Inflammation and Healing

- Inflammation is the response of living tissue to injury. It involves a well-organized vascular, humoral, cellular and nervous reactions.

- The roman Cornelius Celcius formulated his famous cardinal signs of inflammation : Calor (heat) , Rubor (redness), Tumor (swelling), Dolor (pain) and Functio laesa (loss of function)

Causes of inflammation

- **Biological agents – viruses, bacteria, fungi, parasites**
- **Physical and chemical agents - mechanical trauma, exposure to excessive amounts of sunlight, x-rays and radioactive materials, corrosive chemicals, extremes of heat and cold.**
- **Hypersensitivity – body reacts against itself**
- **Necrosis - anoxia, trauma**
- **Tumors**

Pathogenesis of inflammation

1. Vascular changes

- a. Changes in vessel caliber
  b. Changes in blood flow
  c. Increased vascular permeability

Changes in vessel caliber

- Short transient arteriolar **vasoconstriction** followed by **vasodilatation** of the capillaries, arterioles and venules.

Changes in blood flow

- Dilatation of arterioles and capillaries leads to **increased blood flow** (active hyperemia). Vascular flow is then **slowed** (passive hyperemia)
- **Stasis** of the blood flow follows and provides a microenvironment that facilitates **leukocytic margination** along the luminal surface of endothelial cells.

Increased vascular permeability

- **Permeability increases** induced by chemical mediators.
- **Molecular concentrations in the tissue increases** because of the leakage of proteins, cellular and bacterial debris fragmented by cellular enzymes out of small blood vessels towar d the tissue.
- **Colloid osmotic pressure** increases leading to extravasation of plasma fluid.

Mediators of inflammation

- Mediators are the substances that initiate and regulate inflammatory reactions.

- Cell derived mediators (like amines and lymphokines)

or

Plasma protein derived mediators (like kinins and complement system)

Vasoactive amines

Histamine

- Mast cells are richest source of histamine
- Histamine is stored as granules and released by degranulation in response to various stimuli:

1. Dilation of vessels
2. Increase of venules permeability
3. Contraction of endothelial and smooth muscle cells
4. Stimulation of exocrine secretions
5. Selective chemotaxis of eosinophilic granulocytes.

Serotonine

- Located in tissues.
- Found in thrombocytes, mast cells, basophilic granulocytes and enterochromaffin cells of brain and intestine.
- Low dose: vasoconstriction
- High dose: vasodilatation and increase in permeability.

Lymphokines

- Family of chemical messengers released by activated **T-lymphocytes**.
- The lymphokines are **non-antibody mediators** that mediate the development of cell-mediated immune responses.
- Lymphokines have many roles, including the attraction of other immune cells, including **macrophages** and other lymphocytes, to an infected site and their subsequent **activation** to prepare them to mount an immune response.
- Play an important role in chronic inflammation and delayed immunological reactions

Lysosomes of neutrophils

1) **Cationic proteins**; increase vascular permeability,
2) **Acid proteases**; degrade proteins in acid medium
3) **Neutral proteases**; activate complement.

Lymphokines

1) **Lymphotoxin**; lyses or damage target cells.
2) **Mitogenic factors**; stimulates cell proliferation.
3) **Lymphocyte activators**;

Activates lymphocytes and

Suppression of anti-inflammatory effects;

lymphokines in this group have 2 effects:

- Effect on inflammatory cells (act on macrophages)

- Effect on permeability (cause lymphocyte migration by increasing the permeability)

Arachidonic Acid Metabolites

Prostaglandins

- Prostaglandins are long-chained lipids derived from arachidonic acid
- Collected in 6 groups A,B,C,D,E and F.
  Groups E and F are strong vasodilators.
  E1 and E2 play important role in acute inflammation.
- Cannot be stored, produced on need.
- Can be found in all organs.
- Cause long-term increased permeability in late stages of inflammation.
- Can stimulate inflammation at low doses and stop the inflammatory reaction at high doses.
- Have pyrogenic effect. Produce pain and increase the pain effect caused by bradykinin

Arachidonic Acid Metabolites

Leukotrienes

- They are synthesized in the leucocytes and mast cells from arachidonic acid (AA) via the actions of 5-lipoxygenase (5-LO).
- Stimulate neutrophils aggregation, and adherence to endothelial cells.
- Mediate bronchospasm, vasoconstriction and increase permeability of venules.

Kinins and their enzymatic activators

Kinins

- Bradykinin and kallidin

  -Cause pain

  -Elevate vasodilatation and vascular permeability

  -Increase smooth muscle contractions

Proteases (Kallikrein)

- Proteolytic and esterolytic enzymes
- Produced by the inactive precursors prekallikreins
- Hold chemotactic effect
- Stimulate neutrophil granulocytes aggregation

Complement system

- **Complement system** is a collection of soluble proteins and membrane receptors.
- The system consists of more than **20 proteins** circulating in the blood and tissue fluids.
- Most of the proteins are normally inactive, but in response to the recognition of molecular components of microorganisms they become sequentially activated in an **enzyme cascade.**
- Plays a critical role in inflammation and defence against some bacterial infections (**opsonisation** and **killing of bacteria**)

2. Liquordiapedesis

- The leakage of fluid that occurs as a consequence of changes in the permeability of the microvasculature.
- The fluid is at first a watery transudate but the permeability changes within the venules and capillaries permit the escape of larger macromolecules forming a protein-rich exudate.
- Decline in plasma protein levels decreases the colloidal-osmotic pressure of plasma and result in (inflammatory) edema.

3. Leucodiapedesis

Leucodiapedesis or leukocyte extravasation, is the movement of leukocytes out of circulating system and towards the site of tissue damage or infection.

The sequence of leukocytic events can be divided into:

1. Margination
2. Rolling
3. Adhesion
4. Emigration
5. Diapedesis
6. Phagocytosis

1. Margination

Leukocytes move out of the central column of blood flow toward the edges of the moving stream of blood.
The cells roll along the walls of the capillaries and venules; this phenomen is known as margination.

2. Rolling

Rolling slows neutrophil movement within capillaries and brings the neutrophil closer to the surface of vascular endothelial cells.

3. Adhesion

Leukocyte adhesion to vascular endothelium

4. Emigration

Neutrophils, crawling between the endothelial cell junctions, escape from the blood to reach the tissue.

5. Diapedesis

Passive extravasation of red blood cells

Chemotaxis

- After the leukocytes are outside the vessel, the movement into a damaged area is called **chemotaxis** and is mediated by substances known as **chemotactic factors**, that diffuse from the area of tissue damage.
- All granulocytes and monocytes respond to chemotactic factors and move along a **concentration gradient** (from an area of lesser concentration of the factor to an area of greater concentration of the factor).
- Chemoattractants can be exogenous or endogenous .
- Chemotatic factors include cytotaxins (direct chemotactic factor) and cytotaxigens (substances that mediates chemotaxis of cells indirectly by inducing cytotaxin formation).

1) Cytotaxins :

Endogenous cytotaxins: Antigen-antibody and complement complexes (immunocomplex), exudate, complement cleavage products and nucleic acid products.

Exogenous cytotaxins: Bacteria, bacterial filtrates, casein and peptone.

2) Cytotaxigens:

Endogenous cytotaxigens: Antigen-antibody complexes, serum plasmin

Exogenous cytotaxigens: Bacterial endotoxins etc.

In some type of inflammations like viral inflammations, little or no leukocytes are present because of the absence of chemotaxis.

6. Phagocytosis

- The process whereby cells ingest solid particles is termed **phagocytosis**.

- The first step in phagocytosis is adhesion of the particle to be phagocytosed to the cell surface. The phagocyte ingests the attached particle by sending out pseudopodia around it. These meet and fuse so that the particle lies in a phagocytic vacuole (also called a **phagosome**) bounded by cell membrane.

Lysosomes, membrane-bound packets containing the toxic compounds, then fuse with phagosomes to form **phagolysosomes**.
It is within these that intracellular killing of microorganisms occurs.

- **Heterophagy** is the digestion within a cell of an exogenous substance phagocytosed from the cell's environment.

- **Autophagy** is the lysosomal digestion of a cell's own cytoplasmic material.