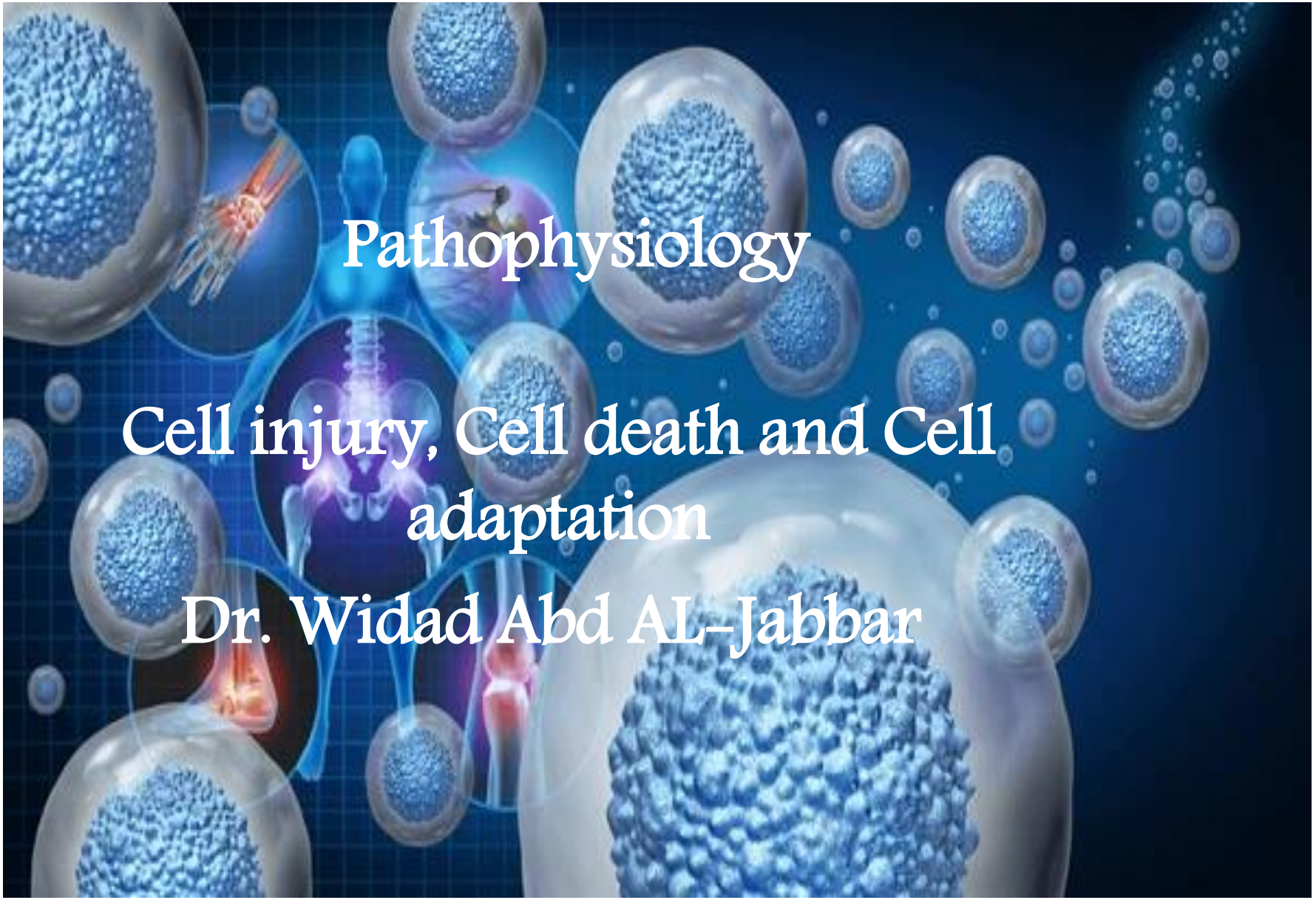


Pathophysiology

Cell injury, Cell death and Cell adaptation

Dr. Widad Abd AL-Jabbar

CELL INJURY

Cells can be damaged in a number of ways, including physical trauma, extremes of temperature, electrical injury, exposure to damaging chemicals, radiation damage, injury from biologic agents, and nutritional factors.

The extent to which any injurious agent can cause cell injury and death depends in large measure on the intensity and duration of the injury and the type of cell that is involved.

Cell injury is usually reversible up to a certain point, after which irreversible cell injury and death occur.

Whether a specific stress causes irreversible or reversible cell injury depends on the severity of the insult and on variables such as blood supply, nutritional status, and regenerative capacity. Cell injury and death are ongoing processes, and in the healthy state, they are balanced by cell renewal

Most injurious agents exert their damaging effects through uncontrolled free radical production, impaired oxygen delivery or utilization, or the destructive effects of uncontrolled intracellular calcium release.

Causes of Cell Injury

Cell damage can occur in many ways. the ways by which cells are injured have been grouped into five categories:

1. Injury from physical agents
2. Radiation injury
3. Chemical injury
4. Injury from biologic agents
5. Injury from nutritional imbalances

1-Injury from Physical Agents

Physical agents responsible for cell and tissue injury include mechanical forces, extremes of temperature, and electrical forces.

• **Mechanical Forces**. Injury or trauma due to mechanical forces occurs as the result of body impact with another object. The body or the mass can be in motion or, as sometimes happens, both can be in motion at the time of impact. These types of injuries split and tear tissue, fracture bones, injure blood vessels, and disrupt blood flow.

• **Extremes of Temperature**. Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems. Exposure to low-intensity heat (43°C to 46°C), such as occurs with partial-thickness burns and severe heat stroke, causes cell injury by inducing vascular injury, accelerating cell metabolism, inactivating temperaturesensitive enzymes, and disrupting the cell membrane. Exposure to cold increases blood viscosity and induces vasoconstriction by direct action on blood vessels and through reflex activity of the sympathetic nervous system.

The resultant decrease in blood flow may lead to hypoxic tissue injury,

• **Electrical Injuries**. Electrical injuries can affect the body through extensive tissue injury and disruption of neural and cardiac impulses

2-Radiation Injury

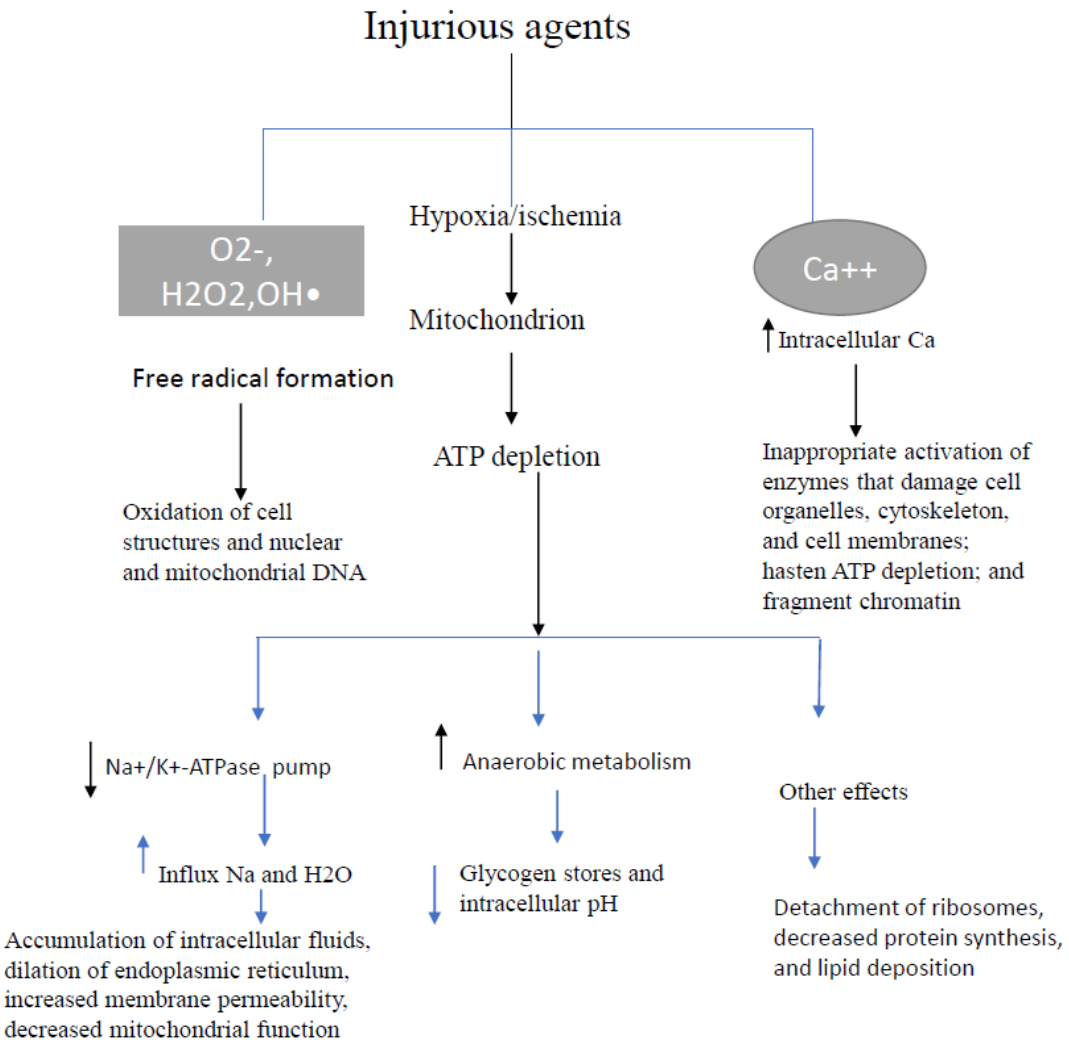
Radiation energy above the ultraviolet (UV) range is called ionizing radiation,

Ionizing radiation: impacts cells by causing ionization of molecules and atoms in the cell. This is accomplished by releasing free radicals that destroy cells and by directly hitting the target molecules in the cell .It can immediately kill cells, interrupt cell replication, or cause a variety of genetic mutations) which may or may not be lethal

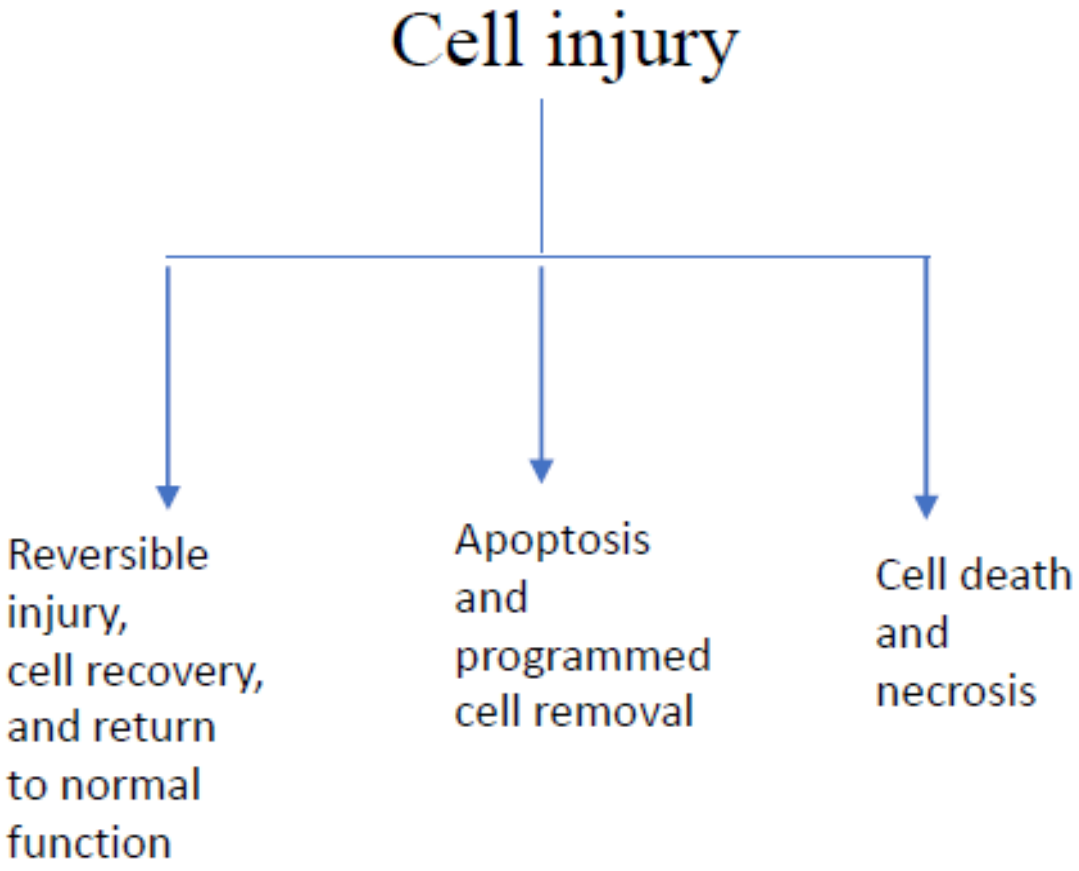
- **Nonionizing radiation: refers to** radiation energy at frequencies below those of visible light Nonionizing radiation includes infrared light, ultrasound, microwaves, and laser energy. Injury from these sources is mainly thermal and, because of the deep penetration of the infrared or microwave rays, tends to involve dermal and subcutaneous tissue injury.
- **Ultraviolet Radiation:** Ultraviolet radiation causes sunburn and increases the risk of skin cancers. The degree of risk depends on the type of UV rays, the intensity of exposure, and the amount of protective melanin pigment in the skin.
- Skin damage produced by UV radiation is thought to be caused by reactive oxygen species (ROS) and by damage to melanin-producing processes in the skin.
- Chemical Injury
- Chemicals capable of damaging cells are everywhere around us. Air and water pollution contains chemicals capable of tissue injury, as does tobacco smoke and some processed or preserved foods. Some of the most damaging chemicals exist in our environment, including gases such as carbon monoxide, insecticides, and trace metals such as lead. Chemical agents can injure the cell membrane and other cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of the cell.
- Corrosive substances such as strong acids and bases destroy cells as the substances come into contact with the body. Other chemicals may injure cells in the process of metabolism or elimination. Carbon tetrachloride (CCl_4), for example, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical ($CCl_3\bullet$). Carbon tetrachloride is extremely toxic to liver cells.
- Injury from Nutritional Imbalances: Nutritional excesses and nutritional deficiencies predispose cells to injury. Obesity and diets high in saturated fats are thought to predispose persons to atherosclerosis.

- Injury from Biologic Agents
- Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects. These agents range from submicroscopic viruses to the large parasites.(Viruses enter the cell and become incorporated into its DNA synthetic machinery. Certain bacteria elaborate exotoxins that interfere with cellular production of ATP. Other bacteria, such as the gram-negative bacilli, release endotoxins that cause cell injury and increased capillary permeability.
- Mechanisms of Cell Injury:
- There seem to be at least three major mechanisms whereby most injurious agents exert their effects:
- Free radical formation
- Hypoxia and ATP depletion
- Disruption of intracellular calcium homeostasis

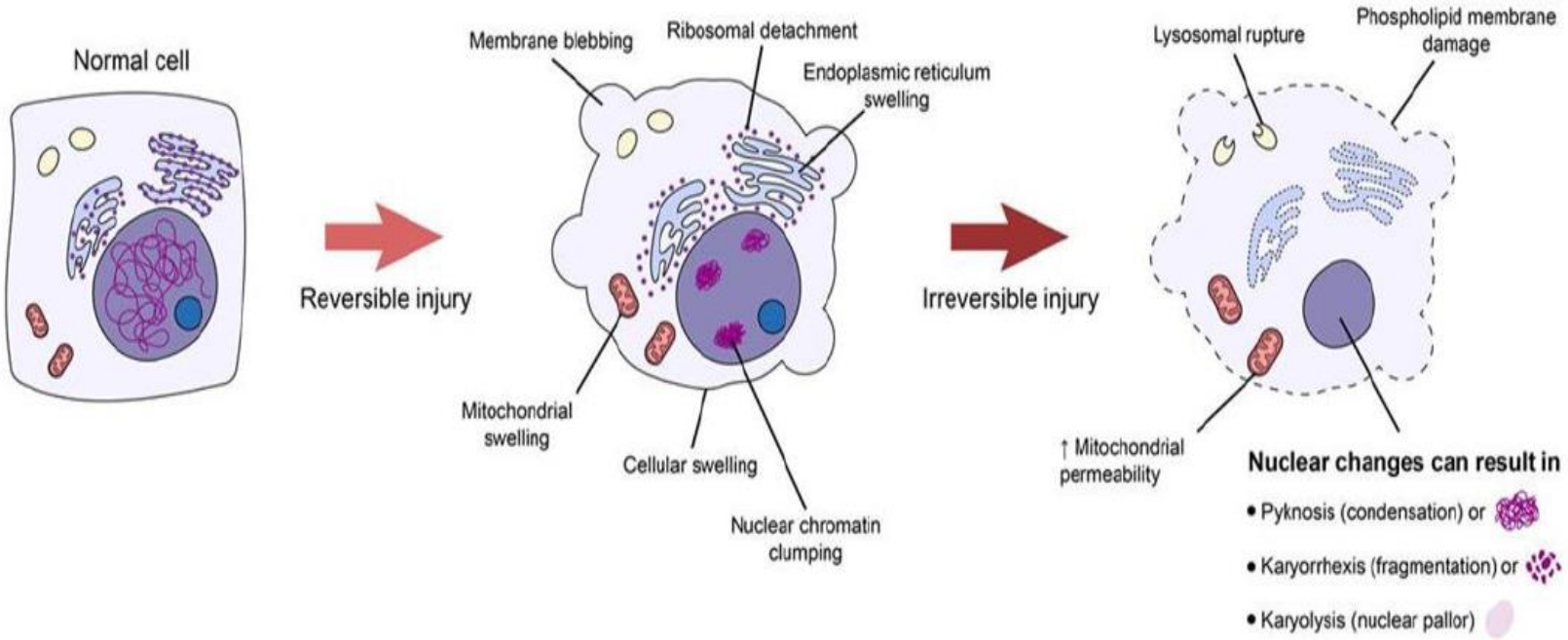
Mechanisms of cell injury



- Reversible Cell Injury and Cell Death
- The mechanisms of cell injury can produce sublethal and reversible cellular damage or lead to irreversible injury with cell destruction or death. Cell destruction and removal can involve one of two mechanisms:
- Apoptosis, which is designed to remove injured or worn-out cells
- Cell death or necrosis, which occurs in irreversibly damaged cells
- Reversible Cell Injury
- Reversible cell injury, although impairing cell function, does not result in cell death. Two patterns of reversible cell injury can be observed under the microscope: cellular swelling and fatty change. Cellular swelling occurs with impairment of the energy-dependent Na^+/K^+–ATPase membrane pump, usually as the result of hypoxic cell injury

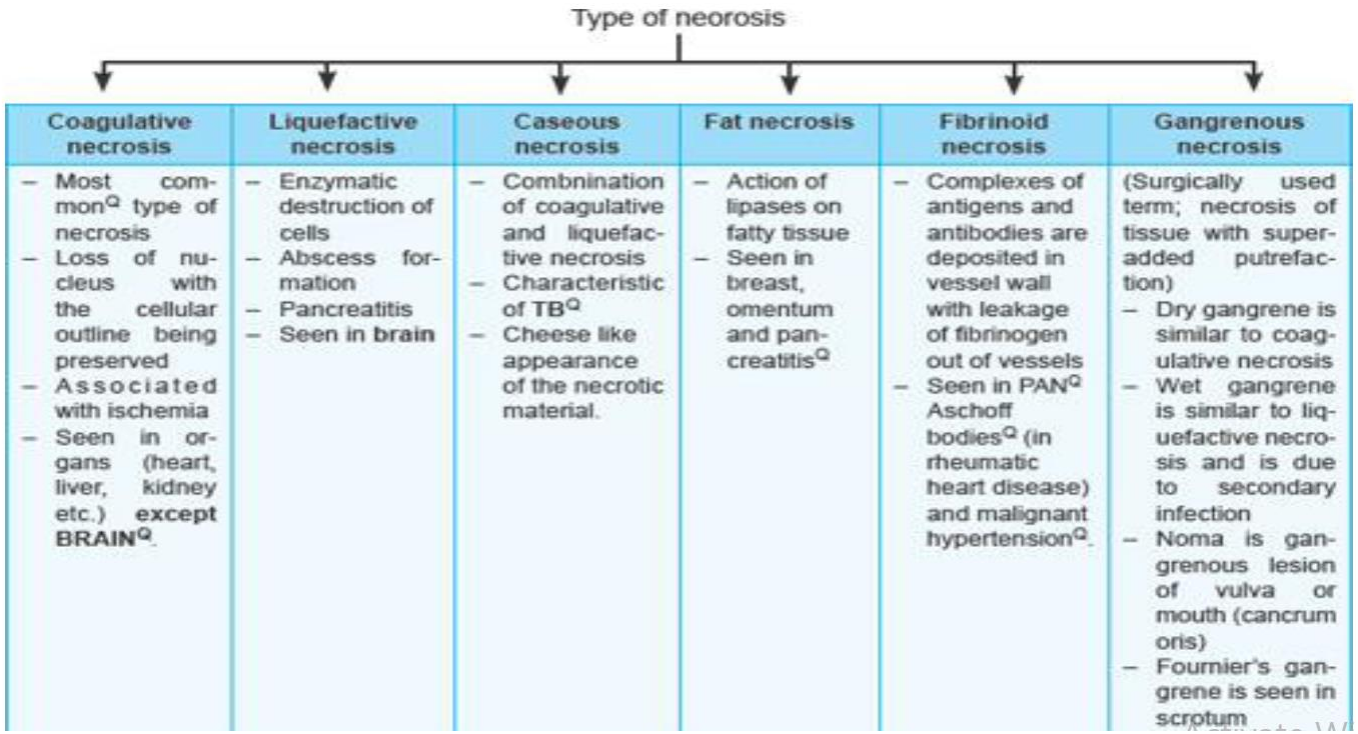

Cell injury
Reversible injury, cell recovery, and return to normal function
Apoptosis and programmed cell removal
Cell death and necrosis

Cell Injury


Normal cell
Reversible injury
Membrane blebbing
Ribosomal detachment
Endoplasmic reticulum swelling
Mitochondrial swelling
Cellular swelling
Nuclear chromatin clumping
Irreversible injury
Lysosomal rupture
Phospholipid membrane damage
↑ Mitochondrial permeability
Nuclear changes can result in
• Pyknosis (condensation) or
• Karyorrhexis (fragmentation) or
• Karyolysis (nuclear pallor)

- Programmed Cell Death(Apoptosis)
- In most normal nontumor cells, the number of cells in tissues is regulated by balancing cell proliferation and cell death.
- Cell death occurs by necrosis or a form of programmed cell death called apoptosis.
- Apoptosis is a highly selective process that eliminates injured and aged cells, thereby controlling tissue regeneration. Cells undergoing apoptosis have characteristic morphologic features as well as biochemical changes.
- Necrosis
- Necrosis refers to cell death in an organ or tissue that is still part of a living organism. Necrosis differs from apoptosis since it causes loss of cell membrane integrity and enzymatic breakdown of cell parts and triggers the inflammatory process .In contrast to apoptosis, which functions in removing cells so new cells can replace them

	Necrosis *(uncontrolled cell death)*	Apoptosis *(programmed cell suicide)*
Size	Cellular swelling	Cellular shrinkage
	Many cells affected	One cell affected
Uptake	Cell contents ingested by macrophages	Cell contents ingested by neighbouring cells
	Significant inflammation	No inflammatory response
Membrane	Loss of membrane integrity	Membrane blebbing, but integrity maintained
	Cell lysis occurs	Apoptotic bodies form
Organelles	Organelle swelling and lysosomal leakage	Mitochondria release pro-apoptotic proteins
	Random degradation of DNA	Chromatin condensation and non-random DNA degradation

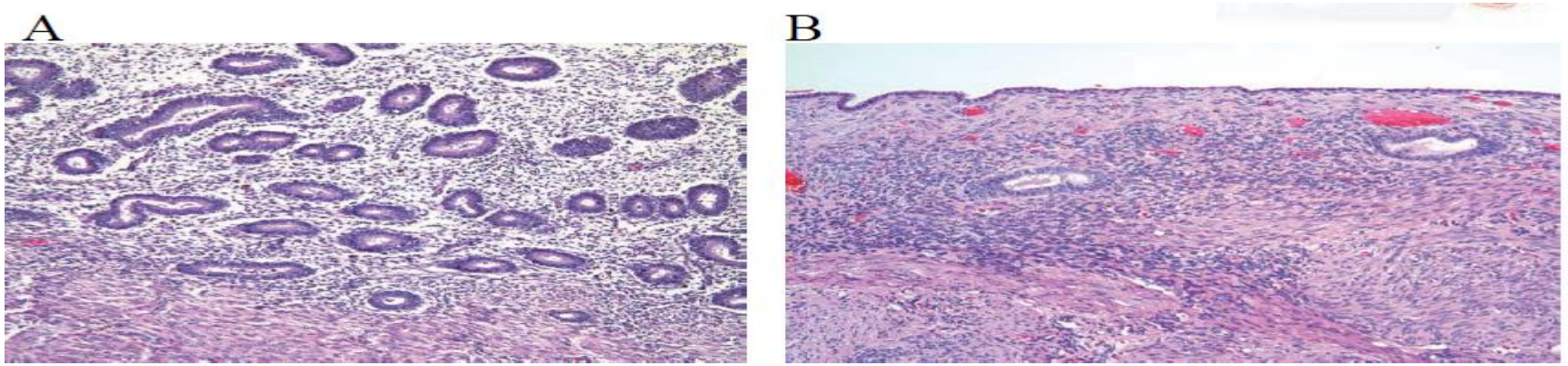


Coagulative necrosis	Liquefactive necrosis	Caseous necrosis	Fat necrosis	Fibrinoid necrosis	Gangrenous necrosis
– Most common[Q] type of necrosis – Loss of nucleus with the cellular outline being preserved – Associated with ischemia – Seen in organs (heart, liver, kidney etc.) **except BRAIN**[Q].	– Enzymatic destruction of cells – Abscess formation – Pancreatitis – Seen in **brain**	– Combnination of coagulative and liquefactive necrosis – Characteristic of TB[Q] – Cheese like appearance of the necrotic material.	– Action of lipases on fatty tissue – Seen in breast, omentum and pancreatitis[Q]	– Complexes of antigens and antibodies are deposited in vessel wall with leakage of fibrinogen out of vessels – Seen in PAN[Q] Aschoff bodies[Q] (in rheumatic heart disease) and malignant hypertension[Q].	(Surgically used term; necrosis of tissue with superadded putrefaction) – Dry gangrene is similar to coagulative necrosis – Wet gangrene is similar to liquefactive necrosis and is due to secondary infection – Noma is gangrenous lesion of vulva or mouth (cancrum oris) – Fournier's gangrene is seen in scrotum

- # Cellular Adaptation, Injury, and Death
- Cells adapt to changes in the internal environment, just as the total organism adapts to changes in the external environment. Cells may adapt by undergoing changes in size, number, and type. These changes, occurring singly or in combination, may lead to:
- • Atrophy
- • Hypertrophy
- • Hyperplasia
- • Metaplasia
- • Dysplasia
- **CELLULAR ADAPTATIONS**
- • Cells are able to adapt to(increased work demands or threats to survival by changing their size) (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia).
- • Normal cellular adaptation occurs in response to an appropriate stimulus and ceases once the need for adaptation has ceased.
- **Atrophy:** decrease in size of a body part, cell, organ, or other tissue, due to decrease in work demands or adverse environmental conditions, Cells that are atrophied reduce their oxygen consumption and other cellular functions by decreasing the number and size of their organelles and other structures, When a sufficient number, of cells are involved, the entire tissue or muscle atrophies.
- Cell size, particularly in muscle tissue, is related to workload. As the workload of a cell declines, oxygen consumption and protein synthesis decrease.

The general causes of atrophy can be grouped into five categories:

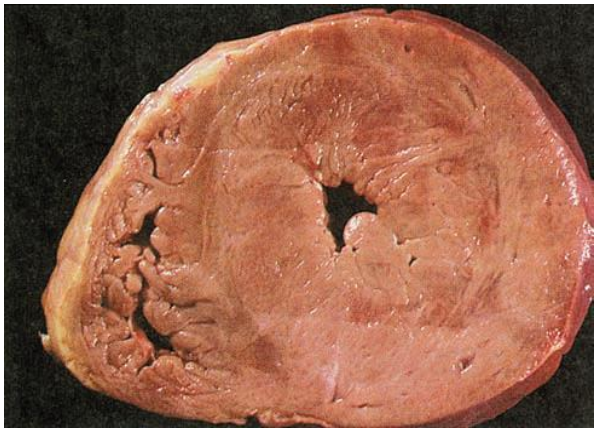
1. Disuse
2. Denervation
3. Loss of endocrine stimulation
4. Inadequate nutrition
5. Ischemia or decreased blood flow



Atrophy of cells in endometrium. (A) This illustrates a piece of a woman of reproductive age who has a normal thick endometrium. (B) This section of endometrium is of a 75-year-old woman that shows atrophic cells and cystic glands

- Disuse atrophy occurs when there is a reduction in skeletal muscle use. An extreme example of disuse atrophy is seen in the muscles of extremities that have been encased in plaster casts. Because atrophy is adaptive and reversible, muscle size is restored after the cast is removed and muscle use is resumed.
- Denervation atrophy is a form of disuse atrophy that occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation produces a form of disuse atrophy. In women, the loss of estrogen stimulation during menopause results in atrophic changes in the reproductive organs.
- With malnutrition and decreased blood flow, cells decrease their size and energy requirements as a means of survival.
- **Hypertrophy:** represents an increase in cell size and with it an increase in the amount of functioning tissue mass It
- results from an increased workload imposed on an organ or body part and is commonly seen in cardiac and skeletal muscle tissue, which cannot adapt to an increase in workload through mitotic division and formation of more cells.
- It involves an increase in the functional components of the cell that allows it to achieve equilibrium between demand and functional capacity. For example, as muscle cells hypertrophy, additional actin and myosin filaments, cell enzymes, and adenosine triphosphate (ATP) are synthesized.
- Hypertrophy may occur as the result of normal physiologic or abnormal pathologic conditions.
- The increase in muscle mass associated with exercise is an example of physiologic hypertrophy.
- Pathologic hypertrophy occurs as the result of disease conditions and may be adaptive or compensatory.
- Examples of adaptive hypertrophy(are the thickening of the urinary bladder from long-continued obstruction of
- urinary outflow and the myocardial hypertrophy that results from valvular heart disease or hypertension).
- Compensatory hypertrophy is the enlargement of a remaining organ or tissue after a portion has been surgically
- removed or rendered inactive. For instance, if one kidney is removed, the remaining kidney enlarges to compensate
- for the loss.

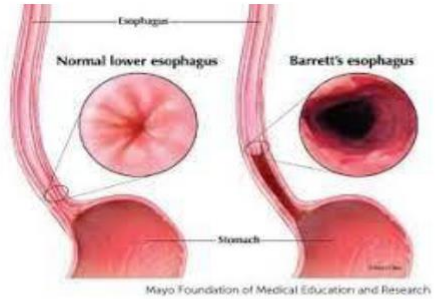
- Research suggests that certain signal molecules can alter gene expression controlling the size and assembly of the contractile proteins in hypertrophied myocardial cells. For example, the hypertrophied myocardial cells of well-trained athletes have proportional increases in width and
- length. This is in contrast to the hypertrophy that develops in dilated cardiomyopathy, in which the hypertrophied cells have a relatively greater increase in length than width.

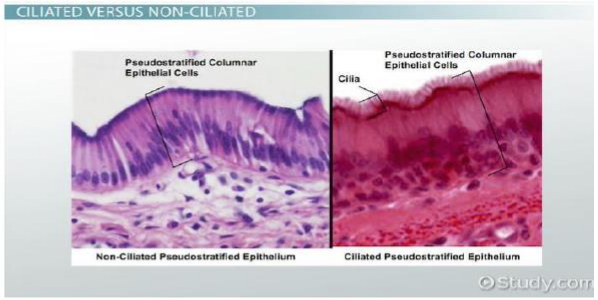


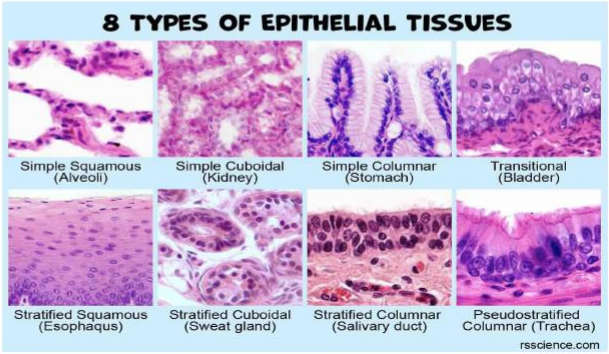
Myocardial hypertrophy.
Cross section of the heart with left ventricular hypertrophy.

- Hyperplasia:
- Hyperplasia refers to an increase in the number of cells in an organ or tissue. It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue. Certain cells, such as neurons, rarely divide and therefore have little capacity.
- As with other normal adaptive cellular responses, hyperplasia is a controlled process that occurs in response to an appropriate stimulus and ceases after the stimulus has been removed. The stimuli that induce hyperplasia may be physiologic or non physiologic. There are two common types of physiologic hyperplasia: hormonal and compensatory.(Breast and uterine enlargements during pregnancy are examples of a physiologic hyperplasia that results from estrogen stimulation). The regeneration of the liver that occurs after partial hepatectomy (i.e., partial removal of the liver) is an example of compensatory hyperplasia.
- Hyperplasia is also an important response of connective tissue in wound healing.
- Most forms of non physiologic hyperplasia are due to excessive hormonal stimulation or the effects of growth factors on target tissues, For example, excessive estrogen production can cause endometrial hyperplasia and abnormal menstrual bleeding. Endometrial hyperplasia is considered a high risk for developing endometrial cancer and is a condition that is monitored carefully.
- Benign prostatic hyperplasia (BPH), which is a common disorder of men older than 50 years of age, is related to the action of androgens. BPH is a nonmalignant condition that causes lower urinary tract symptoms. BPH sometimes develops into prostate cancer.
- Skin warts are another example of hyperplasia caused by growth factors produced by certain viruses, such as the papillomaviruses.

- Metaplasia
- Metaplasia represents a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. Metaplasia is thought to involve the reprogramming of undifferentiated stem cells that are present in the tissue undergoing the metaplastic changes Metaplasia usually occurs in response to chronic irritation and inflammation and allows for substitution of cells that are better able to survive under circumstances in which a more fragile cell type might succumb. However, the conversion of cell types never oversteps the boundaries of the primary tissue type (e.g., one type of epithelial
- cell may be converted to another type of epithelial cell, but not to a connective tissue cell). An example of metaplasia is the adaptive substitution of stratified squamous epithelial cells for the ciliated columnar epithelial cells in the trachea and large airways of a habitual cigarette
- smoker.
- Barrett esophagus is a premalignant condition that occurs in the esophagus of people with chronic gastroesophageal reflux disease (GERD).
- Barrett esophagus is the primary risk factor for developing esophageal adenocarcinoma


Esophagus
Normal lower esophagus
Barrett's esophagus
Stomach
Mayo Foundation of Medical Education and Research


CILIATED VERSUS NON-CILIATED
Pseudostratified Columnar Epithelial Cells
Pseudostratified Columnar Epithelial Cells
Cilia
Non-Ciliated Pseudostratified Epithelium
Ciliated Pseudostratified Epithelium
Study.com


8 TYPES OF EPITHELIAL TISSUES
Simple Squamous (Alveoli)
Simple Cuboidal (Kidney)
Simple Columnar (Stomach)
Transitional (Bladder)
Stratified Squamous (Esophaqus)
Stratified Cuboidal (Sweat gland)
Stratified Columnar (Salivary duct)
Pseudostratified Columnar (Trachea)
rsscience.com

Dysplasia

- Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and organization. Minor degrees of dysplasia are associated with chronic irritation or inflammation.
- The pattern is most frequently encountered in areas of metaplastic squamous epithelium of the respiratory tract and uterine cervix. Although dysplasia is abnormal, it is adaptive in that it is potentially reversible after the irritating cause has been removed.