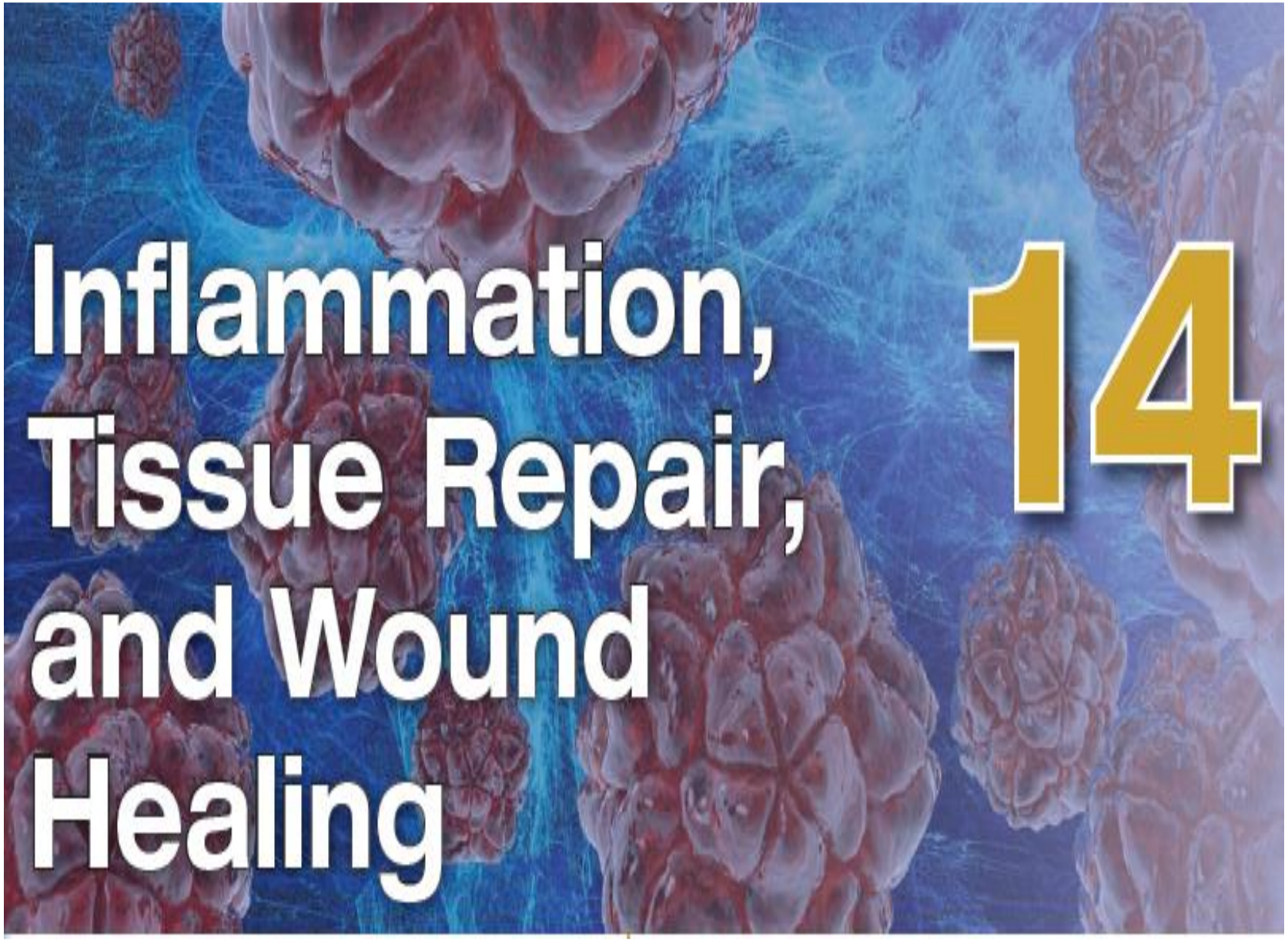

Inflammation,
Tissue Repair,
and Wound
Healing
14

Inflammation

• **Inflammation:** is a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from that injury (facilitate healing process).
• It accomplishes this by diluting, destroying, or otherwise neutralizing the harmful agents and induce repair.
• It is a beneficial host response. However, it can be potentially harmful, because the components of the inflammatory reaction that destroy and eliminate microbes and dead tissue are capable of also injuring normal tissue. This happens if the reaction is very strong (e.g., when the infection is severe), prolonged (e.g., when the eliciting agent resists eradication) or inappropriate (e.g., when it is directed against self-antigens in autoimmune diseases or against harmless environmental antigens in allergic reactions).

• It is due to for example
chemical agents
cold, heat
trauma
invasion of microbes

Inflammatory conditions are commonly named by adding suffix (itis) to the affected organ or system (appendicitis , pericarditis,

Inflammation

- Inflammation can be divided into two basic patterns: acute and chronic.
- Acute inflammation is relatively short duration, lasting from a few minutes to several days, and is characterized by the exudation of fluid and plasma components and emigration of leukocytes, predominantly neutrophils into the extravascular tissue.
- Chronic inflammation: is a longer duration lasting from days to years and is associated with the presence of lymphocytes and macrophages, proliferation of blood vessels, fibrosis (scarring) and tissue necrosis.

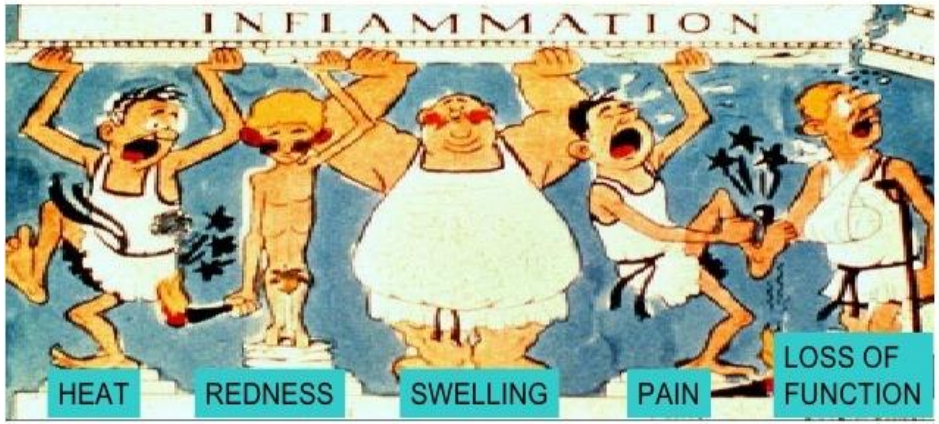
Table 2–1 Features of Acute and Chronic Inflammation

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local and systemic signs	Prominent	Less prominent; may be subtle

Manifestation of inflammation

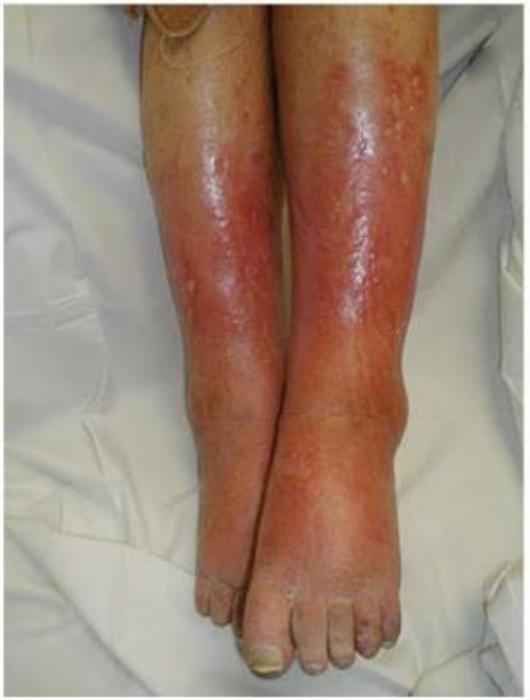
SIGNS AND SYMPTOMS OF INFLAMMATION

- The inflammatory response can be either acute or chronic, but the local reactions are described as the cardinal signs and symptoms of inflammation:



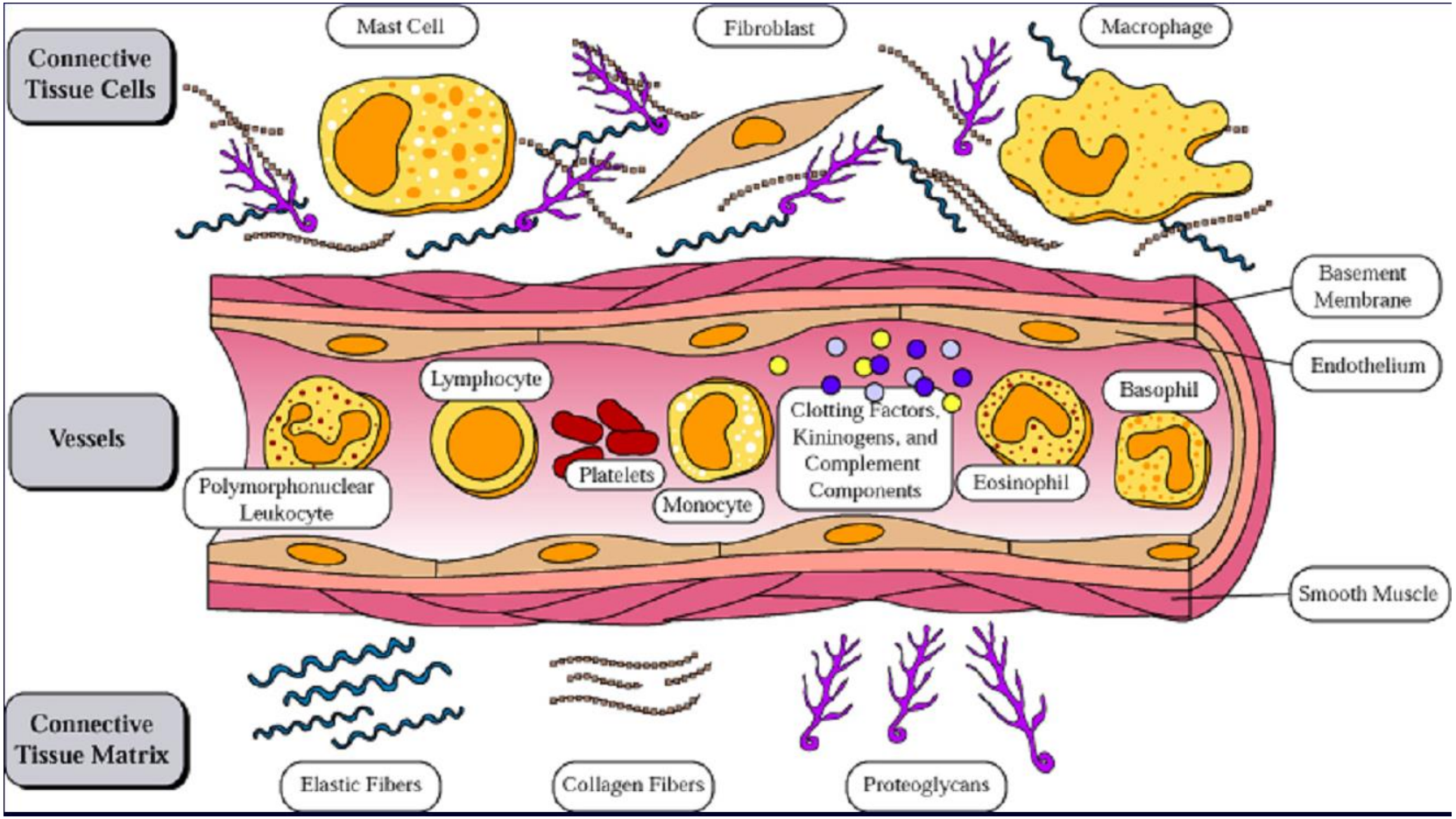
Calor	Rubor	Tumor	Dolor	Functio laesa

The external manifestation of inflammation called cardinal signs which result from vascular changes and cell recruitment.



Cellulitis: Severe bilateral inflammation and swelling of the legs

Inflammatory cells
cells involved in inflammatory responses



Components of acute and chronic inflammation

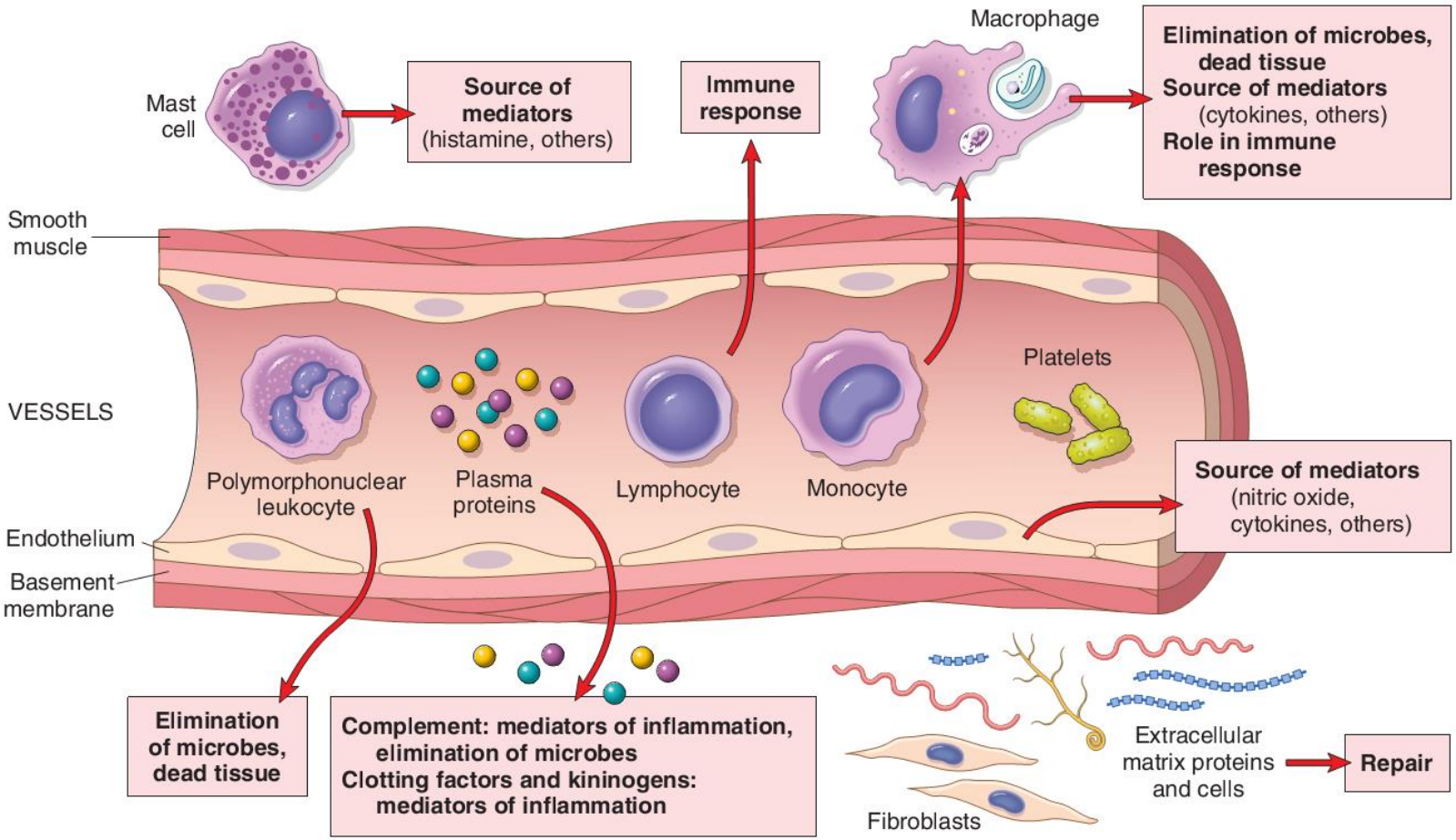


Figure 2–1 The components of acute and chronic inflammatory responses and their principal functions. The roles of these cells and molecules in inflammation are described in this chapter.

Acute Inflammation

- Acute inflammation is a rapid and initial response to injury or microbes that is designated to deliver leukocytes and plasma proteins to sites of injury. Leukocytes clear the invaders and begin the process of digestion and getting rid of necrotic tissues.

- Acute inflammation involves two major component; the vascular and cellular stages. Both the vascular and cellular reactions of the inflammatory response are mediated by chemical factors that are derived from plasma protein or cells and are produced in response to or activated by the inflammatory stimulus.

- Main components: – Vascular changes • Vasodilation • Vascular permeability • Increased adhesion of white blood cells – Cellular events • Cellular recruitment and activation of neutrophils (polymorphonuclear leukocytes)

Vascular stage

- The vascular changes that occur with inflammation begin almost immediately after infection or injury and are initiated by a momentary constriction of small vessels in the area.
- The vasoconstriction is followed rapidly by vasodilation that is induced by chemical mediators such as histamine..
- Vasodilation involves the arterioles and venules with a resultant increase in capillary blood flow, causing heat and redness.
- This is accompanied by an increase in vascular permeability with outpouring of protein-rich fluid (exudate) into the extravascular spaces. The loss of proteins reduces the capillary (intravascular) osmotic pressure and increases the interstitial osmotic pressure. This, coupled with an increase in capillary pressure, causes a marked outflow of fluid and its accumulation in the tissue spaces, producing the swelling, pain, and impaired function that represent the other cardinal signs of acute inflammation.
- Increased vascular permeability is induced by:

1. histamine, bradykinin, leukotrienes and many other chemical mediators that bind with their receptors causing contraction of endothelial cells and consequently the formation of intracellular gaps in the venules.
2. Direct injury to endothelial cells causing endothelial cell necrosis and detachment or leukocytes mediated endothelial injury as a consequence of accumulation of leukocytes along vessel wall following stasis. Activated leukocytes release many toxic mediators that may cause endothelial injury and detachment.

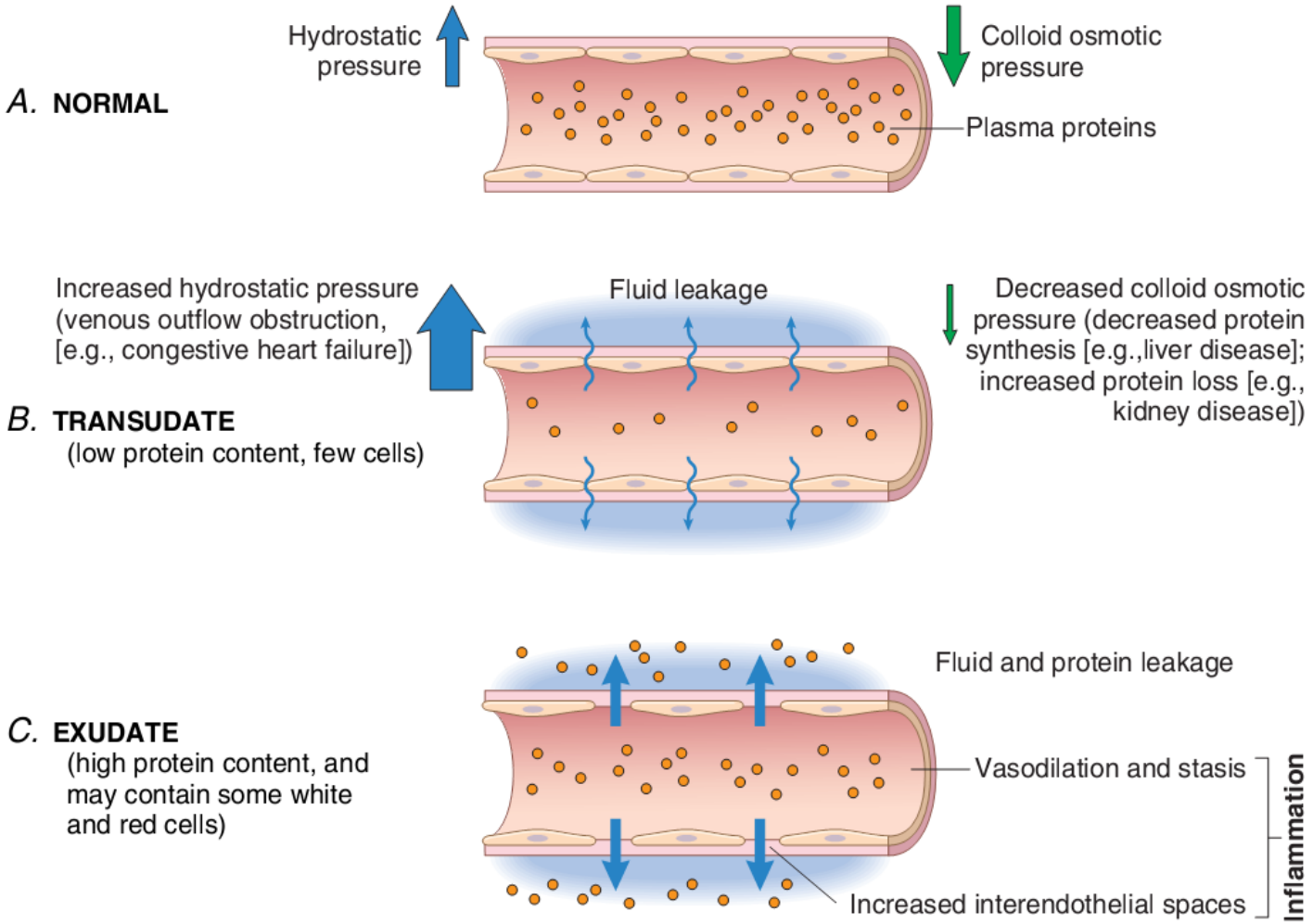


Figure 2–4 Formation of transudates and exudates. *A*, Normal hydrostatic pressure (*blue arrows*) is approximately 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (*green arrows*), which is nearly equal to the mean capillary pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. *B*, A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure. *C*, An exudate is formed in inflammation because vascular permeability increases as a result of the increase in interendothelial spaces.

Cellular Phase (leukocyte recruitment)

- The cellular phase of acute inflammation involves the delivery of leukocytes, mainly neutrophils, to the site of injury followed by the activation process so that they can perform their normal functions of host defense.

- The delivery of leukocytes from vascular lumen to the extravascular space can be divided into the following steps:

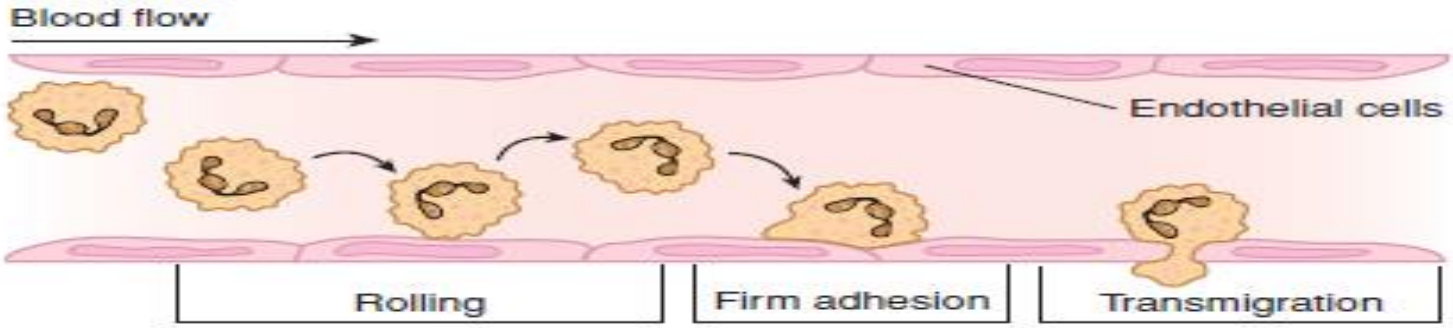
1. Margination and rolling.
2. Firm adhesion and transmigration across the endothelium.
3. Chemotaxis.

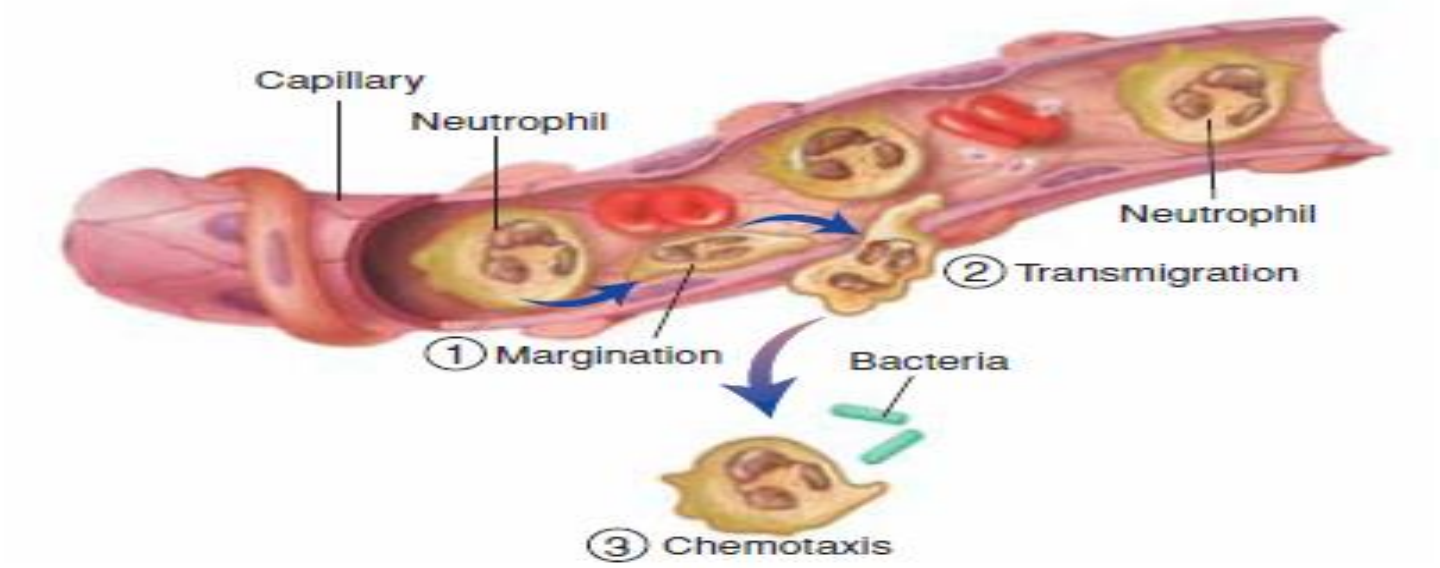
- The recruitment of leukocytes to the precapillary venules, where they exit the circulation, is facilitated by the slowing of blood flow and margination along the vessel surface. Leukocyte adhesion and transmigration from the vascular space into the extravascular tissue is facilitated by complementary adhesion molecules (e.g., selectins, integrins) on the leukocyte and endothelial surfaces. After extravasation, leukocytes migrate in the tissues toward the site of injury by chemotaxis, or locomotion oriented along a chemical gradient.

- The functions of leukocytes is to:

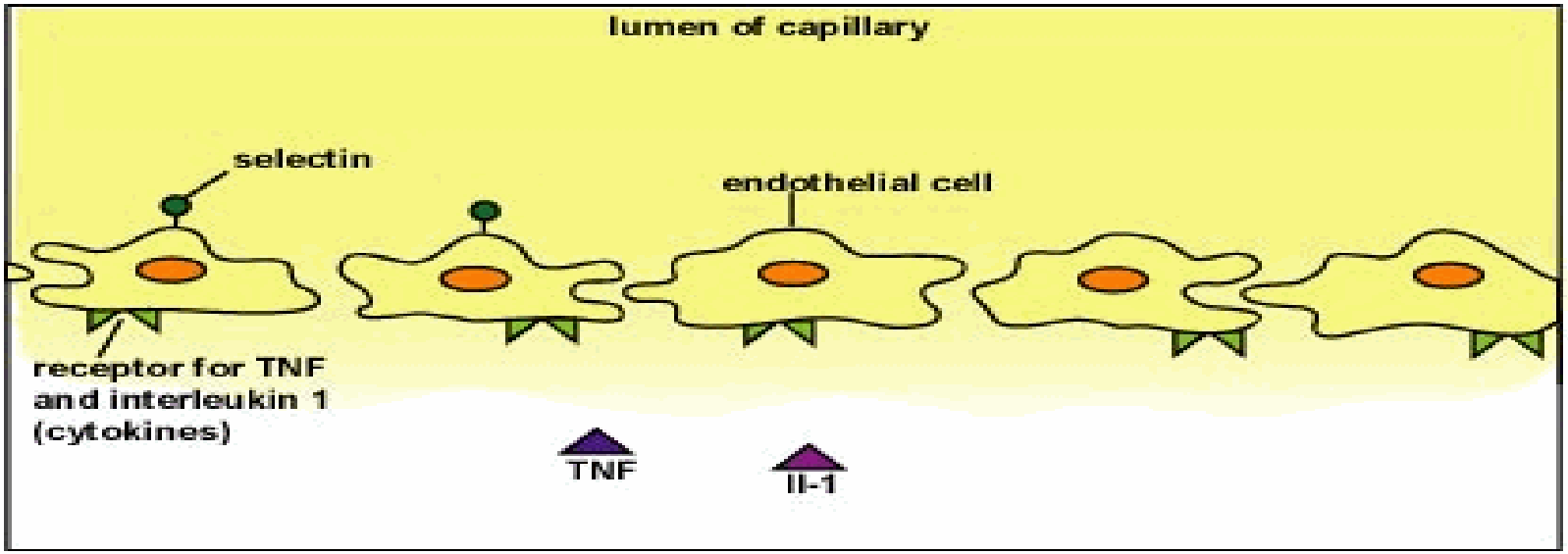
1. Ingesting offending agents.
2. Killing bacteria and other microbes.
3. Eliminating necrotic tissue and foreign substances.

- Bad consequences of that activation is that the activated leukocytes may induce tissue damage and prolong inflammation since their products that destroy microbes can also injury normal host tissues.
- Therefore, key to the normal function of leukocytes in host defense is to ensure that they are recruited and activated only when needed (i.e., in response to foreign invaders and dead tissue)


Blood flow
Endothelial cells
Rolling
Firm adhesion
Transmigration


Capillary
Neutrophil
Neutrophil
② Transmigration
① Margination
Bacteria
③ Chemotaxis

margination*, *adhesion with ***leukodiapedesis (animation)***



- Cytokines such as TNF and Interleukin-1 induce the production of selectins, chemokines, and adhesion molecules on the inner surface of the endothelial cells that line the blood vessels. Eventually integrins on the surface of the leukocyte bind to adhesion molecules (ligands) on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells, leaving the blood vessels and entering the tissue.

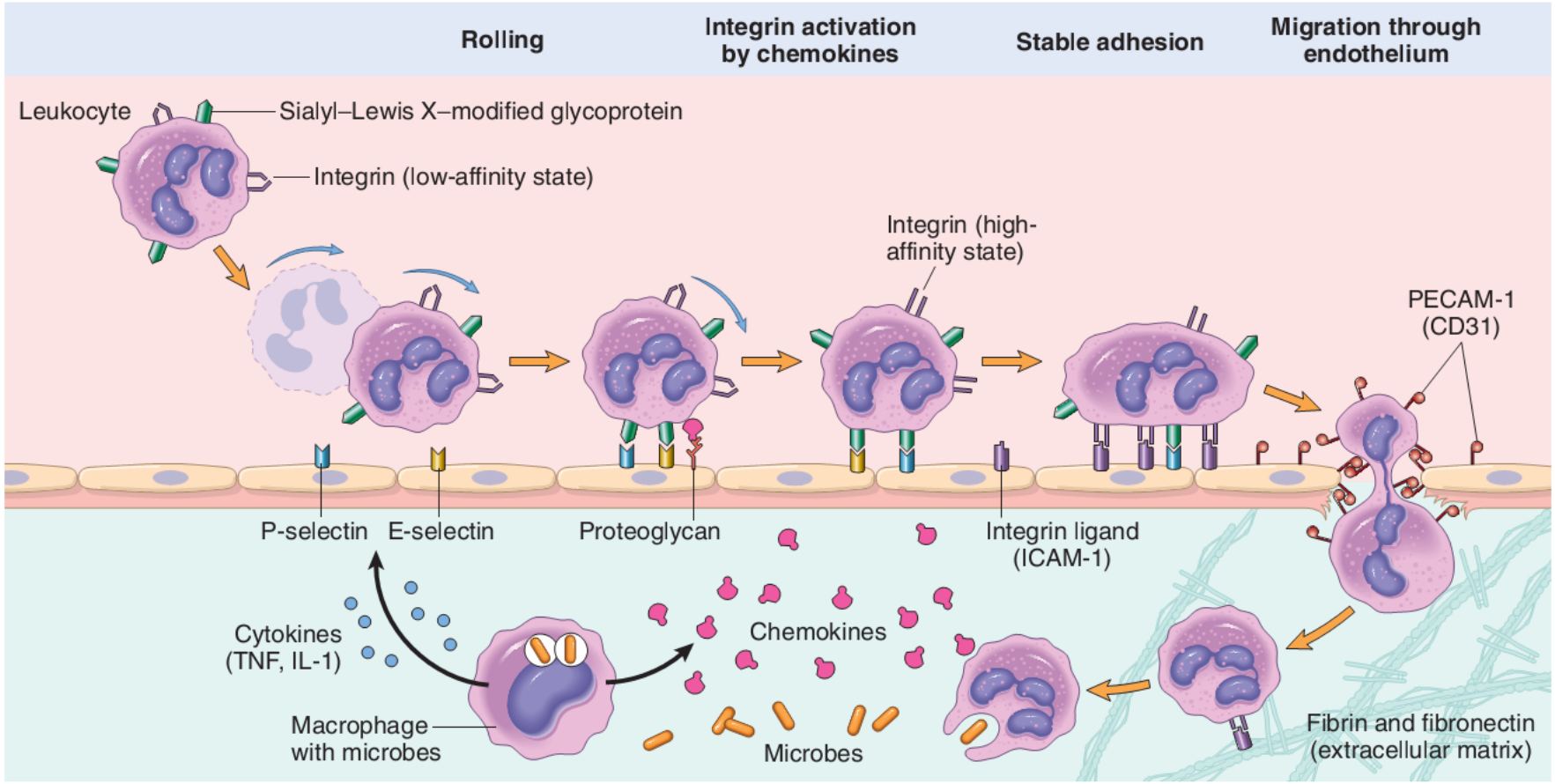


Figure 2–5 Mechanisms of leukocyte migration through blood vessels. The leukocytes (neutrophils shown here) first roll, then become activated and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and migrate toward chemoattractants emanating from the source of injury. Different molecules play predominant roles in different steps of this process: selectins in rolling; chemokines (usually displayed bound to proteoglycans) in activating the neutrophils to increase avidity of integrins; integrins in firm adhesion; and CD31 (PECAM-1) in transmigration. ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1; PECAM-1, platelet endothelial cell adhesion molecule-1; TNF, tumor necrosis factor.

leukocyte recruitment

1. Margination and rolling:

- Smaller red blood cells tend to move faster than the larger white cells. As a result, leukocytes are pushed out of the central axial column and thus have a better opportunity to interact with lining endothelial cells. The accumulation of leukocytes at the periphery of vessels is called ***margination***.
- ***Rolling*** occurs subsequently in which the leukocytes tumble on (fall quickly without control) the endothelial surface and transiently and weakly adhering (sticking) along the way. The adhesion process involved in rolling is mediated by **selectin** family of adhesion molecules.
- ***Selectin***

1. are receptors expressed on endothelial cells which facilitate leukocyte binding.
2. Selectins bind oligosaccharides (sialyl-Lewis X modified glycoprotein) that are present on the leukocytes.
3. The endothelial selectins are expressed at low levels or are not present at all on normal cells. They are up-regulated after stimulation by specific mediators. Therefore, binding of leukocytes is largely restricted to endothelium at sites of infection or tissue injury (where the mediators are produced).

2. Firm adhesion and transmigration:

- ***Firm adhesion*** to endothelial surfaces is mediated by integrins expressed on leukocytes cell surfaces interacting with their ligands on endothelial cells.
- **Integrins** are transmembrane glycoproteins that function as cell receptors. They are normally expressed on leukocyte membrane in a low-affinity form and do not adhere to their ligands until leukocytes are activated by chemokines.

Continue……

- **Chemokines** are chemoattractant cytokines that are secreted by many cells at sites of inflammation and displayed bound to proteoglycans on the endothelial surface. When the adherent leukocytes encounter the displayed chemokines the cells are activated and their integrins undergo conformational changes and cluster together thus converting to a high affinity form.
- At the same time, other cytokines (TNF, IL-1) activate endothelial cells to increase their expression of ligand to integrins. Examples of these ligands (ICAM).
- **The net result of chemokines-stimulated increased integrin affinity and increased expression of integrin ligands is stable attachment of leukocytes to endothelial cells at site of inflammation.**

3. Transmigration

- After being arrested on the endothelial surface, leukocytes migrate through the vessel wall primarily by squeezing between endothelial cells at intercellular junctions. Migration is driven by chemokines produced in extravascular tissues which stimulate movement of the leukocytes toward their chemical gradient. In addition, PECAM-1 also called CD31 which is a cellular adhesion molecule expressed on leukocytes and endothelial cells, mediate the binding events needed for leukocytes to transverse the endothelium.

4. Chemotaxis

- After extravasating from the blood, leukocytes migrate toward sites of infection or injury along chemical gradient. Both exogenous and endogenous substances can be chemotactic for leukocytes including bacterial products, cytokines (from chemokine family), etc.

Cellular Phase (Leukocyte Activation)

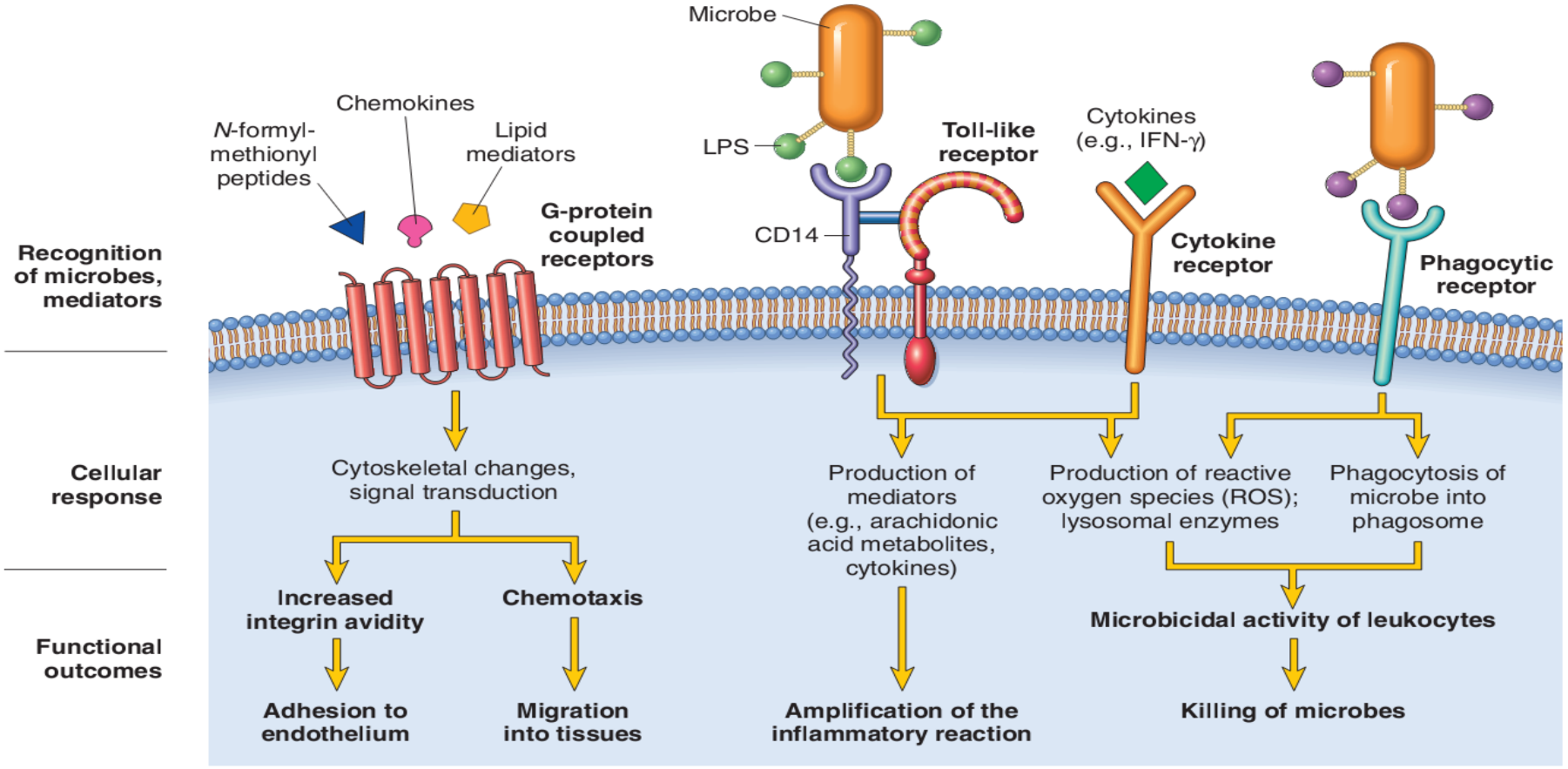


Figure 2–7 Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted (see text for details). Lipopolysaccharide (LPS) first binds to a circulating LPS-binding protein (*not shown*). IFN-γ, interferon-γ.

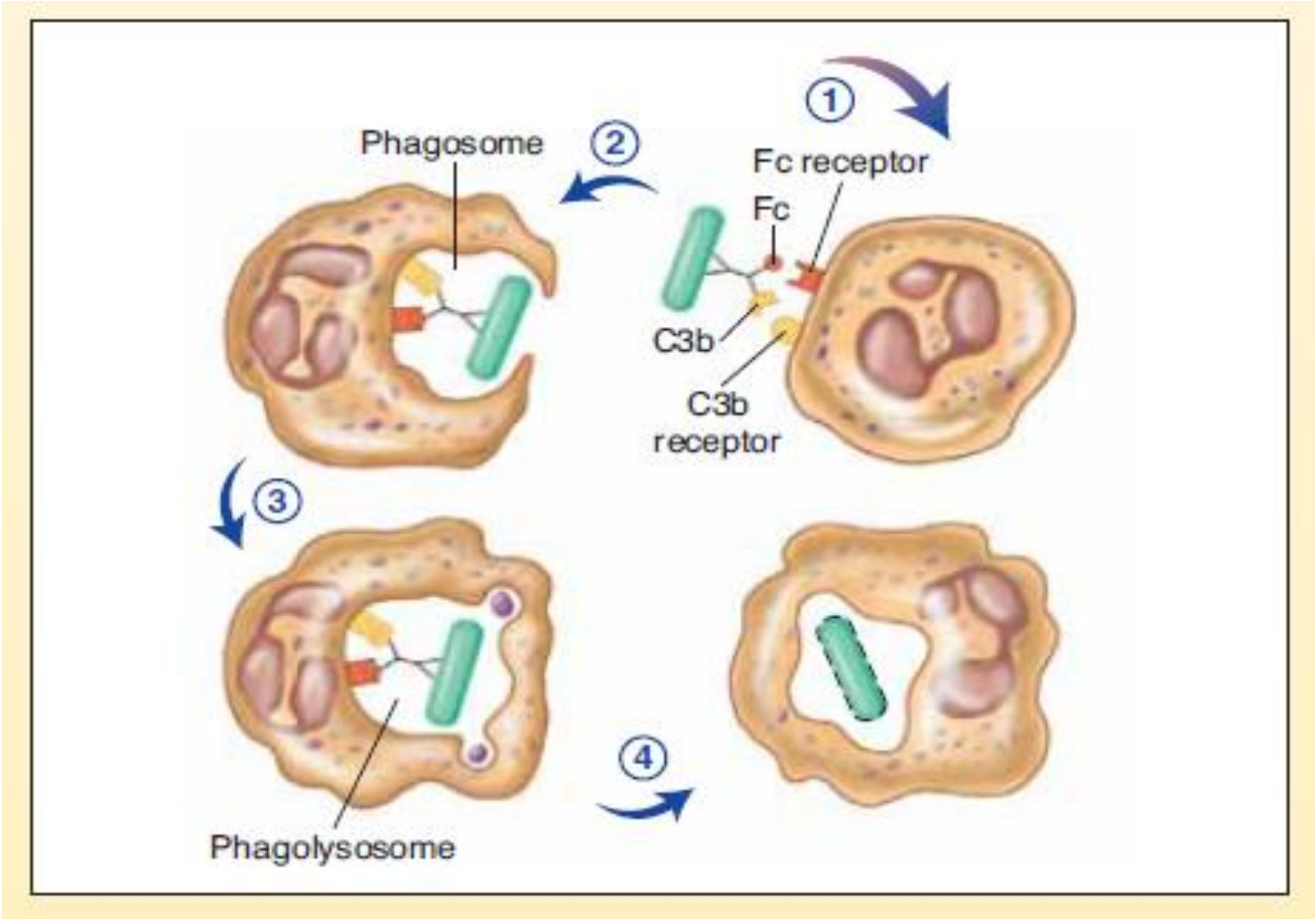
Leukocytes express on their surface different kinds of receptors that sense the presence of microbes. These include 1. TLR which recognise endotoxin (LPS) and many other bacterial and viral products 2. G-protein coupled receptor which recognise bacterial peptides and mediators produced in response to microbes.

Engagement of these receptors by microbial products or various mediators of inflammation induces a number of responses in leukocytes that are part of their normal defensive functions and are grouped under the term of leukocytes activation.

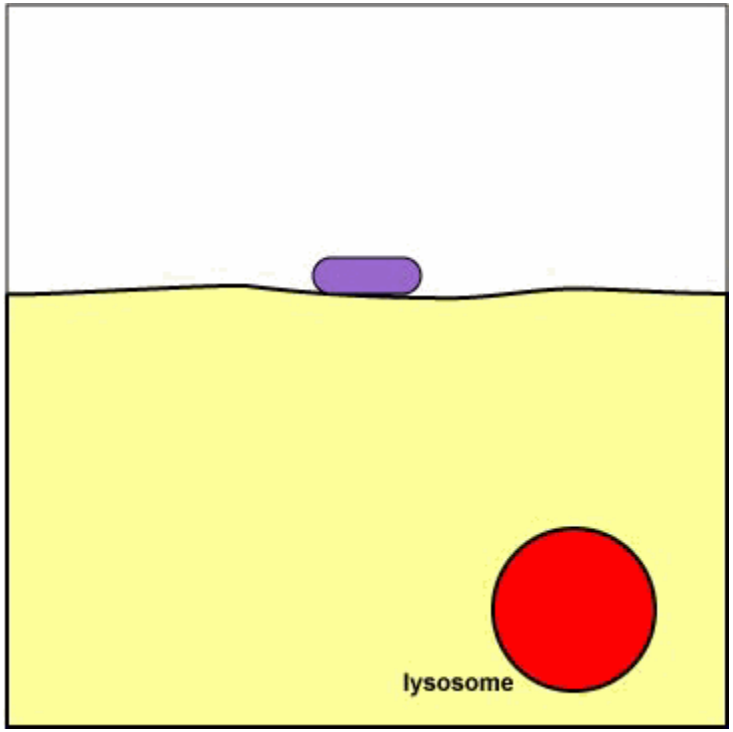
Cellular Phase (Phagocytosis)

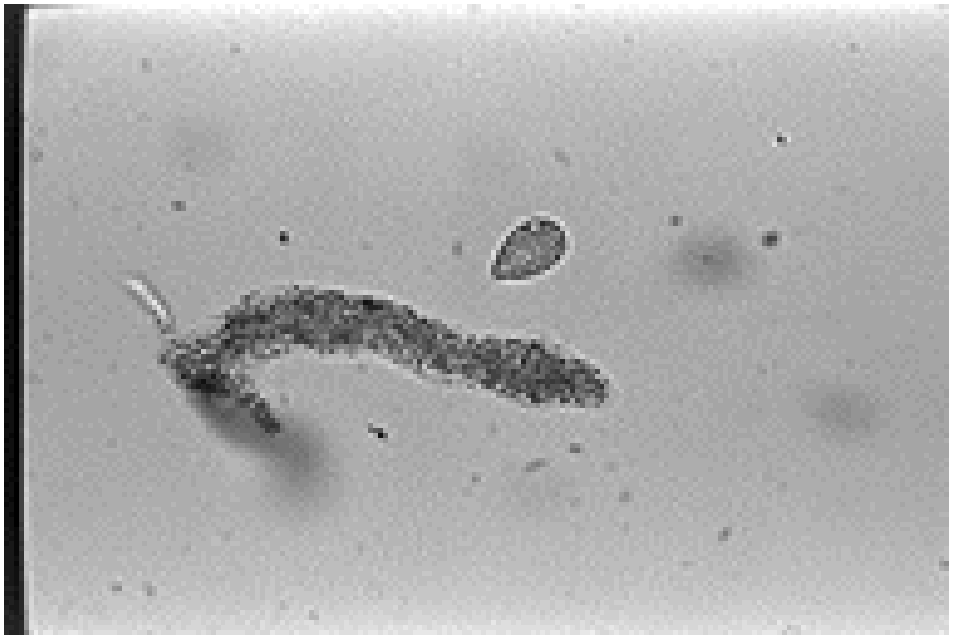
- Once at the site of injury, the products generated by tissue injury trigger a number of leukocyte responses, including phagocytosis and cell killing. Neutrilizing of microbes (1) by complement factor C3b and antibody facilitates recognition by neutrophil C3b and the antibody Fc receptor.
  Receptor activation (2) triggers intracellular signaling and actin assembly in the neutrophil, leading to formation of pseudopods that enclose the microbe within a phagosome.
  The phagosome (3) then fuses with an intracellular lysosome to form a phagolysosome into which lysosomal enzymes and oxygen radicals (4) are released to kill and degrade the microbe.

Phagocytosis

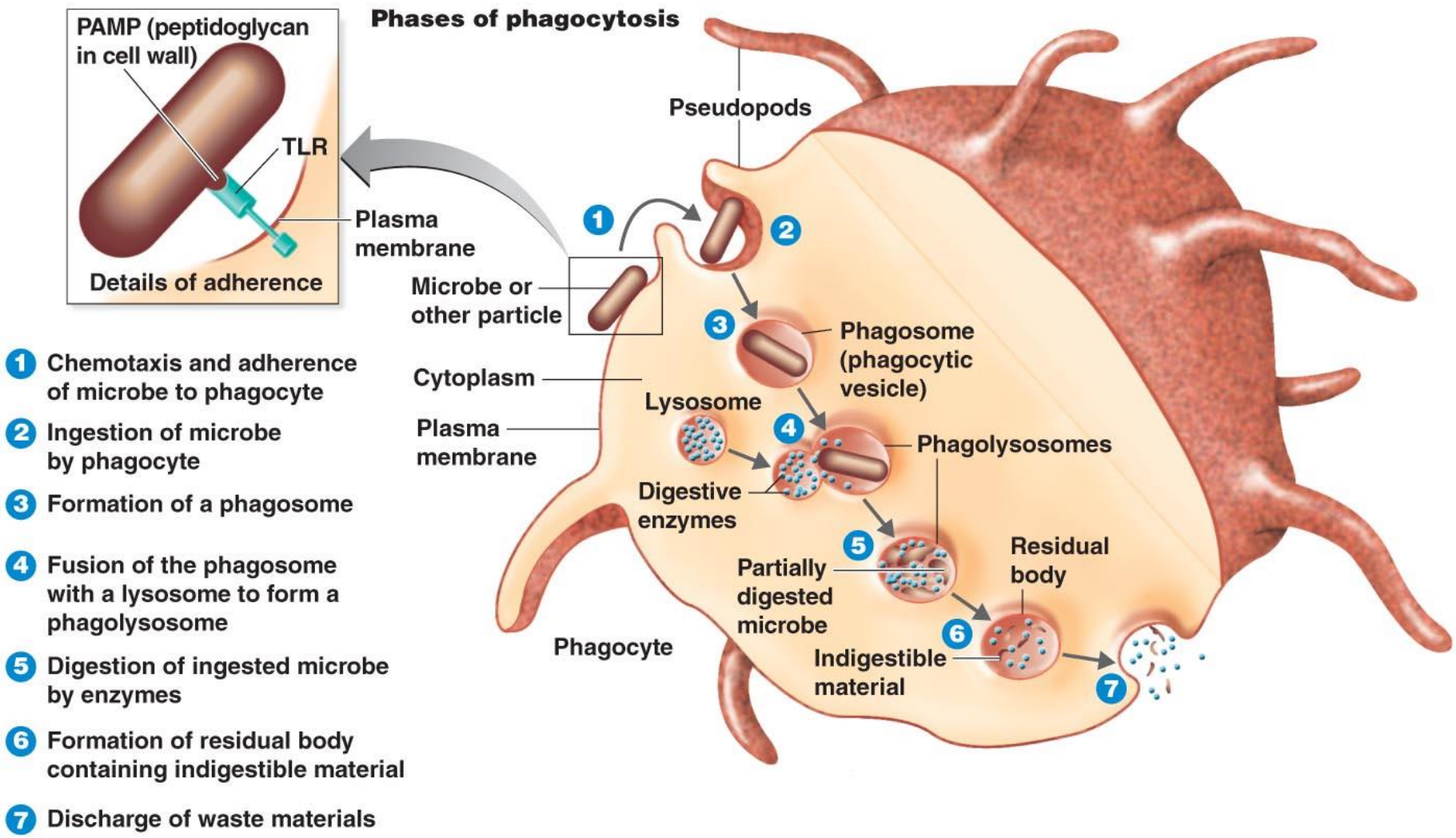


Phagocytosis Animation





Phagocytosis

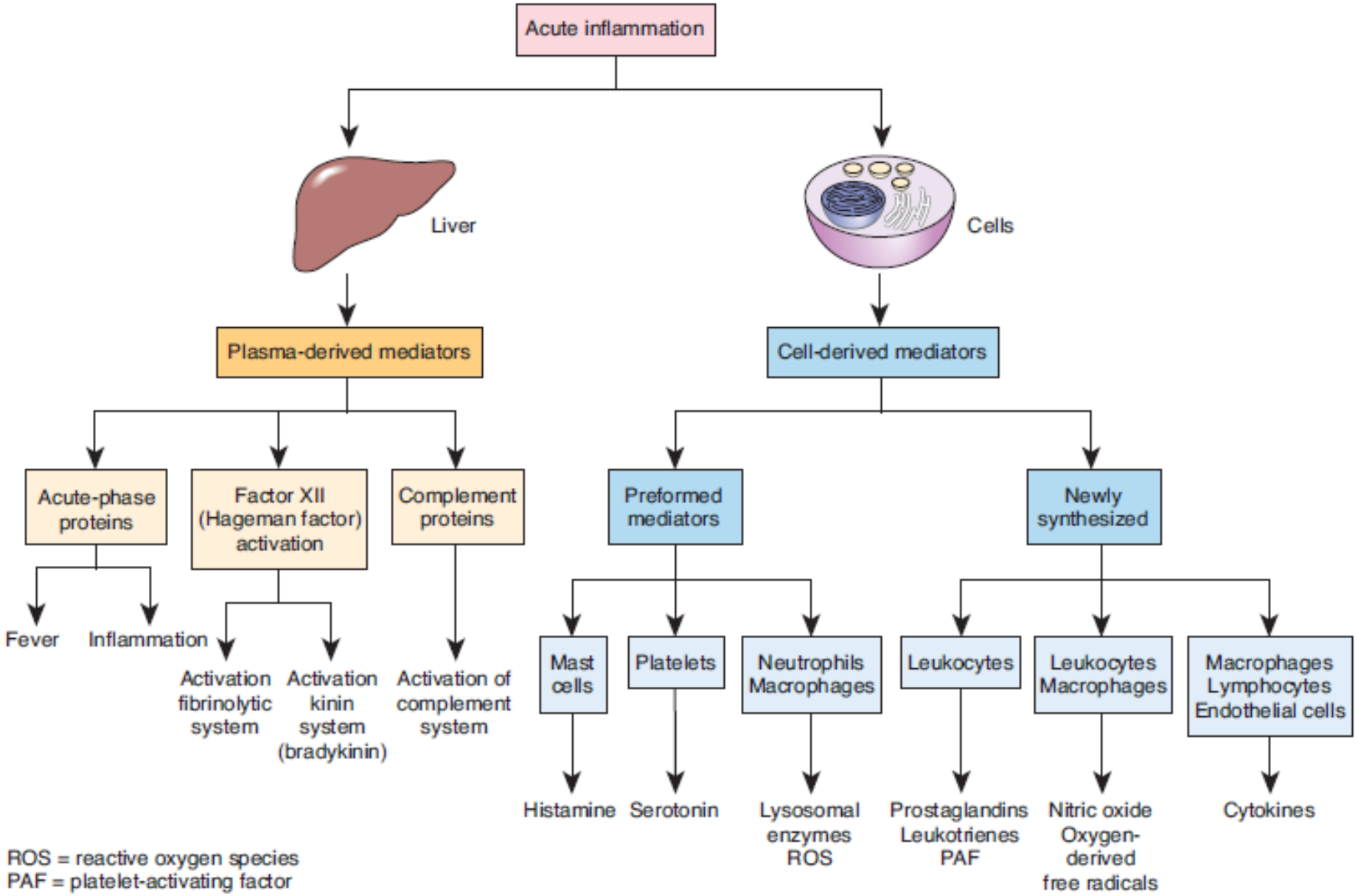


Inflammatory mediators

- Inflammatory mediators may be derived from the plasma or they may be produced locally by cells at the site of inflammation. The ***plasma derived*** *mediators*, which are synthesized in the liver, include the acute-phase proteins, coagulation factors, and complement proteins. These mediators are present in the plasma in a precursor form that must be activated by a series of proteolytic processes, to acquire their biologic properties.

- ***Cell-derived*** *mediators* are normally sequestered in intracellular granules that need to be secreted (e.g., histamine from mast cells) or newly synthesized (e.g., cytokines) in response to a stimulus. The major sources of these mediators are platelets, neutrophils, monocyte/macrophages, and mast cells, but most endothelial cells, smooth muscle cells, and fibroblasts can be induced to produce some of the mediators.

Inflammatory mediators



ROS = reactive oxygen species
PAF = platelet-activating factor

Manifestation of inflammation

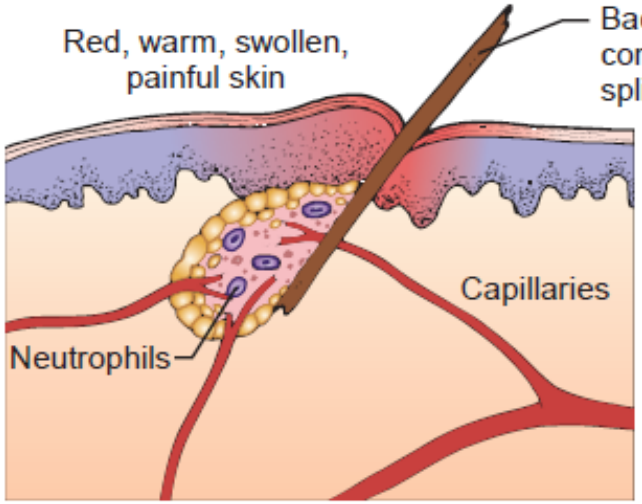
✓ **Local manifestation:**

- The local manifestations of acute inflammation, which are determined by severity of the reaction, its specific cause, and the site of involvement, can range from mild swelling and redness to abscess formation or ulceration.
- P*urulent or suppurative exudate and abscess formation*
- Characteristically, the acute inflammatory response involves the production of exudates. These exudates vary in terms of fluid type, plasma protein content, and the presence or absence of cells. P*urulent or suppurative exudate contains pus, which is* composed of degraded white blood cells, proteins, and tissue debris. An abscess is a localized area of inflammation containing a purulent exudate that may be surrounded by a neutrophil layer. Fibroblasts may eventually enter the area and wall off the abscess. Because antimicrobial agents cannot penetrate the abscess wall, surgical incision and drainage may be required to effect a cure.

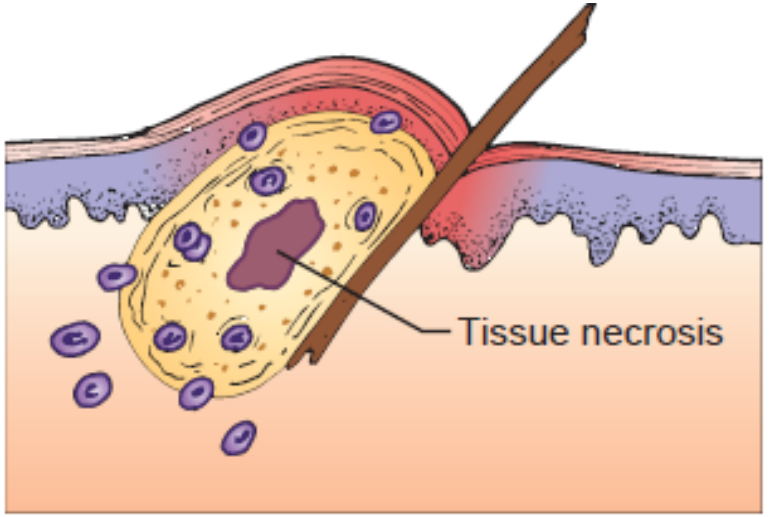
- Ulceration may occur as the result of traumatic injury/ necrosis to the epithelial surface (*e.g., peptic* ulcer) or because of vascular compromise/ circulatory disturbances that predispose to extensive necrosis (*e.g., foot ulcers* associated with diabetes).

- As part of the normal defense reaction, inflammation can also injure adjacent tissues. In some infections such as tuberculosis and certain viral infections, the host response can cause more damage than the microbe itself.
- As a normal attempt to clear damaged and dead tissues (e.g., after a myocardial infarction), the inflammatory response may prolong and exacerbate the injurious consequences of the infarction.

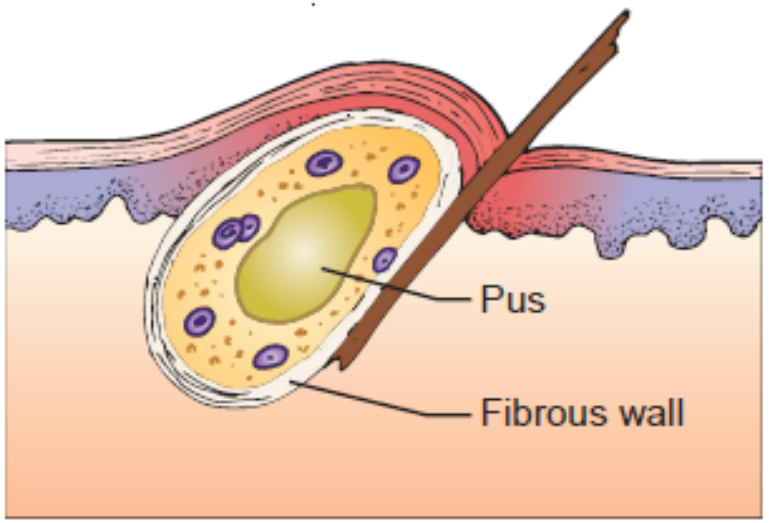
Abscess formation



A Inflammation
Capillary dilation, fluid exudation, neutrophil migration



B Suppuration
Development of suppurative or purulent exudate containing degraded neutrophils and tissue debris



C Abscess formation
Walling off of the area of purulent (pus) exudate to form an abscess

Abscess formation. (A) Bacterial invasion and development of inflammation. (B) Continued bacterial growth, neutrophil migration, liquefaction tissue necrosis (dissolution of dead cells and transformation into a liquid viscous mass), and development of a purulent exudate. (C) Walling off of the inflamed area and its purulent exudate to form an abscess.

Manifestation of inflammation

✓ Systemic manifestation

- Under optimal conditions, the inflammatory response remains confined to a localized area. In some cases, however, local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation. The most prominent systemic manifestations of inflammation include the acute-phase response, alterations in white blood cell count (leukocytosis or leukopenia), and fever. Localized acute and chronic inflammation may extend to the lymphatic system and lead to a reaction in the lymph nodes that drain the affected area. Painful palpable nodes are more commonly associated with inflammatory processes, whereas non-painful lymph nodes are more characteristic of neoplasms.

Some certain features of inflammation

- Serous inflammation e.g. pleural tuberculosis effusion, skin burn blister. It is characterised by outpouring (large volume) of watery protein-poor fluid that derives from the serum or from the secretions of mesothelial cells lining the pleural cavity. Fluid in a serous cavity is called effusion.

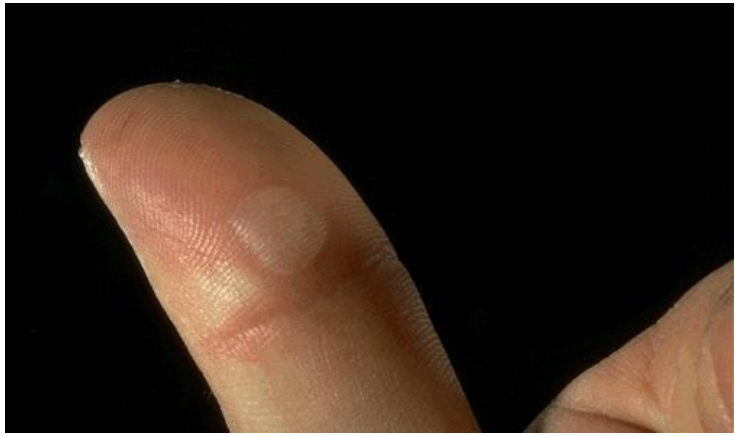
- Fibrinous inflammation e.g. fibrinous pericarditis after acute myocardial infarction. It occurs as a consequence of more sever injuries resulting in greater vascular permeability that allows large molecules (such as fibrinogen) to pass the endothelial barrier. Fibrinous exudate is characteristic of inflammation in the lining of body cavities such as the meninges, pericardium and pleura.

- Suppurative or purulent inflammation e.g. pyogenic staphylococcal abscess. It is manifested by the presence of large amounts of purulent exudate (pus) consisting of neutrophils, necrotic cells, and edema fluid.

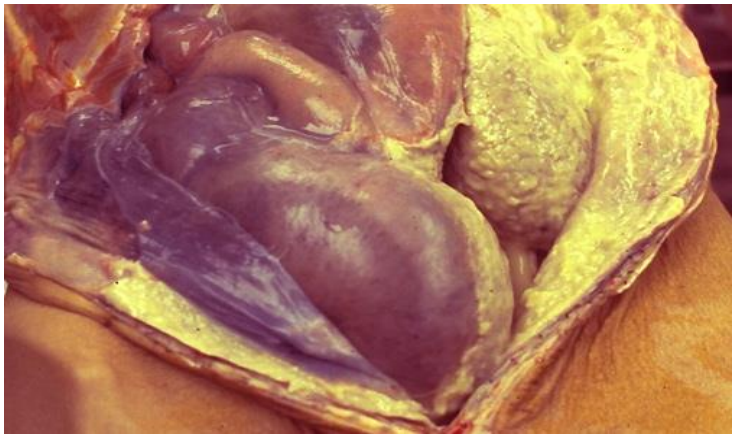
- Abscesses are collection of pus that my be caused by seeding of pyrogenic organisms into a tissue or by secondary infection of necrotic foci. They have a central necrotic region, rimmed by a layer of preserved neutorphils with surrounding zone of dilated vessels and fibroblastic proliferation.

- Ulcer is a local defect for the surface of an organ or tissue that is produced by necrosis of cells or sloughing of inflammatory necrotic tissue.

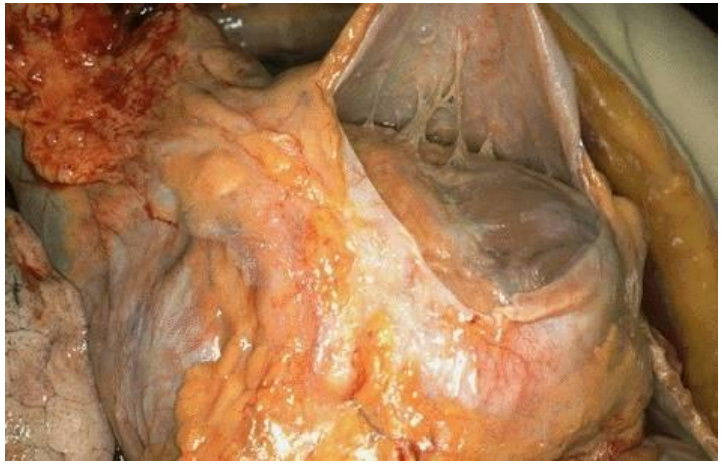
Different morphological patterns of acute inflammation can be found depending on the cause and extend of injury and site of inflammation



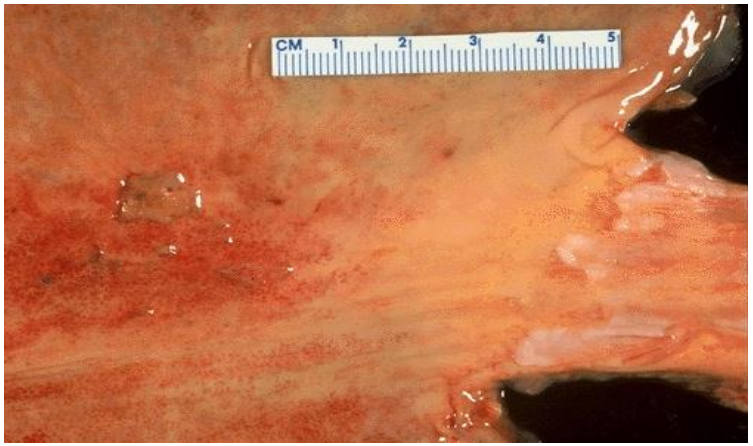
Serous inflammation



Purulent inflammation



Fibrinous inflammation



ulcers

Outcomes of acute inflammation

- Complete resolution
- Healing by scarring
- Progression to chronic inflammation

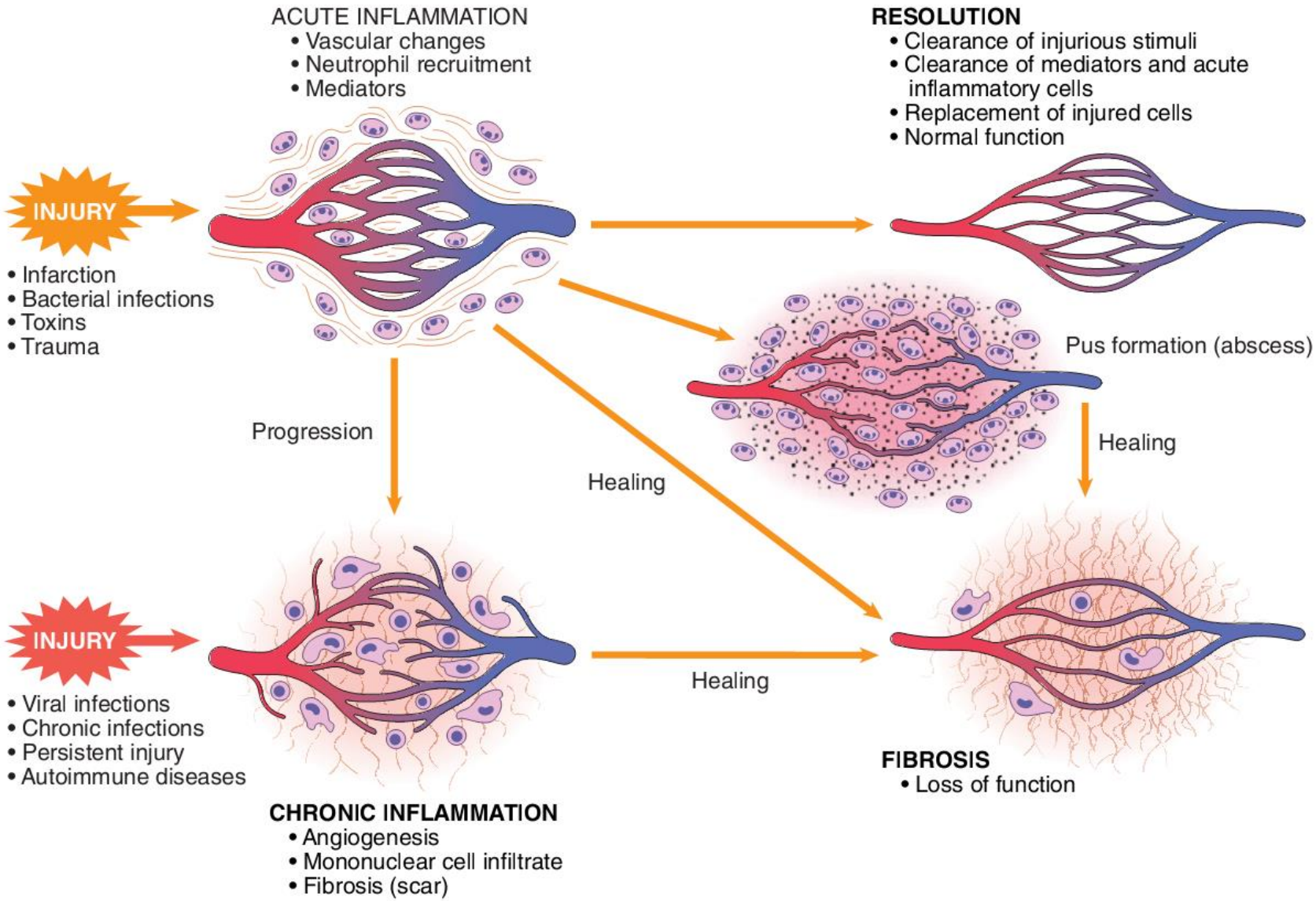


Figure 2–10 Outcomes of acute inflammation: resolution, healing by scarring (fibrosis), or chronic inflammation (see text).

Chronic Inflammation

- Chronic inflammation is inflammation of prolonged duration (weeks to months to years) in which active inflammation (infiltration), tissue injury (destruction), and healing (repair) proceed simultaneously.

1. Acute inflammation may progress to chronic inflammation when the acute response cannot be resolved either because of the persistent of the injurious agents that are difficult to eradicate or are non-degredable Or because of recurrent bouts (short period of injury) of injury that interfere with and interrupt the normal process of healing. For example, a peptic ulcer of the duodenum initially shows acute inflammation followed by the beginning stages of resolution. However, recurrent bouts of duodenal epithelial injury interrupt this process and results in a lesion characterised by both acute and chronic inflammation. Another example is bronchial asthma where the eliciting agent cannot be eliminated and induces immune response.
2. Some forms of injury cause a response that involves chronic inflammation from the onset (viruses and autoimmune diseases).

Histologic characteristics of chronic inflammation

- Infiltration by mononuclear cells (macrophages, lymphocytes and plasma cells)
- Proliferation of fibroblasts (forming fibrosis) and blood vessels (a process called angiogenesis)
- Tissue destruction induced by the products of the inflammatory cells.

Granulomatous inflammation

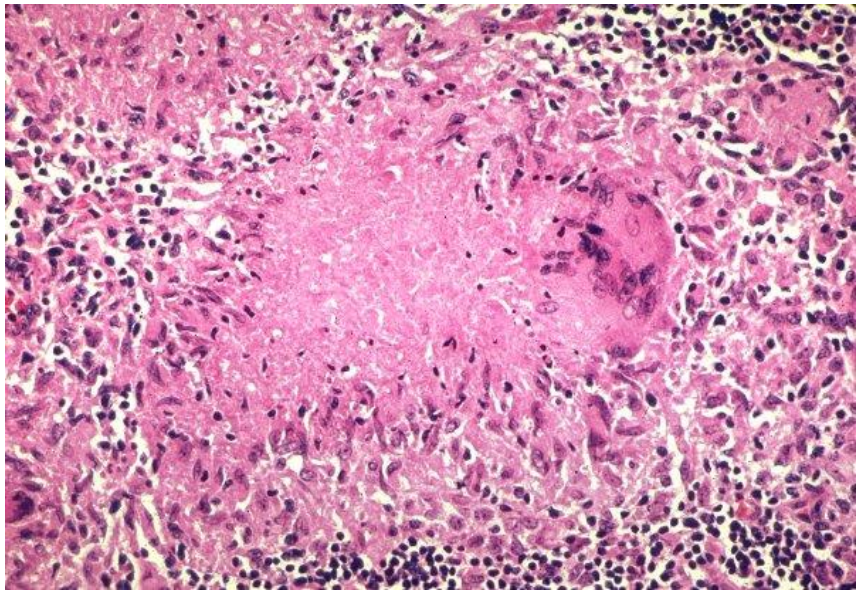
- A granulomatous lesion is a distinctive form of chronic inflammation. A *granuloma* typically is a small, 1- to 2-mm lesion in which there is a massing of macrophages surrounded by lymphocytes. These modified macrophages resemble epithelial cells and sometimes are called *epithelioid cells.* Like other macrophages, these epithelioid cells are derived originally from blood monocytes.
- Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, deep fungal infections, and brucellosis. These types of agents have one thing in common: they are poorly digested and usually are not easily controlled by other inflammatory mechanisms. The epithelioid cells in granulomatous inflammation may clump in a mass or coalesce, forming a multinucleated giant cell that attempts to surround the foreign agent. A dense membrane of connective tissue eventually encapsulates the lesion and isolates it. The epithelioid cells are often referred to as *foreign body giant cells*.

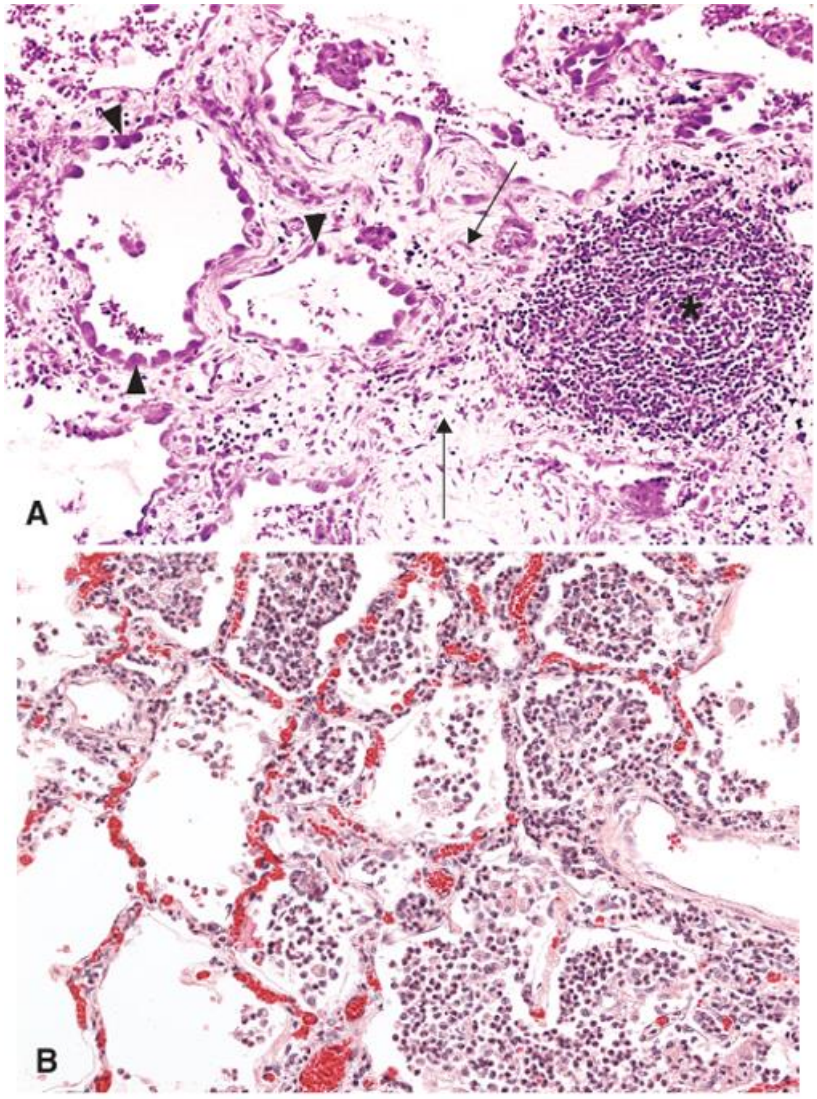
Chronic granulomatous inflammation

- It is characterized by granulomas (small collection of modified macrophages called epitheloid cells, lymphocytes, plasma cells, neutrophils and central necrosis may also be present.
- Types according to the cause:

1. Foreign body granulomas due to inert foreign body e.g. mineral dust (silicosis)
2. Immune granuloma
3. Infectious granuloma e.g. tuberculosis
4. Granuloma of unknown cause e.g. sarcoidosis

Tuberculosis





A, Chronic inflammation in the lung, showing the characteristic histologic features: collection of chronic inflammatory cells (*asterisk*), destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, *arrowheads*), and replacement by connective tissue (fibrosis, *arrows*).

B, By contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.