Inflammation

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DEFINITION

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.

Thus, *inflammation is distinct from infection*—while inflammation is a protective response by the body to variety of etiologic agents (infectious or non-infectious),while infection is invasion into the body by harmful microbes and their resultant ill-effects by toxins.

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SIGNS OF INFLAMMATION.

the famous 4 *cardinal signs of inflammation* as:

- *rubor* (redness);
- *tumor* (swelling);
- *calor* (heat); and
- *dolor* (pain).
    - *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.

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

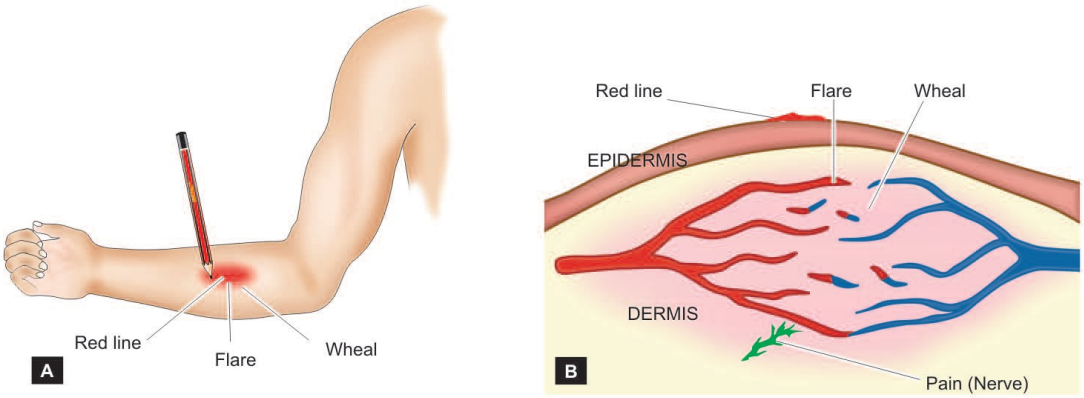
2. Next follows **persistent progressive vasodilatation** which involves mainly the arterioles, but to a lesser extent, affects other components of the microcirculation like venules and capillaries. This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume 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.

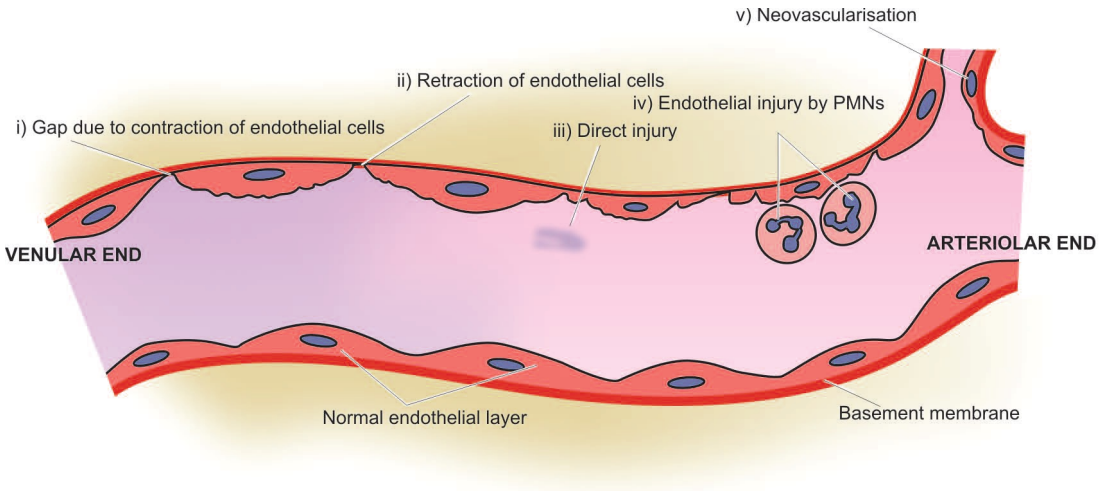
Altered Vascular Permeability

PATHOGENESIS. In and around the inflamed tissue, there is accumulation of oedema fluid in the interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed.



In the initial stage, the escape of fluid is due to vasodilatation and consequent elevation in hydrostatic pressure. This is transudate in nature. But subsequently, the characteristic inflammatory oedema, exudate, appears by increased vascular permeability of microcirculation.

MECHANISMS OF INCREASED VASCULAR PERMEABILITY.
In acute inflammation, normally non-permeable endothelial layer of microvasculature becomes leaky.
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 gap 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). (immediate transient effect)
ii) Retraction of endothelial cells. In this mechanism, there is structural re-organisation of the cytoskeleton of endothelial cells that causes

reversible retraction at the intercellular junctions. This change too affects venules and is mediated by cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF)-□. The onset of response takes 4-6 hours after injury and lasts for 2-4 hours or more *(delayed and prolonged leakage)*.

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iii) Direct injury to endothelial cells. Direct injury to the endothelium causes cell necrosis and appearance of physical gaps at the sites of detached 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 *(immediate sustained leakage)*, or may occur after a delay of 2-12 hours and last for hours or days *(delayed prolonged leakage).*

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 and is a *late response*.

v) Leakiness in neovascularisation. In addition, the newly formed capillaries under the influence of vascular endothelial growth factor (VEGF) during the process or repair and in tumours are excessively leaky.

II. CELLULAR EVENTS

The cellular phase of inflammation consists of 2 processes:
1. exudation of leucocytes; and
2. phagocytosis.

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.

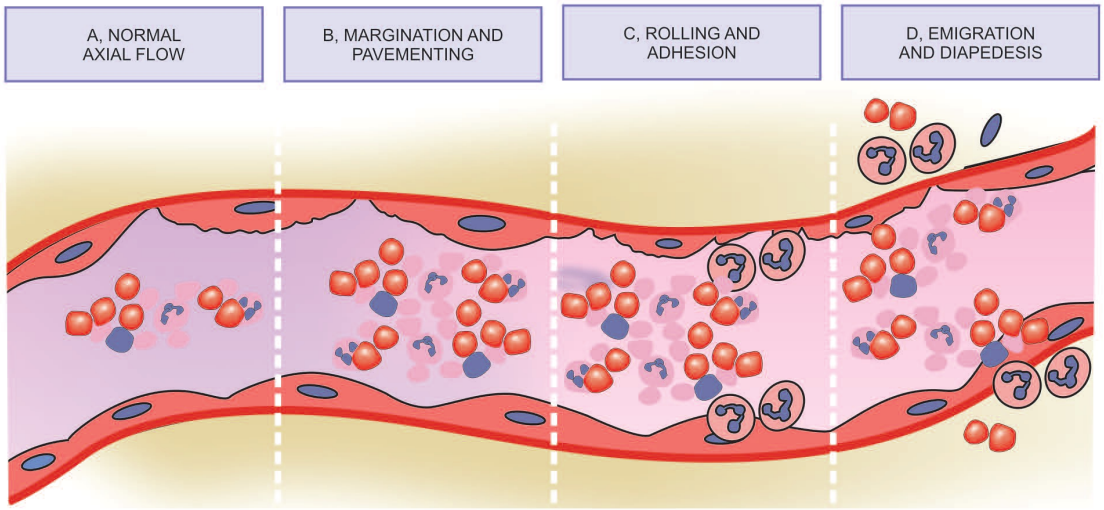
The changes leading to migration of leucocytes are as follows

1. CHANGES IN THE FORMED ELEMENTS OF BLOOD. In the early stage of inflammation, the rate of flow of blood is increased due to vasodilatation. But subsequently, there is slowing or stasis of bloodstream. The normal axial flow consists of central stream of cells comprised by leucocytes and RBCs and peripheral cell-free layer of plasma close to vessel wall. Due to slowing and stasis, the central stream

of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as *margination*. As a result of this redistribution, the neutrophils of the central column come close to the vessel wall; this is known as *pavementing*.

2. ROLLING AND ADHESION. Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cells lining the vessel wall *(rolling phase)*. This is followed by the transient bond between the leucocytes and endothelial cells becoming firmer *(adhesion phase).* The following molecules bring about rolling and adhesion phases:

i) **Selectins**



ii) **Integrins**.

iii) **Immunoglobulin gene superfamily adhesion molecule** such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) and Platelet endothelial cell adhesion molecule-1 (PECAM-1) .

3. EMIGRATION. After sticking of neutrophils to endothelium, the former move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out cytoplasmic pseudopods. Subsequently, the neutrophils lodged between the endothelial cells and basement membrane cross the basement membrane by damaging it locally with secreted collagenases and escape out into the extravascular space; this is known as *emigration*. The damaged basement membrane is repaired almost immediately. As already mentioned, neutrophils are the dominant cells in acute inflammatory exudate in the first 24 hours, and monocytemacrophages appear in the next 24-48 hours. However, neutrophils are short-lived (24-48 hours) while

monocytemacrophages survive much longer Simultaneous to emigration of leucocytes.

4. CHEMOTAXIS. The chemotactic factor-mediated transmigration of leucocytes after crossing several barriers (endothelium, basement membrane, perivascular myofibroblasts and matrix) to reach the interstitial tissues is called chemotaxis.
The following agents act as potent chemotactic substances or *chemokines* for neutrophils:
i) Leukotriene B4 (LT-B4), a product of lipooxygenase pathway of arachidonic acid metabolites
ii) Components of complement system (C5a and C3a in particular)
iii) Cytokines (Interleukins, in particular IL-8)
iv) Soluble bacterial products (such as formylated peptides).

Phagocytosis

Phagocytosis 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*.
Neutrophils and macrophages on reaching the tissue spaces produce several proteolyitc enzymes—lysozyme, protease, collagenase, elastase, lipase, proteinase, gelatinase, and acid hydrolases. These enzymes degrade collagen and extracellular matrix. The microbe undergoes the process of phagocytosis by polymorphs and macrophages and involves the following 3 steps **:**
1. Recognition and attachment
2. Engulfment
3. Killing and degradation

1. RECOGNITION AND ATTACHMENT
Phagocytosis is initiated by the expression of surface receptors on macrophages which recognise microorganisms:
mannose receptor and *scavenger receptor*. The process of phagocytosis is further enhanced when the microorganisms are coated with specific proteins, *opsonins*, from the serum or they get opsonised. Opsonins establish a bond between bacteria and the cell membrane of phagocytic cell. The main opsonins present in the serum and their corresponding

receptors on the surface of phagocytic cells (PMNs or macrophages) are as under:

i) *IgG opsonin* is the Fc fragment of immunoglobulin G; it is the naturally occurring antibody in the serum that coats the bacteria while the PMNs possess receptors for the same.

ii) *C3b opsonin* is the fragment generated by activation of complement pathway. It is strongly chemotactic for attracting PMNs to bacteria.

iii) *Lectins* are carbohydrate-binding proteins in the plasma which bind to bacterial cell wall.

2. ENGULFMENT

The opsonised particle bound to the surface of phagocyte is ready to be engulfed. This is accomplished by formation of cytoplasmic pseudopods around the particle due to activation of actin filaments beneath cell wall, enveloping it in a phagocytic vacuole. Eventually, the plasma membrane enclosing the particle breaks from the cell surface so that membrane lined phagocytic vacuole or phagosome lies internalised and free in the cell cytoplasm. The phagosome fuses with one or more lysosomes of the cell and form bigger vacuole called phagolysosome.

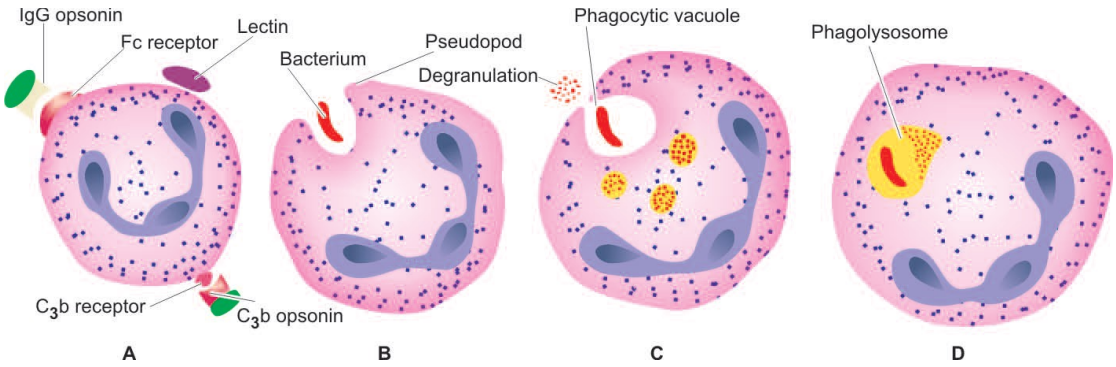
3. KILLING AND DEGRADATION

. The microorganisms after being killed by antibacterial substances are degraded by hydrolytic enzymes. Either by:

A. *Intracellular mechanisms:*

B.Extracellular mechanism

radicals



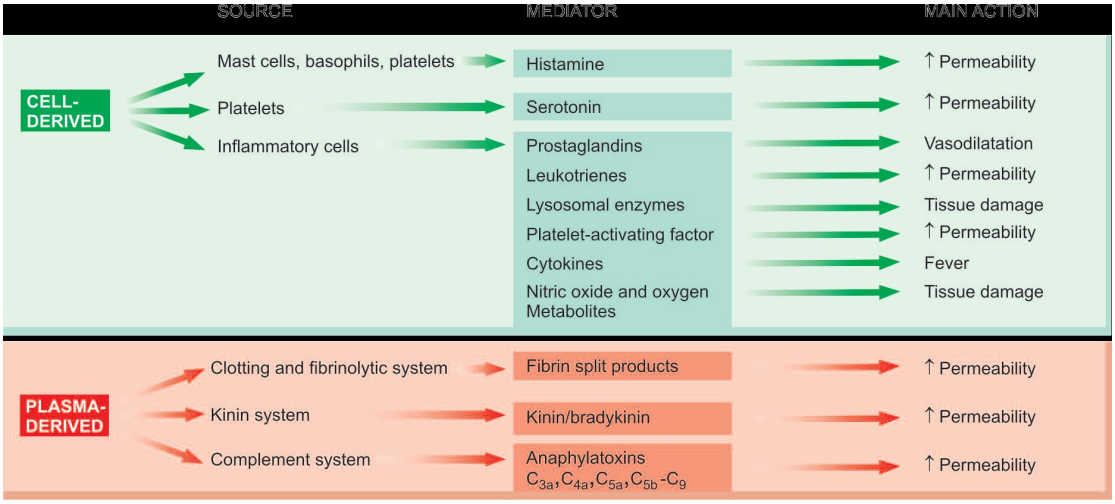
CHEMICAL MEDIATORS OF INFLAMMATION

An inflammatory mediator is **a messenger that acts on blood vessels and/or cells to promote an inflammatory response**..

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.



Type of Exudation

The appearance of escaped plasma determines the morphologic type of inflammation as under:

i) Serous, when the fluid exudate resembles serum or is watery e.g. pleural effusion in tuberculosis, blister formation in burns.

ii) Fibrinous, when the fibrin content of the fluid exudates is high e.g. in pneumococcal and rheumatic pericarditis.

iii) Purulent or suppurative exudate is formation of creamy pus as seen in infection with pyogenic bacteria e.g. abscess, acute appendicitis.

iv) Haemorrhagic, when there is vascular damage e.g. acute haemorrhagic pneumonia in influenza.

v) Catarrhal, when the surface inflammation of epithelium produces increased secretion of mucous e.g. common cold.

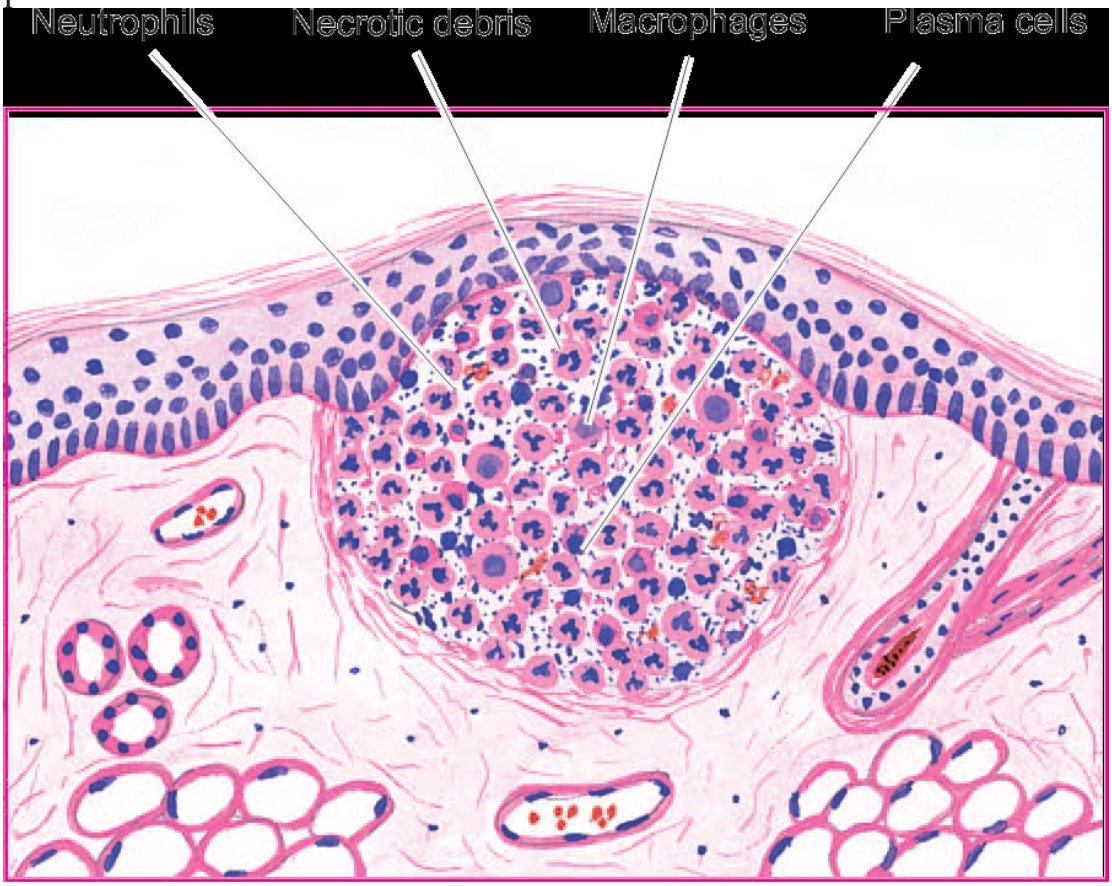
Ulcer

Ulcers are local defects on the surface of an organ produced by inflammation. Common sites for ulcerations are the stomach, duodenum, intestinal ulcers in typhoid fever, intestinal tuberculosis, bacillary and amoebic dysentery, ulcers of legs due to varicose veins etc. In the acute stage, there is infiltration by polymorphs with vasodilatation while long-standing ulcers develop infiltration by lymphocytes, plasma cells and macrophages with associated fibroblastic proliferation and scarring.

Suppuration (Abscess Formation)

When acute bacterial infection is accompanied by intense neutrophilic infiltrate in the inflamed tissue, it results in tissue necrosis. A cavity is formed which is called an abscess and contains purulent exudate or pus and the process of abscess formation is known as suppuration. The bacteria which cause suppuration are called pyogenic.

Microscopically, pus is creamy or opaque in appearance and is composed of numerous dead as well as living neutrophils, some red cells, fragments of tissue debris and fibrin. In old pus, macrophages and cholesterol crystals are also present .
An abscess may be discharged to the surface due to increased pressure inside or may require drainage by the surgeon. Due to tissue destruction, resolution does not occur but instead healing by fibrous scarring takes place.



Cellulitis.

It is a diffuse inflammation of soft tissues resulting from spreading effects of substances like hyaluronidase released by some bacteria.

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

1. Fever occurs due to bacteraemia.
2. Leucocytosis commonly accompanies the acute inflammatory reactions.
3. Lymphangitis-lymphadenitis is one of the important manifestations of localised inflammatory injury. The lymphatics and lymph nodes that drain the inflamed tissue show reactive inflammatory

changes in the form of lymphangitis and lymphadenitis. This response represents either a nonspecific reaction to mediators released from.

4. Shock may occur in severe cases. Massive release of cytokine TNF-□, a mediator of inflammation, in response to severe tissue injury or infection results in profuse systemic vasodilatation, increased vascular permeability and intravascular volume loss.

FATE OF ACUTE INFLAMMATION

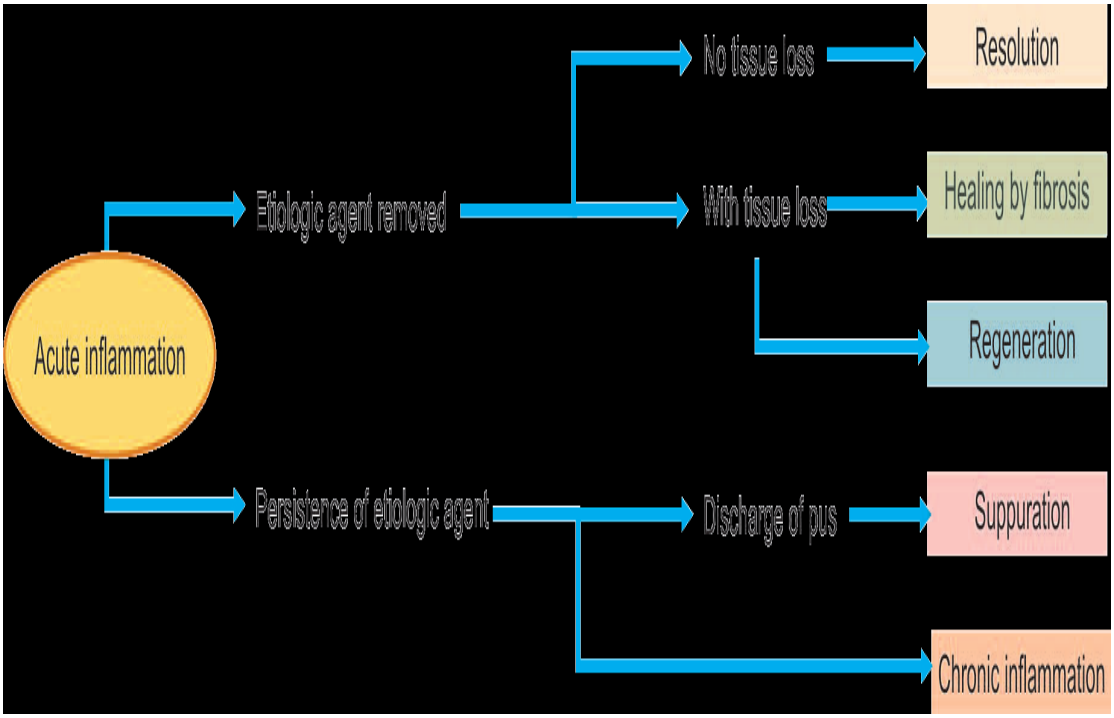
The acute inflammatory process can culminate in one of the following outcomes :

1. Resolution. It means complete return to normal tissue following acute inflammation. This occurs when tissue changes are slight and the cellular changes are reversible e.g. resolution in lobar pneumonia.

2. Healing. Healing by fibrosis takes place when the tissue destruction in acute inflammation is extensive so that there is no tissue regeneration. But when tissue loss is superficial, it is restored by regeneration.

3. Suppuration. When the pyogenic bacteria causing acute inflammation result in severe tissue necrosis, the process progresses to suppuration. Initially, there is intense neutrophilic infiltration. Subsequently, mixture of neutrophils, bacteria, fragments of necrotic tissue, cell debris and fibrin comprise pus which is contained in a cavity to form an abscess. The abscess, if not drained, may get organised by dense fibrous tissue, and in time, get calcified.

4. Chronic inflammation. Persisting or recurrent acute inflammation may progress to chronic inflammation in which the processes of inflammation and healing proceed side by side.


Acute inflammation
Etiologic agent removed
No tissue loss
Resolution
With tissue loss
Healing by fibrosis
Regeneration
Persistence of etiologic agent
Discharge of pus
Suppuration
Chronic inflammation