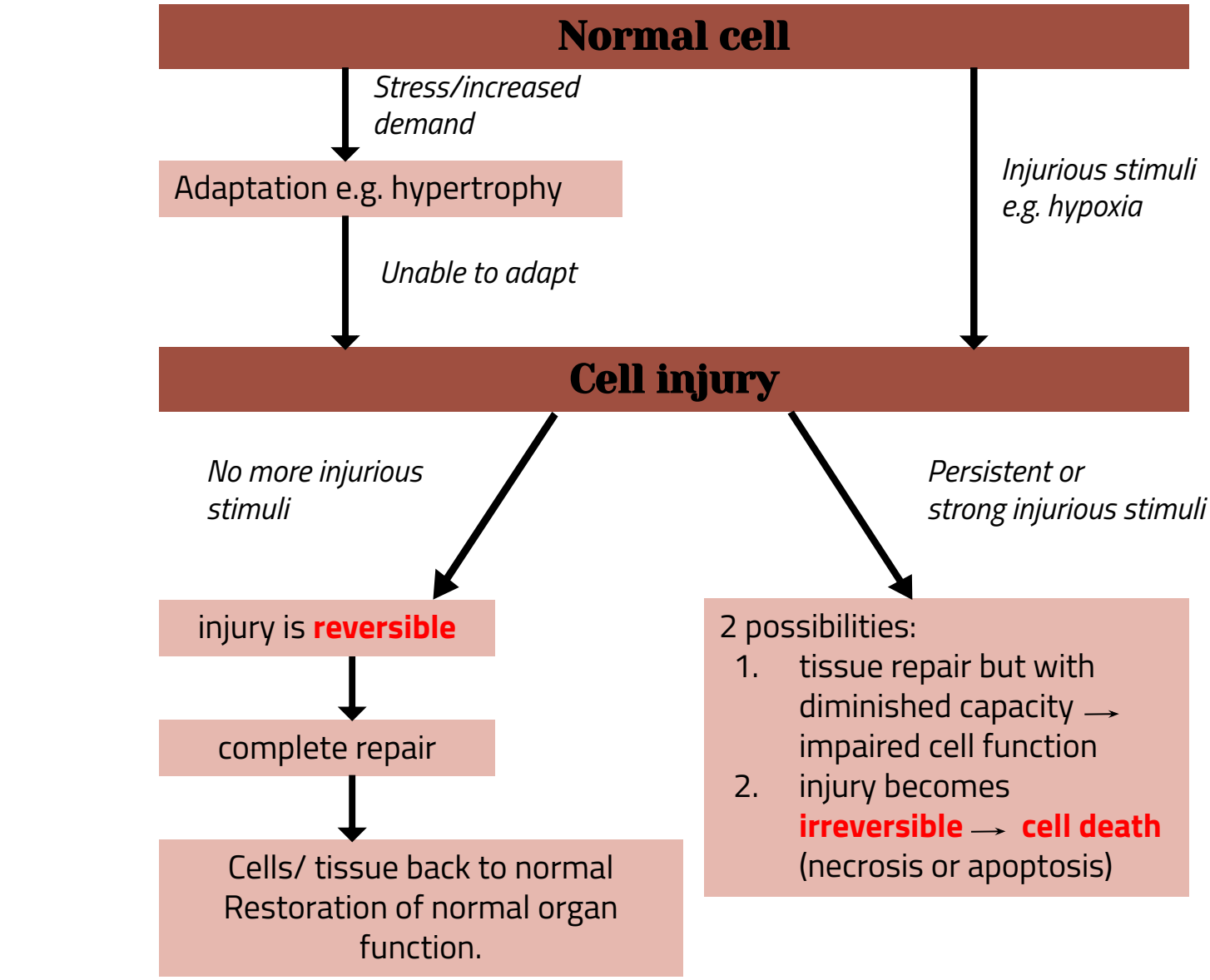
Osseous metaplasia	It is the formation of new bone at sites of tissue injury, cartilaginous metaplasia may also occur.
Myeloid metaplasia	proliferation of hematopoietic tissue in sites other than the bone marrow such as liver or spleen.

Summary

Change in size of cells	
Atrophy	Reduction in the size of cells
Hypertrophy	Increase in the size of cells
Change in number of cells	
Involution	Decrease in the number of cells
Hyperplasia	Increase in the number of cells
Change in differentiation of cells	
Metaplasia	Stable change to another cell type

Note:
-hypoplasia refers to an organ that does not reach its full size.
-aplasia is the failure of cell production.





Cell Injury

DEFINITIONS

- When the cell is exposed to an injurious agent/stress/stimulus, and it leads to injury of the cell, it is termed cell injury.
- Cell injury is reversible up to a certain point, but if the stimulus persists or is severe from the start, the cell reaches a point of no return and suffers irreversible cell injury and ultimately cell death.
- Cell death is death of a cell as a result of cell injury.

cont. Cell Injury

There are 2 principal patterns of cell death :

- **Necrosis** is the type of cell death that occurs due to disease, injury, or failure of the blood supply (ischemia) and it is always pathologic.
- **Apoptosis** occurs when a cell dies through activation of an internally controlled suicide program.

Causes of Cell Injury

Causes of injury (are the same for both reversible and irreversible):

1) Oxygen Deprivation (hypoxic cell injury). It is a common cause of cell injury and cell death. Hypoxia can be due to:

Pathoma: ischemia can also be because of reduced venous drainage or hypoperfusion (eg. shock)

i. Ischemia (obstruction of arterial blood flow), e.g. in myocardial infarction and atherosclerosis.
ii. Inadequate oxygenation of the blood e.g. lung disease and carbon monoxide poisoning
iii. Decreased oxygen-carrying capacity of the blood e.g. anemia
iv. Inadequate tissue perfusion due to cardiorespiratory failure, hypotension, shock etc.

Also some cell types are more vulnerable to hypoxic injury than others e.g. neurons are most susceptible followed by cardiac muscle, hepatocytes and then skeletal muscles.

2) Physical Agents e.g. mechanical trauma, burns and deep cold, sudden changes in atmospheric pressure, radiation, and electric shock.

3) Toxins. Potentially toxic agents are encountered daily in the environment; these include air pollutants, insecticides, CO, asbestos, cigarette smoke, ethanol, and drugs

4) Infectious Agents.

5) Immunologic agents e.g. thyroid damage caused by autoantibodies.

6) Genetic Derangements eg sickle cell anemia.

7) Nutritional Imbalances.

8) Aging

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Mechanism of Cell Injury

1. **Depletion of ATP.**
2. **Cell membrane damage/defects in membrane permeability.**
3. **Mitochondrial damage**:
   It is seen specially in hypoxic injury and cyanide poisoning.
4. **Ribosomal damage:**
   It is seen in alcohol damage of liver cells and with antibiotic use.
5. **Nuclear and DNA damage.**
6. **Influx of intracellular calcium leading to loss of normal calcium balance:**
   ischemia causes an increase in intracellular calcium concentration, which leads to the activation of several enzymes which cause damage.
7. **Free radical injury.**

Free Radical Injury

DEFINITIONS

Free radical injury (oxidative stress): is due to excess accumulation of oxygen-derived free radicals.
Free radicals: are highly reactive and harmful atoms that have a single unpaired electron in the outer orbit. These atoms are called reactive oxygen species (ROS) /free radicals.
unpaired electrons that have been produced by our bodies and basically would pair with anything making troubles.

They always ask questions about free radical injury in the test.

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cont. Free Radical Injury

The free radicals are produced in our cells by various mechanisms called (free radical generating systems). They are produced by:

1. **Normal metabolism/ respiration**: produce free radicals as a bi-product of mitochondrial respiration during normal respiration (reduction-oxidation reactions that occur in normal metabolism).
2. **Ionizing radiation injury** e.g. UV light, x-rays result in production of free radicals.
3. **Chemical toxicity**: enzymatic metabolism of exogenous chemicals or drugs produce free radicals.
4. **Oxygen therapy and reperfusion injury produce free radicals.**
5. **Immune response or inflammation** (neutrophilic oxidative burst)
6. **Transition metals** such as iron and copper can trigger production of free radicals.

The names of the common free radicals are:

1. Superoxide anion radical (O2-)
2. Hydrogen peroxide (H2O2)
3. Hydroxyl ions (OH)
4. Nitric oxide (NO) is an important chemical mediator generated by various cells and it can also act as free radical.

Free radicals cause damage to lipids, proteins, and nucleic acids:

Lipids	**Lipid peroxidation of membrane → damage of cell membrane and organelles**
Proteins	**Oxidative modification of proteins → protein fragmentation**
Nucleic Acid	**DNA damage → cell aging and malignant transformation of cells**

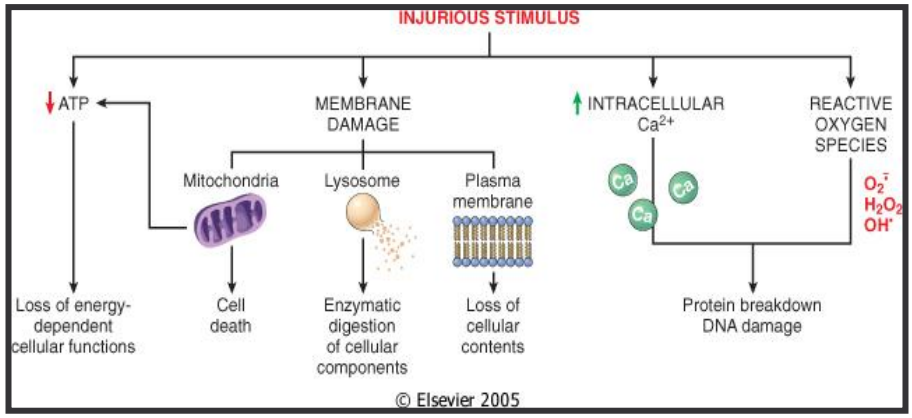
How does our body fight the free radicals? Certain substances in the cells remove or inactivate the free radicals in order to minimize injury caused by them. They are called "**free radical scavenging system**".

These substances are:

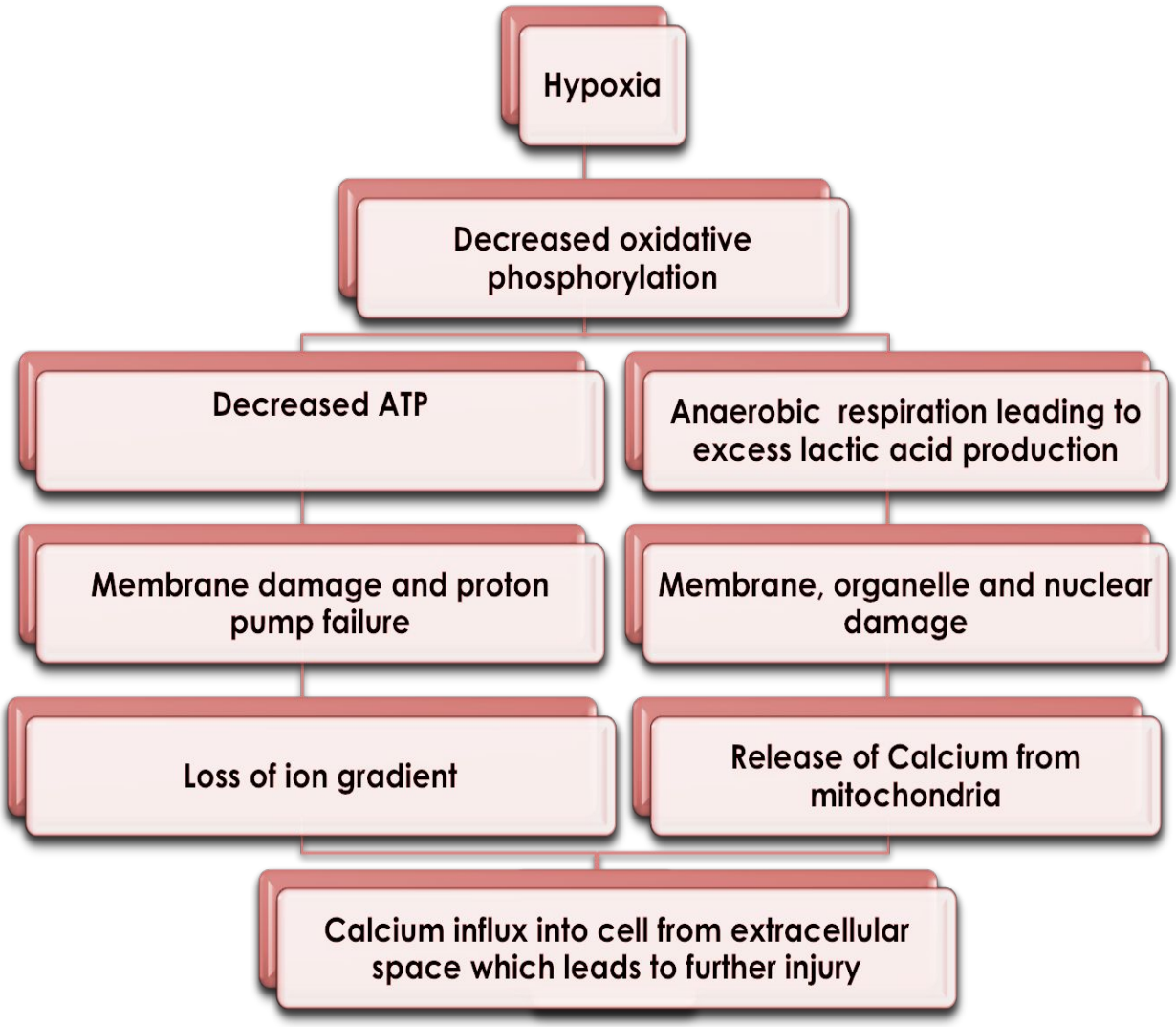
- Antioxidants: e.g. **vitamins E, A and C** (ascorbic acid).
- Enzymes: which break down hydrogen peroxide and superoxide anion e.g. **Catalase, Superoxide dismutases, Glutathione peroxidase and mannitol.**

Remember these names they might come in the exam, you should know the names of the free radicals and what neutralize them.

NOTE: Any imbalance between free radical-generating and free radical-scavenging systems results in oxidative stress causing cell injury.



Mechanism in hypoxic cell injury



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Reversible Cell Injury

Cell injury can be *reversible* or *irreversible*.

Factors that will determine the extent of cell damage (i.e. whether the injury is reversible or irreversible):

1) The type of injury. **2) The time duration of injury.**
3) The severity of injury.

Reversible Cell Injury: initially cell injury is reversible. If the injurious stimulus is removed the damage can be reversed.

- The two main morphological correlates of reversible cell injury are **cellular swelling** and **fatty change**.

- **Cellular swelling** is commonly seen in cell injury associated with increased permeability of the plasma membrane. Microscopic examination may show small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum (ER). This pattern of nonlethal injury is sometimes called hydropic change or vacuolar degeneration.

- **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.
2- Mitochondrial changes such as swelling.
3- Dilation of the ER with detachment of ribosomes and dissociation of polysomes, defect in protein synthesis.
4- Nuclear alterations, such as clumping of chromatin.
5- Mild eosinophilia of cytoplasm (due to decrease in cytoplasmic RNA)

The cytoplasm may contain so-called "myelin figures," which are collections of phospholipids resembling myelin sheaths that are derived from damaged cellular membranes.

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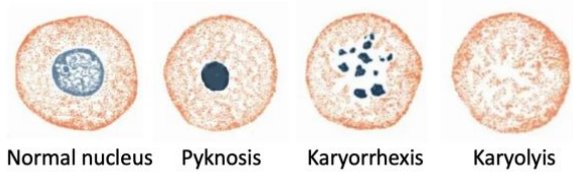
Irreversible Cell Injury

Persistent or excessive injury causes cells to pass into **irreversible injury**.

Irreversible injury is marked by:

1. Severe mitochondrial damage with the appearance large, amorphous densities in mitochondria.
2. Severe plasma/cell membrane damage.
3. Increased eosinophilia.
4. Numerous myelin figures.
5. Rupture of lysosomes leakage and enzymatic digestion of cellular contents.
6. Nuclear damage:
   i. pyknosis (shrinkage).
   ii. karyolysis (dissolution).
   iii. karyorrhexis (break down or fragmentation).

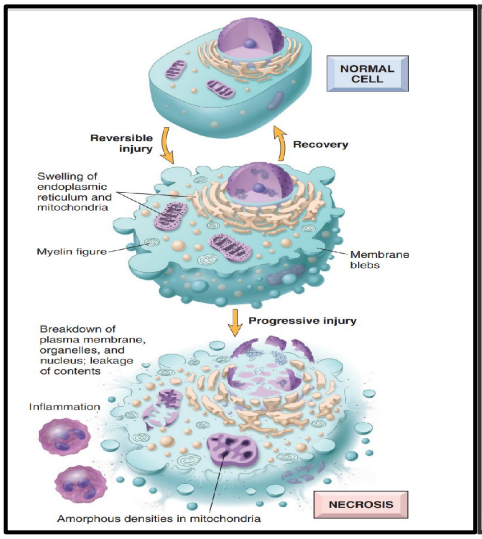


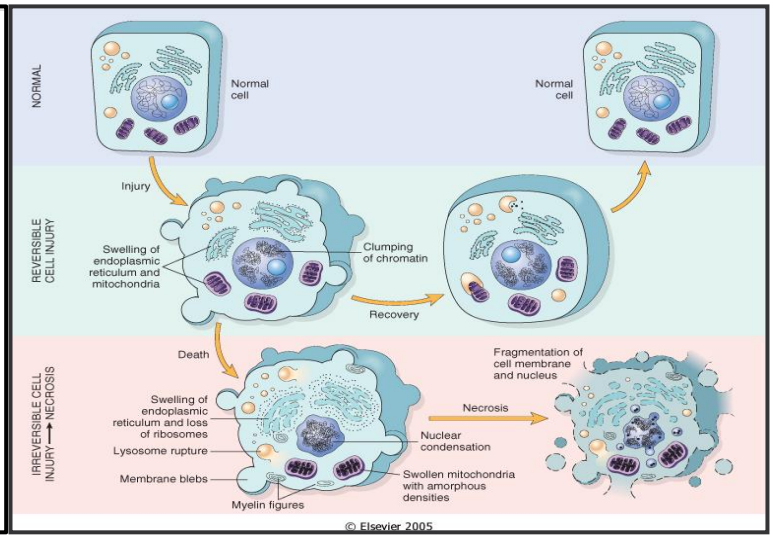
in other sources it is ordered as:

i. pyknosis (shrinkage).

ii. karyorrhexis (break down or fragmentation).

iii. karyolysis (dissolution).





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Reversible vs irreversible cell injury

	Reversible	irreversible
cell membrane/plasma	alteration in plasma	severe damage in both
Mitochondrial changes	swelling	severe, with the appearance of large amorphous densities
nucleus/chromatin	alteration such as clumping of chromatin	nuclear damage: • pyknosis • karyolysis • karyorrhexis
Cytoplasm	Mild eosinophilic (due to decreased RNA)	increased eosinophilia
Organelles	Dilation of the ER with detachment of ribosomes and dissociation of polysomes, defect in protein synthesis.	rupture of lysosome leakage and enzymatic digestion of cellular contents
Myelin figures	may contain	Numerous

***Important: They may give you some of the ultrastructural changes associated with each one and ask you is it reversible or irreversible.**

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MCQs

1. **Which of the following is most likely to be affected by hypoxia?**

A. Hepatocytes | B. Skeletal muscles | C. neurons

2. **What kind of cell adaptation happens in benign nodular prostatic hyperplasia?**

A. Hyperplasia & Hypertrophy | B. Hyperplasia | C. Hypertrophy & Aplasia

3. **What is karyolysis?**

A. Nuclear shrinking | B. Nuclear dissolution | C. Nuclear fragmentation

4. **What of the following is the result of the loss of endocrine stimulation ?**

A. Hypertrophy | B. Hyperplasia | C. Atrophy

5. **What are the two patterns of reversible cell injury visible under the light microscope?**

A. Cellular swelling and fatty change. | B. Swelling and disruption of lysosomes and fatty acids . | C. Pyknosis and membrane blebbing.

1	2	3	4	5
C	A	B	C	A

6 **The reduction of cell number** (only in female slides)

A. Hypoplasia | B. Aplasia | C. Involution

7 **An important chemical mediator generated by various cells and it can act as a free radical**

A. H2O | B. Nitric oxide | C. Carbon Tetrachloride

8 **Myeloid metaplasia occurs**

A. Bone Marrow | B. Liver | C. Respiratory tract

9 **A 35-year-old man is a habitual smoker. If a biopsy is taken from the respiratory tract in this man, the epithelium of respiratory tract is most likely to show:**

A. columnar metaplasia | B. Stratified squamous metaplasia | C. Squamous cell anaplasia

10 **Metapalsia**

A. can be caused by vitamin B12 deficiency | B. is an increase in the number and size of cells in a tissue | C. describes the underlying pathology of Barrett's oesophagus

11 **Which of the following is antioxidant?**

A. Vitamin B | B. Vitamin D | C. Vitamin E

6	7	8	9	10	11
C	B	B	B	C	C

Pathology Team444

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