Inflammation

definition and causes: Inflammation is defined as the local response of living mammalian tissues to injury due to 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. The agents causing inflammation may be as under:

1. *Infective agents* like bacteria, viruses and their toxins, fungi, parasites.

2. *Immunological agents* like cell-mediated and antigenantibody reactions.

3. *Physical agents* like heat, cold, radiation, mechanical trauma.

4. *Chemical agents* like organic and inorganic poisons.

5. *Inert materials* such as foreign bodies.

"immunity or immune reaction" and "inflammatory response" by the host are both protective mechanisms in the body—inflammation is the visible response to an immune reaction, and activation of immune response is almost essential before inflammatory response appears.

SIGNS OF INFLAMMATION

1- *rubor* (redness)
2- *tumor* (swelling)
3- *calor* (heat)
4- *dolor* (pain).
5- *functio laesa* (loss of function)

TYPES OF INFLAMMATION:

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

A. *Acute inflammation* is of short duration (lasting less than 2 weeks) and represents the early body reaction, resolves quickly and is usually followed by healing.

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.

Sometimes, the acute inflammatory response may be quite severe and is termed as *fulminant acute inflammation.*

B. *Chronic inflammation* is of longer duration and occurs 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.

The characteristic feature of chronic inflammation is presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages, granulation tissue formation, and in specific situations as granulomatous inflammation.

In some instances, the term *subacute inflammation* is used for the state of inflammation between acute and chronic.

ACUTE INFLAMMATION

Acute inflammatory response by the host to any agent is a continuous process but for the purpose of discussion, it can be divided into following two events:

I. Vascular events.

II. Cellular events.

I. VASCULAR EVENTS

Alteration in the microvasculature (arterioles, capillaries and venules) is the earliest response to tissue injury. These alterations include: haemodynamic changes and changes in vascular permeability.

Haemodynamic Changes

The earliest features of inflammatory response result from changes in the vascular flow and calibre of small blood vessels in the injured tissue. The sequence of these changes is as under:

1. Irrespective of the type of injury, immediate vascular response is of **transient vasoconstriction** of arterioles. With mild form of injury, the blood flow may be re-established in 3-5seconds while with more severe injury the vasoconstriction may last for about 5 minutes.

2. Next follows **persistent progressive vasodilatation** which involves mainly the arterioles, but to a lesser extent, affects other components of the microcirculation like venules and capillaries. This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume in microvascular bed of the area, which is responsible for redness and warmth at the site of acute inflammation.

3. Progressive vasodilatation, in turn, may elevate the **local hydrostatic pressure** resulting in transudation of fluid into the extracellular space. This is responsible for swelling at the local site of acute inflammation.

4. **Slowing or stasis** of microcirculation follows which causes increased concentration of red cells, and thus, raised blood viscosity.

5. Stasis or slowing is followed by **leucocytic margination** or peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium. The leucocytes stick to the vascular endothelium briefly, and then move and migrate through the gaps between the endothelial cells into the extravascular space. This process is known as *emigration***.**

Altered Vascular Permeability

i) **Contraction of endothelial cells**: This is the most common mechanism of increased leakiness that affects venules exclusively while capillaries and arterioles remain unaffected. The endothelial cells develop temporary gaps between them due to their contraction resulting in vascular leakiness. It is mediated by the release of histamine, bradykinin and other chemical mediators. The response begins immediately after injury, is usually reversible, and is for short duration (15-30 minutes).

ii) **ii) Retraction of endothelial cells:** This change too affects venules and is mediated by cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF)-α. The onset of response takes 4-6 hours after injury and lasts for 2-4 hours or more .

iii) **iii) Direct injury to endothelial cells.** The change affects all levels of microvasculature (venules, capillaries and arterioles). The increased permeability may either appear immediately after injury and last for several hours or days, or may occur after a delay of 2-12 hours and last for hours or days

iv) **iv) Endothelial injury mediated by leucocytes.** Adherence of leucocytes to the endothelium at the site of inflammation may result in activation of leucocytes. The activated leucocytes release proteolytic enzymes and toxic oxygen species which may cause endothelial injury and increased vascular leakiness. This form of increased vascular leakiness affects mostly venules.

v) **v) Leakiness in neovascularisation.** Occur during the process of repair and in tumours are excessively leaky.

II. CELLULAR EVENTS

The cellular phase of inflammation consists of 2 processes:

1- exudation of leucocytes
The escape of leucocytes from the lumen of microvasculature to the interstitial tissue is the most important feature of inflammatory response. In acute inflammation, polymorphonuclear neutrophils (PMNs) comprise the first line of body defense, followed later by monocytes and macrophages.

2- Phagocytosis: It is defined as the process of engulfment of solid particulate material by the cells (cell-eating). The cells performing this function are called *phagocytes*. There are 2 main types of phagocytic cells:

i) Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response, sometimes called as *microphages*.\

ii) Circulating monocytes and fixed tissue mononuclear phagocytes, commonly called as *macrophages*.

CHEMICAL MEDIATORS OF INFLAMMATION

They are play important role in processes of acute inflammation like (vasodilatation, chemotaxis, fever, pain and tissue damage). The substances acting as chemical mediators of inflammation may be released from the cells, the plasma, or damaged tissue itself. They are broadly classified into 2 groups:

i) mediators released by cells; and

ii) mediators originating from plasma.

I. 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

i) Histamine. It is stored in the granules of mast cells, basophils and platelets.

ii) 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.

iii) Neuropeptides. include (substance P, neurokinin A, vasoactive intestinal polypeptide (VIP) and somatostatin). These small peptides are produced in the central and peripheral nervous systems.

The major proinflammatory *actions* of these neuropeptides is as follows:

a) Increased vascular permeability.

b) Transmission of pain stimuli.

c) Mast cell degranulation.

2. ARACHIDONIC ACID METABOLITES (EICOSANOIDS).

Arachidonic acid metabolites or eicosanoids are the most potent mediators of inflammation, much more than oxygen free radicals. 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.

3. LYSOSOMAL COMPONENTS: The inflammatory cells—neutrophils and monocytes, contain lysosomal granules which on release elaborate a variety of mediators of inflammation.

4. PLATELET ACTIVATING FACTOR (PAF): It is released from IgE-sensitised basophils or mast cells, other leucocytes, endothelium and platelets. Apart from its action on platelet aggregation and release reaction

5. CYTOKINES. Cytokines are polypeptide substances produced by activated lymphocytes *(lymphokines)* and activated monocytes *(monokines).*

6. FREE RADICALS: OXYGEN METABOLITES AND NITRIC OXIDE.

II. Plasma-derived Mediators (Plasma Proteases)

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

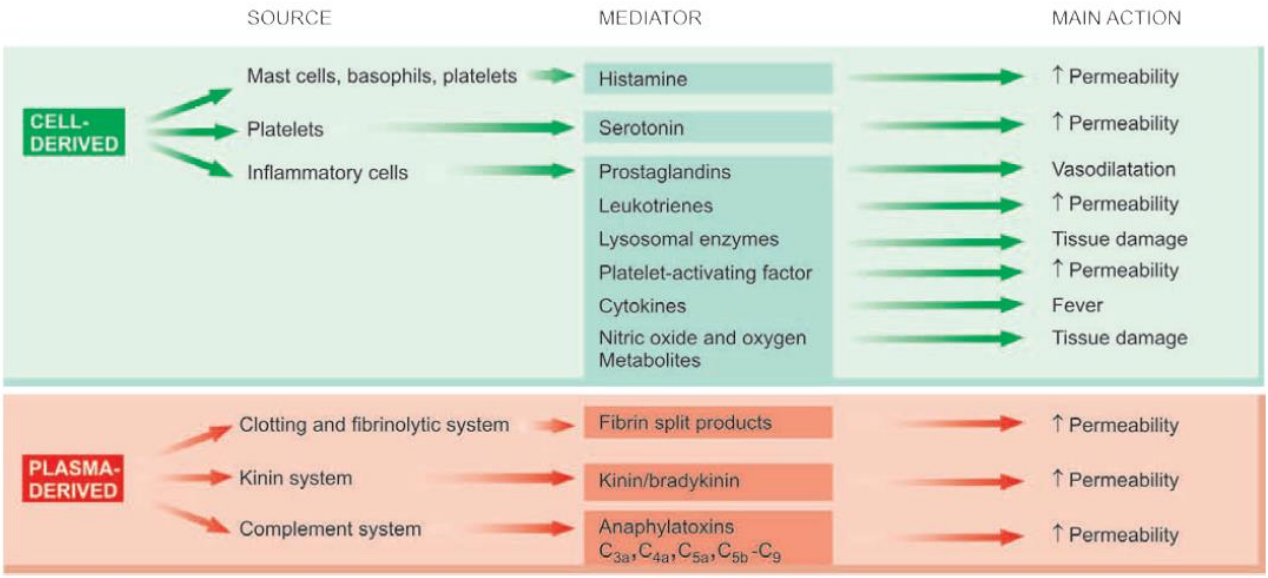

Figure 6.7 Chemical mediators of inflammation.

THE INFLAMMATORY CELLS

The cells participating in acute and chronic inflammation are circulating leucocytes, plasma cells and tissue macrophages.

1. Polymorphonuclear Neutrophils (PMNs)

Commonly called as neutrophils or polymorphs, these cells along with basophils and eosinophils are known as granulocytes due to the presence of granules in the cytoplasm. These granules contain many substances like proteases, myeloperoxidase, lysozyme, esterase, aryl sulfatase, acid and alkaline phosphatase, and cationic proteins. The diameter of neutrophils ranges from 10 to 15 μm and are actively motile. These cells comprise 40-75% of circulating leucocytes and their number is increased in blood (neutrophilia) and tissues in acute **bacterial** infections.

The functions of neutrophils in inflammation are: **1- Initial phagocytosis 2-Engulfment 3-Harmful effect**

2. Eosinophils

These are larger than neutrophils but are fewer in number, comprising 1 to 6% of total blood leucocytes**.** Eosinophils have bactericidal and toxic action against **helminthic parasites**.

3. Basophils (Mast Cells)

The basophils comprise about 1% of circulating leucocytes and are morphologically and pharmacologically similar to mast cells of tissue. The basophile granules has heparin and histamine. Basophils and mast cells have receptors for IgE and degranulate when cross-linked with antigen. Play role in immediate and delayed type of **hypersensitivity** reactions.

4. Lymphocytes

Next to neutrophils, these cells are the most numerous of the circulating leucocytes (20-45%). In addition to blood, lymphocytes are present in large numbers in spleen, thymus, lymph nodes and mucosa-associated lymphoid tissue (MALT). They have scanty cytoplasm and consist almost entirely of nucleus**.** Their role in antibody formation (B lymphocytes) and in cell-mediated immunity (T lymphocytes).

i) *In tissues*, they are dominant cells in chronic inflammation and late stage of acute inflammation.

ii) *In blood*, their number is increased (lymphocytosis) in chronic infections like tuberculosis.

5. Plasma Cells

These cells are larger than lymphocytes. Plasma cells are normally not seen in peripheral blood. They develop from B lymphocytes These cells are most active in **antibody synthesis**.

6. Mononuclear-Phagocyte System

(Reticuloendothelial System)

This cell system includes cells derived from 2 sources with

common morphology, function and origin **(Table 6.3,B).**

These are as under:

Blood monocytes. These comprise 4-8% of circulating

leucocytes.

Tissue macrophages. These include the following cells in different tissues:

a. Macrophages in inflammation.
b. Histiocytes which are macrophages present in connective tissues.
c. Kupffer cells are macrophages of liver cells.
d. Alveolar macrophages (type II pneumocytes) in lungs.
e. Macrophages/histiocytes of the bone marrow.
f. Tingible body cells of germinal centres of lymph nodes.
g. Littoral cells of splenic sinusoids.
h. Osteoclasts in the bones.
i. Microglial cells of the brain.
j. Langerhans' cells/dendritic histiocytes of the skin.

k. Hoffbauer cells of the placenta.
l. Mesangial cells of glomerulus.

7 .Giant Cells

A few examples of multinucleate giant cells exist in normal tissues (e.g. osteoclasts in the bones, trophoblasts in placenta، megakaryocytes in the bone marrow). However, in chronic inflammation when the macrophages fail to engulf invaders, they fuse together and form multinucleated giant cells.

Type of Exudation

1- **Serous**: when the fluid exudate resembles serum or is watery e.g. pleural effusion in tuberculosis, blister formation in burns.
2- **Fibrinous**: when the fibrin content of the fluid exudate is high e.g. in pneumococcal and rheumatic pericarditis.
3- **Purulent or suppurative exudate:** is formation of creamy pus as seen in infection with pyogenic bacteria e.g. abscess, acute appendicitis.
4- **Haemorrhagic**: when there is vascular damage e.g. acute haemorrhagic pneumonia in influenza.
5- **Catarrhal**: when the surface inflammation of epithelium produces increased secretion of mucous e.g. common cold.

CHRONIC INFLAMMATION

It is prolonged process in which tissue destruction and inflammation occur at the same time. Chronic inflammation can be caused by one of the following 3 ways:

1 .Chronic inflammation following acute inflammation like. osteomyelitis, pneumonia.

2 .Recurrent attacks of acute inflammation like in recurrent urinary tract infection leading to chronic pyelonephritis, repeated acute infection of gallbladder leading to chronic cholecystitis.

3 .Chronic inflammation starting de novo like infection with Mycobacterium tuberculosis.

GENERAL FEATURES OF CHRONIC INFLAMMATION

1 .MONONUCLEAR CELL INFILTRATION: Chronic inflammatory lesions are infiltrated by mononuclear inflammatory cells like phagocytes and lymphoid cells. Phagocytes are represented by circulating monocytes, tissue macrophages, epithelioid cells and sometimes، multinucleated giant cells. The macrophages comprise the most important cells in chronic inflammation. These may appear at the site of chronic inflammation from:

Other chronic inflammatory cells include lymphocytes، plasma cells, eosinophils and mast cells. In chronic inflammation، lymphocytes and macrophages influence each other and release mediators of inflammation.

2 .TISSUE DESTRUCTION OR NECROSIS: Tissue destruction and necrosis are central features of most forms of chronic inflammatory lesions.

3 .PROLIFERATIVE CHANGES: As a result of necrosis، proliferation of small blood vessels and fibroblasts is stimulated resulting in formation of inflammatory granulation tissue. Eventually, healing by fibrosis and collagen laying takes place.

SYSTEMIC EFFECTS OF CHRONIC INFLAMMATION

Chronic inflammation is associated with following systemic features:

1 .**Fever**: there is mild fever, often with loss of weight and weakness.

2 .**Anaemia**: chronic inflammation is accompanied by anaemia of varying degree.

3 .**Leucocytosis**: chronic inflammation also has leucocytosis but generally there is relative lymphocytosis in these cases.

4 .**ESR**: ESR is elevated in all cases of chronic inflammation.

5 .**Amyloidosis**: Long-term cases of chronic suppurative inflammation may develop secondary systemic amyloidosis.