INFLAMMATION

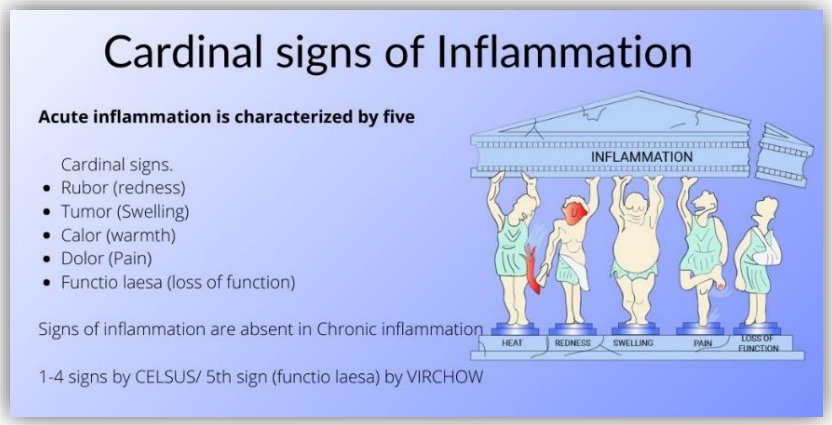
Acute and Chronic inflammation, Chemical mediators

I. Acute and Chronic

Inflammation is a complex *protective* response of the host's immune system towards an injurious factor. Generally, most of the agents that cause cell injury or necrosis can also cause inflammation, e.g. diseases, chemical and physical irritation, or microbial pathogens, injury, etc. Inflammation is not a disease but usually a manifestation of the disease.

The inflammatory response is generated and propagated through *chemical mediators* produced by host cells. Its characterized by increased blood flow to the tissue causing raised *temperature*, *redness*, *swelling*, and *pain*, in addition to *possible loss of function*, these are called the **FIVE cardinal signs of** "acute" **inflammation.**

The suffix (-itis) added to tissue or organ's name indicates inflammation (Gingivitis; Tonsillitis).



Consequences of inflammation

The main purpose of inflammation is *useful*:

1) to *recognize and remove injurious stimuli* (pathogen, wall-off an abscess or inactivate toxins) or its effects (necrotic cells and tissues),

2) *initiating tissue repair, healing* and reconstruction processes.

Inflammation may also cause *harmful* effects by

1) increasing *organ damage* through chronic inflammatory response and consequent fibrosis as seen in rheumatoid diseases and atherosclerosis.

2) causing *life-threatening hypersensitivity* reaction (anaphylaxis).

Generally, inflammation may be

1) *Acute* (short-term: symptoms of acute inflammation last up to 72-hours) or
2) *chronic* (when symptoms lasts continue for months and/or years)

However, some classification considers *sub-acute* inflammation when it lasts 2-6 *weeks*.

Acute inflammation	**Chronic** inflammation
Early onset (seconds – minutes)	Delayed onset (days)
Short duration (minutes – days)	Longer duration (weeks – years)
Fluid exudation (edema)	Blood vessels proliferation and scarring
Polymorph nuclear leukocyte emigration (neutrophils)	lymphocytes & macrophages infiltration

Inflammatory features

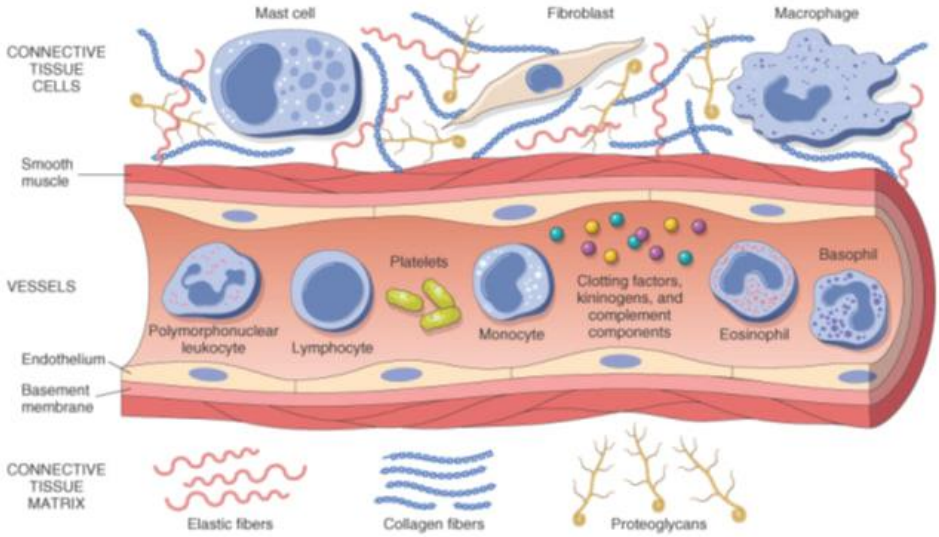
I. Two groups of *response components*
   - Vascular wall response.
   - Inflammatory cell response.

II. Two sets of *inflammatory mediators*, which effects of inflammation
   - Circulating plasma proteins
   - Locally produced factors by vessel wall or inflammatory cells.

III. Termination of inflammatory response: Active anti-inflammatory mechanism
   - Once the causative agent is eliminated
   - Then the secreted mediators are removed

Components of acute and chronic inflammatory responses include:

1) Circulating leukocytes: (neutrophils, monocytes, eosinophils, lymphocytes, basophils) in addition to platelets.
2) Circulating plasma proteins
3) Blood vessels
4) Cells and proteins of the extracellular matrix (ECM).
   Structural proteins (collagen, elastin),
   Adhesive glycoproteins (fibronectin, laminin),
   proteoglycans.
5) Connective tissue cells: mast cells, fibroblasts, macrophages, and lymphocytes.



Studies frequently measure *cellular biomarkers* such as:

Activated monocytes, cytokines, chemokines, various adhesion molecules, adiponectin, non-specific markers such as C-reactive protein (CRP), fibrinogen, serum amyloid alpha.

Key inflammatory pathways include:

- Sympathetic activity,
- Oxidative stress,
- Nuclear factor kappaB (NF-kB) activation,
- Pro-inflammatory cytokine production.

ACUTE INFLAMMATION

An immediate and early response to an injurious agent that serves to deliver mediators of host defense, leukocytes and plasma proteins, to the site of injury. It is marked by the release of fluid and blood plasma proteins and the arrival of leukocytes at the site of injury, which initially comprises neutrophils and later macrophages. An inflammatory response means the innate (non-specific) immune system is 'fighting against something that may turn out to be harmful.'

Remember! Inflammation does not necessarily mean that there is an infection, but an infection can cause inflammation.

Causes of inflammation

- Infections (bacterial, viral, fungal, parasitic).
- Trauma (blunt & penetrating)
- Physical & chemical agents (thermal injury, irradiation, chemicals toxicity, etc.)
- Immune (hypersensitivity) reactions against exogenous substances or self-tissues.
- Tissue necrosis that result from ischemia as in myocardial infarction.
- Foreign bodies.

The acute inflammatory process is a **4-stage processes** that begins with:

I. The *Initiation phase*, triggered by the injury. Involves changes to the microcirculation, leading to fluid loss and migration of white blood cells (WBCs) to the injured area.
II. The *amplification phase*, follows when chemical substances direct additional types of white blood cells to the site, enhancing the response.
III. The *destruction phase* is characterized by the rapid neutralization of the injury and debris removal. Finally,
IV. The *termination phase* requires the action of chemical substances to halt or regulate the inflammatory process, preventing excessive damage if unchecked

Two major components of acute inflammation

1. VASCULAR CHANGES

Vasodilation is an early response, triggered by various mediators (mainly histamine, acting on vascular smooth muscle). *TWO main vascular responses* that are designed to bring blood cells and proteins to the site of injury leading to, will be initiated:

A. change in vascular caliber and blood flow

Initially, there is a transient vasoconstriction, followed by vasodilation that increases blood flow to the injury site causing hotness and redness.

B. Increased Vascular Permeability (i.e. Vascular Leakage)

Increased vascular permeability leads to the leakage of a protein-rich fluid **(**exudate**)** from plasma into the extravascular space. This protein loss reduces the intravascular osmotic pressure and increases the interstitial fluid osmotic pressure, leading to edema (swelling).

The increase in *vascular permeability* occurs through two common mechanisms:

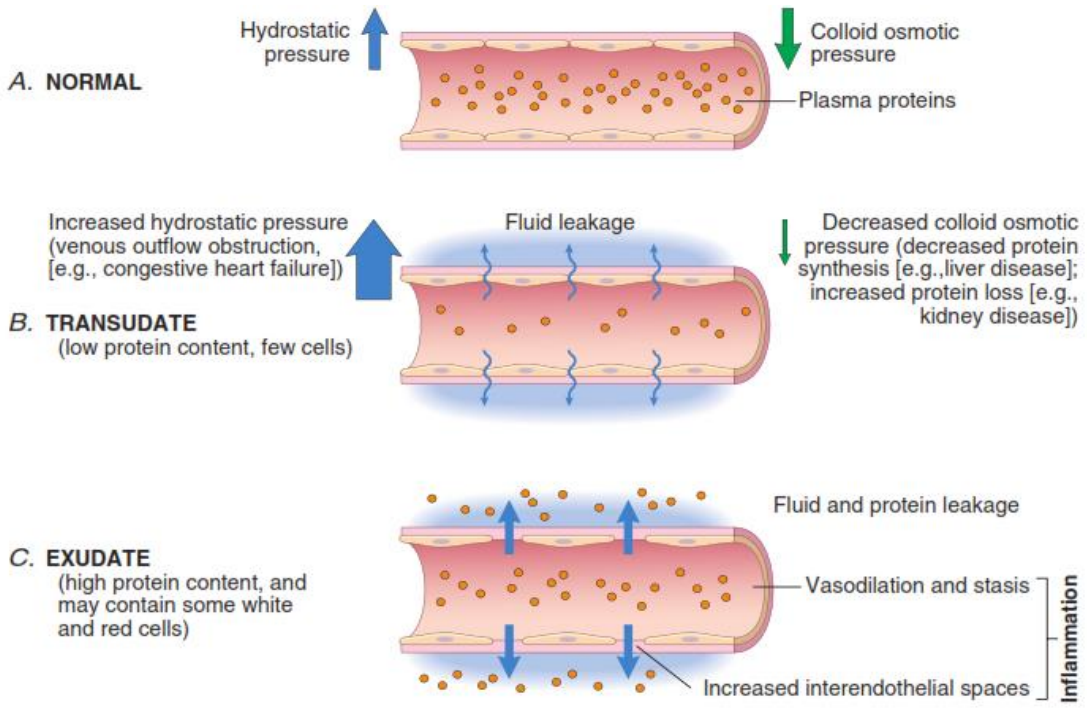
a. Formation of **endothelial gaps** in venules facilitated by contraction of endothelial cells in the vessel wall. This contraction is provoked by *histamine, bradykinin, leukotrienes*, as well as many other classes of chemical mediators.
b. **Endothelial injury** resulting from the causative factor that triggered the inflammation process as seen in burns or infections.

Edema: is excessive fluid in the interstitial tissue or body cavities which may be either *exudates* or *transudate.*

Exudate: An inflammatory extravascular fluid that has a high protein concentration and cellular debris.

Transudate: A fluid with *low protein* content caused by high hydrostatic pressure as a consequence of reduced venous return. It accumulates in non-inflammatory conditions.

Purulent exudates: An inflammatory exudate rich in leukocytes (mostly neutrophils), debris of dead cells and, in many cases, microbes.



2. CELLULAR CHANGES:

LEUKOCYTE RECRUITMENT AND ACTIVATION

A later response in inflammation, will be delivering leukocytes to the site of injury and then activate them to execute their role in host defense. A large number of neutrophils migrate and accumulate along the peripheral zone of the endothelium.

The predominant cells of acute inflammatory response are polymorphonuclear neutrophils (PMNs). The cellular response has the following **FOUR** stages:

Stage 1. Margination, rolling, pavementing, and adhesion of leukocytes

a. Margination: In inflammation, blood flow will slow (stasis) due to the loss of intravascular fluid and increased plasma viscosity. This causes the leukocytes (mainly neutrophils) to take a peripheral position along the endothelial cells lining the blood vessels. This process is called **margination.**

b. Rolling: Rows of leukocytes interact with endothelial cells so that leukocytes can be further activated by chemokines and other pro-inflammatory agents on the of the endothelial cells surfaces.

These leukocytes express adhesion molecules and begin to **flip over**. These weak and transient interactions mediated by **selectin** family of adhesion molecule

c. Pavementing: When neutrophils mainly line with the endothelial lining of the blood vessels, it gives an appearance that is called pavementing. This process occurs explicitly in venules.

d. Adhesion. next leukocytes bind or adhere with endothelial cell surfaces. This phenomenon is facilitated by cell adhesion molecules (CAMs) such as *selectins*, immunoglobulins, and *integrins* expressed on leukokocyte cell surfaces interacting with their ligands on endothelial cells.

Stage 2. Transmigration of leukocytes

Trans-endothelial Migration (TEM) of Leukocytes occurs when they squeeze themselves in an amoeboid fashion, and extend pseudopodia, through the gap created between endothelial cells. This process is called diapedesis, and is driven by chemokines produced in extravascular tissues

The most important mechanism of leukocyte emigration is the widening of inter endothelial junctions after endothelial cell contractions.

Stage 3. Chemotaxis

Chemotaxis occurs when an extracellular gradient of chemicals determines the direction of a cell's locomotion, toward the injury site along soluble chemical mediators' gradients (chemotactic factors). Granulocytes, monocytes and, to a lesser extent, lymphocytes respond to chemotactic stimuli with varying speed.

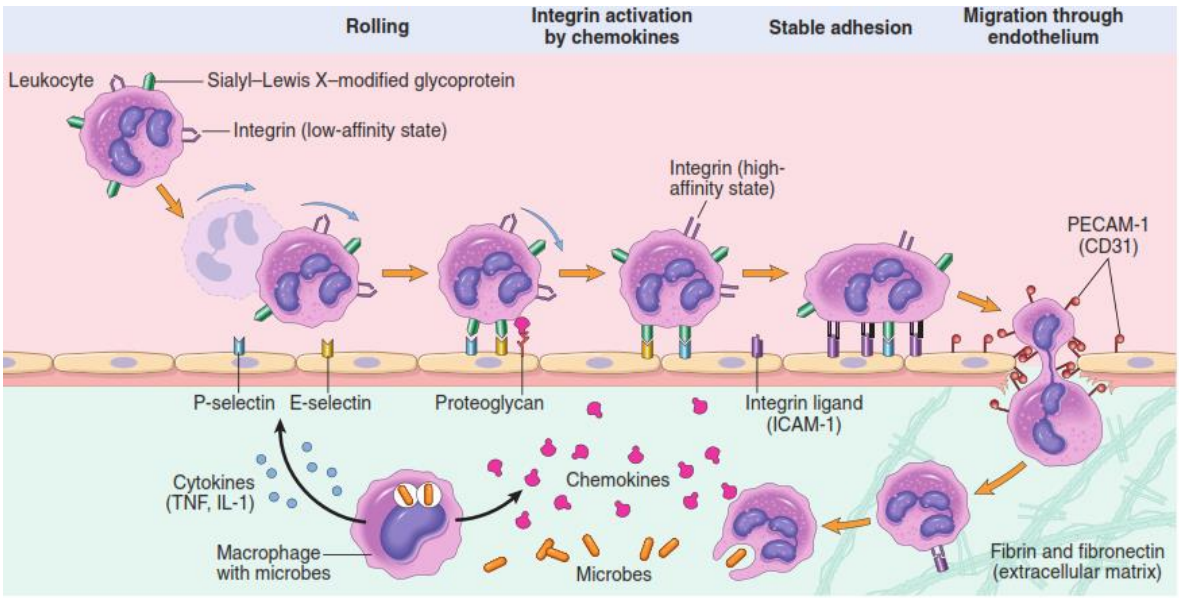
Chemo-attractants that facilitate chemotaxis may be exogenous or endogenous substances. The commonest exogenous attractants are bacterial products.

Endogenous chemo-attractants, include several chemical mediators:

- components of the complement system, particularly C5a.
- products of the lipoxygenase pathway, mainly leukotriene B_4 (LTB_4).
- *cytokines*, particularly those of the chemokine family (e.g., IL-8).

At early stages (first 6 to 24 hours) of acute inflammatory stimulus; *neutrophils* predominate in the inflammatory infiltrate. Once they enter tissues, neutrophils; undergo apoptosis within 24 to 48 hours.

At later stages (in 24 to 48 hours) neutrophils will be replaced by *monocytes*.



Different stages of leukocyte migration through blood vessels.

Leukocyte Activation

Once leukocytes have been recruited to the site of infection or tissue necrosis, they must be activated to perform their functions. **Stimuli for activation include** microbes, products of necrotic cells, and several mediators

Stage 4. Phagocytosis

Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which include invading microorganisms, damaged cells, and tissue debris. These phagocytic cells include polymorphonuclear leukocytes (mainly neutrophils), monocytes, and tissue-resident macrophages.

Phagocytosis involves 3 different but interrelated steps.

Step 1. Recognition and attachment

Recognition and attachment of the particles by receptors expressed on the leukocyte surface; these receptors recognize microbes and host protein, called *opsonization*. During this process the antigen is coated with antibody or complement in order to enhances or increases the binding of the antigen to the leukocyte cell membrane. This step is essential for trapping the agent and triggering the final steps of phagocytosis.

Certain proteins called opsonins, which are detected by high-affinity receptors expressed by phagocytes, greatly increase the efficiency of phagocytosis. Leukocyte receptors identify major opsonins, which include **IgG** antibodies, the **C3b** fragment of complement breakdown, and particular **plasma lectins**.

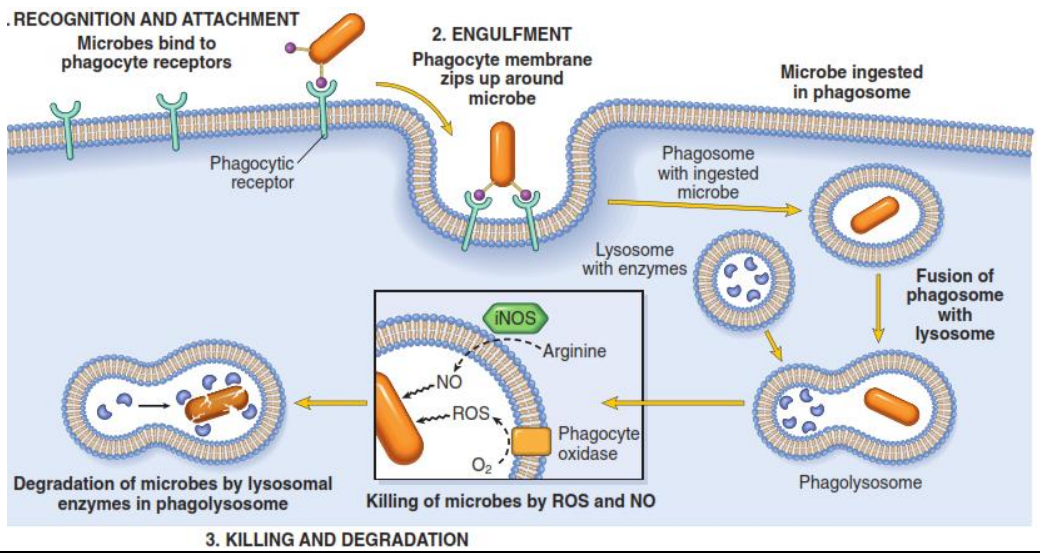
Step 2. Engulfment

Once recognized by a neutrophil or macrophage, a foreign particle is engulfed by the phagocytic cell. This cell extends their cytoplasm (create pseudopods) to form a membrane-bound vacuole around the particle called a phagosome. This phagosome fuses with lysosomes to create a phagolysosome that will contain lysosomal degradation granules.

Step 3. Killing or degradation of the particle to be ingested by leukocytes

The final step in phagocytosis is killing of infectious agent and degradation. There are two forms of: Oxygen-independent and oxygen-dependent mechanisms.

- Oxygen-independent mechanism: mediated by the polymorphonuclear leukocytes such as Lysozymes, Lactoferrin, and Major basic protein (MBP).
- oxygen-dependent due to the formation of reactive oxygen species such as hydrogen peroxide (H_2O_2), superoxide (O_2), hydroxyl ion (HO^-), and possibly single oxygen ($^1O_2$).



Phagocytosis of a particle. (*1*) attachment and binding of the particle to receptors on the leukocyte surface, (2) engulfment and fusion of the phagocytic vacuole with granules (lysosomes), and (*3*) destruction of the ingested particle.

iNOS: inducible nitric oxide synthase; **NO**: nitric oxide; **ROS**: reactive oxygen species.

Outcomes of Acute Inflammation depends on

- The nature and intensity of the injury.
- The site and tissue affected.
- The reaction of the host.

Outcomes of acute inflammation

Resolution

Regaining normal histological & functional tissue. It occurs when there is:

- Limited or short lived injury.
- Minimal or no tissue damage.
- Tissue which is capable of replacing any irreversibly injured cells.

Progression to chronic inflammation: Occurs when:

- The offending agent is not removed.
- There is continuing tissues injury.
- The affected tissue has reduced capacity to regenerate.

Chronic inflammation may be followed by restoration of the normal structure and function or may lead to scarring.

Suppuration: i.e. pus formation

Pus: A purulent inflammatory exudate caused by pyogenic infections. It is a mixture of living & dead neutrophils, bacteria, cellular debris and edema fluid.

Abscesses are focal collections of pus with a necrotic central region surrounded by a layer of conserved neutrophils with a zone of dilated vessels and fibroblast.

Scarring and fibrosis

Replacement of the injured tissue by fibrous connective tissue. This occurs when tissue destruction is extensive or if the affected tissue cannot regenerate.

