PATHOLOGY

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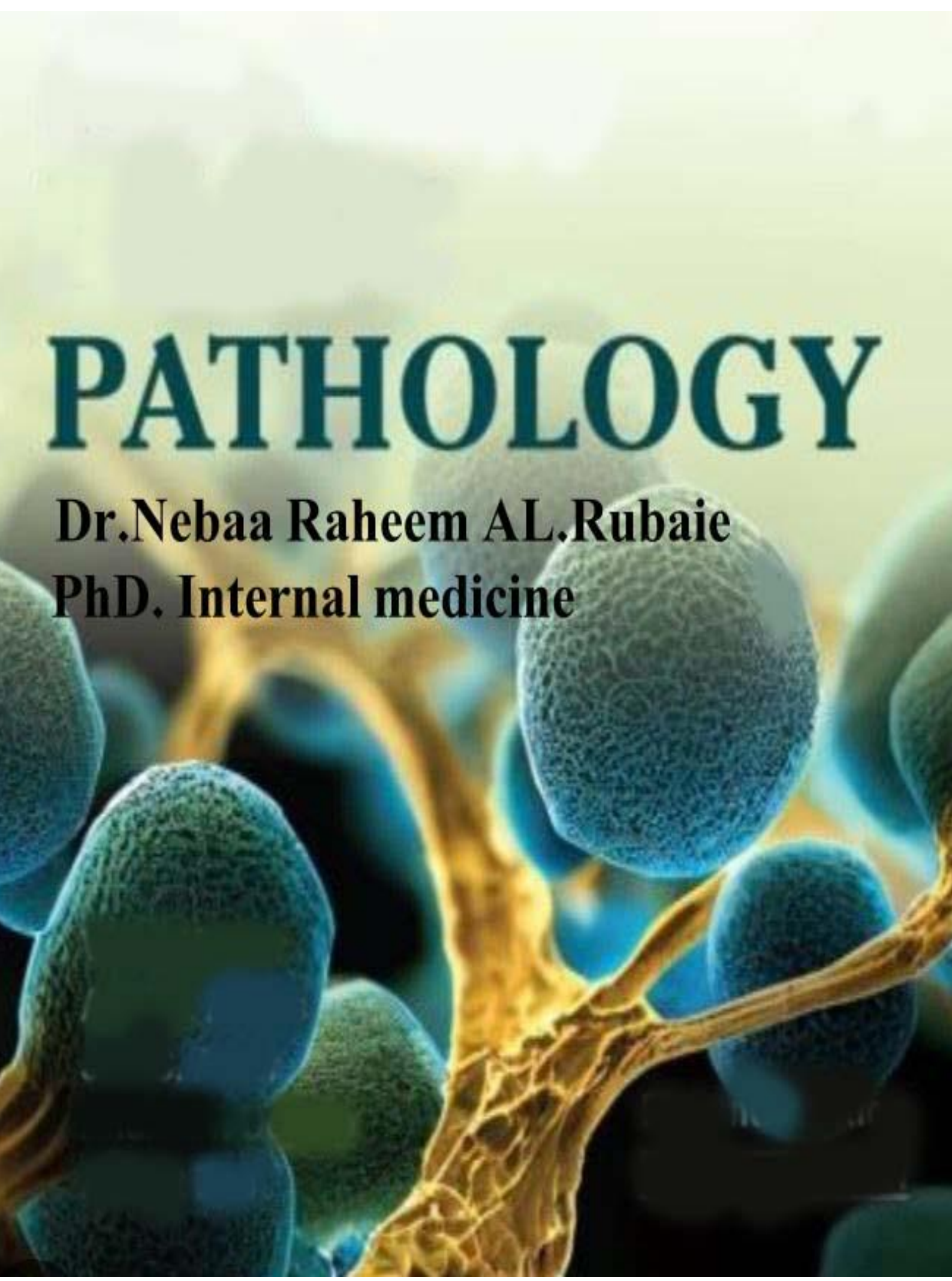

Introduction to pathology

Pathology:

Derived from Greek words 'pathos' meaning suffering or disease and logos' meaning study

Definition:

The study of the structural and functional changes in cells, tissues and organs that underlie the disease.

Pathology is the scientific study of structure and function of body in disease.

Pathology divided in to :

1. General pathology:

It deals with the basic reaction of cells and tissues to abnormal stimuli that underlie the disease.

2. Systemic(special) pathology:

It deals with the specific responses of specialized organs and tissues to more or less well defined stimuli.

There are 4 aspects of a disease process that form the core of pathology They are:

1. Its cause **(Etiology).**
2. Mechanisms of its developments (**Pathogenesis**).
3. Structural alterations induced in the cells and organs of the body (**morphologic changes**).
4. **Functional consequences of the morphologic** changes that are observed clinically.

- **Etiology** : is the origin of a disease, including the underlying causes and modifying factors.

They are divided into 2 classes:

1. **Intrinsic or genetic :** example cancer
   genetically determined disease is due to some abnormalities in the DNA of the fertilized ovum that is inherited from one or both parents
   a. Acquired disease : is due to effect of some environmental factors like:
   1. Deficiency disease e.g., iron deficiency anemia
   2. Physical agents e.g., trauma, heat, cold, electricity, irradiation….etc.
   3. Chemical factors e.g., poison, toxins…..etc.
   4. Infective organisms e.g., bacteria, virus, fungi ….etc.
   5. Immunological factors e.g. hypersensitivity.
   6. Psychogenic factors e.g., depression, psychosomatic disorders like essential hypertension.
   7. Endocrine factors e.g., diabetes.

Pathogenesis :

It refers to the sequence of events in the response of cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease.

- **Morphologic changes :**

  It refers to the structural alterations in cells or tissues that are either characteristic of the disease or diagnostic of the etiologic process .

- **Functional derangements and clinical manifestations:**

  The nature of the morphologic changes and the distribution in different organs or tissues influence normal function and determine the clinical features (symptoms and signs), course and prognosis of the disease.

Common Terminologies :

- **Disease:** is any illness or abnormal state of health either of the whole body or specific parts of organs having characteristic symptoms. It is due to distribution, alteration, or impairment of function or structure or both.
- **Patient:** is the person affected by the disease
- **Lesions:** are the characteristic changes in tissues and cells produced by disease in an individual or experimental animal.
- **Gross or macroscopic changes:** the pathologic changes that can be recognized by naked eye.
- **Etiology:** causal factors of disease(´why' of disease)
- **Pathogenesis:** mechanism by which lesions are developed (how' of disease).
- **Symptoms:** functional implications of the disease felt by patient
- **Signs:** objective indication of disease, especially some evidence discovered during physical examination.
- **Clinical features:** is the manifestation of certain symptoms on the person due to a disease condition.
- **Diagnosis:** the clinical significance of the morphologic and functional changes together with results of other investigations help to arrive at an answer to what is wrong.
- **Syndrome:** is a complex of symptoms occurring together, which characterized on disease or lesion. OR it is a complete group of symptoms which occur together and present a definite basis foe accurate diagnosis.
- **Prognosis:** a prediction as to the progress, course and outcome of a disease(what is going to happen).
- Treatment: what can be done about it
- **Prevention:** what should be done to avoid complications and spread of disease**.**

Subdivisions of pathology :

Based on species studied

a) Human pathology
b) Animal pathology
c) Plant pathology
d) Veterinary pathology
e) Poultry pathology

Human pathology is the largest branch of pathology.

Subdivisions of pathology :

- **Histopathology :** Diagnosis of disease by gross & microscopic examination of tissue.
- **Cytopathology :** Diagnosis of disease on cellular level, by examination of isolated cell
- **Haematology** : Blood related disorder
- **Clinical pathology :** Diagnosis of disease based on laboratory analysis of bodily fluids such as urine, ascetic fluid
- **Chemical pathology :** Diagnosis of disease by using the tools of chemistry.
- **Immunopathogy :** Diagnosis of disease by detecting Ag-Ab specific reaction.
- **Forensic pathology :** Concerned with determining cause of death.
- **Molecular pathology :** Diagnosis of disease through the examination of molecules within organs, tissues or bodily fluids.

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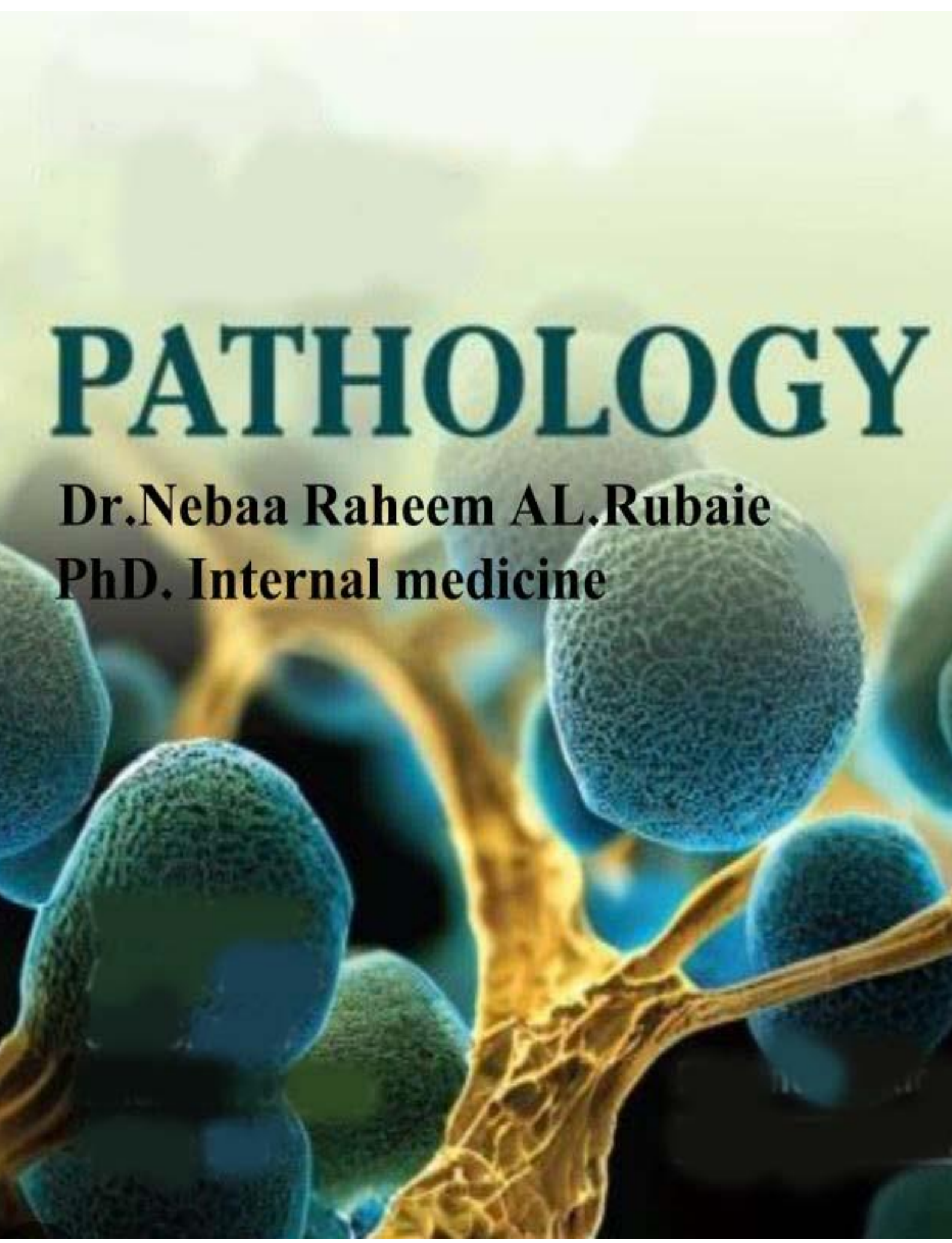


Cellular injury

Introduction

The environment around cells is dynamic and constantly changing In this fluid environment, cells are exposed to numerous stimuli, some of which may be injurious. To survive, cells must have the ability to adapt to variable conditions.

When a cell is exposed to an injurious agent, the possible outcomes are:

1. The cell may adapt to the situation or
2. The cell may acquire a reversible injury or
3. The cell may obtain an irreversible injury & may die. The cell may die via one of two ways: either by necrosis or by apoptosis. This process of adaptation can involve changes in cellular size, number or type.

Types Cellular adaptation :

1. Atrophy :

Decrease in size of a cell or tissue. Decreased size results in decreased oxygen consumption and metabolic needs of the cells and may increase the overall efficiency of cell function.

Atrophy can be caused by:

1. Disuse
2. Under nutrition
3. Decreased endocrine stimulation
4. Denervation
5. Old age.

2. **Hypertrophy :**

Hypertrophy is increase in the size of cells. Increased workload leads to increased protein synthesis & increased size & number of intracellular organelles which, in turn, leads to increased cell size. The increased cell size leads to increased size of the organ.

Examples: the enlargement of the left ventricle in hypertensive heart disease & the increase in skeletal muscle during sternous exercise.

3**. Hyperplasia :**

Hyperplasia is an increase in the number of cells. It can lead to an increase in the size of the organ. It is usually caused by hormonal stimulation. It can be physiological as in enlargement of the breast during pregnancy or it can pathological as in endometrial hyperplasia.

4. Metaplasia :

Metaplasia is the replacement of one differentiated tissue by another differentiated

tissue. There are different types of metaplasia. Examples include:

Squamous metaplasia

This is replacement of another type of epithelium by squamous epithelium. For

example, the columnar epithelium of the bronchus can be replaced by squamous

epithelium in cigarette smokers

5. Dysplasia :

• A derangement of cell growth that leads to tissues with cells of

varying size, shape and appearance.

• Dysplasia may be a strong precursor to cancer in certain instances

such as in the cervix or respiratory tract.

Cell Injury:

injury is manifested as functional and morphologic changes that are.

- **Reversible :** if the damaging stimulus is removed , With continuing damage, the injury becomes.
- **Irreversible :** at which time the cell cannot recover resulted in cell death.

Causes of Cell Injury :

1. Hypoxia: is a lack of oxygen in cells and tissues that generally results from ischemia. During periods of hypoxia, aerobic metabolism of the cells begins to fail. This loss of aerobic metabolism leads to dramatic decreases in energy production (ATP) within the cells.

2. **Physical agents:** Including trauma, extremes of temperatures, radiation, electric shock, and sudden changes in atmospheric pressure.

3. **Chemicals and drugs:** Any chemical agent may cause cell injury by altering membrane permeability, osmotic homeostasis or the integrity of the enzyme cofactor.

4. **Microbiologic agents:** ranging from viruses to tapeworms.

5**. Immunologic reactions:** The immune system of the body may cause cell injury, e.g. anaphylactic reaction.

6. **Genetic defects:** e.g. Down's syndrome, sickle cell anæmia.

7. **Nutritional imbalances:** Protein-calorie insufficiency, vitamin deficiencies. Diets rich in animal fat has been strongly implicated in the pathogenesis of atherosclerosis.

8. **Aging.**

Patterns of Acute Cell Injury:

- **Reversible Cell Injury**
- **Irreversible Injury:**

Manifestations of cellular injury

1. Cellular swelling

Caused by an accumulation of water due to the failure of energy driven ion pumps. Breakdown of cell membrane integrity and

accumulation of cellular electrolytes may also occur. Cellular swelling is considered to be a reversible change.

2. Intra Cellular accumulations

Normal cells may accumulate abnormal substances in various circumstances, either transiently or permanently, being harmful or injurious, and may locate in the cytoplasm or within the nucleus. It may be synthesized by the affected cell or produced elsewhere. Intracellular accumulation can be subdivided into three categories:

1. A normal endogenous substance produced at a normal or increased rate with an inadequate rate of metabolism. E.g. fatty change of the liver.

2. A normal or abnormal endogenous substance which can not be metabolized by genetic enzymatic defect, these diseases are called storage diseases.

3. An abnormal exogenous substance deposit because the cell has neither the enzymatic machinery nor the ability to transport it to other sites.

Fatty Change (Steatosis):

Is an abnormal accumulation of triglycerides within parenchymal cells. Fatty change is most often seen in the liver, and is reversible, but it may also occur in the heart, skeletal muscle, kidney and other organs. It may be caused by toxins, diabetes mellitus, protein malnutrition, obesity and anoxia. Excess acuumulation of triglycerides may result from defects at any step from fatty acid entry to synthesis of lipoproteins.

When fatty change is mild, it may have no effect on cellular function, more severe changes may transiently impair cellular function. Grossly the liver

enlarges and become progressively yellow. It is first seen by light microscope as small vacuoles in the cytoplasm around the nucleus, these vacuoles coalesce to create clear spaces displacing the nucleus to the periphery**.**

Cholesterol And Cholesterol Esters:

Macrophages in contact with lipid debris of necrotic cells may become stuffed with lipid because their phagocytic activities, appearing as foamy cells. In atherosclerosis, the smooth muscle cells and macrophages are filled with lipid vacuoles composed of cholesterol and cholesterol esters. Xanthomas are accumulation of fat within macrophages of subcutaneous connective tissues, appearing as white nodules**.**

Proteins:

Are less commonly seen, e.g. in glomerular diseases with proteinuria, accumulating in proximal convoluted tubules**.**

Glycogen:

Seen in cases of abnormal metabolism of glucose or glycogen, and appear under the light microscope as vacuoles.

Pigments:

Are colored substances either exogenous or endogenous. Endogenous pigments as: Melanin accumulate in basal cells of the epidermis resulting in freckles or in dermal macrophages ,Hæmosiderin is a hæmoglobin-derived granular pigment, golden brown, accumulates in tissues when there is local or systemic excess iron. Bilirubin is derived from hemoglobin but contains no iron. Its normal formation and excretion are vital to health, and jaundice is a common clinical disorder caused by excesses of this pigment within cells and tissues**.**

Pathologic Cacification:

It is an abnormal accumulation of calcium salts, with smaller amounts of iron, magnesium and other minerals. When deposition occurs in dead or dying tissues it is called dystrophic calcification, despite normal serum levels of calcium and in the absence of calcium metabolic derangement. It is encountered in areas of necrosis anywhere, seen in atheromas of advanced atherosclerosis on areas of intimal injuries of large arteries. It is also seen in aging and in aortic valves. It appears as intracellular or extracellular basophilic deposits, sometimes heterotopic bone may be formed.

- **Irreversible Injury: Is seen as**

1. Severe vacuolization of mitochondria and accumulation of calcium particles**.**
2. Extensive damage of plasma membrane.
3. Swelling of lysosomes.
4. Reperfusion of oxygen results in calcium mediated injury.
5. Continued loss of proteins, coenzymes and RNA from the hyperpermeable membranes, with leak of lysosomal enzymes into the cytoplasm, where they are activated by the reduced pH starting degrading the cytoplasmic components.
6. . Dead cells may be replaced by whorled masses of phospholipids (myelin figures).

Mechanisms of Irreversible Injury:

1. Progressive loss of membrane phospholipids.
2. Cytoskeletal abnormalities: Activation of proteases and increased calcium may result in detachment of the cell membrane.
3. Toxic oxygen free radicals: generated after reperfusion of the ischæmic area released by influxed neutrophils.
4. Lipid breakdown products: have detergent effects.

Free radical injury

• Free radicals are highly reactive chemical species that have one or

more unpaired electrons in their outer shell.

• Examples of free radicals include Superoxide ($O2^-$),hydroxyl radicals (OH^-) and hydrogen peroxide ($H2O2$).

• Free radicals are generated as by-products of normal cell metabolism

and are inactivated by free radical–scavenging enzymes within the

body such as *catalase* and *glutathione peroxidase*. When excess free

radicals are formed from exogenous sources or the free radical protective

mechanisms fail, injury to cells can occur.

• Free radicals are highly reactive and can injure cells through:

1. Peroxidation of membrane lipids

2. Damage of cellular proteins

3. Mutation of cellular DNA

• Exogenous sources of free radicals include tobacco smoke, organic solvents, pollutants, radiation and pesticides.

• Free radical injury has been implicated as playing a key role in the normal aging process as well as in a number of disease states such as diabetes mellitus, cancer, atheroscelrosis, Alzheimer's disease and rheumatoid arthritis.

Cell death

There are two principal patterns of cell death:

1. Necrosis: Occurs after exposure to noxious conditions, and characterized by cell swelling, protein denaturation and organelles breakdown.

2. Apoptosis: Is a programmed cell death occurring in the normal or physiologic conditions.

Necrosis:

Refers to a sequence of morphologic changes that follow cell death in living tissue, and is the gross and the histologic terms of cell death occurring in the setting of irreversible exogenous injury. The morphologic appearances of necrosis is the result of two processes: enzymatic digestion of the cell and denaturation of proteins.

The hydrolytic enzymes may be derived from the dead cells themselves (autolysis) or from lysosomes of the infiltrating leukocytes (heterolysis).

Cytoplasmic changes: Eosinophilia and glassy appearance due to loss of glycogen, cytoplasmic vacuolation and calcification.

Nuclear changes:

1. Karyolysis: due to digestion of DNA.

2. Pyknosis: nuclear shrinkage and increased basophilia, seen mainly in apoptosis.

3. Karyorrhexis: The pyknotic nucleus fragments.

Types of Necrosis:

1. **Coagulative necrosis:** Preservation of the structural outlines of the coagulated cell or tissue for days. The injury and acidosis denatures the enzymes that block cellular hydrolysis. The prime example is myocardial infarction appearing as acidophilic coagulated anucleated cells. The necrotic cells are removed by

fragmentation and phagocytosis by leukocytes. Coagulative necrosis is characteristic of hypoxic death in all tissues except in the brain.

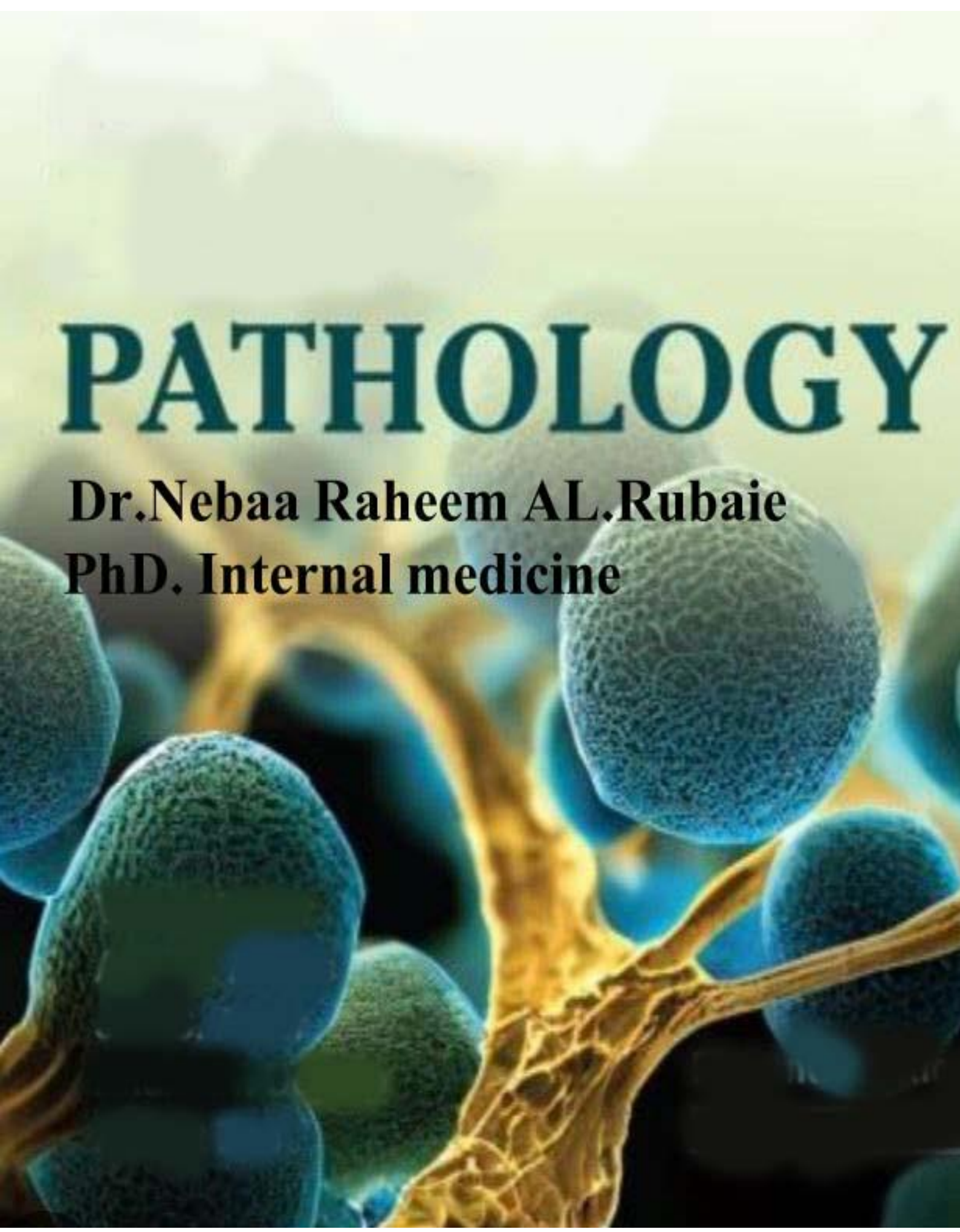
2. **Liquefactive necrosis:** Caused by focal bacterial or fungal infection with accumulation of white cells. Hypoxic cell death in the CNS also results in liquefactive necrosis.

3. **Gangrenous necrosis:** is not a distinctive pattern of necrosis, but is still being used in surgical practice, referring to ischæmic coagulative necrosis with superimposed infection and liquifactive necrosis, called "wet gangrene".

4. **Caseous necrosis:** Seen in tuberculous infection, derived from the cheesy, white gross appearance of the central necrotic area. Microscopically, it is composed of structureless amorphous granular debris within granulomatous inflammation.

5. **Fat necrosis:** It describes focal areas of fat destruction following acute pancreatitis, resulting from release of activated pancreatic enzymes with resultant hydrolysis of triglyceride esters within fat cells of the peritoneal cavity.

6. Fibrinoid necrosis : seen in immune reactions involving blood vessels ,deposition of immune complex with fibrin that has leaked out of vessels results in bright pink & amorphous appearance in H&E stains as necrosis in polyarteritis nodosa .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Inflammation

Definition*:*

Inflammation is a local response (reaction) of living vasculaized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury.
Thus, inflammation is a physiologic (protective) response to injury.

Nomenclature*:*

The nomenclatures of inflammatory lesion are usually indicated by the suffix 'itis'.Thus, inflammation of the appendix is called appendicitis and that of meninges as meningitis, conjunctivitis, etc.…
However, like any rule, it has its own exceptions examples pneumonia.

Causes:

Causes of inflammation are apparently causes of diseases such as

- **physical agents** - mechanical injuries, alteration in temperatures and pressure, radiation injuries.
- **chemical agents**- including the ever increasing lists of drugs and toxins.
- **biologic agents (infectious)**- bacteria, viruses, fungi, parasites
- **immunologic disorders**- hypersensitivity reactions, autoimmunity,immunodeficiency states etc
- **genetic/metabolic disorders**- examples gout, diabetes mellitus etc…

Types of inflammations :

Local and systemic inflammation

1. **local inflammation** :the inflammatory response to a localized infection or tissue damage. Although even local reactions may have systemic manifestations (e.g., fever in the setting of bacterial or viral pharyngitis), the inflammation is largely confined to the site of infection or damage.

2. **systemic inflammation** : In rare situations, such as some disseminated bacterial infections, the inflammatory reaction is systemic and causes widespread pathologic abnormalities. This reaction has been called ***sepsis***, which is one form of the systemic inflammatory response syndrome.

Classification :

Inflammation is classified crudely based on duration of the lesion and histologic appearances into acute and chronic inflammation.

Acute inflammation

Acute inflammation is an immediate and early response to an injurious agent and it is relatively of short duration, lasting for minutes, several hours or few days. It is characterized by exudation of fluids and plasma proteins and the emigration of predominantly neutrophilic leucocytes to the site of injury.

The five cardinal signs of acute inflammation : are

- **Redness** (rubor) which is due to dilation of small blood vessels within damaged tissue as it occurs in cellulitis.
- **Heat** (calor) which results from increased blood flow (hyperemia) due to regional vascular dilation.
- **Swelling** (tumor) which is due to accumulation of fluid in the extravascular space which, in turn, is due to increased vascular permeability.
- **Pain** (dolor), which partly results from the stretching & destruction of tissues due to inflammatory edema and in part from pus under pressure in as abscess cavity.Some chemicals of acute inflammation, including bradykinins, prostaglandins and serotonin are also known to induce pain.
- **Loss of function**: The inflammed area is inhibited by pain while severe swelling may also physically immobilize the tissue.

- **Events of acute inflammation:**

  Acute inflammation is categorized into an early vascular and a late cellular responses.

1) The **Vascular response** has the following steps:

a) Immediate (momentary) vasoconstriction in seconds due to neurogenic or chemical stimuli.

b) Vasodilatation of arterioles and venules resulting in increased blood flow.

c) After the phase of increased blood flow there is a slowing of blood flow & stasis due to increased vascular permeability that is most remarkably seen in the post-capillary venules. The increased vascular permeability oozes protein-rich fluid into extravascular tissues. Due to this, the already dilated blood vessels are now packed with red blood cells resulting in stasis. The protein-rich fluid which is now found in the extravascular space is called exudate. The presence of the exudates clinically appears as swelling. Chemical mediators mediate the vascular events of acute inflammation.

2) **Cellular response**

The cellular response has the following stages:

A. Migration , rolling, pavementing , & adhesion of leukocytes

B. Transmigration of leukocytes

C. Chemotaxis

D. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increased vascular permeability more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) **Migration, rolling, pavementing, and adhesion of leukocytes**

Margination is a peripheral positioning of white cells along the endothelial cells.Subsequently, rows of leukocytes tumble slowly along the endothelium in a process known as rolling In time, the

endothelium can be virtually lined by white cells. This appearance is called pavementing. Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell adhesion molecules such as selectins, immunoglobulins, integrins, etc which result in adhesion of leukocytes with the endothelium.

B). **Transmigration of leukocytes**

Leukocytes escape from venules and small veins but only occasionally from capillaries.The most important mechanism of leukocyte emigration is via widening of interendothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed thereafter immediately.

C). **Chemotaxis:**

A unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) is called chemotaxis.The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines (IL-8). All granulocytes,monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.

How do leukocytes "see" or "smell" the chemotactic agent? This is because receptors on cell membrane of the leukocytes react with the chemoattractants resulting in the activation of phospholipase C that ultimately leads to release of cytocolic calcium ions and these ions trigger cell movement towards the stimulus.

D) **Phagocytosis :** Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which includes invading microorganisms, damaged cells, and tissue debris. These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophiles), monocytes and tissue macrophages.

Chemical mediators of inflammation

Chemical mediators account for the events of inflammation.

Sources of mediators:

The chemical meditors of inflammation can be derived from plasma or cells.

a) Plasma-derived mediators:

1) Complement activation

- increases vascular permeability (C3,C5)
- activates chemotaxis (C5)
- opsoninization (C3,C3b)

2)Factor XII activation :

Its activation results in recruitment of four systems: the kinin, the clotting, the fibrinolytic and the compliment systems.

b) Cell-derived chemical mediatos:

A mediator may be defined as an endogenous chemical agent which takes an active part in the development of the inflammatory response.

Table 3.8 Role of Mediators in Different Reactions of Inflammation

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

IL-1, Interleukin-1; *TNF*, tumor necrosis factor.

Morphology of acute inflammation

Characteristically, the acute inflammatory response involves production of exudates.

- An **exudate** is an edema fluid with high protein concentration, which frequently contains inflammatory cells.
- A **transudate** is simply a non-inflammatory edema caused by cardiac, renal, undernutritional, & other disorders.

Morphologic types of acute inflammation:

1) Serous inflammation

This is characterized by an outpouring of a thin fluid that is derived from either the blood serum or secretion of mesothelial cells lining the peritoneal, pleural, and pericardial cavities ,It resolves without reactions

2) Fibrinous inflammation

More severe injuries result in greater vascular permeability that ultimately leads to exudation of larger molecules such as fibrinogens through the vascular barrier. Fibrinous exudate is characteristic of inflammation in serous body cavities such as the pericardium (butter and bread appearance) and pleura.

3) Suppurative (Purulent) inflammation

This type of inflammation is characterized by the production of a large amount of pus. Pus is a thick creamy liquid, yellowish or blood stained in colour and composed of

- A large number of living or dead leukocytes (pus cells)
- Necrotic tissue debris
- Living and dead bacteria
- Edema fluid

Abscess formation:

An abscess is a circumscribed accumulation of pus in a living tissue. It is encapsulated by a so-called pyogenic membrane, which consists of layers of fibrin, inflammatory cells and granulation tissue.

Abscesses: localized collections of pus

- **Ulcers:** Alocal defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue. Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface. It is most common in (1) the mucosa of the mouth, stomach, intestines, or genitourinary tract, and (2) the skin and subcutaneous tissue of the lower extremities in individuals with disorders that predispose to vascular insufficiency, such as diabetes, sickle cell anemia, and peripheral vascular disease.

Course of acute inflammation

Acute inflammation may end up in:

1. Complete resolution.

2. Healing by connective tissue replacement (scarring, or fibrosis).

3. Progression of the response to chronic inflammation.

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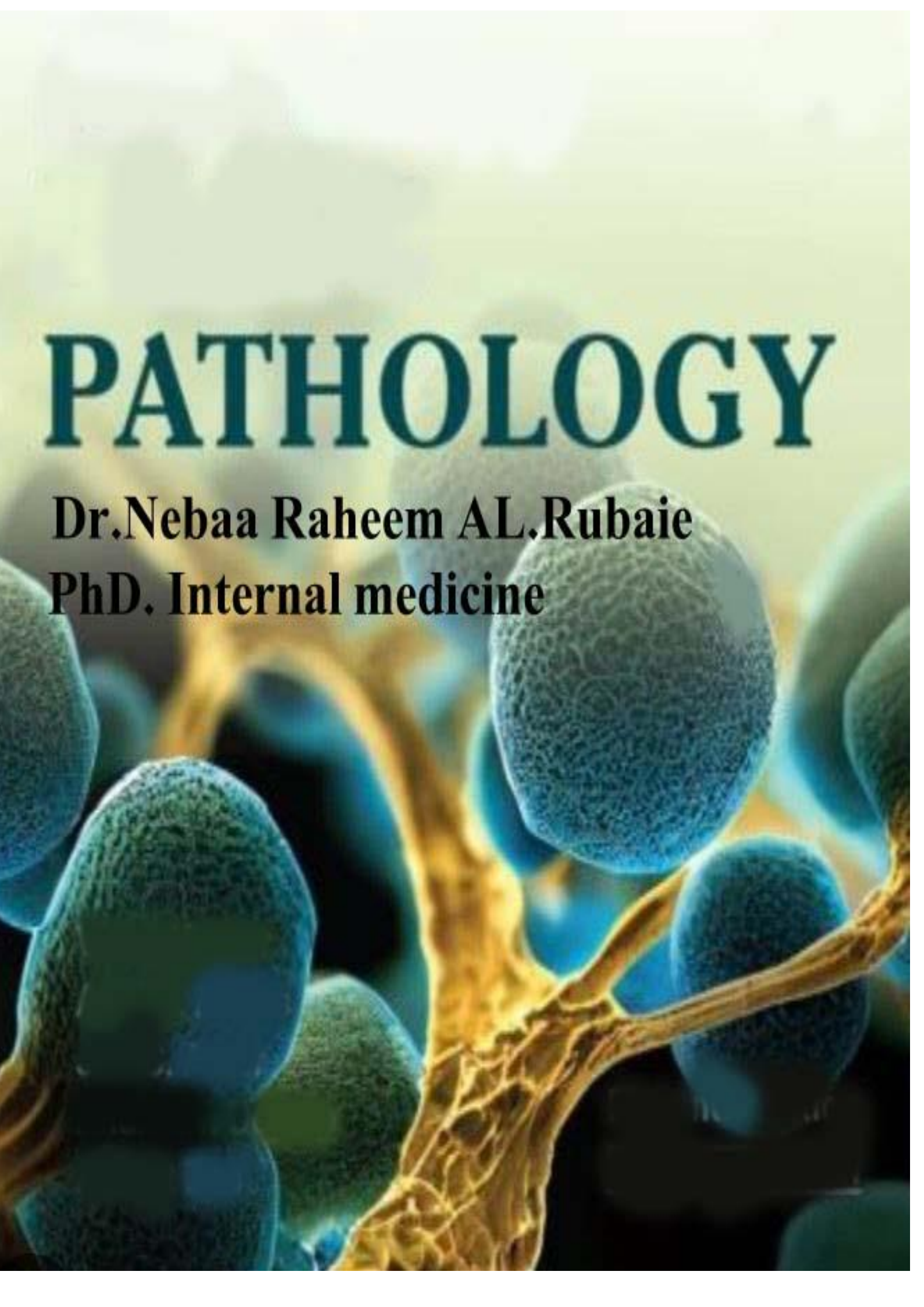


Chronic Inflammation

Definition: Chronic inflammation can be defined as a prolonged inflammatory process (weeks or months) where an active inflammation, tissue destruction and attempts at repair are proceeding simultaneously.

It may follow acute inflammation, as described earlier, or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestations of a preceding acute reaction. Different stimuli may cause variations in the morphological appearances but, overall, in the chronic inflammatory infiltrate lymphocytes, macrophages and plasma cells predominate, in contrast to acute inflammation where the major cell type is the neutrophil.

Causes of chronic inflammation:

1. **Persistent infections** : Certain microorganisms that are difficult to eradicate, associated with intracellular infection such as tuberculosis, leprosy, certain fungi and parasites. characteristically cause chronic inflammation.These organisms are of low toxicity and evoke delayed hypersensitivity reactions.

2. Prolonged exposure to nondegradable but partially toxic substances either endogenous lipid components which result in atherosclerosis is a chronic inflammatory process of the arterial wall induced, at least in part, by excessive production and tissue deposition of endogenous cholesterol and other lipids. or exogenous substances such as silica, asbestos.

3. Progression from acute inflammation: Acute inflammation almost always progresses to chronic inflammation following a Persistent suppuration as a result of uncollapsed abscess cavities, foreign body materials (dirt, cloth, wool, etc).

4. Autoimmuniy : Chronic inflammation plays an important role in a group of diseases that are caused by excessive and inappropriate activation of the immune system. Under certain conditions, immune reactions develop against the individual's own tissues, leading to autoimmune diseases. In these diseases, autoantigens trigger a self-perpetuating immune reaction that results in chronic tissue damage and inflammation example of Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis are chronic inflammations from the outset.

Morphological Features :

In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, chronic inflammation is characterized by the following:

• Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.

• Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.

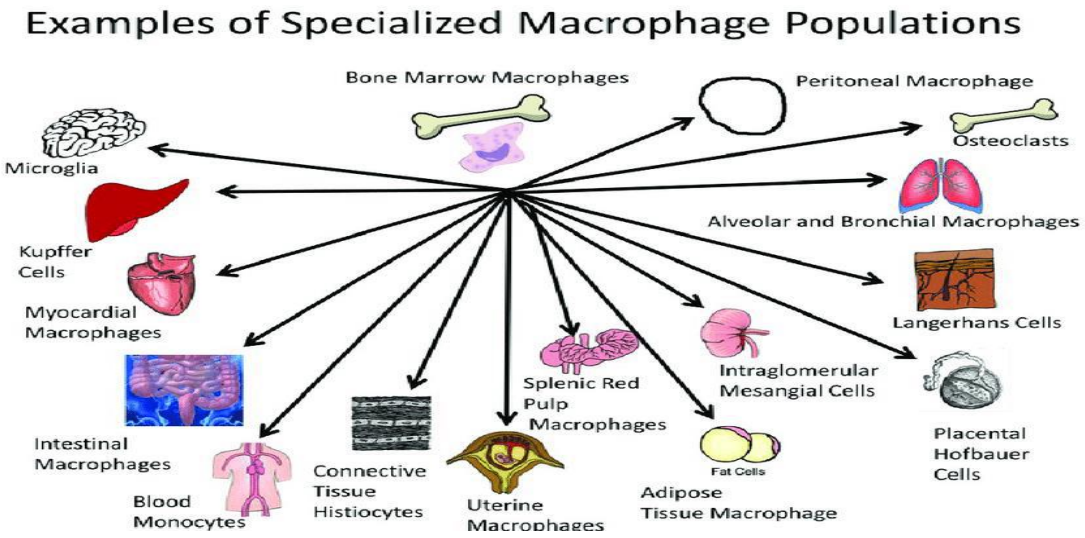
• Attempts at healing by connective tissue replacement of damaged tissue, accomplished by angiogenesis (proliferation of small blood vessels) and, in particular, fibrosis.

Cells of chronic inflammation:

- **Monocytes and Macrophages** are the (primary cells) in chronic

inflammation. Macrophages arise from the common precursor cells in the bone marrow, which give rise to blood monocytes. These cells are then diffusely scattered in various parts of the body, in the liver (Kupffer cells), spleen, lymph nodes (sinus histiocytes), lungs (alveolar macrophages), bone marrow, brain (microglia), skin (Langerhan's cells), etc…. These cells constitute the mononuclear-phagocytic system.

Macrophages are scavenger cells of the body.



Other cells in chronic inflammation:

1. **T-Lymphocytes** are primarily involved in cellular immunity with lymphokine production, and they are the key regulator and effector cells of the immune system.

2. **B-lymphocytes and Plasma cells** produce antibody directed either against persistent antigen in the inflammatory site or against altered tissue components.

3. Mast cells and eosinophils appear predominantly in response to parasitic infestations & allergic reactions.. Thus, the overall differentiation points between acute and chronic inflammations include:

Characteristics	**Acute inflammation**	**Chronic inflammation**
Duration	Short	Relatively long
Pattern	Stereotyped	Varied
Predominant cell	Neutrophils	Macrophages, Lymphocytes, Plasma cell

Tissue destruction	Mild to moderate	Marked
Fibrosis	Absent	Present

Classification of chronic inflammation:

Chronic inflammation can be classified into the following two types based on histologic features:

1) Nonspecific chronic inflammation: This involves a diffuse accumulation of macrophages and lymphocytes at site of injury that is usually productive with new fibrous tissue formations. E.g. Chronic cholecystitis.

2) Specific inflammation (granulomatous inflammation):

Definition: Granulomatous inflammation is characterized by the presence of granuloma. A granuloma is a microscopic aggregate of epithelioid cells. Epithelioid cell is an activated macrophage, with a modified epithelial cell-like appearance (hence the name epithelioid). The epitheloid cells can fuse with each other & form multinucleated giant cells. So, even though, a granuloma is basically a collection of epithelioid cells, it also usually contains multinucleated giant cell & is usually surrounded by a cuff of lymphocytes and occasional plasma cells. There are two types of giant cells:

a. **Foreign body-type giant cells** which have irregularly scattered nuclei in presence of indigestible materials.

b. **Langerhans giant cells** in which the nuclei are arrange peripherally in a horse –shoe pattern which is seen typically in tuberculosis, sarcoidosis etc…Giant cells are formed by fusion of macrophages perhaps by a concerted attempt of two or more cells to engulf a single particle.

Pathogenesis:

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

A. **Foreign body granuloma**

These granulomas are initiated by inert foreign bodies such as talc, sutures (nonabsorbable),fibers, etc… that are large enough to preclude

phagocytosis by a single macrophage and do not incite an immune response.

B. **Immune granulomas**

Antigen presenting cells (macrophages) engulf a poorly soluble inciting agent. Then, the macrophage processes and presents part of the antigen to the T helper 1 cells which become activated. The activated T-cells produce cytokines (IL-2 and interferon gamma).The IL-2 activates other T helper cells and perpetuates the response while IFN-γ is important in transforming macrophages into epitheloid cells and multinucleated giant cells. The cytokines have been implicated not only in the formation but also in the maintenance of granuloma.

MORPHOLOGY

1. The aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes.

2. Older granulomas may have a rim of fibroblasts and connective tissue.

3. multinucleated giant cells 40 to 50 μm in diameter are found in granulomas; these are called *Langhans giant cells*. They consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages.

4. In granulomas associated with certain infectious organisms (most classically Mycobacterium tuberculosis) a combination of hypoxia and free radical–mediated injury leads to a central zone of necrosis.

5. Grossly, this has a granular, cheesy appearance and is therefore called caseous necrosis

6. **Microscopically**, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with complete loss of cellular details (as opposed to coagulative necrosis, in which cell outlines are preserved).

7. The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating.

8. Healing of granulomas is accompanied by fibrosis that may be extensive in involved organs

Major causes of granulomatious inflammation include:

a) **Bacterial:** Tuberculosis, Leprosy, Syphilis.

b) **Fungal**: Histoplasmosis, Cryptococcosis, Coccidioidomycosis.

c) **Helminthic**: Schistosomiasis

d) **Protozoal:** Leishmaniasis, Toxoplasmosis

e) **Inorganic material**: silicosis

f) **Idiopathic:** Cohn’s disease, Primary biliary cirrhosis

SYSTEMIC EFFECTS OF INFLAMMATIONS

The systemic effects of inflammation include:

1. Fever
2. Endocrine & metabolic responses
3. Autonomic responses
4. Leukocytosis
5. Leukopenia
6. Weight loss

1. **Fever** is the most important systemic manifestation of inflammation. It is coordinated by the hypothalamus & by cytokines (IL -1, IL-6, TNF- α) released from macrophages and other cells.

2. **Endocrine and metabolic responses** include:

The liver secrets acute phase proteins such as:

-C-reactive proteins

-Complement and coagulation proteins

- Glucocorticoids (increased)

3. **Autonomic** responses include:

- Redirection of blood flow from the cutaneous to the deep vascular bed.

- Pulse rate and blood pressure (increased)

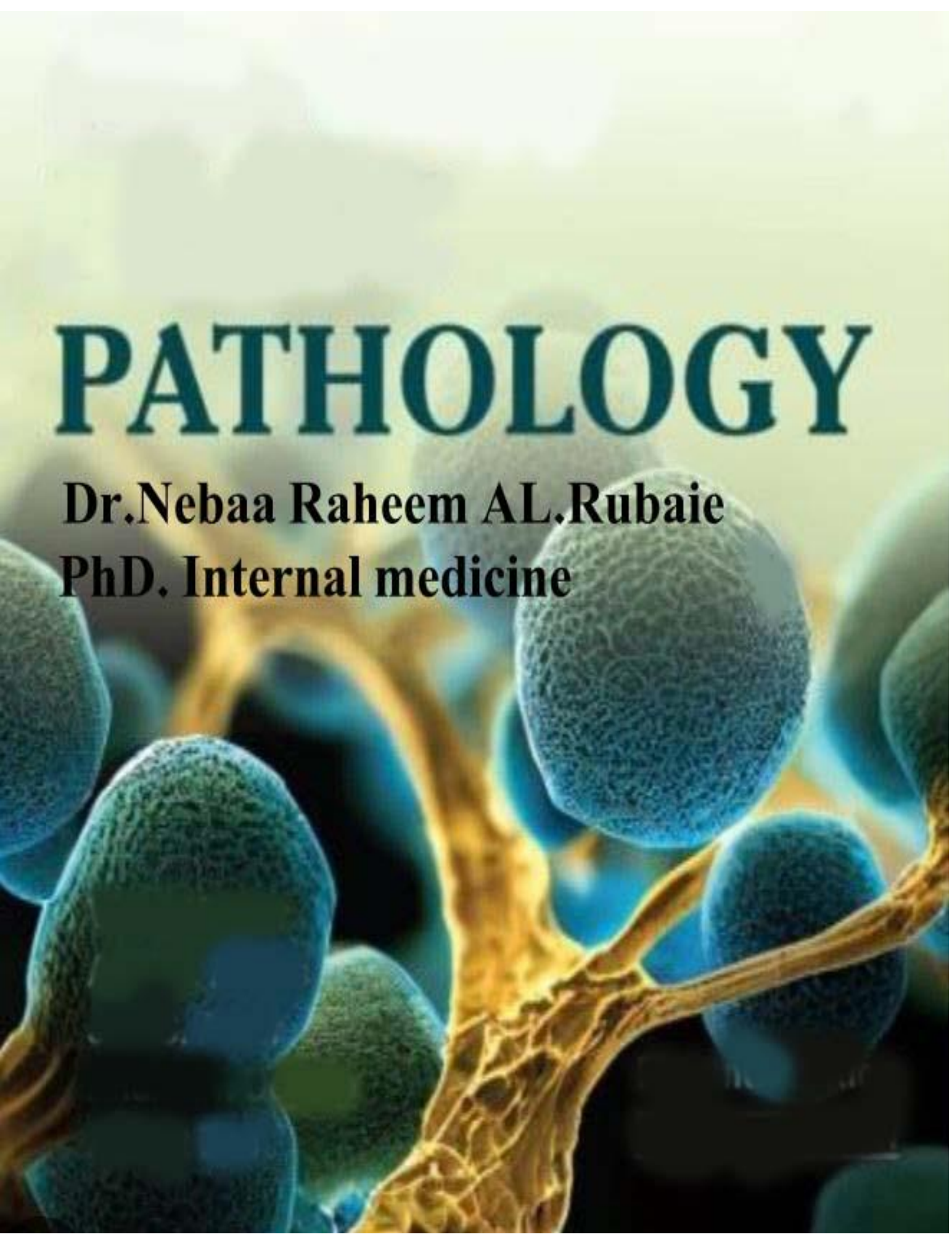
- Sweating (increased)

4. **Leucocytosis is** also a common feature of inflammation, especially in bacterial infections. Its usual count is 15,000 to 20,000 cells/mm3. Most bacterial infections induce neutrophilia. Some viral infections such as infectious mononucleosis, & mumps cause

lymphocytosis. Parasitic infestations & allergic reactions such as bronchial ashma & hay fever induce **eosinophilia**.

5. **Leukopenia** is also a feature of typhoid fever and some parasitic infections.

6. **Weight loss** is thought to be due to the action of IL-1 and TNF- α which increase catabolism in skeletal muscle, adipose tissue and the liver with resultant negative nitrogen balance.


PATHOLOGY
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Healing and tissue Repair

Definition of Healing

Repair, also called healing, refers to the restoration of tissue architecture and function after an injury**.**

The term Repair is used for parenchymal and connective tissue

The term Healing is used for surface epithelia

The Healing process involves two distinct processes:

1. **Regeneration:**

the replacement of lost tissue by tissues similar in type.

2. **Repair (healing by scaring):**

the replacement of lost tissue by granulation tissue which matures to form scar tissue. Healing by fibrosis is inevitable when the surrounding specialized cells do not possess the capacity to proliferate.

Whether healing takes place by regeneration or by repair (scarring) is determined partly by the type of cells in the damaged organ & partly by the destruction or the intactness of the stromal frame work of the organ. Hence, it is important to know the types of cells in the body.

Types of the cell :

Based on their proliferative capacity there are three types of cells.

1. Labile cells

These are cells which have a continuous turn over by programmed division of stem cells. They are found in the surface epithelium of the gastrointestinal treat, urinary tract or the skin. The cells of lymphoid and haemopoietic systems are further examples of labile cells .The chances of regeneration are excellent.

2. Stable cells

Tissues which have such type of cells have normally a much lower level of replication and there are few stem cells. However, the cells of such tissues can undergo rapid division in response to injury. For example, mesenchymal cells such as smooth muscle cells, fibroblasts, osteoblasts and endothelial cells are stable cells which can proliferate. Liver, endocrine glands and renal tubular epithelium has also such type of cells which can regenerate. Their chances of regeneration are good.

3. Permanent cells

These are non-dividing cells. If lost, permanent cells cannot be replaced, because they don not have the capacity to proliferate. For example: adult neurons, striated muscle cells, and cells of the lens.

Healing by regeneration

Definition: Regeneration (*generare=bring to life*) is the renewal of a lost tissue in which the lost cells are replaced by identical ones. Tissues formed of labile and stable cells can regenerate provided that stromal framework are intact.

Repair (Healing by connective tissue)

Definition:- Extensive deposition of collagen fibers (scar formation) a process by which lost tissue is eventually replaced by a scar.

Factors determined type of repair :

1) The tissue capacity for proliferation.

2) severity of damage to stromal framework (ECM) 4**C**

cells involved in tissue Repair :

Several cell types involved during tissue repair. These include

1. The remnants of the injured tissue (which attempt to restore normal structure)

2. Vascular endothelial cells (to create new vessels that provide the nutrients for the repair process)
3. Fibroblasts (the source of the fibrous tissue that fill defects).

The proliferation of the above cell types is driven by growth factors**.**

THE CELL CYCLE

The cell cycle represents the sequence of events that control DNA replication & mitosis in the proliferation of cells. It consists of a series of steps at which the cell checks for the accuracy of the process and instructs itself to proceed to the next step.

The cycle consists of:

the presynthetic growth phase 1 *(G1)*
the DNA synthesis phase *(S)*
the premitotic growth phase 2 *(G2)*
and the mitotic phase *(M)*.

Non-dividing cells are either in cell cycle arrest in G1 or they exit the cycle to enter a phase called G0.

Any stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the G0/G1 transition and the entry of cells into the G1. Further progression is determined by the ability of the cell to pass through an intrinsic quality control mechanism for cell integrity. known as checkpoint control. Checkpoint controls prevent DNA replication or mitosis of damaged cells and either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis**.**

Stem cells :

The original embryonic cells that have the inherent property of proliferation.

• Characteristic features:

1- Prolonged self-renewal capacity.

2- After each cell division, one cell will be differentiated while other cell remain undifferentiated, retaining their self-renewal capacity.

3- They have very broad differentiation capabilities, being able to generate any cell. (fat, cartilage, bone, endothelium, and muscle).

Factors that Control cell proliferation:

Cell proliferation can be triggered by:

1. Chemical mediators: Growth factors, Hormones, Cytokines work on stimulation or inhibition of cell growth

Growth factor are produced by (Leukocytes ,Connective tissue cells)

Growth factor: (specialized Protein)

- Stimulate cell division.
- Promoting cell survival.
- Stimulate migration.
- Stimulate differentiation.
- Enhance the synthesis of collagen in fibroblasts.

2. Extracellular matrix (ECM) and cell-matrix interactions:

ECM:Dynamic, constantly remodeling macromolecular complex synthesized locally as a network surrounding the cells. ECM occurs in two basic forms:-

1. Interstitial matrix.
2. Basement membrane.

ECM send signals controlling cell proliferation.

ECM occurs in two basic forms:

1.Interstitial matrix: Present in the spaces between mesenchymal (connective tissue) cells, and between epithelium and supportive vascular & smooth muscle structures. It is synthesized by the mesenchymal cells (e.g., fibroblasts). Its major constituents are: Collagens (fibrillar and nonfibrillar), Fibronectin, Elastin, Proteoglycans, Hyaluronate & Other elements.

2. Basement membrane: Which lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells Its major constituents are amorphous nonfibrillar type IV collagen and laminin.

Components of the Extracellular Matrix :

1. Fibrous structural proteins (collagens and elastins).

2. Water-hydrated gels (proteoglycans and hyaluronan).

3. Adhesive glycoproteins (that include fibronectin and adhesive receptors (selectins, integrins and coadherins).

Functions of the ECM :

1.Mechanical support for cell anchorage and migration, and maintenance of cell polarity

2. Control of cell growth by signaling through cellular receptors

3. Maintenance of cell differentiation through the type of ECM proteins.

4. Scaffolding for tissue renewal: the maintenance of normal tissue structure requires a basement membrane or stromal scaffold.

5. Establishment of tissue microenvironments: basement membrane acts as a boundary between epithelium and underlying connective tissue and also forms part of the filtration apparatus in the kidney.

6. Storage and presentation of regulatory molecules. For example, growth factors like FGF is excreted and stored in the ECM in some tissues. This allows the rapid release of growth factors after local injury, or during regeneration.

Wound healing

Healing process in general involve:

(1) Inflammation

(2) Formation of granulation tissue

(3) ECM deposition and remodeling

Types of Wound healing

1. Healing by First Intention (primary union).
2. Healing by Second Intention (secondary union).

1. Healing by First Intention (primary union):

- Healing of a clean, uninfected small wound **(**Surgical incision approximated by surgical sutures).

In Primary union there's (Focal disruption of epithelial basement membrane continuity) and (Death of few epithelial &connective tissue cells)

epithelial regeneration > fibrosis.

(Very small scar is formed + minimal wound contraction)

Steps of primary union

- In the first step The incision space is filled with fibrin clotted blood Then It is rapidly invaded by granulation tissueThen Covered by new epithelium,
- Within 24 hours Neutrophils migrate toward the fibrin clot. Basal cells increased mitotic activity at the cut edge of the epidermis
- After 24 up to 48 hours Epithelial cell migrate from both edges & proliferate along the dermis depositing basement membrane components.Cells meet in the midline beneath the surface cut Forming a thin but continuous epithelial layer.
- By the 3rd day

-Neutrophils replaced by macrophages.

-The granulation tissue progressively invades the incision space .

-Collagen fibers are now evident at the incision margins.

-Epithelial cell proliferation continues, forming a thick epidermal covering layer.

 By 5th day

-Neovascularization reaches its peak

-Collagen fibrils more abundant.forming a bridge in the area of incision.

-The epidermis recovers its normal thickness with surface keratinization.

 in the Second week

-Collagen continue to accumulation--Fibroblast continue to proliferation.--Decrease leukocyte infiltrate, edema, vascularity--Decrease collagen deposition--Regression of vascular channels—Blanching

.

By the end of the 1st month Features of the scar:

1. Formed of cellular connective tissue
2. Devoid of inflammatory cells
3. Covered by normal epidermis

2. Healing by Second Intention (secondary union):

Secondary union occurs in :

1. Extensive tissue loss (large wounds)
2. Chronic inflammation
3. Abscess formation
4. Ulceration

In Secondary union there is :(differences' from primary union)

1.large fibrin clot
2.more necrotic debris and exudate
3.Intense inflammatory reaction.
4.Abundant development of granulation tissue.
5-Large scar formation.

6.Wound contracts by action of myofibroblasts.

Begins within 24 hours of injury Start by Emigration of fibroblasts Induction of fibroblast and endothelial cell proliferation.

By 3rd – 5th days

Granulation tissue formation: Specialized type of tissue that is characteristic of healing. The term granulation tissue derives from the pink, soft, granular gross appearance.

Histologic appearance:

1. Proliferation of fibroblasts
2. Formation of new thin-walled, delicate capillaries (angiogenesis)
3. Loose ECM

Steps of scar formation

Repair by connective tissue deposition

consists of four sequential processes:

1- Formation of new blood vessels (angiogenesis)
2- Migration & proliferation of fibroblasts with deposition of ECM.
3- Maturation and reorganization of the fibrous tissue (remodeling)
4- Wound contraction**.**

Factors causes delay wound healing :

Systemic factors :

1. **Nutritional deficiency:** Vitamin C deficiency, inhibits collagen synthesis.

2. **metabolic derangement:** ex DM .associated with delay wound healing.

3. **Hormones :** Glucocorticoids: Steroids = anti-inflammatory

4. **Circulatory status :** Diminished blood supply impaired wound healing.

Local factors :

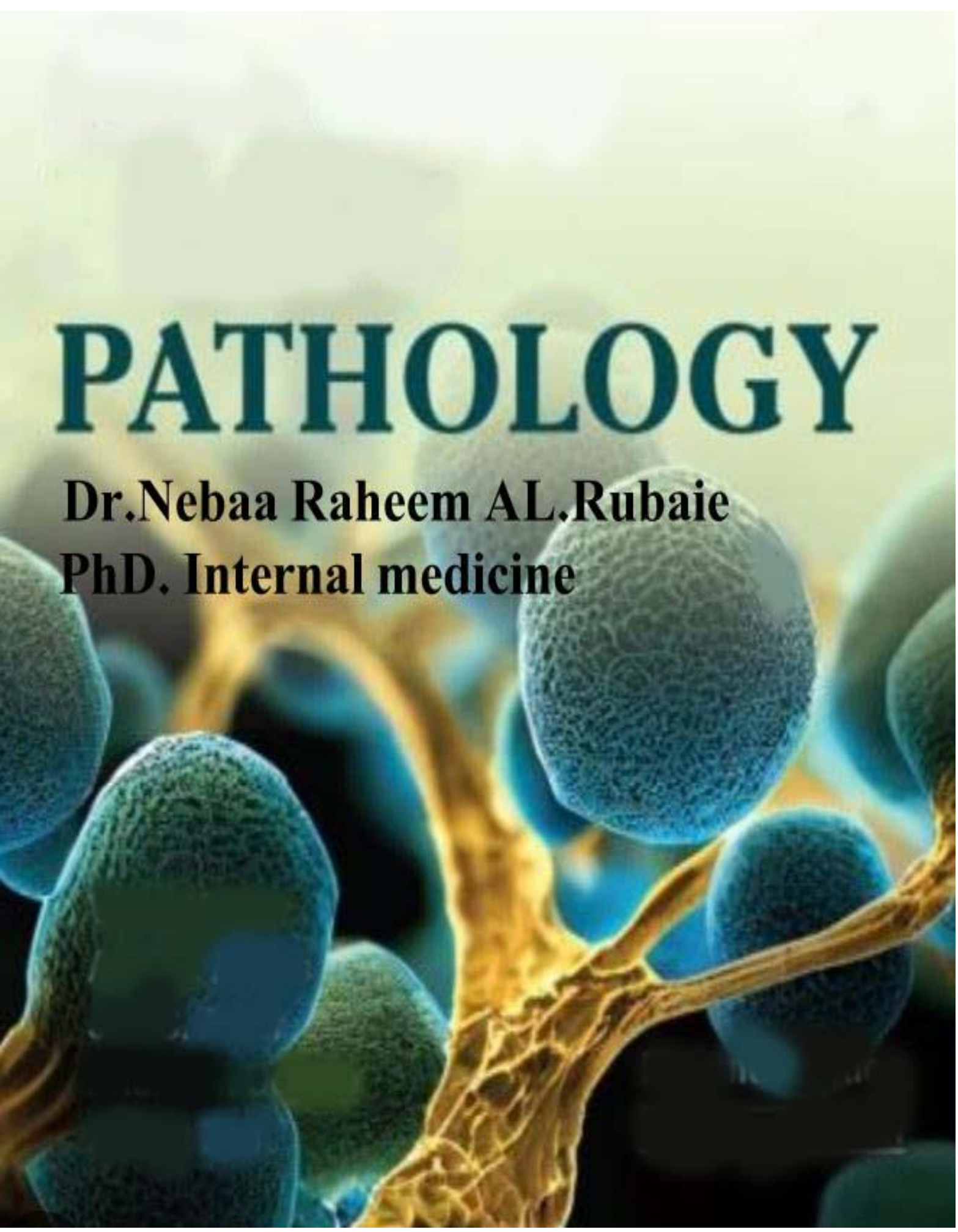
1. **Infection:** Prolongs the inflammation + increases the local tissue injury.

2. **Mechanical injuries:** Increased local pressure, torsion.

3. **Foreign bodies:** Fragments of steel, glass, or fractured bone.

4. **Size and shape of the wound** (clear cut surgical wound heals quickly).

5. **Location of the wound** (wound in the face heals quickly).


PATHOLOGY
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Hemodynamic Disorder I

The health and well-being of cells & tissues depend not only on an intact circulation to
deliver nutrients but also on normal fluid hemostasis. This lecture reviews the major
disturbances involving the hemodynamic system.

I. OEDEMA

Definition

- Oedema is the accumulation of excessive extracellular fluid

Location: interstitial vs body cavities

- Fluid accumulation in the interstitial space is called oedema
- Fluid can also collect in the various body cavities, e.g. pleural effusion, pericardial effusion, peritoneal effusion (ascites)

Mechanisms: Pathophysiologic categories of oedema

- Approximately 60% of the lean body weight is water, two-thirds of which is intracellular with the remainder in the extracellular compartment.The capillary endothelium acts as a semipermeable membrane and highly permeable to water & to almost all solutes in plasma with an exception of **proteins**. Proteins in plasma and interstial fluid are especially important in controlling plasma & interstitial fluid volume.

- **Edema formation** is determined by the following factors:
  1) Hydrostatic pressure
  2) Oncotic pressure
  3) Vascular permeability
  4) Lymphatic channels
  5) Sodium and water retention

Oedema develops as a result of :

- **increased hydrostatic pressure**: pulmonary and peripheral oedema due to congestive heart failure.
- **reduced plasma oncotic pressure**: protein loss due to nephrotic

-
- syndrome, reduced albumin production due to chronic liver disease and protein malnutrition.
- **increased vascular permeability**: due to inflammatory conditions
- **Lymphatic obstruction** e.g. due to inflammation, neoplastic infiltration or post-surgical/ radiation effect, can also lead to oedema.
- **Conditions causing primary salt and water retention** e.g. excessive salt intake in the setting of kidney disease.

Localized vs Generalized oedema

- Causes of **localized oedema**: DVT leading to oedema of the affected lower limb; localized skin infection and inflammation with oedema in the vicinity
- Causes of **generalized or systemic oedema**: congestive heart failure, hypoproteinaemia states renal failure.

Morphology of edema:

Microscopy

- Manifests only as subtle cell swelling. Clearing & separation of extracellular matrix.

II. HYPERAEMIA AND CONGESTION

Definition: Both of them can be defined as a local increase in volume of blood in a particular tissue.

hyperaemia vs congestion

- Hyperaemia is active process its due to arteriolar vasodilation resulting in increased blood flow and hence blood volume within the vasculature of the organ.
- Hyperaemia can be **physiological** e.g. increased blood flow to muscles during exercise, or **pathological** e.g. increased blood flow to an area of inflammation
- Congestion is 'passive' in nature and is due to venous outflow obstruction resulting in increased blood volume within the vasculature of the organ (note: congestion that is sufficiently severe and unrelieved may lead to hypoxaemia and necrosis of the affected organ.)

Localized vs generalized forms of congestion

- Localized types of congestion: e.g. DVT resulting in congestion and oedema of the affected lower limb

-
- Generalized or systemic type of congestion: pulmonary and systemic venous congestion due to congestive heart failure

Morphology and Clinical correlations, e.g. congestion in the lungs and liver

- Grossly, congested organs tend to be enlarged, **heavy** and **cyanotic** (due to increasing deoxyhaemoglobin); in contrast, hyperaemic tissue is typically **red** or erythematous
- In the lungs, acute congestion (e.g. heart failure) leads to interstitial vascular **congestion**, **oedema**.
- In the liver, acute congestion (e.g. heart failure) features central vein and sinusoidal dilatation, and centrilobular hepatocyte degeneration.

III. HAEMOSTASIS

- **Definition:** Hemostasis is the maintainence of the clot-free state of blood & the prevention of blood loss via the formation of hemostatic plug**.**

Hemostasis depends on three general components:

a) Vascular wall

b) Platelets

c) Coagulation pathways

Whenever a vessel is ruptured or injured, hemostasis is achieved by several mechanisms:

A. Vascular spasm (vasoconstriction)

B. Formation of platelet plug

C. Formation of blood clot as a result of blood coagulation

D. Eventual growth of fibrous tissue in to the blood clot to close the hole in the vessel

permanently.

- **Platelet** adhesion, activation and aggregation – **primary haemostasis**
- **Coagulation cascade** activation with formation of thrombin and thereafter fibrin. Polymerized fibrin and platelets aggregates constitute **secondary haemostasis**
- Counter-regulatory mechanisms (e.g. via tissue plasminogen activator t-PA) limits the haemostasis to the affected site.

IV. HAEMORRHAGE

Definition: Hemorrhage is extravasation of blood outside the blood vessel.

Types of haemorrhage

- Can be spontaneous or traumatic

Causes of haemorrhage

Due to abnormalities of platelets, coagulation factors or blood vessel wall:

- **platelet defects** Defects in primary haemostasis quantitative or qualitative Manifests as **petechiae** (1-2 mm in size) skin, mucous membranes .
- **abnormalities in coagulation factors** Defects in secondary haemostasis: can be congenital/ genetic or acquired and involve**.** Manifests as bleeding into joints or soft tissue.
- **blood vessel wall abnormality:** defects involving small blood vessels most often due to **vasculitis** or vascular fragility e.g. scurvy, resulting 1-2 cm sized **bruises** or **ecchymoses** (if palpable mass – haematoma).

Effects of haemorrhage: depend on the rate and amount of blood loss:

· If > 20% the total blood volume is rapidly lost from the body, it may lead to hypovolumic shock & death.

· Chronic loss of blood leads to anaemia.

V. SHOCK

Definition

- Systemic hypoperfusion and cellular hypoxia as a result of either reduction in cardiac output or effective circulating blood volume.

Types of shock

- **Cardiogenic shock**: common causes include myocardial pump failure due to **myocardial infarction**, arrythmia, pericardial tamponade and outflow
-
- obstruction due to massive pulmonary thromboembolism
- **Hypovolaemic shock**: common causes include **severe blood loss** due to trauma, marked fluid loss due to vomiting, diarrhoea and extensive burns
- **Septic shock:** due to marked vasodilation and blood pooling ('distributive' shock) as a result of microbial infection and the haemodynamic effects of the inflammatory-immune responses

  Other **distributive shock** aetiologies: **anaphylaxis** due to severe IgE-mediated allergic reaction,
- **neurogenic** shock due to central nervous system trauma and ensuing loss of vascular tone.

Compensatory mechanisms

- **Neurohumoral responses**: sympathetic nervous system stimulation and effects of catecholamines, leading to vasoconstriction, increased heart rate and myocardial contractility
- Other neurohumoral responses: activation of **renin-angiotensin-aldosterone system** and antidiuretic hormone release, keeping water in the circulatory system
- **Diversion of blood** from cutaneous and splanchnic circulations to critical organs (e.g. brain, heart, kidney)
- **Fluid shift** to the intravascular compartment
- Increased haematopoietic (erythrocytic) cell production by the bone marrow

Septic shock: background, pathogenesis and outcome

- Initially raised cardiac output, but ultimately systemic **vasodilation**, endothelial cell activation and hypercoagulable state lead to tissue hypoperfusion and multiorgan damage
- **Inflammatory responses**, stimulation of leukocytes (macrophages) and release of inflammatory cytokines and other factors; coagulation cascade and complement activation also contribute to the inflammatory state
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-
- **Endothelial cell (EC) activation** and injury: increased vascular permeability and oedema. EC also releases NO and other mediators leading to vasodilation
- **Promotion of procoagulant state**: EC activation contributes to eventual disseminated intravascular coagulation (DIC)
- **Multiorgan dysfunction / failure** occurs: e.g. myocardial contractility can be reduced, and also adult respiratory distress syndrome (shock lung)

Stages of shock

- **Non-progressive phase**: compensatory neurohumoral mechanisms to maintain perfusion of vital organs
- **Progressive phase**: Increasing **circulatory and metabolic disturbances** arise; lactic acidosis from anaerobic respiration inhibits vasomotor responses resulting in vasodilation
-
- **Irreversible phase**: **Multiorgan failure** and death is inevitable even though perfusion might be restored by treatment efforts

Effects on major organs

- **Kidney shutdown** (**renal tubular necrosis**) occurs resulting in oligo- or anuria with critical electrolyte abnormalities.
- **Ischaemia of intestines** cause the loss of fluids and escape of bacteria into the blood circulation.
- **Myocardial ischaemia** and necrosis, reducing cardiac output
- **Liver necrosis**
- **Acute respiratory distress syndrome** or diffuse alveolar damage (shock lung)
- **Brain ischaemia** and necrosis

Clinical consequences

- Shock is characterized by tachycardia, tachypnoea and cold and clammy skin; except early septic shock typified by warm and reddish complexion due to cutaneous vasodilation.
- **Major organ dysfunctions** as described in preceding section leads to **vicious cycle** and deterioration of the shock
- For survivors of initial complications of shock, there could be renal insufficiency with ensuing **fluid and electrolyte imbalances.**
- Prognosis of shock depends on type of shock, premorbid status of patient and timeliness of appropriate treatment: hypovolaemic shock in the young with aggressive treatment has reasonable survival chances while elderly with **cardiogenic or septic shock have much worse prognosis.**

Definition

- **Inappropriate intravascular blood clotting** without preceding significant vascular injury

Virchow's triad

- Thrombosis occurs due to endothelial injury, alterations in normal blood flow or hypercoagulable state

- **Endothelial injury**: e.g. due to **atherosclerosis**, or other physical or chemical injuries; results in platelets coming into contact with ECM and becoming activated, increased production of procoagulants (e.g. tissue factor) or decreased inhibitors of coagulation (e.g. PGI_2)
- **Altered blood flow: stasis or turbulence**: stasis e.g. in veins, cardiac or aortic aneurysms, atrium during atrial fibrillation) – disrupts laminar blood flow and allows platelets to come into contact with endothelium; turbulence – generates eddy currents and pockets of stasis, and also injures endothelium, resulting in thrombosis.
- **Hypercoagulable states: Inherited** (e.g. Factor V and prothrombin mutations; antithrombin III, proteins C and S deficiency) and **acquired** causes (oestrogen-containing pills, pregnancy, heparin and its adverse effects on platelets, antiphospholipid antibodies)

Morphology

- **Venous thrombi** (e.g. DVT) occur mostly due to stasis, are occlusive and are dark red in colour.
- **Aortic or cardiac thrombi** occur often due to endothelial injury and are non-occlusive; smaller arterial thrombi may be occlusive (e.g. coronary thrombosis)

- Arterial and cardiac thrombi may have alternating light and dark-coloured laminations (lines of Zahn)
- Valvular thrombi: main types are vegetations of infective endocarditis, nonbacterial thrombotic endocarditis and Libman-Sacks endocarditis (due to SLE).

Fates of a thrombus

- Propagation
- Embolization (*vide infra*)
- Organization and recanalization
- Microbial infection leading to septic emboli or mycotic aneurysm
-

Clinical features: Venous, Cardiac and Arterial thrombi

- Thrombi in superficial leg veins predispose to skin infections and **venous ulcers**; DVT give rise to limb swelling, congestion and pain, but most dangerously, possibility of pulmonary embolization.
- Clinical states predisposing to DVT: post-major surgery, **prolonged bed rest**, post-partum state, severe trauma, burns and cancer (with production of pro-coagulants)
- **Cardiac thrombosis** can occur as a consequence of **myocardial infarction** because of endothelial injury and abnormality in intracardiac blood flow; mitral valve disease with scarring and stenosis e.g. due to rheumatic heart disease, also may cause atrial dilatation, and with contribution by atrial fibrillation, may lead to stasis and thrombosis within the atrium.
- Arterial thrombosis most often arise as a consequence of atherosclerosis with plaque rupture and ulceration.
- Cardiac and arterial thrombi can **embolize** to various arteries causing **infarcts** in the brain, kidney, spleen etc.

Disseminated intravascular coagulation (DIVC)

- Formation of **widespread fibrin microthrombi** in the blood circulation
- Triggering conditions include obstetric complications, burns, sepsis and advanced malignancy
- As a result of widespread vascular **thrombotic occlusion,** ischaemic damage to the heart, lungs, liver, kidney, brain can occur.
- The consumption of platelets and coagulation factors and the activation of fibrinolysis can lead to the occurrence of uncontrolled **bleeding**.

VII. EMBOLISM

Definition

- Intravascular solid, liquid or gaseous material carried by the bloodstream to a site distant from its point of origin.
- Most common form is **thromboembolism**; other materials include air bubbles, fat globules, foreign body, tumour fragments, bone marrow, septic/ infective material Causes vascular occlusion where it ultimately lodges resulting in ischaemia or infarction; septic emboli leads to abscess formation.

Pulmonary thromboembolism

- Occurs in up to 0.4% of hospitalized patients and accounts for many deaths.
- Most common origin is **DVT**; many smaller thrombi/ thromboemboli are silent or asymptomatic
- Can be single and massive, or showers of smaller emboli.

-
- Massive main pulmonary arterial trunk or **saddle embolus** (sitting on
- bifurcation) results in acute right heart failure and **sudden death**
- Embolus lodging in small or medium-sized arterial branches give rise to **pulmonary haemorrhage** or sometimes infarct
- Multiple of repeated smaller emboli occurring over time can result in widespread occlusion of the pulmonary circulation, with ensuing **pulmonary hypertension** and right heart failure

Systemic thromboembolism

- Common origins for such thromboemboli are the ventricular cavity adjacent to myocardial infarction, from left atrium that is dilated or undergoing fibrillation, vegetations of infective endocarditis and venous thromboemboli crossing from the right heart to the left, via septal defects (paradoxical embolism)
- Arterial origins of thromboemboli are most often from atheromatous plaques or aortic aneurysms.
- Outcome of such systemic thromboembolisms depend on degree of collateral blood supply, tissue vulnerability to ischaemia, prior presence of anaemia or heart failure, and calibre of vessel. Critical organ infarcts are the dreaded outcome.
- Cerebral infarct and lower limb ischaemia and gangrene are the most common affected target sites; embolism to the kidneys, intestines, spleen and upper limbs also occur but are less frequent.

Fat and marrow embolism

- Typically occurs a few days after **bone fractures** or other musculoskeletal injuries, when bone marrow or fat globules gain access to the blood stream; often asymptomatic
- Patients present with petechial haemorrhages, drowsiness, seizures, cough or breathlessness as a result of fat **emboli to the skin, brain and lungs**; condition may be fatal

- Released fatty acids are toxic to the endothelium, and together with free radicals and chemical mediators released from leukocytes, cause further tissue damage, haemorrhage and oedema; platelet activation and RBC aggregation occur and may form microthrombi

Air embolism

- Occurs when air bubbles get access or form in the blood circulation; causes include incidents during head and neck, thoracic or gynaecological surgery
- Classically occurs as diving accident – **decompression disease** – when diving in deep waters, air is dissolved in the blood; whereupon on rapid surfacing, **air bubbles form in the blood stream** and embolize to the muscles and bone (causing pain - ***bends)***, pulmonary circulation (breathlessness, cough - ***chokes)*** and cerebral circulation (drowsiness, disorientation - ***staggers)***Caisson disease a rare cause of
-
- avascular necrosis of the femoral head due to chronic decompression disease

Amniotic fluid embolism

- Very rare obstetric complication (1:40000 births) where amniotic fluid and its content enters the uterine veins and embolize; very high reported fatality
- Leads to embolization to the pulmonary circulation and **sudden cardiac collapse**; if patient survives, diffuse alveolar damage and **DIVC** may develop because of release of injurious fatty acids and thrombogenic substances present in the amniotic fluid
- Autopsy and microscopic examination may show hair, mucin and fetal squames in pulmonary capillaries