Pathogenesis ,clinical manifestations,functional consequences & prognosis

→Pathogenesis:

-The mechanism of development of the disease .

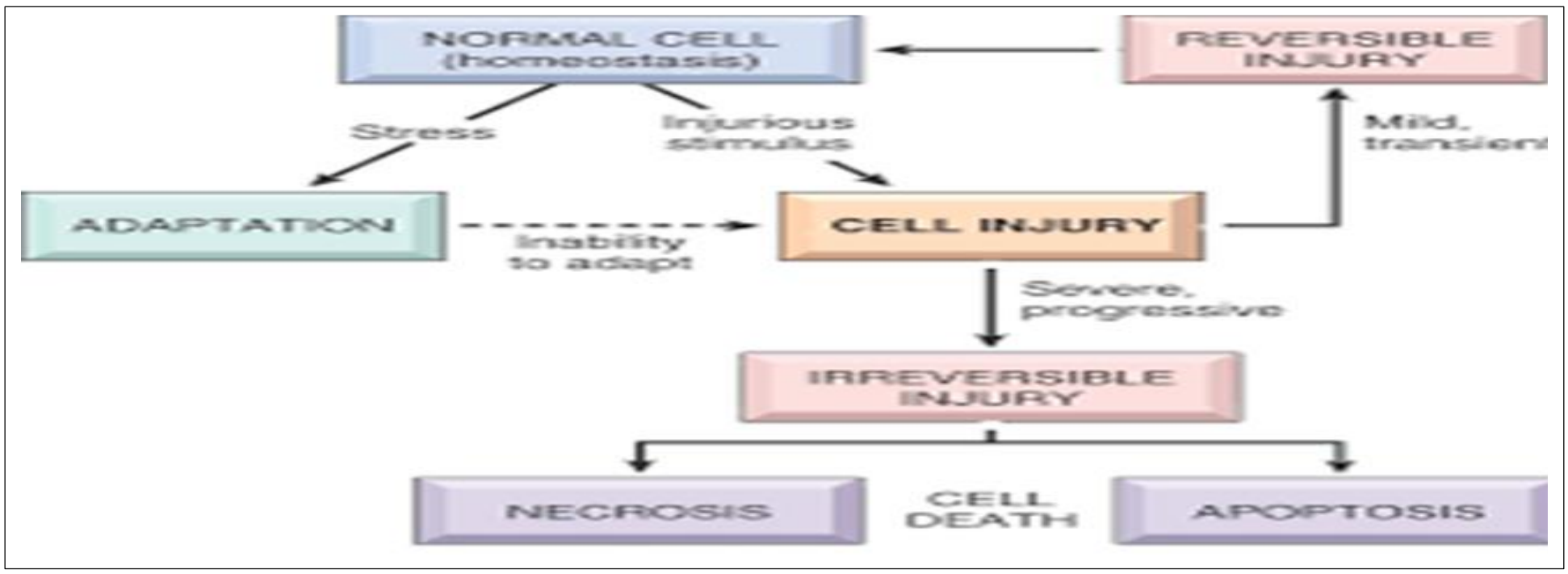
→ Pathological and clinical manifestations :

-The structural and functional features of the disease .

Functional consequences

-Morbidity of the disease :	-Is the sum of the disease effects on the patient, morbidity **may or may not** result in disability of the patient. e.g. **non-fatal cardiac** infraction impairs **heart contractility and predisposes** to heart failure . -This is morbidity patients disability results from breathlessness and restriction on patient's activities.
-Complications and sequel:	The secondary systemic or remote consequences or the disease.
-**Prognosis:**	The anticipated course of the disease in terms of **cure ,remission or fa**te of the patient . -Prognosis is subject to **change by medical or surgical** interventions e.g. a disease with poor or good prognosis.

Cellular adaptations & responses to stress



-Cells tend to maintain their internal environment physiologically stable to maintain **homeostasis.**

-As cells encounter physiologic stresses; they make **adaptation** achieve a new steady state and preserve viability and function .

-**The principal adaptive response are** :

1-Hyperatropy. 2-Hyperplasia .

3-Atrophy . 4-Metaplasia.

-If adaptive capability is exceeded or if the external stress is harmful; cell injury develops within certain limits injury is **reversible** and cells return to a **stable baselin**e ; however; **severe or persistent stress** results in irreversible injury and death of the affected cells.

Cellular adaptation to stress

1-Hyper trophy:

-An increase in **size of cells** resulting in increase in the **size of the organ** .

-In hypertrophy there are **no news cells,** just **bigger cells**; enlarged by an increased amount of **structural proteins and organelle**s.

-Hypertrophy can be **physiologic or pathologic** and is caused either by increased

functional demand or by specific hormonal stimulation

a)Physiologic Hyper trophy	b)Pathologic Hypertrophy
-Weight-lifter can develop hypertrophy of individual **skeletal muscle** cells induced by an increased **workload .**	-The cardiac **enlargement** that occurs with hypertension or aortic valve disease -Cardiac hypertrophy is an adaptation to **increase myocardial contractile force.** -However; if the stress is not relieved (e.g. the hypertension, or aortic valve disease); the ventricle would eventually **fail and becomes dilated resulting in heart failure** .

2-Hyper plasia

-Hyperplasia is characterized by an **increase in cell number** .

-Hyperplasia is an adaptive response in **cells capable of replication** (un like hypertrophy which occurs when cells are in **capable of dividing**).

-**Hypertrophy and hyperplasia** can also **occur together**; resulting in an enlarged (hypertrophic) organ.

-Example: the massive physiologic enlargement of the **uterus during pregnancy** occurs as a consequence of estrogen-stimulated smooth muscle hypertrophy and smooth muscle hyperplasia.

Physiologic Hyperplasia		Pathologic Hyperplasia
Hormonal	**Compensatory**	-Due to **excessive hormones** or growth factors or **hormonal imbalance** . e.g. if the balance between e**strogen** and **progesterone** is disturbed ,endometrial **hyperplasia exaggerates**. -a common cause of **abnormal menstrual bleeding .** -**Pathologic hyperplasia** stops once the **hormonal stimulator** is removed (un like cancer cells which don't stop division after removal of the original stimulator .
e.g proliferation of the glandular epithelium of the **female breast at puberty and during pregnancy.**	1-that occurs when a portion of the tissue is -removed or diseased. for example ,**when a liver is partially resected ,mitotic activity** in the remaining cells begins as early as 12 hours later, eventually **restoring the liver to its normal weight** 2-wound healing	

3-Atrophy

-Atrophy is **shrinkage** in the size of the cell due to the loss of cellular substance .

-Some times the **entire tissue or organ** diminishes in size ; becoming (atrophic).

-Although atrophic cells may **have diminished function** ,the are not **dead .**

→Mechanism :

-Atrophy results from **decreased** protein synthesis and increased protein **degradation** in cells .

-e.g.1 **Renal reflux** due to defect in the urinary bladder sphincter.

-e.g.2 **Atrophic brain** of 82 years old man.

→Causes of atrophy :

1-Decreased work load (e.g ; immobilization of a limb to permit healing of a fracture)

2-loss of innervation

3-Diminished blood supply Inadequate nutrition

4-Loss of endocrine stimulation (e.g. in menopause)

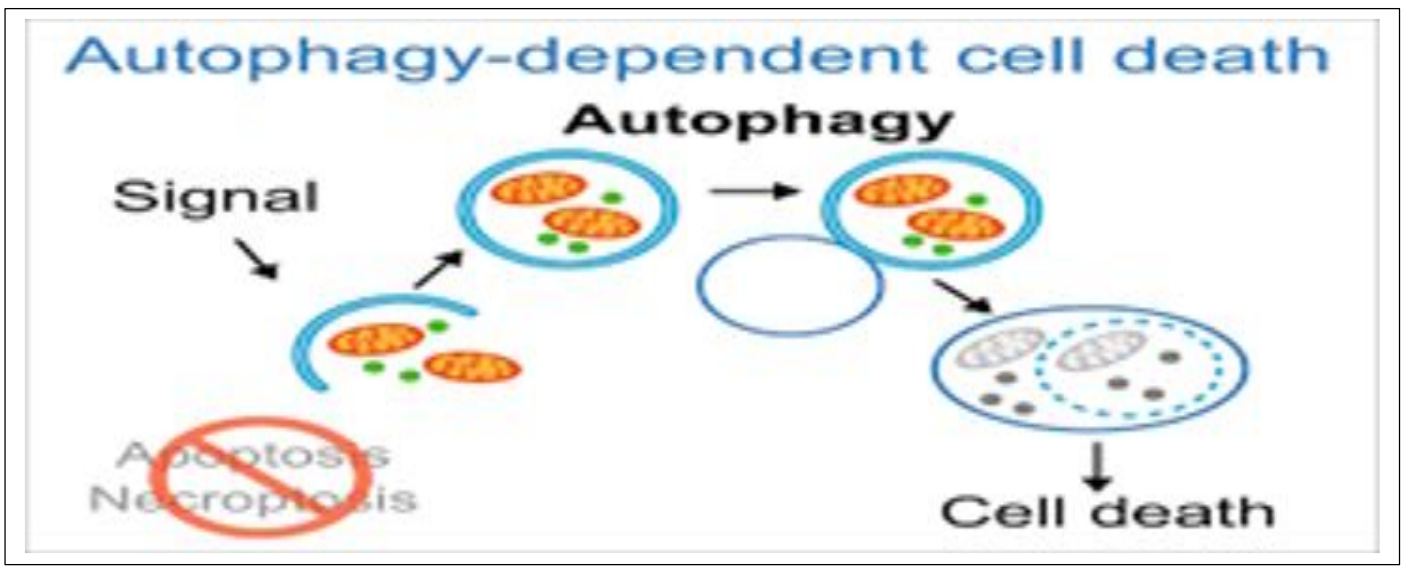
5-Aging (senile atrophy)

-Atrophy and autophagy :

-In many situations atrophy is also **accompanied** by increased **autophagy** with resulting increase in the number of autophagic vacuoles.

-**Autophagy (self eating**) is the process in which the starved cell eats its own components in an attempt to find nutrients and survive .

-Autophagy refers to a **group of processes** that involve degradation of **cytoplasmic components** including cytosol, macromolecular complexes , and organelles , within the vacuole or the lysosome .



4- Metaplasia

-Metaplasia is **reversible change** in **which adult cell type** (epithelial or mesenchymal)is replaced by another **adult cell type** .

-Cells sensitive to a **particular stress** are replaced by other cell types which are able better to **withstand this stress .**

→Mechanism : it seems to be induced by **altered differentiation pathway** of tissue stem cells *(genetic reprogramming of stem cells rather than trans differentiation of already differentiated cells) .*

Types of metaplasia

Epithelial Metaplasia	Connective tissue Metaplasia
a)Metaplasia occurring in the **respiratory epithelium** in habitual **cigarette smokers** →the **normal ciliated columnar** epithelial cells of the **trachea and bronchi** are replaced by **stratified squamous epithelial cells .** b)**Vitamin A deficiency** may also induce squamous metaplasia in the respiratory epithelium. →Although the **metaplastic squamous** epithelium has **survival advantages** but ,important protective mechanisms are lost such as **mucus secretion and ciliary clearance of particulate** matter →**Metaplastic transformation**; if persistent, may predispose to **malignant** transformation of epithelium i.e.(lung cancer).	-Cartilage to bone in old age . -Occasional bone formation at site of injury . -Muscle tissue to bone in traumatic **myositis ossificans**.

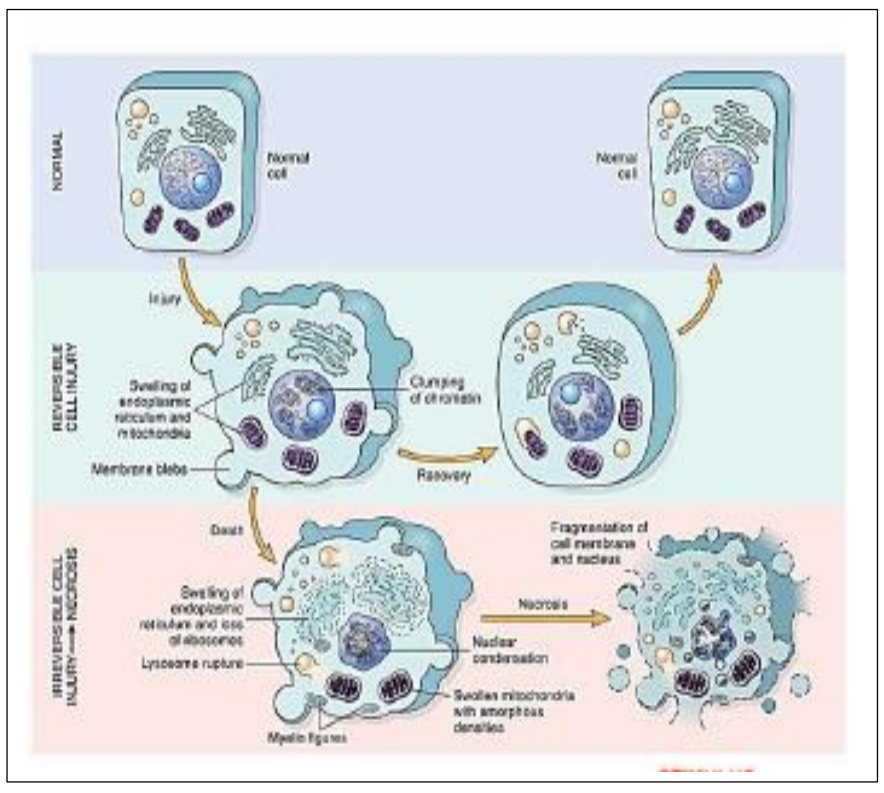
Cell Injury

→Causes of cell injury

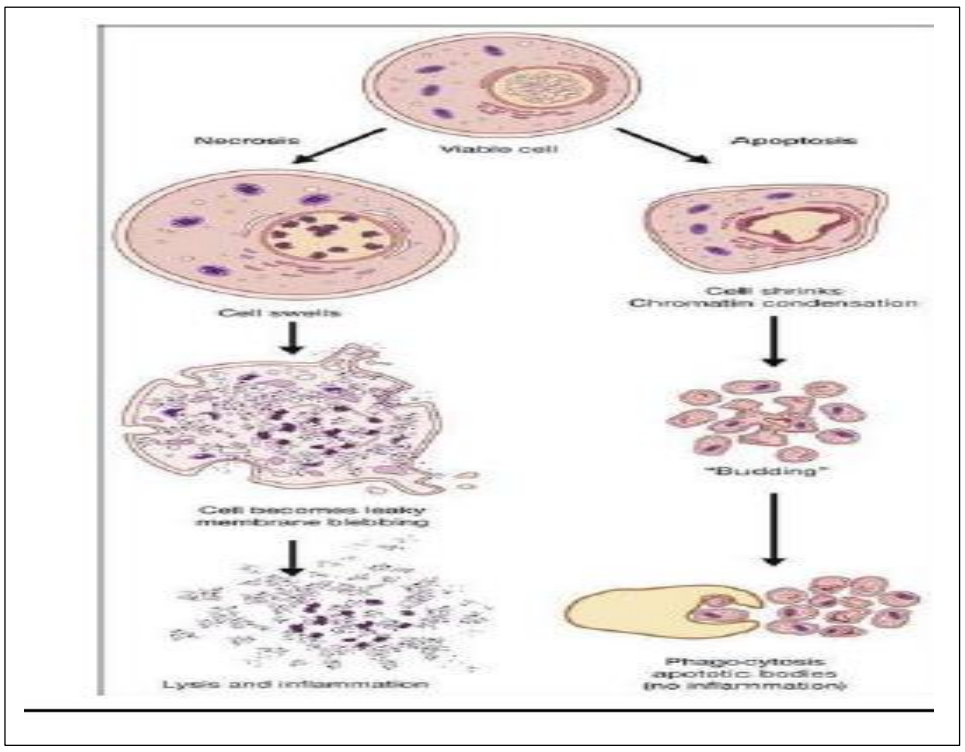
1-Hypoxia	-Oxygen **deficiency** , different from i**schemi**a . **-Ischemia** :is a **loss** of **body supply** in a tissue due **to inadequate arterial flow** or reduced **venous drainage** . - i**schemia** is the most common cause of **hypoxia** .
2-Immunologic reaction	-**Autoimmune reactions** against one's one tissues and **allergic reactions** against environmental substances .
3-Genetic defects	-Single gene **defect results** in **defective enzyme** or accumulation of damaged DNA or **misfolded proteins.**
4-Chemical agent	e.g. drugs
5-Infectious agent	viruses, bacteria , fungi and parasites .
6-Nutritional imbalance	-Both mal **nutrition and obesity** can cause cell damage . -**Obesity** increases the risk for **type 2 diabetes mellitus** .
7-Physical agents	-e.g trauma , extremes of temperature, radiation, electric shock , and **sudden changes in atmospheric pressure** .
8-Aging	-**Cellular senescence** leads to alterations in **replicative and repair abilities** of cells and tissues ,this results in a reduced ability to respond to **damage and eventually , cell death** .

Reversible &Irreversible cell injury

Reversible cell injury		Irreversible cell injury
-In **early stages or mild forms** of injury , the functional and morphologic changes are **reversible** if the damaging stimulus is **removed .**		-**Continuing damage** leads **to irreversible** cell injury where the cells cannot recover and **they die .** -There are **two types** of cell death : **necrosis and apoptosis (programmed cell death).**
	Reversible cell injury	**Irreversible Cell injury**
Morphological characters	**→Two main morphologic manifestations**: **a)Cellular swelling** is the result of **failure of energy – dependent ion pumps** in the plasma membrane , leading to an inability to **maintain ionic and fluid** homeostasis. **b)Fatty change** occurs in hypoxic injury and toxic injury , and is manifested by the appearance of **small or large lipid vacuoles in the cytoplasm .** -It occurs mainly in cells involved in and dependent on **fat metabolism , such as hepatocytes and myocardial cells** .	-Dead cells may be replaced by large **, phospholipid masses , called myelin figures , originating from damaged cellular membranes.** →***These phospholipid masses are either :*** a)Phagocytosed . b)Degraded into fatty acids , calcification of such fatty acid residues results in the formation of **calcium soaps** , thus the dead cells may become calcified .
Ultra-structural changes	1- Plasma membrane alterations such a **blebbing.** 2- Mitochondrial changes such as swelling and appearance of **phospholipid – rich amorphous densities**. 3- **Dilation of the ER** with detachment of ribosomes. 4-**Nuclear alterations , with clumping of chromatin.**	1- Inability to reverse **mitochondrial dysfunction** (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury 2- Major **" disturbance in membrane function** **Injury to lysosomal** membranes results in **enzymatic dissolution** of the injured cell, Enzymes responsible for digestion of the cell are derived from the **lysosomes** of the **dying cells themselves or from the lysosomes of** leukocytes that are recruited as part of the inflammatory reaction to the dead cells.



Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → Karyorrhexis → Karyolysis	Fragmentation into nucleosome-size fragment
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	pathologic (due to irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage.



Subcellular responses in cell injury

Autophagy & heterophagy

→Autophagy: (self-eating).

-Stressed cells **digest internal organelles** to provide source of energy under **starved conditions**, It involves **lysosomal digestion** of the cell's own components.

-It is a survival mechanism when there is nutrients deprivation .

→ Heterophagy:

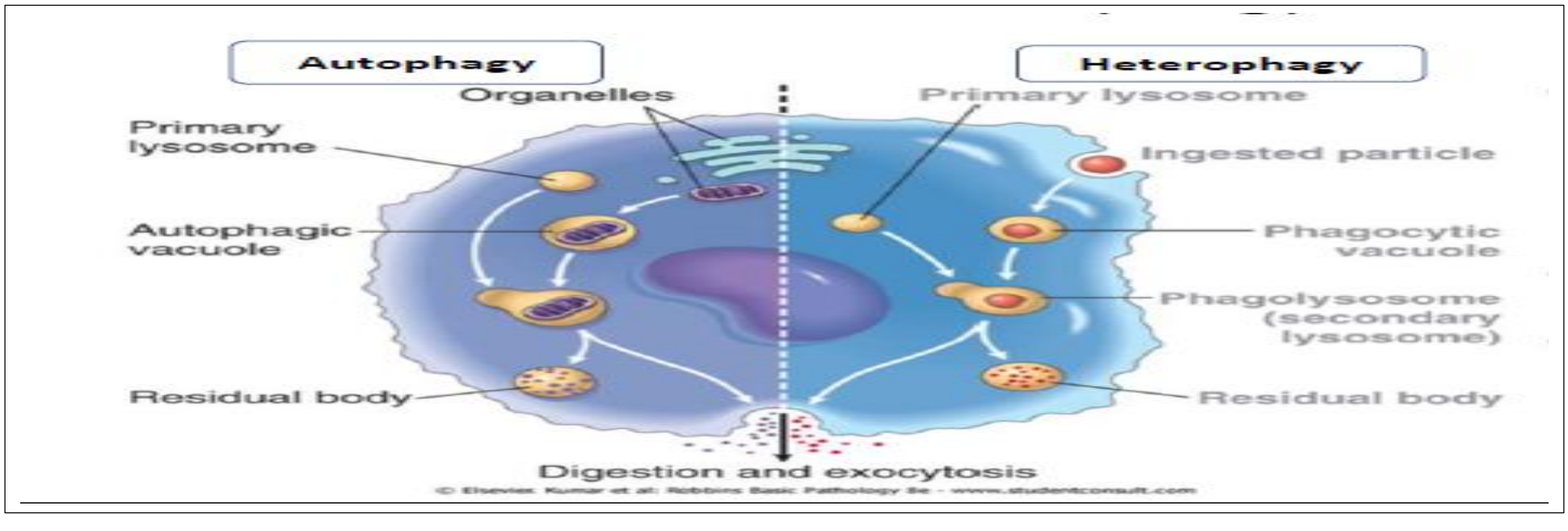
-A macrophage ingests extracellular substances by the process of phagocytosis.

-The enzymes in **Lysosomes** can break down most proteins and carbohydrates, but some **lipids may remain undigested**.

-**Lysosomes** with **undigested debris** may persist within *cells* as ***residual bodies*** or may be **extruded**.

a)***Lipofuscin pigment*** granules represent indigestible material resulting from lipid peroxidation.

b) **Carbon particles inhaled** from the atmosphere or inoculated pigment in tattoos, can persist in phagolysosomes for decades.



-The principle cellular and biochemical sites of damage in cell injury:

-In case of Injurious stimulus it will affect:

a)**DNA damage** or **accumulation of misfolded proteins** which will lead to Apoptosis.

b)**Cytoskeleton damage or membrane damage** including the Mitochondria leading to decrease **in ATP production** ,if lysosomal membrane damage will lead to cell lysis.

c)If damage in the **plasma membrane** it will lead to loss of the intracellular contents **leading to Necrosis.**

→The cellular response to injurious stimuli depends on:

1)the type of injury, 2) its duration, and 3) its severity.

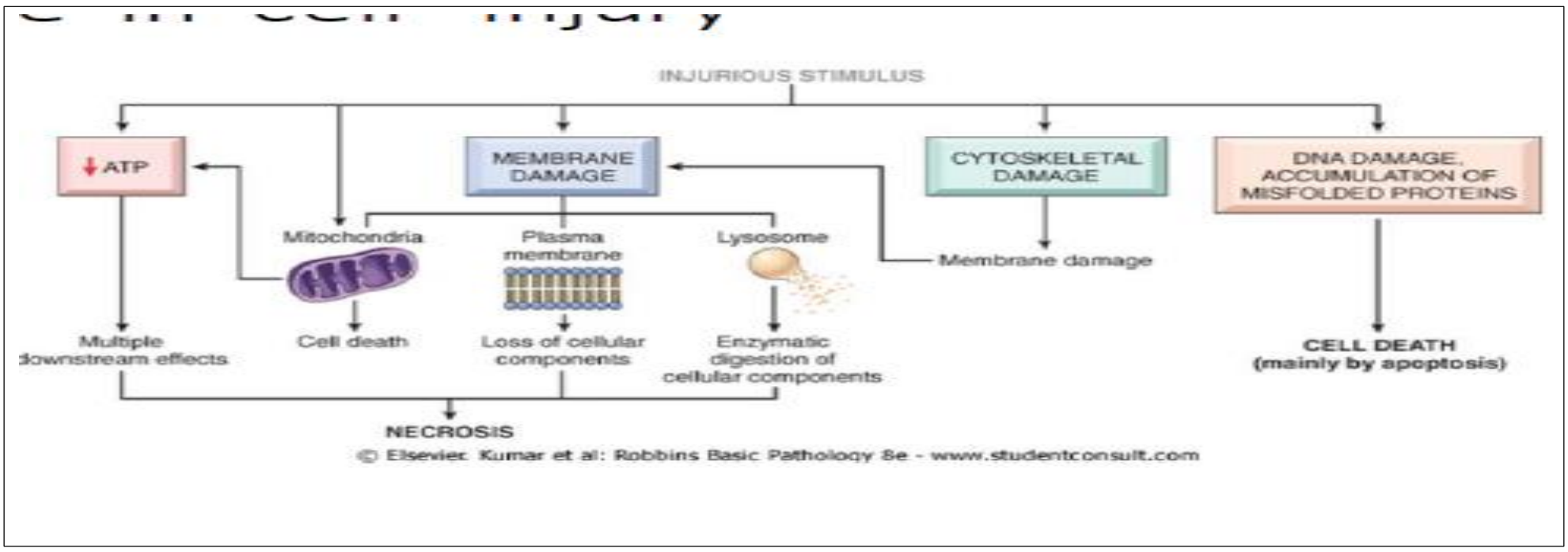
- Thus, **low doses of toxins** or a brief duration of ischemia may lead to **reversible cell injury**, whereas **larger toxin doses** or longer **ischemic intervals** may result in **irreversible** injury and cell death.

-The consequences of an injurious stimulus depend on:

1)the type, 2)status, 3)adaptability, and 4) genetic makeup of the injured cell.

-**The same injury** has **different outcomes** depending' on the cell type; thus,

striated skeletal muscle in the leg accommodates complete ischemia for 2 to 3 hours without irreversible injury, whereas cardiac muscle dies after only 20 to 30 minutes.



Miscellaneous forms of cell injury

Cellular aging

-Cellular aging is the result of a **progressive decline** in the **proliferative capacity** and life span of cells and the effects of continuous exposure to exogenous factors that cause accumulation of cellular and molecular damage.

Mechanisms of cellular aging

1.Increasing DNA damage and reduced DNA repair activity:

-DNA damage may happen during normal *DNA replication or enhanced by free radicals*. Although **most DNA damage is repaired** by DNA repair enzymes, **some persists and accumulates** as cells age.

-In animal models, it was found that **calorie restriction** imposes a level of stress that **activates proteins** of the Sirtuin family, such as Sir2, that **activate DNA repair enzymes**, thus stabilizing the DNA.

2-**Decreased cellular replication (Replicative senescence):**

-All normal cells have a **limited capacity** for replication, and after a fixed number of divisions, cells stop to divide, entering a non-dividing state, known as ***replicative senescence***.

-Aging is associated with **progressive replicative senescence** of cells. Cells from children have the capacity to undergo more rounds of replication than do cells from older people.

-Mechanism of replicative senescence involves **incomplete replication** and **progressive shortening** of telomeres, which results in **cell cycle arrest.**

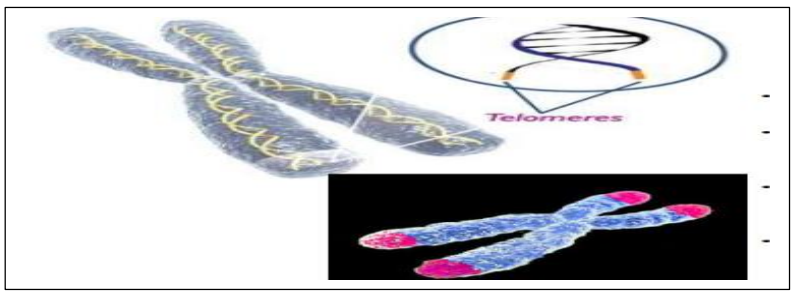
Telomeres

→*Telomeres* are short repeated sequences of DNA present at the linear ends of chromosomes .

-They are important for **ensuring the complete replication of chromosome** ends and for protecting the ends from degradation .

-When cells replicate, a small section of the telomere **not duplicated**, and telomeres become **progressively shortened .**

-As the telomeres become shorter, **the ends of chromosomes cannot** be **protected** and are broken, which signals cell cycle arrest .



Telomerase

-The lengths of the telomeres are normally maintained by **nucleotide addition** mediated by an enzyme called **telomerase .**

-Telomerase activity is expressed in germ cells and is present at **low levels in stem** cells, but it is usually **absent** in **most somatic tissues**. Therefore, as cells age their telomeres become shorter resulting in an inability to cell replication .

-Conversely, **in immortal cancer cells, telomerase is reactivated** and telomeres are not shortened, suggesting that **telomere elongation might be an important essential step in tumor formation.**