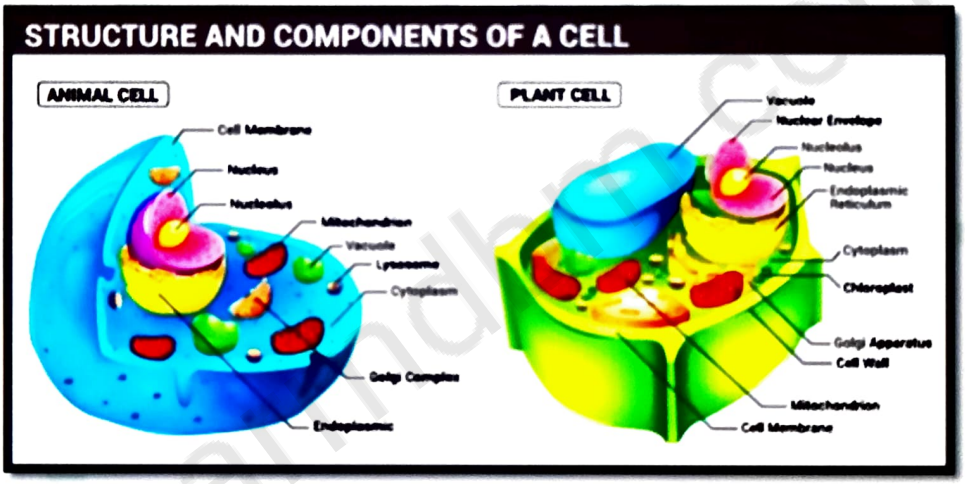
UNIT-I (PART-1-CELL INJURY & ADAPTATION)

Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ DEFINITIONS
- ❑ HOMEOSTATIS
  - ❖ COMPONENTS OF HOMEOSTATIC SYSTEM/ FEEDBACK SYSTEMS
  - ❖ TYPES OF FEEDBACK SYSTEMS
- ❑ CAUSES OF CELLULAR INJURY
- ❑ PATHOGENESIS OF CELL INJURY
- ❑ MORPHOLOGY OF CELL INJURY
- ❑ CELL SWELLING
- ❑ INTRACELLULAR ACCUMULATION
- ❑ CALCIFICATION
- ❑ ENZYME LEAKAGE
  - ❖ CELL DEATH ACIDOSIS
- ❑ ELECTROLYTE IMBALANCE

❑ INTRODUCTION

- **Cells** are the **basic units** of tissues, which form **organs** and **systems** in the human body.
- Traditionally, Body cells are divided in to two main types: **epithelial** and **mesenchymal cells**.
- In health, the cells remain in accord with **each other.**
- In **1859, Virchow** first published **cellular theory of disease**, bringing in the concept that diseases occur due to abnormalities at the level of cells.
- Since then, study of **abnormalities** in structure and function of cells in disease has remained the focus of attention in understanding of diseases.
- Thus, most forms of diseases begin with cell injury followed by consequent **loss** of **cellular function.**



❑ DEFINITIONS

S. NO	TERMINOLOGY	COMMENTS
1.	**Anaplasia**	Morphological and functional alteration of mature cell
2.	**Azotemia**	Characterized by abnormally high levels of nitrogen-containing compounds (such as urea, creatinine, various body waste compounds, and other nitrogen-rich compounds) in the blood
3.	**Aneurysm**	Permanent abnormal dilatation of blood vessel (Arteries)
4.	**Apnea**	A potentially serious sleep disorder in which breathing repeatedly stop and start

5.	**Amenorrhea**	**Absence of menstrual period**
6.	**Acromegaly**	**Over production of Growth Hormone in adults**
7.	**Agranulocytosis**	**happens when your body doesn't make enough white blood cells (called neutrophils)**
8.	**Atrophy**	**Decrease in cell size and tissue mass**
9.	**Apoptosis**	**A controlled, preprogrammed cell death occur with aging**
10.	**Granulocytopenia**	**A marked decrease in the number of granulocytes.**
11.	**Anaphylaxis**	**A severe potentially life-threatening allergic reaction**
12.	**Aplastic anemia**	**Is a condition that occurs when your body stops producing enough new**
13.	**Anisocytosis**	**Abnormal variation of RBC in size**
14.	**Angiogenesis**	**Formation of new blood vessels**
15.	**Brucellosis**	**Bacterial infection spread from animal to humans**
16.	**Bronchitis**	**Inflammation of the bronchi**
17.	**Candidiasis**	**Fungal infection caused by candida**
18.	**Cholestasis**	**A decrease or blockage in the flow of bile.**
19.	**Chemotaxis**	**The movement of an organism in response to a chemical stimulus.**
20.	**Chorio-carcinoma**	**Fast growing cancer that occur in women's uterus(womb)**
21.	**Catalepsy**	**Condition characterized by lack of response to external stimuli and muscular rigidity**
22.	**Cyanosis**	**Bluish discoloration of the skin and mucous membrane due to lack of oxygen in blood**
23.	**Dyspnea**	**Shortness of breath**
24.	**Dysmenorrhea**	**Cramps and pelvic pain with menstruation**
25.	**Dysplasia**	**The abnormal growth or development of a tissue or organ.**
26.	**Dysgeusia**	**An altered or impaired sense of taste**
27.	**Erythropoiesis**	**The process through which new red blood cells are created; it begins in the bone marrow.**

29.	**Emphysema**	Destruction of alveolar walls and permanent dilation of airspaces distal to terminal bronchioles
30.	**Fibrosis**	Slightly rise in serum transaminase level
31.	**Gestational hypertension**	Pregnancy induced Hypertension
32.	**Hepatitis**	Elevated liver function
33.	**Hypocorticism (Addison's Disease)**	A disorder in which adrenal gland doesn't produce enough adrenocortical hormones
34.	**Hypercorticism (Cushing's syndrome)**	A condition that occurs from exposure to high cortisol level for long time
35.	**Hypoxia**	Absence of enough oxygen in the tissues
36.	**Hemostasis**	Stoppage of bleeding or hemorrhage
37.	**Hemangiosarcoma**	A rapidly growing, highly invasive variety of tumor that arises from the cell lining blood vessel.
38.	**Hemolytic anaemia**	Red blood cells are destroyed faster than they can be made
39.	**Hemosiderin**	It is an iron-storage complex that is composed of partially digested ferritin and lysosomes
40.	**Hematopoiesis**	It is the production of all of the cellular components of blood and blood plasma.
41.	**Hypertrophy**	Increase in cell size and tissue mass
42.	**Hyperplasia**	It is increased cell production in a normal tissue or organ
43.	**Integrins**	Family of proteins consist of alpha and beta subtype
44.	**Leukopenia**	A low white blood cell count in blood.
45.	**Malignant melanoma**	A kind of Skin cancer
46.	**Methaemoglobinaemia**	In this the hemoglobin iron is in the oxidized or ferric state and can-not reversibly bind oxygen
47.	**Myalgia**	Muscle aches and pain
48.	**Myositis**	Inflammation of the muscle
49.	**Metaplasia**	Change in cell type
50.	**Metastasis**	Ability to spread to part of organs (cancer)
51.	**Neuralgia**	Pain that travels along the length of a nerves
52.	**Neuroglia**	They are non-neuronal cell in the CNS

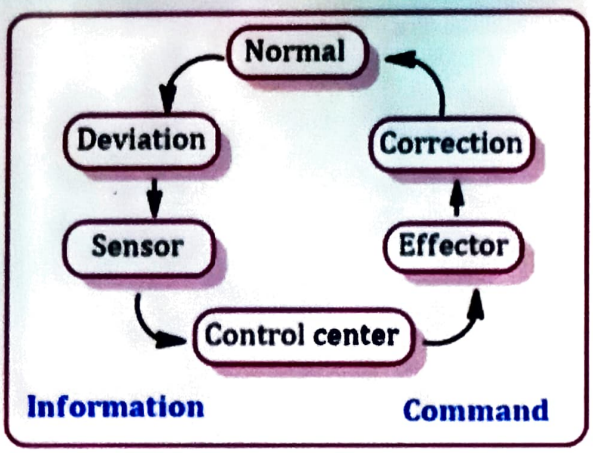
❑ HOMEOSTATIS

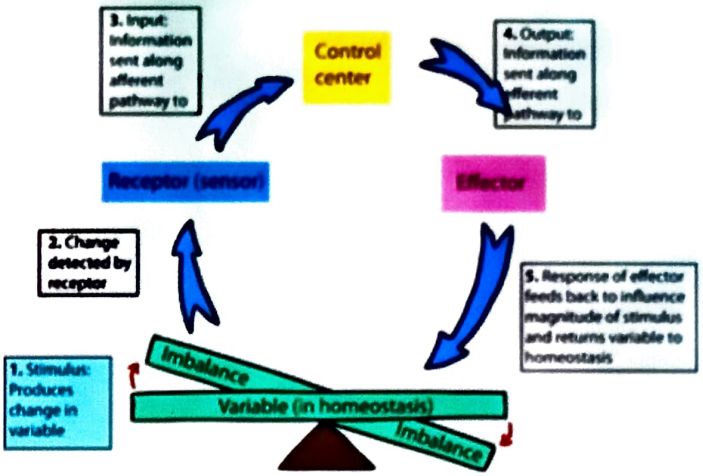
- Homeostasis refers to the maintenance of constant internal environment of the body **(Homeo= same; stasis = standing).**
- Importance of internal environment was notified by the great biologist of **19th century Claude Bernard** the fact that multicellular organisms including man live in a perfectly organized and controlled internal environment, which he called **'milieu interieur'.**
- The word 'homeostasis' was introduced by **Harvard Professor, Walter B Cannon in 1930.**
- The concept of homeostasis forms basis of physiology because it explains why various **physiological functions** are to be maintained within a **normal range** and in case if any **function** deviates from this range how it is brought back to **normal.**
- Understanding the concept of homeostasis also forms the basis for **clinical diagnostic procedures.** For example, increased body temperature beyond normal range as in the case of fever, indicates that something is wrong in the heat production-heat loss mechanism in the body.
- It induces the physician to go through the diagnostic proceedings and decide about the treatment.

❖ Components of Homeostatic System/Feedback systems

- Homeostatic system in the body acts through self regulating devices, which operate in a cyclic manner . This cycle includes four components:

1. **Sensors** or **detectors,** which recognize the deviation.
2. Transmission of this message to a **control center.**
3. Transmission of information from the control center to the effectors for correcting the deviation Transmission of the message or information may be an electrical process in the form of impulses through nerves or a chemical process mainly in the form of hormones through blood and body fluids.
4. **Effectors,** which correct the deviation.





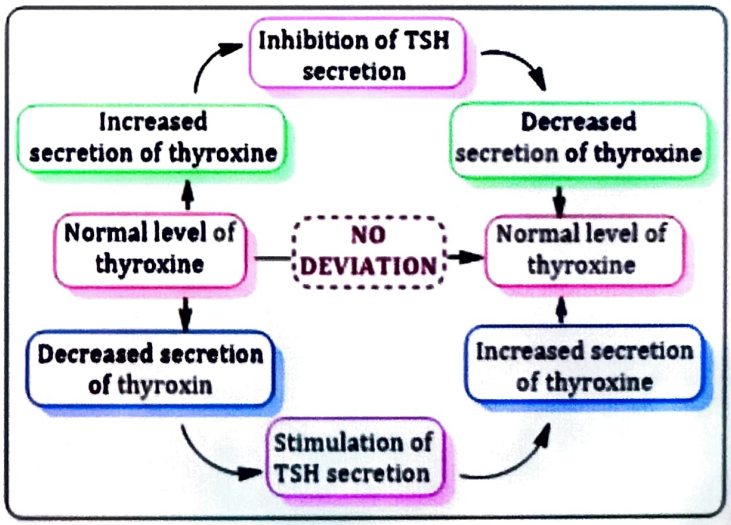
❖ Types of Feedback systems

- **Homeostatic mechanism** in the body is responsible for maintaining the **normalcy** of various body systems.
- This is achieved by means of **feedback signals.**

- Feedback is a process in which some proportion of the output signal of a system is fed (passed) back to the input.
- This is done more often intentionally in order to control the behavior pattern of the system.
- Whenever any change occurs, system receives and reacts to two types of feedback:
  1. **Negative feedback**
  2. **Positive feedback**

1. Negative feedback

- Negative feedback is the one to which the **system** reacts in such a way as to **arrest** the **change** or **reverse** the direction of change.
- After receiving a message, **effectors** send **negative feedback signals** back to the **system.**



- Now, the system stabilizes its own **function** and makes an attempt to maintain **homeostasis.**

2. Positive feedback

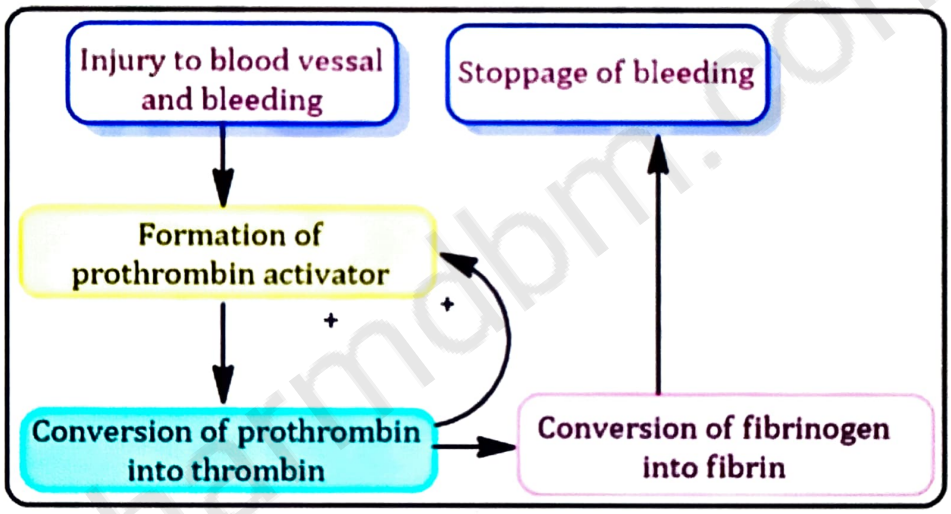
- It is the one to which the system reacts in such a way as to increase the intensity of the change in the same direction.
- Positive feedback is less common than the negative feedback. However, it has its own significance during emergency conditions.
- One of the positive feedbacks occurs during the blood clotting. Blood clotting is necessary to arrest bleeding during injury and it occurs in three stages.

The three stages are:

i. Formation of prothrombin activator

ii. Conversion of prothrombin into thrombin

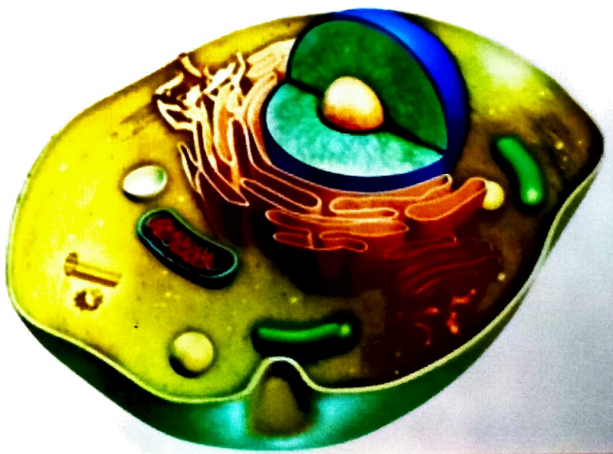
iii. Conversion of fibrinogen into fibrin.

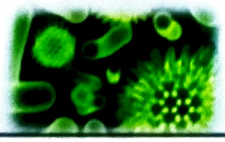


❑ CAUSES OF CELLULAR INJURY

- A variety of stresses of factors may be responsible for cell injury. They are-

1. Hypoxia and ischemia
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



S.NO	CAUSES	EXPLANATION
1.	**HYPOXIA AND ISCHAEMIA** 	• Cells of different tissues essentially require oxygen to generate energy and perform metabolic functions. • Deficiency of oxygen or hypoxia results in failure to carry out these activities by the cells.
2.	**PHYSICAL AGENTS**	• Physical agents in causation of disease are as under: i) Mechanical trauma (e.g. road accidents) ii) Thermal trauma (e.g. by heat and cold) iii) Electricity iv) Radiation (e.g. Ultraviolet and ionizing) v) rapid changes in atmospheric pressure
3.	**CHEMICALS AND DRUGS** 	Important examples include the following: i. Chemical poisons such as cyanide, arsenic, mercury ii. Strong acids and alkalis iii. Environmental pollutants iv. Insecticides and pesticides v. Oxygen at high concentrations vi. Hypertonic glucose and salt vii. Social agents such as alcohol and narcotic drugs viii. Therapeutic administration of drugs
4.	**MICROBIAL AGENTS** 	Injuries by microbes include infections caused by bacteria, rickettsiae, viruses, fungi, protozoa, metazoa, and other parasites.
5.	**IMMUNOLOGIC AGENTS**	It protects the host against various injurious agents but it may also turn lethal and cause cell injury e.g: i) Hypersensitivity reactions ii) Anaphylactic reactions iii) Autoimmune diseases

6.	NUTRITIONAL DERANGEMENTS	• A deficiency or an excess of nutrients may result in nutritional imbalances.
7.	AGEING	• Cellular ageing or senescence leads to impaired ability of the cells to undergo replication and repair, and ultimately lead to cell death.
8.	PSYCHOGENIC DISEASES	• Problems of drug addiction, alcoholism, and smoking result in various organic diseases such as liver damage, chronic bronchitis, lung cancer, peptic ulcer, hypertension, ischemic heart disease etc.

❑ PATHOGENESIS OF CELL INJURY

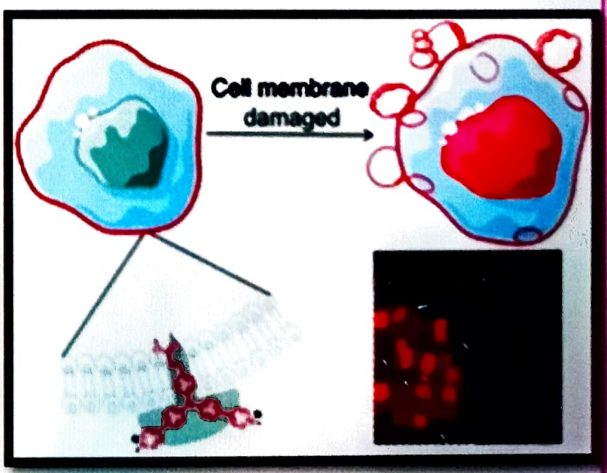
- Injury to cells may have many causes. In such case **oxygen** plays a central role in the cell injury.
- Mechanisms of cell injury include-

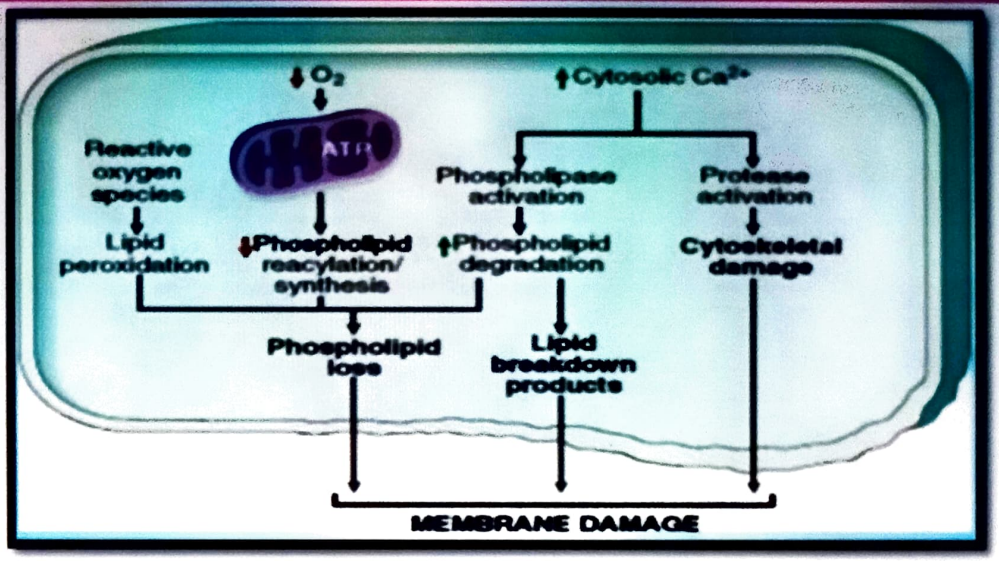
❖ Hypoxic & Ischemic cell injury

- ✓ **Cell membrane damage**
- ✓ **Mitochondrial damage**
- ✓ **Ribosome damage**
- ✓ **Nuclear damage**

1. Cell membrane damage

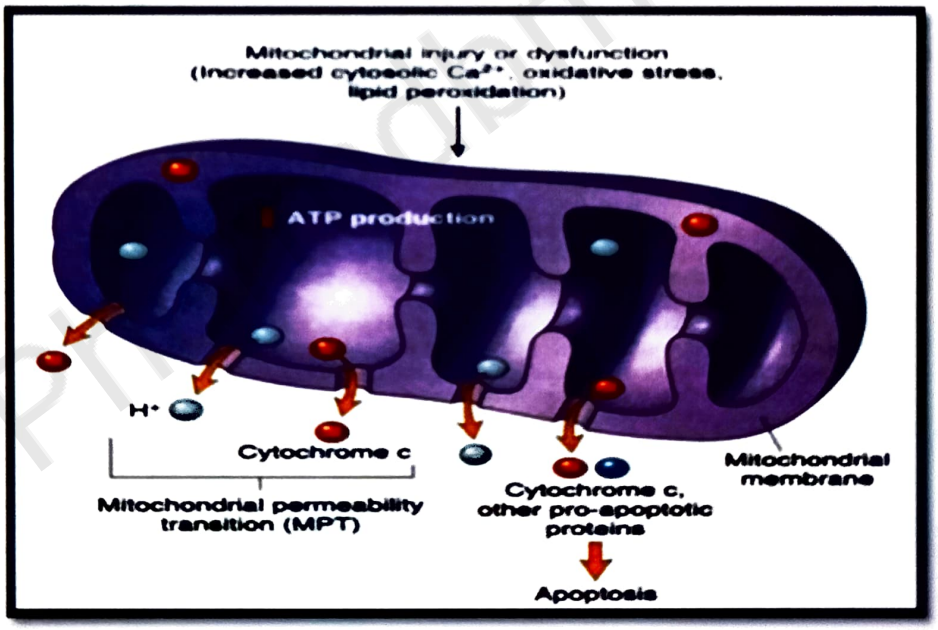
- **Physical agents** such as heat or radiation can damage a cell by literally **cooking** or **coagulating** their **contents**.
- **Impaired nutrient supply**, such as lack of oxygen or glucose, or impaired production of adenosine triphosphate (ATP) may deprive the cell of **essential materials needed to survive.**





2. Mitochondrial damage

- Increases in **cytosolic Calcium**, coupled by an increase in **inorganic phosphate** and **certain fatty acids.**
- **High inorganic phosphate and fatty acids** alone cannot damage the mitochondria but coupled with **high Ca^{2+}** are **extremely damaging** to a cell. Note that high Calcium alone can still **damage mitochondria.**



3. Ribosome damage

- Leading to **altered protein synthesis.**
- If hypoxia continues, **intracellular protein synthesis decreases due** to damage to **ribosomes** and **polysomes. Continue hypoxia causes cytoskeleton changes** with loss of **microvilli and formation of blebs** on the surface of the cell.
- This swelling results in swelling at mitochondria and ER (endoplasmic reticulum).

4. Nuclear damage

- The **decrease** in cellular ATP and **increase** in **adenosine monophosphate** (AMP) also stimulates the **enzyme phosphofructokinase glycolysis** in order to maintain the cells energy source by generating the ATP from **glycogen**.
- This stage is **reversible** if oxygen is restored.

❖ Free Radical Mediation of Cell Injury

- Free radicals are **chemical species** that have a **single unpaired electron** in **outer orbit**. Free radicals initiate **autocatalytic reaction**.
- It is mainly occur in **reperfusion** of the **ischemic cell**. There are many more causes like **chemical injury**, cellular aging, hyperoxia, killing of exogenous biological agents, destruction of tumor cells, inflammatory damage, chemical injuries, ionization, artherosclerogenesis.
- There are some radicals, like **superoxide radicals, hydroxyl ions, peroxide ions**, very destructive to cells which cause **lipid peroxidation,** oxidation of protein, DNA damage, cytoskeleton damage etc.

❑ MORPHOLOGY OF CELL INJURY –ADAPTIVE CHANGES (ATROPHY, HYPERTROPHY, HYPERPLASIA , METAPLASIA,DYSPLASIA)

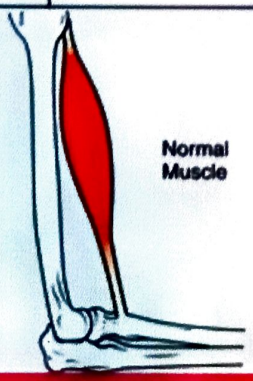
- Adaptive changes are the adjustments which the cells make in **response** to **stresses** which may be for **physiologic needs** *(physiologic adaptation)* or a response to **non-lethal pathologic injury** *(pathologic adaptation)*.
- Such **physiologic** and **pathologic** adaptations occur by following processes:
  - **Decreasing** or **increasing** their size i.e. ***atrophy*** and ***hypertrophy*** respectively, or by increasing their number i.e. ***hyperplasia.***
  - Changing the pathway of **phenotypic differentiation** of cells i.e. **metaplasia** and **dysplasia**.
- In general, the adaptive responses are reversible on withdrawal of stimulus. However, if the irritant stimulus persists for long time, the cell may not be able to survive and may either die or progress further.

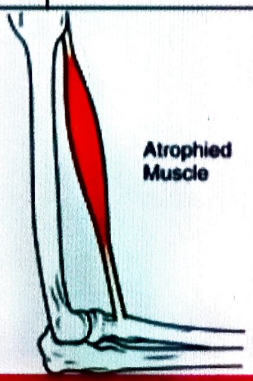
Various mechanisms which may be involved in adaptive cellular responses include the following:

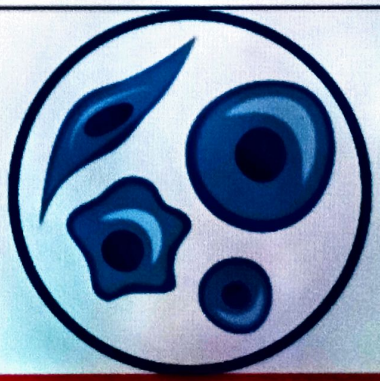
- **Altered cell surface receptor binding.**
- **Alterations in signal for protein synthesis.**
- **Synthesis of new proteins by the target cell such as heat shock proteins (HSPs).**

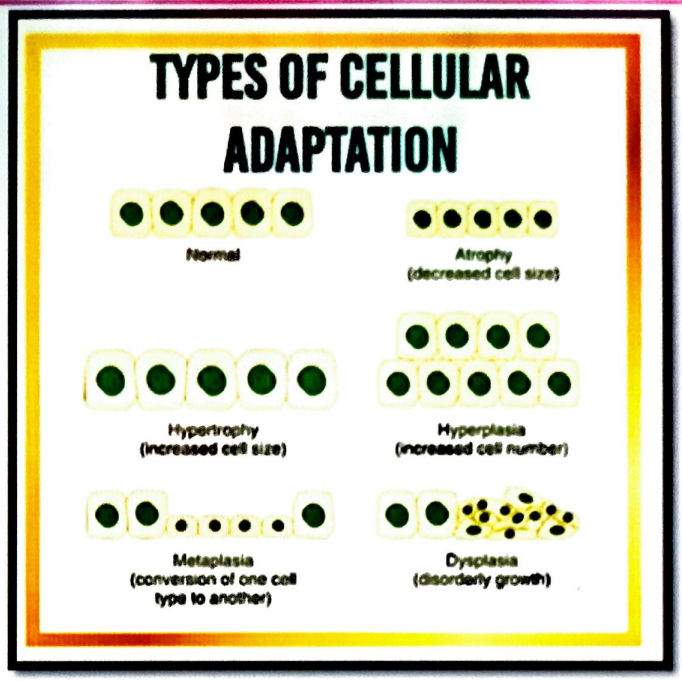
- Common forms of cellular adaptive responses along with examples of physiologic and pathologic adaptations are briefly discussed here:

S.NO	ADOPTATION	FEATURES
1	ATROPHY	Decrease in cell size
2	HYPERTROPHY	Increase in cell size
3	HYPERPLASIA	Increase in cell number **Physiologic Hyperplasia:** occurs when there hormonal stimulation. eg.- Occurs in puberty and pregnancy. **Compensatory Hyperplasia**: Occurs in organs that are capable of regenerating lost tissues. eg.- When part of liver is destroyed. **Pathologic Hyperplasia** - is seen in abnormal stimulation of organs with cells that are capable of regeneration. eg. - Enlargement of Thyroid gland due to TSH from pituitary gland
4	METAPLASIA	Conversion of one type of an adult cell type to another adult cell type
5.	DYSPLASIA	Development of an abnormal type of epithelial cells







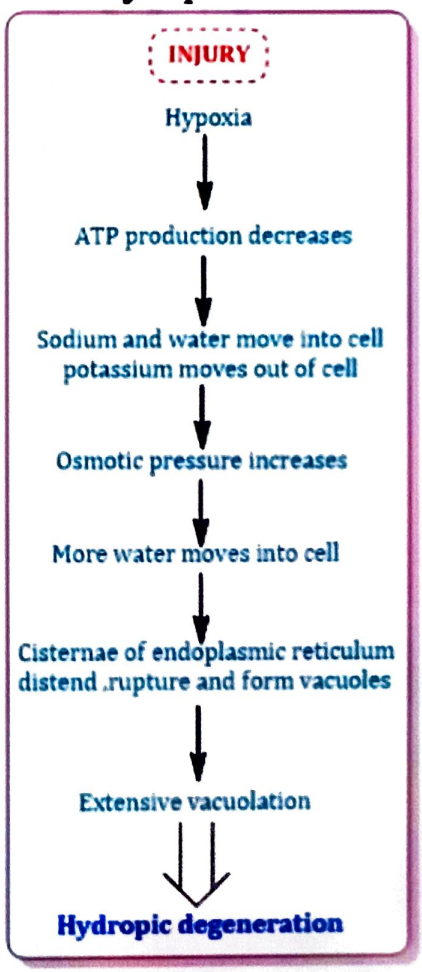


❑ CELL SWELLING

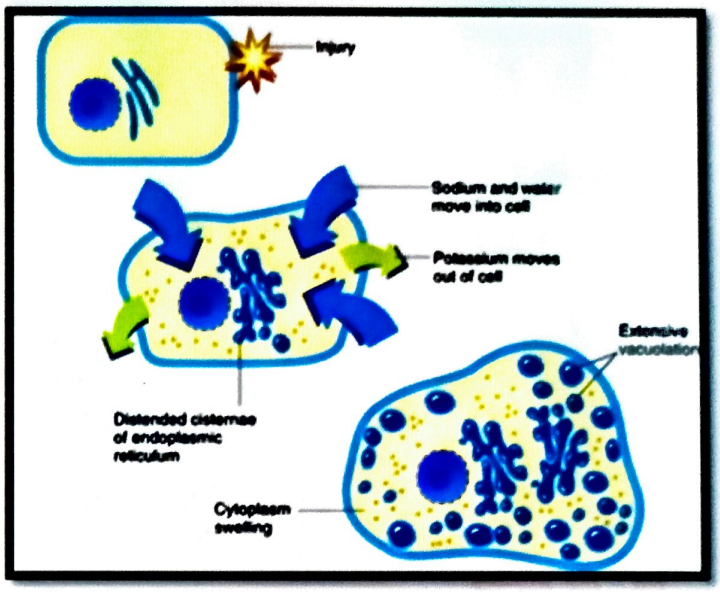
- Normally, it is called **Hydropic changes**, which refers to **excessive water accumulation in the cytoplasm of a cell.**
- Cell swelling is the general term used for the gross appearance of the **affected organ.**
- It is called **vacuolization** when it occurs within the cytoplasm.

❖ Etiology

- Cell selling may be caused by the following factors:
  - ✓ **High fever**
  - ✓ **Poison**
  - ✓ **Burns**
  - ✓ **A hypertonic glucose solution or saline solution is administered intravenously.**
  - ✓ **Bacterial toxins**
  - ✓ **Chemical agents**
  - ✓ **An acute cellular swelling (Cellular oedema) is primarily caused by ATP depletion.**



❖ Pathogenesis



- In healthy cells, **sodium** and **potassium** are controlled at the cell membrane level to prevent **cloudy swelling.**
- It leads to an **accumulation** of sodium **inside** the cell and the **escape** of potassium from the cell.
- Thus, **rapid infiltration** of water in to the cell causes **cellular swelling.**
- This, in turn, leads to **iso-osmotic conditions** being maintained within the cell. **Calcium** is also inflexed into the cell.

❖ Morphology

- An **enlarged kidney, liver, pancreas,** or **heart muscle** is the result of **swollen cells** in these organs. After swelling of the cells of the kidney, the following structure is observed:
  - ✓ **Vacuolar degeneration** is a condition in which the **tubular epithelial cells** become swollen, their cytoplasm containing small clear vacuoles, hence the term. Endoplasmic reticulum cisternae distended in these vacuoles.
  - ✓ **The cytoplasm** may contain **small blebs.**
  - ✓ There may be a **pale appearance** to the **nucleus.**
  - ✓ In the **interstitial space**, swollen tubular cells have compressed the **microvasculature.**

❑ INTRACELLULAR ACCUMULATION

- As a result of abnormal accumulation of substance, the normal cell may suffer **permanent damage or have temporary damage that is potentially harmful.**
- **Cellular phagolysosomes** and **nuclei** are the sites of these **accumulations.** A reversible or permanent accumulation may occur.

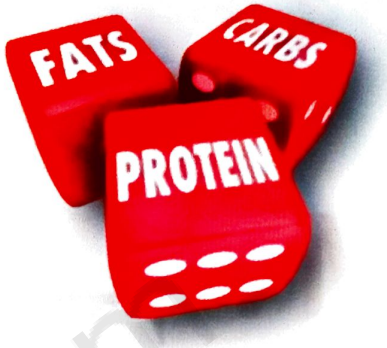
❖ Categories of Accumulation

✓ **Components of normal cell metabolism accumulated in cells include:**

- Proteins
- Carbohydrates
- Fats

✓ **A substance accumulated by abnormal cell metabolism:**

- Inborn error of metabolism
- Storage disease



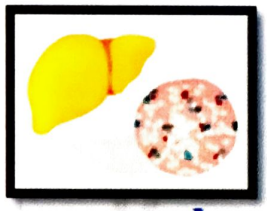
✓ **Pigment accumulation :**

- Exogenous pigments
- Endogenous pigments

❖ Mechanism

✓ **Due to overproduction**

- **Excess accumulation** of **normal endogenous** on a normal or **increased rate**, but the rate does not allow them to be broken down adequately.
- **Example - fatty changes in liver.**

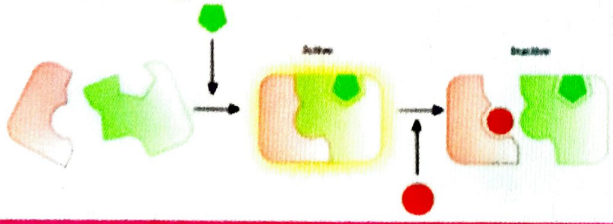


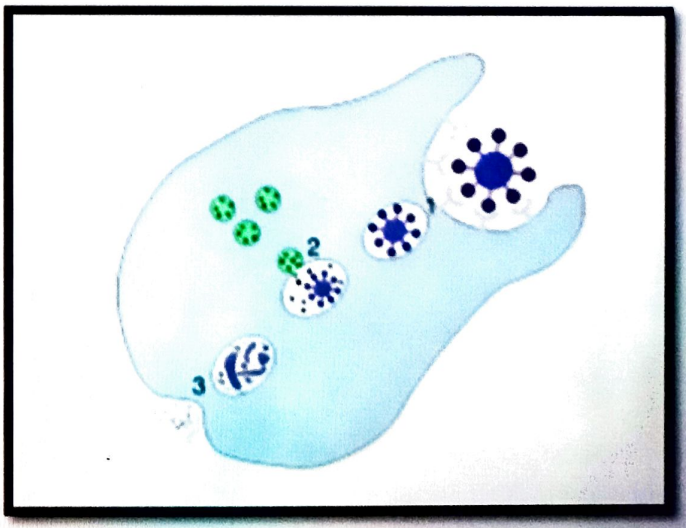
✓ **Inadequate enzymes to remove**

- An **abnormal deposit of exogenous substances are deposited** and accumulate due to the **lack of enzymes that can degrade the substances or the inability to transport them to other sites.**
- Particles of **carbon** and **chemical substances** like silica that cannot be metabolized accumulate.

✓ **Due to inadequate metabolism**

- Endogenous substances accumulate when **enzymes that block specific metabolic pathways prevent them from being metabolized.**





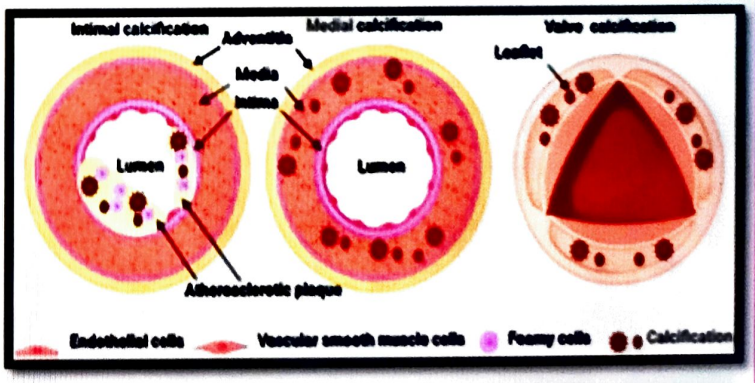
❑ CALCIFICATION

- The **buildup of calcium** in tissues, blood vessels, or organs is referred to as **calcification.**
- The accumulation can **harden** and **interfere** with **normal body functions.**
- **Blood** carries **calcium** throughout the body and **all cells** contain calcium.
- Calcification has the effect of occurring in almost any part of the body. Eventually, this can lead to **health problems.**

❖ Types

- Many places in your body can develop calcium deposits, including:
  - ✓ **Heart valves**
  - ✓ **Bladder, kidney, and gall bladder**
  - ✓ **Brain, here it is known as brain calcification**
  - ✓ **Knee joints and rotator cuff tendons are examples of joints and tendons**
  - ✓ **Soft tissues such as fats, breasts, and muscles**
- **The buildup of calcium isn't always harmful.**
- It is believed that the body produces these deposits as a **result of inflammation, injury, or other biological processes.**
- The calcification of certain organs and the deterioration of blood vessels can disrupt their functions.

❖ Causes

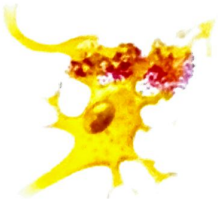


- Calcification is caused by a variety of factors. They are:
  - ✓ **Persistent inflammation**
  - ✓ **Infections**
  - ✓ **Hypercalcemia (excess blood calcium) is caused by calcium metabolism disorders.**
  - ✓ **Diseases of the skeleton and connective tissues caused by genetic or autoimmune factors**

- Calcium rich diets are commonly thought to cause calcifications.
- Calcium oxalate is the most common component of kidney stones.
- The urine of people who get calcium oxalate stones contains more calcium than urine from people who do not develop them.

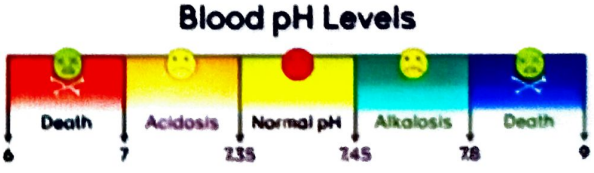
❑ ENZYME LEAKAGE

- The enzyme has covalent bonds with itself and also with the membrane.
- A lower level of the enzyme is typically found in the bloodstream.
- If damage or injury occurs to the heart muscles, these enzymes are released into the bloodstream in greater quantities, which is termed "Enzyme leakage".
- Cell death is a natural process. Cells have a certain lifespan.
- When the tissues or fluids of the body contain **higher levels of acid**, it is known as acidosis. Acidosis is usually caused by malfunctioning kidneys or lungs.
- When an individual has a **high level of alkaline** in their tissues or fluids, the condition is known as alkalosis.



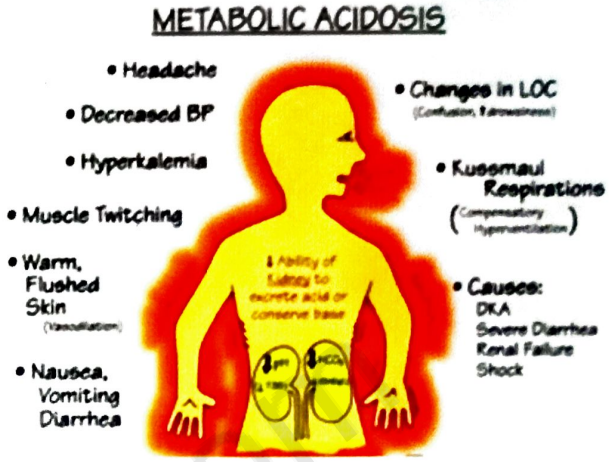
❖ Cell death Acidosis & Alkalosis

- Body fluids are acidotic when there is too much acid in them.
- The body's pH becomes out of balance if your kidneys or lungs cannot maintain it.
- Your body produces acid as a byproduct of many processes.
- If your kidneys or lungs don't work properly, you can have excess acid in your body to compensate for slight pH imbalances.
- Acidity or basicity of your blood is determined by the pH of your blood.
- A lower pH indicates more acidic blood, while a higher pH indicates more basic blood.
- Ideally, blood should have a pH of 7.4.
- An acidic condition is defined as a pH lower than 7.35.
- The pH level of alkalosis should be at or above 7.45.
- A person suffering from acidosis may be suffering from one of two types. it will be categorized as respiratory or metabolic.



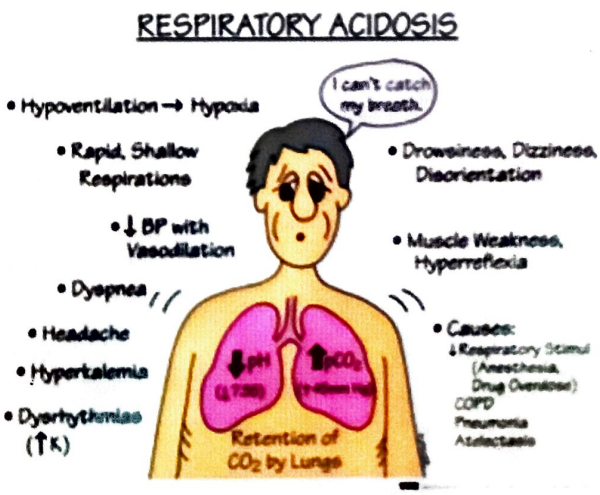
1. Respiratory acidosis

- Respiratory Acidosis occurs as a result of too much CO_2 accumulation in the body.
- While you breathe, CO_2 is normally expelled from the lungs. But sometimes it cannot remove enough CO_2.
- Possible reasons include :
  - ✓ **Sedative misuse**
  - ✓ **Deformed chest structure**
  - ✓ **Alcohol overuse**
  - ✓ **Obesity**
  - ✓ **Asthma**



2. Metabolic acidosis

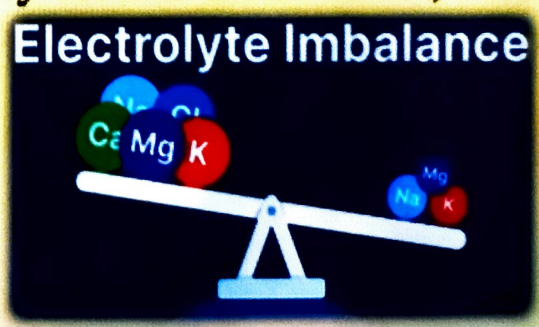
- Metabolic acidosis takes place in the **kidneys**.
- This happens when the acid isn't eliminated enough, or if the base is eliminated too much.
- Metabolic acidosis can be classified as follows:
  - ✓ Diabetes patients with **poorly controlled blood sugars** are at risk of diabetic acidosis. **Lack of insulin** causes the body to produce ketones, which make the **blood acidic.**
  - ✓ An excess of **sodium bicarbonate** is the cause of hyperchloremic acidosis. Blood is kept neutral by sodium bicarbonate. **Vomiting** and **diarrhea** can both lead to this condition.
  - ✓ A person with **lactic acidosis** has an abundance of lactic acid in their body. In addition to **chronic alcohol consumption**, heart failure, cancer, seizures, liver failure, prolonged oxygen deprivation, and low blood sugar can cause it.
  - ✓ When the kidney's ability to **excrete acids** into the urine is **impaired**, renal tubular acidosis results.



❑ ELECTROLYTE IMBALANCE

- Bloodstream contains **many chemicals** that are involved in many of your body's functions. **Electrolytes** are one of these chemicals.
- Ions have a **positive** and a **negative charge** when they are dissolved in water.
- For **nerve reactions** and **muscle function**, these electrolytes ions must be exchanged **properly** inside and outside the **cell**.
- **Calcium, magnesium, potassium, sodium**, and **calcium** are examples of electrolytes.
- These substances can cause a variety of symptoms when they are out of balance.

- **Many factors can contribute to electrolyte imbalances. The following are a few:**
  - ✓ Vomiting, diarrhea, sweating, high fever, or prolonged vomiting result in a loss of body fluids
  - ✓ Kidney disease
  - ✓ Lack of nutrients from food and inadequate diet.
  - ✓ There may be reasons why your body cannot absorb these electrolytes, such as a stomach disorder, medication, or how you eat.
  - ✓ Disorders of the hormones or endocrine system.
  - ✓ Tumor lysis syndrome is one of the complications of chemotherapy. This occurs when tumor cells are rapidly broken down after chemotherapy, reducing calcium levels in the blood, elevating potassium levels, and causing other electrolyte imbalances.
- **Electrolyte imbalance can be caused by certain medications, such as:**
  - ✓ Antibiotics (amphotericin B)
  - ✓ Chemotherapy drugs (cisplatin)
  - ✓ Corticosteroids (hydrocortisone)
  - ✓ Diuretics



UNIT-I (PART-2- INFLAMMATION & REPAIR)

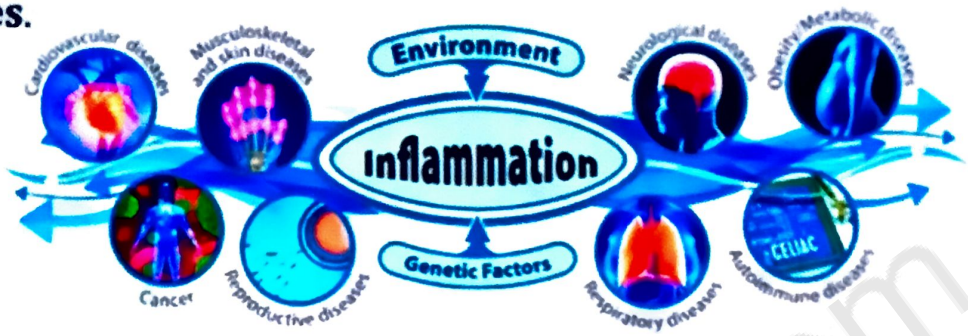
Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ CLINICAL SIGNS OF INFLAMMATION
- ❑ DIFFERENT TYPES OF INFLAMMATION
- ❑ MECHANISM OF INFLAMMATION
  - ❖ ALTERATION IN VASCULAR PERMEABILITY AND BLOOD FLOW
  - ❖ MIGRATION OF WBC'S
- ❑ MEDIATORS OF INFLAMMATION
- ❑ BASIC PRINCIPLES OF WOUND HEALING IN THE SKIN
- ❑ PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

❑ INTRODUCTION

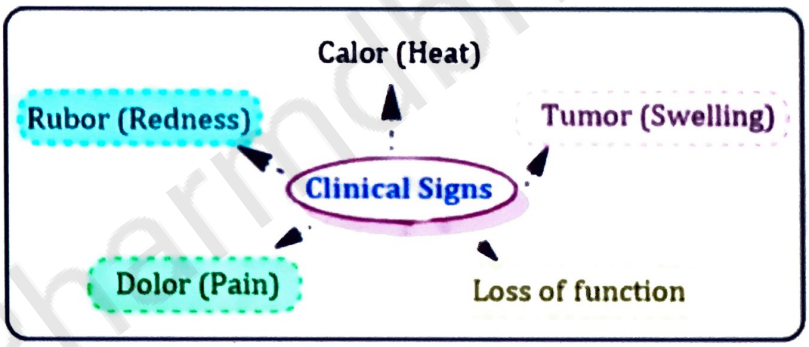
❖ Definition

- Inflammation is defined as the **local response** of **living mammalian tissues** to injury from **any agent.**
- It is a **body defense reaction** in order to eliminate or limit the spread of **injurious agent**, followed by removal of the necrosed **cells** and **tissues.**



❖ Clinical Signs of inflammation

- The physical signs of acute inflammation were described by using the **Latin words :**



1.	**Redness**	An acutely inflamed tissue appears red, for example, skin affected by sunburn, cellulitis due to bacterial infection or acute conjunctivitis. This is due to dilation of small blood vessels within the damaged area.
2.	**Heat**	Increase in temperature is seen only in peripheral parts of the body, such as the skin. It is due to increased blood flow 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.

3.	Swelling:	Swelling results from oedema - the accumulation of fluid in the extravascular space as part of the fluid exudate and, to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area
4.	Pain	Pain is one of the 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.
5.	Loss of function	Loss of function, a well-known consequence of inflammation, was added by Virchow (1821-1902) to the list of features drawn up to Celsius. Movement of an inflamed area is consciously and reflex inhibited by pain, while severe swelling may physically immobilize the tissues.

❖ Different types of inflammation

- Depending upon the defense capacity of the host and duration of response, inflammation can be classified as **acute** and **chronic**:

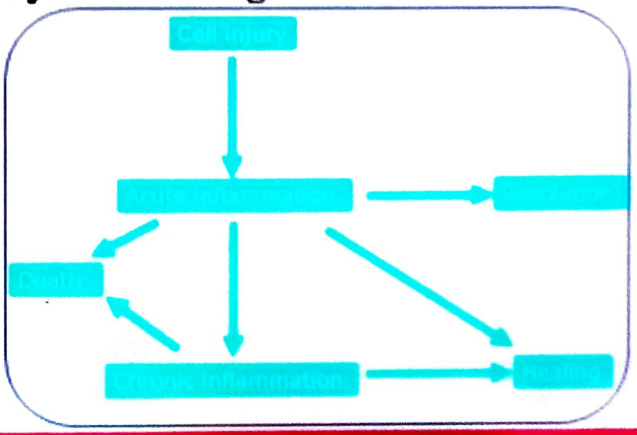
S.NO	ACUTE INFLAMMATION
1.	Is of short duration (lasting less than 2 weeks)
2.	Represents the early body reaction
3.	Resolves quickly and is usually followed by healing
S.NO	**THE MAIN FEATURES OF ACUTE INFLAMMATION ARE**
1.	Accumulation of fluid and plasma at the affected site
2.	Intravascular activation of platelets
3.	Polymorphonuclear neutrophils as inflammatory cells

S.NO	CHRONIC INFLAMMATION
1.	Is of longer duration
2.	Occurs after delay, either after the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning
3.	A variant, *chronic active inflammation*, is the type of chronic inflammation in which during the course of disease there are acute exacerbations of activity.

S.NO	THE MAIN FEATURES OF CHRONIC INFLAMMATION ARE
1.	Presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages, granulation tissue formation, and in specific situations as granulomatous inflammation.

❑ MECHANISM OF INFLAMMATION

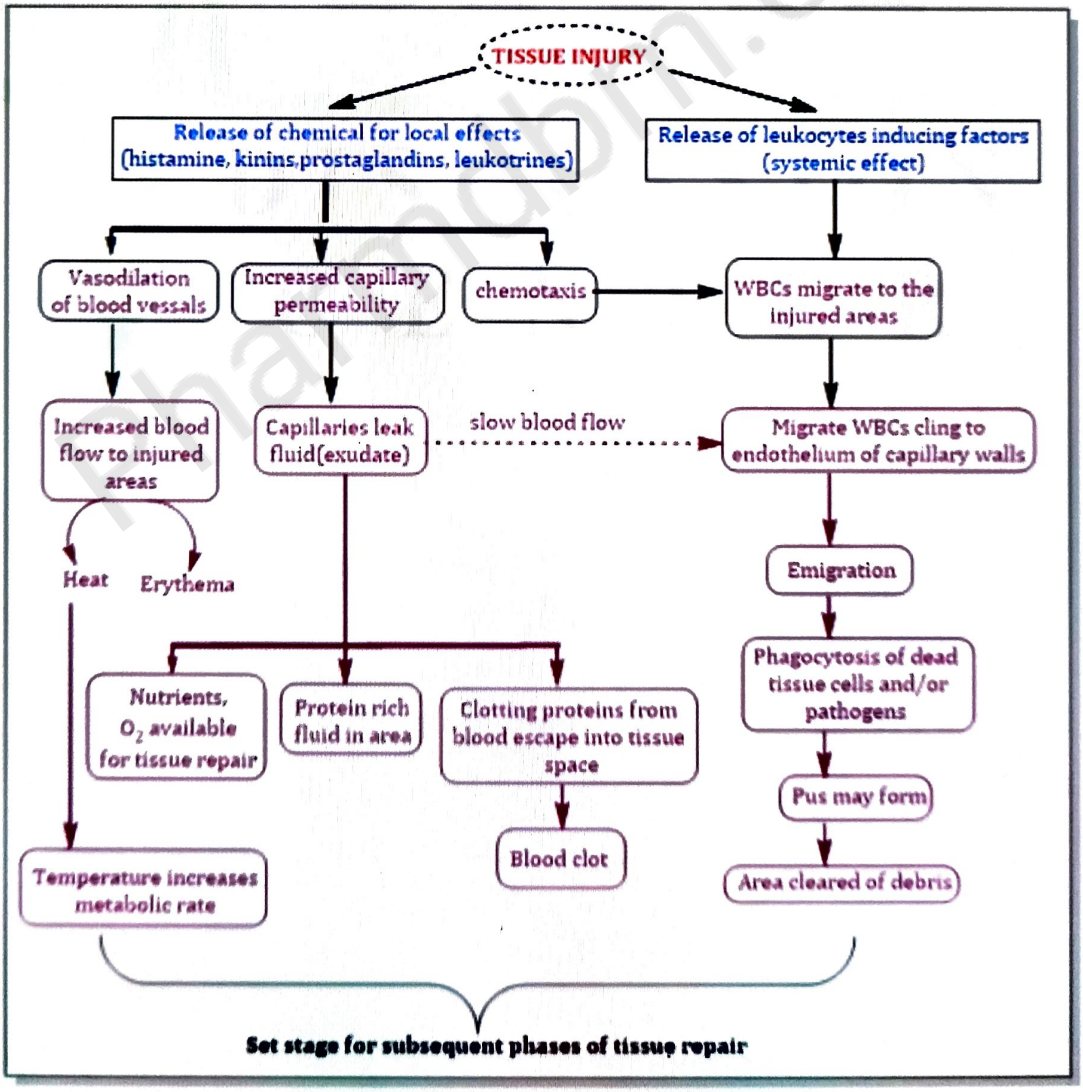
- Inflammation is a process by which the **body's white blood cells** and **chemicals** protect the **body infection** and **foreign substances** such as **bacteria** and **viruses**.
- The body's defense mechanism (immune system) inappropriately triggers an **inflammatory response** when there are **no foreign substances** to fight off, these are called **autoimmune diseases**, where the body's normally **protective immune system** causes damage to its **own tissues.**
- When the tissue injury releases the **inflammation mediators** cause inflammation. These chemicals release from the **site of injury** such as **histamine, kinin, prostaglandins leukotrienes** and **white blood cells** are released to protect or repair the body from foreign substances.
- The inflammatory responses are due to **circulating cells** and **plasma proteins, vascular cells** and **extracellular matrix** of the surrounding connective tissue.



❖ Components of Vascular Smooth Muscles Involved in Inflammation

S.NO	TYPE OF CELL/COMPONENT	EXAMPLES
1.	CONNECTIVE CELLS	Mast cells, Fibroblasts, lymphocytes
2.	CIRCULATING CELLS	Neutrophills, Basophills, eosinophills, Lymphocytes, Monocytes ,platelets
3.	STRUCTURAL FIBROUS PROTEINS	Collagen, Elastin
4.	ADHESIVE GLYCOPROTEINS	Fibronectin, Entactin, Tenascin
5.	VASCULAR WALL CELLS	Endothelial Cells

- All these parameters interact to or resolve a local injury and restore normal tissue function.



The outline mechanism of inflammation

❖ Alteration in Vascular permeability and blood flow

- In the early stages, oedema fluid, fibrin and neutrophil polymorphs accumulate in the extracellular spaces of the damaged tissue.
- The presence of the cellular component, neutrophil polymorph, is essential for a histological diagnosis of acute inflammation. The acute inflammatory response involves three processes:

1. **Changes in vessel caliber** and consequently flow
2. **Increased vascular permeability** and formation of the fluid exudates
3. **Formation of the cellular exudate** - emigration of the neutrophil polymorphs into the extravascular space.

1. Changes in vessel caliber and consequently flow

- The microcirculation consists of the network of **small capillaries** lying between **arterioles**, which have a **thick muscular wall, and thin-walled venules.**
- Capillaries have no smooth muscle in their walls to control their caliber and are so narrow that red blood cells must pass through them
- The smooth muscle of arteriolar walls forms **precapillary sphincters** which regulate blood flow through the capillary bed.
- In blood vessels larger than capillaries, blood cells flow mainly in the **center of the lumen (axial low),** while the area near the vessel wall carries only plasma (plasmatic zone).
- This feature of normal blood flow keeps blood cells away from the vessel wall.

2. Increased vascular permeability and formation of the fluid exudates

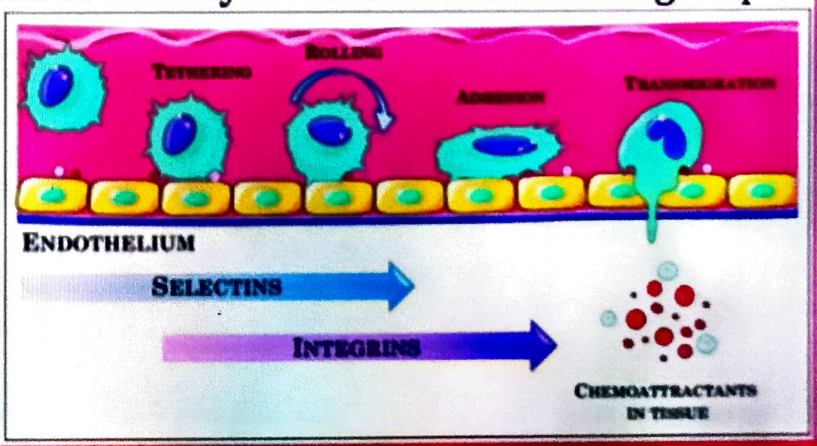
- Small blood vessels are lined by a **single layer of endothelial cells.**
- In some tissues, these form a complete layer of **uniform thickness** around the vessel wall, while in other tissues there are areas of endothelial cell thinning, known as **fenestrations.**
- Walls of small blood vessels act as a **microfilter**, allowing the passage of water and solutes but blocking that of large molecules and cells.

- Oxygen, carbon dioxide and some nutrients transfer across the wall by diffusion, but the main transfer of fluid and solutes is by **ultrafiltration**,
- The high colloid osmotic pressure inside the vessel, due to plasma proteins, favours the fluid return to the vascular compartment.
- Under normal circumstances, **high hydrostatic pressure** at the arteriolar end of capillaries forces fluid out into the **extravascular space,** but this fluid returns into the capillaries at their venous end, where hydrostatic pressure is **low**.
- In acute inflammation, not only is **capillary hydrostatic pressure** increased, but there is also escape of plasma proteins into the **extravascular space**, increasing the colloid osmotic pressure there.
- Much more fluid **leaves** the vessels than is **returned** to them.
- The net escape of protein-rich fluid is called **exudation**; hence, the fluid is called the **fluid exudate.**

❖ Migration of WBC's or Leukocytes

- The main inflammatory cells are **polymorphonuclear leukocytes (neutrophils/heterophils, eosinophils, basophils), mast cells, mononuclear cells (monocytes/macrophages, lymphocytes, plasma cells), and platelets.**
- Most cells, except for plasma cells, macrophages & mast cells, are normal inhabitants of the circulating blood.
- The total leukocyte (WBC) count in peripheral blood and the relative proportions of different white blood cells may be greatly modified in the systemic response to inflammation and can, therefore, be used as a diagnostic tool. The migration of leukocytes involves in following Steps. These are :

1) **Margination**
2) **Rolling & Adhesion**
3) **Emigration**
4) **Chemotaxis**
5) **Phagocytosis**



✓ **Margination:**

- In the normal blood circulation, White blood cells are traveled generally to the **central (axial) stream** in blood vessels, and do not flow in the peripheral (plasmatic) zone near to the endothelium.
- However, loss of intravascular fluid and increase in plasma viscosity with **slowing** and **stagnation** of the flow occurs due to vasodilatation and increased **vascular permeability.**
- The Leukocytes fall out of the **central column** and tumble slowly to the periphery of the **vascular lumen** until they come in contact with the surface of endothelial cells of capillaries and post-capillary venules.

✓ **Rolling & Adhesion:**

1. Adhesion

- Marginated leukocytes line of the endothelium.
- Leukocytes start to become adhered to the surface of endothelial cells through various adhesion molecules.
- The adhesion of leukocyte to vascular endothelium is at first loose, allowing the leukocytes to roll along the endothelial surface.
- The adhesion becomes firmer, the leukocytes become stationary and can then begin to migrate through the endothelium and into the site of injury.
- Leukocyte randomly contacts the endothelium in normal tissues, but do not adhere to it. The process of adhesion molecules of which there are 4 main groups -

1. **Selectins:** (P-selectin and E-selectin on endothelium and L-selectin on leukocytes)
2. **Mucin:** like ligands (Sialyl-Lewis X, etc. on leukocytes)
3. **Integrins:** (CD11/CD18, etc. on leukocytes)
4. **Immunoglobulin** superfamily adhesion molecules: IgSAM's (ICAM, VCAM, MadCAM, etc on endothelium, and PECAM on endothelium and leukocytes)

- Increased leukocyte adhesion results from the interaction between paired adhesion molecules on leukocyte and endothelial surfaces.

2. Rolling:

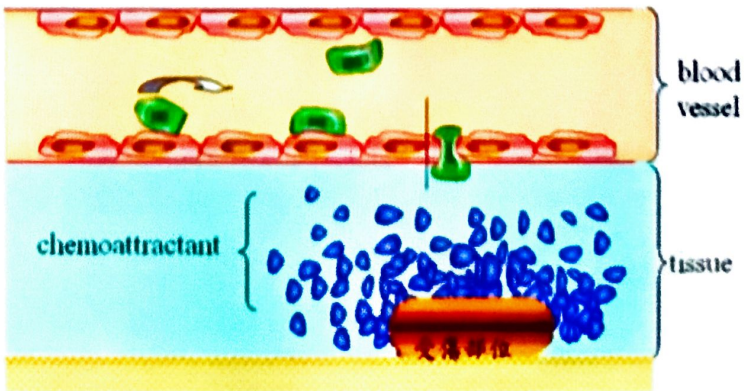
- **P-selectin** is first to become activated due to release of histamine, thrombin & Platelet Activating Factor (PAF).
- **E-selectin** follows in 1-2 hours, stimulated by the secretion of TNF-alpha and IL-1 by macrophages, mast cells and/or damaged endothelial cells.

✓ **Emigration of leukocyte:**

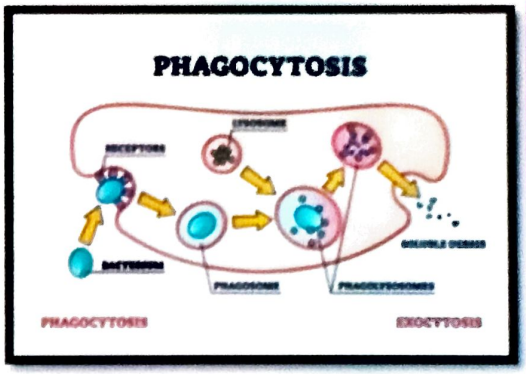
- The process by which leukocytes escape from the **blood to perivascular tissues;** moving to the site of inflammation.
- After firm adhesion the **leukocytes** insert large cytoplasmic extensions into endothelial gaps.
- The vascular gaps have been created by actions of histamine and other **chemical mediators** as well as by the leukocytes themselves.
- The leukocyte pass through the **basement membrane** of the vessel, the emigration occurs in the postcapillary venule because it is there that adequate numbers of inter-endothelial gaps and receptors are found
- In viral infections, lymphocytes are the first to arrive and in some hypersensitivity reactions, eosinophils arrive first.

✓ **Chemotoxins:**

- The initial margination of neutrophils and mononuclears is potentiated by slowing of blood flow and by **increased 'stickiness'** of the endothelial surface.
- After penetration of the vessel wall, the subsequent movement of the leucocytes is controlled by chemotaxis.
- The **cell moves** in response to an increasing concentration gradient of the particular **chemotactic agent**, usually a **protein** or **polypeptide**.



✓ Phagocytosis:

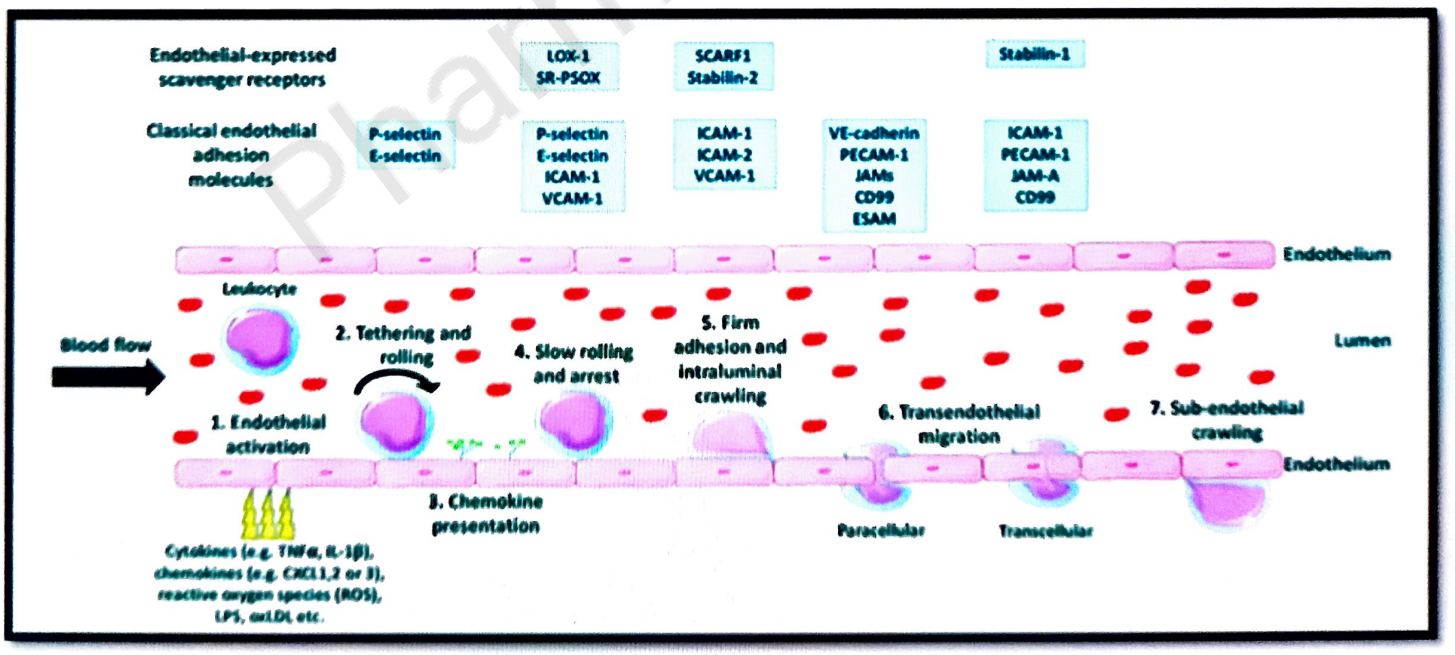


- Phagocytosis is a process of engulf, kill and degrade foreign material; most commonly bacteria.
- In this process, the neutrophils and macrophages clear the injurious agent.
- The aimed at engulfing an injurious agent include following steps.

a) **Recognition and attachment of agent** (in case of bacteria): Mannose on the bacterial wall is recognized directly by the leukocyte's mannose receptor or bacteria are opsonized by antibodies and complement (C3b) fragments that are then recognized by specific receptors on leukocytes.

b) **Engulfment**: Small cytoplasmic extensions (pseudopods) project from the leukocyte. Pseudopods wrap around the attached particle until it is engulfed. Pseudopods meet and fuse, forming a phagosome.

c) **Phagolysosome formation:** The fusion of lysosomal granules with phagosome to forms the phagolysosome. The phagosome killed and digested the bacteria.



❑ MEDIATORS OF INFLAMMATION

- These are a **large** and **increasing** number of endogenous chemical substances which mediate the process of acute inflammation.
- Mediators of inflammation have some common properties as under:

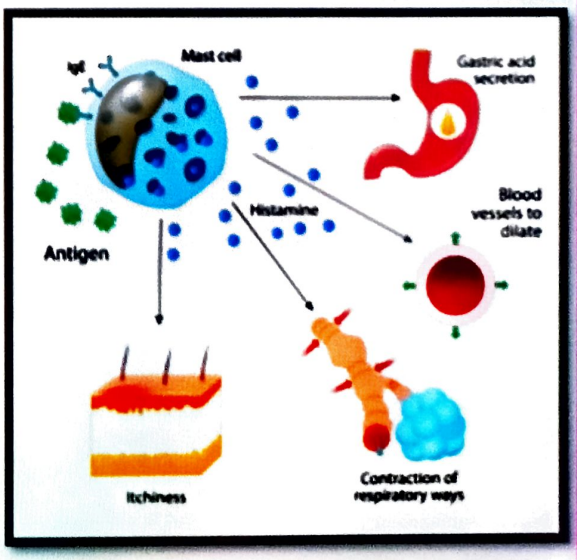
1.	These mediators are released either from the cells or are derived from plasma proteins.
2.	All mediators are released in response to certain stimuli. These stimuli may be a variety of injurious agents, dead and damaged tissues, or even one mediator stimulating release of another
3.	Mediators act on different targets. They may have similar action on different target cells or differ in their action on different target cells. They may act on cells which formed them or on other body cells.
4.	Range of actions of different mediators are: increased vascular permeability, vasodilatation, chemotaxis, fever, pain and tissue damage.
5.	Mediators have short lifespan after their release.

A. CELL-DERIVED MEDIATORS

1. VASOACTIVE AMINES

- Two important pharmacologically active amines that have role in the early inflammatory response (first one hour) are **histamine** and **5-hydroxytryptamine (5-HT) or serotonin**; another addition to this group is **neuropeptides**.

HISTAMINE	It is stored in the granules of mast cells, basophils and platelets.
	The main actions of histamine are: vasodilatation, increased vascular (venular) permeability, itching and pain.



5-HYDROXYTRYPTAMINE (5-HT OR SEROTONIN)	**It is present in tissues like chromaffin cells of GIT, spleen, nervous tissue, mast cells and platelets.**
	The actions of 5-HT are similar to histamine but it is a less potent mediator of increased vascular permeability and vasodilatation than histamine.

NEUROPEPTIDES	Another class of vasoactive amines is tachykinin neuropeptides such as substance P, neurokinin A, vasoactive intestinal polypeptide (VIP) and somatostatin

2. ARACHIDONIC ACID METABOLITES (EICOSANOIDS)

- Arachidonic acid is a **fatty acid, eicosatetraenoic acid.**
- Arachidonic acid is a constituent of the phospholipid cell membrane, besides its presence in some constituents of diet.
- Arachidonic acid is released from the cell membrane by **phospholipases**.
- It is then activated to form arachidonic acid **metabolites** or **eicosanoids**.

3. LYSOSOMAL COMPONENTS

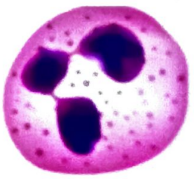
- The inflammatory cells—neutrophils and monocytes, contain lysosomal granules which on release elaborate a variety of mediators of inflammation e.g.

i) Granules of neutrophils- Neutrophils have 3 types of granules:

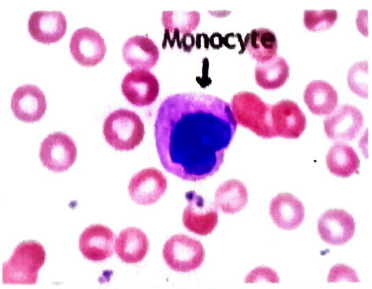
a) Primary or azurophil granules

b) Secondary or specific granules

c) Tertiary granules or C particles



ii) Granules of monocytes and tissue macrophages- These cells on degranulation also release mediators of inflammation like acid proteases, collagenase, elastase and plasminogen activator.



4. PLATELET ACTIVATING FACTOR (PAF)

- It is released from **IgE-sensitized basophils** or **mast cells,** other leucocytes, endothelium and platelets. Apart from its action on platelet aggregation and release reaction, the actions of PAF as mediator of inflammation are:

1.	Increased vascular permeability
2.	Vasodilatation in low concentration and vasoconstriction otherwise
3.	Bronchoconstriction
4.	Adhesion of leucocytes to endothelium
5.	Chemotaxis

5. CYTOKINES

- Cytokines are polypeptide substances produced by activated lymphocytes (lymphokines) and activated monocytes (monokines).

6. FREE RADICALS: OXYGEN METABOLITES AND NITRIC OXIDE

- Free radicals act as potent mediator of inflammation:

i) Oxygen-derived metabolites are released from activated neutrophils and macrophages and include superoxide oxygen (O'2), H2O2, OH' and toxic NO products. These oxygen-derived free radicals have the following actions in inflammation:

a) Endothelial cell damage and thereby increased vascular permeability.

b) Activation of protease and inactivation of antiprotease causing tissue matrix damage.

c) Damage to other cells.

ii) Nitric oxide (NO) NO plays the following roles in mediating inflammation:

a) Vasodilatation

b) Anti-platelet activating agent

c) Possibly microbicidal action.

B. PLASMA PROTEIN-DERIVED MEDIATORS (PLASMA PROTEASES)

- These include various products derived from activation and interaction of 4 interlinked systems: kinin, clotting, fibrinolytic and complement.

1. THE KININ SYSTEM

- This system on activation by factor XIIa generates bradykinin, so named because of the slow contraction of smooth muscle induced by it.
- Bradykinin acts in the early stage of inflammation and its effects include:
  - i) **Smooth muscle contraction**
  - ii) **vasodilatation**
  - iii) **increased vascular permeability**
  - iv) **pain**

2. THE CLOTTING SYSTEM

- Factor XIIa initiates the cascade of the clotting system resulting information of fibrinogen which is acted upon by thrombin to form fibrin.
- The actions of fibrinopeptides in inflammation are:
  - i) **increased vascular permeability**
  - ii) **chemotaxis for leucocyte**
  - iii) **anticoagulant activity**

3. THE FIBRINOLYTIC SYSTEM

- This system is activated by **plasminogen activator**, the sources of which include **kallikrein** of the **kinin system**, **endothelial cells** and **leucocytes**.
- The actions of plasmin in inflammation are as follows:

  i) Activation of factor XII to form prekallikrein activator that stimulates the kinin system to generate bradykinin;

  ii) splits off complement C3 to form C3a which is a permeability factor; and

  iii) degrades fibrin to form fibrin split products which increase vascular permeability and are chemotactic to leucocytes

4. COMPLEMENT SYSTEM:

- The activation of complement system can occur either:
  i) By *classic pathway* through antigen-antibody complexes; or
  ii) By *alternate pathway* via non-immunologic agents such as bacterial toxins, cobra venoms and IgA.
- Complement system on activation by either of these two pathways yields activated products which include **anaphylatoxins** (C3a, C4a and C5a), and **membrane attack complex (MAC)** i.e. C5b,C6,7,8,9.

❑ BASIC PRINCIPLES OF WOUND HEALING

- Wound healing is a **complex** and **dynamic process**
- Knowledge of the physiology of the normal wound healing trajectory through the phases of **hemostasis, inflammation, granulation** and **maturation** provides a framework for understanding the basic principles of wound healing.
- Research regarding acute wounds in animal models demonstrates that wounds heal in 4 phases. It is believed that chronic wounds also undergo 4 basic phases of healing. These are
  - ✓ **Hemostasis**
  - ✓ **Inflammation**
  - ✓ **Proliferation** (also known as granulation and contraction)
  - ✓ **Remodeling** (also known as maturation)

1. Hemostasis-

- Hemostasis, the **first phase of healing**, begins at the onset of injury, and the objective is to stop the bleeding.
- In this phase, the body activates its **emergency repair system, the blood clotting system, and forms a dam to block the drainage.**
- During this process, platelets come into contact with **collagen**, resulting in activation and **aggregation**.
- An enzyme called **thrombin** is at the center, and it initiates the formation of a fibrin mesh, which strengthens the **platelet clumps into a stable clot.**

2. Inflammatory Phase

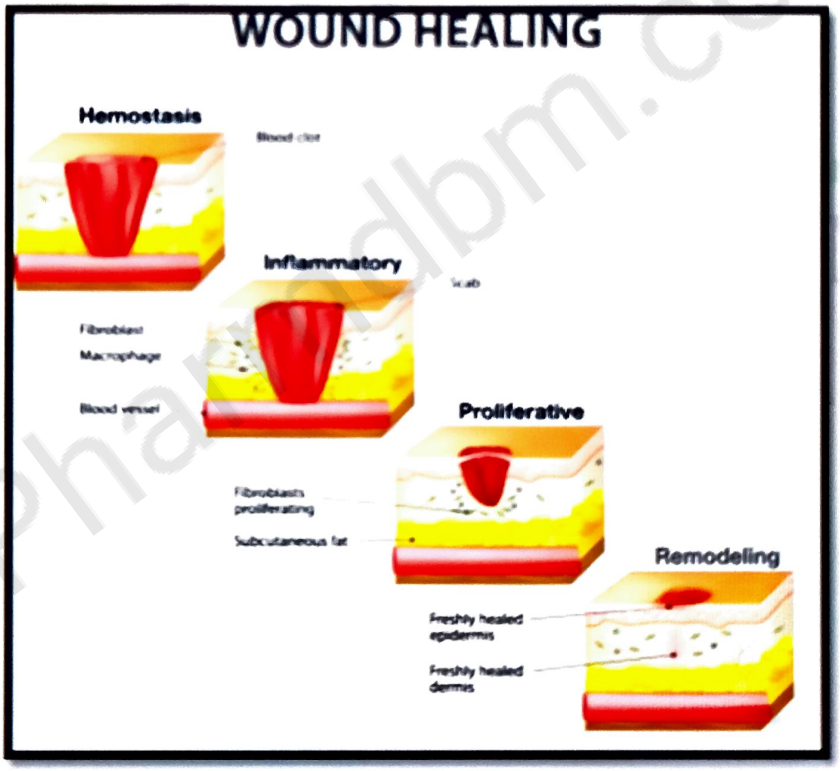
- If Phase 1 is primarily about coagulation, the second phase, called the **Defensive/Inflammatory Phase, focuses on destroying bacteria and removing debris—essentially preparing the wound bed for the growth of new tissue.**
- During Phase 2, a type of white blood cells called neutrophils enter the wound to **destroy bacteria** and **remove debris.**
- These cells often reach their peak population between **24 and 48 hours** after injury, reducing greatly in number after three days.
- As the white blood cells leave, specialized cells called **macrophages** arrive to continue **clearing debris.**
- These cells also secrete **growth factors** and **proteins** that attract immune system cells to the wound to facilitate tissue repair.
- This phase often lasts four to six days and is often associated with **edema, erythema (reddening of the skin), heat and pain.**

3. Proliferative Phase

- Once the wound is cleaned out, the wound enters Phase 3, the **Proliferative Phase, where the focus is to fill and cover the wound.**
- The Proliferative phase features three distinct stages:
  1) **filling the wound;**
  2) **contraction of the wound margins; and**
  3) **covering the wound (epithelialization).**
- During the first stage, shiny, deep red granulation tissue fills the wound bed with connective tissue, and new blood vessels are formed.
- During contraction, the wound margins contract and pull toward the center of the wound.
- In the third stage, epithelial cells arise from the wound bed or margins and begin to migrate across the wound bed in leapfrog fashion until the wound is covered with epithelium.
- The Proliferative phase often lasts anywhere from **four to 24 days**

4. Maturation Phase

- During the Maturation phase, the new tissue slowly **gains strength and flexibility.**
- Here, collagen fibers **reorganize**, the **tissue remodels** and **matures** and there is an overall increase in **tensile strength.**
- The Maturation phase varies greatly from wound to wound, often lasting anywhere from **21 days to two years.**
- The healing process is remarkable and complex, and it is also susceptible to interruption due to **local** and **systemic factors**, including **moisture**, **infection**, and **maceration (local)**; and age, nutritional status, body type (systemic).
- When the right healing environment is established, the body works in wondrous ways to heal and replace devitalized tissue.



❑ PATHOPHYSIOLOGY OF ATHEROSCERELOSIS

- Atherosclerosis is caused by **plaque deposits (fatty deposits) that stack up in the arteries.**
- **Cholesterol, fatty substances, calcium, and fibrin are the ingredients of plaques such as cholesterol, fatty substances, and waste products.**
- The incidence of atherosclerosis cannot be accurately estimated since it is primarily asymptomatic.

- **Cardiovascular diseases** are mostly caused by atherosclerosis. Coronary artery disease and ischemic stroke are the two main types of atherosclerotic cardiovascular disease.
- Typically, atherosclerosis occurs as a result of **chronic inflammation** at vulnerable areas of the **arteries** due to the **continuous process** of arterial wall **lesions** caused by lipid retention by the intima, resulting from the trapping of lipids by a matrix (e.g., proteoglycans).
- The aorta, coronary and carotid arteries exhibit similar **systemic changes in atherosclerosis**. It is usually understood that atherosclerosis is a continuous process that involves a series of histologic developments and lesions.

1. The fatty streak

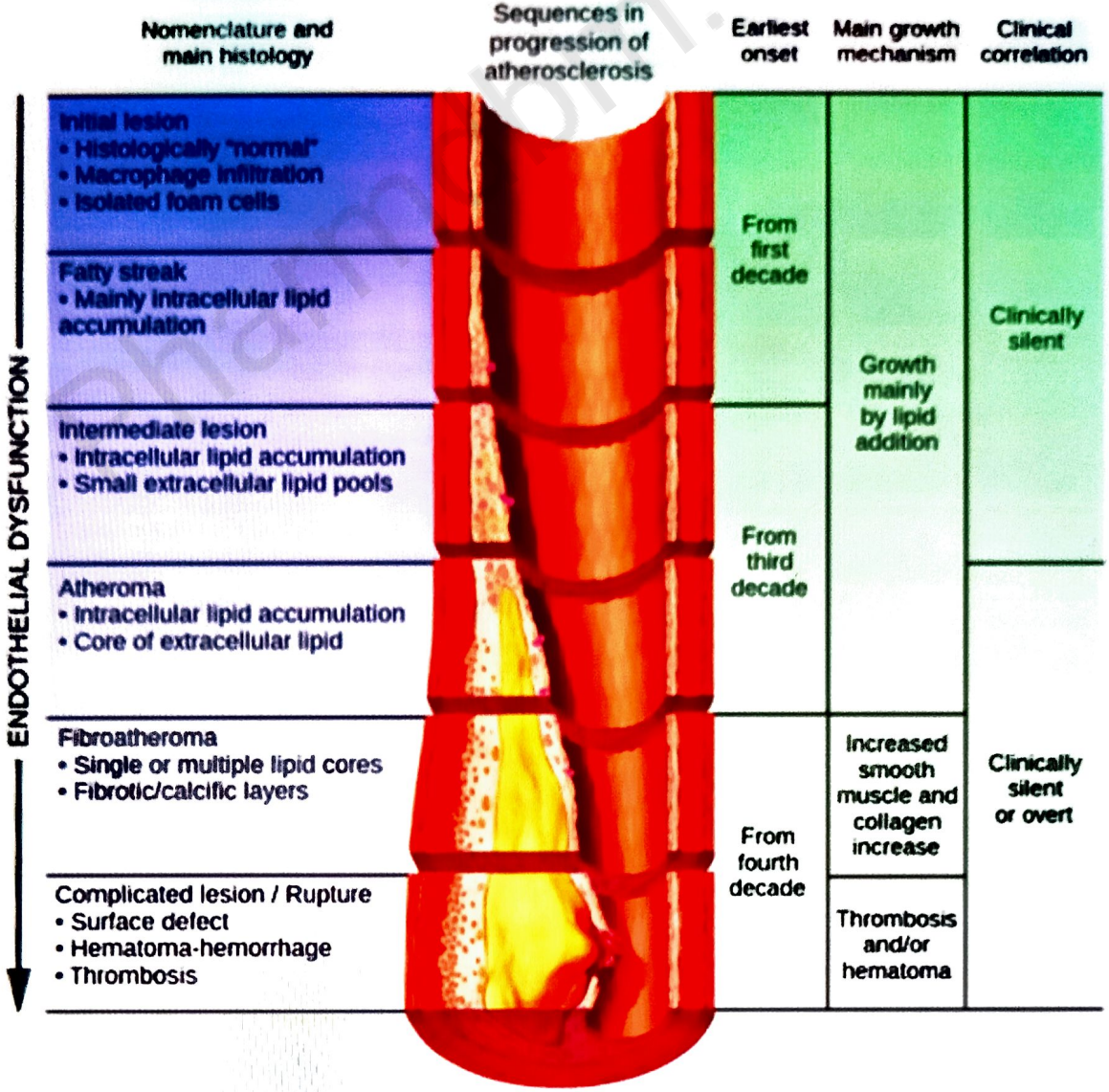
- The **aorta** and **carotid arteries,** which are major arteries, appear with **brown spots.**
- **Macrophages** (types of white blood cells) and **smooth muscle cells** are present in this streak.
- **Fibrotic plaques** are a more harmful form of atherosclerosis that develops after the **fatty streak phase.**

2. Fibrous plaque

- Fibrous plaques form on the **inner lining of vessels.**
- Plaques like this are formed of macrophages, smooth muscle cells, and lymphocytes (more aggressive types of white blood cells).
- Cells with cholesterol are found in this plaque. Growing fibrous plaques begin to protrude into the vessels in which blood flows.

3. Complicated lesion

- The underlying cause of atherosclerosis is a series of **risky events.**
- When a fibrous plaque is broken up, cholesterol and connective tissue are **exposed** beneath it. Within seconds of an injury being detected, a **blood-clotting cell** is sent to the scene.
- Both the **blockage** and the **clot** make the situation particularly **hazardous**, as blood flow is now restricted.
- A ruptured plaque combined with a blood clot form a **compound lesion.**


Nomenclature and main histology
Sequences in progression of atherosclerosis
Earliest onset
Main growth mechanism
Clinical correlation
ENDOTHELIAL DYSFUNCTION
Initial lesion
• Histologically "normal"
• Macrophage infiltration
• Isolated foam cells
Fatty streak
• Mainly intracellular lipid accumulation
Intermediate lesion
• Intracellular lipid accumulation
• Small extracellular lipid pools
Atheroma
• Intracellular lipid accumulation
• Core of extracellular lipid
Fibroatheroma
• Single or multiple lipid cores
• Fibrotic/calcific layers
Complicated lesion / Rupture
• Surface defect
• Hematoma-hemorrhage
• Thrombosis
From first decade
From third decade
From fourth decade
Growth mainly by lipid addition
Increased smooth muscle and collagen increase
Thrombosis and/or hematoma
Clinically silent
Clinically silent or overt