GENERAL PATHOLOGY

INFLAMMATION

Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but it may also cause tissue damage.

The main components of inflammation are a vascular reaction and a cellular response, both activated by mediators that are derived from plasma proteins and various cells. The mediators of defense include *phagocytic leukocytes*, *antibodies*, and *complement proteins.*

Without inflammation, infections would go unchecked, wounds would never heal, and injured tissues might remain permanent festering sores.

The suffix *-itis* after an organ denotes inflammation in that site, such as appendicitis, conjunctivitis, or meningitis.

Causes of Inflammation

Inflammatory reactions may be triggered by a variety of stimuli:

1. Infections (bacterial, viral, fungal, parasitic) and microbial toxins are among the most common and medically important causes of inflammation.
2. Tissue necrosis elicits inflammation regardless of the cause of cell death. Cells may die because of ischemia (reduced blood flow, the cause of myocardial infarction), trauma, and physical and chemical injury (e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals).
3. Foreign bodies (splinters, dirt, sutures) may elicit inflammation by themselves or because they cause traumatic tissue injury or carry microbes. Even endogenous substances can be harmful if they deposit in tissues; such substances include urate crystals (in gout), cholesterol crystals (in atherosclerosis), and lipids (in obesity associated metabolic syndrome).
4. Immune reactions (also called hypersensitivity) are reactions in which the normally protective immune system damages the individual's own tissues. The injurious immune responses may be inappropriately directed against self-antigens, causing autoimmune diseases, or may be reactions against environmental substances, as in allergies, or against microbes. Inflammation is a major cause of tissue injury in these diseases.

Fundamental Properties of Inflammation:

- **components of inflammation**

1.Plasma fluid proteins.
2. blood vessels.
3.*The circulating leukocytes include:*__neutrophils, monocytes, eosinophils, lymphocytes, basophils, in addition to platelets.
4. *The connective tissue cells are:* mast cells, fibroblasts, macrophages, and lymphocytes.
5. The extracellular matrix consists of: Structural proteins (collagen, elastin), Adhesive glycoproteins (fibronectin, laminin), Proteoglycans.

- ***Harmful consequences of inflammation***

1. local tissue damage and its associated signs and symptoms (e.g., pain and functional impairment) these harmful consequences are self-limited and resolve, leaving little or no permanent damage. or inflammatory reaction is misdirected (e.g., against self-tissues in autoimmune diseases), occurs against normally harmless environmental substances (e.g., in allergies), or is inadequately controlled.
2. Inflammatory reactions underlie common chronic diseases such as rheumatoid arthritis, atherosclerosis, and lung fibrosis, as well as life-threatening hypersensitivity reactions to insect bites, foods, drugs, and toxins.
3. Inflammation also may contribute to a variety of diseases that are thought to be primarily metabolic, degenerative, or genetic, such as type 2 diabetes, Alzheimer disease, and cancer.

Types of inflammations

- *Local and systemic inflammation*

1.the inflammatory response to a localized infection or tissue damage. Although even local reactions may have systemic manifestations (e.g., fever in the setting of bacterial or viral pharyngitis), the inflammation is largely confined to the site of infection or damage.

2.In rare situations, such as some disseminated bacterial infections, the inflammatory reaction is systemic and causes widespread pathologic abnormalities. This reaction has been called *sepsis,* which is one form of the systemic inflammatory response syndrome.

- *Mediators of inflammation*

The vascular and cellular reactions of inflammation are triggered by soluble factors that are produced by various cells or derived from plasma proteins and are generated or activated in response to the inflammatory stimulus.

Table 3.5 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules) Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

IL, Interleukin; *TNF*, tumor necrosis factor.

- ***Acute and chronic inflammation***

The typical inflammatory reaction develops through a series of sequential steps:

(1) recognition of the injurious agent,
(2) recruitment of leukocytes,
(3) removal of the agent,
(4) regulation(control) of the response, and
(5) repair (resolution).

ACUTE INFLAMMATION:

It is a rapid, often self-limited, response to offending agents that are readily eliminated, such as many bacteria and fungi, and dead cells.

The cardinal signs (clinical features) are:

- *redness (rubor) caused by hyperaemia*
- *swelling (tumor) caused by fluid exudation and hyperaemia*
- *heat (calor) caused by hyperaemia*
- *pain (dolor) resulting from release of bradykinin and PGE2.*
- *loss of function (functio laesa) caused by the combined effects of the above.*

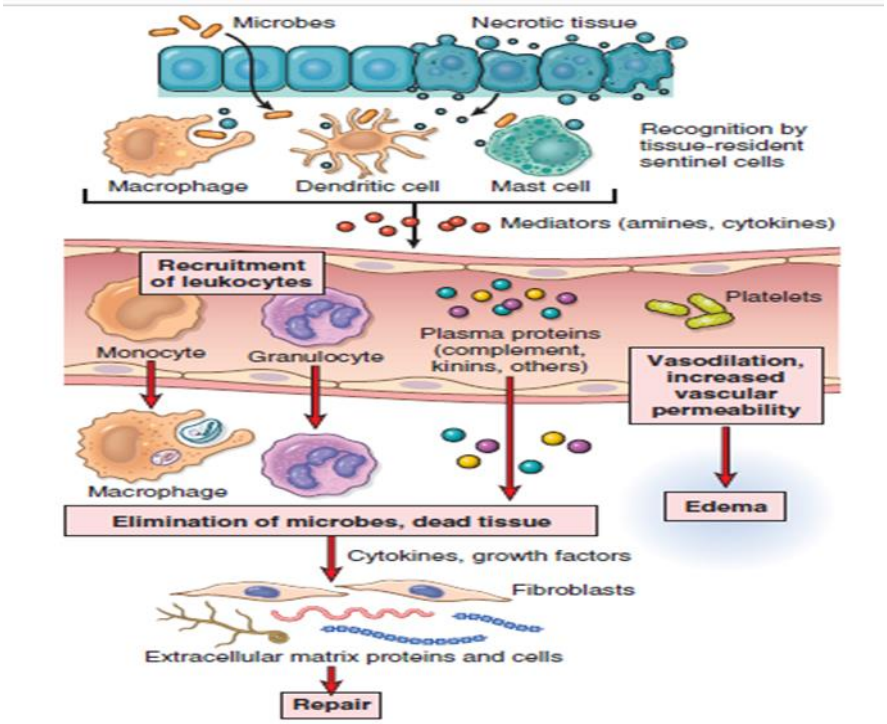


Figure 3.1 Sequence of events in an inflammatory reaction. Sentinel cells in tissues (macrophages, dendritic cells, and other cell types) recognize microbes and damaged cells and liberate mediators, which trigger the vascular and cellular reactions of inflammation.

Acute inflammation has three major components:

(1) dilation of small vessels leading to an increase in blood flow.
(2) increased permeability of the microvasculature enabling plasma proteins and leukocytes to leave the circulation.
(3) emigration of leukocytes from the microcirculation, their accumulation in the focus of injury, and their activation to eliminate the offending agent.

VASCULAR REACTIONS IN ACUTE INFLAMMATION

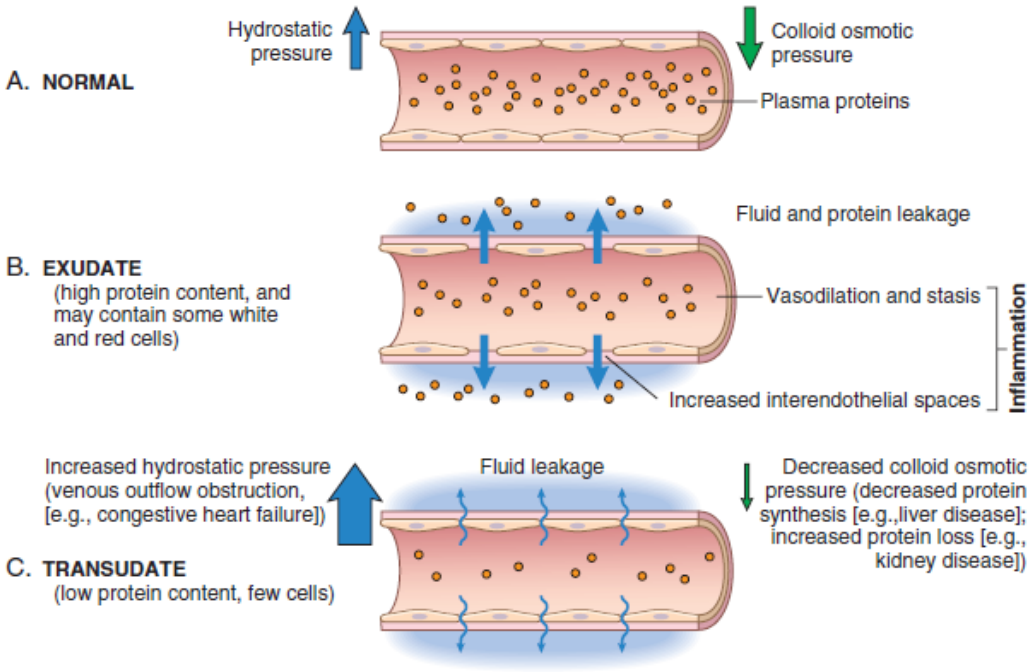
The vascular reactions of acute inflammation consist of changes in the flow of blood and the permeability of vessels, both designed to maximize the movement of plasma proteins and leukocytes out of the circulation and into the site of infection or injury.

Edema (which is the cause of swelling) means an excess of fluid in the interstitial tissue or serous cavities; it can be either an exudate or a transudate.

Exudate is an extravascular fluid that has a high protein concentration and contains cellular debris. Its presence implies the existence of *an inflammatory process* that has, increased the permeability of small blood vessels.

Pus, a purulent exudate, is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells, and, in many cases, microbes.

transudate is a fluid with low protein content (most of which is albumin), little or no cellular material, and low specific gravity. transudate is accumulating in non-inflammatory conditions.



A. Changes in Vascular Flow and Caliber: begin early after injury and consist of the following:

- Vasodilation induced by chemical mediators such as histamine and is the cause of erythema and increased blood flow.
- increased permeability of the microvasculature, with the outpouring of protein-rich fluid into the extravascular tissues.
- The loss of fluid and increased vessel diameter lead to slower blood flow, concentration of red cells in small vessels, and increased viscosity of the blood. a condition termed *stasis*, which is seen as vascular congestion and localized redness of the involved tissue.
- As stasis develops, blood leukocytes, *principally neutrophils*, accumulate along the vascular endothelium. Leukocytes then adhere to the endothelium, and soon afterward they migrate through the vascular wall into the interstitial tissue.

B. *Increased Vascular Permeability (Vascular Leakage)*

Several mechanisms are responsible for the increased permeability of post capillary venules.

- *Contraction of endothelial cells* resulting in opening of interendothelial gaps is the most common mechanism of vascular leakage. It is the immediate transient response because it occurs rapidly after exposure to the mediator and is usually short-lived (15 to 30 minutes). It is elicited by histamine, bradykinin, and leukotrienes.

- *Endothelial injury* resulting in endothelial cell necrosis and detachment. in severe physical injuries, for example, in thermal burns, or is induced by the actions of microbes and microbial toxins that damage endothelial cells. Neutrophils that adhere to the endothelium during inflammation may also injure endothelial cells and thus amplify the reaction.

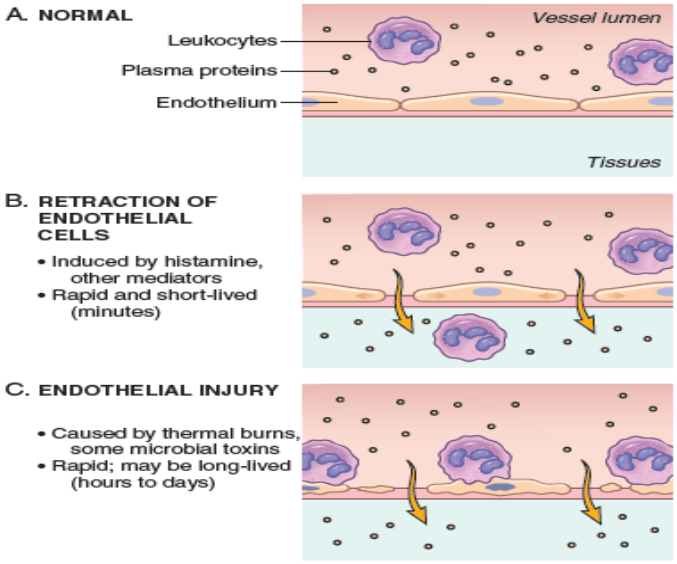


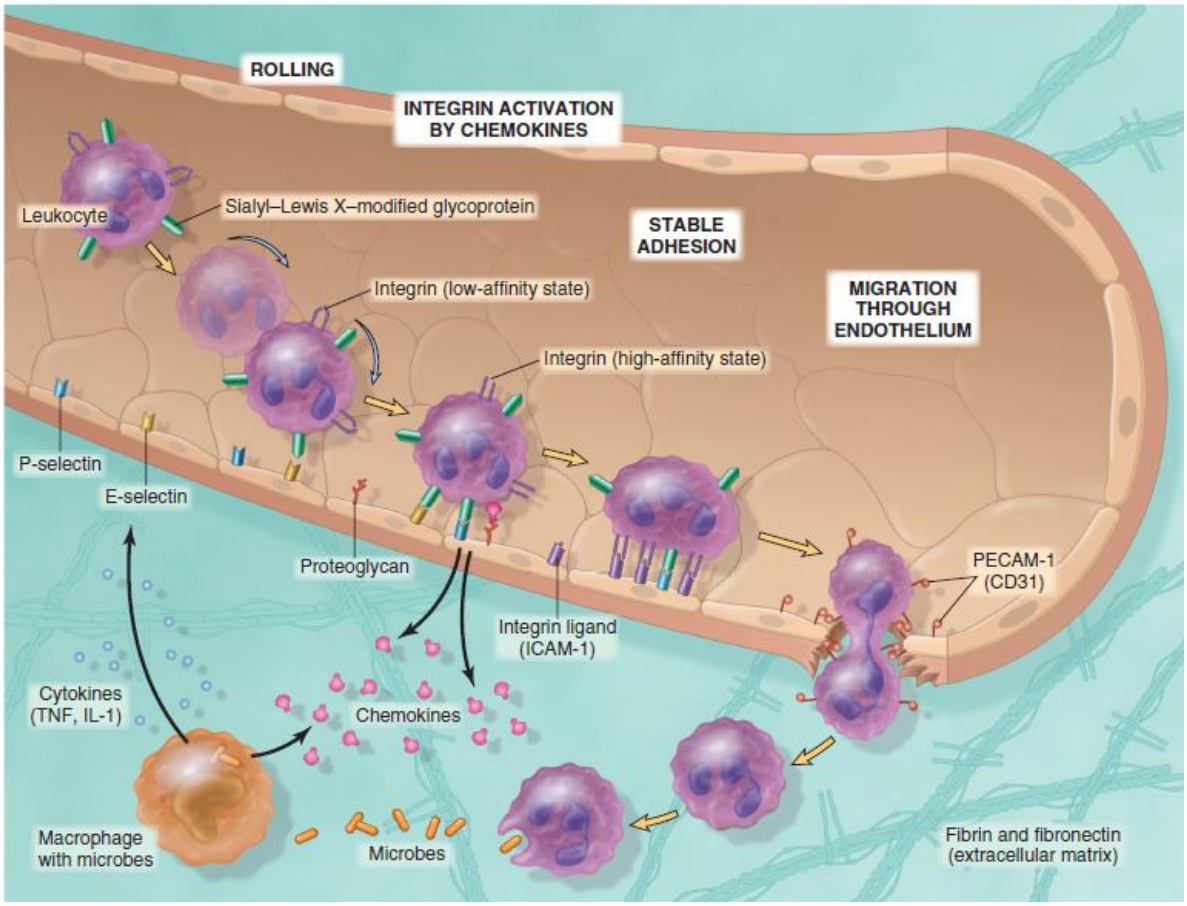
Figure 3.3 Principal mechanisms of increased vascular permeability in inflammation and their features and underlying causes.

Lymphatic vessels and lymph nodes are also involved in inflammation and often show redness and swelling. inflamed lymphatic channels and are diagnostic of lymphangitis; it may be accompanied by painful enlargement of the draining lymph nodes, indicating lymphadenitis.

LEUKOCYTE RECRUITMENT TO SITES OF INFLAMMATION:

The journey of leukocytes from the vessel lumen to the tissue is a multistep process that is mediated and controlled by adhesion molecules and cytokines called chemokines. This process can be divided into sequential phases.

1. In the lumen: *margination, rolling, and adhesion* to endothelium.
2. *Migration across the endothelium* and vessel wall (*transmigration* or *diapedesis*).
3. *Migration in the tissues* toward a *chemotactic* stimulus (locomotion along a chemical gradient.



Leukocyte Activation

Once leukocytes (particularly neutrophils and monocytes) are recruited to a site of infection or cell death, they must be activated by receptors to perform their functions through the phagocytosis and destroy the microbes.

Phagocytosis and Clearance of the Offending Agent

The functional responses that are most important for destruction of microbes and other offenders are phagocytosis and intracellular killing. two major phagocytes are neutrophils and macrophages.

Phagocytosis involves sequential steps:

• Recognition and attachment of the particle to be ingested by the leukocyte;

• Engulfment, with subsequent formation of a phagocytic vacuole; and

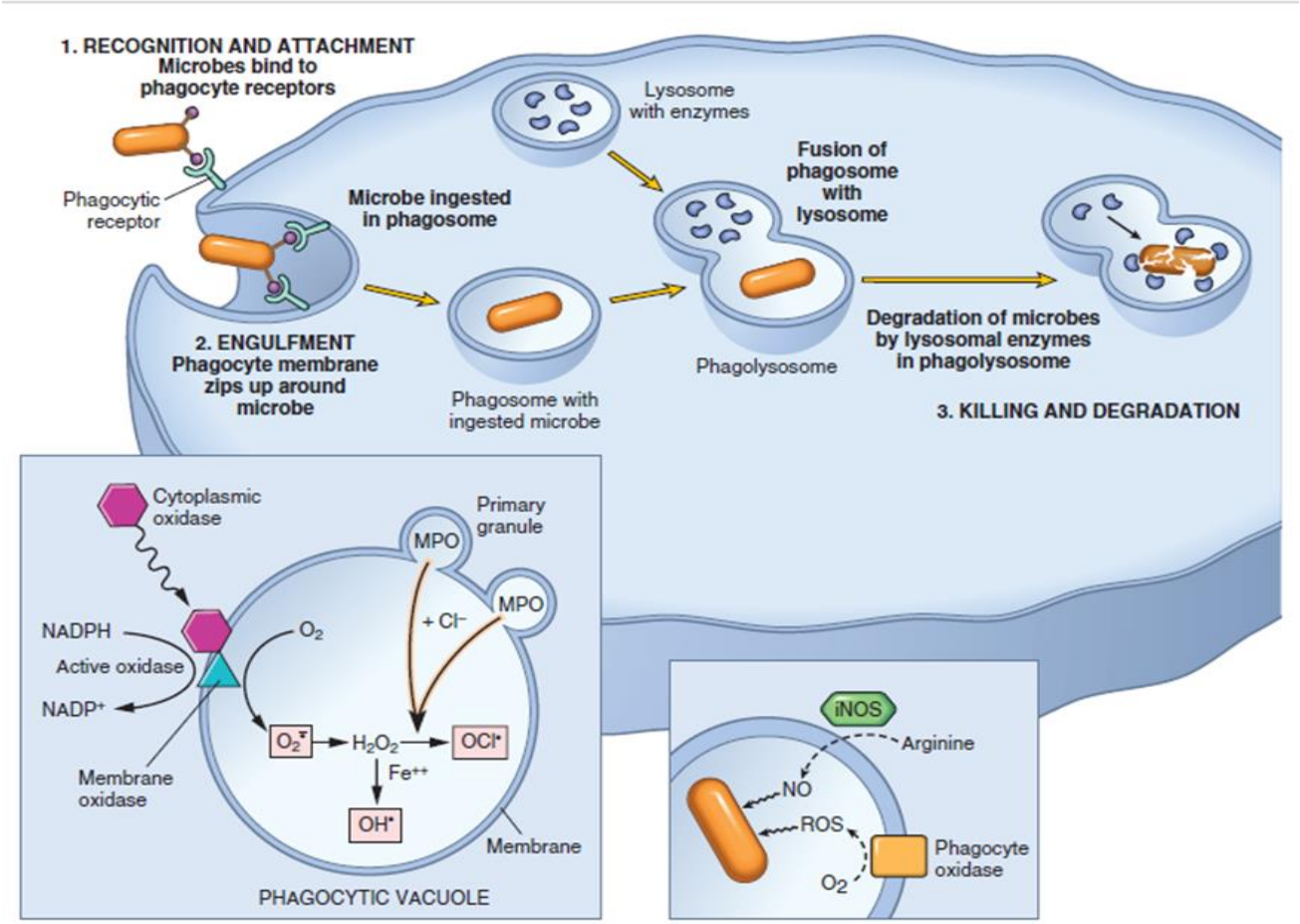
• Killing of the microbe and degradation of the ingested material.

1. Recognition and attachment of the particle to be ingested by the leukocyte; The efficiency of phagocytosis is greatly enhanced when microbes are coated with *opsonins* for which the phagocytes express high-affinity receptors. The major *opsonins* are

immunoglobulin G (IgG) antibodies, the C3b breakdown product of complement, and certain plasma lectins, notably mannose-binding lectin and *collectins*, all of which are recognized by specific receptors on leukocytes.

2. Engulfment. After a particle is bound to phagocyte receptors, extensions of the cytoplasm flow around it, and the plasma membrane pinches off to form an intracellular vesicle (phagosome) that encloses the particle. The phagosome then fuses with a lysosomal granule, which discharges its contents into the phagolysosome. During this process the phagocyte may also release lysosome contents into the extracellular space.

3. Killing of microbes is accomplished by reactive oxygen species (ROS), also called reactive oxygen intermediates, and reactive nitrogen species, mainly derived from nitric oxide (NO), and these as well as lysosomal enzymes destroy phagocytosed materials.



Morphologic Patterns of Acute Inflammation

Many variables may modify the basic inflammatory response; these include:

1. The nature and intensity of the injury

2. The site and tissues affected

3. The responsiveness of the host

Serous Inflammation

Fibrinous Inflammation

Suppurative Inflammation

1. *Serous Inflammation:* is marked by the exudation of cell poor fluid into spaces created by cell injury or into body cavities lined by the peritoneum, pleura, or pericardium. accumulation of fluid in these cavities is called an effusion. (Effusions also occur in non-inflammatory conditions, such as reduced blood outflow in heart failure or reduced plasma protein levels in some kidney and liver diseases.)
2. *Fibrinous Inflammation:* A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus (e.g., caused by cancer cells). A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium. Histologically, fibrin appears as an eosinophilic meshwork of threads or sometimes as an amorphous coagulum. If the fibrin is not removed, over time it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue is called organization.
3. Purulent (Suppurative) Inflammation and Abscess: Purulent inflammation is characterized by the production of pus, an exudate consisting of neutrophils, the liquefied debris of necrotic cells, and edema fluid. The most frequent cause of purulent (also called suppurative) inflammation is infection with bacteria that cause liquefactive tissue necrosis, such as staphylococci; these pathogens are referred to

as pyogenic (pus-producing) bacteria. A common example of an acute suppurative inflammation is acute appendicitis.

Abscesses are localized collections of pus caused by suppuration buried in a tissue, an organ, or a confined space. They are produced by seeding of pyogenic bacteria into a tissue. Abscesses have a central liquefied region composed of necrotic leukocytes and tissue cells. There is usually a zone of preserved neutrophils around this necrotic focus, and outside this region there may be vascular dilation and parenchymal and fibroblastic proliferation, indicating chronic inflammation and repair. In time the abscess may become walled off and ultimately replaced by connective tissue.

Ulcers

An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue. Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface. It is most common in

(1) the mucosa of the mouth, stomach, intestines, or genitourinary tract, and

(2) the skin and subcutaneous tissue of the lower extremities in individuals with disorders that predispose to vascular insufficiency, such as diabetes, sickle cell anemia, and peripheral vascular disease.

Outcomes of Acute Inflammation:

acute inflammatory reactions typically have one of three outcomes:

1.Complete resolution. In a perfect world, all inflammatory reactions, once they have succeeded in eliminating the offending agent, would end with restoration of the site of acute inflammation to normal. This is called *resolution* and is the usual outcome when the injury is limited or short-lived. Resolution involves removal of cellular debris and microbes by macrophages and resorption of edema fluid by lymphatics, followed by regeneration of the damaged tissue.

2. Healing by connective tissue replacement (scarring, or fibrosis).

This occurs after substantial tissue destruction, when the inflammatory injury involves tissues that are incapable of regeneration, or when there is abundant fibrin exudation in tissue or in serous cavities (pleura, peritoneum) that cannot be adequately cleared in all these situations, connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue, a process also called organization.

3. Progression of the response to chronic inflammation

Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, as a result of either the persistence of the injurious agent or some interference with the normal process of healing.

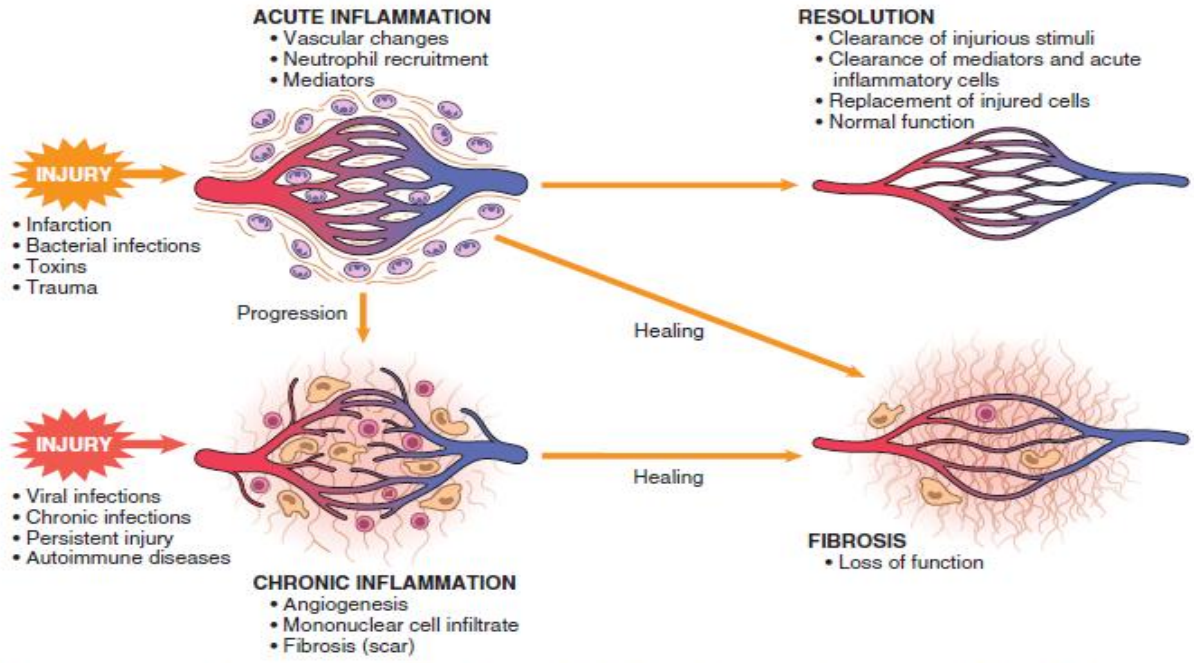


Figure 3.17 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.