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.

Review Structure and Function of Normal Cells

Almost all normal cells of the human body have some common features and consist of the same basic components. These include the nucleus, the cytoplasm, and the cell (plasma) membrane:

Nucleus:

The nucleus is the essential component of most living cells. All human cells, except the erythrocytes and platelets, need a nucleus for survival.

It consists of nucleic acids deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and nuclear proteins that surrounded by nuclear membrane. The DNA of the nucleus contains essential genetic material that is identical to all somatic cells of the tissues and organs of

the body. DNA consists of genes that are differentially expressed in various tissues and organs. Differential expression of genes allows the cells to assume unique features in various tissues and organs, and to perform specialized functions.

The genetic information encoded in the DNA is transcribed by the messenger RNA (mRNA) and transmitted by transfer RNA (tRNA) into the cytoplasm where the ribosomal RNA (rRNA) serves as a template for translating the genetic messages into amino acids for protein synthesis.

Protein synthesis is essential for the maintenance of life:

1. Proteins act as structural elements, maintaining the cell's shape and the internal organization of the cytoplasm
2. Proteins are needed for cellular growth and replication
3. Proteins are needed for cellular metabolism and respiration

Cytoplasm

All cells have a cytoplasm that represent the ground substance of all cells, it consists of an amorphous matrix called hyaloplasm and a fibrillar meshwork called cytoskeleton. Each cell is also enclosed by an outer plasma membrane, which forms the border between the cytoplasm and the extracellular space.

The principal cytoplasmic organelles are the mitochondria, ribosomes, endoplasmic reticulum, Golgi apparatus, and lysosomes. Some cells have organelles for specialized functions for example the muscle cells have myofilaments composed of actin and myosin which are essential for contraction; glandular cells have secretory granules, which contain enzymes or mucus.

Mitochondria

They are cytoplasmic organelles contain oxidative enzymes (e.g., cytochrome oxidase) that participate in cellular respiration, their function primarily is generation of energy by production of energy-rich compounds adenosine triphosphate (ATP), this process is called oxidative phosphorylation. ATP generated by the mitochondria is essential for all other cellular functions. Cells with complex functions, such as liver cells and nerve cells,

require a considerable amount of energy and therefore contain numerous mitochondria. By comparison, many malignant tumor cells have few mitochondria.

Ribosomes

Ribosomes are small granules composed of RNA. Some of them are attached to the membranes of the rough endoplasmic reticulum (RER) and others are float freely in the cytoplasm called polysomes or free ribosomes. The ribosomes are involved in protein synthesis. Structural proteins and enzymes needed for the maintenance of basic cell functions ("proteins for internal purposes") are synthesized on the free ribosomes. Those intended for excretion ("export or luxury proteins") are synthesized on the RER and discharged from cells through the cisternae lined by the membranes of the RER.

Endoplasmic Reticulum

The endoplasmic reticulum is a meshwork of membranes that is continuous with the outer plasma membranes on one side and the nuclear membrane on the other. There are two forms of endoplasmic reticulum:

- **Rough endoplasmic reticulum (RER):** it is the site of protein synthesis for export and secretion. For ex; Liver cells synthesize blood proteins (such as albumin and the blood clotting factors), plasma cells synthesize immunoglobulins.
- **Smooth endoplasmic reticulum (SER):** it is site for catabolism (metabolic degradation) of drugs, hormones, and various nutrients and site for synthesis of steroid hormones. For ex; liver cells have a well-developed SER used in metabolic degradation of many chemicals, including drugs and hormones, adrenocortical cells that synthesize steroid hormones (e.g., estrogens, androgens, and corticosteroids).

Golgi Apparatus

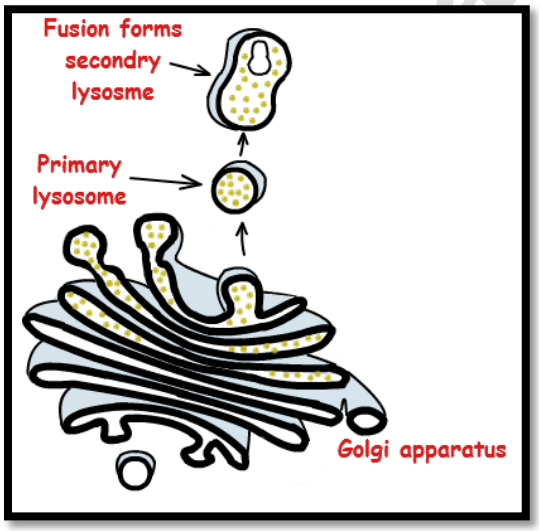
The Golgi apparatus is a synthetic organelle that is responsible for transporting, modifying, and packaging proteins and lipids into vesicles for delivery to targeted destinations.

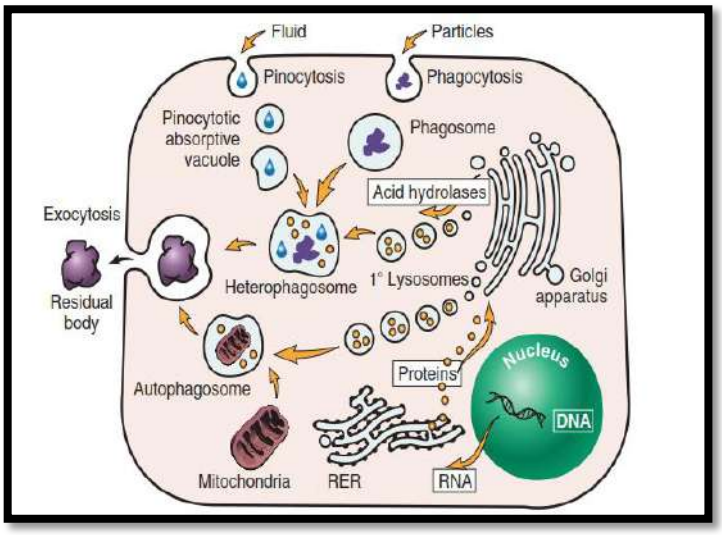
Lysosomes

They are membrane-bound organelles that are rich in lytic enzymes. They originate as small vesicles budding from the lateral sides of the Golgi apparatus. Lysosomes contain digestive enzymes (acid hydrolases, proteases, nucleases and lipases) that are maximally active in an acidic environment. Under normal circumstances, if some lysosomal content is spilled into the cytoplasm, the acid hydrolases would cause little damage in normal cytoplasm, which has a neutral pH. However, if the cell is injured and the pH of the cytoplasm becomes acidic, enzymes released from lysosomes could cause damage, as we will see in cell injury.There are three types of lysosomes:

- **Primary lysosomes** are formed from the Golgi apparatus (GA)
- **Secondary lysosomes** (autophagosomes) are formed from the fusion of primary lysosome and phagocytotic vesicle (phagosome)
- **Tertiary lysosomes** are old secondary lysosomes contain only waste materials may remain within the cytoplasm as "residual bodies." These residual bodies typically contain a lipid-rich brown pigment known as lipofuscin.

Lipofuscin is also known as the brown pigment of aging, because it is commonly found in aging cells. Formation of autophagosomes and the orderly removal of worn out organelles are also well regulated in healthy cells. In damaged or abnormal cells, autophagy may escape control and lead to cell destruction ("cell death by autophagy").





Plasma Membrane

It forms the outer surface of the cell and is composed of proteins, lipids, and carbohydrates arranged in a polarized complex bilayer that has an internal and external surface. On the internal side, the plasma membrane is in continuity with the membrane of the endoplasmic reticulum and the cell membrane also serves as an anchorage site for cytoskeletal filaments.

The external surface of the plasma membrane serves as the site of contact between the cell and the environment. The interaction is maintained through the action of specialized portions of the cell membrane that serve as receptors, adhesion molecules, transducers of signals, or metabolic channels.

The plasma membrane is a living structure that is maintained by constant supply of ATP. The structural integrity of the plasma membrane is important demand for the maintenance of all essential cellular functions. Rupture or major damage of the cell membrane that cannot be repaired leads to cell death.

Integration and Coordination of Cell Functions and Response to Injury

Cells of the human body are arranged into tissues, and these tissues form organs. The integration of cells, tissues and organs into functional units is achieved through several mechanisms:

- **Autocrine stimulation:** is a chemical messenger that secrets from cell and binds to autocrine receptors on the same cell, leading to changes in the cell. For example, T lymphocytes secrete cytokines, which stimulate the growth of other cells, such as fibroblasts, but at the same time act on the cells that produced them, act as their own growth factors (self-stimulation).
- **Paracrine stimulation:** is cell signaling or cellular communication which a cell produces a signal to induce changes in nearby cells (local action).
- **Endocrine stimulation:** is a cellular communication (hormonal messenger released by glands directly into the circulatory system regulating distant target organs.

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.

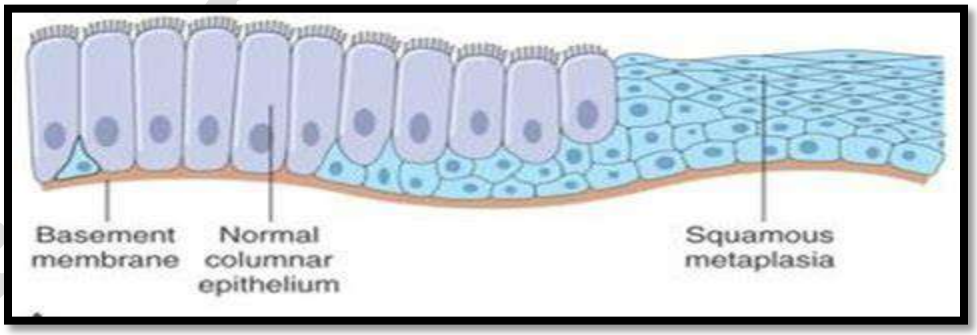
Causes of atrophy include a decreased workload (e.g., immobilization of a limb to permit healing of a fracture), loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging.

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.



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Cellular responses to injury

Homeostasis: is the ability of cells or human body to maintain internal stability to compensate for the environmental changes.

Cell injury: is the effect of a variety of stresses on a cell resulting in changes in its internal and external environment.

Etiology of cell injury:

A. Genetic causes

B. Acquired causes: 1. Hypoxia and ischaemia. 2. Physical agents. 3. Chemical agents and drugs. 4. Microbial agents. 5. Immunologic agents, 6. Nutritional derangements. 7. Ageing 8. Psychogenic diseases. 9. Iatrogenic factors. 10. Idiopathic diseases.

Cells require oxygen to generate energy and perform metabolic functions. Deficiency of oxygen or results in failure of cells activities (e.g. anaemia, carbon monoxide poisoning).

Hypoxia: is partial reducing of oxygen in tissue level.

Anoxia: is complete lack of oxygen in tissue level.

Hypoxemia: low level of oxygen in blood.

Ischemia: is reduction of blood flow to the organ which affects both oxygen and substrate delivered to the tissue.

The cellular response to stress may vary and depends upon following two variables:

i) Host factors i.e. the type of cell and tissue involved. For example, a cerebral neuron is much more vulnerable to damage following hypoxia than a fibroblast. Another example an individual who has an immunodeficiency disorder or poor nutrition is more likely to affect with infection than an individual with a normal immune response.

ii) Factors pertaining to injurious agent i.e. extent and type of cell injury.

Types of cellular responses to injury

1. Cellular adaptations
2. Reversible cell injury
3. Irreversible cell injury (cell death)
4. Intracellular accumulations

Cellular adaptation

It refers to changes made by a cell in response to environmental stimuli (pathological or physiological stimuli), it include the following changes:

- **Hypertrophy:** it is an increase in the size of the individual cells and ultimately the entire organ, for example; Myocardium subjected to persistent increased load in hypertension or with a narrowed (stenotic) valve, adapts by undergoing pathological hypertrophy. Heart and skeletal muscles hypertrophy in weightlifting as a physiological adaptation.

- **Hyperplasia:** it is increase in number of cells occur in tissue capable of replication, for example; hormonal hyperplasia glandular epithelium of the female breast at puberty and during pregnancy. Compensatory hyperplasia occur when part of a liver is resected mitotic activity in the remaining cells begins as early as 12 hours later restoring the liver to its normal weight. Pathologic hyperplasia are caused by excessive hormonal or growth factor stimulation occur in cancer and viral infection.

- **Atrophy:** shrinkage in the size of the cell by the loss of cell substance, although atrophic cells may have diminished function, they are not dead. 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** is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type, for example normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelial cells in order to survive the noxious chemicals in cigarette smoke. Moreover, the influences that induce metaplastic change, if persistent, may predispose to malignant transformation of the epithelium.

Reversible cell injury

If the harmful injury is of short duration (as ischemia or hypoxia), the effects may be reversible on rapid restoration of circulation, the sequential biochemical and ultrastructural changes in reversible cell injury are:

1. **Decreased generation of cellular ATP:** If there is impaired in blood supply, aerobic respiration and glucose availability are affected causes accumulation of metabolic waste products in the cells. If hypoxia occurs due to lung diseases or RBC disorders causes limit the supply of oxygen to the cells, anaerobic glycolytic ATP generation continues, and thus cell injury is less severe. However, highly specialized cells such as myocardium, proximal tubular cells of the kidney, and neurons of the CNS are dependent solely on aerobic respiration for ATP generation thus these tissues are severely and rapidly affected.

2. **Intracellular lactic acidosis:** anaerobic glycolytic pathway results in accumulation of lactic acid lowering the intracellular PH (i.e. intracellular lactic acidosis) and clumping of nuclear chromatin.

3. **Damage to plasma membrane pumps (Hydropic swelling):** Lack of ATP interferes in generation of phospholipids from the cellular fatty acids which are required for continuous repair of membranes. This events lead to failure of sodium-potassium pump mechanism (normally, the energy (ATP)-dependent sodium pump allows active transport of sodium out of the cell and diffusion of potassium into the cell) accumulation of sodium in the cell leads to increase in intracellular water (i.e. hydropic swelling) and disturbance in the calcium ion exchange across the cell membrane (i.e. calcium influx).

4. **Reduced protein synthesis:** As a result of continued hypoxia, membranes of endoplasmic reticulum and Golgi apparatus swell up leading to detached ribosomes and dispersed in the cytoplasm and inactivating their function and reduced protein synthesis occurs in Golgi apparatus.

Morphologic changes of reversible cell injury are:

1. Hydropic change (cloudy swelling or cytoplasmic vacuolation): means accumulation of water within the cytoplasm of the cell, it is reversible change upon removal of the injurious agent.
2. Hyaline change: means glassy, homogeneous, eosinophilic appearance of protein material in haematoxylin and eosin-stained sections.
3. Mucoid change: is deposition of mucinous material in epithelial and connective tissues in excessive amounts.
4. Fatty change (steatosis): is the intracellular accumulation of neutral fat within epithelial cells.

Irreversible cell injury (cell death)

Persistence of ischaemia or hypoxia results in irreversible damage and cell death. Two characterstic features distinguish irreversible from reversible cell injury mitochondrial and cell membrane function dysfunctions. The ultrastructural changes of the cell are:

- Calcium influx collects lead to mitochondrial damage and degrade membrane phospholipids progressively.
- Damage normal cytoskeleton of the cell (microfilaments, micro tubules and intermediate filaments) which anchors the cell membrane due to degradation by activated proteases.
- Nuclear damage results from activated lysosomal enzymes such as proteases and endonucleases. Damaged DNA activates proapoptotic proteins leading the cell to death. Irreversible damage to the nucleus can be in three forms:
  i) Pyknosis Condensation and clumping of nucleus which becomes dark basophilic.
  ii) Karyorrhexis: Nuclear fragmentation in to small bits dispersed in the cytoplasm.
  iii) Karyolysis: Dissolution of the nucleus.
- Activation of hydrolytic lysosomal enzymes due to lack of oxygen in the cell and acidic pH (e.g. hydrolase, RNAase, DNAase, protease, glycosidase, phosphatase, lipase, amylase, cathepsin etc) on activation bring about enzymatic digestion of cellular components and hence cell death.

Liberated enzymes leak across the abnormally permeable cell membrane into the serum, the estimation of which may be used as clinical parameters of cell death. For example, in myocardial infarction, estimation of elevated serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), isoenzyme of creatine kinase (CK-MB), and cardiac troponins (cTn) are useful guides for death of heart muscle.

While cell damage from oxygen deprivation by above mechanisms develops slowly, taking several minutes to hours, if the cells restore the blood supply what is happened?

Ischemia-Reperfusion Injury and Free Radical-Mediated Cell Injury

Depending upon the duration of injury, the regaining of blood flow may result in the following 3 different consequences:

1. If the duration of ischemia is short, reperfusion with resupply of oxygen restores the structure and function of the cell i.e. reversible cell injury.
2. If the duration of ischemia is long, restore blood flow or reperfusion is not helpful, it lead to further accumulation of intracellular sodium and calcium ions due to persistent cell membrane damage (cell death).

3. If ischemia is for somewhat longer duration, the cells are injured but still viable, reperfusion injury occurs due to excessive accumulation of free radicals or reactive oxygen species (Superoxide anion Ǒ2, Hydrogen peroxide (H2O2), Hydroxyl radical (OH–) and Nitric oxide). Normal cell generates free radicals as a consequence products from oxidation process in mitochondria, generally oxygen radicals are unstable and are destroyed spontaneously by the catalytic action of certain enzymes. The injured effect of free radical (oxidative stress) depends upon the rate of their formation and rate of their elimination.
The injured cell has low ATP, calcium overload stored and dysfunction membrane, in addition reactive oxygen species react with cell proteins leading to damage to DNA and cytoskeleton.

Stress Proteins in Cell Injury

When cells are exposed to stress of any type, a protective response by the cell is by release of proteins that move molecules within the cell cytoplasm; these are called stress protein. There are 2 types of stress-related proteins: heat shock proteins (HSP) and ubiquitin. These proteins play an important role in cancer and a variety of human degenerative diseases, especially in the nervous system in ageing.

Morphology of irreversible cell injury (Cell Death)

Autolysis

Is self-digestion of the cell by its own hydrolytic enzymes liberated from lysosomes. The term is generally used for postmortem change but it can occur in the living body as in inflammatory reaction. In histopathology, autolysis is identified by homogeneous and eosinophilic cytoplasm with loss of cellular details and remains of cell as debris.

Necrosis

It is cell death that is associated with loss of membrane integrity and leakage of cellular contents resulting in degradation of cell. It may elicit host reaction (inflammation) that attempts to eliminate the dead cells and start the subsequent repair process. Based on etiology and morphologic appearance, there are 5 types of necrosis:

- **Coagulative necrosis** is a form of necrosis in which the underlying tissue architecture is preserved for at least several days. The affected tissues take on a firm texture. In this type of

necrosis the denaturation involve both structural proteins and enzymes blocking the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks. Leukocytes are recruited to the site of necrosis, and the dead cells are digested by the action of lysosomal enzymes of the leukocytes. The cellular debris is then removed by phagocytosis. Coagulative necrosis is characteristic of infarcts (areas of ischemic necrosis) in all of the solid organs except the brain.

- **Liquefactive necrosis** is seen in bacterial infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest the tissue transforming the tissue into a liquid viscous mass. Hypoxic death of cells within the central nervous system evokes liquefactive necrosis.
- **Gangrenous necrosis** refers to the condition of a limb that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers. When bacterial infection is superimposed, coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes (resulting in so-called wet gangrene).
- **Caseous necrosis:** means "cheese-like," appear as friable yellow-white area of necrosis, the tissue architecture is completely obliterated and cellular outlines cannot be discerned. The area of caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma.
- **Fat necrosis:** refers to fat destruction by release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. It occur as abdominal emergency known as acute pancreatitis. The released fatty acids combine with calcium to produce grossly visible chalky white areas (fat saponification).
- **Fibrinoid necrosis** is deposition of fibrin with immune reactions complexes of antigens and antibodies in the walls of arteries produce a bright pink and amorphous appearance on H&E called fibrinoid.

Apoptosis

It is a form of coordinated and programmed cell death (cell suicide). Unlike necrosis, apoptosis is not accompanied by any inflammation and collateral tissue damage. Because apoptosis cannot stop once it has begun, it is a highly regulated process. Apoptosis can be initiated through one of two pathways. In the intrinsic pathway the cell kills itself because it senses cell stress, while in the extrinsic pathway the cell kills itself because of signals from other cells. Both pathways induce cell death by activating caspases, which are proteases, or enzymes that degrade proteins

Apoptosis occurs in a variety of physiologic conditions:

1. Organized cell destruction during development of embryo.

2. Physiologic involution of cells in hormone-dependent tissues e.g. endometrial shedding, regression of lactating breast after withdrawal of breast-feeding.
3. Normal shedding followed by replacement proliferation such as in intestinal epithelium.

Apoptosis occurs in a variety of pathologic Processes:

1. Cell death in tumors exposed to chemotherapeutic agents.
2. Cell death by cytotoxic T cells in immune mechanisms such as in graft rejection.
3. Cell death in viral infections and progressive depletion of CD4+T cells in AIDS.
4. Pathologic atrophy of organs and tissues on withdrawal of stimuli.
5. Degenerative diseases of CNS (Alzheimer's disease, Parkinson's disease and dementias).
6. Heart diseases, acute myocardial infarction (20% necrosis and 80% apoptosis).

Morphologic changes in apoptosis:

1. Involvement of single cells or small clusters of cells in viable tissue.
2. Apoptotic cells are round to oval shrunken with intensely eosinophilic cytoplasm containing shrunken or almost-normal organelles.
3. Nuclear chromatin is condensed under the nuclear membrane i.e. pyknosis.
4. The cell membrane may show blebs or projections on the surface.
5. Formation of spherical bodies containing condensed organelles called apoptotic bodies.
6. No acute inflammatory reaction around apoptosis.
7. Macrophages phagocyte the apoptotic.

Table 1–1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size 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

DNA, deoxyribonucleic acid.

INFLAMMATION

Inflammation is a protective response involving host cells, blood vessels, and proteins and other mediators that intended to eliminate the initial cause of injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.

Inflammation is induced by chemical mediators that are produced by host cells in response to injurious stimuli, Inflammation is normally controlled and self-limited but it cause harmful effect to the tissue.

Inflammation may have beneficial effects, such as the destruction of invading micro-organisms and the walling-off of an abscess cavity preventing spread of infection and initiate healing process. Equally, it may produce harmful effect; for example, an abscess in the brain would act as a space-occupying lesion compressing vital surrounding structures that may distort the tissues and permanently alter their function. It can cause life-threatening hypersensitivity reaction. It can cause progressive organ damage from chronic inflammation and subsequent fibrosis like rheumatoid arthritis and atherosclerosis.

Inflammation is usually classified according to its time course as:

- Acute inflammation: the initial and often transient series of tissue reactions to injury
- Chronic inflammation: the subsequent and often prolonged tissue reactions following the initial response.

ACUTE INFLAMMATION

It is the initial tissue reaction to a wide range of injurious agents; it may last from a few hours to a few days. The process is usually described by the suffix '-itis', preceded by the name of the organ or tissues involved. For example:

Pulpitis : inflammation of pulp
Gingivitis: inflammation of gingiva
Hepatitis: inflammation of liver
Appendicitis: inflammation of appendix

CAUSES OF ACUTE INFLAMMATION

- Microbial infections: Viruses lead to death of individual cells by intracellular multiplication. Bacteria release specific exotoxins or endotoxins.

• Hypersensitivity reactions, inappropriate or excessive immune reaction that damages the tissues e.g. parasites, tubercle bacilli
• Physical agents, e.g. trauma, ionising radiation, heat, cold ('frostbite')
• Chemicals, e.g. corrosives, acids, alkalis, reducing agents, bacterial toxins
• Tissue necrosis, e.g. ischaemic infarction.
- Forign bodies (dirt ,suture)

THE PHYSICAL CHARACTERISTICS OF ACUTE INFLAMMATION

These characteristics were formulated by Celsus (30 bc–ad 38) using the Latin words rubor, calor, tumor and dolor. Loss of function is also characteristic

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Redness (rubor): An acutely inflamed tissue appears red, for example skin affected by sunburn, cellulitis due to bacterial infection or acute conjunctivitis. This is due to dilatation of small blood vessels within the damaged area.

Heat (calor): Increase in temperature is seen only in peripheral parts of the body due to increased blood flow (hyperaemia) through the region, resulting in vascular dilatation and the delivery of warm blood to the area. Systemic fever, which results from some of the chemical mediators of inflammation, also contributes to the local temperature.

Swelling (tumor): Swelling results from oedema (the accumulation of fluid in the extravascular space as part of the fluid exudate).

Pain (dolor): it is one of the best-known features of acute inflammation. It results partly from the stretching and distortion of tissues due to inflammatory oedema and, in particular, from pus under pressure in an abscess cavity. Some of the chemical mediators of acute inflammation, including bradykinin, the prostaglandins and serotonin, are known to induce pain.

Loss of function: a well-known consequence of inflammation, physically immobilise the tissues in inflamed area due to pain and severe swelling.

EXUDATE is an inflammatory extravascular fluid that has a high protein concentration. It found in the area of injury.

PURULENT EXUDATES (PUS) is an inflammatory extravascular fluid (exudate) rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes.

TRANSUDATE is a fluid with low protein content that results from increase hydrostatic pressure as a consequence of reduced venous return. transudate is accumulate in non inflammatory conditions.

EDEMA Excessive fluid in the interstitial tissue or body cavities which may be either exudates or transudate.

ACUTE INFLAMMATION HAS TWO MAJOR COMPONENTS

VASCULAR CHANGES: increased blood flow (vasodilation) and increased vascular permeability, migration of the leukocytes through the vessel wall these events induced by histamine, kinins, and other mediators that produce gaps between endothelial cells resulting in erythema and stasis of blood flow and edema.

CELLULAR EVENTS: emigration of the leukocytes from the circulation and accumulation in the focus of injury (cellular recruitment) by chemotaxis, followed by activation of the leukocytes, enabling them to eliminate the offending agent.

VASCULAR CHANGES

1. Direct endothelial injury (as in burns or infections) stimulates mast cell and other immune cells to release histamine, bradykinin, leukotrienes, and many other chemical mediators as the response to injury.
2. The chemical mediators affect the endothelial cell (contraction)
3. Contracted endothelial cell result in initial transient vasoconstriction that followed by vasodilation causing increasing in blood flow to the area of injury. (This is the cause of heat and redness).
4. Increased vascular permeability result in escape of a protein-rich fluid **(exudate)** into the extravascular tissue.
5. The loss of protein from the plasma reduces the intravascular osmotic pressure and increases the osmotic pressure of the interstitial fluid leading to formation of **edema (swelling).**

CELLULAR EVENTS

Chemotaxis: it is a process of movement of leukocytes toward sites of infection or injury by the effect of exogenous or endogenous chemotactic substances including bacterial products, cytokines (TNF, IL-1 and components of the complement system).

1. Margination of neutrophils: loss of intravascular fluid and increase in plasma viscosity with slowing of flow at the site of acute inflammation allow neutrophils to flow in this plasmatic zone.
2. Pavementing of neutrophils: adhesion of neutrophils to the vascular endothelium that occurs at sites of acute inflammation.
3. Neutrophil emigration: Pass between endothelial cells, Leukocytes migrate by active amoeboid movement through the walls of blood vessles to the surrounding area of injury.

MEDIATORS OF INFLAMMATION:

1. CELL-DERIVED MEDIATORS

1. Vasoactive amines (Histamine, 5-hydroxytryptamine, neuropeptides)
2. Arachidonic acid metabolites by : cyclo-oxygenase pathway (ex: prostaglandins), lipo-oxygenase pathway (ex: leukotrienes)
3. Lysosomal components from PMNs, macrophages
4. Platelet activating factor
5. Cytokines (IL-1, IL-6, IL-8, IL-12, IIL-17, TNF-a, TNF-b, IFN-g)
6. Free radicals (Oxygen metabolites, nitric oxide)

2. PLASMA PROTEIN-DERIVED MEDIATORS the products of The kinin system, the clotting system, the fibrinolytic system, and the complement system

The steps of the inflammatory response

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

Neutrophils predominate the first 6 to 24 hours and are later replaced by monocytes/ macrophages in 24 to 48 hours. Leukocytes can eliminate microbes and dead cells by phagocytosis; recognization and attachment of microbs by specific surface receptors called opsonins (the opsonization process) which either are present in the blood ready or are produced

in response to the microbes, the most important opsonins are IgG, complement protein C3 and plasma carbohydrate lectins that bind to microbial cell wall sugar groups. Engulfment by formation of a phagocytic vacuole then killing and degradation of the ingested material by formation phagosomes (phagocytic vacuole, microbicidal substances ex: reactive oxygen species (ROS) and lysosomal enzymes).

MORPHOLOGIC APPEARANCE OF ACUTE INFLAMMATION IS:

Serous inflammation
Fibrinous inflammation
Suppurative (purulent) inflammation
Abscess
Ulcer.

CHRONIC INFLAMMATION MAY ARISE IN THE FOLLOWING:

1. Persistent infections
2. Immune-mediated inflammatory diseases (hypersensitivity ,allergic reactions, and autoimmune diseases).
3. Prolonged exposure to potentially toxic agents.
4. many diseases include Alzheimer disease, atherosclerosis, metabolic syndrome type 2 diabetes and cancer.

Chronic Inflammatory Cells and Mediators

Neutrophils: are found in acute and chronic inflammation may continue.
Macrophages: are the dominant cells of chronic inflammation which derived from circulating blood monocytes after their emigration from the bloodstream. Macrophages are normally diffusely scattered in most connective tissues and are also found in organs such as the liver (Kupffer cells), spleen and lymph nodes (histiocytes), central nervous system (microglial cells), and lungs (alveolar macrophages).
Lymphocytes: Both classes of lymphocytes migrate into inflammatory sites. In the tissues, B lymphocytes may develop into plasma cells which secrete antibodies and T lymphocytes are activated to secrete cytokines. **Other Cells:** Eosinophils, Mast cells.

Granulomatous inflammation: is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages with scattered lymphocytes. Granulomas

are characteristic of certain specific pathologic states: Tuberculosis, Leprosy, Syphilis, Cat-scratch disease, Sarcoidosis, Crohn disease.

Feature	acute	chronic
Duration	short duration (lasting less than 2 weeks)	longer duration
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local and systemic signs	Prominent	Less prominent; may be subtle
Characteristic features	Edema, intravascular activation of platelets, presence of acute inflammatory cells neutrophils	presence of chronic inflammatory cells such lymphocytes, plasma cells and macrophages, granulation tissue formation or granuloma
The outcome	tissue repair or chronic inflammation or scarring.	Scaring and fibrosis

Sub-acute inflammation: is term used for the state of inflammation between acute and chronic.
Fulminant acute inflammation: it is sever acute inflammatory response
Chronic active inflammation: is the type of chronic inflammation during the course of acute exacerbations activity of disease.

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Lec 7 **General Pathology** **Dr.Afrah Adnan**

Diseases of immune system

Hypersensitivity reactions

It is defined as an exaggerated or inappropriate state of normal immune response with adverse effects on the body. These lesions are termed as hypersensitivity reactions or immunologic tissue injury, of which 4 types are described:
Type I: immediate hypersensitivity
Type II: antibody to cell--bound antigen
Type III: immune complex reactions
Type IV: delayed hypersensitivity mediated by T--cells

Hypersensitivity reactions are grouped in general into:

1. Immediate type: the reaction occurs immediately on administration of antigen (within seconds to minutes). Immune response in this type is mediated by humoral antibodies (B cell mediated). Immediate types of hypersensitivity reactions include type I, II and III.
2. Delayed type: in which the reaction is slower in onset and develops within 24-48 hours and the effect is prolonged. It is mediated by cellular response (T cell mediated) and it includes Type IV reaction.

TYPE I: ANAPHYLACTIC (Allergic) REACTION

It is as a state of rapidly developing anaphylactic type of immune response to an antigen (i.e. allergen) to which the individual is previously sensitized. The reaction appears within 15-30 minutes of exposure to antigen. It is mediated by humoral antibodies of IgE type in response to antigen. Following etiological hypotheses have been proposed:
1. Genetic basis: There is evidence that ability to respond to antigen and produce IgE are both linked to genetic basis. For example, there is a 50% chance that a child born to both parents allergic to an antigen, may have similar allergy.
2. Environmental pollutants: environmental pollutants increase mucosal permeability and thus may allow increased entry of allergen into the body, which in turn leads to raised IgE level.
3. Concomitant factors: type I allergic reaction may be linked to certain viral infections of upper respiratory tract in a susceptible individual.

Pathogenesis

i) In response to initial contact with antigen, activation of the TH2 subset of CD4+ helper T cells by environmental antigens which activated circulating B lymphocytes and differentiates to form IgE-secreting plasma cells. IgE antibodies bind to the Fc receptors present on the surface of mast cells and basophils.

ii) Degranulation of mast cells and basophils (released granules) contain important chemicals and enzymes with proinflammatory properties— histamine, serotonin, vasoactive intestinal peptide (VIP), chemotactic factors of anaphylaxis for neutrophils and eosinophils, leukotrienes , prostaglandins and platelet activating factor. **The effects of these agents are:**

i) Early vasoconstriction followed by vasodilatation
ii) increased vascular permeability
iii) smooth muscle contraction
iv) increased gastric secretion
v) increased nasal and lacrimal secretions
vi) shock

Examples of type I reaction

The manifestations of type I reaction may be variable in severity and intensity. It may manifest as a local irritant (skin, nose, throat, lungs etc), or sometimes may be severe and life-threatening anaphylaxis. Common allergens which may incite local or systemic type I reaction are as under:

Systemic anaphylaxis:

The clinical features of systemic anaphylaxis include itching, erythema, contraction of respiratory bronchioles, diarrhoea, pulmonary oedema, pulmonary haemorrhage, shock and death.

i) Administration of antisera e.g. anti-tetanus serum (ATS).
ii) Administration of drugs e.g. penicillin.
iii) Sting by wasp or bee.

Local anaphylaxis:

i) Hay fever (seasonal allergic rhinitis) to pollen sensitization of conjunctiva and nasal passages.
ii) Bronchial asthma due to allergy to inhaled allergens like house dust.
iii) Food allergy to ingested allergens like fish, cow's milk, eggs etc.
iv) Cutaneous anaphylaxis due to contact of antigen with skin.
v) Angioedema, inherited disorder characterized by laryngeal oedema, oedema of eyelids, lips, tongue and trunk.

TYPE II: ANTIBODY-MEDIATED (CYTOTOXIC) REACTION

Type II or cytotoxic reaction is defined as reaction by antibodies (IgG and IgM) that attack surface antigens on the specific cells and tissues and cause lysis of target cells. It appears generally within 15-30 minutes after exposure to antigen but in myasthenia gravis and thyroiditis appear after longer duration.

PATHOGENESIS

i) The antigen on the surface of cell (foreign cell) attracts and binds Fab portion of the antibody (IgG or IgM) forming antigen-antibody complex.

ii) The unattached Fc fragment of antibodies (IgG or IgM) forms a link between the antigen and complement that causes activation of classical pathway of complement system.

iv) Antigen-antibody complex also activates complement system and exposes membrane attack complex (MAC) that attracts phagocytes to the site of cell injury and initiates phagocytosis and destroys the target cell.

Examples of type II reaction

1. **Blood Transfusion reactions** due to incompatible or mismatched blood transfusion.
2. Haemolytic disease of the newborn (**erythroblastosis foetalis**) in which the foetal red cells are destroyed by maternal isoantibodies crossing the placenta.
3. **Pemphigus vulgaris** Proteins in intercellular junctions of epidermal cells (epidermal desmoglein) causes Skin vesicles (bullae)
4. **Graves' disease** (primary hyperthyroidism),autoantibody is formed which reacts with the TSH receptor to cause hyperfunction and proliferation.
5. **Myasthenia gravis**, antibody to acetylcholine receptors of skeletal muscle is formed which blocks the neuromuscular transmission at the motor end-plate (muscle weakness).
6. **In male sterility**, antisperm antibody is formed (impaired motility and cellular injury).
7. **Type 1 diabetes mellitus**, autoantibodies are formed which react against islet cell tissue.
8. **Hyperacute rejection reaction**, antibodies are formed against donor antigen.

TYPE III: IMMUNE COMPLEX MEDIATED (ARTHUS) REACTION

It results from deposition of antigen-antibody IgG and IgM complexes on tissues (Arthus reaction), which is followed by activation of the complement system and inflammatory reaction resulting in tissue injury. The onset of type III reaction takes place about 6 hours after exposure to the antigen.

Note: both type II and type III reactions have antigen-antibody complex formation but the two can be distinguished—antigen in type II is tissue specific while in type III it is not so.

PATHOGENESIS

1. Immune complexes are formed by interaction of soluble antibody IgG and IgM and soluble or insoluble antigen.
2. Immune complexes which fail to get removed from body fluid get deposited into tissues.
3. Fc component of antibody links with complement and activates classical pathway of complement system result in formation of C3b, C5a and membrane attack complex.
4. C3b stimulates release of histamine from mast cells and its resultant effects of increased vascular permeability and oedema.
5. C5a releases proinflammatory mediators and chemotactic agents for neutrophils and macrophages in the tissue release cytokines and result in tissue destruction.

Examples of type III reaction

1. Immune complex glomerulonephritis in which the antigen may be glomerular basement membrane (GBM) or exogenous agents (e.g. Streptococcal antigen).
2. Rheumatoid arthritis.
3. Serum sickness caused by various proteins (e.g., foreign serum protein such as horse antithymocyte globulin) result in arthritis, vasculitis, nephritis.

TYPE IV: DELAYED HYPERSENSITIVITY (T CELL-MEDIATED) REACTION

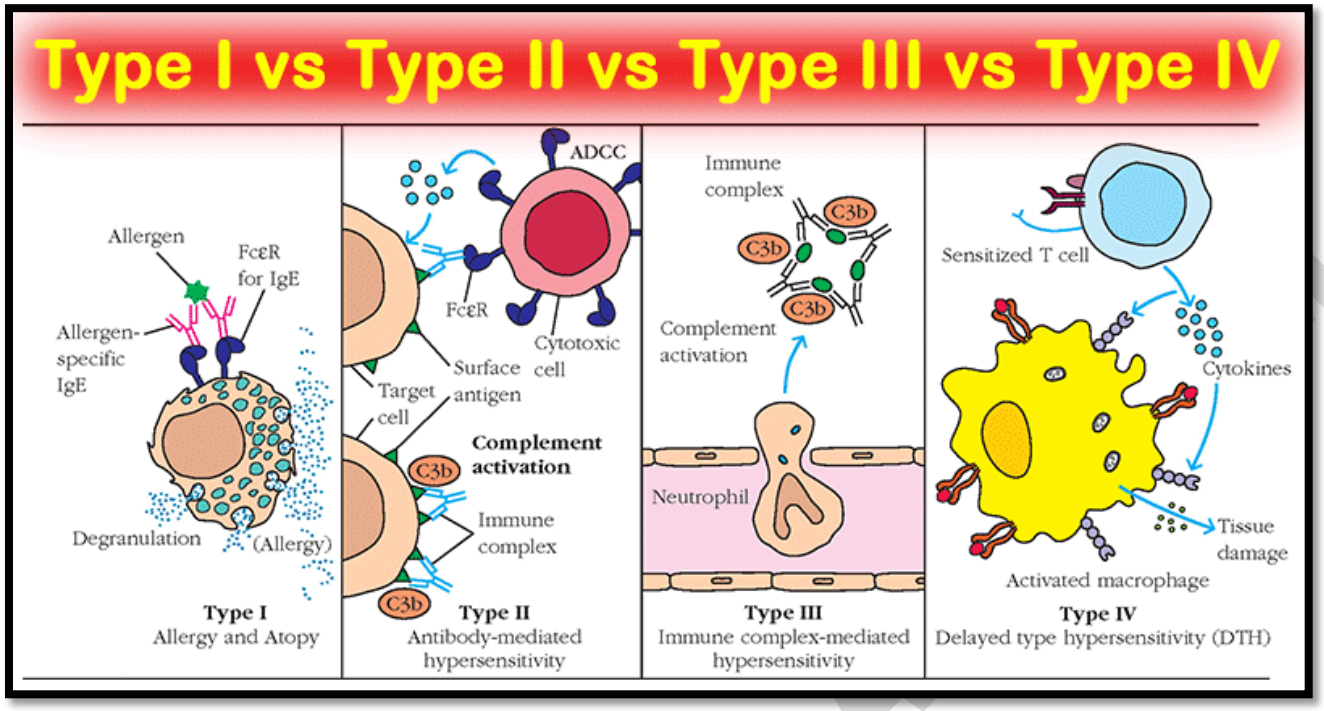
It is tissue injury by T cell-mediated immune response without formation of antibodies with a slow and prolonged response. The reaction occurs about 24 hours after exposure to antigen and the effect is prolonged which may last up to 14 days.

PATHOGENESIS

1. The antigen is recognised by CD8+ T cells (cytotoxic T cells) and is processed by antigen presenting cells.
2. Antigen-presenting cells migrate to lymph node where antigen is presented to helper T cells (CD4+ T cells).
3. Helper T cells release cytokines that stimulate T cell proliferation and activate macrophages.
4. Activated T cells and macrophages release proinflammatory mediators and cause cell destruction.

Examples of type IV reaction

1. Reaction against virally infected cells and mycobacterial infection e.g. tuberculosis, leprosy.
2. Contact dermatitis.
3. Reaction against malignant cells in the body.
4. Reaction against organ transplantation e.g. transplant rejection, graft versus host reaction.



Immunodeficiency diseases

A. Primary immunodeficiencies: genetic or developmental abnormality of the immune system.
B. Secondary immunodeficiencies: acquired suppression of the immune system, the most important example being acquired immunodeficiency syndrome (AIDS).

Primary immune deficiency states are fortunately rare, most primary immune deficiencies come to attention early in life (between the ages of 6 months and 2 years), usually because the affected infants are susceptible to recurrent infections. Examples:

- X-linked agammaglobulinemia (XLA), or Bruton disease, is characterized by the failure of pre-B cells to differentiate into B cells resulting in absence of antibodies in the blood.
- DiGeorge syndrome results from a congenital defect in thymic development with deficient T cell maturation this defect is extremely vulnerable to viral, fungal, and protozoal infections.
- Selective immunoglobulin A (IgA) deficiency is a genetic immunodeficiency, a type of hypogammaglobulinemia. People with this deficiency lack immunoglobulin A (IgA), a type of antibody that protects against infections of the mucous membranes lining the mouth as IgA is the only immunoglobulin secreted in the saliva, airways, and digestive tract. It is defined as an undetectable serum IgA level in the presence of normal serum levels of IgG and IgM, in persons older than 4 years. It is the most common of the

primary antibody deficiencies. Most such persons remain healthy throughout their lives and are never diagnosed.

HIV & AIDS is caused by an RNA (retrovirus) virus called human immunodeficiency virus (HIV). Transmission of HIV infection occurs by one of following routes: Sexual contact, Transmission via blood and blood products and Perinatal transmission. HIV has been isolated and identified from a number of body fluids such as saliva, tears, sweat, urine, semen, vaginal secretions, cervical secretions, breast milk, CSF, synovial, pleural, peritoneal and pericardial fluid, there is no definite evidence that HIV transmission can occur by any of these fluids.

The pathogenesis of HIV infection is largely related to the depletion of CD4+ T cells (helper T cells) resulting in profound immunosuppression.

1. HIV has a selective tropism for CD4+ T cells (T helper cells) via molecule receptor gp120 envelope glycoprotein of HIV.
2. Once HIV has combined with CD4 receptor, gp41 glycoprotein of envelope is integrated in the CD4+ T cell membrane.
3. Virion has entered the T cell cytoplasm and start to form a single-stranded DNA from its RNA while destroying the original RNA of the host.
4. DNAViral integration into the the host cell DNA termed as HIV provirus
5. Multiplication of viral facilitated release of cytokines from T helper cells where they acquire protein coating and responsible for spread of infection to other body sites, in particular to CNS

Viral DNA so formed has frequent mutations making the HIV quite resistant to anti-retroviral therapy. There after inactive infected T cell are formed, CD4+ T cell destruction, Viral dissemination.

Progression of HIV Infection

The clinical stages of HIV infection include an acute phase (which is only partly controlled by the host immune response), a chronic phase (or latency period), and AIDS.

During the acute phase, the patient may be asymptomatic or exhibit a self-limited acute retroviral syndrome but he exhibit high levels of viremia and extremely infectious. Typically develops within 1 to 6 weeks after exposure in 50-70% of infected patients (generalized lymphadenopathy, sore throat, fever, maculopapular rash, headache, myalgia, arthralgia, diarrhea, photophobia, and peripheral neuropathies). Oral changes may include mucosal erythema and focal ulcerations. During this initial phase, HIV infection often is not considered or investigated, and HIV antibodies are not yet detectable.

During the chronic phase (or latency period) an immune response is developed, viremia declines, and the patient enters a clinical latency period. Latency may last from several months to more than 15 years. Without treatment, the median duration is approximately 10 years (shorter in infants, children, or those infected via blood transfusion).
Most patients are asymptomatic, but some patients have persistent generalized lymphadenopathy, chronic fever, weight loss, diarrhea, oral candidiasis, herpes zoster, and/or oral hairy leukoplakia. This presentation has been termed **AIDS-related complex (ARC)**.

AIDS (acquired immunodeficiency syndrome) dramatic increase in viremia, and the CD4+ cell count declines, signs and symptoms described under **AIDS-related complex** are often present with an increasing number of opportunistic infections or neoplastic processes.
Pneumonia, disseminated cytomegalovirus infection, severe herpes simplex virus infection, atypical mycobacterial infection, cryptococcal meningitis, and CNS toxoplasmosis (AIDS-dementia complex).

Amyloidosis

It is the term used for a group of diseases in which an abnormal protein called amyloid accumulates in body tissues and organs. The protein deposits can be in a single organ or dispersed throughout the body. The disease causes serious problems in the affected areas.

Over the years, amyloidosis has been classified in a number of ways:

- Based on cause, into primary (with unknown cause and the deposition is in the disease itself) and secondary (as a complication of some underlying known disease; tuberculosis, rheumatoid arthritis).
- Based on extent of amyloid deposition, into systemic (generalised) involving multiple organs and localised amyloidosis involving one or two organs or sites.
- Based on clinical location, into pattern I (involving tongue, heart, bowel, skeletal and smooth muscle, skin and nerves), pattern II (principally involving liver, spleen, kidney and adrenals) and mixed pattern (involving sites of both pattern I and II).
- Based on precursor biochemical proteins, into specific type of serum amyloid proteins.

There are about 30 different types of amyloidosis, each due to a specific protein misfolding. Some are genetic while others are acquired. They are grouped into localized forms, and systemic ones. The four most common types of systemic amyloidosis are light chain (AL),

inflammation (AA), dialysis-related ($A\beta_2M$), and hereditary and old age (ATTR and familial amyloid polyneuropathy.

AL amyloidosis is caused by an abnormality in plasma cells that result in production of abnormal forms of light chain proteins, which enter the bloodstream and can form amyloid deposits. Healthy people have normal light chain proteins in their blood that are part of their natural antibody proteins. These help protect the body from infection.

The abnormal light chains in patients with AL amyloidosis clump together into thread (amyloid fibrils) that the body cannot clear away easily. Over time, amyloid fibrils build up as AL amyloid deposits in tissues and organs. This gradually stops them functioning properly, causing the many symptoms of AL amyloidosis. Unlike some other types of amyloidosis, AL amyloidosis is not inherited, so a person with the condition cannot pass it on to their children.

As a result, people with amyloidosis in different body parts may experience different physical problems:

- **Tongue enlargement**
- **Brain** – Dementia
- **Heart** - Heart failure, heart rhythm, and enlarged heart
- **Kidneys** - Kidney failure, protein in the urine
- **Nervous system** - Numbness, tingling or weakness from nerve disease
- **Digestive system** - Intestinal bleeding, intestinal obstruction, poor nutrient absorption
- **Blood** -Low blood counts, easy bruising or bleeding
- **Pancreas** - Diabetes
- **Musculoskeletal system** - Joint pain or swelling, weakness
- **Skin** - Lumps or purple discoloration

There is not currently a cure for amyloidosis. The amyloid deposits cannot be directly removed. But there are treatments to stop more of the abnormal proteins being produced and treat your symptoms. These treatments can give your body time to gradually clear the deposits before they build up again. This can help prevent organ damage.

In most cases, the treatment will involve having chemotherapy. Chemotherapy damages abnormal bone marrow cells and stops them producing the abnormal proteins that form amyloid deposits. Steroids are usually given together with chemotherapy to boost the effect of the chemotherapy drugs. They may also lessen your chances of having a bad reaction to chemotherapy.

Lec 6 **General Pathology** **Dr. Afrah Adnan**

Immunopathology

Immunity is a double-edged sword i.e. it is a defense mechanism but it can be harmful to the human body in a variety of ways. Immunity is divided into natural (innate) and specific (adaptive) which are interlinked to each other in their functions.

Natural or innate immunity is non-specific and is considered as the first line of defense without antigenic specificity. It has 2 major components:

- Humoral: represented by complement.
- Cellular: consists of neutrophils, macrophages, and natural killer (NK) cells.

Specific or adaptive immunity is specific and is characterized by antigenic specificity. It too has 2 main components:

- Humoral: consisting of antibodies formed by B cells.
- Cellular: mediated by T cells.

The major functions of immune system are as under:

i) Recognition of self from non-self
ii) Induced a specific response against non-self
iii) Memory of what was earlier recognized as non-self
iv) Antibody formation
v) Cell-mediated reactions

While normal function of immunity is for body defense, its failure or derangement in any way results in diseases of the immune system which are broadly classified into 4 groups:

1. Immunodeficiency disorders: are deficient or absent cellular and/or humoral immune functions. It may be primary or secondary immunodeficiency diseases.

2. Hypersensitivity reactions: are characterized by hyperfunction or inappropriate response of the immune system.

3. Autoimmune diseases: occur when the immune system fails to recognise 'self' from 'non-self' antigen.

4. Transplant rejection.

Review the normal structure and function of the immune system

An antigen (Ag): is as a substance (usually protein in nature) which when introduced into the tissues stimulates antibody production.

Hapten: is a non-protein substance which has no antigenic properties, but on combining with a protein can form a new antigen capable of stimulating antibodies.

An antibody (Ab): is a protein substance produced as a result of antigenic stimulation. Circulating antibodies are immunoglobulins (Igs) of which there are 5 classes: IgG, IgA, IgM, IgE and IgD.

ORGANS OF IMMUNE SYSTEM

a) Primary lymphoid organs:

i) Thymus

ii) Bone marrow

b) Secondary lymphoid organs:

i) Lymph nodes

ii) Spleen

iii) MALT (Mucosa-Associated Lymphoid Tissue located in the respiratory tract and GIT).

CELLS OF IMMUNE SYSTEM

Lymphocytes

Lymphocyte is the master of human immune system, lymphocytes appear as a homogeneous group but functionally three major groups (T, B and NK natural killer).

All three subtypes of lymphocytes are formed from lymphoid precursor cells in the bone marrow, lymphocytes undergo maturation and differentiation in the bone marrow (B cells) and thymus (T cells) and acquire certain genetic and immune surface characters which determine

their type and function; this is based on cluster of differentiation (CD) molecule on their surface. CD surface protein molecules, about 350 different CD markers have been identified; B and T lymphocytes proliferate into 'memory cells' for long lasting immunity against specific antigens. B cells differentiate into plasma cells which form specific antibodies. T cells get functionally activated on coming in contact with appropriate antigen.

How can T lymphocytes activated?

If macrophage coming in contact with antigen, the major histocompatibilty complex (MHC) in the macrophage determine whether the invading antigen is to be presented to B cells or T cells. Some strong antigens that cannot be dealt by antibody response from B cells such as certain microorganisms (e.g. viruses, mycobacteria M. tuberculosis and M. leprae), cancer cells, tissue transplantation antigen etc, are presented to T cells.

T cells about 75-80% of lymphocytes, they are inciting cell-mediated immunity and delayed type of hypersensitivity, destroying cells infected with viruses, foreign cells and tumor cells.

T cells have two major subtypes: T helper (CD4+) cells and T suppressor (CD8+) cells. CD8 (suppressor T cells or cytotoxic T lymphocytes) are directly cytotoxic to the antigen.

CD4+ cells in circulation are about twice the number of CD8+ cells (CD4+/CD8 ratio 2:1).

T helper cells (also termed as T-regulatory cells) are promote and enhance the immune reaction and act by elaboration of variety of cytokines that are further of two subclasses:

- TH 1 cells elaborate IL-2 and interferon (IFN).
- TH 2 cells elaborate IL-4, IL-5, IL-6, and IL-10.

How can B lymphocytes activated?

B cells about 10-15% of lymphocytes, involved in humoral immunity by inciting antibody response, macrophage presented invading antigen to B cells (e.g. invading microorganims) B cells activated to proliferate and transform into plasma cells.

How can NK lymphocytes activated?

They are about 10-15% of circulating lymphocytes. They are morphologically distinct from B and T cells in being large granular lymphocytes and they play role in natural or innate immunity. These cells recognize antibody-coated target cells and kill the target directly; this process is termed as antibody-dependent cell-mediated cytotoxicity (ADCC).

Monocytes and Macrophages

Circulating monocytes are immature macrophages form about 5% of peripheral leucocytes. They remain in circulation for about 3 days then they enter tissues to become macrophages.
The macrophage subpopulations as the dendritic cells (in the lymphoid tissue) and Langerhans' cells (in the epidermis) are characterized by the presence of dendritic cytoplasmic processes.

Functions of macrophages are:

1. Antigen recognition: by their surface receptors bind to cytokines, component of complement (C3b), selectins, integrins and Fc of antibody. Antigen to become recognizable are coated by antibodies or complement, the process being termed as opsonisation.

2. Phagocytosis Antigen: antigen that recognized by macrophages are engulfed.

3. Secretory function: Macrophages secrete substances as:

a. **Cytokines** (IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor) and prostaglandins (thromboxane-A, leukotrienes) which are chemical mediators of inflammation and activate other leucocytes.

b. **Proteins** involved in wound healing e.g. collagenase, elastase, fibroblast growth factor, angiogenesis factor.

c. **Acute phase reactants** e.g. fibronectin, microglobulin, complement components.

4. Antigen presentation: they act as antigen-presenting cells for T cells (subtype CD4+ or CD8+ cells), or to B cells.

Basophils and Mast Cells

Basophils form (0-1%) of circulating granulocytes while mast cells are their counterparts seen in tissues. Basophils and mast cells have IgE surface receptor; thus if they are in contact with antigen binding to IgE (e.g. allergic reaction to parasites), these cells get activated and release granules (degranulate). These granules contain active substances such as histamine, platelet activating factor, heparin and certain chemical mediators (e.g. prostaglandins,leukotrienes).
Mast cells and basophils are mediating inflammation in allergic reactions.

Neutrophils

Polymorphonuclear neutrophils (PMNs) are the most numerous of the circulating leucocytes (40-75%). The cytoplasm of PMNs contains lysosomal granules that act similar to macrophages, PMNs are first line of defense against an invading foreign organism in the body.

Eosinophils

They are form (1-6%) of circulating granulocytes. They play a role in allergic reactions and in intestinal helminthiasis. The granules of eosinophils contain lysosomal enzymes, peroxidases,

and chemical mediators of inflammation (e.g.prostaglandins, leukotrienes). When IgE opsonised antigen (e.g. helminths), eosinophils degranulate and incite inflammation.

Cytokines are immunomodulators consist of soluble proteins, peptides and glycoproteins secreted by many cells in response to stimuli. They are grouped into 3 main categories:

i) Haematopoietin family: G-CSF, GM-CSF, erythropoietin, thrombopoietin, Various interleukins (IL) such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9.
ii) IL-1, tumour necrosis factor (TNF), platelet-derived growth factor (PDGF), transforming growth factor (TGF) family.
iii) Chemokine family: They regulate movement of cells e.g. IL-8, monocyte chemokine protein (MCP), eotaxin, platelet factor (PF).

ACTION OF CYTOKINES

Cytokines may act as autocrine or paracrine or endocrine ways.
Cytokines are involved in following actions:
1. Regulation of growth
2. Inflammatory mediators
3. Activation of immune system
4. Cytokine storm

HLA SYSTEM AND MAJOR HISTOCOMPATIBILITY COMPLEX

Human Leucocyte Antigen system is gene on chromosome 6 represented as complexes of proteins on the surface of all nucleated cells of the body and platelets. These complexes are important in matching donor and recipient for organ transplant.
Depending upon the characteristics of MHC, they have been divided into 3 classes:

I. Class I MHC antigens: it is identified by CD8+ (T suppressor) lymphocytes.
II. Class II MHC antigens: it is identified by B cells and CD4+ (T helper) cells.

MHC antigens present on the cell surface help the macrophage in its function of recognition of bacterial antigen i.e. they help to identify self from foreign, and accordingly present the foreign antigen to T cells (CD4+ or CD8+) or to B cells.

ROLE OF HLA COMPLEX

1. Organ transplantation: matching donor and recipient for tissue transplantation.
2. Regulation of the immune system cellular and humoral immunity.
3. HLA association with diseases (Autoimmune disorders e.g. rheumatoid arthritis, Sjogren's syndrome, SLE, type 1 diabetes mellitus and myasthenia gravis)

Transplant rejection

According to the genetic relationship between donor and recipient, transplantation of tissues is classified into 4 groups:

1. Autografts are grafts in which the donor and recipient is the same individual.
2. Isografts are grafts between the donor and recipient of the same genotype.
3. Allografts are those in which the donor is of the same species but of a different genotype.
4. Xenografts are those in which the donor is of a different species from that of the recipient.

All types of grafts have been performed in human beings but xenografts have been found to be rejected invariably due to genetic disparity.

Skin grafts, kidney, heart, lungs, liver, pancreas, cornea and bone marrow are transplanted recently. For any successful tissue transplant without immunological rejection, matched major histocompatibility locus antigens (HLA) between the donor and recipient are importance.

The greater the genetic disparity between donor and recipient in HLA system, the stronger and more rapid will be the rejection reaction. Besides the rejection reaction, a serious problem occurring especially in bone marrow transplantation is graft-versus-host (GVH) reaction.

Graft-versus-host (GVH) reaction

In humans, GVH reaction results when immunocompetent cells are transplanted to an immunodeficient recipient. The clinical features of GVH reaction include: fever, weight loss, anaemia, dermatitis, diarrhoea, intestinal malabsorption, pneumonia and hepatosplenomegaly. The intensity of GVH reaction depends upon the extent of genetic disparity between the donor and recipient.

Mechanisms of graft rejection

Rejection of allografts involves both cell-mediated and humoral immunity.

1. Cell-mediated immune reactions

These are mainly responsible for graft rejection and are mediated by T cells. The lymphocytes of the recipient sensitised tissue HLA antigens of the donor are in case of incompatibility. Sensitised T cells in the form of cytotoxic T cells (CD8+) as well as by hypersensitivity reactions initiated by T helper cells (CD4+) attack the graft and destroy it.

2. Humoral immune reactions

Pre-sensitisation of the recipient before transplantation lead to production of circulating antibodies e.g. by blood transfusions and previous pregnancies.

Types of rejection reactions

Based on the underlying mechanism and time period, rejection reactions are classified into 3 types: hyperacute, acute and chronic.

1. Hyperacute rejection

- It appears within minutes to hours of placing the transplant and destroys it.
- It is mediated by preformed humoral antibody against donor-antigen.

Grossly, hyperacute rejection is recognised by the surgeon soon after the vascular anastomosis of the graft is performed to the recipient's vessels. The organ becomes swollen, oedematous, haemorrhagic, purple and cyanotic rather than gaining pink colour.

Histologically, the characteristics of Arthus reaction are present. There are numerous neutrophils around dilated and obstructed capillaries which are blocked by fibrin and platelet thrombi, Necrosis of much of the transplanted organ, hemorrhages are common.

2. Acute rejection

- This usually becomes evident within a few days to a few months of transplantation.
- Acute graft rejection may be mediated by cellular or humoral mechanisms.
- Acute cellular rejection is more common than acute humoral rejection.

Microscopically:

i) Acute cellular rejection is characterized by extensive infiltration in the interstitium of the transplant by lymphocytes (mainly T cells), a few plasma cells, monocytes and polymorphs. There is damage to the blood vessels and there are foci of necrosis in the transplanted tissue.

ii) Acute humoral rejection appears due to poor response to immunosuppressive therapy. It is characterised by acute rejection vasculitis and foci of necrosis in small vessels. The mononuclear cell infiltrate is less marked as compared to acute cellular rejection and consists mostly of B lymphocytes.

3. Chronic rejection

- Chronic rejection may follow repeated attacks of acute rejection or may develop slowly over a period of months to a year or so.
- The underlying mechanisms of chronic rejection may be immunologic or ischaemic. Patients with chronic rejection of renal transplant show progressive deterioration in renal function as seen by rising serum creatinine levels.

Microscopically, changes are fibrosis and atrophy.

Autoimmunity

The body's immune system fails to distinguish between 'self' from 'non-self', characterized by formation of autoantibodies against one's own tissue antigens.
In other words, there is loss of tolerance to own tissues.

Immune tolerance is defined as the ability of an individual to recognize self-tissues and antigens, it is a normal phenomenon present since fetal life and.

Immunological tolerance to different self-antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs as the bone marrow and thymus, a process called central tolerance, or when mature lymphocytes encounter self-antigens in peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance.

The process of eliminate self-reactive lymphocyte before it become functionally competent is called Negative selection which is done by the following mechanisms:

1. Clonal elimination during embryonic development, T cells maturing in the thymus acquires the ability to distinguish self from non-self. Abnormal T cells are eliminated by apoptosis.

2. Concept of clonal anergy T lymphocytes which have acquired the ability to distinguish self from non-self are not eliminated but instead become non-responsive and inactive.

3. Suppressor T cells the tolerance is achieved by a population of specific suppressor T cells which do not allow the antigen-responsive cells to proliferate and differentiate.

Pathogenesis of autoimmunity

- **Release of Sequestered antigen:** Lymphoid cells may not educate self-antigens during their differentiation: testes, brain and eye.
- **Escape of auto-reactive clones:** The negative selection in the thymus may not be fully functional to eliminate self-reactive cells.
- **Lack of regulatory T cells**
- **Cross reactive antigens:** Antigens on certain pathogens may trigger cross react with self-antigens lead to antibodies against tissue antigens, ex: developing of heart damage after a post streptococcal infection nephritis or rheumatic fever.
- **Failure of Activation apoptosis (Induced Cell Death).**
- **Genetic factors**

TYPES AND EXAMPLES OF AUTOIMMUNE DISEASES

Autoimmune diseases are classified into 2 groups:

1. Organ specific (Localised) the diseases when autoantibodies react specifically against an organ or target tissue component and cause its chronic inflammatory destruction. The tissues affected are endocrine glands, alimentary tract, blood cells and various other tissues and organs.

2. Organ non-specific (Systemic) these are diseases in which a number of autoantibodies are react with antigens in many tissues and thus cause systemic lesions. The examples of this group are various systemic collagen diseases.

Systemic Lupus Erythematosus (SLE)

SLE is the classical example of systemic autoimmune (collagen diseases). The disease derives its name 'lupus' from the Latin word meaning 'wolf' since initially this disease was believed to affect skin only and eat away skin like a wolf.

Now 2 forms of lupus erythematosus are described:

1. Systemic or disseminated form is characterised by acute and chronic inflammatory lesions widely scattered in the body and there is presence of various nuclear and cytoplasmic autoantibodies in the plasma.
2. Discoid form is characterised by chronic and localised skin lesions involving the bridge of nose and adjacent cheeks without any systemic manifestations. Rarely, discoid form may develop into disseminated form.

ETIOLOGY The exact etiology of SLE is not known. Genetic and enviromental factors that play role in increase the susceptibility of an individual to develop disease. These factors are certain drugs, certain viral infections (EBV infection); and certain hormones e.g. estrogen.

Morphologic features The manifestations of SLE are widespread in different visceral organs and as erythematous cutaneous eruptions.

Histologically, the characteristic lesion in SLE is fibrinoid necrosis

Clinical features, is more common in women in their 2nd to 3rd decades of life. SLE is a multisystem disease and thus a wide variety of clinical features may be present. The severity of disease varies from mild to intermittent to severe. Usually targeted organs are musculoskeletal system, skin, kidneys, nervous system, lungs, heart and blood vessels, GI system, and haematopoietic system. Fatigue and myalgia are present in most cases throughout the course of disease. Severe form of illness occurs with fever, weight loss, anaemia and organ related manifestations. The disease usually runs a long course of flare-ups and remissions; renal failure is the most frequent cause of death.

Scleroderma (Systemic Sclerosis)

This disease characterized by progressive fibrosis involving the skin, gastrointestinal tract, and other tissues**.** 2 main types are recognized:

1. Diffuse scleroderma: widespread involvement of skin and may progress to visceral structures.
2. CREST syndrome characterised by Calcinosis (C), Raynaud's phenomenon (R), Esophageal hypomotility (E), Sclerodactyly (S) and Telangiectasia (T)

Clinical features Systemic sclerosis is more common in middle-aged women. The clinical manifestations include:
i) claw-like flexion deformity of hands;
ii) Raynaud's phenomenon;
iii) Esophageal fibrosis causing dysphagia and hypomotility;
iv) Malabsorption syndrome;
v) Respiratory distress;
vi) Malignant hypertension;
vii) Pulmonary hypertension
viii) Biliary cirrhosis.

Sjögren's Syndrome

Sjögren's syndrome is characterised by the triad of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and rheumatoid arthritis. The combination of the dry eyes and mouth is called sicca syndrome.

Morphologic features: In early stage, the lacrimal and salivary glands show periductal infiltration by lymphocytes and plasma cells, this at times may form lymphoid follicles (pseudolymphoma). In late stage, glandular parenchyma is replaced by fat and fibrous tissue. The ducts are also fibrosed and hyalinised.

Clinical features The disease is common in women in 4th to 6th decades of life. It is clinically characterised by the following:
i) Symptoms related to dryness of eyes (blurred vision, burning and itching).
ii) Symptoms related to xerostomia (fissured oral mucosa, dryness, difficulty in swallowing).
iii) Symptoms related to systemic involvement referable to lungs, CNS and skin.

LEC 8 GENERAL PATHOLOGY DR. AFRAH ADNAN

INFECTIOUS DISEASES

Microorganisms are present everywhere in the soil, water, atmosphere and on the body surfaces, and are responsible for a large number of infectious diseases in human beings.

Infectious disease caused by wide agents ranging from very small size prion protein (under 20 nm) to 10m tapeworms.

Vaccines have been successful in controlling or eliminating some diseases (ex; smallpox and measles), similarly, insecticides have helped in controlling malaria. However, infections still rank very high as a cause of death in the world because:

i) Development of newer antibiotic-resistant strains of microorganisms.

ii) Administration of immunosuppressive therapy to patients with malignant tumors and transplanted organs making them susceptible to opportunistic infections.

iii) Developing hospital-acquired infections.

iv) Acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV).

Dental students need a basic understanding of general concept of infectious diseases and a detailed knowledge of clinical oral microbiology in order to diagnose oral microbial infections, which are intimately related to the overall treatment plan for their patients.

CHAIN IN TRANSMISSION OF INFECTIOUS DISEASES

i) Reservoir of pathogen: It may be a human being (e.g. in influenza virus), animal (e.g. dog for rabies), insect (e.g. mosquito for malaria), or soil (e.g. enterobiasis).

ii) Route of infection: Infection is transmitted from the reservoir to the human being by different routes, usually from breach in the mucosa or the skin.

iii) Mode of transmission: The organism may be transmitted directly by physical contact or indirectly by fomites (e.g. insect bite).

iv) Susceptible host: The organism would colonies the host if the host has good immunity but such a host can pass on infection to others. However, if the host is old, debilitated, malnourished, or immunosuppressed, he is susceptible to have manifestations of infection.

FACTORS RELATING TO INFECTIOUS AGENTS

1. Mode of entry: ex. ingestion; inhalation; perinatally (vertical transmission); by direct contact; by contaminated water, food, soil, environment or from an animal host (zoonotic infections).

2. Spread of infection further through the phagocytic cells, blood vessels and lymphatic.

3. Virulence of organisms Many species and strains of organisms may have varying virulence e.g. the three strains of C. diphtheriae (gravis, intermedius and mitis) produce the same diphtherial exotoxin but in different amounts.

4. Production of toxins Bacteria liberates endotoxins on lysis of the bacterial cell while exotoxins are secreted by bacteria and have effects at distant sites too.

5. Product of organisms Some organisms produce enzymes that help in spread of infections e.g. streptokinase by streptococci, staphylokinase and coagulase by staphylococci.

✓ **Virulence is the ability of pathogen to cause damage to a host (degree of toxicity).**

FACTORS RELATING TO HOST

1. Physical barrier a break in the continuity of the skin or mucous membranes allows the microorganisms to enter the body.
2. Chemical barrier mucus secretions of the oral cavity and the alimentary tract and gastric acidity prevent bacterial colonization.
3. Effective drainage natural passages of the hollow organs like respiratory, gastrointestinal and urinary systems provide a way to drain the excretions effectively. Obstruction in any of these passages promotes infection.
4. Immune defense mechanisms these include polymorphs and monocytes in blood and other phagocyte cells in tissues.

METHODS OF IDENTIFICATION

1. Gram stain (bacteria)
2. Acid fast stain (Mycobacteria)
3. Giemsa stain (Malaria, Leishmania)
4. Periodic acid-Schiff (Amoebae, Most fungi)
5. Silver stain (Most fungi)
6. Culture (bacteria)
7. In situ hybridization (virus)
8. DNA analysis (virus)
9. Polymerase chain reaction (PCR) (virus)

Spread and Dissemination of Microbes within the Body

• Direct invasion by secrete lytic enzymes to destroy tissue.
• Transported in blood or lymph.
• Spread locally from cell to cell by replication or transport within nerves.

MECHANISMS OF BACTERIAL INJURY

- Bacterial Virulence: it is the ability of bacteria to adhere and invade host`s cells and deliver toxins to become harmful pathogenic bacteria.
- Plasmids and bacteriophages viruses are genetic agents that spread between bacteria converted nonpathogenic bacteria into virulent ones and converted an antibiotic susceptible bacterium into a resistant one, making effective therapy difficult.

- Various bacteria can act together in coordination that alters their virulence. Communities of bacteria can form biofilms which is a viscous layer of extracellular polysaccharides and various microorganisms that adhere to host tissues or devices making bacteria inaccessible to immune mechanisms and antimicrobial drugs.

BACTERIAL TOXINS

Bacterial endotoxin: is a lipopolysaccharide (LPS) that is a component of the outer membrane of gram-negative bacteria. It plays role in development of septic shock.

Bacterial exotoxins: are secreted proteins that cause cellular damage. They can be classified by their mechanism and site of action ex: proteases, hyaluronidases, coagulases, neurotoxins (produced by Clostridium tetani), and enterotoxins (affect GIT causing nausea, vomiting and diarrhea in cholerae).

DISEASES CAUSED BY BACTERIA

PLAGUE

Plague has been a great killer since 14th century (black death).

Causative agent: Yersinia pestis (Gram-negative coccobacillus) produce pesticin exotoxin and lipopolysaccharide endotoxin.

Pathogenesis: Plague is spread by rodents that enter human body by inhalation than get in the bloodstream and replicate, within 24-48 hours of infection they produce lymphadenopathy, chills, fever, myalgia, nausea and vomiting, if untreated, death occurs from disseminated intravascular coagulation (DIC) within 1 to 2 days with development of widespread petechiae and ecchymoses leading to gangrene, and hence the name black death or death results from toxaemia lead to multi-organ failure.

Treatment: Antibiotic therapy.

ANTHRAX

Anthrax is a bacterial disease that spreads from animals (cattle and Sheep) to human.

Causative agent: Bacillus anthracis (gram-positive, aerobic bacillus) that forming spores. The disease occurs by contact with soil or animal products contaminated with spores.

The characteristic lesions of anthrax are haemorrhage, oedema and necrosis at the portal of entry. The disease classify into cutaneous anthrax (is the most common), pulmonary anthrax (wool-sorters' disease) occurring from inhalation of spores and intestinal anthrax is rare in human beings and is quite similar to that seen in cattle.

STAPHYLOCOCCAL INFECTIONS

Staphylococci are gram-positive cocci which are present in the skin and mucous membrane. Most staphylococcal infections are caused by Staph. aureus. Staphylococcal infections are among the commonest antibiotic-resistant hospital-acquired infection in surgical wounds.

A wide variety of suppurative diseases are caused by Staph. aureus includes the following:

- Folliculitis: infection of hair follicle with obstruction of sweat or sebaceous gland duct.
- Cellulitis: spread of infection horizontally under the skin and subcutaneous tissue.
- Impetigo: common in school children in which there are multiple pustular lesions on face forming honey-yellow crusts.
- Osteomyelitis: staph. Infection spread in bone marrow.
- Bacterial endocarditis.
- Infections of respiratory tract: commonly occur in patient under 2 years of age including: pharyngitis, bronchopneumonia, and staphylococcal pneumonia.
- Bacterial meningitis: infection of CNS.
- Septicaemia: it occurs in patients with lowered resistance or impaired immunity.

STREPTOCOCCAL INFECTIONS

Streptococci are also gram-positive, streptococci have been identified in different diseases:

- β-haemolytic streptococci: are causing upper respiratory tract infection, cutaneous infections (erysipelas) and rheumatic heart disease (RHD) and septicaemia .
- Enterococci are causing of urinary tract infection.
- α-haemolytic streptococci such as Streptococcus viridans constitute the normal flora of the mouth and may cause bacterial endocarditis.

TETANUS

Tetanus or ‘lock jaw’ is a severe acute neurologic syndrome caused by tetanus toxin, tetanospasmin which is a neurotoxic exotoxin elaborated by Clostridia. tetani. The spores of the microorganism present in the soil enter the body through a wound. Neurotoxin causes neuronal stimulation and spasm of muscles. The incubation period of the disease is 1-3 weeks. The earliest manifestation is lock-jaw or trismus, rigidity of muscles of the back and death occurs due to spasm of respiratory and laryngeal muscles.

DIPHTHERIA

It is a life-threatening infection produced by Corynebacterium diphtheriae. Humans are the reservoir and the infection is acquired through contact with an infected person or carrier. The bacterium produces a lethal exotoxin that causes tissue necrosis, thereby providing nutrients for further growth and leading to peripheral spread.

The initial systemic symptoms appear after 1-5 days, which include low-grade fever, headache, malaise, anorexia, sore throat and vomiting, mucoid or hemorrhagic discharge affects mucosal surfaces and may produce exudates of the nasal, tonsillar, pharyngeal, laryngotracheal, conjunctival, or genital areas. The severity of the infection correlates with the spread of the membrane.

SYPHILIS (LUES DISEASE)

Syphilis is a worldwide chronic infection produced by Treponema pallidum. the primary modes of transmission are sexual contact or from mother to fetus. The infection evolution classically through three stages. A syphilitic patient is highly infectious and pregnant women may transmit the infection to the fetus, the clinical changes secondary to the fetal infection are known as congenital syphilis (Hutchinson's triad: ● Hutchinson's teeth ● Ocular interstitial keratitis ● Eighth nerve deafness)

Primary syphilis is characterized by chancre ulcer that develops at the site of inoculation 3- 90 days after the initial exposure. Secondary (disseminated) syphilis and is discovered clinically 4 to 10 weeks after the initial infection. The lesions of secondary syphilis may arise before the primary lesion has resolved, painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever, and musculoskeletal pain. A consistent sign is a diffuse, painless, maculopapular cutaneous rash, patients enter a period in which they are free of lesions and symptoms, known as latent syphilis. This period of latency may last from 1 to 30 years; tertiary syphilis develops includes the most serious of all complications (CNS, ocular and heart complications) also characterized by granulomatous inflammation, known as a gumma.

TUBERCULOSIS (TB)

It is a chronic infectious disease caused by Mycobacterium tuberculosis. Tuberculosis generally affects the lung, but can also affect other parts of the body. Infections are the result of direct person-to-person spread through airborne droplets from a patient with active disease. There are two forms of the disease:

- **Latent TB.** The Mycobacterium germs in body but the immune system keeps them from spreading. The patient doesn't have any symptoms, and he is not contagious. But the infection is still alive and can one day become active.
- **Active TB.** The Mycobacterium germs multiply and make the patient sick. Very contagious disease.

Oral lesions of TB are uncommon, with most cases appearing as a chronic painless ulcer.

DISEASES CAUSED BY FUNGI

Many of the human fungal infections are opportunistic i.e. they occur in conditions with impaired host immune mechanisms. Such conditions include defective neutrophil function, administration of corticosteroids, immunosuppressive therapy and immunodeficiency states (congenital and acquired).

CANDIDIASIS

It is an opportunistic fungal infection caused most commonly by Candida albicans, Candida species are present as normal flora of the skin and mucocutaneous areas, intestines and vagina. The organism becomes pathogenic when the balance between the host and the organism is disturbed. Various predisposing factors are: impaired immunity, prolonged use of oral contraceptives, long-term antibiotic therapy, corticosteroid therapy, diabetes mellitus, obesity, pregnancy etc.

Cutaneous candidiasis and Oral thrush is the commonest forms of candida lesions consist of creamy white pseudo membrane composed of fungi covering the tongue, soft palate, and buccal mucosa. In severe cases, ulceration may be seen.

Systemic candidiasis: Invasive candidiasis is rare and is usually associated with impaired immune system.

Deep fungal infections

Histoplasmosis: causative agent is Histoplasma capsulatum.

Mucormycosis (Zygomycosis): Zygomycetes organisms are the causative agents may cause symptoms related to cranial nerve involvement (e.g., facial paralysis, blindness, lethargy, and seizures may develop, followed by death.). .

Aspergillosis: Aspergillus organisms are the causative agents. The patient may acquire such infections in the hospital ("nosocomial" infection), especially if remodeling or building construction is being performed in the immediate area.

Toxoplasmosis: causative agent is Toxoplasma gondii, cats are considered to be the definitive host. The organism cause Congenital toxoplasmosis.

All these organisms are found throughout the world, growing in their natural state on a variety of decaying organic materials, soil or water and transmitted by spore. Usually the infection appear in immunosuppressed individuals and in uncontrolled diabetics, clinically presented as large, irregular, necrotizing ulcers may resemble squamous cell carcinoma, the lesion persist until treatment of systemic disease.

Diagnosis: biopsy specimen (scattered epithelioid macrophages admixed with lymphocytes and plasma cells. Some macrophages contain organisms), culture and serologic.

Treatment: Surgical debridement, Amphotericin B or anti-fungal infection (Ketoconazole, fluconazole)

DISEASES CAUSED BY VIRUSES

Viruses are intracellular parasites that depend on the host cell's metabolic machinery for their replication. They consist of a nucleic acid genome surrounded by a protein coat (called a capsid), they are classified by their nucleic acid genome (DNA or RNA but not both). Some viral components and particles aggregate within infected cells and form characteristic inclusion bodies, which may be seen with the light microscope and are useful for diagnosis ex; cytomegalovirus (CMV) and herpesviruses.

Many viruses cause transient illnesses (e.g., colds, influenza). Other viruses are not eliminated from the body and persist within cells of the host for years, either continuing to multiply (e.g., chronic infection with hepatitis B virus) or surviving in latent form with potential to be reactivated later. Viral tropism means that viruses bind to specific cell surface proteins

(receptors) for ex: HIV binds to CD4 on T cells, chemicals and temperature affect tissue tropism (ex: Rhinoviruses infect cells only within the upper respiratory tract because they replicate optimally at the lower temperatures characteristic of this site).

Viruses can enter, replicated and directly damage host cells by direct cytopathic effects; or indirectly by stimulation cytotoxic T lymphocytes which are important for defense against viral infections but also can be responsible for tissue injury. Oncogenic viruses can stimulate cell transformation, growth and survival of infected cells into benign or malignant tumor cells.

How can the virus escape from immune system?

1. Amino acid replacements (mutation) leading to changes of virus epitopes result in structural changes in antibody/virus contact sites.
2. Several viruses bypass clearance processes by the Fc portion of antibodies by encoding and expressing Fc receptor analogs.
3. Blocking MHC class II antigen presentation and synthesis of viral MHC class I homologs.
4. Down regulation of cellular CD4 or its degradation.
5. Interference with cytokine effector functions

Steps in Viral Pathogenesis

1. Viral entry into the host
2. Primary viral replication
3. Viral spread
4. Cellular injury
5. Host immune response
6. Viral clearance or establishment of persistent infection
7. Viral shedding.

HUMAN HERPESVIRUSES

A large family of double-stranded DNA viruses; herpes simplex virus (HSV type 1 and HSV type 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus. Humans are the only natural reservoir for these viruses which are endemic worldwide. All types cause a primary infection and remain latent within specific cell types for the life of the individual. On reactivation, these viruses cause recurrent infections that may be symptomatic or asymptomatic.

HSV-1 is spread predominantly through infected saliva or active perioral lesions and adapted best to the oral (Acute herpetic gingivostomatitis), facial, and ocular areas. The pharynx, intraoral mucosa, lips, eyes, and skin above the waist are involved most frequently.

HSV-2 is infected the genital zones, is transmitted predominantly through sexual contact, and typically involves the genitalia and skin below the waist.

The primary infection is established after incubation period 3-9 days, the virus is taken up by sensory nerves and transported to the associated sensory ganglia where the virus remains in a latent state. Recurrent (secondary) infection occurs with reactivation of the virus. Old age, ultraviolet light, physical or emotional stress, fatigue, heat, cold, pregnancy, allergy, trauma, dental treatment, respiratory illnesses, fever, menstruation, systemic diseases, and malignancy have been associated with reactivation.

Herpes labialis ("cold sore" or "fever blister") is the most common site of recurrence for HSV-1 in the vermilion border and adjacent skin of the lips, prodromal signs and symptoms arise 6-24 hours before the lesions develop (e.g., pain, burning, itching, tingling, localized warmth, and erythema of the involved epithelium), multiple small vesicles develop that rupture and crust within 2 days. Healing usually occurs within 7 to 10 days.

Herpetic whitlow is a primary or recurrent HSV infection of the fingers, Recurrent digital infection may result in paresthesia and permanent scarring.

Varicella (chickenpox) represents primary infection with the varicella-zoster virus, after latency recurrence is possible as herpes zoster. The incubation period about 15 days, the symptoms appear (malaise, pharyngitis, headache, myalgia, nausea, anorexia and vomiting) then A maculopapular, cutaneous rash begins on the face and trunk and spreads to the extremities and rapidly progresses into vesicles that rapture and crust (the vesicular stage is the classic presentation). Reactivation of the virus with the distribution of the affected sensory nerve that the virus remains latent in nerve ganglia is herpes zoster that appear as numerous crusting vesicles in the skin with neuronal necrosis and severe neuralgia travel along the nerve. Ocular involvement if present cause permanent blindness.

The Epstein–Barr virus, is one of herpes family that cause infectious mononucleosis "glandular fever". It is also associated Burkitt lymphoma, Hodgkin's lymphoma; gastric cancer, nasopharyngeal carcinoma, hairy leukoplakia and central nervous system lymphomas.

Cytomegalovirus (CMV) is a common virus. Once infected, your body retains the virus for life. Most people don't know they have CMV because it rarely causes problems in healthy people. Women who develop an active CMV infection during pregnancy can pass the virus to their babies (congenital CMV; hearing loss, developmental delay and vision problems.), people who have weakened immune systems (organ, stem cell or bone marrow transplant), CMV infection can be fatal. CMV spreads from person to person through body fluids, such as blood, saliva, urine, semen and breast milk (perinatal CMV). There is no cure, but there are medications that can help treat the symptoms.

INFLUENZA VIRUS INFECTION

It is an important and common form of viral disease, its general clinical features range from a mild illness fever, headache, myalgia, malaise, chills and respiratory tract manifestations such as cough, sore throat to a more severe form of acute respiratory illness and lymphadenopathy. Three types of influenza viruses affect humans: Type A, Type B, and Type C, the virus is spread through the air from coughs or sneezes and by touching surfaces contaminated by the virus and then touching the eyes, nose, or mouth. Various forms of influenza virus infections have occurred as an outbreak at different times, sometimes with alarming morbidity and mortality in the world {Spanish influenza in 1918 (17–100 million deaths), Asian influenza in 1957 (1–4 million deaths), Hong Kong influenza in 1968 (1–4 million deaths) and Russian flu in 1977 (700,000 deaths)}. Seasonal flu vaccine is administered to population at high risk in developed countries.

What are the difference between flu and common cold?

	Influenza (flu)	**Common cold**
Virus type	the human parainfluenza viruses, which are RNA	virus is a rhinovirus belong to

	viruses belonging to the paramyxovirus family	picornavirus family
Transmission	transmitted via airborne droplets (aerosols), direct contact with infected nasal secretions, or contaminated objects.	
Symptoms	the symptoms of influenza are more severe and last longer than cold.	the symptoms of cold are less severe and shorter than flu.
Symptoms	fever and chills, Cough, Nasal congestion, Runny nose, Sore throat, Hoarseness, Muscle pains, Fatigue, Headache, Irritated, watering eyes, Reddened eyes, skin (especially face), mouth, throat and nose, Petechial rash, In children, gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain (may be severe in children with influenza B)	typical symptoms of a cold include cough, runny nose, sneezing, nasal congestion, and a sore throat, sometimes accompanied by muscle ache, fatigue, headache, and loss of appetite.
Section .01 Treatment for colds and flu	Antibiotics don't work against a cold or flu, Stay home, get rest and sleep, drinking plenty of fluids (particularly water) and eating soft foods that are easy to swallow.Medication is available to help relieve headaches, muscles aches and fever and see your doctor if you have a cough and high fever (38°C or more) that is not improving, trouble breathing, chest pain, or if you have any other concerns about your symptoms.	

Avian influenza, or **bird flu**, is influenza caused by viruses adapted to birds, caused by strains of influenza viruses type A virus which is a zoonotic infection with a natural reservoir in birds. Although it is possible for humans to contract the avian influenza virus from birds, human-to-human contact is much more difficult without prolonged contact. However, public health officials are concerned that strains of avian flu may mutate to become easily transmissible between humans. The potential complications of bird flu include: pneumonia; sepsis and organ failure.

Pneumonia resulting from bird flu is aggressive and leads to the development of the so-called acute respiratory distress syndrome. Nearly 60% of the patients with bird flu develop complications.

SECTION .02 DIFFERENCE BETWEEN BIRD FLU AND SWINE FLU

- Bird flu (H5N1) is a type A influenza, an infection affects wild birds. Swine flu (H1N1) is a type A influenza, affecting pigs, or a form of human flu, caused by a related virus.
- Bird Flu People can be infected with the virus by direct contact with infected birds, Swine Flu: The virus spreads from person to person. The infection is transmitted via droplets, coughing or sneezing, it is inhaled or transmitted by hands

- Bird Flu: Nearly 60% of the patients with bird flu develop severe complications and die.Swine Flu: It is considered that the swine flu is no more dangerous than a common influenza virus.

CORONAVIRUSES

Coronaviruses belong to the family Coronaviridae that have characteristic club-shaped spikes that project from their surface, create an image of the solar corona, from which their name derives. They are a group of related RNA virus that causes diseases in mammals and birds; they cause respiratory tract infections that can range from mild to lethal. Mild illnesses in humans include some cases of the common cold (which is also caused predominantly by rhinoviruses), while more lethal varieties can cause SARS, MERS, and COVID-19. In cows and pigs they cause diarrhea, while in mice they cause hepatitis and encephalomyelitis.

SARS: sever acute respiratory syndrome, it produces flu-like symptoms with fever above 38 °C, shortness of breath and pneumonia; either direct viral pneumonia or secondary bacterial pneumonia.

MERS: Middle East Respiratory Syndrome, it is a species of coronavirus which infects humans, bats, and camels. The most common symptoms of MERS are a fever, a cough, and shortness of breath. People may also have gastrointestinal problems, such as diarrhea, nausea, or vomiting. People with severe symptoms may need to spend a long time in the hospital, receiving mechanical ventilation and intensive care.

COVID-19: is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 , Symptoms of COVID-19 are variable, but often include fever, cough, fatigue, breathing difficulties, and loss of smell and taste. Symptoms begin one to fourteen days after exposure to the virus. The virus that causes COVID-19 spreads mainly when an infected person is in close contact with another person. Small droplets and aerosols containing the virus can spread from an infected person's nose and mouth as they breathe, cough, sneeze, sing, or speak. Because some of the symptoms of flu and COVID-19 are similar, it may be hard to tell the difference between them based on symptoms alone, and testing may be needed to help confirm a diagnosis. While more is learned every day about COVID-19 and the virus that causes it, there is still a lot that is unknown.

Ebola

Ebola hemorrhagic fever (EHF); Ebola virus is the causative agent that spreads through direct contact through the air with body fluids, such as blood from infected humans or other animals (Fruit bats are believed to be the normal carrier in nature). Signs and symptoms typically start between 2-21 days after exposures to the virus with a fever, sore throat, muscular pain, headaches, vomiting, diarrhoea , rash with decreased function of the liver and kidneys. At this time, some people begin to bleed both internally and externally. The disease has a high risk of death, killing 50% of those infected due to low blood pressure from fluid loss. Blood samples are tested for viral RNA, viral antibodies or for the virus itself to confirm the diagnosis.

Measles

it is a highly contagious infectious disease caused by measles virus. Symptoms usually develop 10–12 days after exposure to an infected person and last 7–10 days. Initial symptoms typically include fever, often greater than 40 °C, cough, runny nose, and inflamed eyes. Small white spots known as Koplik's spots may form inside the mouth two or three days after the start of symptoms. A red, flat rash which usually starts on the face and then spreads to the rest of the body typically begins three to five days after the start of symptoms. Common complications include diarrhea, middle ear infection, pneumonia, seizures, blindness and inflammation of the brain. Other names include *morbilli*, *rubeola*, *red measles*, and *English measles*.

MUMPS

Mumps is an infection caused by a virus in the family Paramyxoviridae. This infection causes diffuse swelling of the exocrine glands mainly parotid salivary glands, the pancreas, and mature ovaries and testes also are affected frequently. The virus can be transmitted through respiratory droplets, saliva, and urine. The incubation period is about 2-4 weeks. Patients are contagious from 1 day before the clinical appearance of infection to 14 days after its clinical resolution. Mumps most commonly occurs in winter and spring. The lesion appear as enlargement can range from a minimal swelling to a fourfold increase in size. Unilateral involvement is most

common. Complication are testicular atrophy, permanent sterility, meningoencephalitis, cerebellar ataxia, hearing loss, pancreatitis, arthritis and carditis.

HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

HIV is a single-stranded RNA virus belonging to the family Retroviridae. There are two species: HIV-1 (exhibits a worldwide distribution and is responsible for the majority of cases) and HIV-2 (predominates in western Africa and is associated with a somewhat lower risk of transmission and slower disease progression).

The primary target cell of HIV is the CD4+ helper T lymphocyte, although other CD4+ cells (such as, macrophages and dendritic cells) may be infected as well. The virus may become incorporated into the host cell DNA. In people with HIV infection, antibodies against the virus are developed but are not protective. The virus may remain silent, cause cell death or disrupts their normal function. A subsequent decrease in T-helper cell numbers occurs, with a resultant loss of immune function. The normal response to viruses, fungi, and encapsulated bacteria is diminished. In addition, infection of macrophages and microglia in the CNS may lead to neurologic disease manifestations.

The histological features of the host- microbe interaction

Suppurative (Purulent) Inflammation: it is acute tissue damage characterized by increased vascular permeability and leukocytic infiltration. The neutrophils are attracted to the site of infection by release of chemoattractants from the “pyogenic” bacteria and host cells. Neutrophil enzymes cause liquefactive necrosis .

Mononuclear and Granulomatous Inflammation: it is chronic inflammatory damage characterized by diffuse mononuclear, interstitial infiltrates, developed as a response to viruses, intracellular bacteria, or intracellular parasites.

Cytopathic-Cytoproliferative Reaction: it is produced by viruses characterized by cell necrosis or cellular proliferation with inflammatory cells.

Tissue Necrosis: some organisms that secrete powerful toxins can cause rapid and severe necrosis (gangrenous necrosis) that tissue damage is the dominant feature.

Chronic Inflammation and Scarring: Many infections elicit chronic inflammation, which can either resolve with complete healing or lead to extensive scarring.

Prion

Prions are transmissible agents similar to infectious protein particles but lack nucleic acid. These agents are implicated in the etiology of spongiform encephalopathy (or mad cow disease) and Creutzfeldt-Jakob disease.

Lec 3 **General Pathology** **Dr. Afrah Adnan**

Intracellular accumulations & Aging

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 secondary to defects in mechanisms of packaging and transport, as in fatty change in the liver.
2. Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion.
3. Failure to degrade a metabolite due to inherited enzyme deficiencies.
4. Deposition and accumulation of an abnormal exogenous substance when the cells can`t degrade or transport the substance to other sites.

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 toxins, protein malnutrition, diabetes mellitus, obesity, or anoxia. Alcohol abuse and diabetes associated with obesity are the most common causes of fatty change in the liver. 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 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; they may occur when excesses are presented to the cells or if the cells synthesize excessive amounts.

Ex: In nephrotic syndrome there is heavy protein reabsorption and accumulated in vesicles containing this protein in glomerulus giving the histologic appearance of pink, hyaline cytoplasmic droplets.

Ex: Accumulation of newly synthesized immunoglobulins that forming rounded eosinophilic Russell bodies.

Glycogen

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 synthesized within the body itself, such as lipofuscin, melanin, and certain derivatives of hemoglobin.

- **Carbon** (an example is coal dust), is exogenous pigment that inhaled and phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional lymph nodes and aggregates as a black pigments.
- **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.
- **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 radicals interactions with lipid and protein. It is not injurious to the cell but is a marker of past free radical injury.
- **Melanin** is an endogenous, brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation. Various disorders associated with hyperpigmentation of melanin such as Addison's disease , Peutz-Jeghers syndrome and Cäfe-au-lait spots are pigmented patches seen in neurofibromatosis and Albright's syndrome.
- **Hemosiderin** is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or systemic excess of iron such as haemorrhage into tissues due to trauma or chronic haemolytic anaemias.

Pathologic calcification

It is an abnormal deposition of calcium salts. When the deposition occurs in dead tissues, it is called dystrophic calcification. In contrast, the deposition of calcium salts in normal tissues is known as metastatic calcification and is almost always secondary to some derangement in calcium metabolism (hypercalcemia).

Dystrophic calcification is occurs in areas of necrosis of any type. It is formed in advanced atherosclerosis, associated with intimal injury in the aorta and large arteries and characterized by accumulation of lipids. Dystrophic calcification indicate past cell injury resulting in 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.

Metastatic calcification can occur in normal tissues whenever there is hypercalcemia. The major causes of hypercalcemia are:

(1) Increased secretion of parathyroid hormone.
(2) Destruction of bone due to the effects diseases such as Paget disease, multiple myeloma, and leukemia.
(3) Vitamin D related disorders
(4) Renal failure

Cellular Aging

Individuals age because their cells age. Although public attention on the aging process has traditionally focused on its cosmetic manifestations, aging has important health consequences, because age is considered strongest risk factors for cancer, Alzheimer disease, ischemic heart disease and other diseases.

There has been great interest in defining signaling pathways that affect the aging process as a therapeutic potential and as an “elixir of youth”. It is now thought that certain environmental stresses, such as calorie restriction, alter signaling pathways that influence aging.

Cellular aging is the result of a progressive decline in the life span and functional capacity of cells. With ageing, the mechanism of homeostasis is slow; hence the response to various stresses takes longer to revert back to normal structure and function.

There is higher life expectancy in women because men are exposed to many causes like cigarette smoking and alcohol consumption that increase their susceptibility to cardiovascular disease, cancer, cirrhosis and respiratory diseases. In general, the life expectancy of an individual depends upon the following factors:

- Intrinsic genetic process
- Environmental factors
- Lifestyle of the individual

- Age-related diseases

THEORIES OF AGEING

1. Reduced functional capacity to proliferate with age. With every cell division there is progressive shortening of telomere present at the tips of chromosomes, which in normal cell is repaired by the presence of RNA enzyme (telomerase). However, due to ageing there is inadequate presence of telomerase enzyme; therefore lost telomere is not repaired resulting in interference in viability of cell.
2. Genetic control Clock (clk) genes responsible for controlling the rate and time of ageing.
3. Diseases that accelerated ageing.
4. Oxidative stress hypothesis (free radical-mediated injury).The rate of generation of reactive oxygen species is directly correlated with metabolic rate of the organisms. With ageing, there is low metabolic rate with generation of toxic oxygen radicals, which fail to get eliminated causing their accumulation and hence cell damage due to mitochondrial injury. The role of antioxidants in retarding the oxidant damage has been reported in some studies.
5. Hormonal secretion decline of some hormones resulting in their functional decline.
6. Impaired immune function and hence reduced ability to respond to microbes and environmental agents.
7. Failure to renewal of lost cells and accumulation of senescent cells.

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.
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5. Hearing: Disability in hearing due to otosclerosis.
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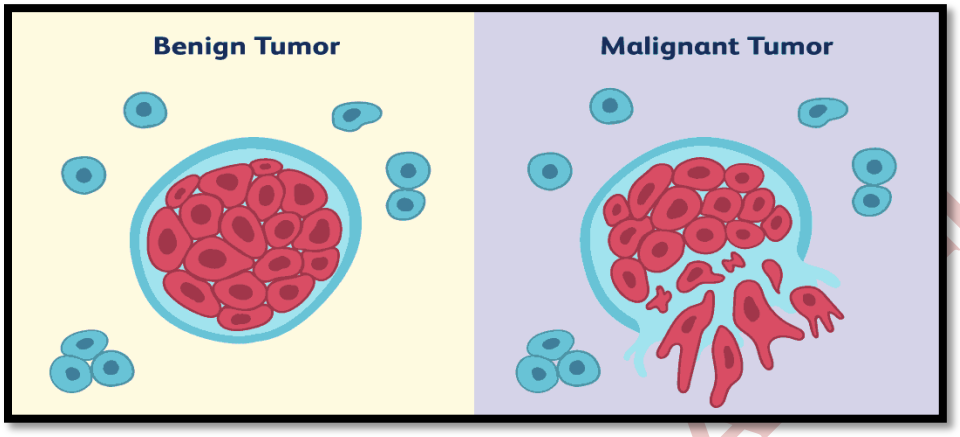
NEOPLASIA

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.

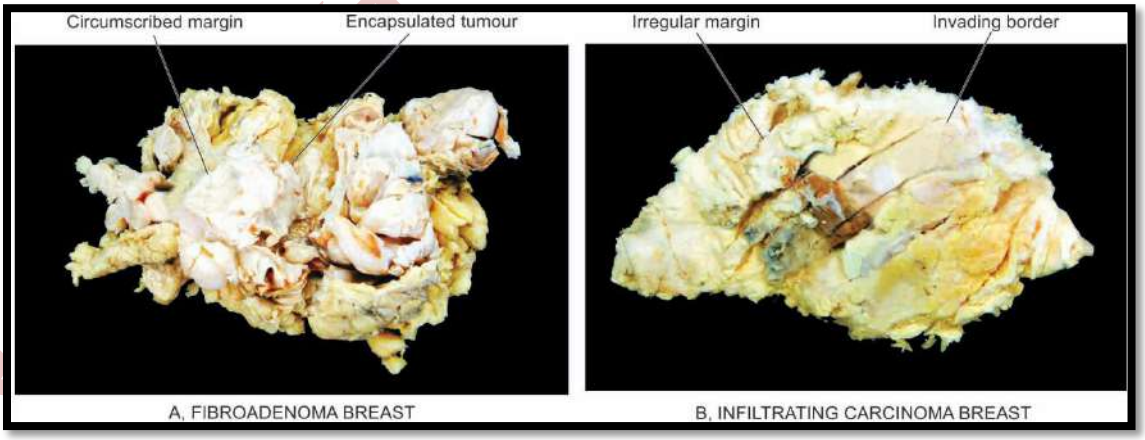
Due to loss of growth controls, cancer cells are genetically unstable and develop newer mutations (polyclonality).

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.

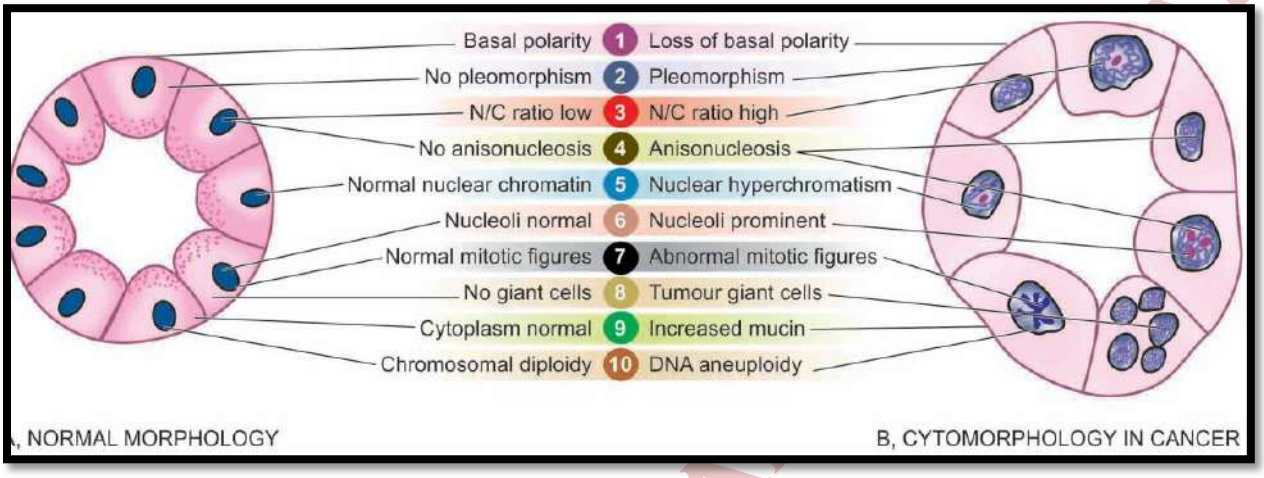
vi) Nucleolar changes: increased nucleoprotein synthesis result in prominent nucleoli.

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

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