Lec1 General Pathplogy Dr.Afrah Adnan

Introduction

The word **'Pathology'** is derived from two Greek words pathos (meaning suffering) and logos (meaning study). Pathology is scientific study of abnormal changes in the structure and function of the body in disease in order to reach specific diagnosis and successful treatment.

Pathology involves the investigation of:

- Etiology of the disease (causes)
- Pathogenesis of the disease (the underlining mechanism that result in signs and symptoms of the disease)
- Morphology (the gross or microscopic identifying changing in cells, tissues and organs)

Latent period: some etiological agents takes some time to manifest the disease (e.g. carcinogenesis) and It varies depending on the disease.

Incubation period: it is the period between exposure to causative agent which is usually infectious (due to bacteria, viruses, etc.) and the development of disease and it is usually ranges from days to weeks.

Basic Pathology in order to study is subdivided into:

- General pathology: study of cellular and tissue responses to pathologic stimuli.
- Systemic pathology: study of particular responses of specialized organs.

Disease: it is abnormal variation in structure or function of any part of the body.

Patient: is the person affected by disease.

Lesions: are the characteristic changes in tissues and cells produced by disease.

Syndrome: The term is used for a combination of several clinical features caused by altered physiologic processes (meaning running together).

General causes of the diseases:

a. Genetic determined diseases: abnormality of DNA that is inherited from one or both parents.

b. Acquired diseases that includes:

1. Deficiency diseases (such as iron deficiency anemia)
2. Physical agents (mechanical injury by heat, cold or irradiation)
3. Chemical and drug injury (cyanide, strong acid and alkalis)
4. Infectious microorganism (bacteria, fungi and viruses)
5. Immunological factors (the harmful effect of immunity due to reaction of antibodies and lymphocyte against microbes and toxic products.
6. Psychologic factors (schizophrenia, depression)
7. Diseases of addiction (alcohol, tobacco and drugs)

Branches of pathology:

- **Histopathology:** examination of the diseased tissues by light or electron microscopes. Sections are routinely cut from tissues and processed by pararffin-embedding. The sections are cut from the tissue by a special instrument called microtome and examined under light microscope. It includes the following subdivisions:
    1. **Surgical pathology:** study of biopsy from surgical resection.
    2. **Experimental pathology:** production of disease in the experimental animal and study of morphological changes in organs after sacrificing the animal.
    3. **Forensic pathology:** examination of autopsy at postmortem for medico-legal work and for determining the underlying sequence and cause of death. 'the dead teach the living'.
- **Cytopathology:** examine the single cells from the patient rather than tissue. The sample is obtained by fine needle aspiration (FNA) or suction or scraping from a surface (exfoliative cytology), which is the technique used for cervical screening (the Pap smear). Fluids such as urine, sputum or a pleural effusion can also be obtained for cytological examination. The resulting specimen is smeared on a glass slide, fixed, stained and examined under the microscope. A major advantage of

cytology examinations is that saving time. However, great skill is required to interpret the appearances of individual cells without the advantage of seeing the tissue architecture.

Hematology: examine the blood diseases.

Clinical Pathology: qualitative and/or quantitative analysis of body fluids (blood, urine, semen, CSF and other).

Clinical Biochemistry: study the biochemical constituents in serum and plasma, and in other body fluids.

Microbiology: study of disease-causing microbes in human. It include: bacteriology, parasitology, mycology, virology etc.

Immunology: study abnormalities in the immune system and immunopathology.

Medical Genetics: study human genetics and link the relationship between heredity and disease.

Molecular Pathology: detect and diagnose the abnormalities at the level of DNA of the cell is included in situ hybridization, PCR and others.

Homeostasis

It is defined as the state of balance between the cells or tissues and the environment. From the environment the cell receives nutrients, oxygen, water, and essential minerals; it generates energy by burning some of the calories derived from the nutrients. This energy is used for integrity and function of the nucleus, cytoplasm, cell organelles, and plasma membranes.

When an equilibrium between the cells and their environment is achieved and maintained, the cells are said to be in a steady state. External stimuli may alter this

equilibrium that cells try to adapt this changes, the adaptation is temporary and the cell may revert to the original steady state after the external demands cease.

If the demands exceed the capacity of the cell to adapt, a cell injury may occur for ex; a pulled muscle that has exceeded its ability to stretch, has ruptured, and cannot contract any more, the cell has passed its point of no return and damaged.

Cellular adaptations to stress

Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment. It is two types:

Physiologic adaptations usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy), or to the demands of mechanical stress (in the case of bones and muscles).

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.

Hypertrophy

It is an increase in the size of cells resulting in an increase in the size of the organ. Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or by growth factor or hormonal stimulation.

Ex; The physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogen stimulated (Hypertrophy and hyperplasia also can occur together)

Increased workload the striated muscle cells in both the skeletal muscle and the heart undergo only hypertrophy because adult muscle cells have a limited capacity to divide.

An example of pathologic hypertrophy is the cardiac enlargement that occurs with hypertension or aortic valve disease

Hyperplasia

It is an increase in the number of cells in an organ, hyperplasia takes place if the tissue contains cell populations capable of replication; it may occur concurrently with hypertrophy and often in response to the same stimuli.

Hyperplasia can be physiologic or pathologic:

Hormonal hyperplasia results in proliferation of the glandular epithelium of the female breast at puberty and during pregnancy, compensatory hyperplasia, in which residual tissue grows after removal or loss of part of liver, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal size.

Pathologic hyperplasia associated with certain viral infections; for example, papillomaviruses cause skin warts.

Atrophy

It is shrinkage in the size of cells by the loss of cell substance. When a sufficient number of cells are involved, the entire tissue or organ is reduced in size, or atrophic.

Causes of atrophy include a decreased workload (e.g., immobilization of a limb to permit healing of a fracture), loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging.

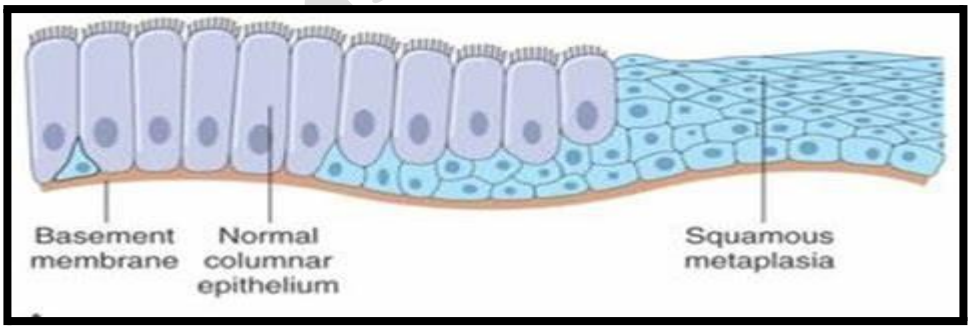
Metaplasia

It is a change in the cell type (epithelial or mesenchymal) and replaced by another cell type. In this type of cellular adaptation, a cell type sensitive to a particular stress is replaced by another cell type better able to withstand the adverse environment.

Ex; metaplasia in the respiratory epithelium of habitual cigarette smokers, in whom the normal ciliated columnar epithelial cells of the trachea and bronchi often are replaced by stratified squamous epithelial cells. Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter. Epithelial metaplasia is therefore a double-edged sword. Another cause of metaplasia in respiratory epithelium is vitamin A deficiency.

Metaplasia the normal stratified squamous epithelium of the lower esophagus may undergo metaplastic transformation to gastric or intestinal-type columnar epithelium in chronic gastric reflux. The influences that induce metaplastic change in an epithelium, if persistent, may predispose to malignant transformation.

Dysplasia is a broad term that refers to the abnormal development of cells within tissues or organs. Dysplasia can occur in any area of the body and can vary in degree of severity. It can lead to a wide range of conditions that involve enlarged tissue or precancerous or cancerous cells. Some of the possible factors contribute to the development of dysplasia include: infections, smoking, and exposure to carcinogenic toxins.



References:

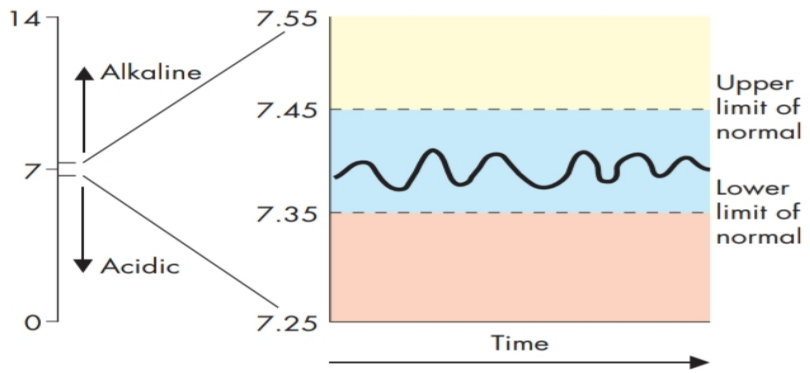
- **Text book of general pathology; Harsh Mohan; 7th edition; 2015 ;Jaypee.**
- **Robbins basic pathology; Kumar etal, 2013; 9th edition; Elsevier.**

Lec 2 General Pathology Dr. Afrah Adnan

Homeostasis

It is defined as the body maintaining stable, constant conditions, despite changes in the environment. The term is derived from homeo (meaning similar) and stasis (meaning steady).

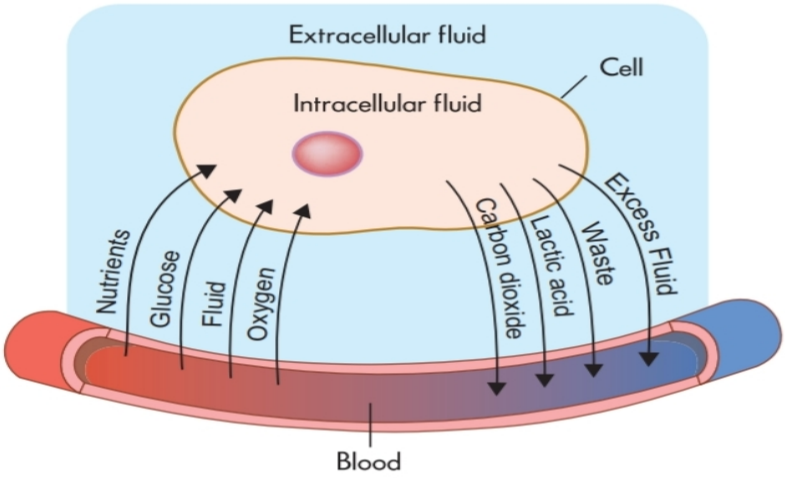
🔗 The normal level for a particular variable is usually a range of values. This is known as the normal range (or reference range), so that slight increases or decreases in value may still be within normal levels. For example, the normal range of blood pH is between 7.35 and 7.45 in a healthy individual.



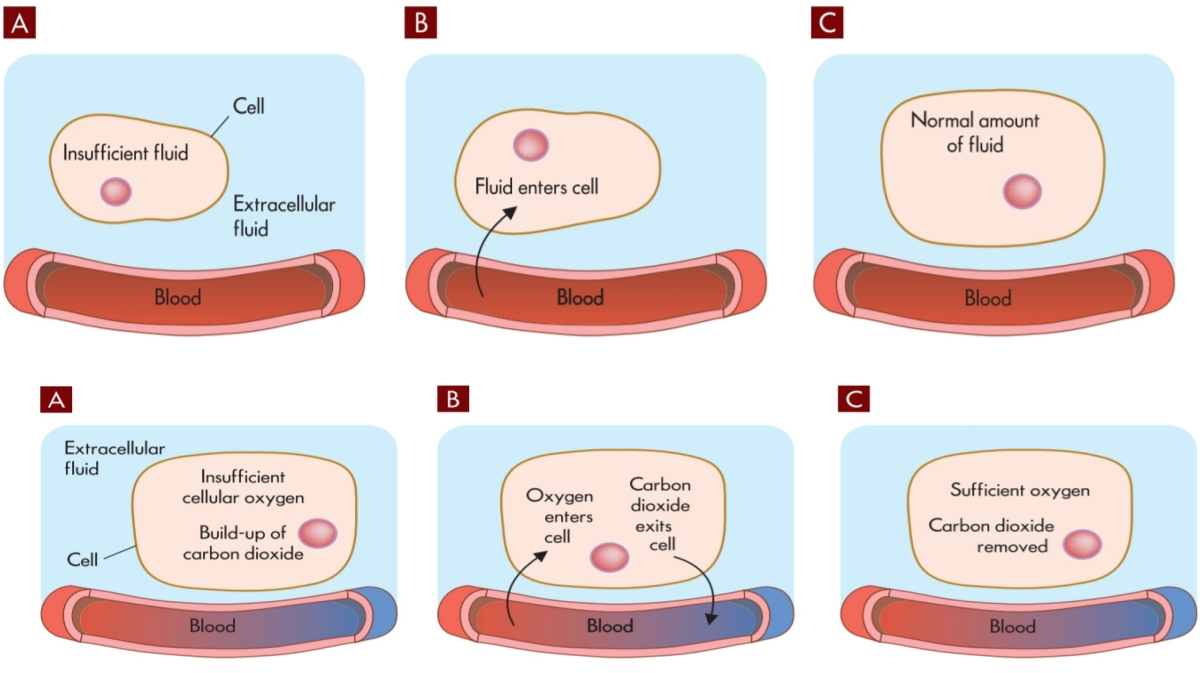
🔗 Homeostasis such as temperature, pressure and amount of nutrients and wastes traveling through the blood and extracellular fluid vary, even in a resting individual. All cells need to have a stable environment to continue functioning normally; thus homeostasis is necessary.

📎 When fluid levels inside the intracellular environment drop, the cell obtains additional fluid from the surrounding extracellular fluid. Similarly, if oxygen levels in the cell are too low and carbon dioxide is allowed to

accumulate, then exchange with the blood and extracellular fluid restores these levels in the cell back to normal.

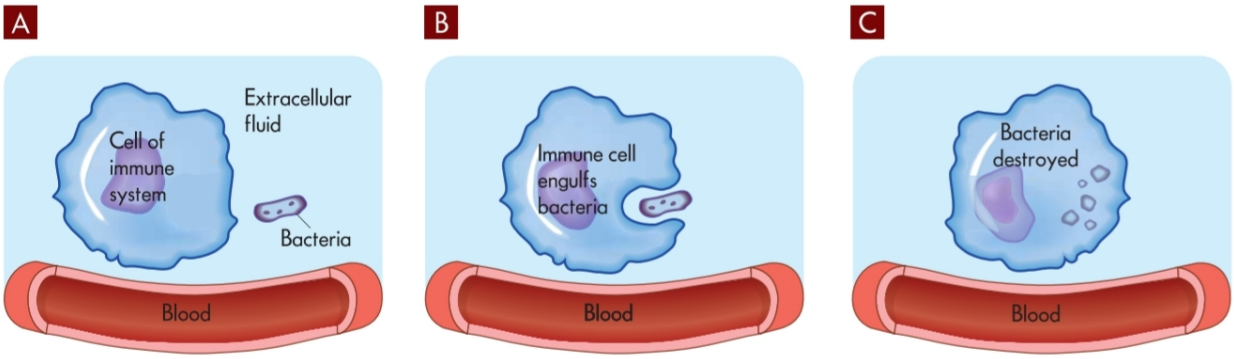


📎 The levels of ions (or electrolytes) within the cell also need to be maintained in the appropriate range for normal cellular function. In particular, the relative proportions of the ions sodium, potassium and calcium are the most critical ions required for neurons (nerve cells) to function.



Homeostasis at the local level

Cells of the immune system function in their environment to maintain local homeostasis by destroying foreign substances such as bacteria. This contributes to homeostasis of not just the cell, but also the local tissues. Other examples of local area homeostasis are wound healing and blood clotting.



Homeostasis at the body level constancy within the cells leads to homeostasis of the whole body in addition to coordination of the central nervous system (the brain and spinal cord), as well as the endocrine system is essential in maintaining the harmony of all body systems. Disturbances of homeostasis lead to pathophysiology

When the body's ability to compensate for changes and maintain homeostasis is exceeded, disorders and disease occur. The original cause of a problem may be a source external to the body, such as use of drugs, or a source internal to the body, such as occurs with aging.

Cellular adaptation

Cells have the ability to adapt under stress, they adapt to their environment to escape and protect themselves from injury. An adapted cell is neither normal nor injured. Cellular adaptation is the ability of cells to respond to various types of stimuli and adverse environmental changes. The most significant adaptive changes in cells are:

- Atrophy, where the cells decrease in size and function
- Hypertrophy, where individual cells increase in size
- Hyperplasia, where the number of cells increases
- Metaplasia, where the cells change from one mature cell type into another type.

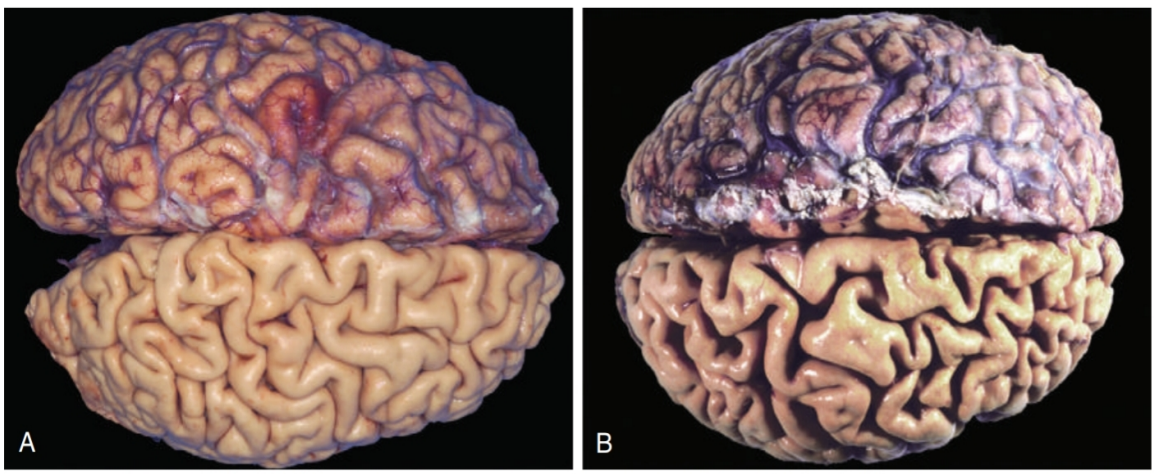
Another change, which is not truly adaptive, is dysplasia. This involves abnormal change in the size, shape and arrangement of mature cells.

Atrophy:

It is a decrease or shrinkage in cellular size and consequently in the size of the affected organ. Atrophy can affect any organ, but it is most common in skeletal muscle, the heart, secondary sex organs and the brain, and is especially related to aging. Cells that have atrophied contain less endoplasmic reticulum and fewer mitochondria than normal cells. These cells also reduce their oxygen consumption, decreased amino acid uptake, decreased protein production, increased protein catabolism (breakdown), or

both. Atrophy can be classified as physiological or pathological:

- Physiological atrophy occurs in early development as an example the thymus gland undergoes the normal process of physiological atrophy during childhood. The reasons for this are unknown.
- Pathological atrophy occurs as a result of decreases in workload, pressure, use, blood supply, nutrition and hormonal and nervous system stimulation. Ex; Individuals immobilized in bed for a prolonged time exhibit a type of skeletal muscle atrophy called disuse atrophy. This is prevalent in hospitalized patients who cannot be mobilized; also in case of patients with multiple bone fractures or significant obesity. Aging causes brain cells to become atrophic and endocrine-dependent organs such as the gonads (testes or ovaries) shrink as hormonal stimulation decreases. Whether atrophy is caused by normal physiological conditions or by pathological conditions, atrophic cells exhibit the same basic changes.



Atrophy as seen in the brain. (A) Normal brain of a young adult. (B) Atrophy of the brain in an 82-year-old man with atherosclerotic

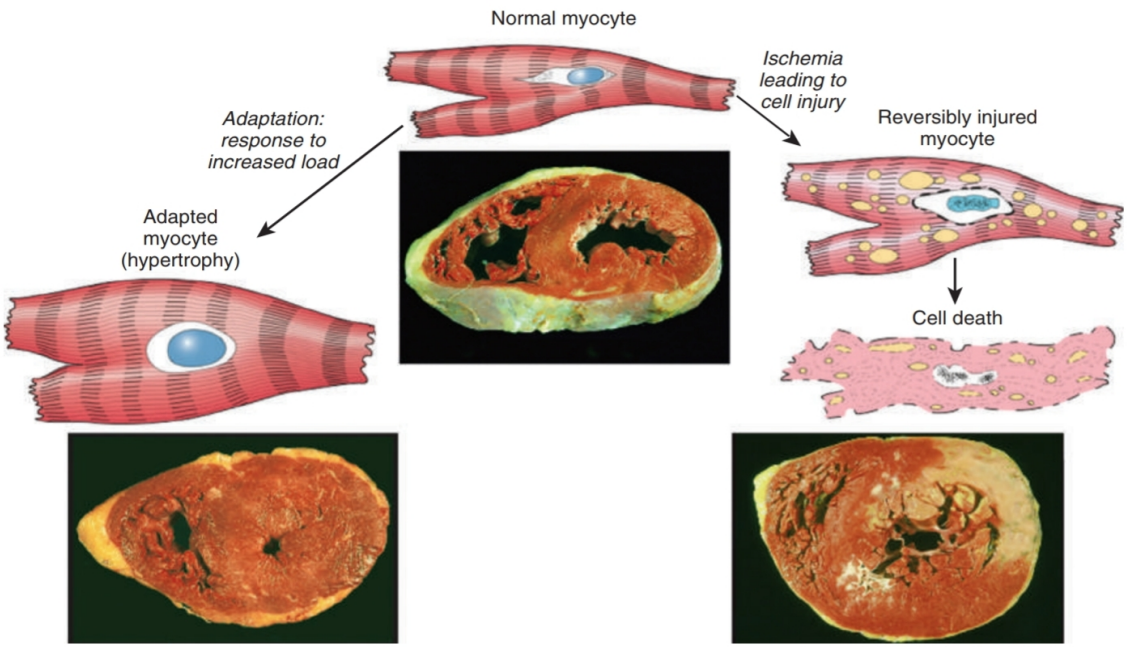
Causes of pathological atrophy:

- **Starvation atrophy:** there is reduction in CHO, fat, followed by protein. There is general weakness, anaemia e.g. Cancer, chronic illness.
- **Ischaemic atrophy ;** Due to decrease in blood supply which leads to shrinkage of the affected organ. gradual obstruction of the renal artery leads to ischaemic atrophy of the kidney , brain atrophy in cerebrovascular diseases.
- **Disuse atrophy:** prolonged immobilization or decrease activity of the affected organ or tissue. e.g. wasting of the limb after fracture
- **Neuropathic atrophy:** damage to the nerve supply e.g.: poliomyelitis .
- **Endocrine atrophy {hormonal atrophy}:** Loss of endocrine regulatory mechanisme.g.hypopitutarism cause atrophyof the Thyroid , atrophy of the adrenals .
- **Pressure atrophy:** prolong pressure on tissue causes atrophy . e.g.: pressure of tumor on the adjacent tissues, pressure on blood vessels etc.
- **Exhaustion atrophy:** Due to over activity of the cell population may end with atrophy e.g.: atrophy of the thyroid, adrenals ....etc
- **Idiopathic atrophy:** the cause is unknown e.g. myopathies.of the bone.

Hypertrophy:

It is an increase in the size of cells and consequently in the size of the affected organ. The cells of the heart and kidneys are particularly prone to enlargement. The increased cellular size is associated with an increased accumulation of protein in the cellular components (the cell membrane, endoplasmic reticulum and mitochondria) and not with an increase in cellular fluid. Hypertrophy, like atrophy, can be physiological or pathological and is caused by specific hormone stimulation, hormonal stimulation or by increased functional demand.

🕯️ Physiological hypertrophy of skeletal muscles occurs in response to heavy work repeatedly. Another example of normal or physiological hypertrophy is the increased growth of the uterus and mammary glands in response to pregnancy.



- Pathological example is pathophysiological hypertrophy of the heart, secondary to mechanical problems, such as faulty heart valves.

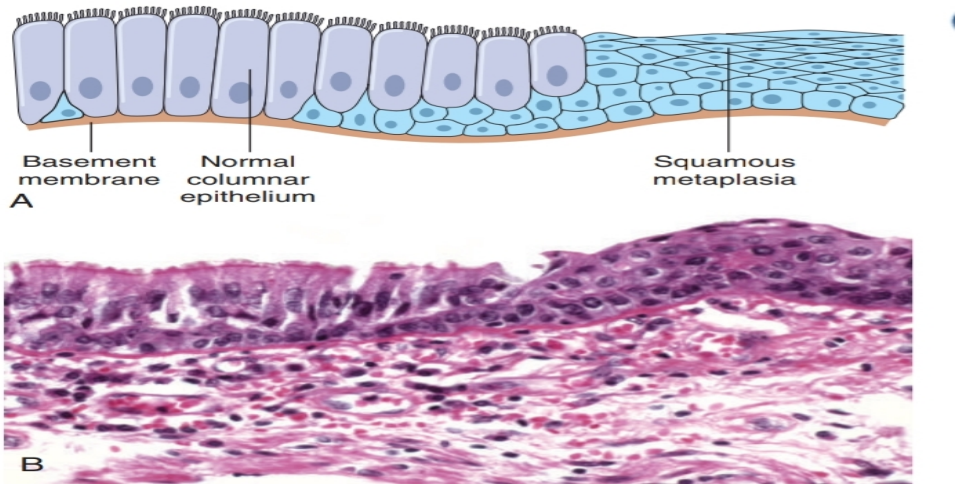
Hyperplasia:

It is an increase in the number of cells resulting from an increased rate of cellular division. Increased cell growth is a multistep process involving the production of growth factors that stimulate the remaining cells to divide. Hyperplasia and hypertrophy often occur together; however, in non-dividing cells only hypertrophy occurs. Two types of normal, or physiological, hyperplasia are:

- **Compensatory hyperplasia:** is an adaptive mechanism that enables certain organs to regenerate. For example, removal of part of the liver leads to hyperplasia of the remaining liver cells (hepatocytes) to compensate for the loss. Even with removal of 70% of the liver, regeneration of the liver occurs over time.
- **Hormonal hyperplasia:** occurs in response to release of a hormone. The most common example of this is enlargement of the uterus in pregnancy.
- **Pathological hyperplasia:** is abnormal proliferation of normal cells usually in response to excessive hormonal stimulation or growth factors on target cells. Ex; enlargement of the prostate which occurs in a significant proportion of males over the age of 60 years.

Metaplasia:

It is the reversible replacement of one mature cell type by another, sometimes less differentiated cell type. It is thought to develop from a reprogramming of stem cells in epithelial or connective tissue. This may be precipitated by a persistent irritant to the cells, such as cigarette smoking. Example; metaplasia occurs when normal epithelial cells lining the upper airways in the lungs (columnar cells) are replaced by stratified squamous epithelial cells that do not secrete mucus or have cilia resulting in loss of a vital protective mechanism. Metaplasia can be reversed if the inducing stimulus is removed. With prolonged exposure to the inducing stimulus, however, dysplasia and cancerous transformation may occur.



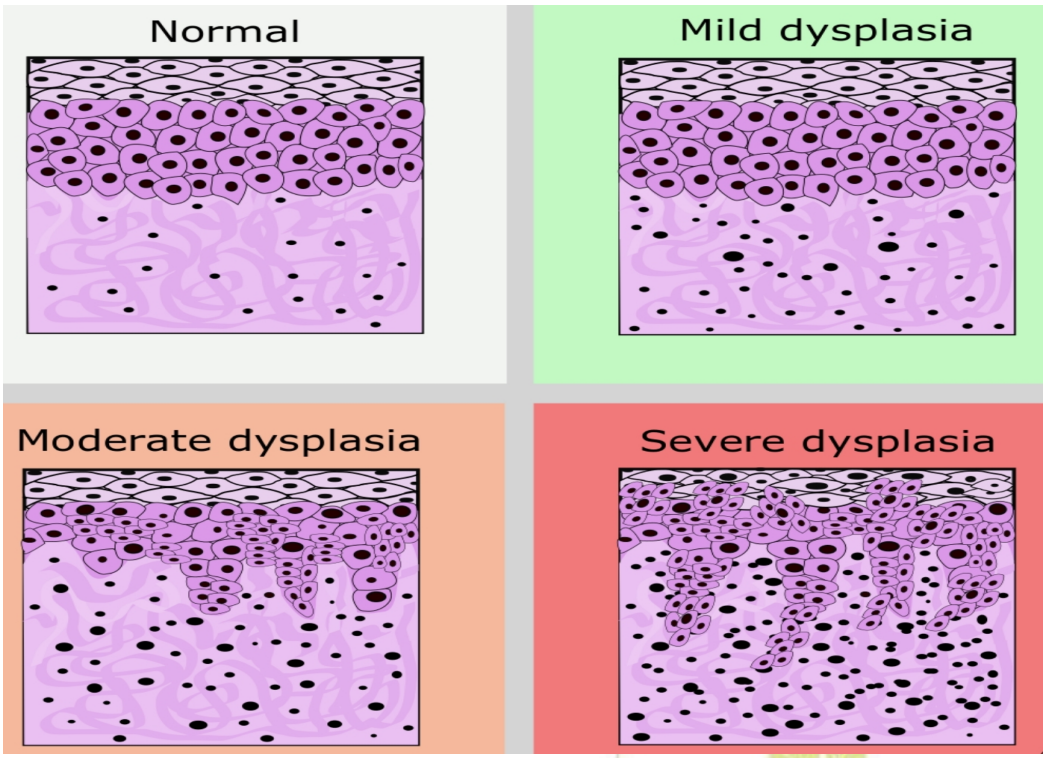
- Squamous metaplasia: pseudostratified ciliated columnar respiratory epithelium due to chronic irritation by habitual cigarette smoking , transitional epithelium of urinary bladder, ureter or renal pelvis due to

chronic irritation by bilharziasis or stones.

- Osseous metaplasia: This replacement of a connective tissue by bone, for example at sites of injury.

Dysplasia:

It refers to abnormal changes in the size, shape and organization and differentiation of mature cells. Dysplasia is not considered a true adaptive process but is related to metaplasia. Dysplastic changes are often encountered in epithelial tissue of the cervix and respiratory tract, where they are strongly associated with cancer development. However, it should be noted that dysplastic cell changes are likely to be adaptive in nature, if the inciting stimulus is removed early enough, dysplastic changes are often reversible.



References:

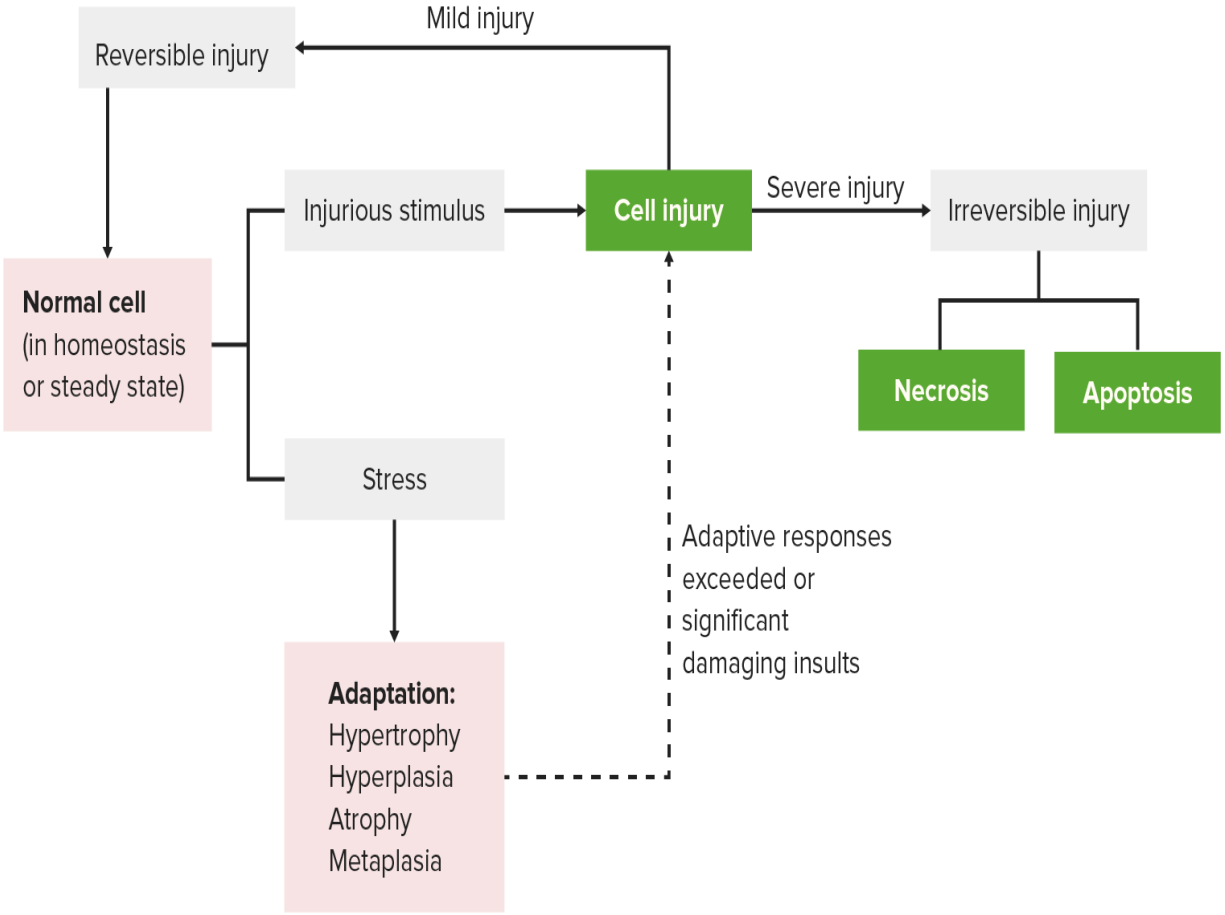
- Understanding pathophysiology. Judy A. Craft & Christopher J. Gordon. 3rd edition. ELSEVIAR. 2019.
- Robin Basic pathology. Kumar, Abbas and Aster .10th edition. ELSEVIAR. 2018
- Porth Essential of pathophysiology. 3rd edition. Wolters Kluwer. 2011.

Lec 3 **Pathophysiology** **Dr. Afrah A. Aldelaimi**

Cell injury, Cell death

As cells face physiologic stresses or injurious conditions they can undergo adaptation, achieving a new steady state and preserving viability and function. If the adaptive capability is exceeded or if the external stress is harmful or excessive, cell injury develops. Within certain limits, injury is reversible, and cells return to their stable baseline; however, if the stress is severe, persistent, or rapid in onset, it results in irreversible injury and death of the affected cells.

Cell injury: Sequence of events that occurs when stresses exceed ability of cells to adapt.



Cell injury divided to:

1. **Reversible cell injury:** cellular changes will regress and disappear when the injurious agent is removed i.e. cells return to normal both morphologically and functionally e.g. cellular swelling (hydropic changes) and fatty changes.
2. **Irreversible cell injury (cell death):**occurs when injury persists or its sever here cell alteration reach point of no return and progress to cell death ,cell death is inevitable e.g. amyloidosis

Factors influencing the severity of cell injury:

- Type, duration & severity of causative agent
- Type of affected cells e.g. : neurons are highly susceptible to an injury while hepatocyte is moderate.

CAUSES OF CELL INJURY

Hypoxia: refers to oxygen deficiency

Ischemia: reduced blood supply including hypoxia and deficiency of essential nutrients with accumulation of toxic metabolites.

Toxins: air pollutants, insecticides, CO, asbestos, cigarette smoke, ethanol,over-the-counter prescibed drugs. Even innocuous substances, such as glucose, salt, water and oxygen, can be toxic. Poisons such as cyanide, can rapidly destroy cells and cause the death of the individual in a very short period of time after exposure.

A biochemical interaction occurs between a toxic substance and the cell membrane leading either to increased permeability or combine with a part of the cell membrane that causes the lipids in the cell membrane to be damaged.

Immunologic reactions: autoimmune diseases and hypersensitivity reactions.

Genetic abnormalities: heredity and congenital malformations such as Down syndrome, thalassemia and sickle cell anemia.

Nutritional imbalances: Protein–calorie insufficiency, specific vitamin deficiencies, excessive dietary intake may result in obesity and also is an important underlying factor in many diseases, such as type 2 diabetes mellitus and atherosclerosis.

Physical agents: Trauma, extremes of temperature, radiation, electric shock, and sudden changes in atmospheric pressure.

Aging: Cellular senescence results in a diminished ability of cells to respond to stress and cell death.

Mechanisms of cellular injury

- **ATP depletion**

ATP is important in every process in the cell like protein synthesis and transport processes. A reduction in ATP levels causes the cell membrane's sodium–potassium (Na+–K+) pump and sodium–calcium exchange to fail, which leads to an intracellular accumulation of sodium and calcium and diffusion of potassium out of the cell.
Sodium and water then can enter the cell freely causing cellular swelling, dilation of the endoplasmic reticulum, detachment of ribosomes and reducing protein synthesis.
It should be noted that these disruptions will be reversed if oxygen is made available and restored. However, if oxygen is not restored, swelling of lysosomes and marked mitochondrial swelling occurs with accumulation of calcium subsequently activating multiple enzyme systems, resulting in membrane damage, cytoskeleton disruption, activation of inflammation, DNA degradation and cell death.

- **Defect in plasma membrane permeability**.

Defect in membrane permeability will result in the change of concentration of metabolites across the cell membrane.

- **Generation of Free Radicals**

Many free radicals are derived from oxygen as a result from cellular metabolism called reactive oxygen species ROS which includes: superoxide anion (O2-) ,hydroxyl radical (OH-), and Hydrogen peroxide (H2 O2). In cell injury such as ischemia ROS accumalted in cell and react with protein, lipids, and carbohydrates, thereby damaging cell membrane, inactivating enzymes, and damaging nucleic acid that make up DNA.
Restoration of oxygen in this point can cause additional injury called reperfusion injury or oxidative stress.

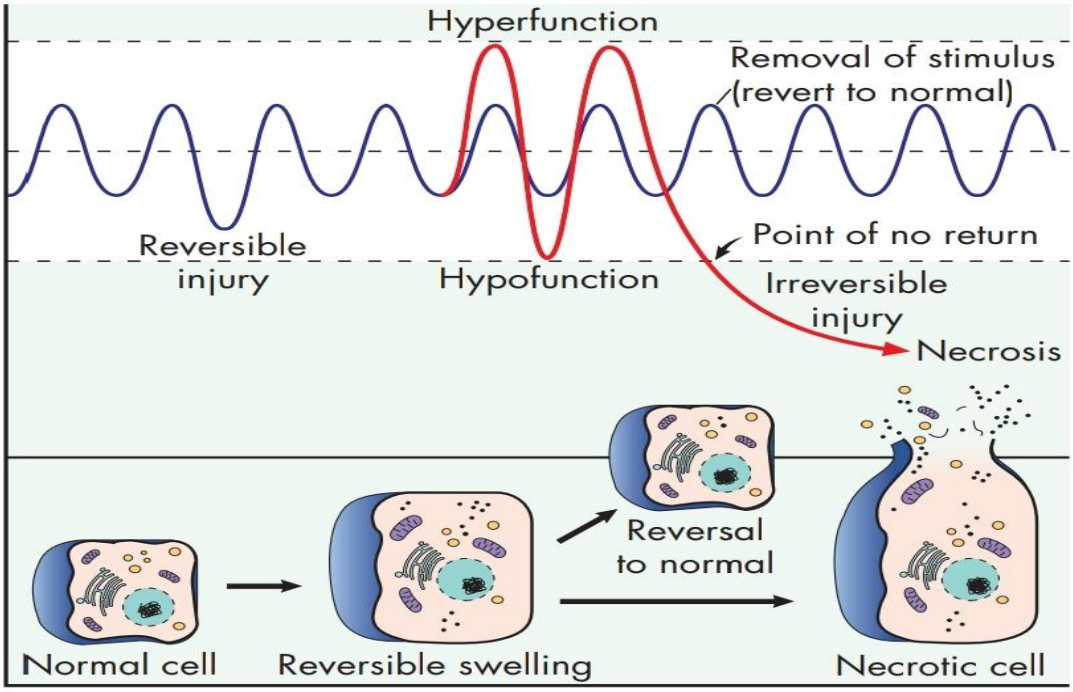
- **Loss of Ca+2 homeostasis**

Normally, the extracellular concentration of Ca is higher than the cytosolic free Ca‘,this is maintained by ATP dependent transport also the Ca normally is stored intracellular at Mitochondria & Endoplasmic Reticulum. Cell injury allow a net influx of extracellular Ca‘ across the cell membrane, follow by release of Ca from intracellular stores & this result in increased cytosolic Ca such increased in the cytosolic Ca will mediate cell injury by activation of many enzymes which include:

- ☐ Phospholipases: cause cell membrane damage.
- ☐ Proteases: catabolizing the structural & membrane proteins.
- ☐ ATPase: accelerating ATP depletion.
- ☐ Endonuclease: fragmented the genetic material.

- **Mitochondrial damage.**

It is an important cause for irreversible cell injury, mitochondria can be damaged by increase in cytoplasmic Ca, Oxidative stress and breakdown of mitochondrial membrane phospholipid by activated phospholipases.



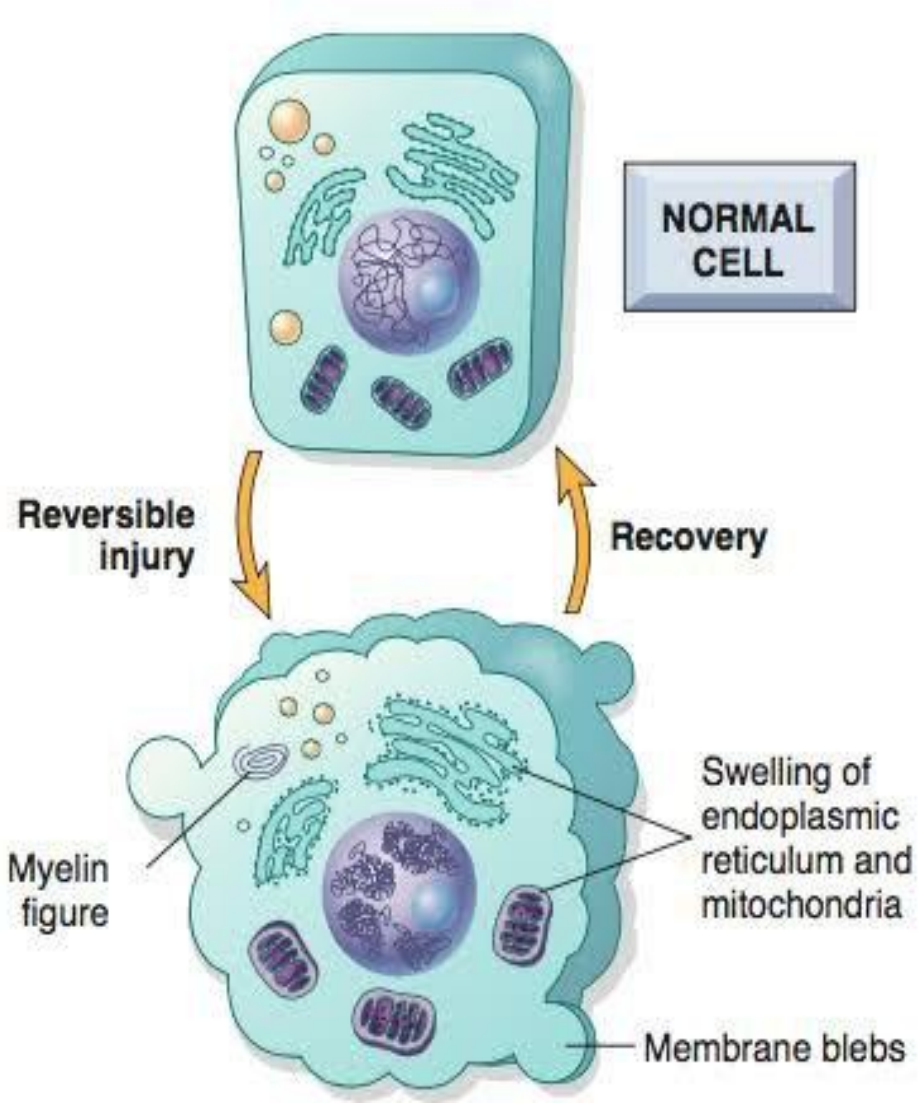
Reversible Cell Injury

It is cell injury at which the deranged function and morphology of the injured cells can return to normal if the damaging stimulus is removed. The main morphologic correlates of reversible cell injury are:

1. **Cellular swelling:** increased permeability of the plasma membrane, plasma membrane alterations such as blebbing and loss of intercellular attachments.
2. **Hydropic change:** accumulation of water within the cytoplasm of the cell. Other synonyms used are cloudy swelling (for gross appearance of the affected organ) and vacuolar degeneration (due to cytoplasmic vacuolation).
3. **Hyaline change:** is a glassy, homogeneous, eosinophilic appearance of proteinaceous material in H&E stained sections.
4. **Mucoid change:** accumulation of mucus-like substances consist of a complex of proteins with mucopolysaccharides.
5. **Fatty change:** It is the intracellular accumulation of neutral fat within parenchymal cells (fatty metamorphosis). Fatty change is particularly

common in the liver but may occur in other non-fatty tissues such as heart, skeletal muscle and kidneys. Liver is the commonest site for accumulation of fat because it plays a central role in fat metabolism.

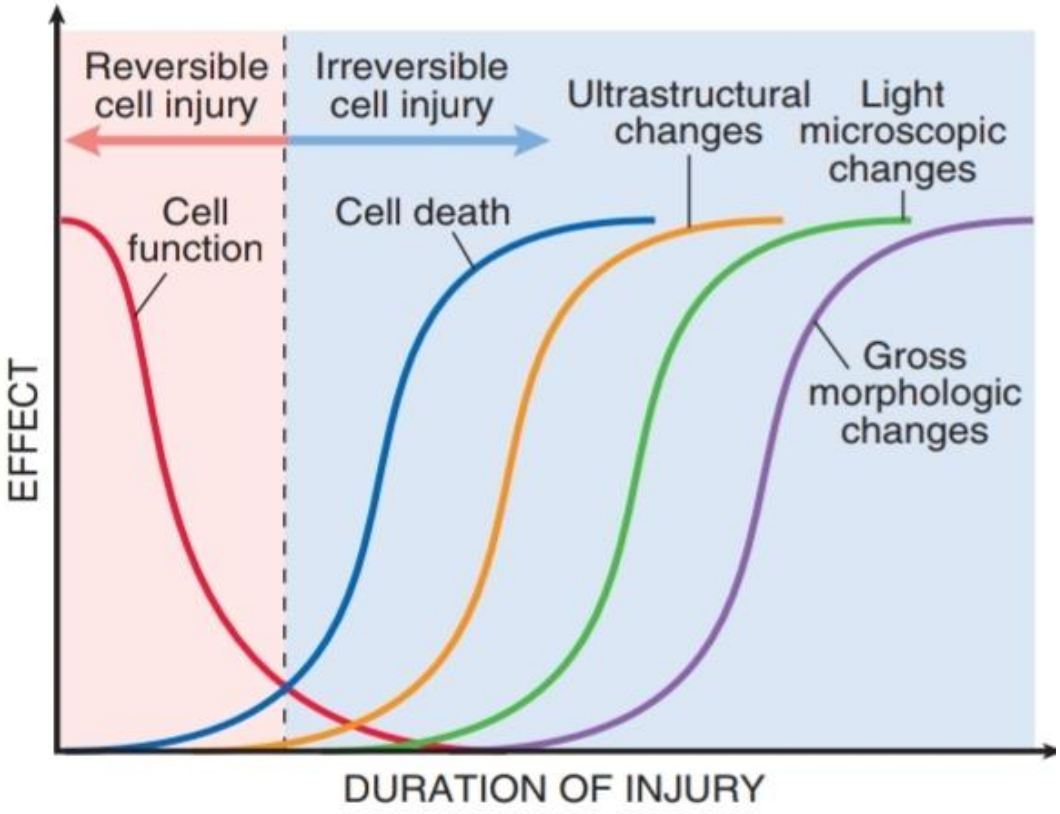
6. **Mitochondrial changes** such as swelling and the appearance of phospholipid-rich amorphous densities
7. **Dilation of the ER with detachment of ribosomes**
8. **Nuclear alterations:** clumping of chromatin.
9. **Myelin figures** in the cytoplasm which are collections of phospholipids resembling myelin sheaths that are derived from damaged cellular membranes.



Irreversible Cell Injury

With persistent noxious exposures, injured cells reach "point of no return" and undergo cell death. The molecular changes in irreversible cell death characterized by three phenomena:

- Mitochondrial changes such as swelling and the inability to restore mitochondrial function (oxidative phosphorylation and adenosine triphosphate [ATP] generation) even after resolution of the original injury.
- Loss of structure and functions of the plasma membrane and intracellular membranes; cytoplasm may contain so-called "myelin figures," which are collections of phospholipids resembling myelin sheaths that are derived from damaged cellular membranes.
- Loss of DNA and chromatin structural integrity



Cell Death

When cells are injured they die by different mechanisms, depending on the nature and severity of the insult and type of injured cells. There are two types of cell death: necrosis and apoptosis.

Necrosis:

A cell death occurs when cellular membranes dissociate and cellular enzymes leak out and finally digest the cell. Necrosis elicits a local host reaction (inflammation) that is induced by substances released from dead cells and which serves to eliminate the debris and start the subsequent repair process.

The enzymes responsible for digestion of the cell are derived from lysosomes and may come from the dying cells themselves or from leukocytes recruited as part of the inflammatory reaction. The nucleus undergoes morphological change of pyknosis, karyorrhexis and karyolysis. Necrosis is the process of cellular self-digestion known as autodigestion, or autolysis.

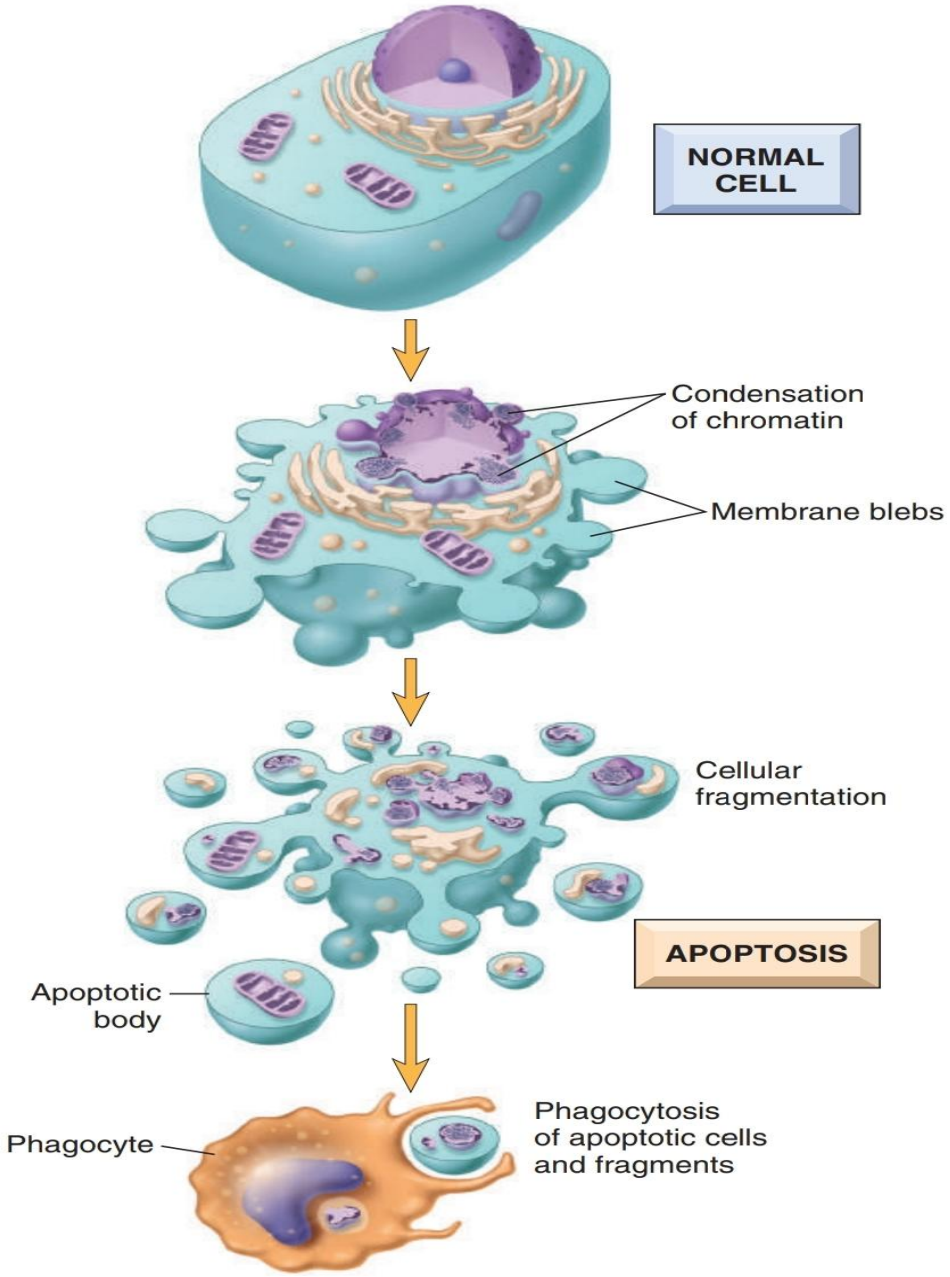
📚 Different types of necrosis tend to occur in different organs or tissues and sometimes can indicate the mechanism or cause of cellular injury:

- **Coagulative necrosis:** Occurs in almost all tissues (except the brain), it commonly results from hypoxia caused by severe ischaemia. Coagulation is caused by protein denaturation (a process that modifies the molecular structure of protein), which causes the protein albumin to change from a gelatinous, transparent state to a firm, opaque state.
- **Liquefactive necrosis:** Commonly results from ischaemic injury to nerve cells in the brain, or from microbial infections. Dead brain tissue is readily affected by liquefactive necrosis because brain cells are rich in digestive enzymes and lipids and the brain contains little

connective tissue. Cells are digested by their own enzymes, so the tissue becomes soft, liquefies and is walled off from healthy tissue.

- **Caseous necrosis:** Usually results from a lung infection that caused tuberculosis. It is a combination of coagulative and liquefactive necrosis. The dead cells disintegrate, but the debris is not completely digested by enzymes. Tissues resemble clumped cheese hence the name caseous, in that they are soft and granular.
- **Fat necrosis:** Fat necrosis is cellular dissolution caused by powerful enzymes, called lipases, that occur in the pancreas and other abdominal structures. Lipases break down triglycerides, releasing free fatty acids, which then combine with calcium, magnesium and sodium ions, creating soaps (called saponification). The necrotic tissue appears opaque and chalk-white.
- **Gangrenous necrosis:** Refers to the death of tissue and results from severe hypoxic injury. This commonly occurs because of blockages of arteries, particularly those in the lower leg. With hypoxia and subsequent bacterial invasion, the tissues undergo necrosis. In dry gangrene the skin becomes very dry and shrinks, resulting in wrinkles, and its colour changes to dark brown or black. Wet gangrene develops when the main white blood cells of the body, neutrophils, invade the site, causing liquefactive necrosis. This usually occurs in internal organs, causing the site to become cold, swollen and black. A foul odour is present, and if systemic symptoms become severe end with death.

Apoptosis: it is a regulated suicide cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and cytoplasmic proteins. The plasma membrane of the apoptotic cell remains intact but the cell is fragmented into apoptotic bodies to be highly "edible," by phagocytes. The apoptotic cell death does not elicit an inflammatory reaction.



Causes of Apoptosis

🍀🍀 Physiologic apoptosis:

- During normal development of an organism (embryogenesis), some cells die and are replaced by new ones.
- Cell lose hormonal stimulation and unwanted cells are eliminated by apoptosis.

- In the immune system, apoptosis eliminates excess leukocytes left at the end of immune responses as well as lymphocytes that recognize self-antigens and could cause autoimmune diseases if they were not purged.

☘☘ Pathologic conditions:

- Apoptosis eliminates cells that are damaged beyond repair seen when there is severe DNA damage, for example, after exposure to radiation and cytotoxic drugs.
- The accumulation of misfolded proteins also triggers apoptotic death
- Certain infectious agents, particularly some viruses, induce apoptotic death of infected cells.

Mechanisms of Apoptosis

Apoptosis is regulated by death- and survival-inducing signals that activate enzymes called caspases. Two distinct pathways converge on caspase activation:

• **The mitochondrial (intrinsic) pathway:** it is responsible for apoptosis in most physiologic and pathologic situations, Mitochondria contain several proteins that are capable of inducing apoptosis, including cytochrome c. When mitochondrial membranes become permeable, cytochrome c leaks out into the cytoplasm, triggering caspase-9 activation ultimately leading to nuclear fragmentation and apoptotic death.

• **The death receptor (extrinsic) pathway of apoptosis:** it is responsible for elimination of self-reactive lymphocytes and damage by CTLs, A surface molecules called death receptors trigger apoptosis by tumor necrosis factor (TNF) receptor and Fas (CD95) that bind with intracellular death domain and activate caspase-8

• **Clearance of apoptotic cells:** Apoptotic fragments producing a number of “eat-me” signals and secrete soluble factors to attract phagocytes. For ex; in normal cells, phosphatidylserine is present on the inner leaflet of the plasma membrane, but in apoptotic cells this phospholipid“flips" to the outer leaflet, where it is recognized by tissue macrophages, leading to phagocytosis of the apoptotic cells.

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
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	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

Other Pathways of Cell Death

Necroptosis: is a programmed form of necrosis or inflammatory cell death. This form of cell death resemble necrosis initiated by engagement of TNF receptors result in the dissolution of the cell, it occurs in inflammatory reactions in which the cytokine TNF is produced.Apoptotic death usually leads to immunologically silent responses whereas necroptotic death releases molecules that promote inflammation, a process referred to as necroinflammation

Pyroptosis. This form of cell death is associated with activation of a cytosolic danger-sensing protein complex called the inflammasome that results in activation of caspases and production of cytokines that induce inflammation, often manifested by fever. It occurs in some infectious disease which ends in formation of plasma membrane pores resulting in cell explosion.

Autophagy ("self-eating"): it refers to lysosomal digestion of the cell's own components. It is a survival mechanism in times of nutrient deprivation, so that the starved cell can live by eating its own contents and recycling these contents to provide nutrients and energy. In some circumstances, autophagy may be associated with atrophy of tissues and may represent an adaptation that helps cells survive lean times. If, however, the starved cell can no longer cope by devouring its contents, autophagy may eventually lead to apoptotic cell death.

Lec 4 Pathology Dr. Afrah Adnan

Intracellular accumulations & Calcification

Under some circumstances cells may accumulate abnormal amounts of various substances, which may be harmless or associated with varying degrees of injury. The substance may be located in the cytoplasm, within organelles, or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere. There are four main pathways of abnormal intracellular accumulations:

1. Inadequate removal of a normal substance accumulated in excess, such as water, lipids, proteins, and carbohydrates.
2. Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion (Failure to degrade a metabolite due to inherited enzyme deficiencies).
3. Deposition and accumulation of an abnormal exogenous substance when the cells can`t degrade or transport the substance to other sites such as a mineral or products of infectious agents, or endogenous, such as a product of abnormal synthesis or metabolism.
4. Pigments.

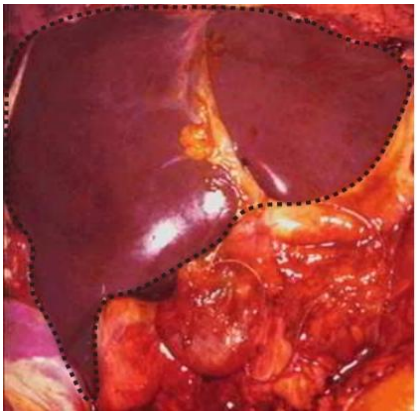
Fatty Change (Steatosis)

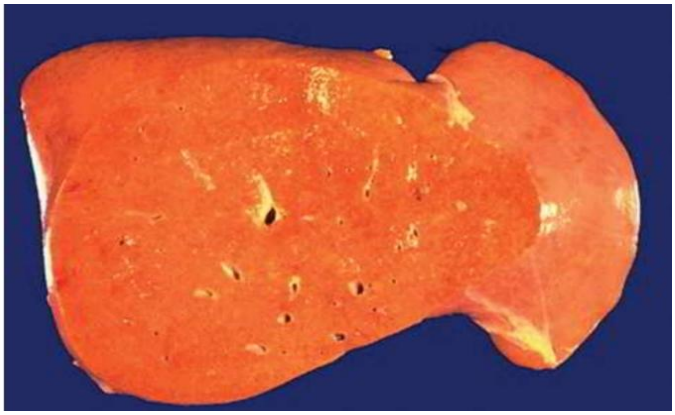
Fatty change refers to any abnormal accumulation of triglycerides within parenchymal cells. It is most often seen in the liver, since this is the major

organ involved in fat metabolism, but it may also occur in heart, skeletal muscle, kidney, and other organs.

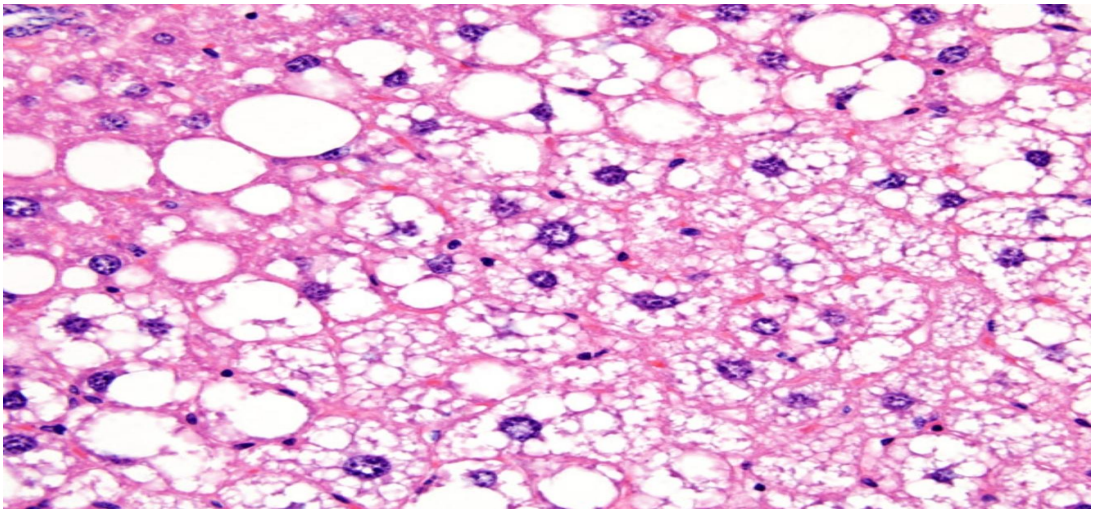
Steatosis may be caused by protein malnutrition, diabetes mellitus, obesity, hypoxia, alcohol abuse, starvation, Hypoxia, Liver toxins like CCL4, Drugs like estrogen, steroid, tetracyclinetoxins.

Morphological features: Grossly, the liver is enlarged, glistening capsule, pale-yellow to yellow and greasy to touch.



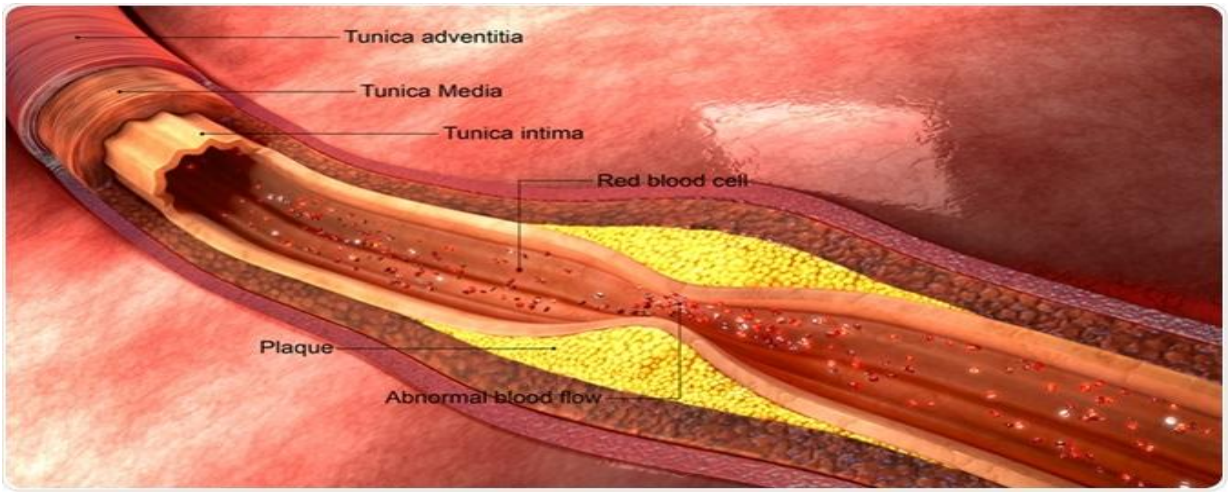


Microscope characteristic feature is the presence of numerous lipid vacuoles in the cytoplasm of hepatocytes that appear as non-staining vacuoles because it is dissolved in organic solvents used in H&E stain.



Cholesterol Deposits

Intracellular deposits of cholesterol in macrophages may occur in hypercholesterolaemia. This turns macrophages into foam cells. This change can be seen in atherosclerosis, xanthomas and xanthelasma.



Intracellular accumulation of proteins

Protein accumulations are much less common than lipid accumulations; intracellular accumulations of proteins usually appear as rounded, eosinophilic droplets, vacuoles, or aggregates in the cytoplasm.

Examples of protein accumulation:

- In the kidney, there is accumulation of albumin in the cytoplasm of tubular cells of proximal tubules, which occur in diseases associated with increased protein filtration through the glomeruli (like nephrotic

syndrome) & increase reabsorption of albumin by the tubular cells, accumulated protein appear as pink, hyaline cytoplasmic droplets, this is reversible process.

- There is marked accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells, resulting in rounded, eosinophilic Russell bodies.
- In alcoholic liver diseases, there is accumulation of intracellular proteins (keratin intermediate filaments) (Mallory body), which appear as an eosinophilic inclusion in the liver cells.
- Neurofibrillary tangle which is aggregation of proteins that are present in the brain of Alzheimer disease.

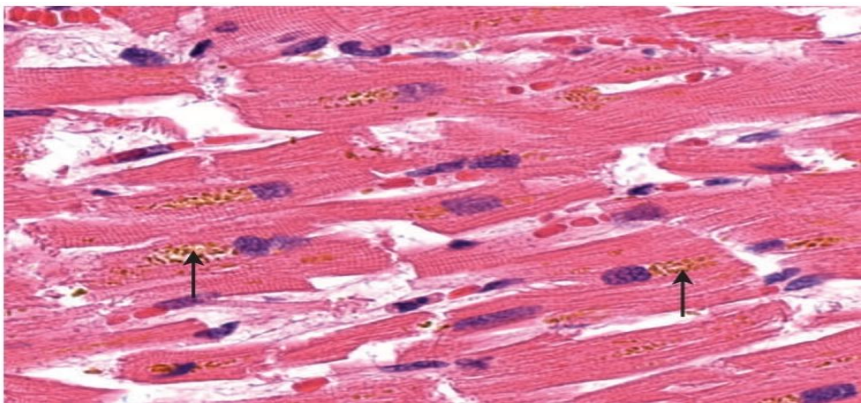
Glycogen accumulation

Excessive intracellular deposits of glycogen are associated with abnormalities in the metabolism of either glucose or glycogen. Ex: in poorly controlled diabetes mellitus and genetic disorders (glycogen storage diseases)

Pigments

Pigments are colored substances that are either exogenous that coming from outside the body, such as carbon, or endogenous that synthesize within the body itself, such as lipofuscin, melanin, and certain derivatives of hemoglobin.

- **Exogenous Carbon** (an example is coal dust), is exogenous pigment that is inhaled and phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional lymph nodes and aggregates as a black pigment. Ex; Anthracosis.
- **Exogenous Injected Pigments** (Tattooing) Pigments like India ink, cinnabar and carbon are introduced into the dermis in the process of tattooing where the pigment is taken up by macrophages and lies permanently in the connective tissue. The examples of injected pigments are prolonged use of ointments containing mercury, dirt left accidentally in a wound, and tattooing by pricking the skin with dyes.
- **Endogenous Lipofuscin,** or “wear-and-tear pigment,” is intracellular insoluble brownish-yellow granules that accumulate in a variety of tissues (heart, liver, and brain) as a sign of age or atrophy. It represents a complex of free radical interactions with lipids and protein. It is not injurious to the cell but is a marker of past free radical injury.

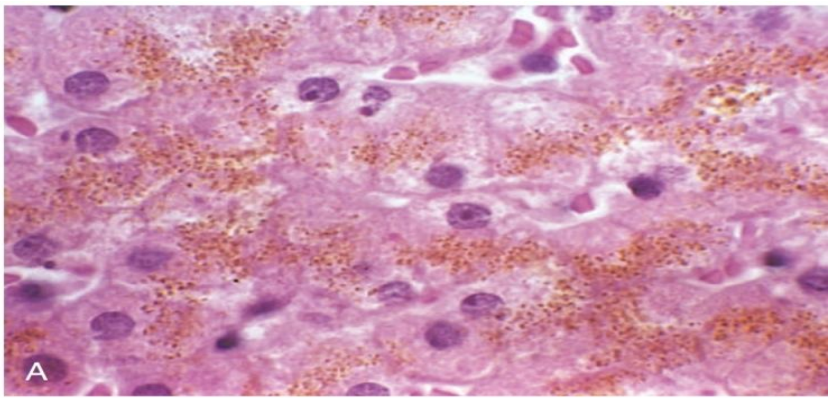


- **Endogenous Melanin** is a brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against

harmful ultraviolet radiation. formed when the enzyme tyrosinase catalyzes the oxidation of tyrosine to dihydroxyphenylalanine in melanocytes in various organs. Excess of melanin can be seen in malignant melanoma. Various disorders associated with hyperpigmentation of melanin such as Addison's disease, Peutz-Jeghers syndrome, neurofibromatosis and Albright's syndrome.

- **Endogenous Hemosiderin** is an aggregation of ferritin (a hemoglobin-derived granular pigment) that is golden yellow to brown and accumulates in tissues when there is a local or systemic iron overlosd.

Local excesses of iron: bruises are due to deposition of hemosiderin in the macrophages). Systemic overload of iron: hemosiderosis.



Pathologic calcification

It is a common process in a wide variety of disease states, and is the result of an abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. It can occur in two ways:

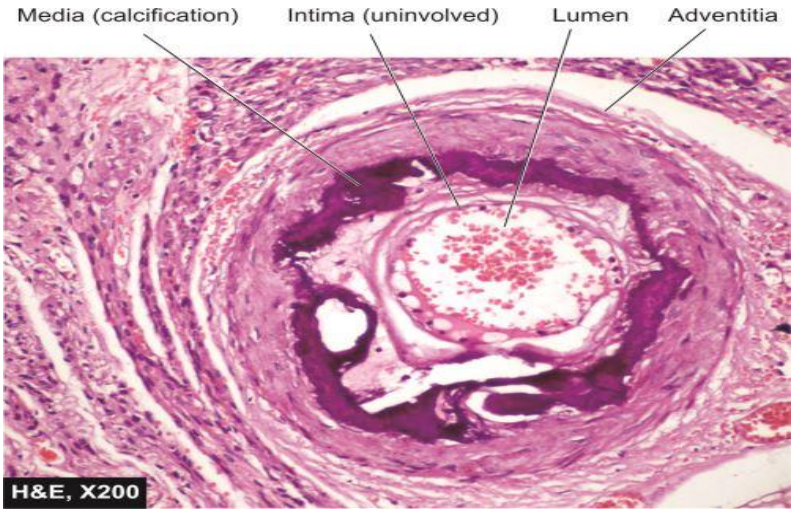
- **Dystrophic calcification:** calcium metabolism is normal but it deposits in injured or dead tissue, such as areas of necrosis of any type (ex; advanced atherosclerosis).

Dystrophic calcification may be a cause of organ dysfunction, for example, calcification can develop in aging or damaged heart valves resulting in severely compromised valve motion. Dystrophic calcification of the aortic valves is an important cause of aortic stenosis in elderly persons.

Dystrophic calcification is derived from intracellular deposition of calcium in the mitochondria of dying cells and phosphate derived from membrane phospholipids.

- **Metastatic calcification:** it is associated with hypercalcemia and can occur in normal tissues. The major causes of hypercalcemia are:

1. increased secretion of parathyroid hormone
2. destruction of bone due to the effects of tumors or diseases (e.g., Paget disease, multiple myeloma and leukemia
3. vitamin D–related disorders (vitamin D intoxication and sarcoidosis)
4. renal failure



Aging and altered cellular function

👵👴 Aging is a normal physiological process that is both universal and inevitable. However, as individuals age, they are continually exposed to agents that may cause cellular injury in addition to what is considered to be general ‘wear and tear’. Microinsults (little insults) caused by continuous exposure to ultraviolet light, environmental temperature changes, infectious agents and chemical reactions in the body that can produce substances like free radicals all may alter cellular structure and function.

📜 Each normal cell may have a finite life span during which it can replicate. This may be in the form of a genetic program that progressively slows or shuts down physiological mechanisms, including mitosis, and so cells are not replaced.

An example of the influence of our genetic programming on the aging process is evidenced by the ages at which females may undergo menopause. For example, a daughter whose mother has undergone early menopause is more likely to undergo the same early menopause herself.

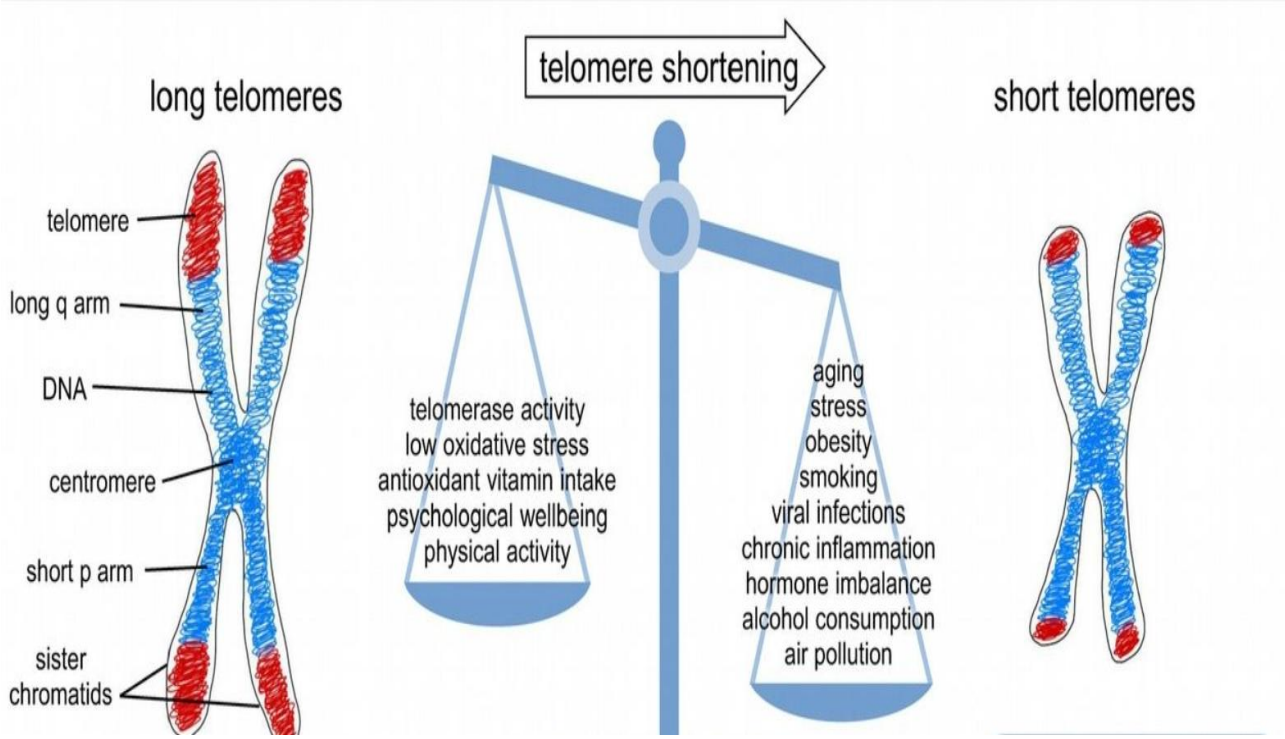
📒 Cellular aging is the result of a progressive decline in functional activity of cells. Several abnormalities contribute to the aging of cells:

- Accumulation of mutations in DNA.
- A limited capacity for replication known as replicative senescence.

Replicative senescence occurs in aging cells because of progressive shortening of telomeres (are short repeated sequences of DNA present at the ends of chromosomes that are important for ensuring the complete replication of chromosome ends and for protecting the ends from fusion

and degradation). Telomere length is maintained by nucleotide addition mediated by an enzyme called telomerase. Telomerase is expressed in germ cells and is present at low levels in stem cells, but absent in most somatic cells.

Therefore, as mature somatic cells age, their telomeres become shorter and they exit the cell cycle, resulting in an inability to generate new cells to replace damaged ones. Conversely, in immortalized cancer cells, telomerase is usually reactivated and telomere length is stabilized, allowing the cells to proliferate indefinitely.



🍔🍡 Defective protein homeostasis: With the passage of time,cells are unable to maintain normal protein homeostasis, because of defective activity of chaperones (which promote normal protein folding) and proteasomes (which destroy misfolded proteins). The concomitant accumulation of misfolded proteins exacerbates the loss of functional proteins and can trigger apoptosis.

🍓🍒 Calorie restriction has been found to slow down aging and prolong life in every species tested from flies to mice. Calorie restriction reduces activation of insulin-like growth factor receptor signaling, which involves a downstream network of kinases and transcription factors. Reduced IGF-1 signaling leads to lower rates of cell growth and metabolism and possibly reduced errors in DNA replication, better DNA repair and improved protein homeostasis. Calorie restriction also serves to improve immunity. All of these inhibit aging.

🌡️ Persistent inflammation: accumulation of damaged cells, lipids, and other endogenous substances may result in persistent low-level inflammation that induces chronic diseases such as atherosclerosis and type 2 diabetes. Cytokines produced during inflammatory reactions may themselves induce cellular alterations that exacerbate aging,and chronic metabolic disorders may accelerate the aging process.

🌻 Clinical observations and epidemiologic studies have shown that physical activity and calorie restriction slow the aging process, whereas stresses, perhaps acting via increased production of glucocorticoids, accelerate aging.

Organ changes in ageing

Although all organs start showing deterioration with ageing, following organs show evident morphologic and functional decline:

1. Cardiovascular system: atherosclerosis and arteriosclerosis
2. Nervous system: atrophy of gyri and sulci, Alzheimer's disease, Parkinson's disease.
3. Musculoskeletal system: bone diseases, fractures, and age-related muscular degeneration.
4. Eyes: cataract and vascular changes in retina.
5. Hearing: Disability in hearing due to otosclerosis.
6. Immune system: Reduced IgG response to antigens, frequent and more severe infections.
7. Skin: Laxity of skin due to loss of elastic tissue.
8. Cancers: 80% of cancers occur in the age range of 50-80 years.

In general any substance improved DNA repair and protein homeostasis and enhanced immunity, all of which inhibit aging.

Lec 4 Pathology Dr.Afrah Adnan
Inflammation

Inflammation: is a response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites of injury to eliminate the causative agents.
The goals of inflammation are to contain and isolate injury, to destroy invading microorganisms and inactivate toxins, and to prepare the tissue for healing and repair.

Inflammation is actually a protective response that is essential for survival.Without inflammation, infections would go unchecked, wounds would never heal, and injured tissues might remain permanent festering sores.In some situations, the inflammatory reaction becomes the cause of disease or life threatening condition ex; autoimmune diseases, allergies, and chronic diseases such as rheumatoid arthritis, atherosclerosis and lung fibrosis.

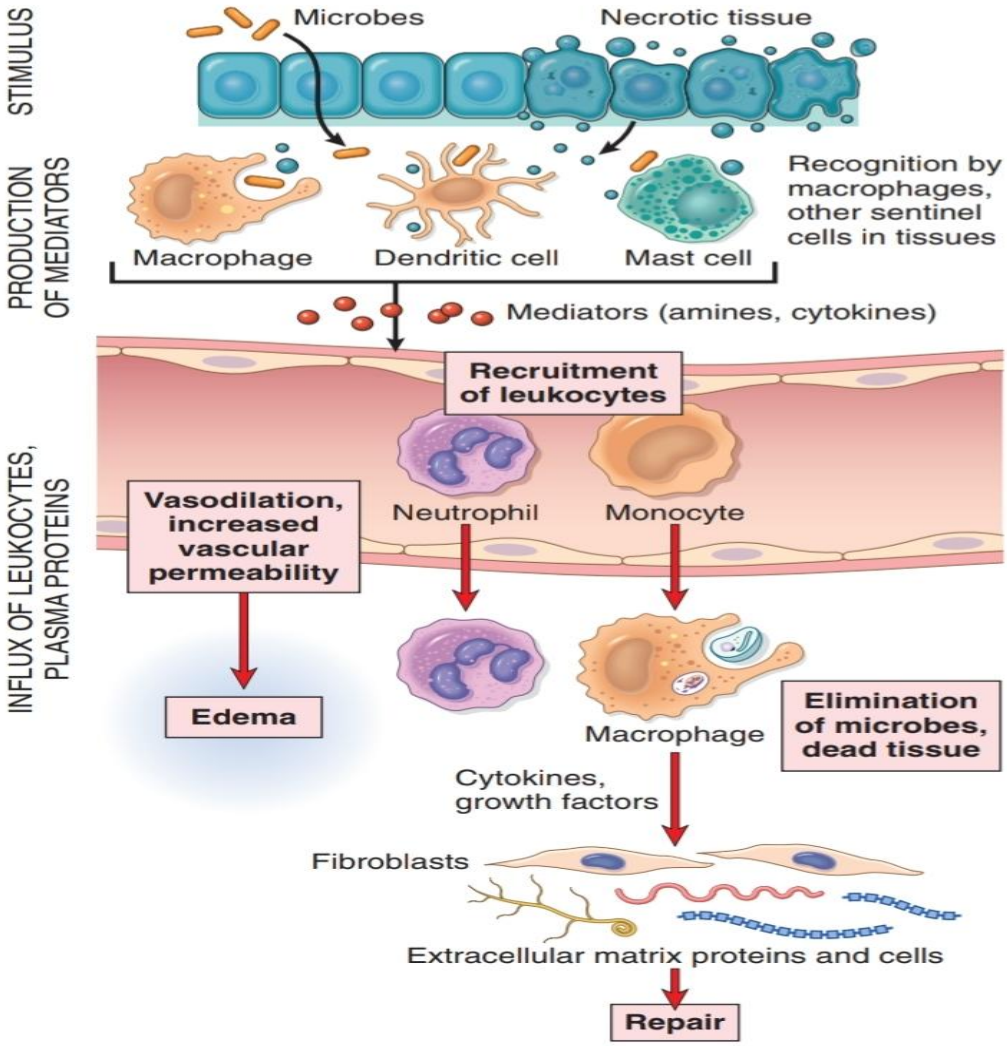
The typical sequential events in inflammatory reaction are 5Rs:

1. Recognition of the injurious agent
2. Recruitment of leukocytes
3. Removal of the agent
4. Regulation (control) of the response
5. Resolution (repair).

Cardinal signs

The external manifestations of inflammation are:

- Heat (calor in Latin)
- Redness (rubor)
- Swelling (tumor)
- Pain (dolor)
- Loss of function (functio laesa).



Causes of inflammation:

- Infections
- Tissue necrosis
- Foreign bodies
- Trauma
- Immune reactions

Recognition of microbes and necrotic cells

🍓🍓 **Cellular receptors for microbes:** Phagocytes and dendritic cells that contain receptors for detection of invaders. Ex; Toll-like receptors (TLRs).

🍐🍐 **Sensors of cell damage:** All cells have receptors to recognize molecules liberated from damaged cells such as uric acid, ATP, intracellular K+ and DNA. Ex; damage-associated molecular patterns (DAMPs).

🍋🍋 **Circulating proteins:** complement system, mannose-binding lectin and collectins.

Inflammation can be divided into two basic types;

- **Acute inflammation:**

Early onset (i.e., seconds to minutes).short duration (i.e., minutes to days), involving fluid exudation (edema) and polymorphonuclear cell (neutrophil) emigration.

The suffix (itis) add to the name of organs signifying acute inflammation, but with some exceptions e.g. colitis, appendicitis

- **Chronic inflammation:**

Later onset (i.e., days) and longer duration (i.e., weeks to years), involving lymphocytes and macrophages, with blood vessel proliferation and fibrosis.

The suffix (osis) add to the name of organs signifying chronic inflammation, e.g. dermatosis, atherosclerosis

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

Acute inflammation

It is a rapid host response that serves to deliver leukocytes and plasma proteins to sites of tissue injury. Acute inflammation has two major components:

- Vascular events
- Cellular events

Vascular events:

The vascular reactions of acute inflammation consist of changes in the flow of blood and the permeability of vessels, both designed to maximize the movement of plasma proteins and leukocytes out of the circulation and into the site of infection or injury.

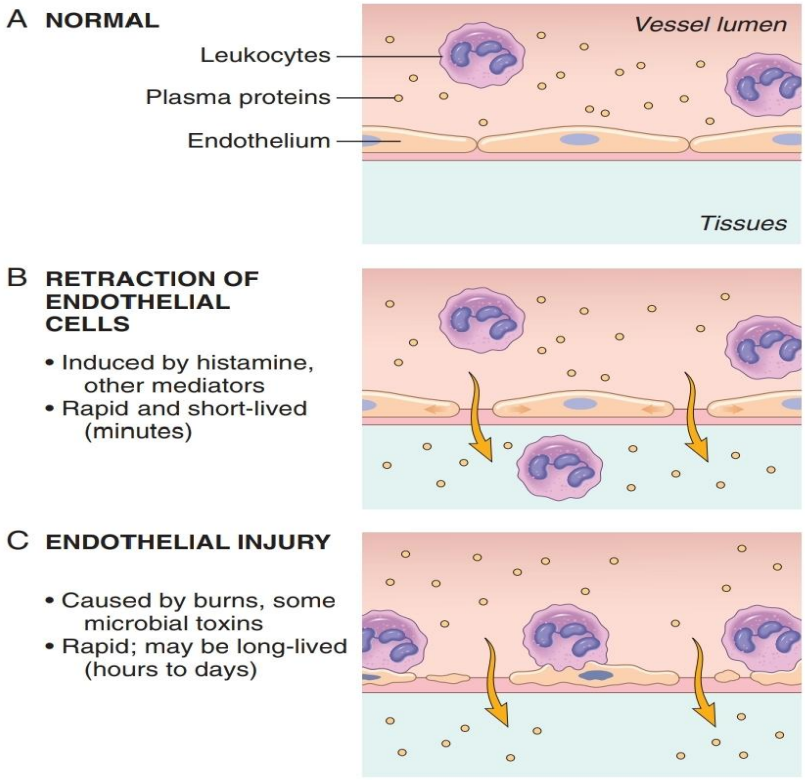
- Transient vasoconstriction in few seconds
- Vasodilation of arterioles and capillaries is induced by histamine and bradykinin.
- Increased blood flow (this is responsible for hotness & redness of area).
- Slowing of blood stream
- Increased capillary permeability by retraction of endothelial cells or injury.
- Movement of protein rich fluid into extravascular areas (exudate)
- Lymphatic vessels and lymph nodes also are involved in inflammation show redness and swelling (reactive or inflammatory lymphadenitis).

Exudate: is a high protein concentration extravascular fluid and contains cellular debris. It occurs typically during an inflammatory reaction (increased vascular permeability).

Transudate: is a fluid with low protein content with little or no cellular material, it is essentially an ultrafiltrate of blood plasma that is produced as a result of osmotic or hydrostatic imbalance across vessels with normal vascular permeability.

Edema: an excess of fluid in the interstitial tissue or body cavities; it can be either an exudate or a transudate.

Pus: a purulent exudate, is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and microbes.



Cellular events:

Leukocytes that are recruited to sites of inflammation perform the key function of eliminating the causative agents, the journey of leukocytes from the vessel lumen to the tissue is a multistep process that is mediated and controlled by adhesion molecules and cytokines.

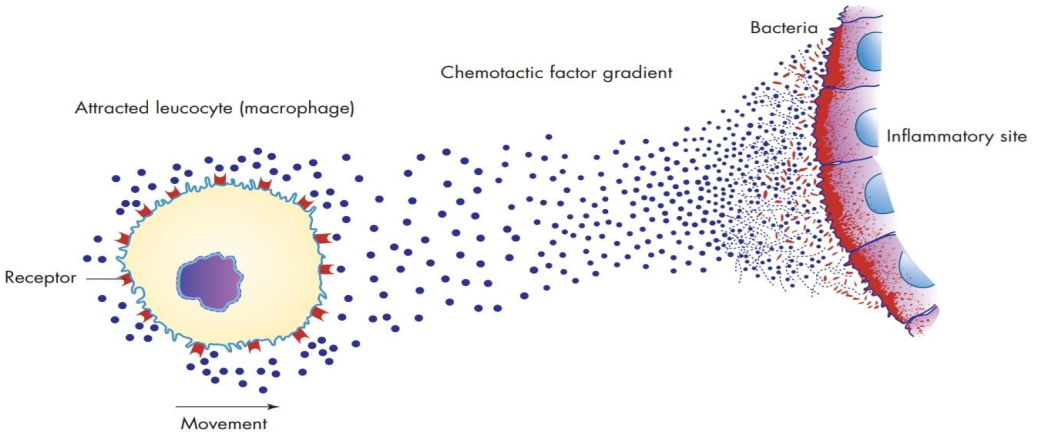
- **Leukocytes margination:** moving close to the vessel wall to detect and react to changes in the endothelium.
- **Leukocytes rolling** on the surface of endothelial cells
- **Leukocytes adhesion:** firm adhesion with the activated endothelial cells (by TNF and IL-1) at the site of injury is mediated selectins and integrins.The surface adhesion molecules assist the phagocytes to undergo diapedesis or emigration of the cells through the endothelial junctions that have retracted in response to inflammatory mediators

- **Leukocytes migration** or Transmigration through the vessel wall primarily by squeezing between cells at intercellular junctions.
- **Chemotaxis:** leukocytes move in the tissues toward the site of injury along a chemical gradient of chemoattractants which including the following: Bacterial products, Cytokines, complement system C5a, Production of Arachidonic Acid metabolites (leukotriene B4 LTB4).

Neutrophils predominate in the early inflammatory infiltrate during the first 6 to 24 hours and are gradually replaced by monocytes and macrophages over 24 to 48 hours. However, exceptions to this are in viral infections, lymphocytes may be the first cells to arrive; some hypersensitivity reactions are dominated by activated lymphocytes, macrophages, and plasma cells (reflecting the immune response); and in allergic reactions, eosinophils may be a prominent cell type.

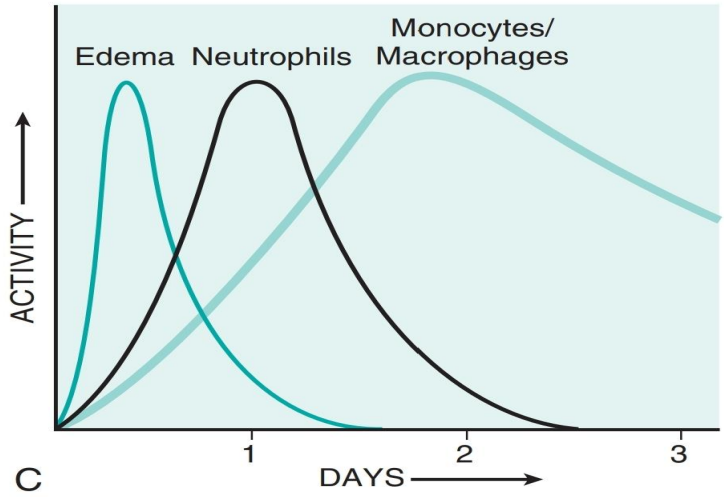
Cytokines: are proteins secreted by many cell types (principally activated lymphocytes, macrophages, and dendritic cells, but also endothelial, epithelial, and connective tissue cells) that mediate and regulate immune and inflammatory reactions, ex; TNF and IL-1.

Chemokines are a family of small proteins that act primarily as chemoattractants for specific types of leukocytes.



Cytokines are large and diverse group of pro- or anti-inflammatory factors that are grouped into families based upon their structural or their receptors. Chemokines are a group of secreted proteins within the cytokine family whose generic function is to induce cell migration.

Note: Agents that block TNF, one of the major cytokines in leukocyte recruitment, are among the most successful therapeutics ever developed for chronic inflammatory diseases.



Phagocytosis and Clearance of Cauative Agent

Include three steps:

- Recognition & attachment of injurious particle to the ingesting leukocytes (by Opsonization)

Opsonization is the process by which injurious particles are coated by specific plasma particles that are called opsonins, to facilitate the recognition & attachment of injurious particles to the killer leukocytes. These opsonins are included IgG, C3b & plasma carbohydrate binding particle called Collectins.

- Engulfment of injurious particle & formation of phagocytic vacuole by Pseudopods of WBC, & then fusion of these vacuoles with the membrane of lysosomes.
- Killing & degradation of injurious particles by production of free radicals (reactive oxygen species, nitrogen species from nitric oxide (NO), and lysosomal enzymes).

Mediators of inflammation

- The mediators of inflammation are the substances that initiate and regulate inflammatory reactions.
- Mediators may be produced locally by cells at the site of inflammation or may be derived from circulating inactive precursors that are activated at the site of inflammation
- The major cell types that produce mediators at the site of inflammation are epithelial cells, tissue macrophages, dendritic cells, mast cells in addition to platelets, neutrophils and endothelial cells.
- Plasma-derived mediators (e.g., complement proteins) are synthesized in liver and present in the circulation as inactive precursors that must be activated, usually by a series of proteolytic cleavages.
- Most of the mediators are short-lived.
- One mediator can stimulate the release of other mediators.

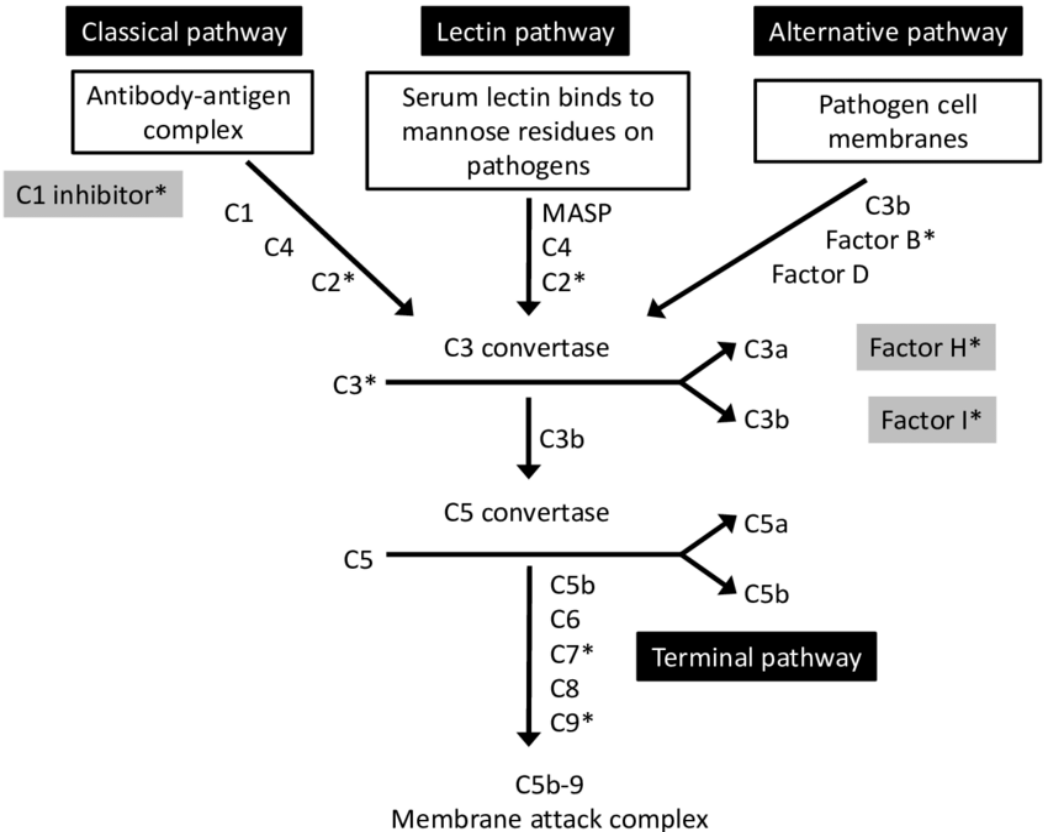
Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

Complement System

It is a collection of soluble proteins that function mainly in host defense against microbes and in pathologic inflammatory reactions. Complement proteins are present in inactive forms in the plasma, and many of them are activated to become proteolytic enzymes that degrade other complement proteins, thus forming an enzymatic cascade.There are more than 20 complement proteins, the critical step in complement activation is the cleavage of C3 can occur by one of three pathways:

- The classical pathway: which is triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen
- The alternative pathway: which can be triggered by microbial surface molecules (e.g., endotoxin, or LPS), complex polysaccharides, and other substances, in the absence of antibody
- The lectin pathway: in which plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1



Outcomes of Acute Inflammation

1. Complete resolution and elimination of causative agent.
2. Healing by connective tissue replacement (scarring or fibrosis). It occurs in huge tissue destruction.
3. Progression to chronic inflammation as a result of either the persistence of the injurious agent or some interference with the normal process of healing.

Chronic inflammation

It is a response of prolonged duration (weeks or months) of inflammation, It may follow acute inflammation or may begin insidious progressive process without any signs of a preceding acute reaction.

Causes of Chronic Inflammation

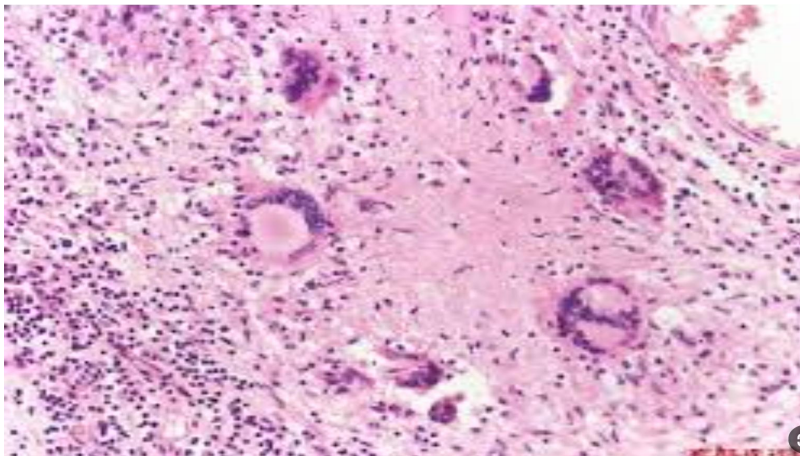
- Persistent infections by microorganisms that are difficult to eradicate, such as mycobacteria and certain viruses, fungi, and parasites.
- Hypersensitivity diseases that include autoimmune and allergic diseases.
- Prolonged exposure to potentially toxic agents, either exogenous or endogenous.
- Some forms of chronic inflammation may be important in the pathogenesis of diseases (Alzheimer disease, type 2 diabetes, and certain cancers).

Chronic inflammation is characterized by the following:

- Infiltration with mononuclear cells include macrophages, lymphocytes, and plasma cells.
- Tissue destruction, induced by the persistent caustive agent or by the inflammatory cells.
- Attempts at healing by connective tissue replacement of damaged tissue, accomplished by angiogenesis (proliferation of small blood vessels) and fibrosis.

Granulomatous Inflammation

It is a form of chronic inflammation characterized by collections of activated macrophages with T lymphocytes, and sometimes associated with central necrosis. The activated macrophages may develop abundant cytoplasm and begin to resemble epithelial cells, and are called epithelioid cells.
Some activated macrophages may fuse, forming multinucleated giant cells. Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate.



There are two types of granulomas, which differ in their pathogenesis:

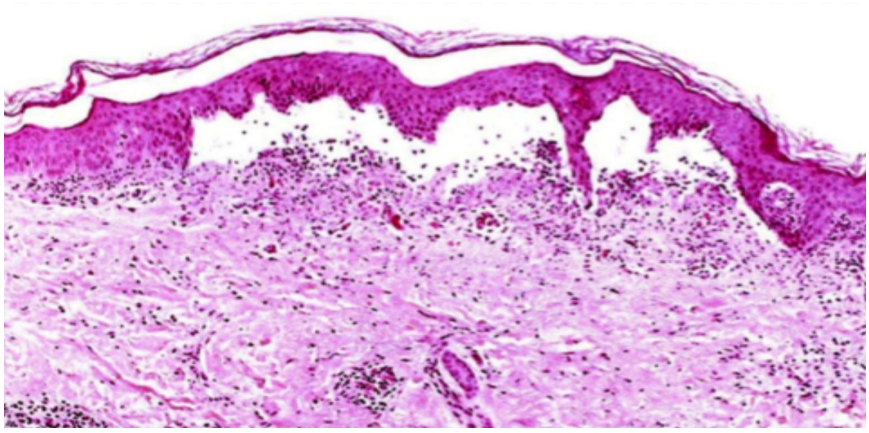
- **Immune granulomas** are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response. , such as a persistent microbe or a self antigen.
- **Foreign body granulomas** are seen in response to relatively inert foreign bodies, in the absence of T cell mediated immune responses. Typically, epithelioid and giant cells are apposed to the surface of the foreign body.

Examples of diseases with granulomatous inflammation:

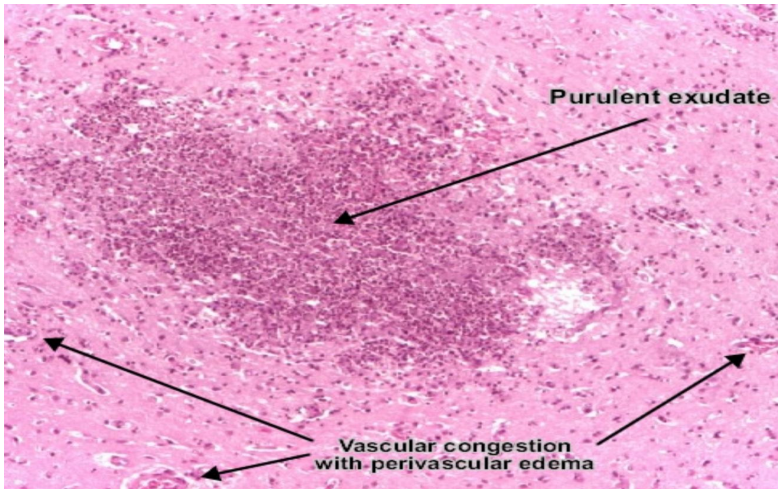
Disease	Cause	Tissue reaction
Tuberculosis	Mycobactrium tuberculosis	Tubercle: Caseating granulomas
Leprosy	Mycobactrium leprosy	Non caseating granuloma
Syphilis	Treponema pallidum	Gumma
Cat-scratch disease	Gram-negative bacillus	Non caseating granuloma
Sarcoidosis	Unknown cause	Non caseating granuloma
Crohn disease	Immune reaction	Non caseating gr.

Morphological patterns of inflammation

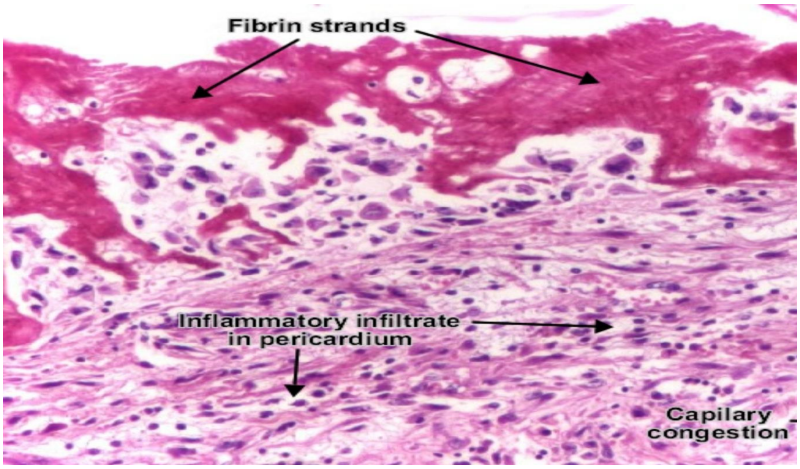
Serous inflammation: is accumulation of fluid into spaces or into body cavities lined by the peritoneum, pleura, or pericardium (effusion). Blister resulting from a burn or viral infection represents accumulation of serous fluid within or immediately beneath the damaged epidermis of the skin.



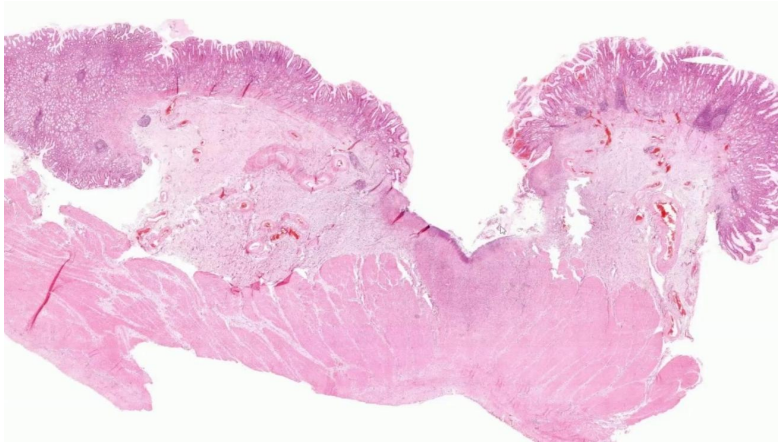
Purulent (Suppurative) Inflammation: it is characterized by the production of pus, an exudate consisting of neutrophils, the liquefied debris of necrotic cells, and edema fluid. Abscess is a localized collection of pus.



Fibrinous Inflammation: A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus and fibrin is formed and deposited in the extracellular space, Fibrinous exudates may be dissolved by fibrinolysis and cleared by macrophages or remain and conversion to scar tissue (organization).



Ulcer: is a local defect or discontinuity of the surface of an epithelial tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue. Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface such as in epithelium of mouth, peptic and duodenal ulcers.



The systemic manifestations of inflammation

It means the effects of acute-phase response include:

- Fever and lethargy
- Increased ESR levels
- Leukocytosis or leukopenia
- Enlargement of the lymph nodes

Lethargy: means mental and physical abnormalities such as drowsy, tiredness, little energy and loss of appetite.

Fever: is characterized by an elevation in body temperature, is one of the most prominent manifestations of the acute-phase response, especially if inflammation is caused by infection.

Fever is produced in response to pyrogens that act by resetting of the hypothalamic thermoregulatory center.

- Endogenous pyrogens (cytokine such as IL-1) found naturally within the body.
- Exogenous pyrogens such as endotoxins from gram-negative bacteria or pyrogenic prions. Exogenous pyrogens or autoimmune diseases either provoke endogenous pyrogen production to create a fever within the body or activate a toll-like receptor (TLR) to create a fever. Clinically, the fever produced by endogenous cytokines is indistinguishable from fever produced by exogenous pyrogens such as LPS.

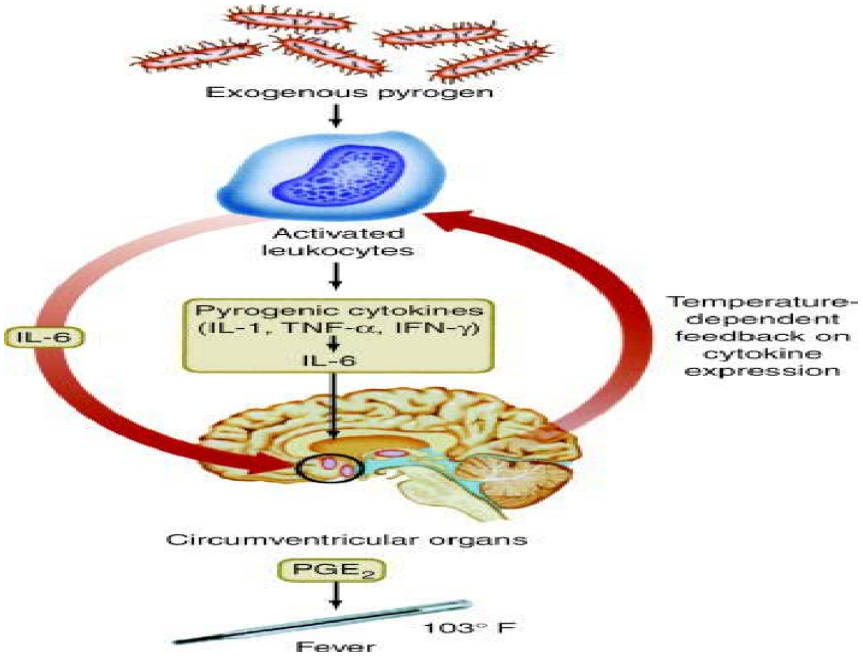
For example, the breakdown products of phagocytosed bacteria that are present in the blood leads to the release of endogenous pyrogens. The endogenous pyrogens are thought to increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E2.

In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established.

The reactions that occur during fever consist of four stages:

1. Prodromal period (nonspecific symptoms: mild headache and fatigue)
2. Chill, during which the temperature rises;
3. Flush, during which the skin becomes warm
4. Defervescence stage, initiation of sweating. Fever manifestations are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source. Fever in children varies depending on the age of the child. Infants and young children have decreased immunologic function and are more commonly infected with virulent organisms. The elderly tend to have a lower baseline temperature, so serious infections may go unrecognized because of the perceived lack of a significant fever.

ESR: is a simple blood test that helps detect inflammation in the body. The test measures the rate of fall (sedimentation) of red blood cells (erythrocytes) in a sample of blood placed in a tall vertical tube. Increased sed rate indicates inflammation, infections, some cancers, and autoimmune diseases.

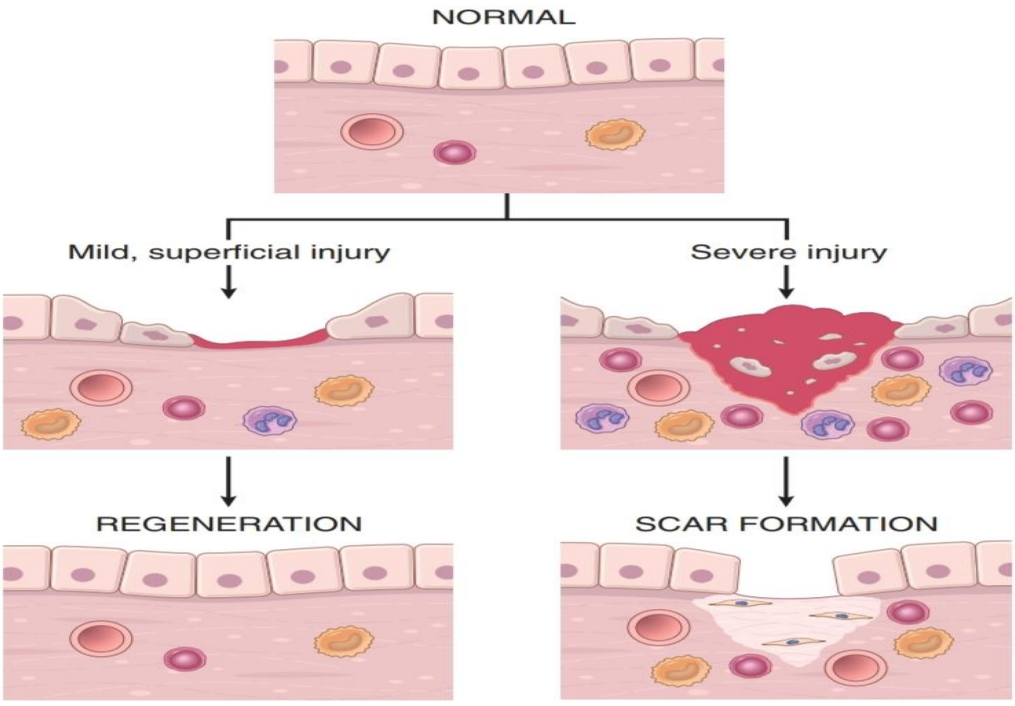


Lec 6 Pathology Dr. Afrah Adnan
Healing and repair

Healing is the attempt of living tissue to restore the function and structure after injury. Healing of damaged tissues occurs by two types of reactions:

• **Regeneration:** tissues are able to replace the damaged components and return to a normal state by proliferation of residual (uninjured) cells and maturation of tissue stem cells.

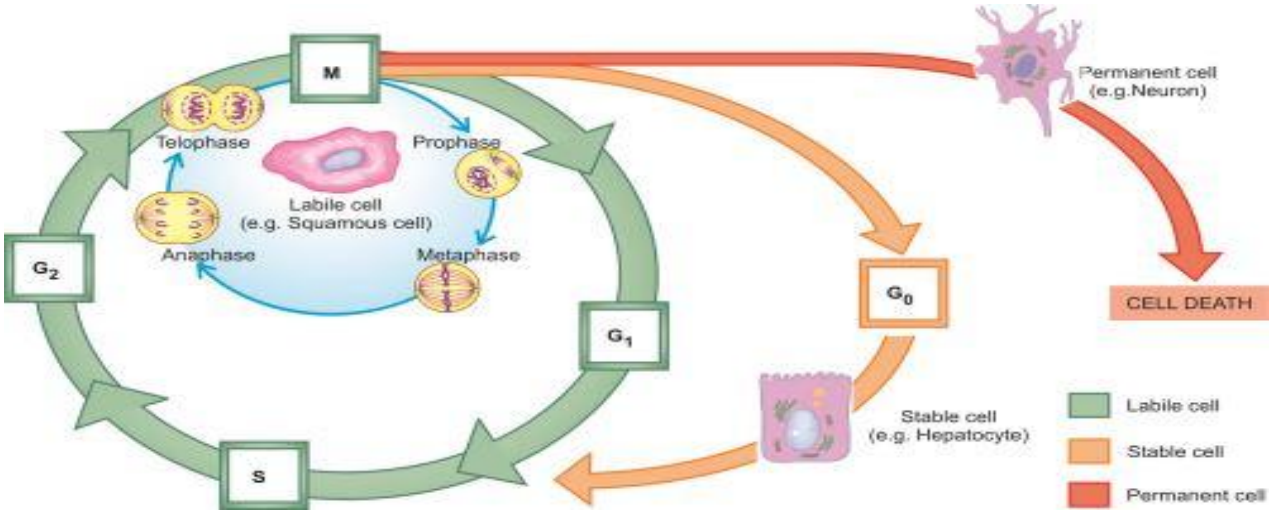
• **Repair by connective tissue deposition (scar formation):** If tissue is severely damaged repair occurs by the laying down of connective (fibrous) tissue and scarring.



- **Cell proliferation** is the process of increasing cell numbers to replacement cells through mitotic cell division.
- **Cell differentiation** is the process of transforming the proliferating cells into more specialized cells in structure and function.

The ability of tissues to repair themselves is determined by their intrinsic proliferative capacity:

- **Labile tissues:** cells are constantly being lost and continually replaced by new cells that are derived from tissue stem cells ex; hematopoietic cells in the bone marrow, surface epithelia that line body cavities and ducts.
- **Stable tissues:** cells that are normally in the G0 stage of the cell cycle and hence not proliferating, but they are capable of dividing in response to injury or loss of tissue mass ex; parenchyma of most solid organs such as liver, kidney, and pancreas.
- **Permanent tissues:** terminally differentiated nonproliferative cells ex; eurons and cardiac muscle cells.



Injury to these tissues is irreversible and results in a scar, because the cells cannot regenerate. Skeletal muscle cells are usually considered nondividing, but satellite cells attached to the endomysial sheath provide some regenerative capacity for muscle.

Continuously dividing labile tissues contain stem cells. Stem cells are undifferentiated cells that have the capacity to generate multiple cell types.

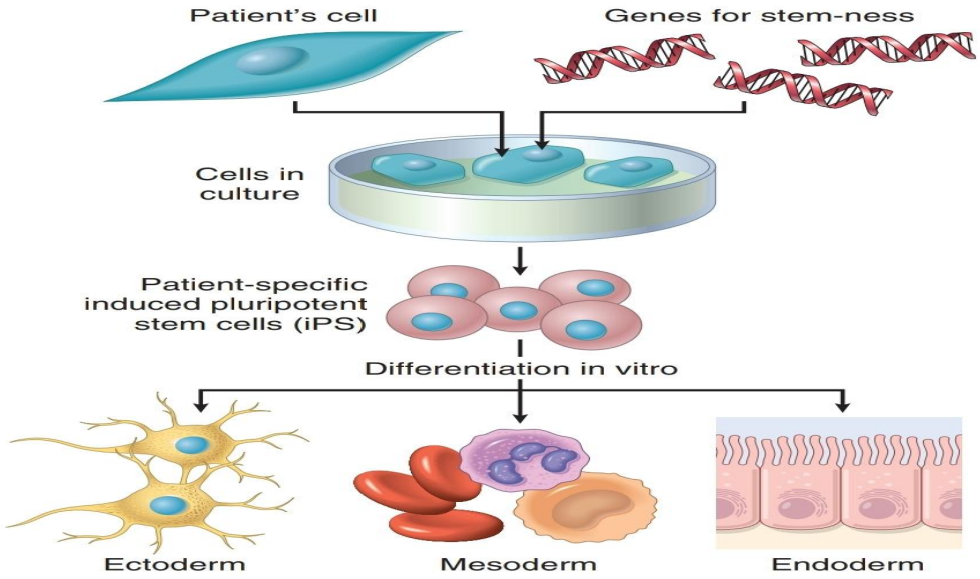
Stem cells are characterized by three important properties:

1. Self-renewal
2. Asymmetric replication
3. Differential potential

Stem cells can be classified in general into two types:

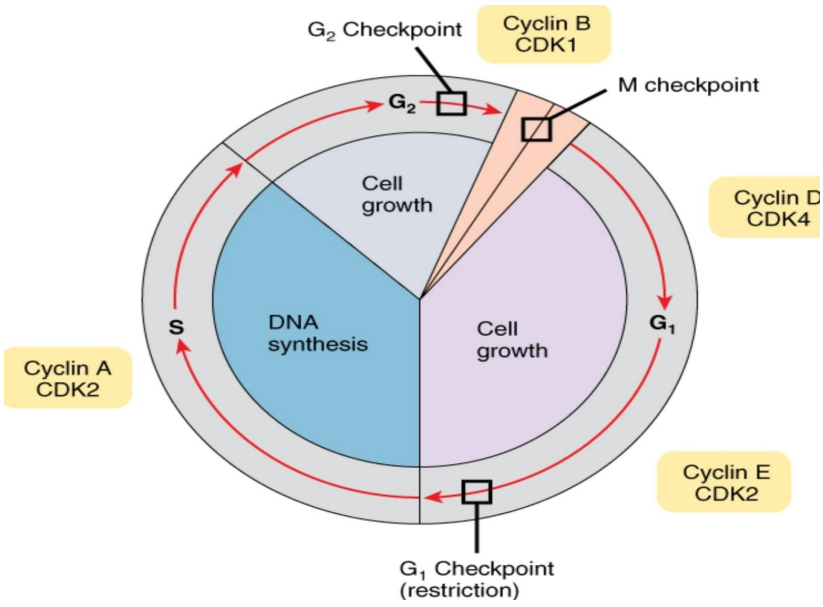
1. **Embryonic stem cells (ES cells):** are the most undifferentiated. They are present in embryos and have limitless cell renewal capacity that can give rise to every cell in the body (totipotent).
2. **Tissue stem cells (adult stem cells):** they have a limited line of differentiated cells that they can generate according to their environment (multipotent).

The ability to identify, isolate, expand, and transplant stem cells has given birth to the new field of regenerative medicine. Pluripotential cells (resembling ES cells), that are derived from the patient somatic cells (e.g., fibroblasts) by reprogramming specific genes to achieve the "stem-ness" of ES cells. Because these cells are derived from the patient can be engrafted without eliciting an immunologically mediated rejection reaction.



Cell cycle is periodic biochemical and structural events occurring during cell proliferation. The cell cycle consists of G1 (presynthetic growth), S (DNA synthesis), G2 (premitotic growth), and M (mitotic) phases; quiescent cells that are not actively cycling are in the G0 state.

The cell cycle is regulated by numerous activators, inhibitors and checkpoints. Cell-cycle progression is driven by proteins called cyclins and cyclin-associated enzymes called cyclin-dependent kinases (CDKs). Cell cycle checkpoints ensure proper progression of replication , the G1 checkpoint (restriction or Major Checkpoint); the G2/M checkpoint; and the metaphase-to-anaphase checkpoint.



Cell proliferation is driven by growth factors produced by cells near the site of damage. The most important sources of these growth factors are macrophages,

epithelial and stromal cells. All growth factors activate signaling pathways that ultimately induce changes in gene expression that drive cells through the cell cycle.

Angiogenesis

It is the process of new blood vessel formation from existing vessels. It is critical in healing, in the development of collateral circulations at sites of ischemia, and in neoplasia. Angiogenesis induced by:

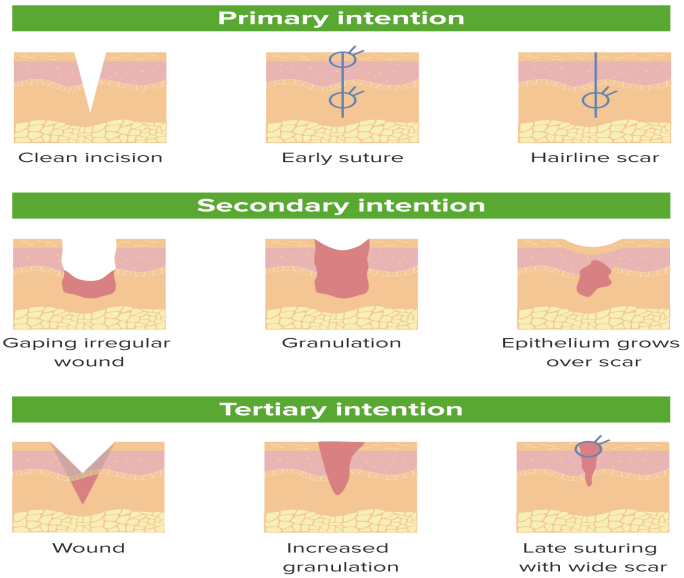
- Vascular endothelial growth factors (VEGF)
- Fibroblast growth factors (FGFs)
- Platelet derived growth factors (PDGF)
- Transforming growth factors beta (TGF-β).

TGF-β is the most important cytokine for the synthesis and deposition of connective tissue proteins. It is produced by most of the cells in granulation tissue, TGF-β stimulates fibroblast migration, proliferation, increases the synthesis of collagen and fibronectin, and decreases the degradation of ECM by inhibiting metalloproteinases. TGF-β also has anti-inflammatory effects by inhibiting lymphocyte proliferation and the activity of other leukocytes.

Healing of skin wounds

It can be classified into healing by:

- **First intention (primary union)** referring to epithelial regeneration with minimal scarring, as in well-apposed surgical incisions.
- **Second intention (secondary union)** referring to larger wounds that heal by a combination of regeneration and scarring.
- **Third intention (tertiary union)** referring to delayed primary wound healing after 4-6 days and the process of secondary unioun is interrupted, it occurs when wound need to be open for drainage or cannot stitched the tissue loss.



Mechanisms of Tissue Regeneration

• **Regeneration of skin and mucous membranes:** injured cells are rapidly replaced by proliferation of residual cells and differentiation of stem cells, the residual epithelial cells produce the growth factors to initiate generation of cells to fill the defect created by the injury .

• **Regeneration of internal organ:** can occur in parenchymal cells that capable of proliferation with limited potential. Ex; Pancreas, adrenal, thyroid, and lung have some regenerative capacity the mechanisms underlying this response are not understood, but they likely involve local production of growth factors and interactions of cells with the ECM.

• **Regeneration of liver:** following partial hepatectomy resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes. This process is driven by cytokines such as IL-6 produced by Kupffer cells, and by growth factors such as hepatocyte growth factor (HGF) produced by many cell types.

Repair by Scarring

This type of healing occurs in severe or chronic injury that results in healing by replacement with connective tissue leading to scar formation. Steps in Scar Formation:

1. **Formation of hemostatic plug** composed of platelets to stop bleeding.
2. **Inflammation:** acute and chronic inflammatory responses to eliminate the causative agents and clear the debris. Macrophages are the central cellular players in the repair process, they clear microbes and necrotic tissue and promote inflammation in a positive feedback loop, and produce growth factors that stimulate the proliferation of many cell types in the next stage of repair.
3. **Cell proliferation** takes up to 10 days including epithelial cells, endothelial and other vascular cells, and fibroblasts, proliferate and migrate to close clean wounds. The combination of proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells, forms a type of tissue that is unique to healing wounds and is called granulation

tissue. This term derives from its pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.

4. **Remodeling;** deposition of fibroblasts to produce the stable fibrous scar. This process begins 2 to 3 weeks after injury and may continue for months or years. There is a shift of the type of collagen deposited from type III collagen early in repair to more resilient type I collagen. In well-sutured skin wounds, strength may recover to 70% to 80% of normal skin by months. Wound contraction is initially caused by myofibroblasts and later by cross-linking of collagen fibers.

Factors That Impair Tissue Repair

Factors that interfere with healing may be extrinsic (e.g., infection) or intrinsic to the injured tissue, and systemic or local:

1. Infection
2. Diabetes
3. Nutritional status
4. Glucocorticoids (steroids) have well-documented antiinflammatory effects, and their administration may result in weak scars because they inhibit TGF-β production and diminish fibrosis. In some instances, however, the

anti-inflammatory effects of glucocorticoids are desirable. For example, in corneal infections, glucocorticoids may be prescribed (along with antibiotics) to reduce the likelihood of opacity due to collagen deposition.

5. Mechanical factors (increased local pressure, torsion, dehisce).
6. Poor perfusion due to arteriosclerosis, diabetes or obstructed venous drainage (e.g., in varicose veins).
7. Foreign bodies such as fragments of steel, glass, or bone.
8. The type and extent of tissue injury (labile, stable or permanent cells).
9. Location of the injury and the character of the tissue in which the injury occurs also are important. Ex, inflammation with small exudates arising in tissue spaces (e.g.,pleural, peritoneal, synovial cavities) may resorbed and digested by the proteolytic enzymes of leukocytes resulting in resolution. However, if exudate is too large to be fully resorbed it undergoes organization, a process during which granulation tissue grows into the exudate, and a fibrous scar ultimately forms.

Defects in Healing:

- **Chronic ulcers formation** ex; venous leg ulcers develop in elderly with severe varicose veins or congestive heart failure, arterial ulcers develop in individuals with atherosclerosis associated with diabetes, pressure sores and diabetic ulcers.

- **Tissue necrosis and failure to heal** due to ischemia, neuropathy, systemic metabolic abnormalities and secondary infections.
- **Wound dehiscence** (wound rupture) occurs most frequently after abdominal surgery due to increased abdominal pressure with vomiting or coughing.
- **Exuberant granulation** formation of excessive amounts of granulation tissue which protrudes above the level of the surrounding skin and blocks reepithelialization (proud flesh), it must be removed by cautery or surgical excision to permit restoration of epithelial continuity.
- **Desmoid tumor** formation or aggressive fibromatoses (benign and malignant low-grade tumors).
- **Wound contraction** is an important part of the normal healing process. An exaggeration of this process gives rise to contracture and results in deformities of the wound and the surrounding tissues. Contractures are particularly prone to develop on the palms, the soles, and the anterior aspect of the thorax. Contractures are commonly seen after serious burns and can compromise the movement of joints.
- **Fibrosis** excessive deposition of collagen and other ECM components in a tissue of internal organs in chronic diseases. It occurs in lungs, liver cirrhosis, kidney, and myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an

inflammatory exudate, it is called organization (as in organizing pneumonia affecting the lung). The basic mechanisms of fibrosis are the same as those of scar formation in the skin during tissue repair. It may be responsible for substantial organ dysfunction and even organ failure. The major cytokine involved in fibrosis is TGF-β.

- **Excessive Scarring** can give rise to **hypertrophic scars** and **keloids**.

The accumulation of excessive amounts of collagen may result in a raised scar known as a hypertrophic scar. These often grow rapidly and contain abundant myofibroblasts, but they tend to regress over several months.

Hypertrophic scars generally develop after thermal or traumatic injury that involves the deep layers of the dermis.

If the scar tissue grows beyond the boundaries of the original wound and does not regress, it is called a keloid. Certain individuals seem to be predisposed to keloid formation, particularly those of African descent.

Healing in bone

Healing of fracture bone by callus formation depends whether the fracture is: ” traumatic (in previously normal bone), or pathological (in previously diseased bone); complete or incomplete like green-stick fracture; and simple (closed), comminuted (splintering of bone), or compound (communicating to skin surface).

However, basic events in healing of any type of fracture are similar and resemble healing of skin wounds to some extent.

” Primary union of fractures occurs when the ends of fracture are approximated surgically by application of compression clamps or metal plates. In these cases, bony union takes place with formation of medullary callus without periosteal callus formation.

” Secondary union is a more common form of fracture healing when the plaster casts are applied for immobilization of a fracture.

Secondary bone union is described under the following 3 headings:

i) Procallus formation ii) Osseous callus formation iii) Remodelling

PROCALLUS FORMATION

1. Haematoma

2. Local inflammatory response

3. Ingrowth of granulation tissue

4. Callus composed of woven bone and cartilage

II. OSSEOUS CALLUS FORMATION lamellar bone is formed.

III. REMODELLING osteoblastic laying and osteoclastic removal are taking place remodelling the united bone ends, which after sometime, is indistinguishable from normal bone.

Complications of Fracture Healing These are as under:

1. Fibrous union may result instead of osseous union if the immobilization of fractured bone is not done. Occasionally, a false joint may develop at the fracture site (pseudo-arthrosis).

2. Nonunion may result if some soft tissue is interposed between the fractured ends.

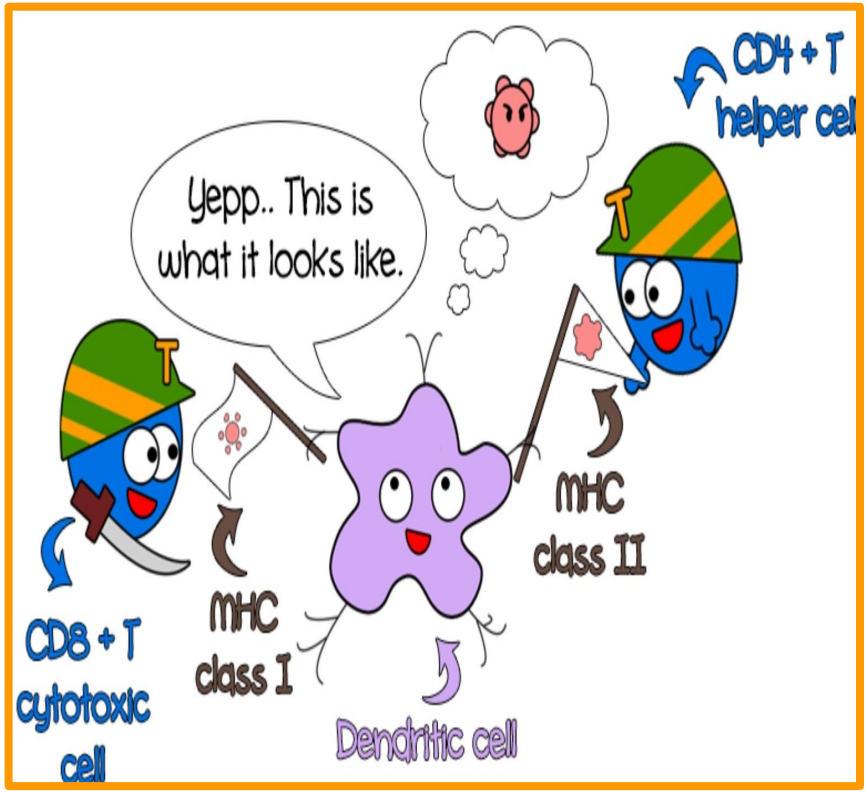
3. Delayed union may occur from causes of delayed wound healing in general such as infection, inadequate blood supply, poor nutrition, movement and old age.

Diseases of Immune system II

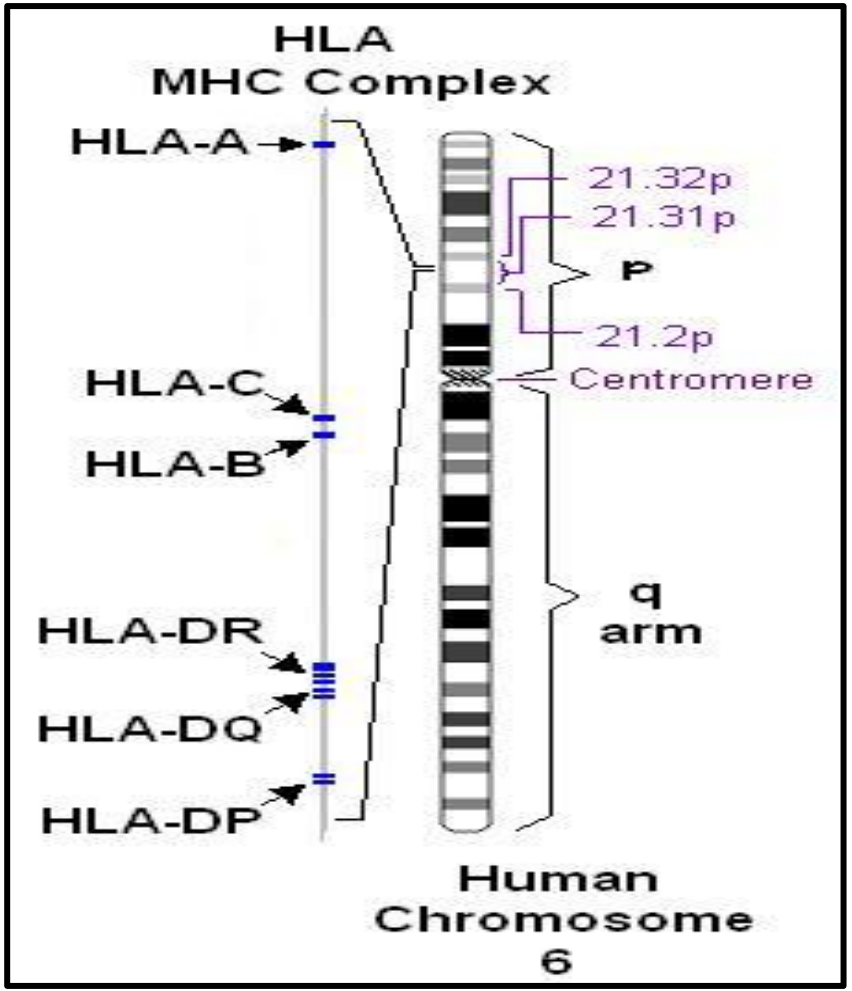
Dr. Afrah Adnan Aldelaimi

Major histocompatibility complex (MHC)

- Group of genes that code for proteins found on the surfaces of cells that help the immune system recognize foreign substances.
- MHC proteins are found in all higher vertebrates.
- In human beings the complex is also called the **human leukocyte antigen (HLA) system.**

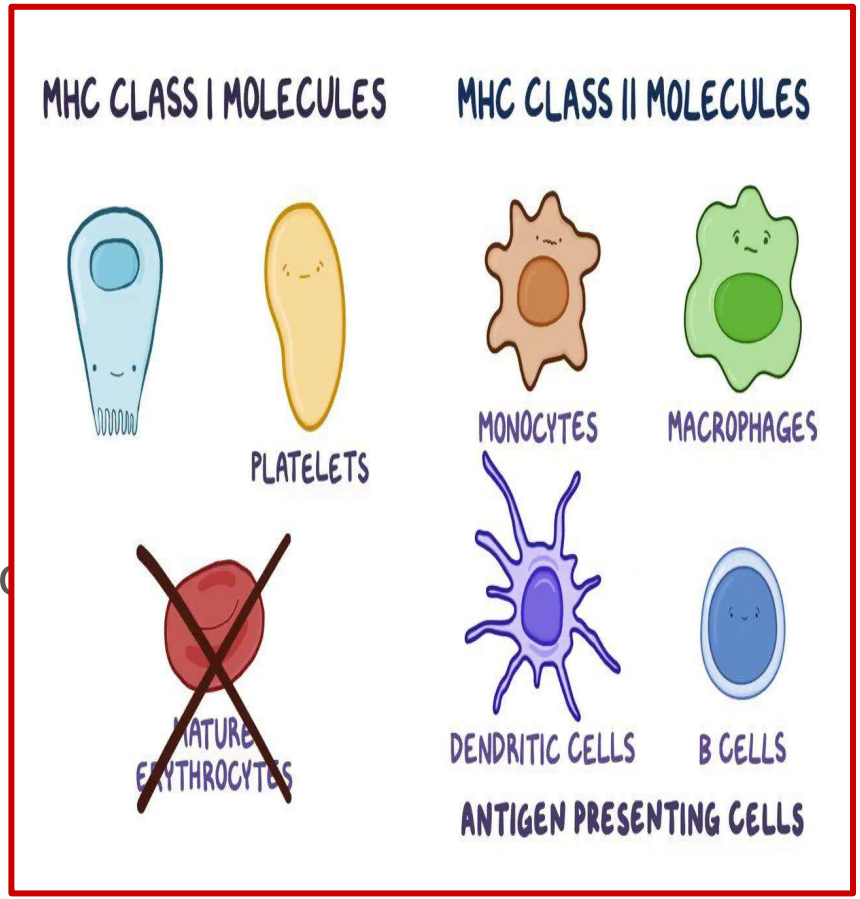


- The genes encoding HLA molecules are clustered on chromosome 6.
- The HLA system is highly polymorphic; thousands of distinct MHC gene alleles in humans, This polymorphism means that no two individuals (other than identical twins) are likely to express the same MHC
- Subsequently, play important role in organ transplantation.



Types of MHC

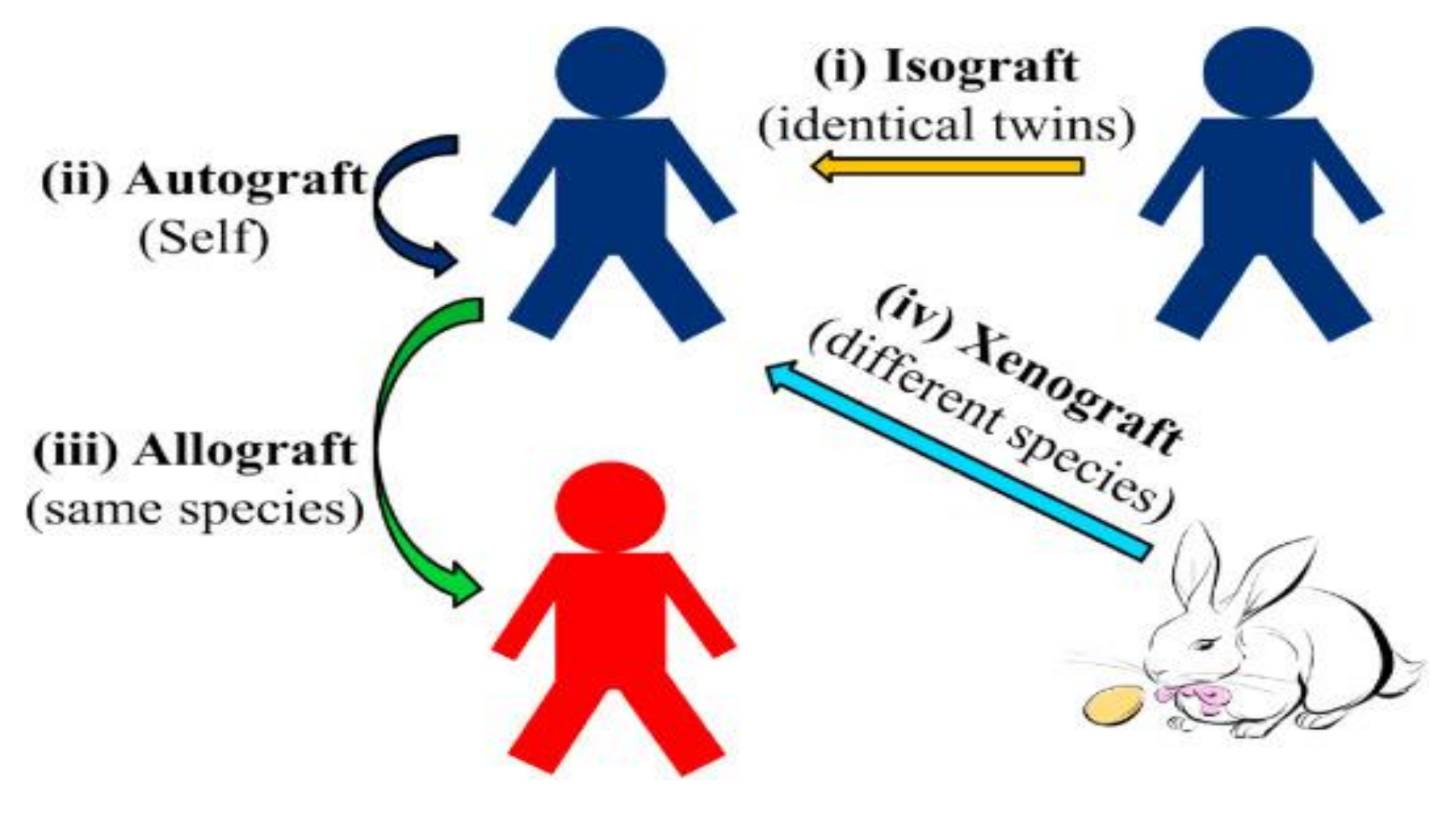
- **MHC Class I** proteins are found on the surface of almost all nucleated cells in the body.
- **MHC Class II** proteins are primarily expressed on antigen-presenting cells, including dendritic cells, macrophages, and B cells.
- MHC I and MHC II are responsible fo distinguishing between self and non-self molecules, allowing the immune system to recognize and eliminate foreign invaders.



Transplantation

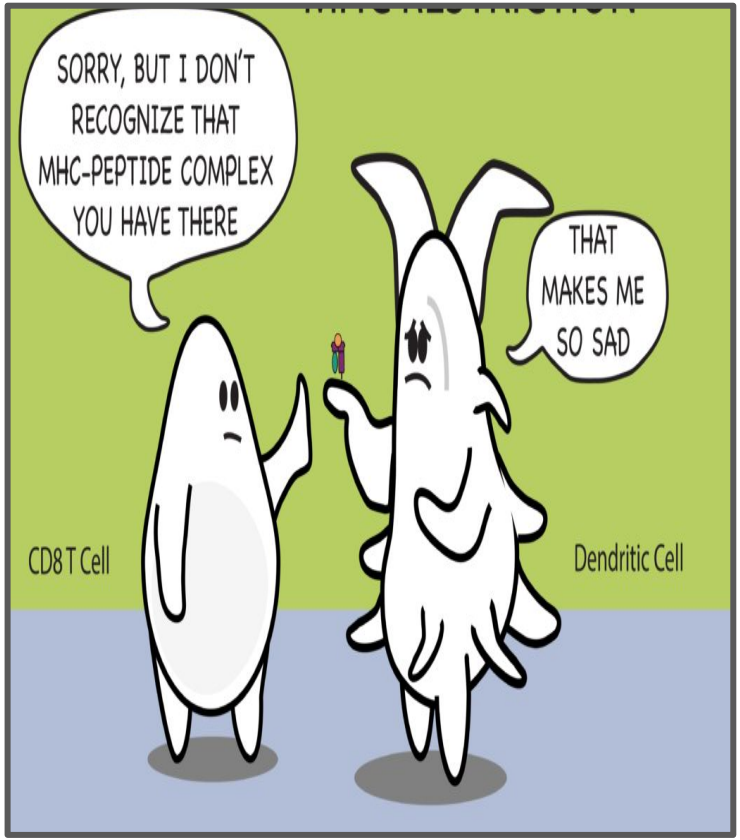
It is a surgical procedure in which an organ, tissue or group of cells are removed from one person (the donor) and transplanted into another person (the recipient), or moved from one site to another in the same person. Transplants can be for:

- **Organs**: heart, kidney, liver, lung, pancreas, stomach and intestine
- **Tissue**: cornea, bone, tendon, skin, pancreas islets, heart valves, nerves and veins
- **Cells**: bone marrow and stem cells
- **Limbs**: hands, arms and feet.


(i) Isograft
(identical twins)
(ii) Autograft
(Self)
(iii) Allograft
(same species)
(iv) Xenograft
(different species)

Transplantation immunopathology:

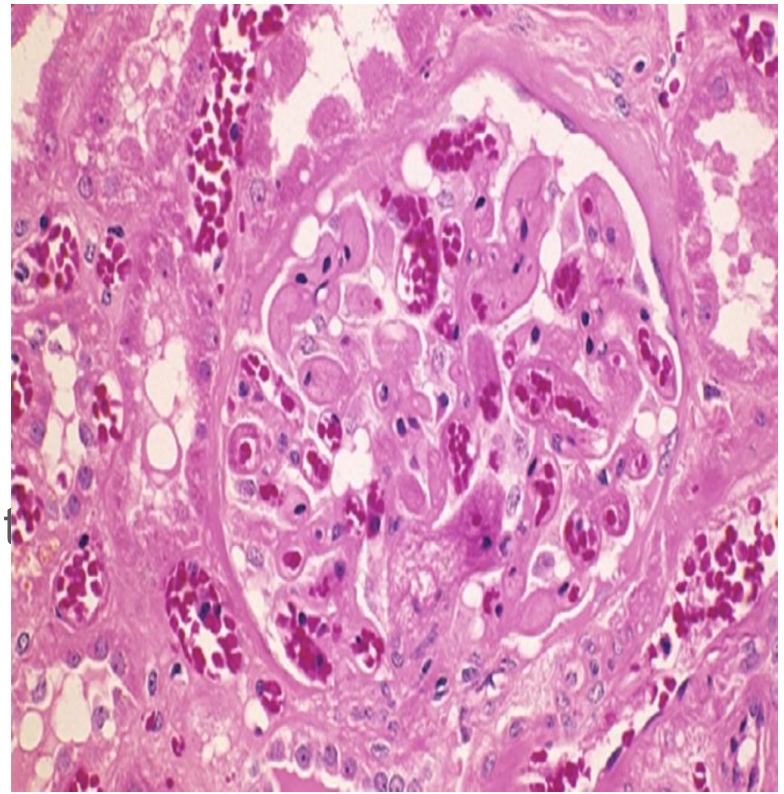
- Rejection is a major problem in transplantation.
- Rejection is a process in which T lymphocytes and antibodies recognizes the graft as being foreign and attacks it.
- The graft antigens are either presented directly to recipient T cells by graft APCs
- Or indirectly the graft antigens are picked up by host APCs, processed (like any other foreign antigen), and presented to host T cells.

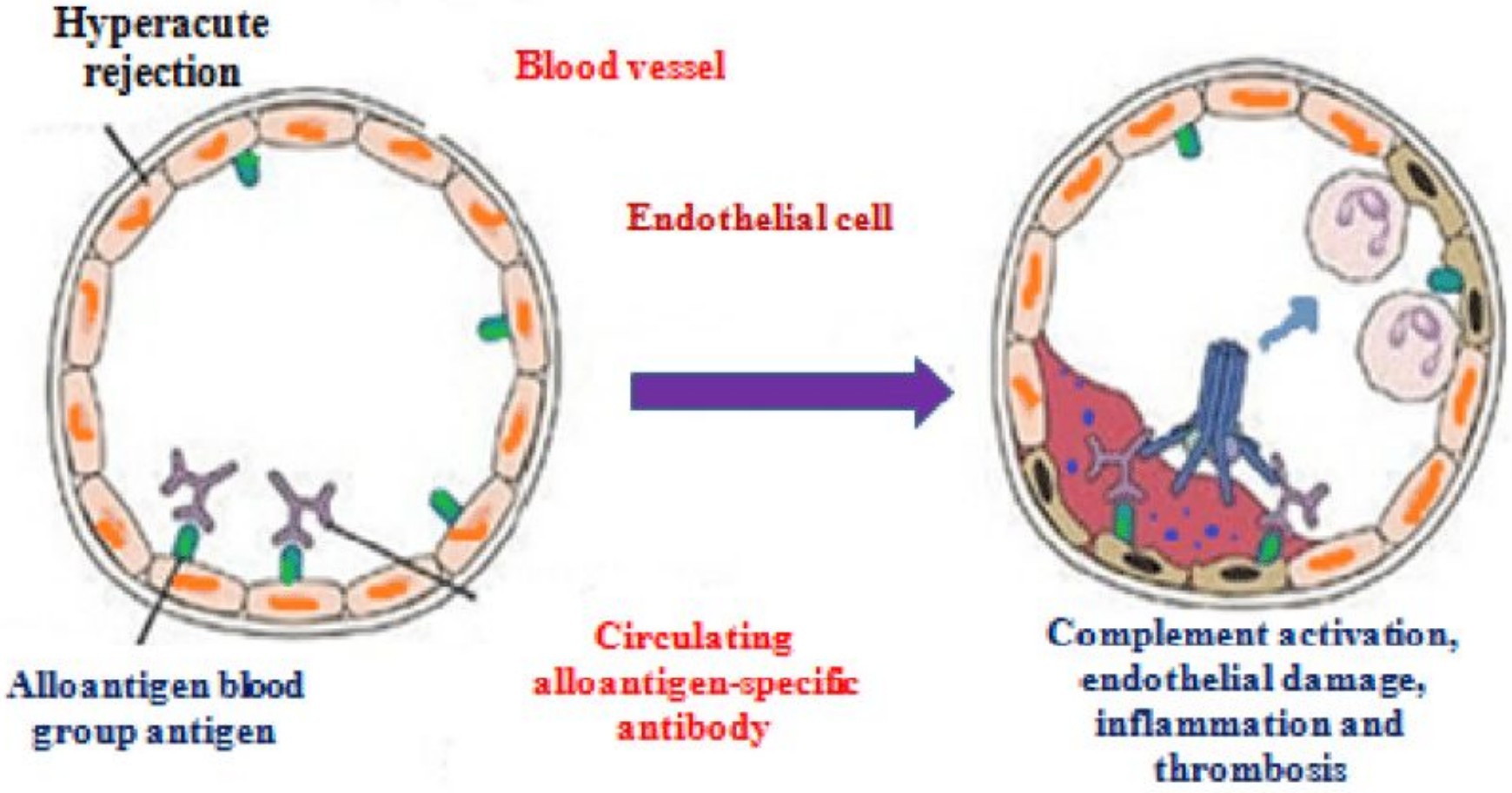


Patterns and Mechanisms of Graft Rejection

Hyperacute rejection

- It is mediated by preformed antibodies specific for antigens on graft endothelial cells.
- Immediately after the graft is implanted and blood flow is restored, the antibodies bind to antigens on the graft vascular endothelium and activate the complement system, leading to endothelial injury, thrombosis, and ischemic necrosis of the graft

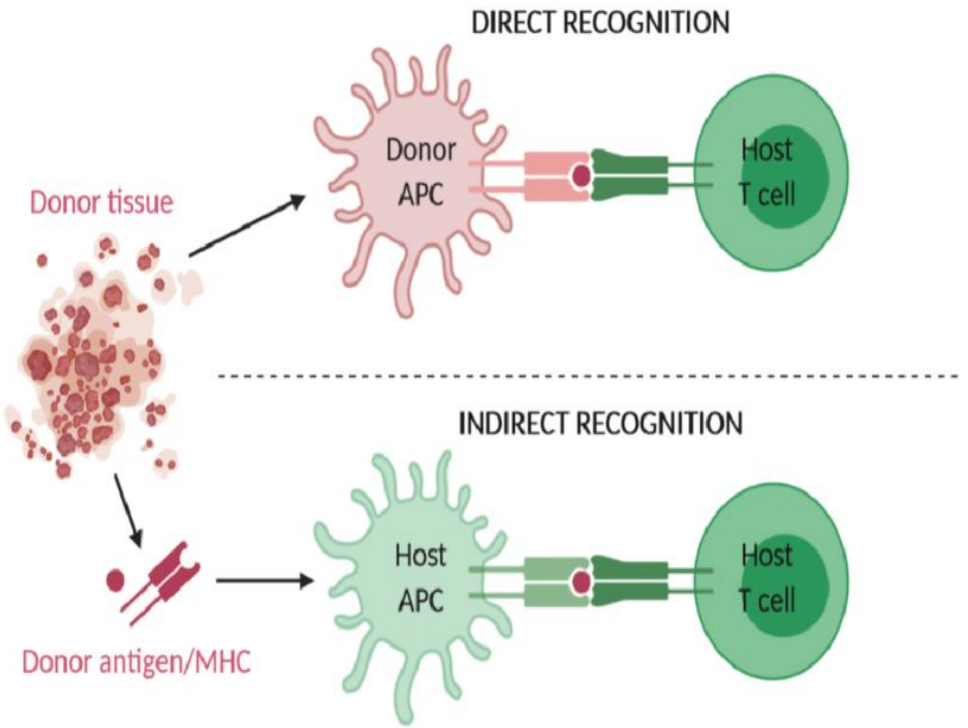



Hyperacute rejection
Blood vessel
Endothelial cell
Alloantigen blood group antigen
Circulating alloantigen-specific antibody
Complement activation, endothelial damage, inflammation and thrombosis

Patterns and Mechanisms of Graft Rejection

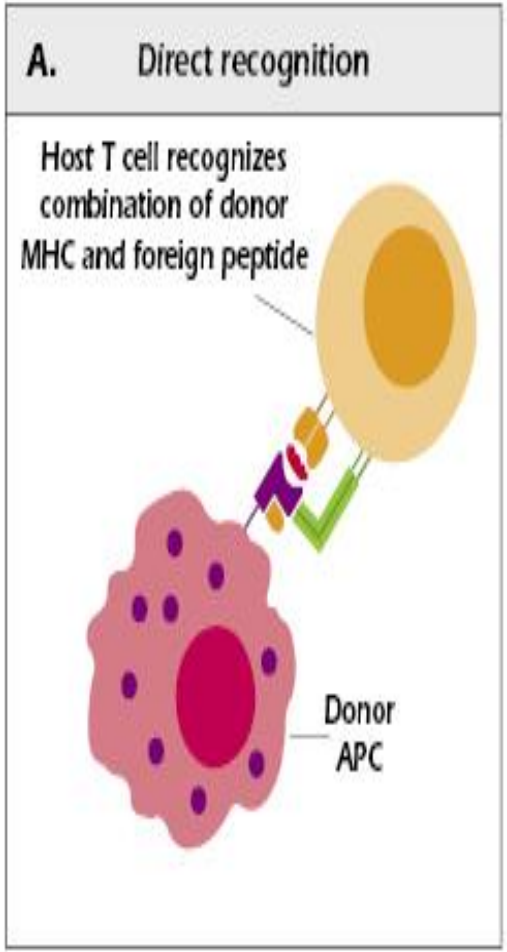
Acute rejection

- It is mediated by T cells or antibodies that are activated by alloantigens in the graft.
- It occurs within days or weeks after transplantation.



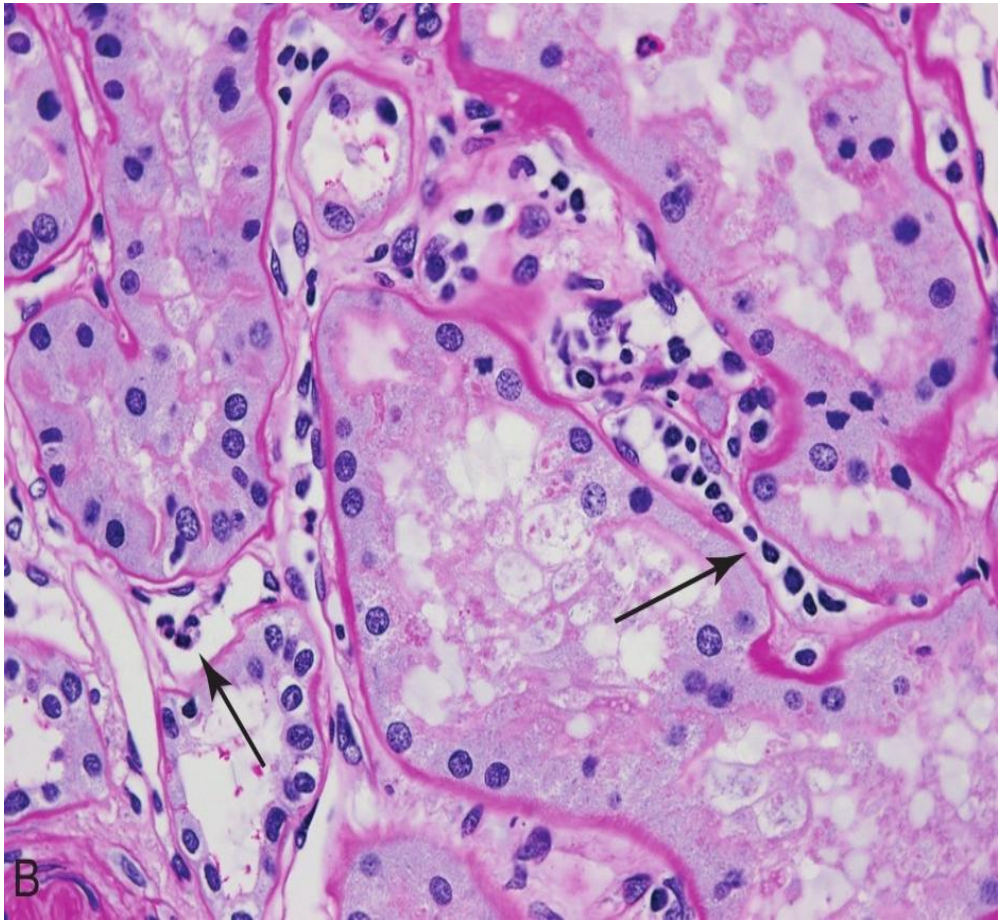
In acute cellular rejection

- CD8+ CTLs may directly destroy graft cells, or CD4+ cells secrete cytokines and induce inflammation, which damages the graft.
- T cells may also react against graft vessels, leading to vascular damage.



In acute antibody-mediated

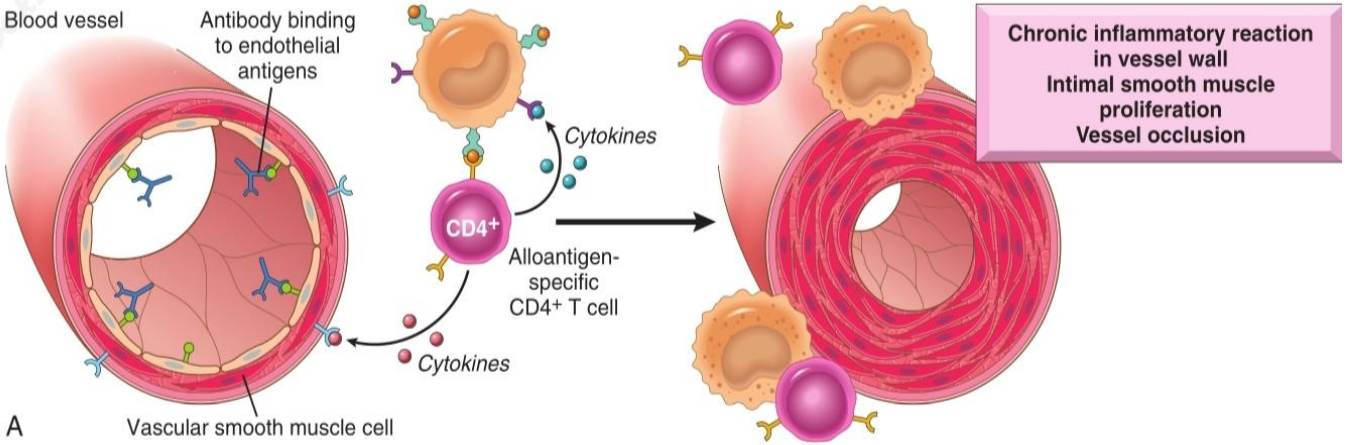
- Antibodies bind to vascular endothelium and activate complement via the classical pathway.
- The resultant inflammation and endothelial damage cause graft failure.



Patterns and Mechanisms of Graft Rejection

Chronic rejection

- is an slower form of graft damage that occurs over months or years, leading to progressive loss of graft function.
- Chronic rejection manifests as interstitial fibrosis and gradual narrowing of graft blood vessels (graft arteriosclerosis).



Immunosuppressive therapy

Immunosuppressive drugs in current use include:

- Steroids (reduce inflammation)
- Mycophenolate mofetil (inhibits lymphocyte proliferation)
- Tacrolimus (inhibits T cell responses).

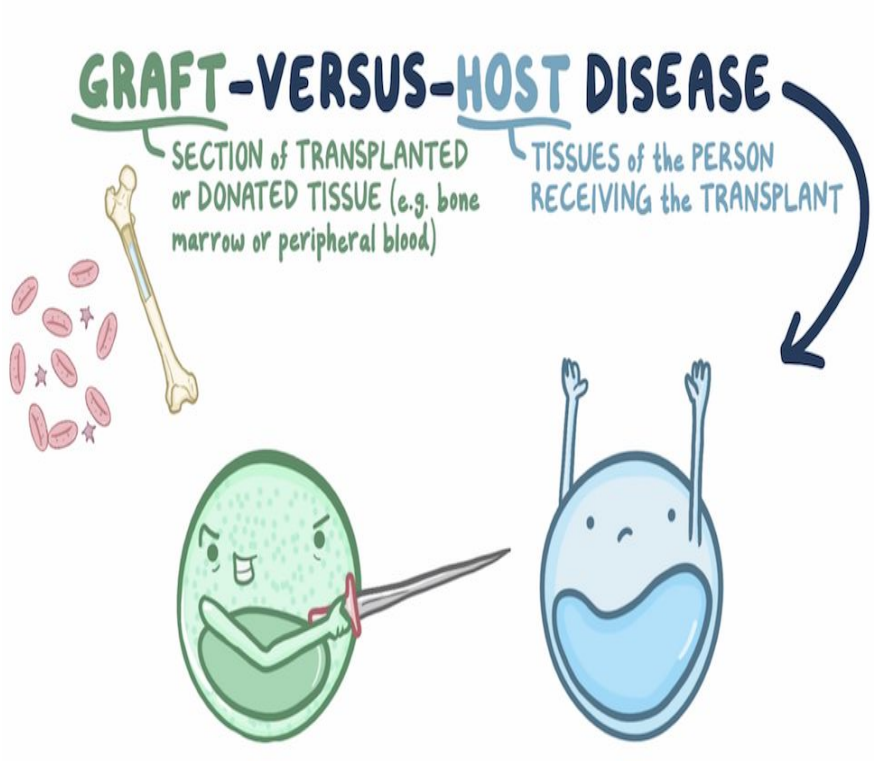
Although immunosuppression prolongs graft survival, it carries its own risks. The price paid in the form of increased susceptibility to opportunistic infections. The most frequent infectious complications is reactivation of polyoma virus, Epstien Barr Virus, human papilloma virus.

Transplantation of Hematopoietic Stem Cells (HSCs)

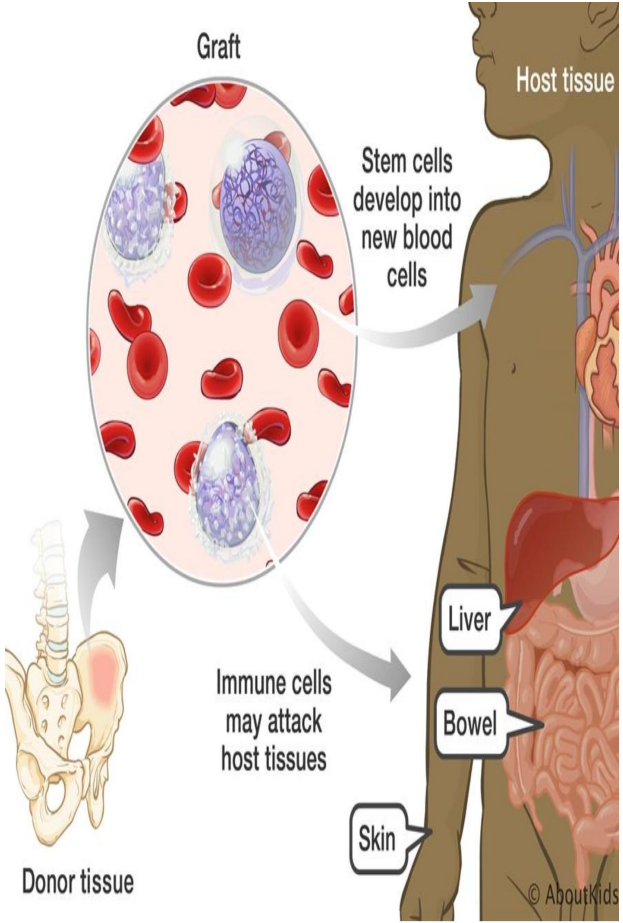
- HSC transplants to treat hematologic malignancies, bone marrow failure syndromes (aplastic anemia), and inherited bone marrow disorders (sickle cell anemia, thalassemia)
- The recipient is irradiated or treated with high doses of chemotherapy to destroy the immune system (sometimes cancer cells)
- Two problems that are unique to HSC transplantation are graft-versus-host disease (GVHD) and immunodeficiency

Graft-versus-host disease (GVHD)

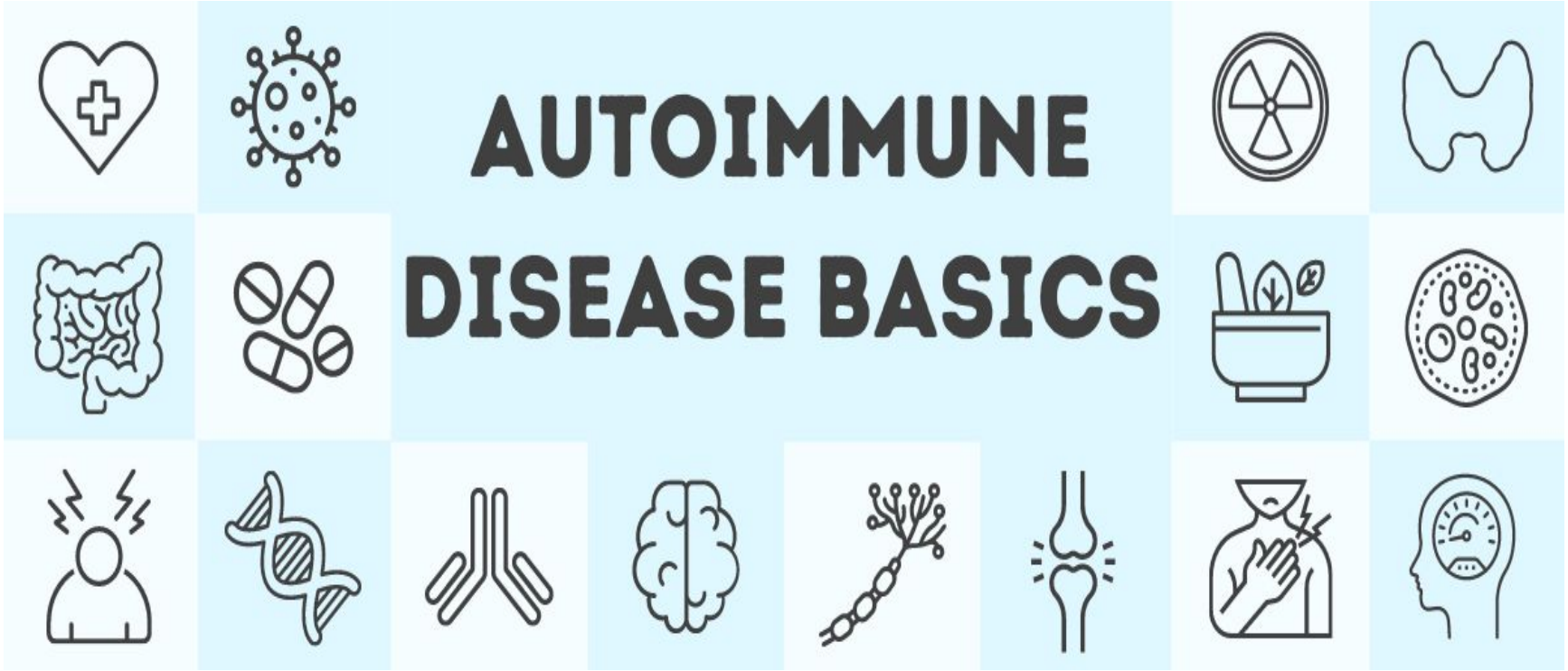
GVHD occurs when immunologically competent cells or their precursors are transplanted into immunologically compromised recipients, and the transferred cells recognize alloantigens in the host and attack host tissues.



- **Acute GVHD** occurs within days to weeks after HSC transplantation, the major clinical manifestations are generalized rash, destruction of small bile ducts gives rise to jaundice, and mucosal ulceration of the gut results in bloody diarrhea.
- **Chronic GVHD** may follow the acute syndrome or may occur insidiously. Clinical manifestations: extensive cutaneous injury and fibrosis, chronic liver disease, jaundice, gastrointestinal tract damage, recurrent and life-threatening infections.

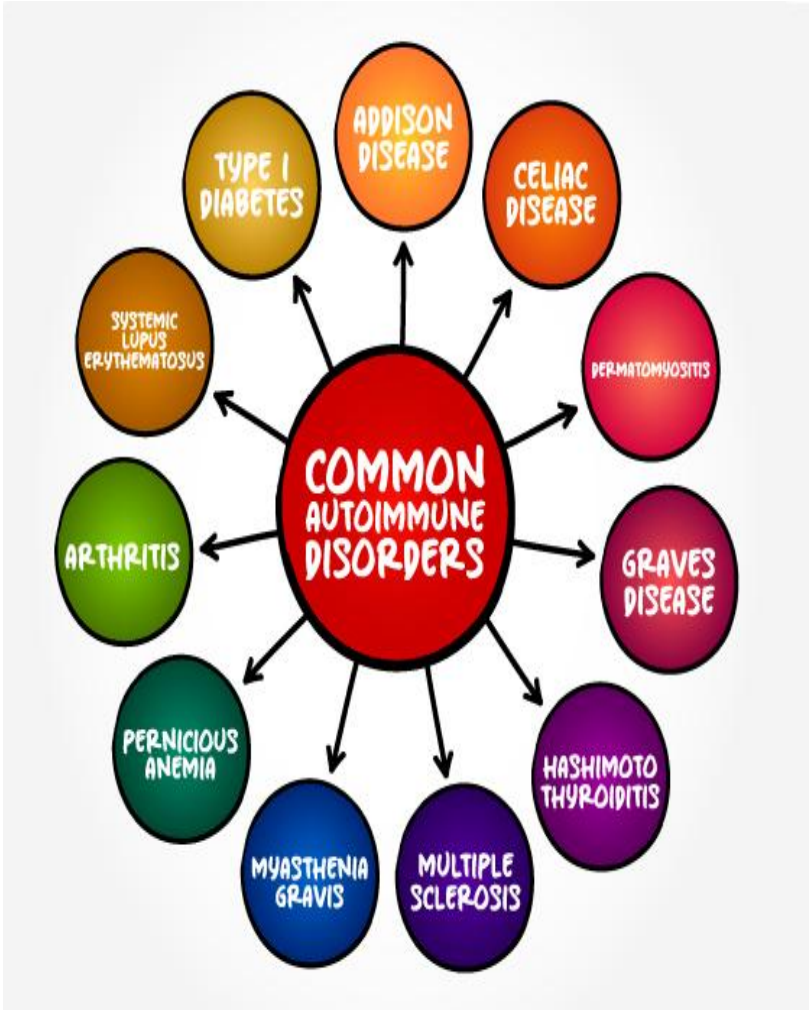


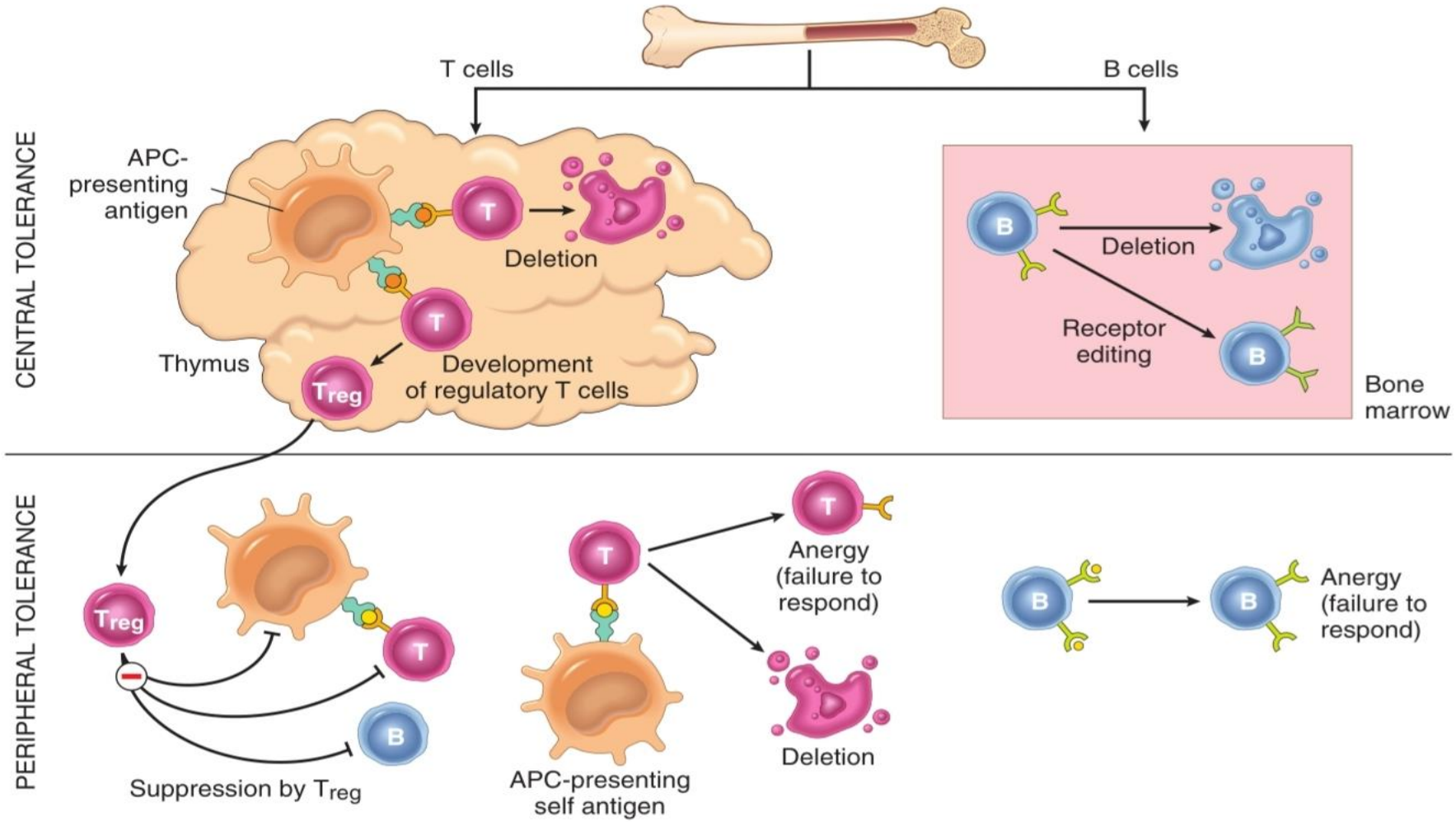
Immune reactions against self antigens



Self-tolerance refers to lack of responsiveness to an individual's own antigens, and it underlies our ability to live in harmony with our cells and tissues.

The mechanisms of self-tolerance can be broadly classified into two groups: central tolerance and peripheral tolerance

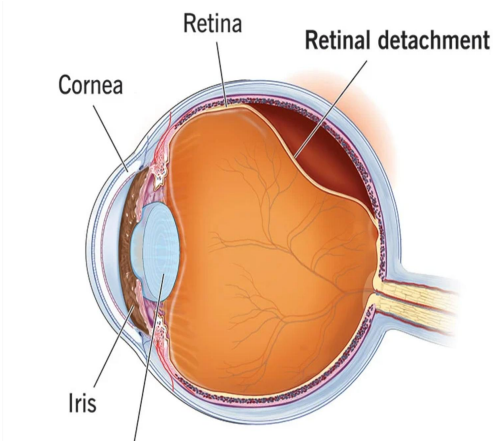


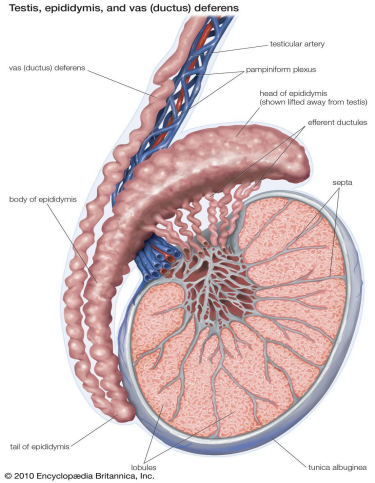

CENTRAL TOLERANCE
T cells
B cells
APC-presenting antigen
T
Deletion
T
Thymus
Treg
Development of regulatory T cells
B
Deletion
Receptor editing
B
Bone marrow
PERIPHERAL TOLERANCE
Treg
T
B
Suppression by Treg
T
Anergy (failure to respond)
Deletion
APC-presenting self antigen
B
B
Anergy (failure to respond)

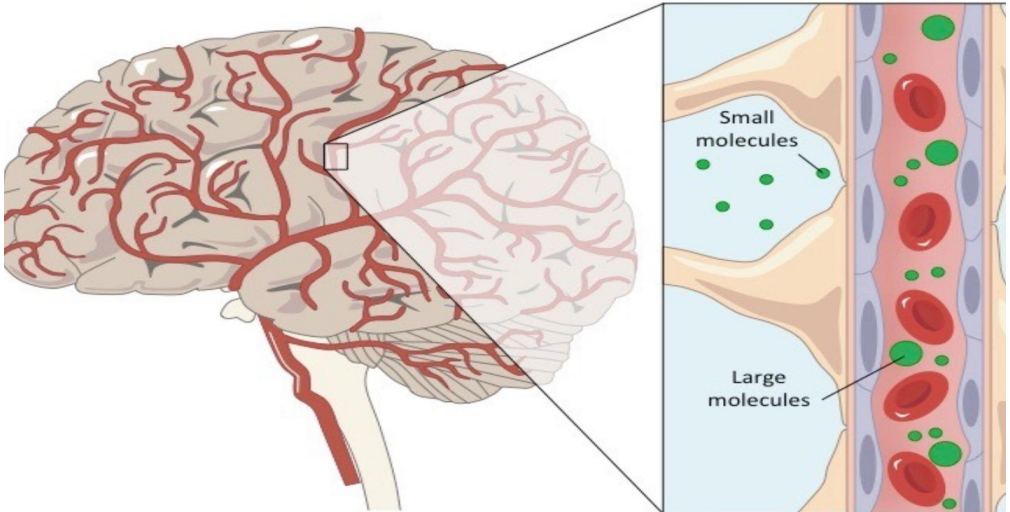
- **Central tolerance:** immature lymphocytes that recognize self antigens in the central (generative) lymphoid organs and bone marrow are killed by apoptosis or change receptor for B lymphocytes, but some lymphocytes escape into the periphery causing autoimmune diseases.
- **Peripheral tolerance:** mature lymphocytes that recognize self antigens in peripheral tissues become functionally inactive (Anergy) or are suppressed by regulatory T lymphocytes, or they die by apoptosis.

Antigen sequestration:

antigens are hidden from the immune system because the tissues, in which these antigens are located, do not communicate with blood and lymph; these organs are also called **immune-privileged sites** because it is difficult to induce immune responses to antigens in these sites

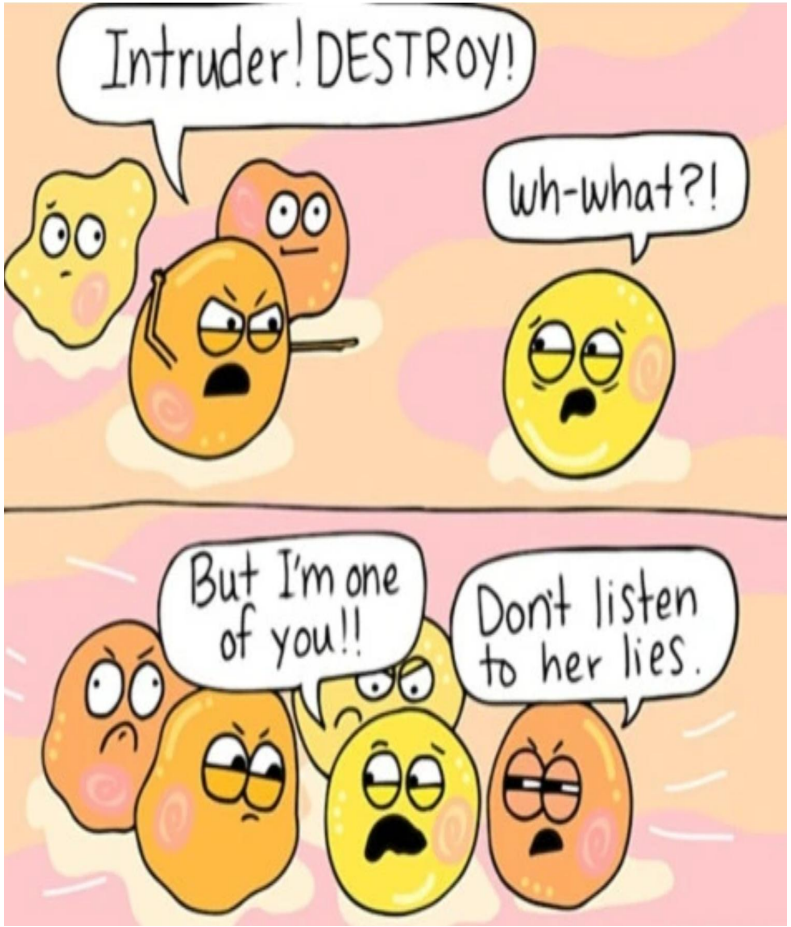






Autoimmune diseases

The breakdown of self-tolerance and the development of autoimmunity are probably related to the inheritance of various **susceptibility genes** (HLA genes) and **changes in tissues**, often induced by infections or injury, that alter the display and recognition of self-antigens.



Role of Infections and Tissue Injury

- **Molecular mimicry**: Viruses and other microbes (particularly streptococci and Klebsiella) may share cross-reacting epitopes with self-antigens, so the body responses to the microbial antigen may attack self-tissues.
- Ex: Rheumatic heart disease, in which an immune response against streptococci cross-reacts with cardiac antigens

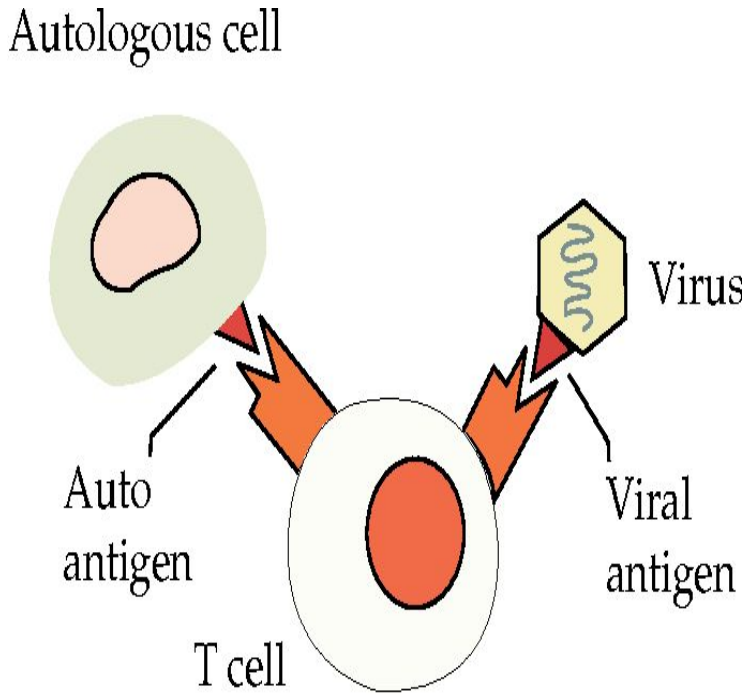
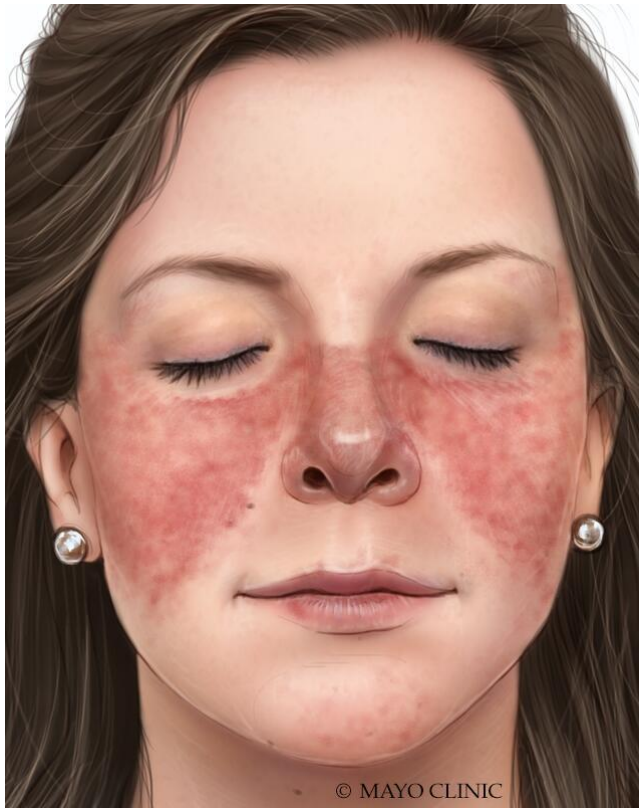


Fig. 1 : Diagram showing Molecular Mimicry Hypothesis. The

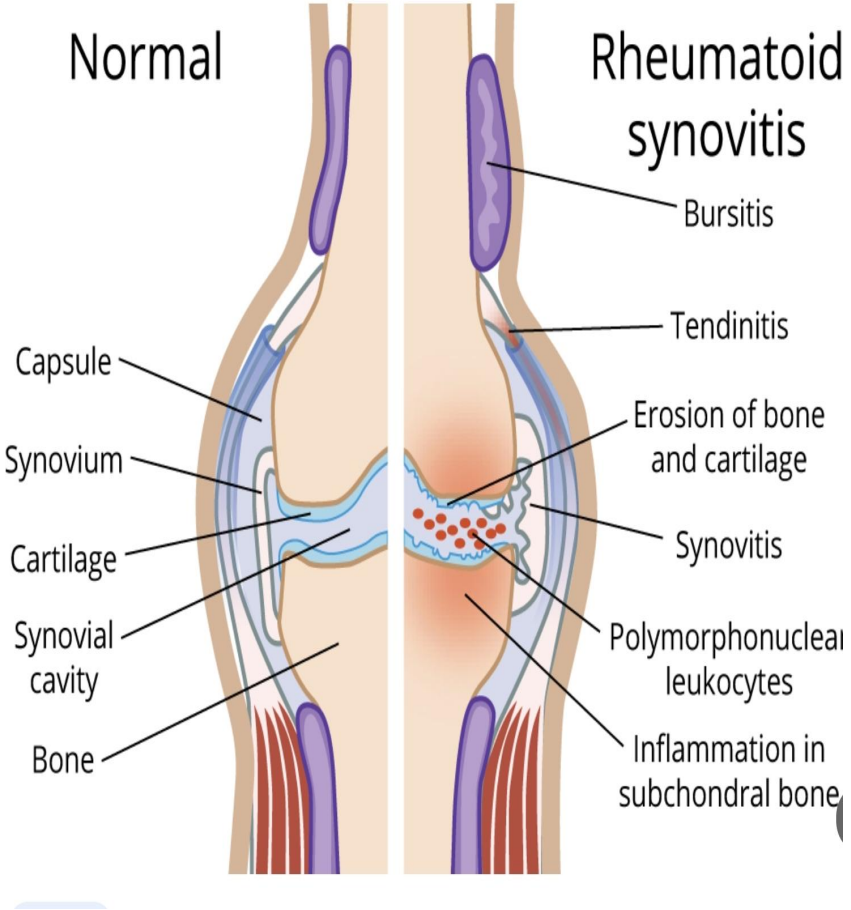
Systemic Lupus Erythematosus SLE

- Caused by autoantibodies directed against nuclear antigens
- Other autoantibodies directed against erythrocytes, platelets, and various complexes of phospholipids with proteins.
- Manifestations: include nephritis, skin lesions like “butterfly” rash on the face and arthritis (caused by the deposition of immune complexes), and hematologic and neurologic abnormalities.



Rheumatoid Arthritis RA

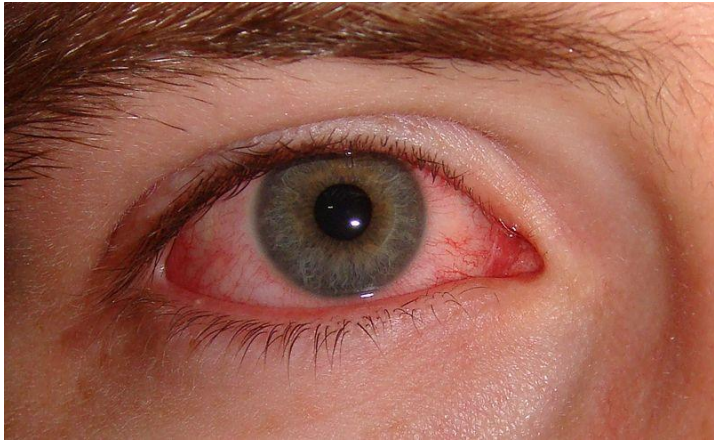
- A chronic inflammatory disease caused by an autoimmune response against an unknown self antigen(s)
- T-cell reactions in the joint with production of cytokines that activate phagocytes that damage tissues and stimulate inflammation of synovial tissues (synovitis).

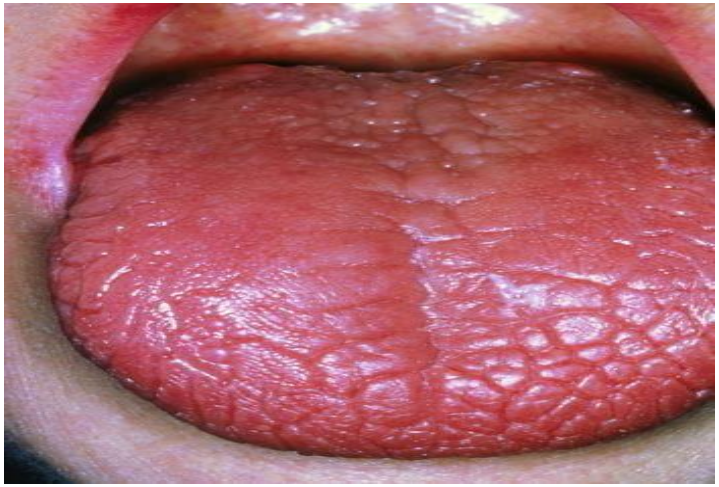


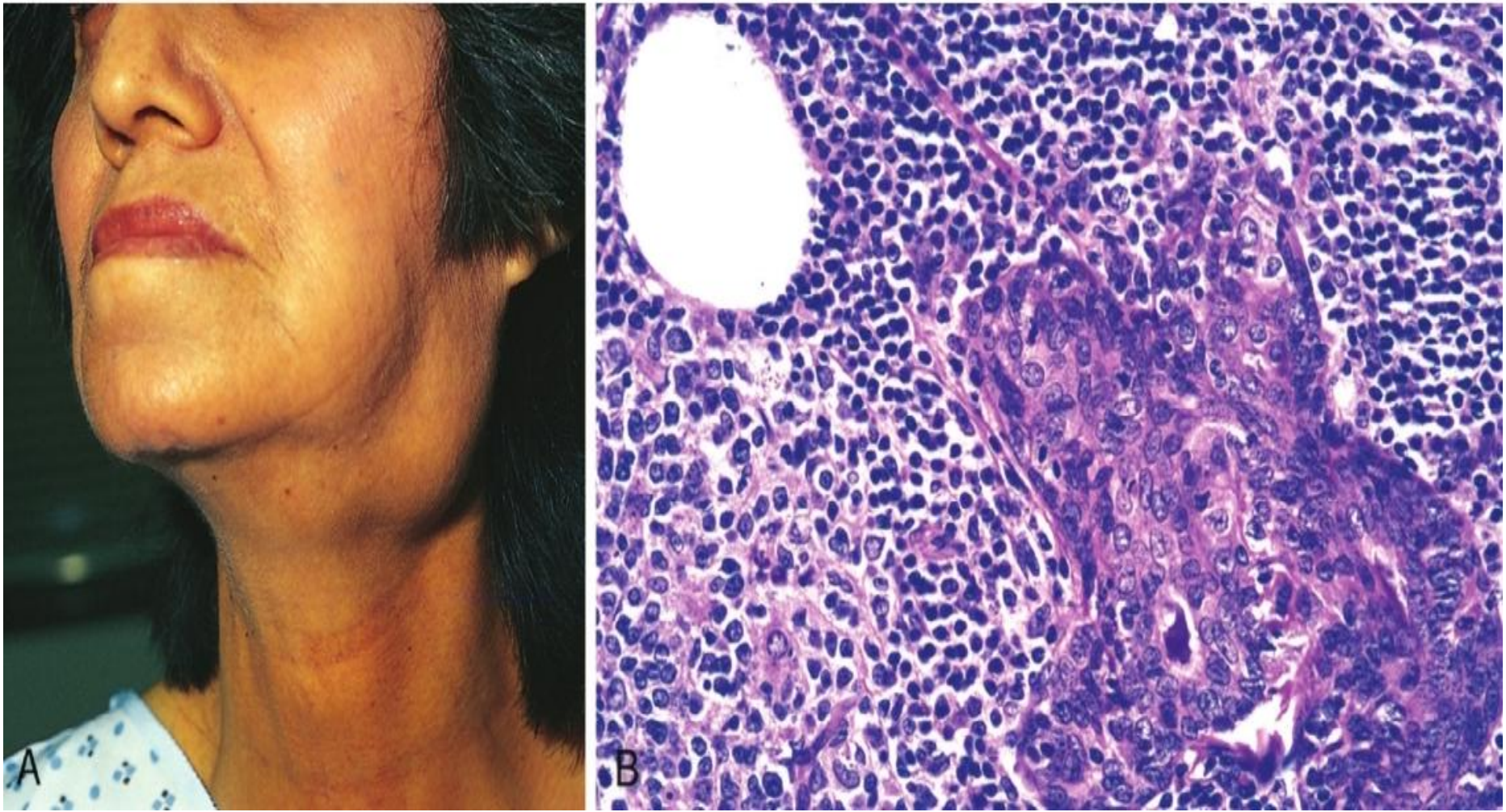
Sjögren syndrome

An autoimmune disease, autoantibodies against the ductal epithelial cells of the exocrine gland resulting from immune-mediated destruction of the lacrimal and salivary glands, characterized by:

- Dry eyes (keratoconjunctivitis sicca)
- Dry mouth (xerostomia)

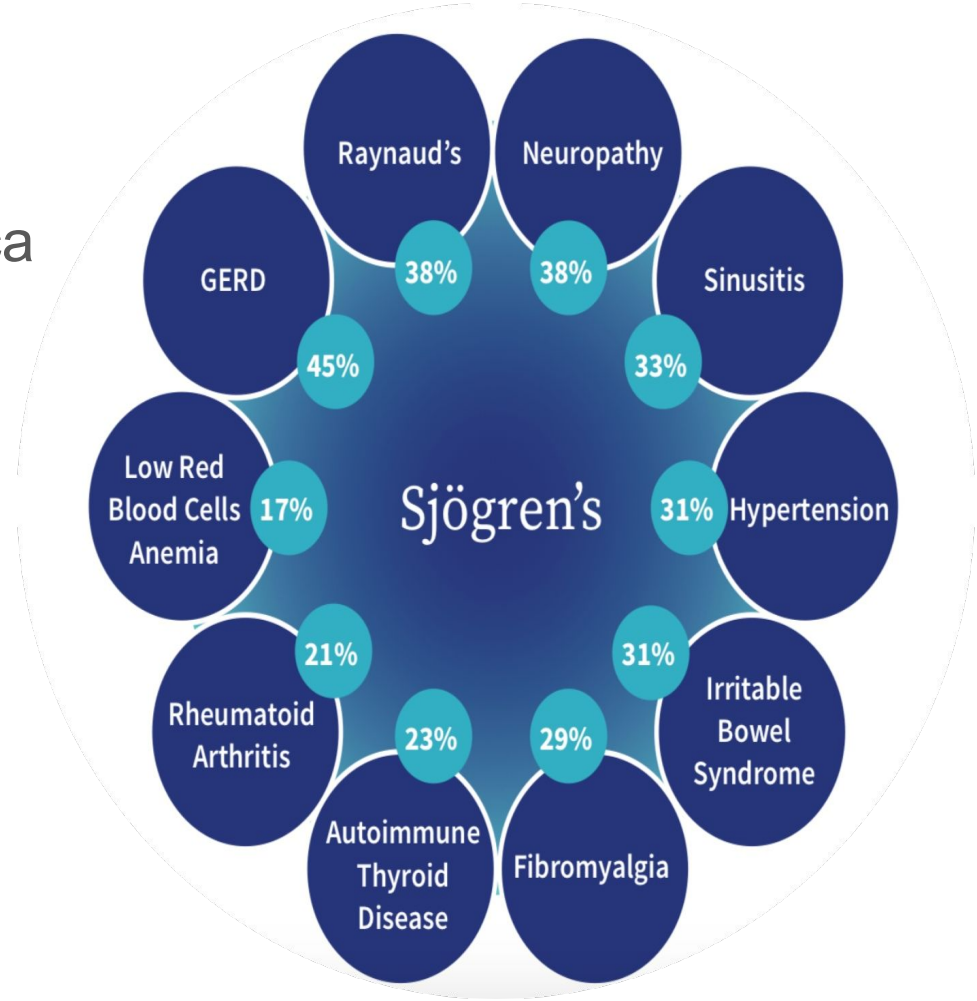





A
B

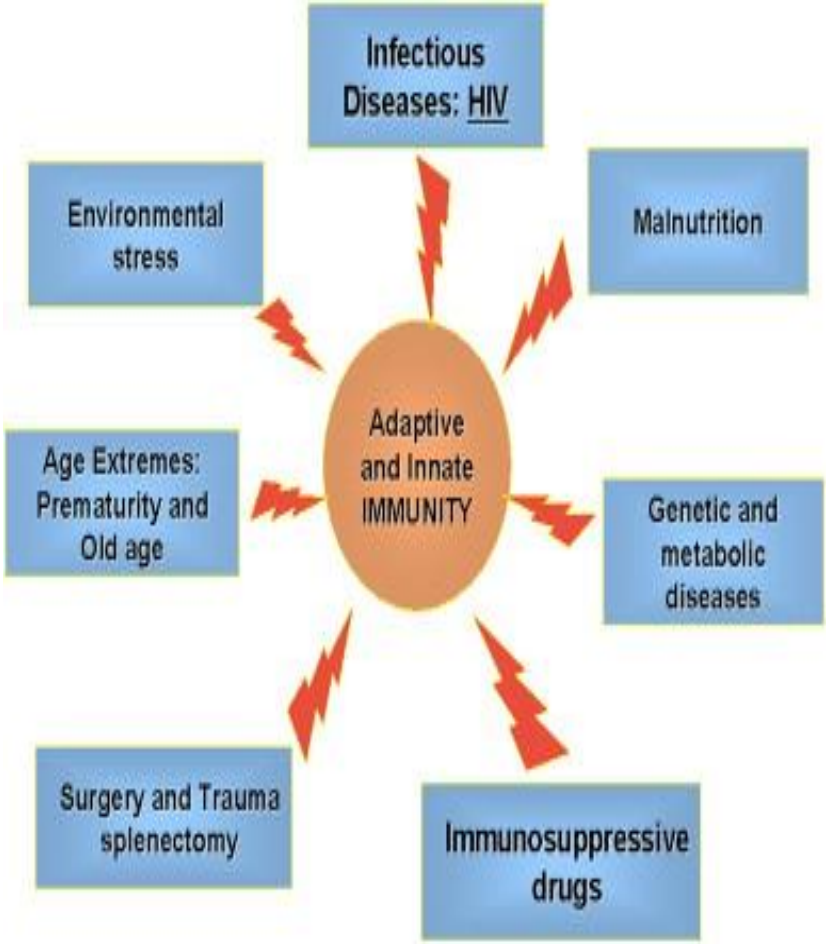
It occurs as two types:

1. Isolated disorder **(primary form),** also known as the sicca syndrome.
2. In association with another autoimmune disease **(secondary form)** RA is the most common, but some patients have SLE, polymyositis, systemic sclerosis, vasculitis, or thyroiditis



Immune deficiency diseases

- Caused by inherited defects in immune system development (primary)
- Acquired defects due to infection, malnutrition, aging, immunosuppression, autoimmunity, or chemotherapy (secondary).
- Increased susceptibility to infections as well as to certain forms of cancer.

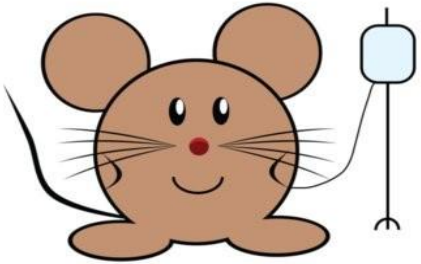


Primary (Congenital) Immune Deficiency Diseases:

- Caused by mutations in genes involved in lymphocyte maturation or function, or in innate immunity.
- They have increased susceptibility to infections in early life

Primary

Due to family history, genetic diagnosis

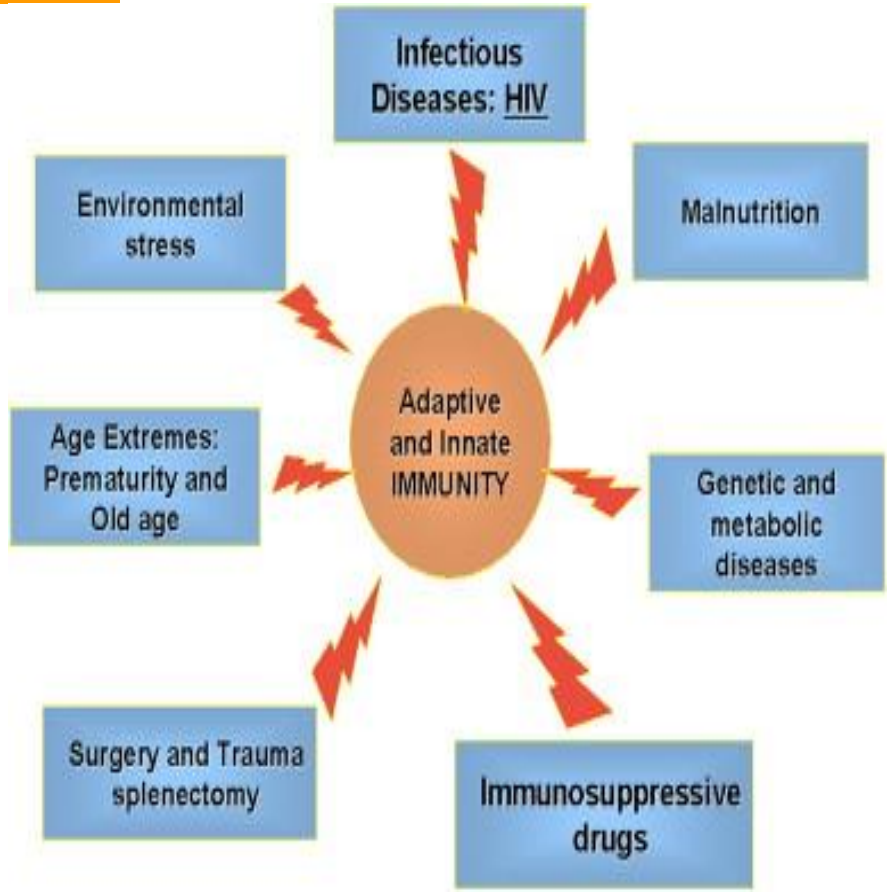


Secondary

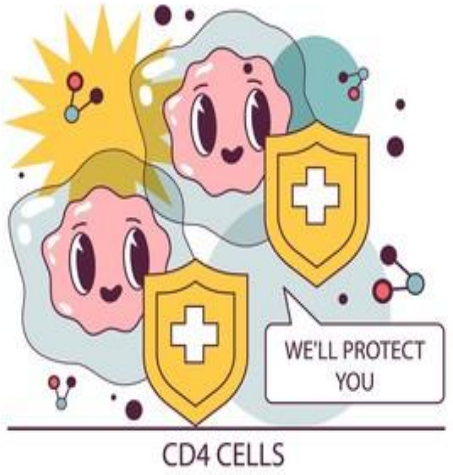
Due to Chemotherapy cancers, organ transplant, disease, medication

Secondary Immune Deficiencies

- More common than the primary (inherited) disorders.
- It occurs in patients with malnutrition, infection, cancer, renal disease, or sarcoidosis, therapy-induced suppression of the bone marrow and of lymphocyte function or viruses in Acquired Immunodeficiency Syndrome (AIDS).

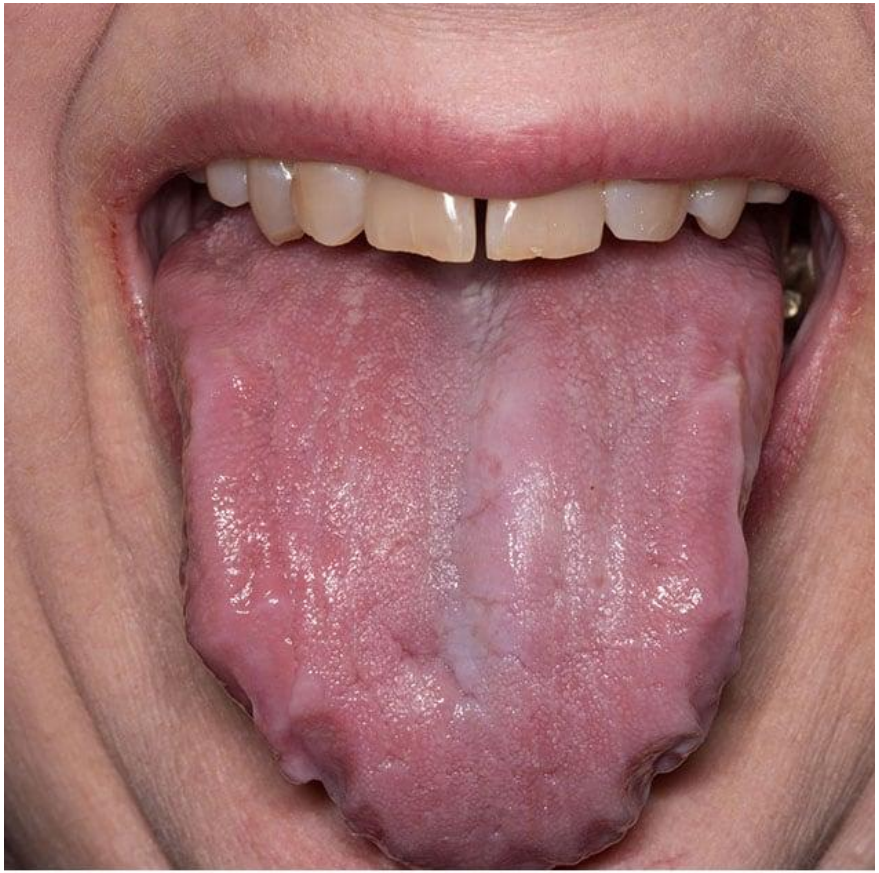


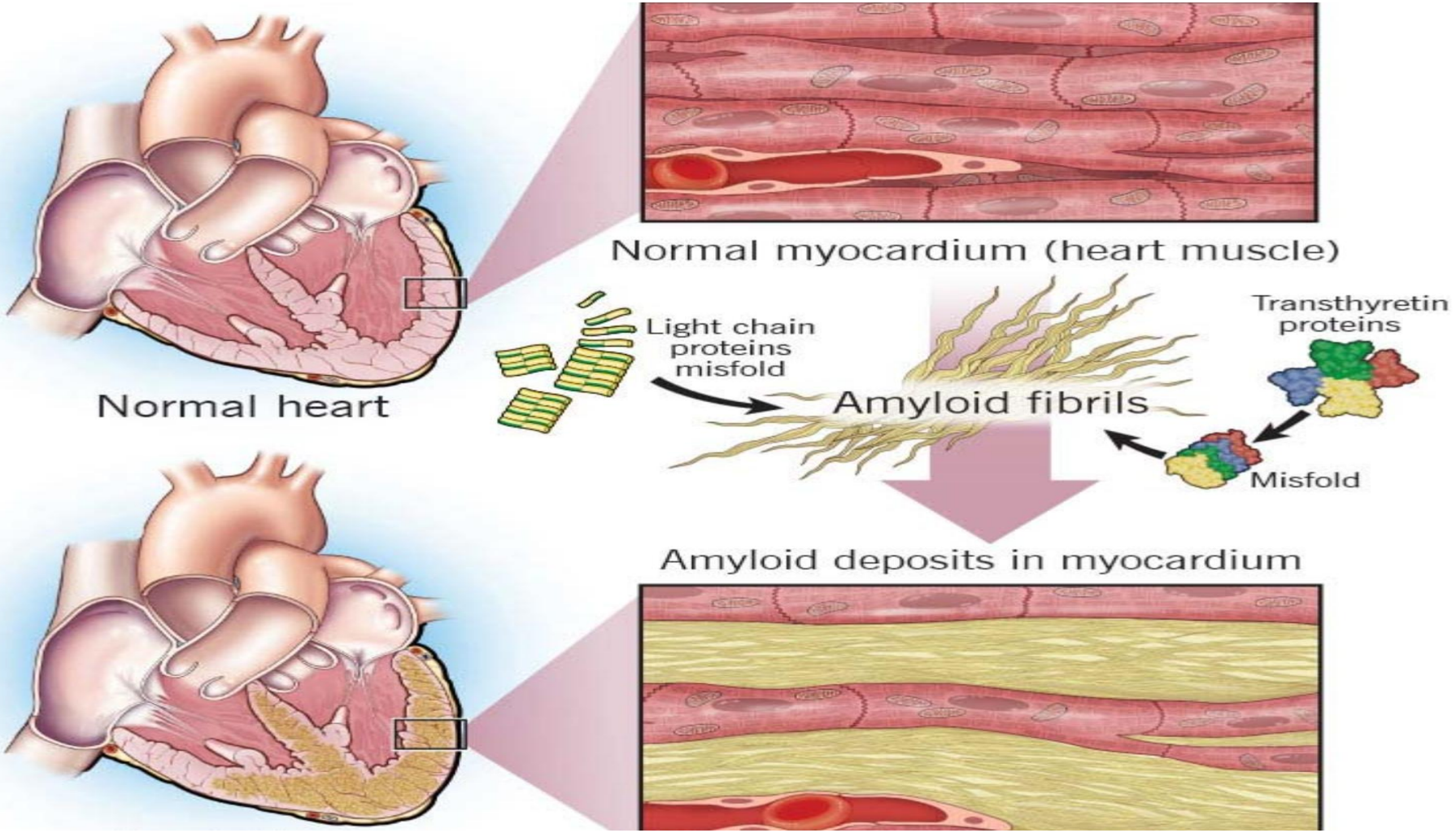
Cause	Mechanism
Human immunodeficiency virus infection	Depletion of CD4+ helper T cells
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Involvement of bone marrow by cancers (metastases, leukemias)	Reduced site of leukocyte development
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Removal of spleen	Decreased phagocytosis of microbes



Amyloidosis

- It is a condition of accumulations of misfolded protein in tissues and leads to organs dysfunction (misfolded proteins that aggregate to form insoluble fibrils).
- It associated with a number of inherited and inflammatory disorders
- They do not evoke an inflammatory response.




Normal myocardium (heart muscle)
Normal heart
Light chain proteins misfold
Amyloid fibrils
Transthyretin proteins
Misfold
Amyloid deposits in myocardium

Arms

- Carpal tunnel syndrome
- Numbness, burning &/or tingling (peripheral neuropathy)
- Weak fingernails

Stomach & Intestines

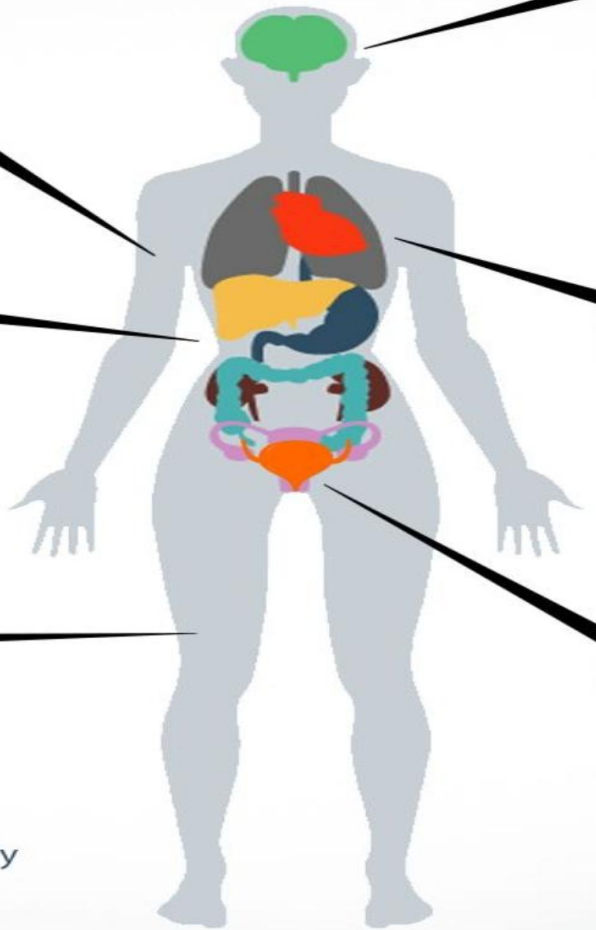
- Poor appetite
- Bloating or excessive gas
- Diarrhea or constipation

Legs

- Swelling of feet or legs
- Numbness, burning &/or tingling (peripheral neuropathy)
- Leg weakness
- Weak toenails

General

- Bruising or bleeding excessively
- Purple color in areas of skin folds



Head & Neck

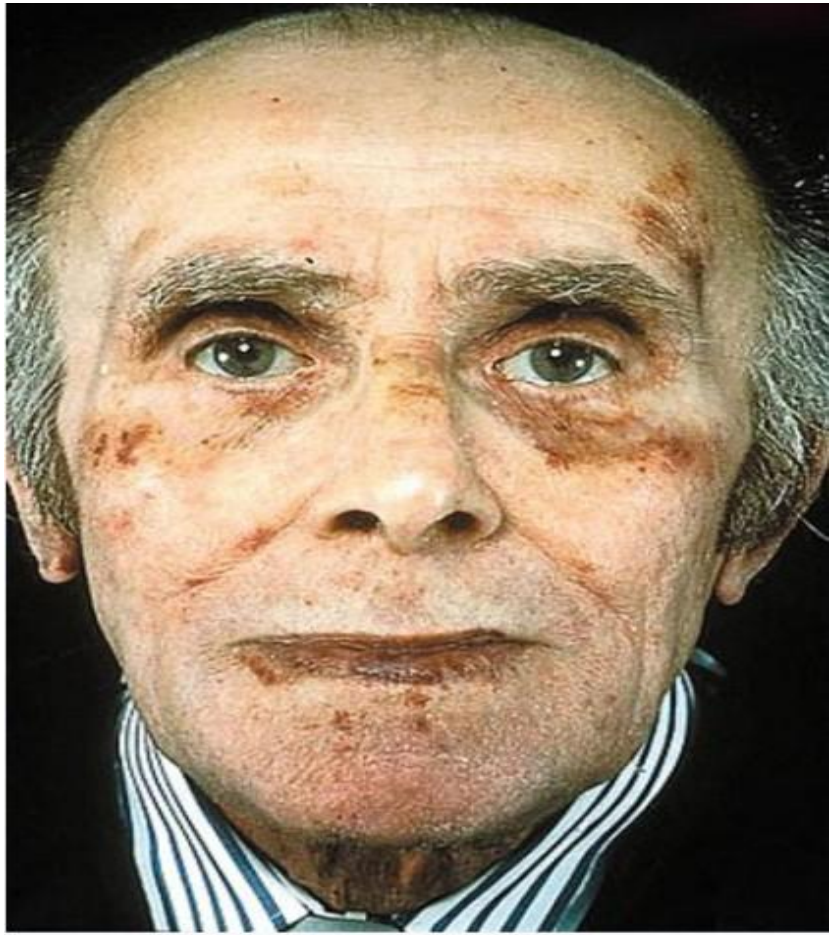
- Light headedness upon standing
- Purple color on the eyelids & /or around the eye
- Enlarged tongue

Heart and Lungs

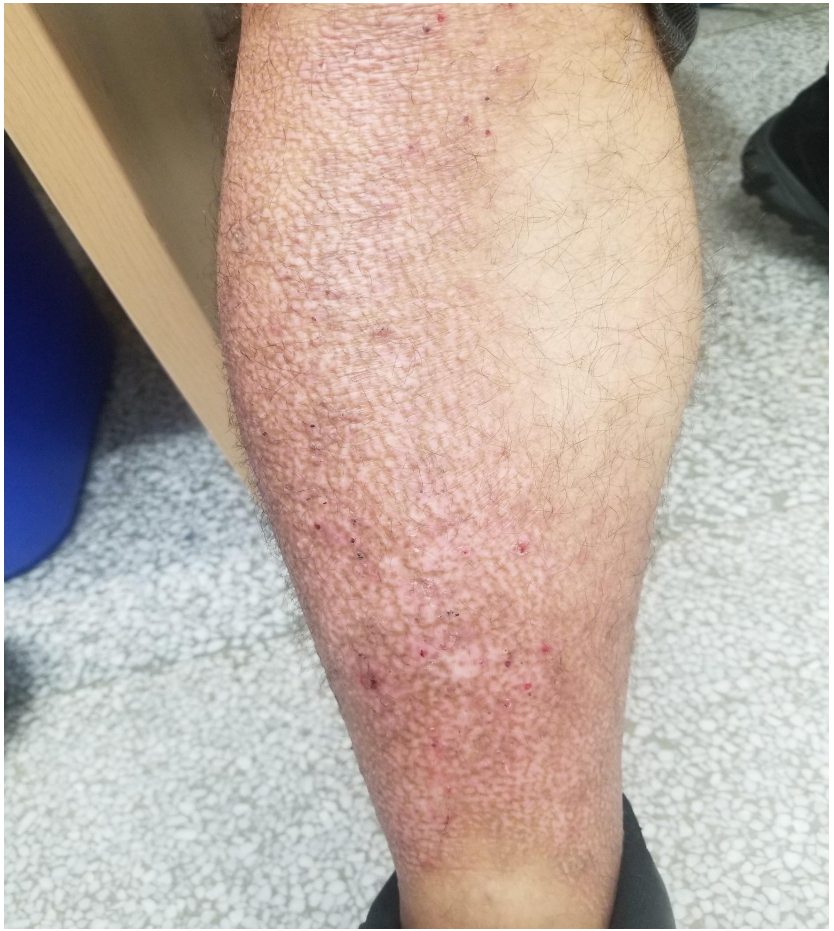
- Shortness of breath
- Palpitations & chest pain
- Fatigue

Kidney and Bladder

- Excessive bubbles in the urine
- Urinating less
- Getting up at night to urinate



Classic facial features of AL amyloidosis with bleeding under the skin around the eyes[1]

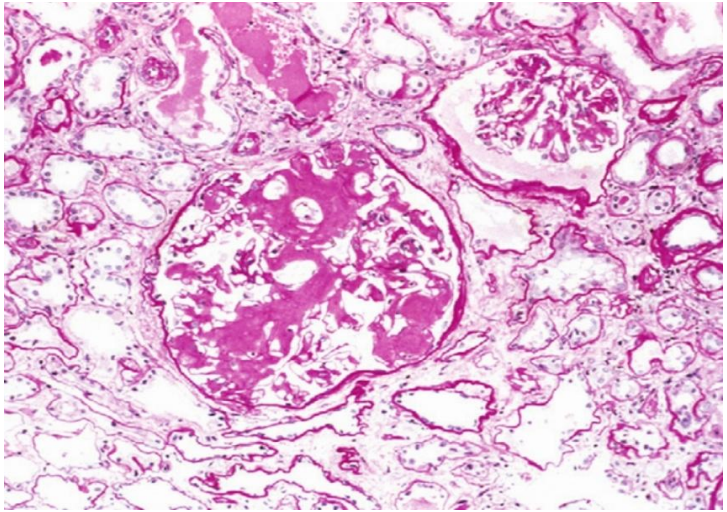


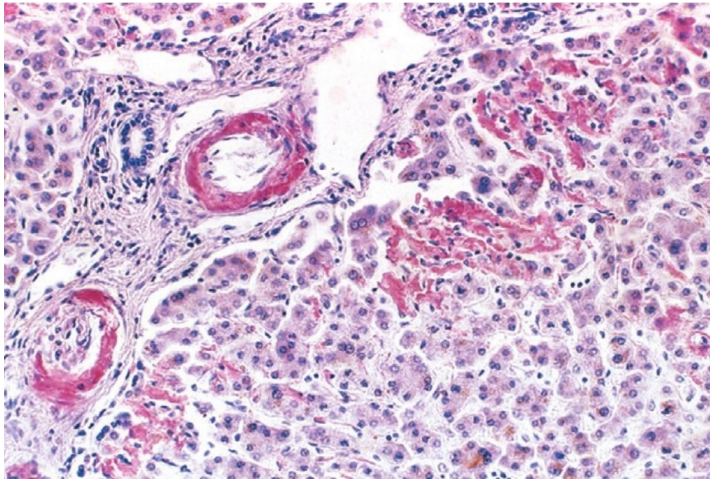
Amyloidosis may be localized or systemic. It is seen in association with a variety of primary disorders, including:

- Monoclonal immunoglobulin light chains deposits occurs in multiple myeloma, lymphoma, or Waldenstorm’s macroglobulinemia.
- Chronic inflammatory diseases such as rheumatoid arthritis
- Alzheimer disease
- Familial conditions in which the amyloid deposits consist of mutants of normal proteins
- Amyloidosis associated with dialysis

Histological appearance:

With the light microscope and standard tissue stains, amyloid appears as an amorphous eosinophilic hyaline extracellular substance that with progressive accumulation will produce pressure atrophy of the adjacent cells. To differentiate between amyloid and other hyaline deposits like collagen and fibrin, a special stain can be used which is, Congo red that give amyloid a pink or red color






Thank
you!

Diseases of the Immune System

Dr. Afrah Adnan Aldelaimi

Immunity

It is protection against infections.

The immune system is the collection of cells and molecules that are responsible for:

- Defending our body against pathogenic microbes
- Prevent the proliferation of cancer cells.
- Mediate the healing of damaged tissue.

Types of immunity:
1. Innate or natural or native immunity

It is mediated by cells and proteins that are always present in the blood or tissue and act immediately against any infection.

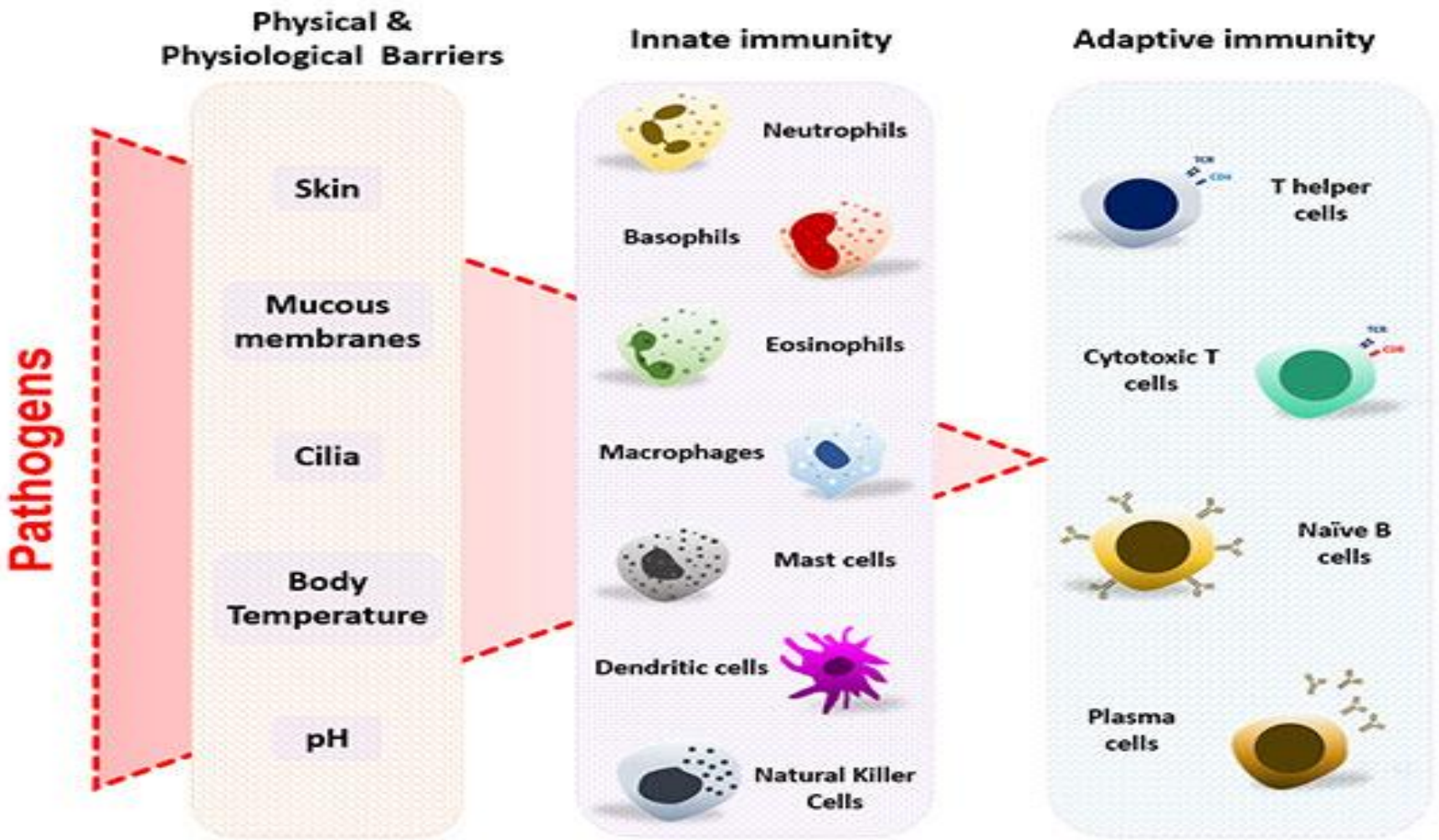
Components of innate immunity are:

- Epithelial barriers of the skin, gastrointestinal tract, and respiratory tract, which prevent microbe entry.
- Phagocytic leukocytes (neutrophils and macrophages).
- A specialized cell type called the natural killer (NK) cell.
- Several circulating plasma proteins, the most important of which are the proteins of the complement system.

Types of immunity:
Adaptive or acquired or specific immunity

It is normally silent and responds to the presence of an infectious microbes by becoming active for neutralizing and eliminating the microbes.

The components of the adaptive immunity are lymphocytes and their products. The terms "immune system" and "immune response" refer to adaptive immunity.

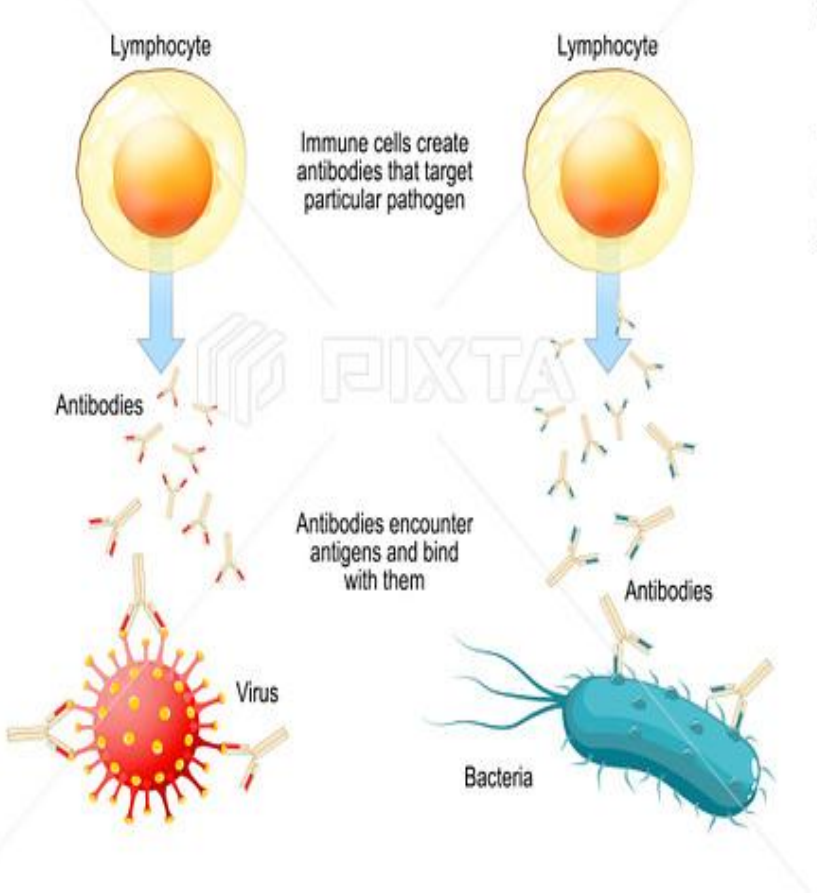

Physical &
Physiological Barriers
Innate immunity
Adaptive immunity
Pathogens
Skin
Mucous membranes
Cilia
Body Temperature
pH
Neutrophils
Basophils
Eosinophils
Macrophages
Mast cells
Dendritic cells
Natural Killer Cells
T helper cells
Cytotoxic T cells
Naïve B cells
Plasma cells

Types of adaptive immunity

Humoral immunity:

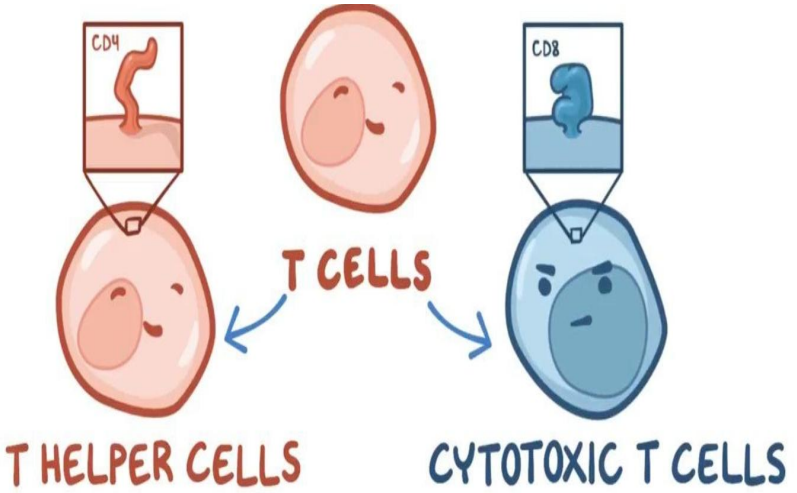
Mediated by soluble antibody proteins that are produced by B lymphocytes (B cells).

Antibodies provide protection against extracellular microbes in the blood, mucosal secretions, and tissues



Types of adaptive immunity:

Cell-mediated (or cellular) immunity: Mediated by T lymphocyte which are important in defense against intracellular microbes.

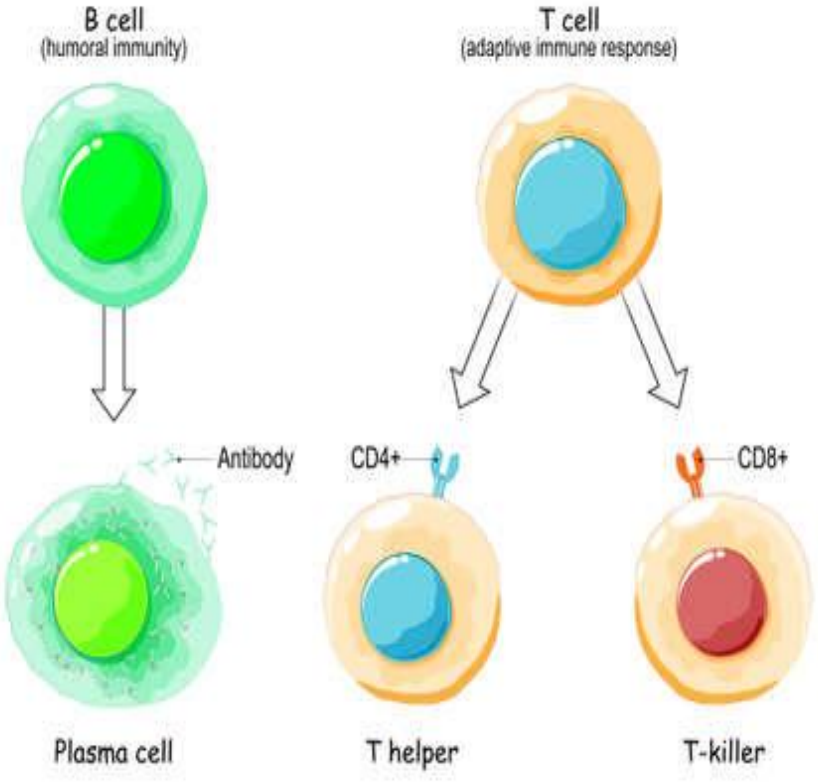


They work by either directly killing infected cells (by cytotoxic T lymphocytes) or by activating phagocytes to kill ingested microbes, via the production of soluble protein mediators called cytokines (made by helper T cells)

Cell & Tissues of Immune System

Lymphocytes:

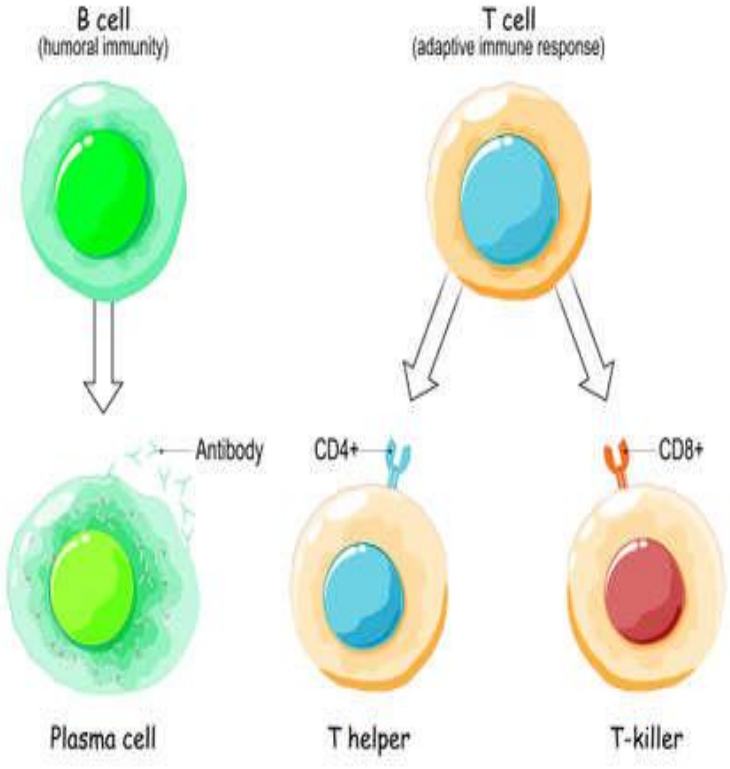
T lymphocytes: mature in thymus, express antigen receptors called T cell receptors (TCRs) that recognize protein antigens that are displayed by MHC molecules on the surface of antigen-presenting cells.



Lymphocytes:

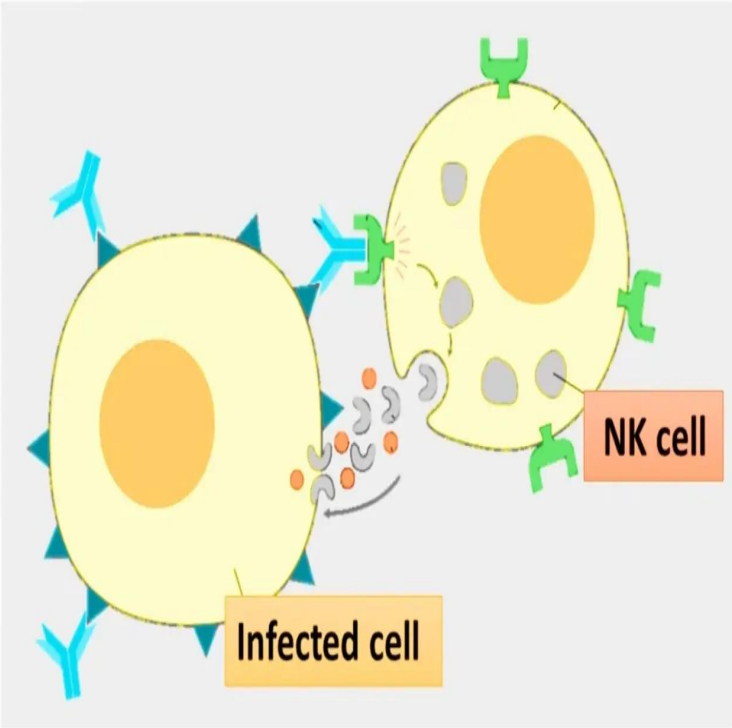
B lymphocytes: mature in bone marrow, express membrane-bound antibodies that recognize a wide variety of antigens.

B cells are activated to become plasma cells, which secrete antibodies or immunoglobulines.



Lymphocytes:

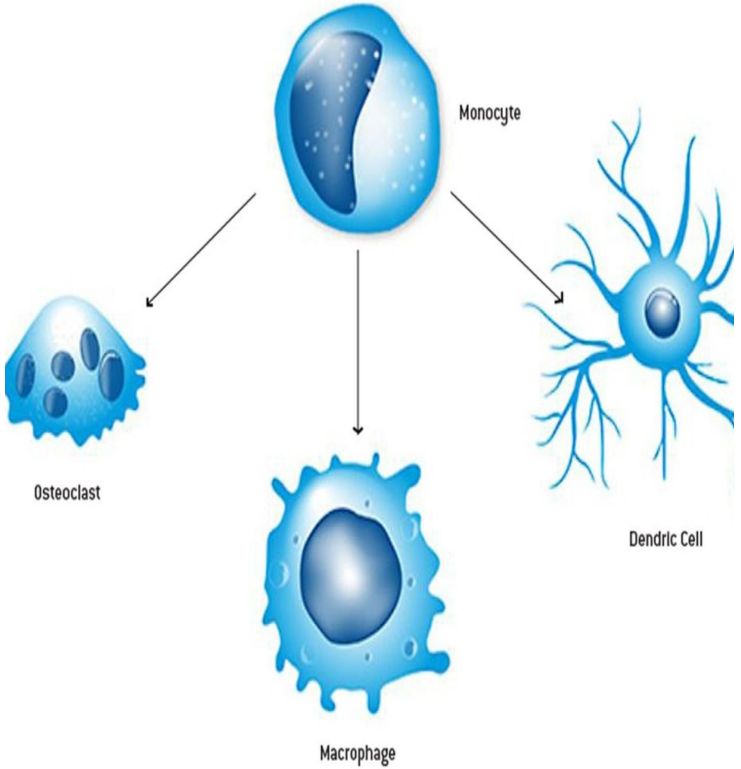
Natural killer: kill cells that are infected by some microbes, or are stressed and damaged beyond repair. NK cells express inhibitory receptors that recognize MHC molecules that are normally expressed on healthy cells, and are thus prevented from killing normal cells.



Antigen-presenting cells (APCs)

APCs capture microbes and other antigens, transport them to lymphoid organs, and display them for recognition by lymphocytes. The most efficient APCs are:

- Dendritic cells: live in epithelia and most tissues
- Macrophages: ingest microbes and other antigens



Under normal conditions, the immune response prevents disease, the inappropriate activation of the immune system can lead to debilitating or life-threatening illnesses, like:

1- Allergic or hypersensitivity reactions.

2- Transplantation immunopathology.

3- Autoimmune disorders.

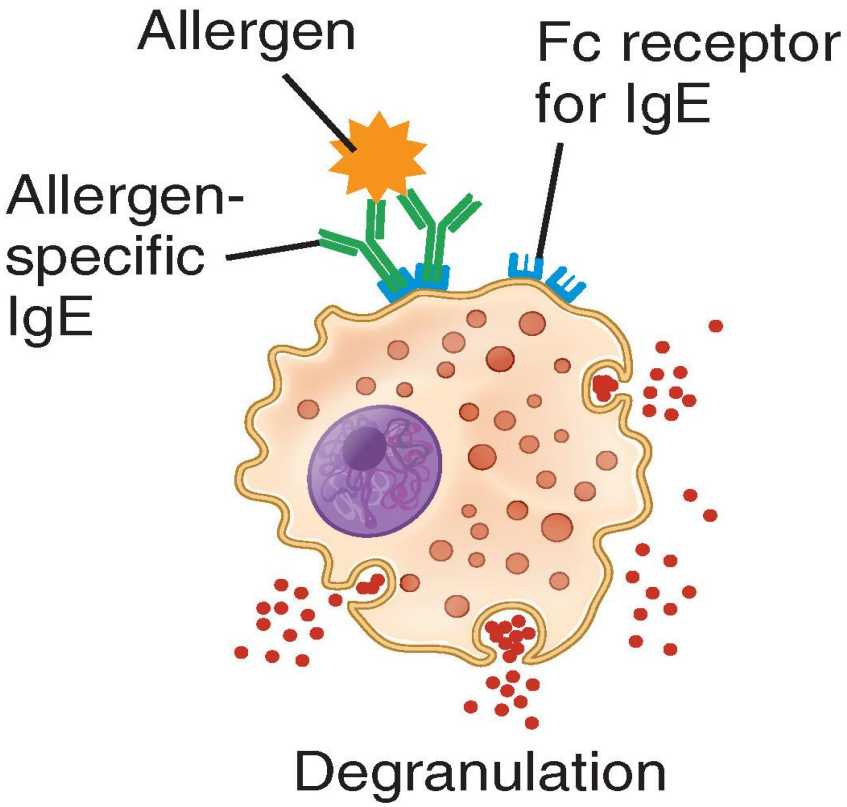
4- Immunodeficiency states.

Allergic
or
Hypersensitivity diseases

Hypersensitivity:

it is an exaggerated immune response to a foreign agent resulting in injury to the host.

It is caused by immune responses to environmental antigens called **allergens** that produce inflammation and cause tissue injury



Allergens:

- Any foreign substances capable of inducing an immune response.
- Many different chemicals of natural and synthetic origin are known as allergens. Complex natural organic chemicals, especially proteins, are more likely to cause an immediate hypersensitivity response, whereas simple organic compounds, inorganic chemicals, and metals more commonly cause delayed hypersensitivity reactions.
- Exposure to the allergen can be through inhalation, ingestion, injection, or skin contact

Hypersensitivity disorders are of four types:

Type I: IgE-mediated disorders.

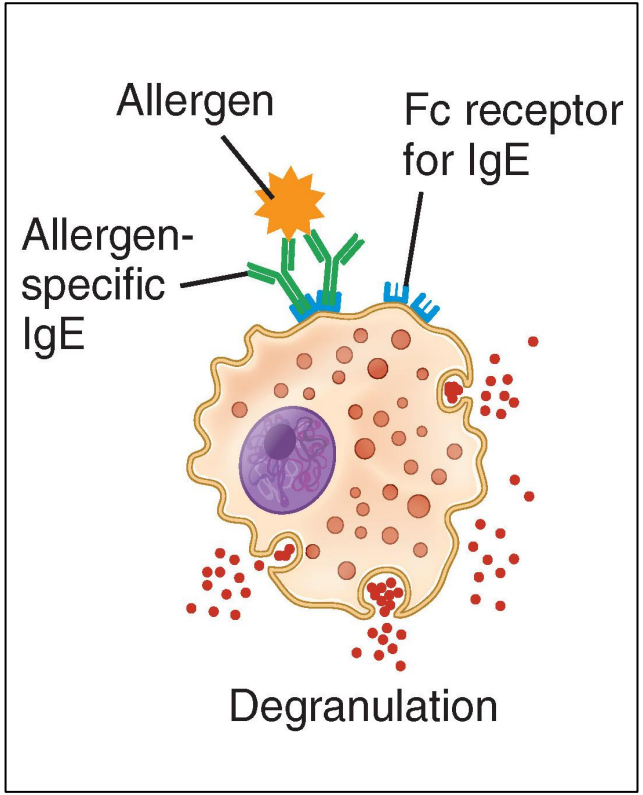
Type II: Antibody-mediated (cytotoxic) disorders.

Type III, Immune-Complex Disorders

Type IV: Cell-mediated hypersensitivity reactions

Type I hypersensitivity reactions
IgE-Mediated Disorders (Immediate type):

- Immediate-type of hypersensitivity reactions
- Triggered by binding of an allergen to IgE found on the surface of mast cells or basophils
- Mast cells and basophil have granules contain potent mediators that degranulated in response to allergen-specific IgE antibodies attach to receptors on the surface of these cells



Mediators of type I hypersensitivity reactions

- **Histamine:** a potent vasodilator that increases the permeability of capillaries and venules, causes bronchoconstriction and increased secretion of mucus.
- **Acetylcholine:** produces bronchial smooth muscle contraction and dilation of small blood vessels.
- **Proteases** generate kinins and cleave complement components to produce additional chemotactic and inflammatory mediators.

Mediators of type I hypersensitivity reactions

- **Leukotrienes and prostaglandins** produce responses similar to those of histamine and acetylcholine, although their effects are delayed and prolonged by comparison.
- **Platelet-activating factor** result in platelet aggregation ,histamine release,and bronchospasm. It also acts as a chemotactic factor for neutrophils and eosinophils.
- **Cytokines** recruit and activate a variety of inflammatory cells

Type I hypersensitivity reactions may present as:

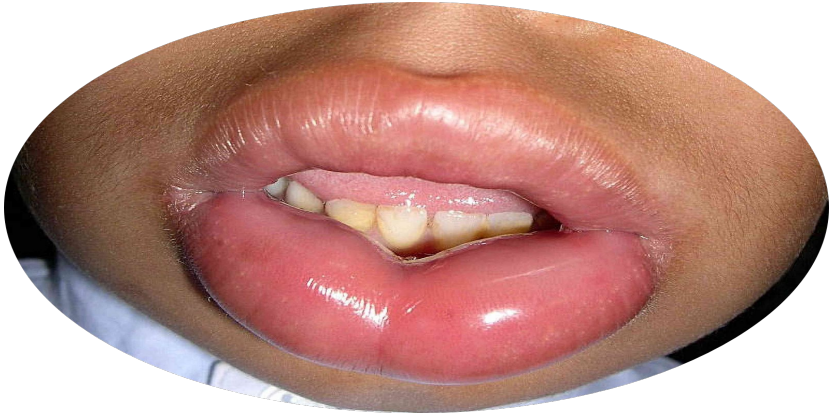
- Systemic disorder (anaphylaxis)
- Localized reaction (atopy).

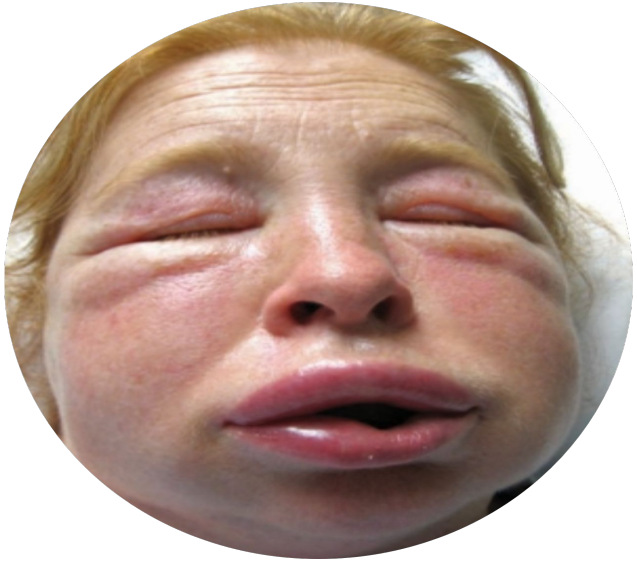
Systemic Anaphylactic Reactions:

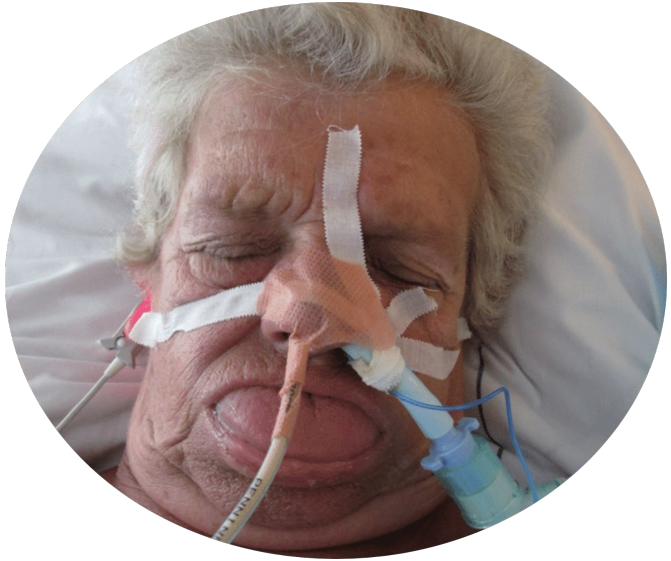
- Result from injected allergens (e.g., penicillin, radiographic contrast dyes, and bee or wasp stings).
- Result from ingested allergens (seafood, nuts, and legumes).

Sign and symptoms: anaphylactic response rapid onset within minutes

- Itching.
- Urticaria.
- Gastrointestinal cramps.
- Difficulty in breathing caused by bronchospasm.
- Angioedema (swelling of face and throat) may develop, causing upper airway obstruction.
- Massive vasodilation may lead to peripheral pooling of blood, sudden hypotension and life-threatening circulatory shock

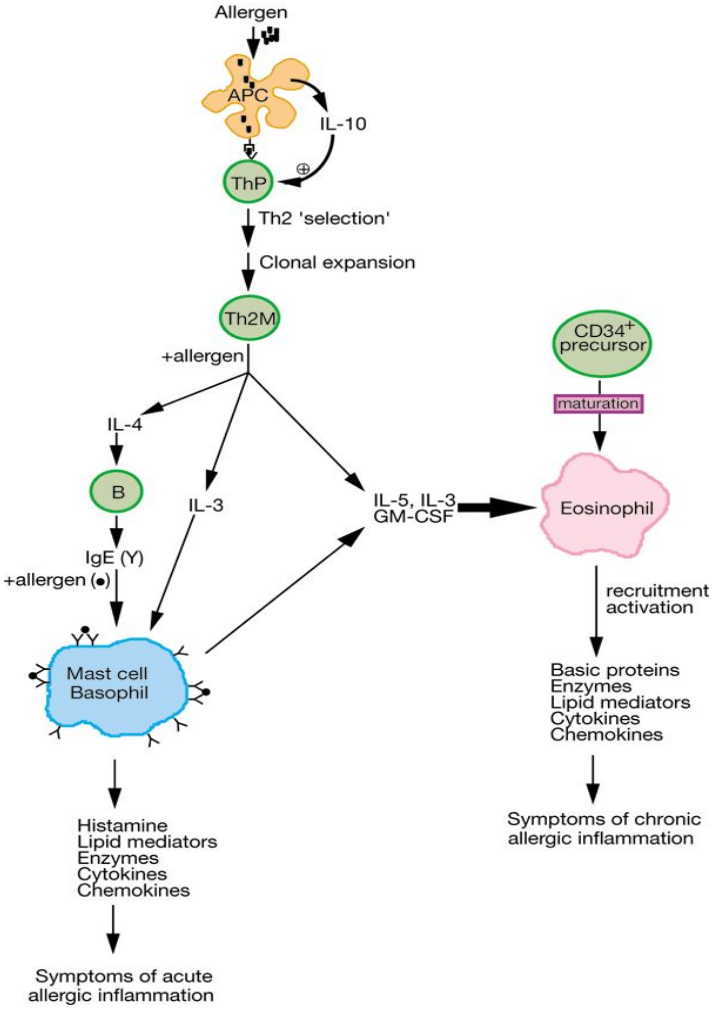






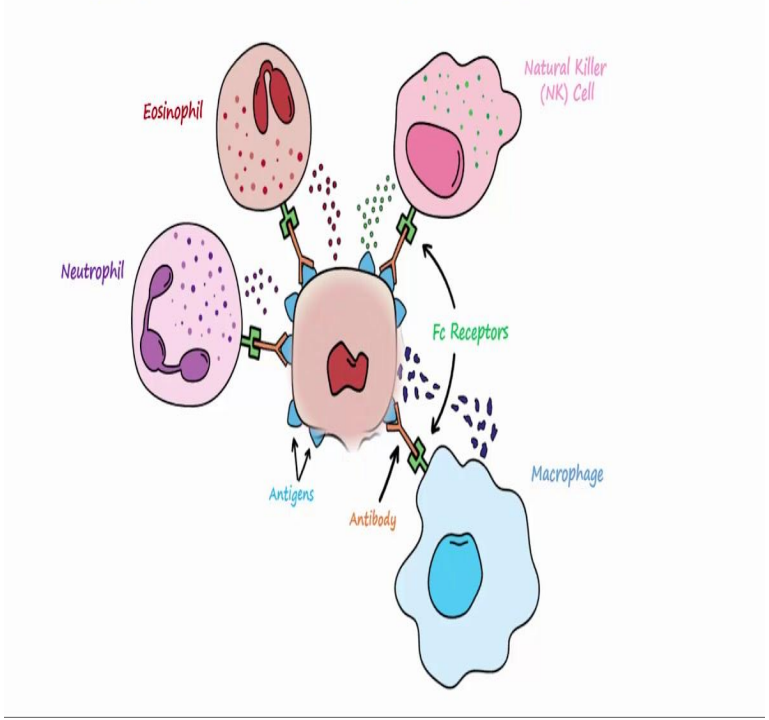
Localized Atopic Disorders:

- Atopy is the genetic predisposition to develop an allergic reaction that produces an exaggerated IgE response when a person is exposed to otherwise harmless environmental substances
- The antigen is confined to a specific site related to the route of exposure.
- Atopic disorders include food allergies, allergic rhinitis (hay fever), allergic dermatitis, and certain forms of bronchial asthma.



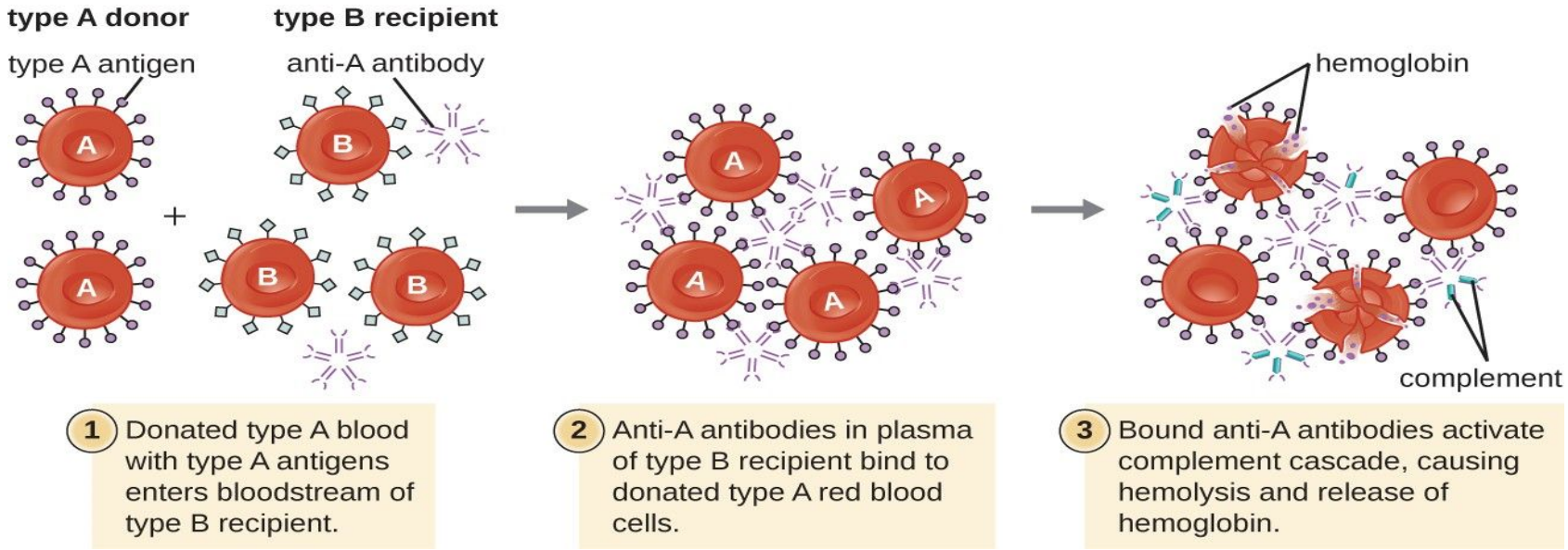
Type II hypersensitivity reactions
Antibody-Mediated Cytotoxic Disorders:

They are the end result of direct interaction between IgG and IgM class antibodies and tissue or cell surface antigens, with subsequent activation of complement- or antibody-dependent cell-mediated cytotoxicity

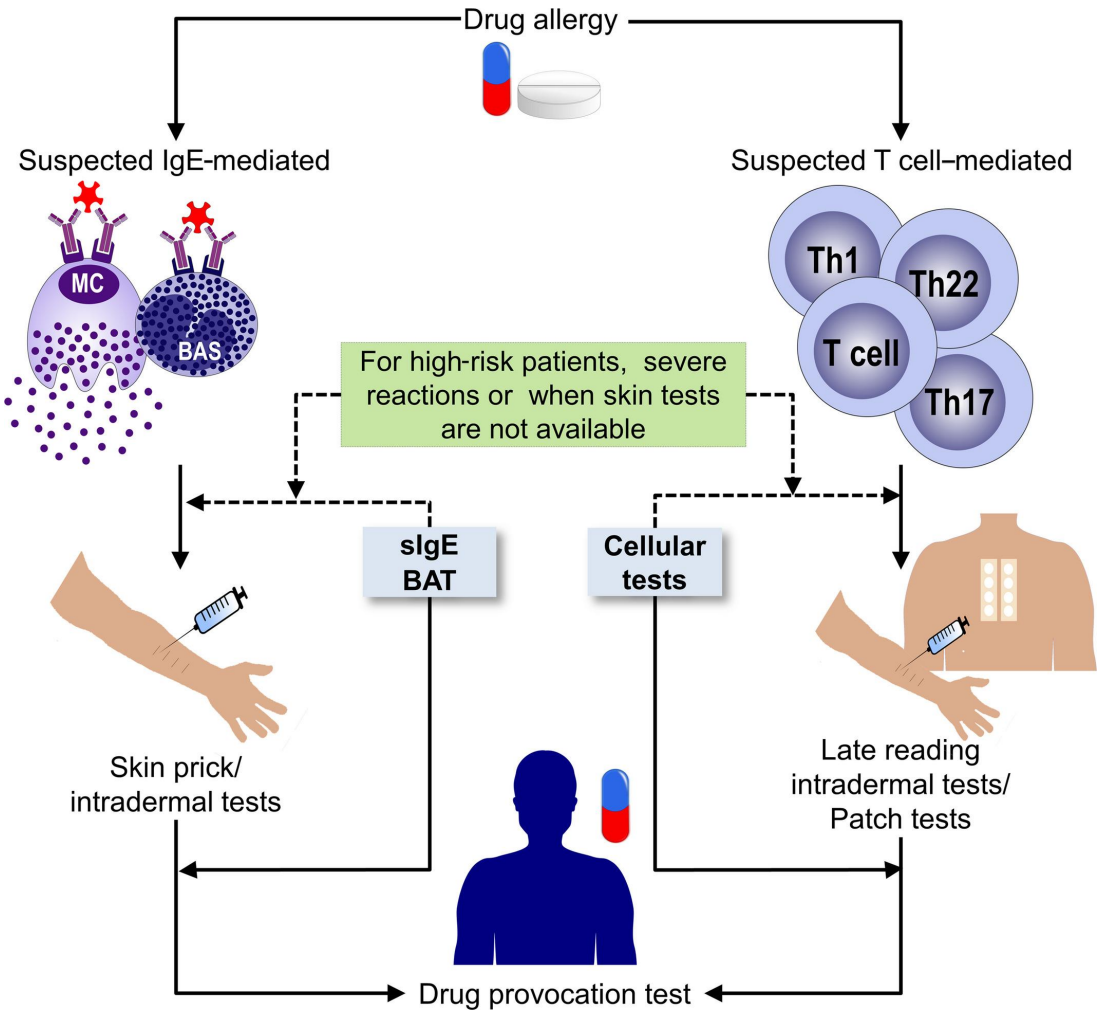


Examples of type II reactions:

Mismatched blood transfusions,hemolytic disease of the newborn caused by ABO or Rh incompatibility.

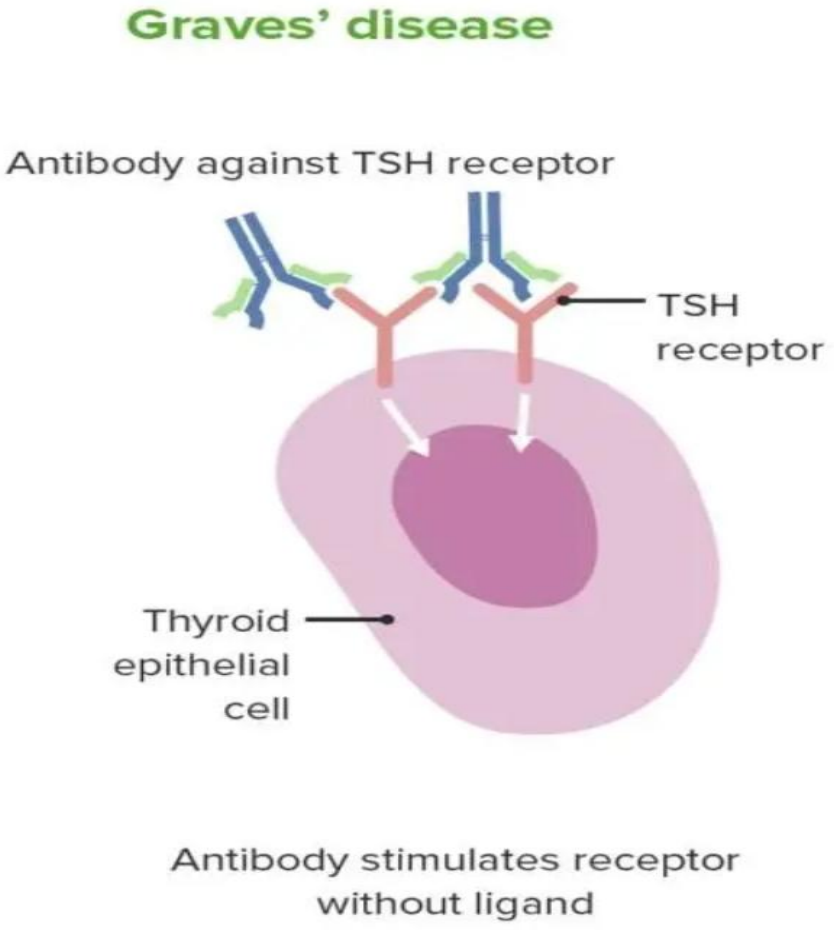


Certain drug reactions, bind to the surface of red or white blood cells elicits an antibody and complement response that lyses the drug-coated cell and produce transient anemia, leukopenia, or thrombocytopenia, which are corrected by the removal of the offending drug.



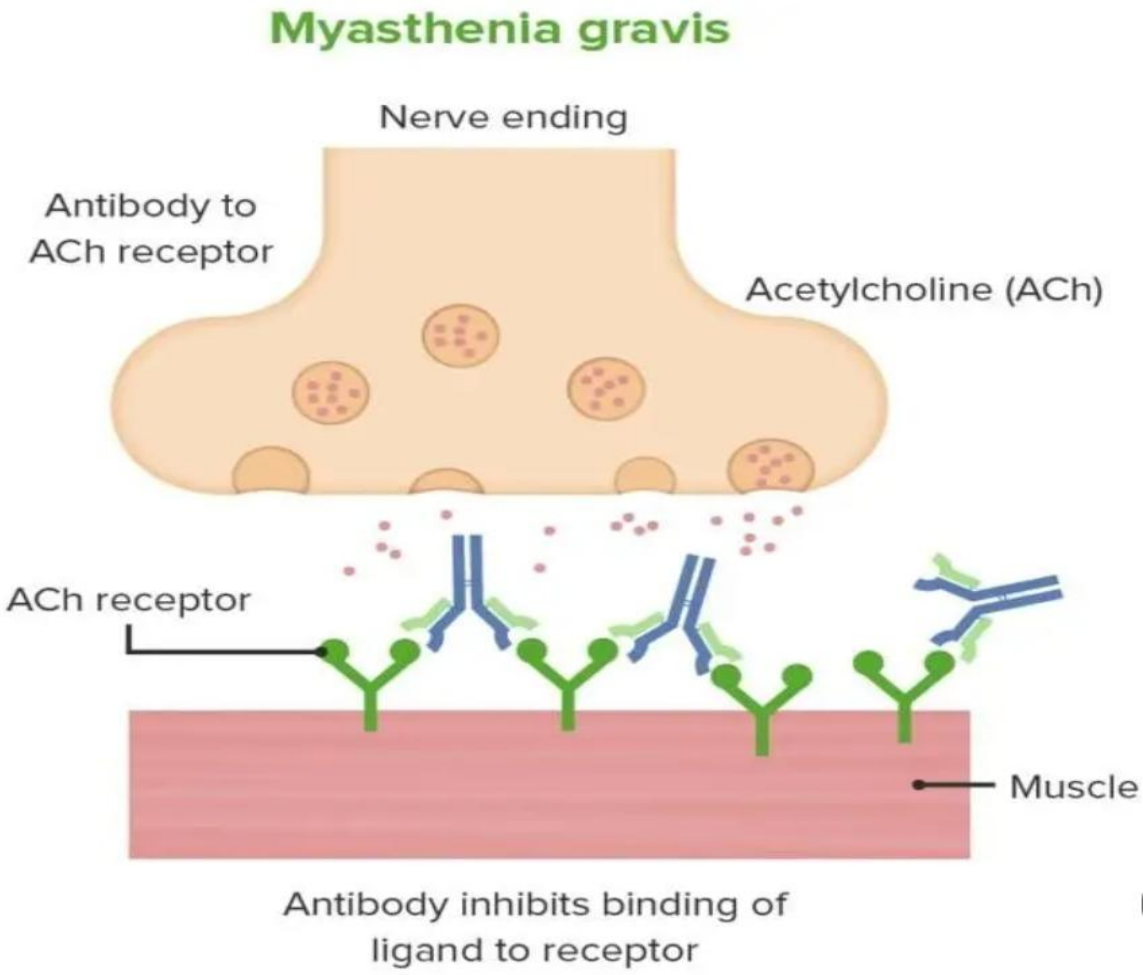
Graves disease

Antibodies against thyroid stimulating hormone receptors lead to exaggerated action of thyroid



Myasthenia gravis

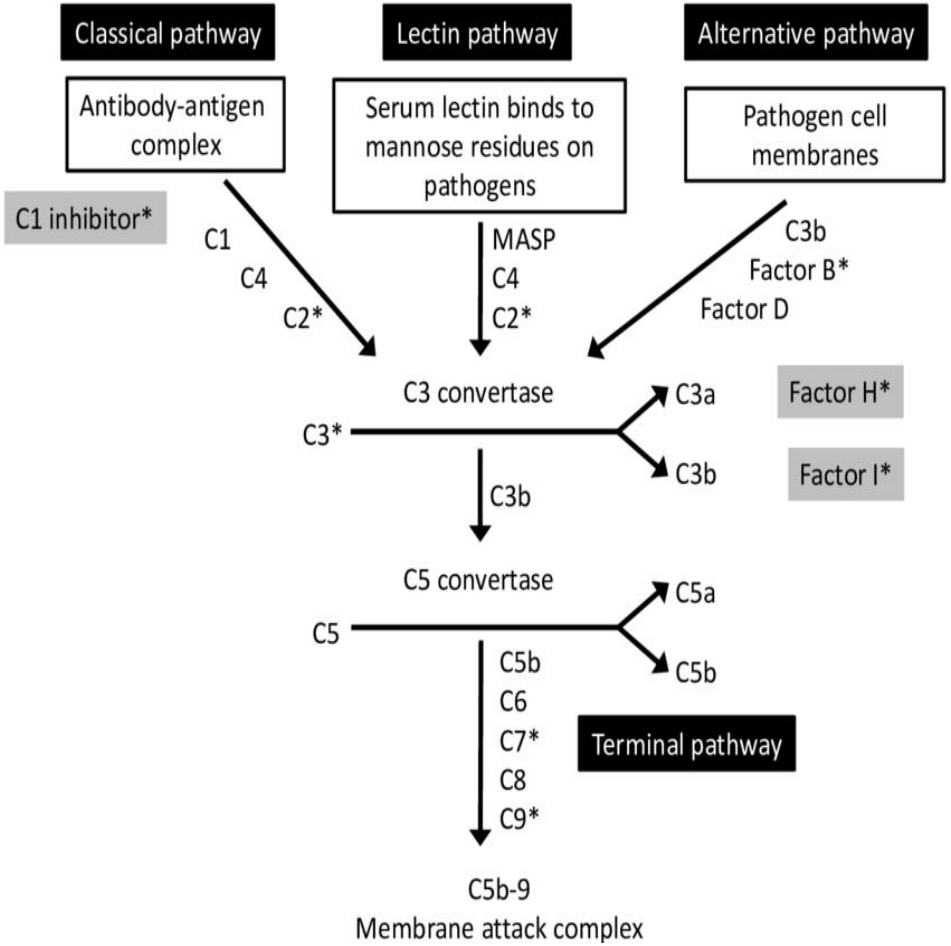
Antibodies destroy neuromuscular connections lead to weakness of muscles and difficultyin breathing and swallowing.



Type III hypersensitivity reactions

Immune-Complex Disorders:

They are mediated by the formation of insoluble antigen-antibody complexes that activate complement and generate inflammatory reaction

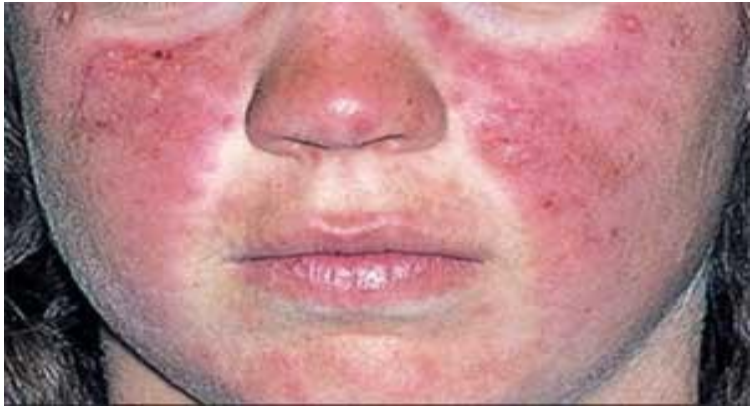


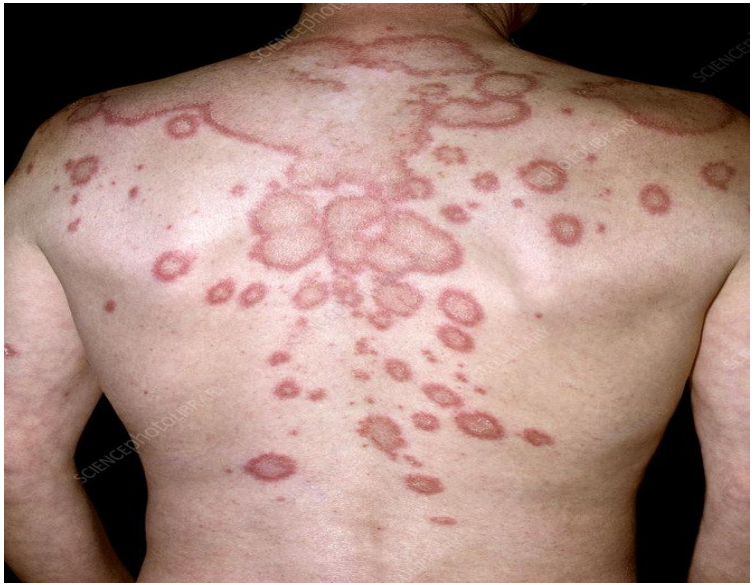
There are two general types of antigens that cause immune complex mediated injury:

- Exogenous antigens such as viral and bacterial proteins.
- Endogenous antigens such a self-antigens associated with autoimmune disorders.

Immune complexes formed in the circulation produce damage when they come in contact with the vessel lining or are deposited in tissues,including the renal glomerulus, skin venules, lung, and joint synovium.

- Acute glomerulonephritis that follows a streptococcal infection
- Systemic lupus erythematosus(SLE).

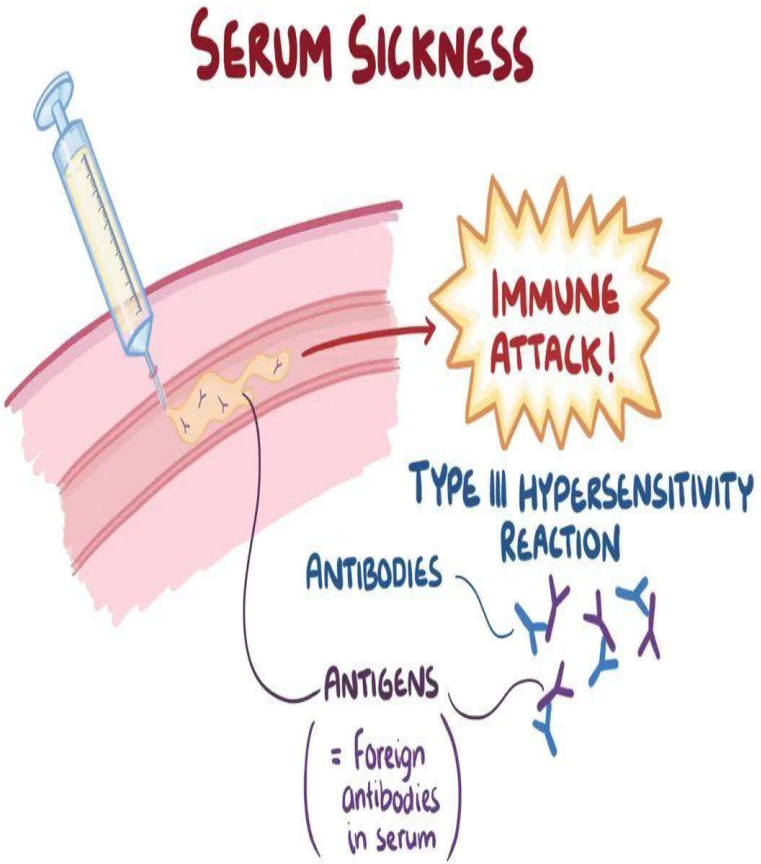




Acute serum sickness

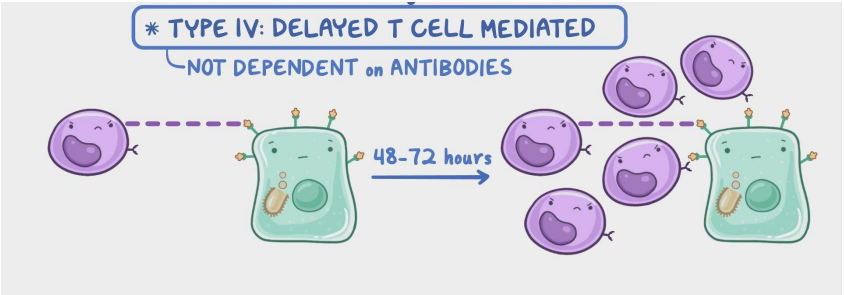
Ab-Ag complex mediated reaction of immune system following exposure to foreign proteins such as in animal serum.

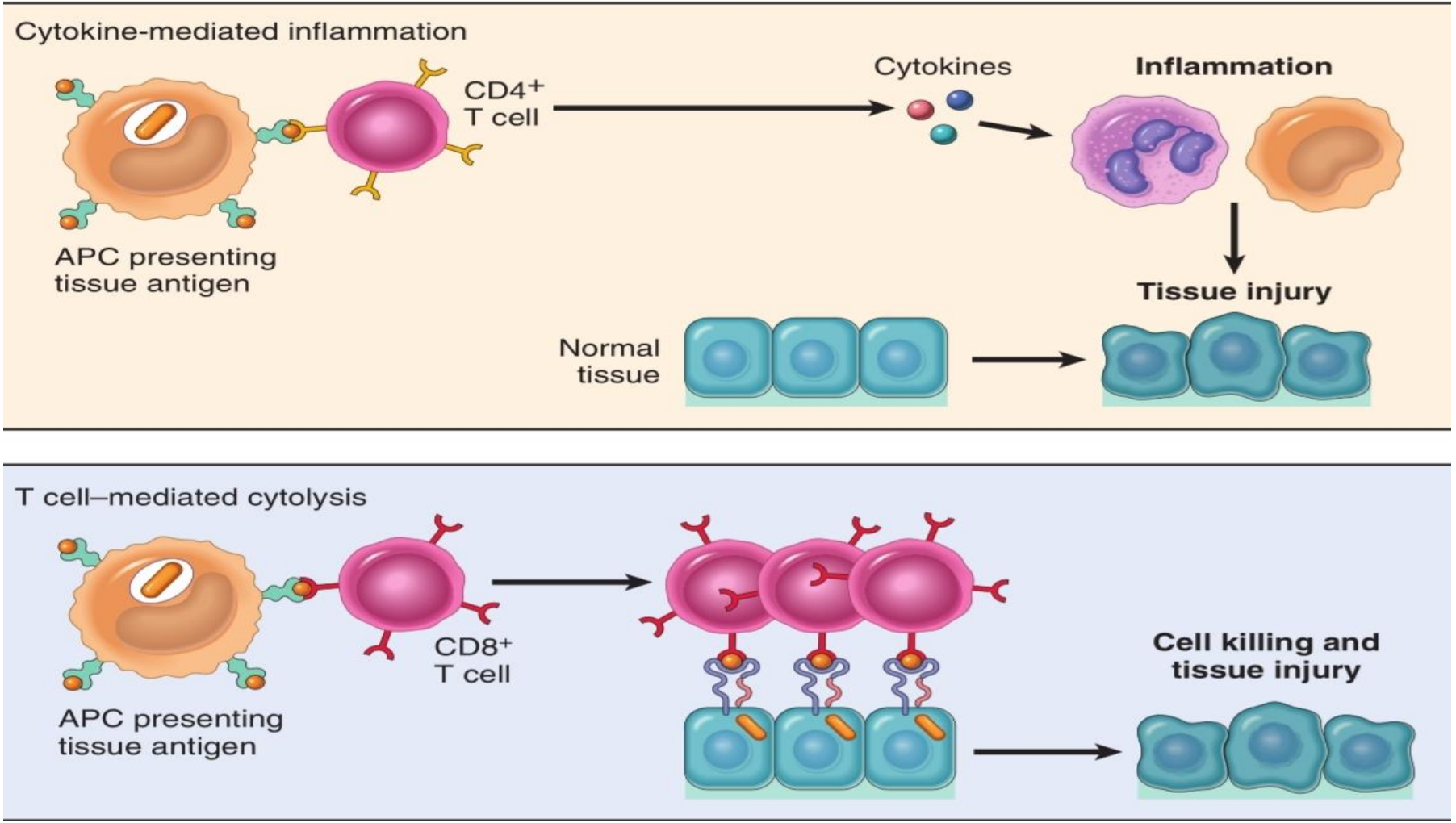
The classical symptoms are: feve, arthralgias, skin purpura or urticaria, lymphadenopathy, nephritis, edema, neuritis



Type IV hypersensitivityreactions
Cell-Mediated Hypersensitivity Disorders:

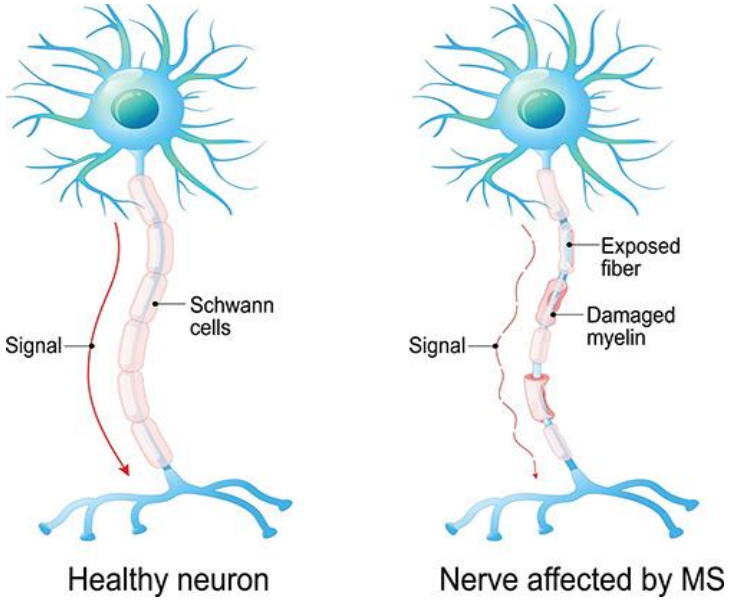
- It is mediated by cells, not antibodies
- It occurs 24 to 72 hours after exposure to antigen.
- Mediated by helper T lymphocytes that are directly cytotoxic or secrete cytokines that attracted other inflammatory cells and activation of macrophages that function as phagocytic and antigen-presenting cells(APCs)

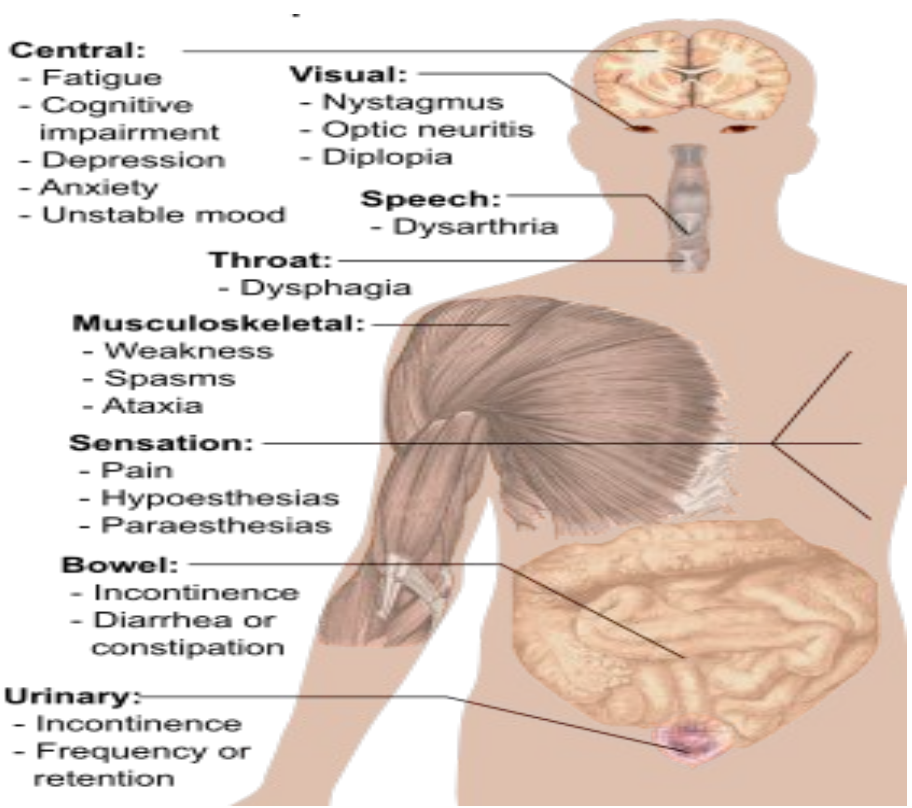



Cytokine-mediated inflammation
CD4+
T cell
Cytokines
Inflammation
APC presenting
tissue antigen
Tissue injury
Normal
tissue
T cell–mediated cytolysis
CD8+
T cell
APC presenting
tissue antigen
Cell killing and
tissue injury

Example of type IV : Multiple sclerosis

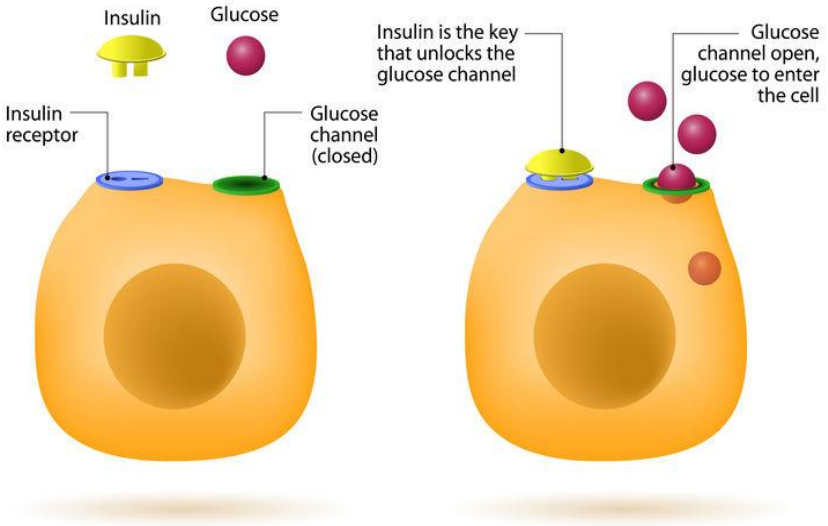
Immune- mediated cytotoxic reaction against myelinated sheath of neurons.

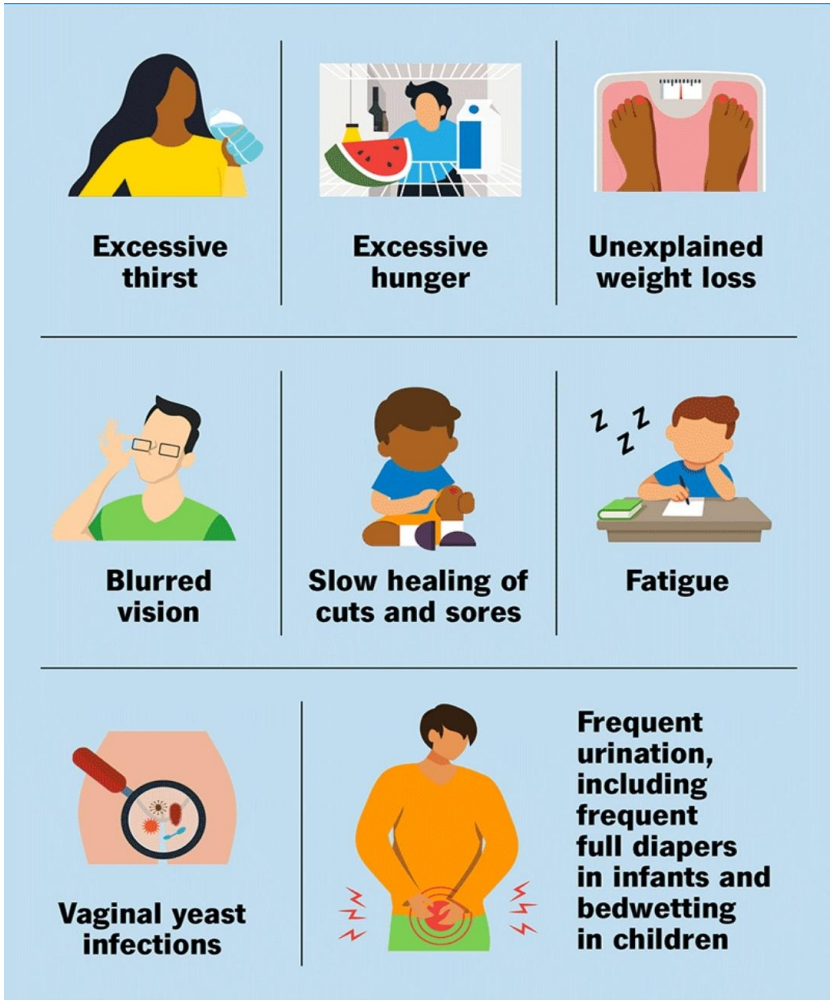




Type 1 diabetes mellitus

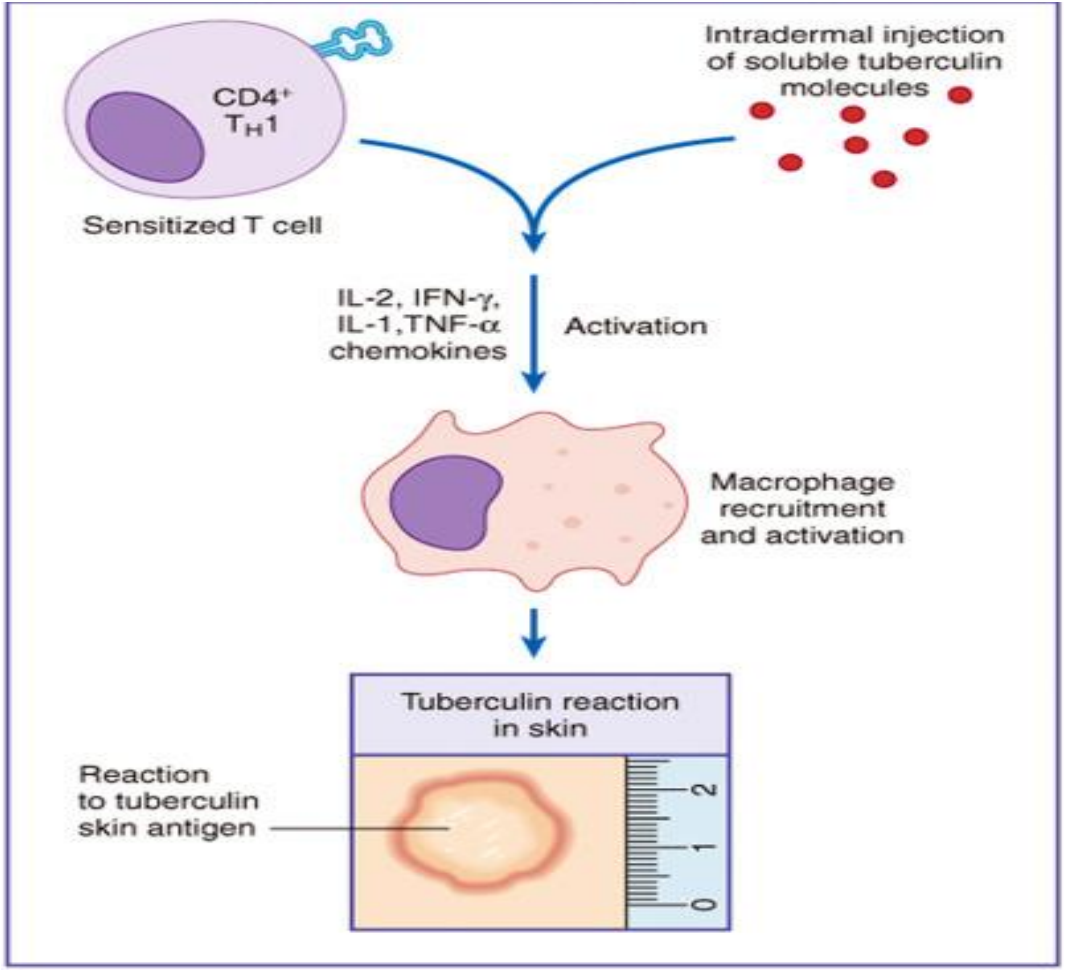
Immune mediated cell cytotoxic reaction against beta pancreatic cells that produce insulin.





Tuberculin test

tuberculin reaction is produced by the intracutaneous injection of purified protein derivative (called tuberculin), a protein-containing antigen of the tubercle bacillus.

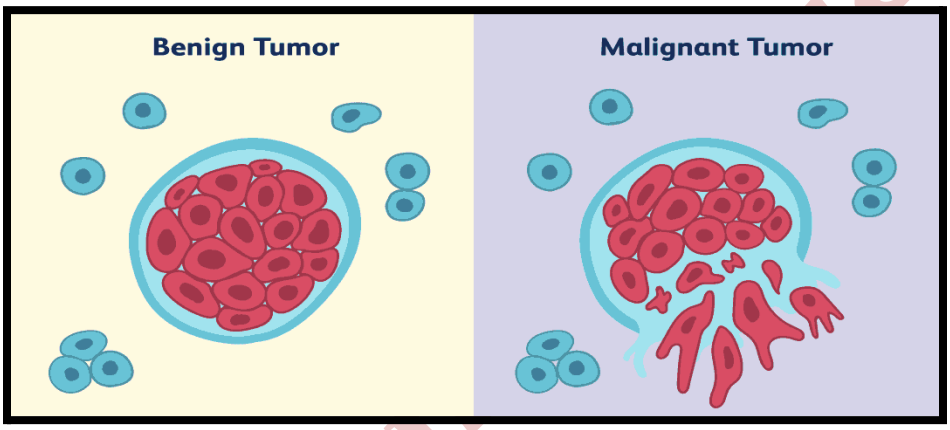


Thank you 

Neoplasia

Neoplasia means new growth; the new growth produced is called 'neoplasm' or 'tumor'. A neoplasm or tumor is define 'a mass of tissue formed as a result of abnormal, excessive, uncoordinated and purposeless proliferation of cells even after cessation of stimulus for growth which caused it'. The branch of science dealing with the study of neoplasms or tumors is called oncology (oncos=tumor, logos=study).

Neoplasms may be 'benign' when they are slow-growing and localized without causing much difficulty to the host or 'malignant' when they proliferate rapidly, spread throughout the body and may eventually cause death of the host. The common term used for all malignant tumors is cancer.



Hippocrates (460-370 bc) coined the term karkinos for cancer of the breast. The word 'cancer' means crab, thus reflecting the true character of cancer since 'it sticks to the part like a crab'.

All tumors, benign as well as malignant, have 2 basic components:

- **Parenchyma:** comprised by proliferating tumor cells; parenchyma determines the nature and evolution of the tumor.
- **Supportive stroma:** composed of fibrous connective tissue and blood vessels; it provides the framework on which the parenchymal tumor cells grow.

The tumors derive their nomenclature on the basis of the parenchymal component comprising them. The suffix '-oma' is added to denote benign tumors. Malignant tumors of epithelial origin are called carcinomas, while malignant mesenchymal tumors are named sarcomas. However, some cancers are composed of highly undifferentiated cells and are referred to as undifferentiated malignant tumors.

Although, this broad generalization regarding nomenclature of tumors usually holds true in majority of instances, some examples contrary to this concept are: melanoma for carcinoma of the melanocytes, hepatoma for carcinoma of the hepatocytes, lymphoma for malignant tumor of the lymphoid tissue, and seminoma for malignant tumor of the testis. Leukaemia is the term used for cancer of blood forming cells.

Mixed tumors: When two types of tumors are combined in the same tumor, ex; Adenosquamous carcinoma is the combination of adenocarcinoma and squamous cell carcinoma. Adenoacanthoma is the mixture of adenocarcinoma and benign squamous elements. Carcinosarcoma is the rare combination of malignant tumor of the epithelium (carcinoma) and of mesenchymal tissue (sarcoma) such as in thyroid. Mixed tumor of the salivary gland (pleomorphic adenoma) is the term used for benign tumor having combination of both epithelial and mesenchymal tissue elements.

Teratomas: These tumors composed of a mixture of various tissue types arising from totipotent cells derived from the three germ cell layers (ectoderm, mesoderm and endoderm). Most common sites for teratomas are ovaries and testis. But they occur at extra-gonadal sites as well, mainly in the midline of the body such as in the head and neck region, mediastinum, retroperitoneum, etc. Teratomas may be benign or mature (most of the ovarian teratomas) or malignant or immature (most of the testicular teratomas).

Blastomas (Embryomas): are malignant tumors arise from embryonal or partially differentiated cells during embryogenesis that occur more frequently in infants and children (under 5 years of age). Ex; neuroblastoma, nephroblastoma (Wilms' tumor), hepatoblastoma, retinoblastoma, medulloblastoma, pulmonary blastoma.

Hamartoma: is benign tumor made of mature but disorganised cells of tissues indigenous to the particular organ e.g. hamartoma of the lung consists of mature cartilage, mature smooth muscle and epithelium.

Choristoma: is an ectopic island of normal tissue (heterotopia) but is not a true tumor.

CHARACTERISTICS OF TUMORS

Majority of neoplasms can be categorized into benign and malignant on the basis of certain clinical features, biologic behavior and morphological characteristics. The characteristics of tumors are described under the following headings:

I. Rate of growth
II. Cancer phenotype and stem cells
III. Clinical and gross features
IV. Microscopic features
V. Spread of tumors: a. Local invasion or direct spread , b. Metastasis or distant spread

I. RATE OF GROWTH

The tumor cells generally proliferate more rapidly than the normal cells. In general, benign tumors grow slowly and malignant tumors rapidly. However, there are exceptions to this generalization. The rate at which the tumor enlarges depends upon 2 main factors:

1. Rate of cell production, growth fraction and rate of cell loss: In general, malignant tumor cells have increased mitotic rate (doubling time) and slower death rate i.e. the cancer cells do not follow normal controls in cell cycle and are immortal.

2. Degree of differentiation of the tumor: The rate of growth of malignant tumor is directly proportionate to the degree of differentiation. Poorly differentiated tumors show aggressive growth pattern as compared to well differentiated tumors.

The regulation of tumor growth is under the control of growth factors secreted by the tumor cells. Out of various growth factors, important ones modulating tumor biology are:

i)Epidermal growth factor (EGF)
ii) Fibroblast growth factor (FGF)
iii)Platelet-derived growth factor (PDGF)
iv) Colony stimulating factor (CSF)
v) Transforming growth factors-b (TGF-b)
vi) Interleukins 1 and 6 (IL-1, IL-6)
vii) Vascular endothelial growth factor (VEGF)
viii) Hepatocyte growth factor (HGF)

II. CANCER PHENOTYPE AND STEM CELLS

Cancer cells originate by clonal proliferation of a single progeny of a cell (monoclonality). These stem cells have the properties of prolonged self-renewal, asymmetric replication and trans-differentiation (i.e. plasticity). These cancer stem cells are called tumor-initiating cells. Ex: acute leukemia.

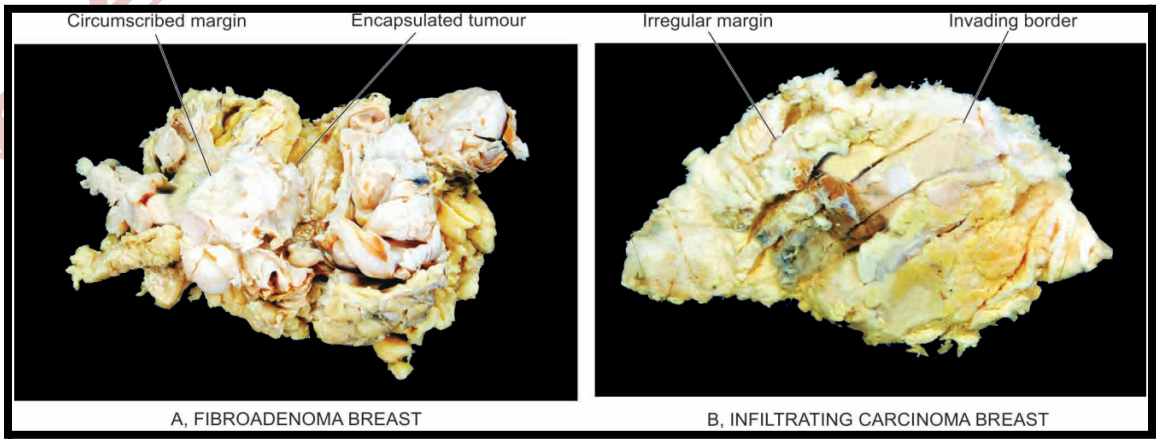
Due to loss of growth controls, cancer cells are genetically unstable and develop newer mutations (polyclonality).

III. CLINICAL AND GROSS FEATURES

Gross appearance of benign and malignant tumors may be quite variable and they have a different color, texture and consistency compared to neighboring normal tissue.

Benign tumors are generally slow growing, asymptomatic depending upon the location or may produce serious symptoms (e.g. meningioma in the nervous system), uniform in shape, encapsulated or well-circumscribed, freely movable, and more often firm unless secondary changes like hemorrhage or infarction.

Malignant tumors grow rapidly, may ulcerate on the surface, invade locally into deeper tissues, may spread to distant sites (metastasis), and also produce systemic features such as weight loss, anorexia and anemia, they are usually irregular in shape, poorly-circumscribed and extend into the adjacent tissues. Secondary changes like hemorrhage, infarction and ulceration are seen more often. Sarcomas typically have fish-flesh like consistency while carcinomas are generally firm.



IV. MICROSCOPIC FEATURES

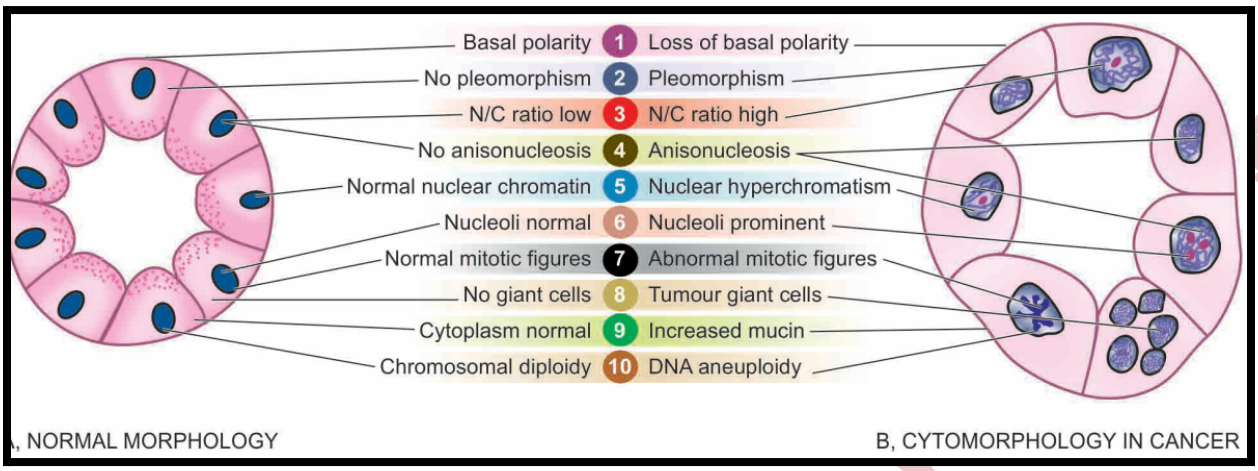
The microscopic characteristics of tumor cells are very importance to diagnosis. Generally, most benign tumors and low grade malignant tumors similar to the normal tissue of origin more closely so that there is little difficulty in identifying them. However, anaplastic tumors differ greatly from the arrangement in normal tissue of origin of the tumor that required close looking to identify the tumor.

Differentiation is defined as the extent of morphological and functional resemblance of parenchymal tumor cells to corresponding normal cells.

Anaplasia is lack of differentiation and is a characteristic feature of most malignant tumors.
Depending upon the degree of differentiation and the extent of anaplasia we classify the tumors:
Well-differentiated tumor: If the deviation of neoplastic cell in structure and function is minimal as compared to normal cell, such as most benign and low-grade malignant tumors.
Poorly differentiated tumor 'undifferentiated' or 'dedifferentiated': are synonymous terms for poor structural and functional resemblance to corresponding normal cell i.e. poorly differentiated malignant tumors have high degree of anaplasia.
Moderately differentiated tumor: is an intermediate stage between well and poor degree of differentiation.

By using higher magnification power of the light microscope, morphological and functional alterations in the neoplastic cells are observed by looking for specific features:
i) Loss of polarity: Normally, the nuclei of epithelial cells are oriented along the basement membrane which is termed as basal polarity. This property is based on cell adhesion molecules (selectins). In malignancy, tumor cells lose their basal polarity so that the nuclei tend to lie away from the basement membrane.
ii) Pleomorphism: it means variation in size and shape of the tumor cells. The extent of cellular pleomorphism generally correlates with the degree of anaplasia.
iii) N:C ratio: the nuclei of malignant tumor cells are enlarged disproportionate to the cell size so that the nucleocytoplasmic ratio is increased from normal 1:5 to 1:1.
iv) Anisonucleosis: the nuclei show variation in size and shape in malignant tumor cells.
v) Hyperchromatism: dark-staining nuclei due to increase in the amount of nucleoprotein and clumping of chromatins.
vi) Nucleolar changes: increased nucleoprotein synthesis result in prominent nucleoli.
vii) Mitotic figures: The parenchymal cells of poorly-differentiated tumors often show large number of mitoses as compared with benign tumors and well-differentiated malignant tumors. As stated above, these appear as either normal or abnormal mitotic figures. Abnormal or atypical mitotic figures are more important in malignant tumors and are identified as tripolar, quadripolar and multipolar spindles.
viii) Tumor giant cells: Multinucleate tumor giant cells are important feature of anaplasia in malignancy.
ix) Functional (Cytoplasmic) changes: functional abnormality may be quantitative, qualitative, or both. Generally, benign tumors and well-differentiated malignant tumors continue to function well qualitatively, but with quantitative abnormality in the product e.g. large or small amount of collagen

produced by benign tumors of fibrous tissue, keratin formation in well-differentiated squamous cell carcinoma. In more anaplastic tumors, there is usually quantitative fall in the product made by the tumor cells e.g. absence of keratin in anaplastic squamous cell carcinoma.



There may be both qualitative and quantitative abnormality of the cellular function in some anaplastic tumors e.g. multiple myeloma producing abnormal immunoglobulin in large quantities, Endocrine tumors may cause excessive hormone production, certain tumors may produce hormones or hormone-like substances this property of tumors is called ectopic hormone production e.g. ectopic erythropoietin may be produced by carcinoma of kidneys and hepatocellular.

x) Chromosomal abnormalities: all tumor cells have genetic abnormality that is includes deviations in both morphology and number of chromosomes. Ex; the most important examples of a consistent chromosomal abnormality in human malignancy is the presence of Philadelphia chromosome (named after the city in which it was first described) in 95% cases of chronic myeloid leukaemia. In this, part of the long arm of chromosome 9 is translocated to part of the long arm of chromosome 22 (t 9; 22). Other examples of neoplasms showing chromosomal abnormalities are Burkitt's lymphoma, acute lymphoid leukaemia, multiple myeloma, retinoblastoma etc.

Prominent inflammatory reaction is present in and around the tumors which result from secondary infection mainly chronic inflammatory reaction (lymphocytes, plasma cells and macrophages). This inflammatory reaction is due to cell-mediated immunologic response by the host in an attempt to destroy the tumor. In some cases, such an immune response improves the prognosis.

V. SPREAD OF TUMOURS

LOCAL INVASION (DIRECT SPREAD)

Most benign tumors form encapsulated or circumscribed masses that expand and push aside the surrounding normal tissues without actually invading, infiltrating or metastasizing.
Malignant tumors are distinguished from benign tumors by invasion, infiltration and destruction of the surrounding tissue, besides spread to distant sites or metastasis. Tumors invasion via the route of least resistance, though tissue spaces, thin-walled capillaries and veins.

METASTASIS (DISTANT SPREAD)

Metastasis is defined as spread of tumor into distant site of the primary tumor. Benign tumors do not metastasize while all the malignant tumors can metastasize (with few exceptions). Generally, larger, more aggressive and rapidly-growing tumors are more likely to metastasize.

Cancers may spread to distant sites by following pathways (Routes of Metastasis):

1. Lymphatic spread: In general, carcinomas metastasize by lymphatic route while sarcomas favor haematogenous route. The involvement of lymph nodes by malignant cells may be by lymphatic permeation of lymphatics walls or by lymphatic tumor emboli so as to be carried along the lymph to the next draining lymph node, regional lymph nodes draining the tumor are involved producing regional nodal metastasis e.g. from carcinoma breast to axillary lymph nodes, from cancer of the thyroid to lateral cervical lymph nodes.

The sentinel lymph node is the first lymph node or group of nodes draining a cancer. In case of established cancerous dissemination it is postulated that the sentinel lymph node/s is/are the target organs primarily reached by metastasizing cancer cells from the tumor.

2. Haematogenous spread: Blood-borne metastasis is the common route for sarcomas but certain carcinomas also frequently metastasize by this mode, especially those of the lung, breast, thyroid, kidney, liver, prostate and ovary. In general, cancers from limbs, head and neck and pelvis are metastasize to the lungs by systemic veins drain blood into vena cava. Tumors from the bowel, spleen and pancreas metastasize into the liver through portal veins. Lung cancer metastasize by pulmonary veins provide into systemic circulation elsewhere in the body.

3. Spread along body cavities: seeding across body cavities is often seen through seeding of peritoneal cavity, pleural and pericardial cavities.

The process of local invasion and distant spread by lymphatic and haematogenous routes (together called lymphovascular spread) by dissolution of extracellular matrix (ECM) at three levels—at the basement membrane of tumor itself, at the level of interstitial connective tissue, and at the basement membrane of microvasculature.

Lec General Pathology Dr. Afrah Adnan

MOLECULAR BASIS OF CANCER

Monoclonality of tumors

Most human cancers arise from a single clone of cells by genetic mutation. For example: multiple myeloma (a malignant disorder of plasma cells), there is production of a single type of immunoglobulin as seen by serum electrophoresis.

Field theory of cancer

In an organ developing cancer, limited numbers of cells only grow into cancer after undergoing sequence of changes under the influence of etiologic agents. This is termed as 'field effect' and the concept called as field theory of cancer.

Carcinogenesis

Is a gradual multi-step process of cancer growth and progression involving many generations of cells. It is a multi-hit process on genetic level results in cell transformation having features of malignancy (excessive growth, invasiveness and metastasis).

Genetic theory of cancer

Normal cell growth is under genetic control. In cancer, there are either genetic abnormalities in the cell, or there are normal genes with abnormal expression. Thus the abnormalities in genetic composition may be from inherited or induced mutations (induced by etiologic carcinogenic agents namely: chemicals, viruses, radiation). Eventually, the mutated cells transmit their characters to the next progeny of cells and result in cancer.

Genetic regulators

In normal cell growth, there are regulatory genes control mitosis as well as cell aging, and cell death, there are 4 regulatory genes:

i) Proto-oncogenes: are growth-promoting genes.

ii) Anti-oncogenes: are growth-inhibiting or growth suppressor genes.

iii) Apoptosis regulatory genes control the programmed cell death.

iv) DNA repair genes: are normal genes which regulate the repair of DNA damage

In cancer, the transformed cells are produced by abnormal cell growth due to genetic damage to these normal controlling genes. Thus, corresponding abnormalities in these 4 cell regulatory genes are as under:

i) Activation of growth-promoting oncogenes causing transformation of cell (mutant form of normal proto-oncogene in cancer is termed oncogene). Gene products of oncogenes are called oncoproteins.

ii) Inactivation of cancer-suppressor genes permitting the cellular proliferation of transformed cells. Anti-oncogenes are active in recessive form i.e. they are active only if both alleles are damaged.

iii) Abnormal apoptosis regulatory genes

iv) Failure of DNA repair genes inability to repair DNA damage resulting in mutations.

Hallmarks of cancer

1. Excessive and autonomous growth: activation of oncogenes.
2. Resistance to growth inhibition: inactivation of suppressing genes.
3. Escaping cell death by apoptosis: inhibition of genes regulating apoptosis.
4. Avoiding cellular ageing: elongation of Telomeres and telomerase activation.
5. Continued perfusion of cancer: Cancer angiogenesis.
6. Invasion and distant metastasis: Cancer dissemination.
7. Damage DNA repair system.
8. Cancer progression and tumor heterogeneity: Clonal aggressiveness.
9. Cancer a sequential multistep molecular phenomenon: Multistep theory.
10. MicroRNAs in cancer: OncomiRs.

1. Excessive and Autonomous Growth:

Mutated form of normal protooncogenes in cancer is called oncogenes; this mutation may occur by three mechanisms:

i) Point mutations (mutation of a single base in the DNA) ex; RAS oncogene.

ii) Chromosomal translocations ex; Philadelphia chromosome seen in chronic myeloid leukemia (t 9:22) and Burkitt's lymphoma (t 8:14).

iii) Gene amplification overexpressed gene product (i.e. oncoproteins) ex; breast, ovarian cancer and neuroblastoma,.

Oncogenes that promote cell proliferation are 5 groups:

i) Growth factors: a cancer cell may synthesize a GF and acquire growth self-sufficiency, ex; Platelet-derived growth factor-b-(PDGF-b), Transforming growth factor-a (TGF-a) and Fibroblast growth factor (FGF)

ii) Growth factor receptors: mutation of these receptors stimulate cell proliferation even without binding to growth factors, ex; EGF receptors and c-KIT receptor

iii) Cytoplasmic signal transduction proteins: mutation in intracellular growth signaling pathways, ex; Mutated RAS gene seen in colon, lung and pancreas carcinoma

iv) Nuclear transduction factors: MYC oncogene causes autonomous cell proliferation as C-MYC oncogene t(8;14) seen in Burkitt's lymphoma

v) Cell regulatory proteins: mutation in cyclins and cyclin-dependent kinases (CDKs) A, B, E and D such as mutated cyclin D protooncogene seen in mantle cell lymphoma, mutated cyclin E in breast cancer and mutated CDK4 seen in malignant melanoma, and sarcomas.

2. Resistance to growth inhibition: inactivation of suppressing genes

Normally tumor suppresser gene act by inducing the dividing cell to enter into G0 (resting) phase. Loss of tumor suppressor genes are due to chromosomal deletions, point mutations and loss of portions of chromosomes. Ex; RB gene mutation seen in retinoblastoma, p53 mutation (two major functions of p53 in the normal cell cycle are blocking mitotic activity by inhibits the cyclins and CDKs to repair the DNA damage and promoting apoptosis and because of these significant roles in cell cycle, p53 is called as 'protector of the genome')

3. Escaping Cell Death by Apoptosis:

Apoptosis in normal cell is guided by cell death receptor (CD95) in addition to other genes that affect apoptosis as pro-apoptotic factors (BAD, BAX, BID and p53) and apoptosis-inhibitors (BCL2, BCL-X). In cancer cells, apoptosis is interfered due to mutations in the above genes. For examples: Mutation in BCL2 gene (increase

expression) is inhibiting the apoptosis seen in B-cell lymphoma, absence of p53 gene reduces apoptotic activity and thus allows cell proliferation. CD95 receptors are depleted in hepatocellular carcinoma causes tumor cells escape apoptosis.

4. Avoiding Cellular Ageing:

Normally, after each mitosis there is progressive shortening of telomeres which are the terminal tips of chromosomes. Telomerase is the RNA enzyme that helps in repair of such damage to DNA and maintains normal telomere length. After repetitive mitosis for a maximum of 60 to 70 times, telomeres are lost in normal cells and the cells cease to undergo mitosis. Cancer cells in most malignancies have markedly up regulated telomerase enzyme, and hence telomere length is maintained. Thus, cancer cells avoid ageing, mitosis does not slow down or cease, thereby immortalizing the cancer cells.

5. Continued Perfusion of Cancer (Tumour Angiogenesis)

Cancers required adequate nourished and perfused to survive, grow and metastasize, the stimulus for angiogenesis is provided by the release of various factors:

i) Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) released from genes in the parenchymal tumor cells.

ii) Mutated form of p53 gene in both alleles results in removal of anti-angiogenic factors thrombospondin-1, angiostatin, endostatin and vasculostatin thus continued angiogenesis.

6. Invasion and Distant Metastasis: Cancer Dissemination

One of the most important characteristic of cancers is invasiveness and metastasis. To gain these properties, the tumor cells must loss the intercellular glue by either loss or inactivation of cell adhesion molecules (CAMs) for ex; E –cadherin. Then the cancer cells loss their attachment to the connective tissue by loss the transmembrane receptors (integrins), after that the cancer cells produce proteinase and metalloprotein-

ases (e.g. collagenases and gelatinase) enzymes to degrade the extracellular matrix and finally dissolve the basement membrane of the vessel wall get a way to migrate into lumen of capillaries or venules.

7. Damage DNA repair system

Normal cells during mitosis suffer from minor damage to the DNA, also mutational damage to the DNA of dividing cell occur by exogenous factors (e.g. radiation, chemical carcinogens etc) which is detected and repaired before mitosis is completed via p53 gene (the guarder of the genum), However, if this system of DNA repair is defective as by inherited mutations (mutator genes), the defect in unrepaired DNA results in cancer. For ex; Hereditary breast cancer, Xeroderma pigmentosum (is an inherited disorder in which there is defect in DNA repair mechanism. Upon exposure to sunlight, the UV radiation damage to DNA cannot be repaired. Thus, such patients are more prone to various forms of skin cancers), Bloom syndrome (is an example of damage by ionizing radiation which cannot be repaired due to inherited defect and the patients have increased risk to develop cancers, particularly leukaemia).

8. Cancer progression and tumor heterogeneity

Tumor progression means increasing size of the tumor, greater anaplasia and dedifferentiation, invasiveness and distant metastasis. Heterogeneity means cancer cells acquire more mutations and more aggressive clones of cancer cells.

9. Cancer a sequential multistep molecular phenomenon: Multistep theory

Multiple steps mutation are involved at genetic level by which cell proliferation of cancer cells is activated, loss of growth suppressors, inactivation of apoptotic mechanisms and escaping cellular ageing.

10. Micro-RNAs in Cancer: Oncomirs

Normally, microRNAs function as the post-translational gene regulators of cell proliferation, differentiation and survival. In cancer, microRNAs have an oncogenic role in initiation and progression and are termed as oncogenic microRNAs, abbreviated as

oncomiRs. These oncogenic microRNAs influence various cellular processes in cancer such as control of proliferation, apoptosis, differentiation, metastasis and metabolism.

CARCINOGENS AND CARCINOGENESIS

Carcinogenesis or oncogenesis or tumorigenesis means mechanism of induction of tumors; agents which can induce tumors are called carcinogens (etiology of cancer). The carcinogens can be discussed under following 3 headings:

A. Chemical carcinogens and chemical carcinogenesis

B. Physical carcinogens and radiation carcinogenesis

C. Biologic carcinogens and viral oncogenesis.

A. CHEMICAL CARCINOGENESIS

The induction of cancer by chemical carcinogens occurs after several years in humans, individual susceptibility (age, sex and nutritional status of the host), dose and mode of administration influence the induction of cancer. Chemical carcinogenesis is a progressive process of cellular transformation by chemical carcinogens that involve 3 stages: Initiation, Promotion and Progression

INITIATION

Chemical initiators of carcinogenesis can be grouped into 2 categories:

I. Direct-acting carcinogens: can induce cellular transformation without undergoing any prior metabolic activation (e.g. alkylating agents, acylating agents).

II. Indirect-acting carcinogens or procarcinogens: These require metabolic conversion within the body (in the liver by the cytochrome P-450 system in the endoplasmic reticulum) so as to become 'ultimate' carcinogens having carcinogenicity e.g. polycyclic aromatic hydrocarbons chewing of tobacco, smoke, fossil fuel, tar, mineral oil, smoked animal foods, industrial and atmospheric pollutants, aromatic amines, azo dyes.

Any gene may be the target molecule in the DNA for the chemical carcinogen. However, it has been observed that most frequently affected growth promoter oncogene is RAS gene mutation and p53 gene mutation. The transformed DNA becomes permanent and fixed only if the altered cell undergoes at least one cycle of proliferation.

PROMOTION

Promoters of carcinogenesis are substances such as phenols, hormones, artificial sweeteners and drugs like phenobarbital. They differ from initiators in:

i) They do not produce sudden change.

ii) They require application or administration for sufficient time and in sufficient dose.

iii) The change induced may be reversible.

iv) They do not mutated DNA but enhance the effect of direct-acting carcinogens.

v) They induce clonal proliferation and expansion of initiated (mutated) cells.

PROGRESSION

It is the stage when mutated proliferated cell shows phenotypic features of malignancy. Such phenotypic features appear only when the initiated cell starts to proliferate rapidly and in the process acquires more and more mutations.

B. PHYSICAL CARCINOGENESIS

Physical agents in carcinogenesis are divided into 2 groups:

Radiation:

the most important physical agent are ultraviolet light and ionizing radiation. The appearance of mutations followed by a long period of latency after initial exposure 10-20 years or even later. Also, radiation may act to enhance the effect of chemical carcinogens. The main source of UV radiation is the sunlight which penetrates the skin for a few millimetres only so that its effect is limited to epidermis. The efficiency of UV light as carcinogen depends upon the extent of light-absorbing protective melanin pigmentation of the skin. UV radiation also induces mutated forms of oncogenes (in particular RAS gene) and anti-oncogenes (p53 gene). In humans, excessive exposure to UV rays can cause various forms of skin cancers—squamous cell carcinoma, basal cell carcinoma and malignant melanoma.

The most important biochemical effect of UV radiation is the formation of pyrimidine dimers in DNA. Such UV-induced DNA damage in normal individuals is repaired, while in the predisposed persons who are excessively exposed to sunlight such damage remain unrepaired (Xeroderma pigmentosum, Ataxia telangiectasia is predisposed to leukaemia, Bloom's syndrome, Fanconi's anaemia).

Ionizing radiation induced cancers of all forms, the risk is increased by higher dose and with high LET (linear energy transfer) such as in neutrons and a-rays than with low LET as in X-rays and g-rays. The evidence in support of carcinogenic role of ionizing radiation is cited in the following examples: Japanese atom bomb survivors of the twin cities of Hiroshima and Nagasaki after World War II have increased frequency of malignant tumors, notably acute and chronic myeloid leukemia, and various solid tumors of breast, colon, thyroid and lung. Accidental leakage at nuclear power plant in 1985 in Chernobyl (in former USSR, now in Ukraine) has caused long-term hazardous effects of radioactive material to the population living in the vicinity.

Mechanism Radiation damages the DNA of the cell either directly or by dislodges ions from water and other molecules of the cell resulting in formation of highly reactive free radicals that cause chromosomal breakage, translocation, or point mutation.

The effect depends upon a number of factors such as type of radiation, dose, dose-rate, frequency and various host factors such as age, individual susceptibility, immune competence, hormonal influences and type of cells irradiated.

2. Non-radiation physical agents

Mechanical injury to the tissues may induce cancers such as:

i) Stones in the gallbladder.

ii) Healed scars following burns or trauma.

iii) Occupational exposure to asbestos (asbestosis) associated with tumors of the lung.

iv) Hardwood cutting workers having high incidence of adenocarcioma of paranasal sinuses.

C. Biologic carcinogens and viral oncogenesis.

Viral and Microbial Oncogenesis: Human papilloma virus (HPV) subtypes 16 and 18 are implicated in the pathogenesis of carcinoma of the cervix and the lower female genital tract. Epstein-Barr virus has been associated with Burkitt lymphoma and nasopharyngeal carcinoma. Hepatitis virus B and C chronic liver disease has been associated with hepatocellular carcinoma. Herpes virus 8 has been isolated from cells of Kaposi sarcoma. Several cancers are now commonly associated with HIV infection or AIDS. These include Kaposi's sarcoma, lymphomas ,non-Hodgkin lymphoma and cancer of the cervix.

H. pylori–induced gastric cancers by chronic inflammation, stimulation of gastric cell proliferation, and production of reactive oxygen species that damage DNA.
H. pylori infection leads to polyclonal B cell proliferations and that eventually a monoclonal B cell tumor (MALT lymphoma) emerges as a result of accumulation of mutations.

Conditions related to cancer development

- **Pre-Existing Abnormalities** chronically inflamed or ulcerated tissues, or severely scarred tissues (Ex; chronic ulcer, severe burn,polyps, papillomas and adenomas*)*
- **Nutritional Deficiencies and Food Habits:** High animal fat content of food appears to be associated with increased risk of some cancers; whilst a diet rich in fresh fruit and vegetables appears to be protective.

Clinical Aspects of Tumors

Cachexia is loss of body weight accompanied by weakness and exhaustion. It may be caused by large tumors that act as parasites draining energy and nutrients. In other cases, tumors inhibit nutrition (e.g., carcinoma of the esophagus prevents swallowing). Other tumors secrete cytokines, such as tumor necrosis factor, which promote catabolism and loss of fat tissue and muscles.
Paraneoplastic syndromes include signs and symptoms caused by tumor effects:
Unrelated to the mechanical effects of the tumor mass or distant metastases
May result from substances released from tumor cells but not found in the normal cells from which the tumor has originated, May result from a series of immunologic and other host reactions to tumor, May have a complex and not fully understood pathogenesis

- **Grading of tumors** is determined by cytological appearance and is based on the idea that behavior and differentiation are related, with poorly differentiated tumors having more aggressive behavior. Cancer grading gives an indication of the

likely aggressiveness of the cancer, Grading of tumors is determined by cytological appearance and is based on the idea that behavior and differentiation are related, with poorly differentiated tumors having more aggressive behavior.

- **Staging of tumors,** determined by surgical exploration or imaging, is based on size, local and regional lymph node spread, and distant metastases. Staging is of greater clinical value than grading because it determine type of treatment modalities and the extent of surgical intervention.

Laboratory Diagnosis of Cancer:

- Biopsy
- cytology
- Immunohistochemistry
- DNA microarray
- Immunofluorescent
- Polymerase chain reaction

References:

- **Wheater`s pathology a text, atlas and review of histopathology; 6th edition, Geraldine O'Dowd etal; 2020, Elsevier.**
- **Text book of general pathology; Harsh Mohan; 7th edition; 2015 ;Jaypee.**
- **Robbins basic pathology; Kumar etal, 2013; 9th edition; Elsevier.**