Inflammation

Inflammation Second line defense When microbes penetrate the first line of defense, they encounter a second line of defense that includes defensive cells, such as

- **phagocytic cells**
- **inflammation**
- **fever**
- **antimicrobial substances**

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Damage to the body's tissues triggers a local defensive response called inflammation, another component of the second line of defense.

The damage can be caused by microbial infection,

- physical agents (such as heat, radiant energy, electricity, or sharp objects),
- chemical agents (acids, bases, and gases).

Certain signs and symptoms are associated with inflammation,

you can remember by thinking of the acronym **PRISH**:

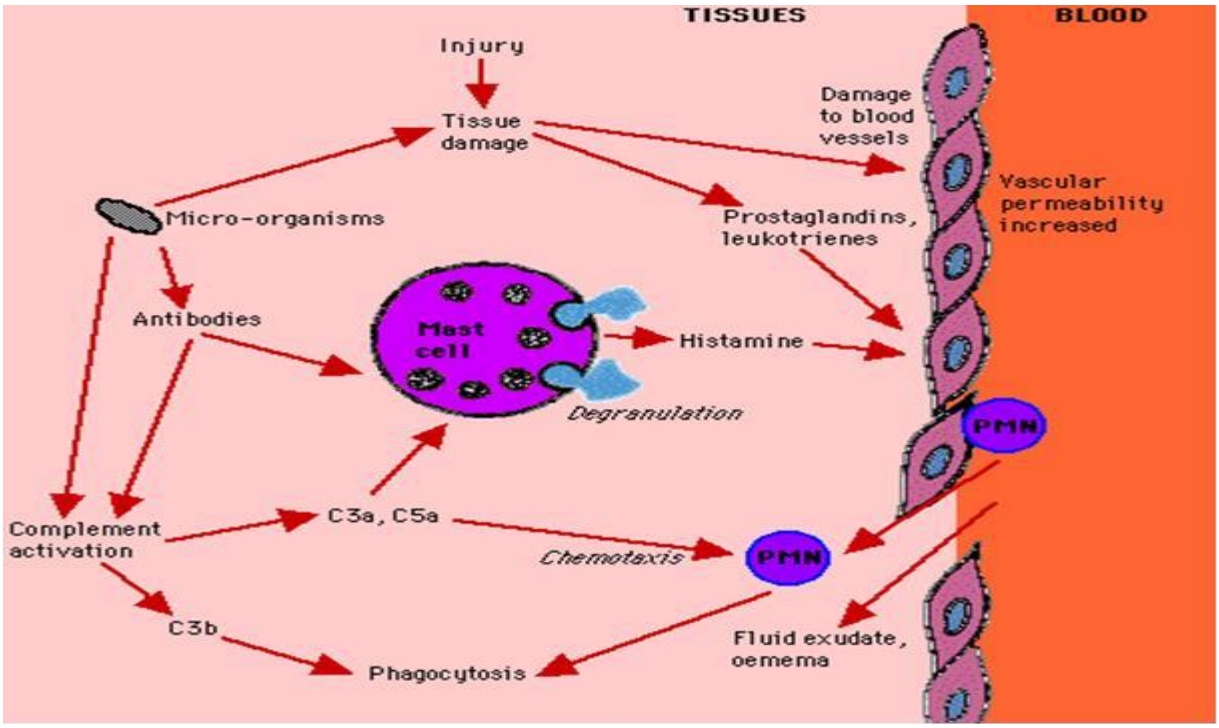
Pain due to the release of certain chemicals.

Redness because more blood goes to the affected area.

Immobility that results from local loss of function in severe inflammations.

Swelling caused by an accumulation of fluids.

Heat, which is also due to an increase in blood flow to the affected area .



Inflammation has the following functions:

(1) to destroy the injurious agent, if possible, and to remove it and its by products from the body.

(2) if destruction is not possible, to limit the effects on the body by confining or walling off the injurious agent and its by-products.

(3) to repair or replace tissue damaged by the injurious agent or its by-products.

Inflammation can be classified depending on a number of factors as acute or chronic.

1-acute inflammation: the signs and symptoms develop rapidly and usually last for a few days or even a few weeks. It is usually mild and self-limiting, and the principal defensive cells are neutrophils. Examples of acute inflammation are a sore throat, appendicitis, cold or flu, bacterial pneumonia, and a scratch on the skin.

2- chronic inflammation: the signs and symptoms develop more slowly and can last for up to several months or years. It is often severe and progressive, and the principal defensive cells are monocytes and macrophages. Examples of chronic inflammation are mononucleosis, peptic ulcers, tuberculosis, rheumatoid arthritis, and ulcerative colitis.

Table 3 : Comparison between acute and chronic inflammation

	Acute	Chronic
Causative agent	Bacterial pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions
Major cells involved	neutrophils (primarily), basophils (inflammatory response), and eosinophils (response to helminthes worms and parasites), mononuclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes

During the early stages of inflammation, microbial structures, such as flagellin, lipopolysaccharides (LPS), and bacterial DNA

stimulate the **Toll-like receptors** of macrophages to **produce cytokines**, such as tumor necrosis factor alpha (TNF- α). In response to TNF-α in the blood,

the liver synthesizes a group of proteins called acute-phase proteins; other acute-phase proteins are present in the blood in an inactive form and are converted to an active form during inflammation.

Acute-phase proteins induce both local and systemic responses and include proteins such as **C-reactive protein,** mannose-binding lectin and several specialized proteins such as fibrinogen for blood clotting and kinins for vasodilation. All of the cells involved in inflammation have receptors for TNF-α and are activated by it to produce more of their own T.N.F -α. This amplifies the inflammatory response.

excessive production of TNF-α may lead to disorders such as rheumatoid arthritis and Crohn's disease. Monoclonal antibodies are used therapeutically to treat such inflammatory disorders. we will divide the process of inflammation into three stages: vasodilation and increased permeability of blood vessels, phagocyte migration and phagocytosis, and tissue repair

Vasodilation and Increased Permeability of Blood Vessels.

Immediately following tissue damage (Figur), blood vessels dilate (increase in diameter) in the area of damage, and their permeability increases. Dilation of blood vessels, called vasodilation,

- is responsible for the redness (erythema) and heat associated with inflammation. Increased permeability permits defensive substances normally retained in the blood to pass through the walls of the blood vessels and enter the injured area.
- The increase in permeability, which permits fluid to move from the blood into tissue spaces, is responsible for the edema (accumulation of fluid) of inflammation.
- The pain of inflammation can be caused by nerve damage, irritation by toxins, or the pressure of edema.

–The blood clots that form around the site of activity prevent the microbe (or its toxins) from spreading to other parts of the body.

-As a result, there may be a localized collection of pus, a mixture of dead cells and body fluids, in a cavity formed by the breakdown of body tissues. This focus of infection is called an abscess. Common abscesses include pustules and boils. Phagocyte Migration and Phagocytosis Generally, within an hour after the process of inflammation is initiated, phagocytes appear on the scene.

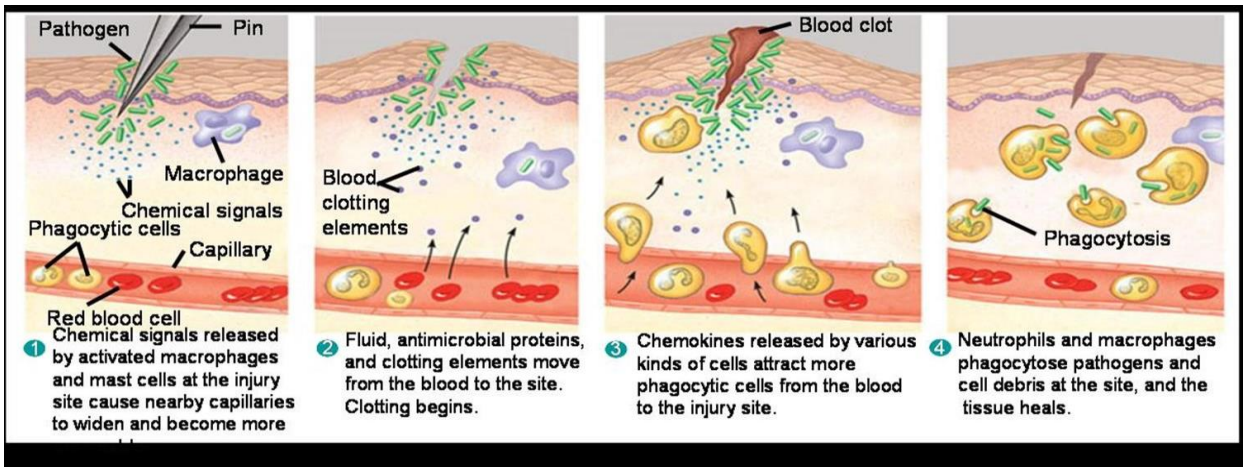
–As the flow of blood gradually decreases, phagocytes (both neutrophils and monocytes) begin to stick to the inner surface of the endothelium (lining) of blood vessels. This sticking process in response to local cytokines is called margination. The cytokines alter cellular adhesion molecules on cells lining blood vessels, causing the phagocytes to stick at the site of inflammation.

–Then the collected phagocytes begin to squeeze between the endothelial cells of the blood vessel to reach the damaged area. This migration, which resembles Amyloid movement, is called diapedesis; it can take as little as 2 minutes.

–The phagocytes destroy microorganisms by phagocytosis.

Chemical Mediators in the Inflammatory Response

Chemical	Source	Major Action
Histamine	Mast cell granules	Immediate vasodilation and increased capillary permeability to form exudate
Chemotactic factors	Mast cell granules	For example, attract neutrophils to site
Leukotrienes	Synthesis from arachidonic acid in mast cells	Later response: vasodilation and increased capillary permeability, chemotaxis
Platelet-activating factor (PAF)	Cell membranes of platelets	Activate neutrophils
		Platelet aggregation
Cytokines (interleukins, (lymphokines	T lymphocytes, Macrophages	Increase plasma proteins, ESR
		Induce fever, chemotaxis, leukocytosis
Prostaglandins (PGs)	Synthesis from arachidonic acid in mast cells	Vasodilation, increased capillary permeability, pain, fever, potentiate histamine effect
Kinins (e.g., bradykinin)	Activation of plasma protein (kinogen)	Vasodilation and increased capillary permeability, pain, chemotaxis
Complement system	Activation of plasma protein cascade	Vasodilation and increased capillary permeability, chemotaxis, increased histamine release



As mentioned earlier, certain chemicals attract neutrophils to the site of injury (chemotaxis). These include chemicals produced by microorganisms and even other neutrophils; other chemicals are kinins, leukotrienes, chemokines, and components of the complement system. Chemokines are cytokines that are chemotactic for phagocytes and T cells and thus stimulate both the inflammatory response and an adaptive immune response. The availability of a steady stream of neutrophils is ensured by the production and release of additional granulocytes from red bone marrow.

As the inflammatory response continues, monocytes follow the granulocytes into the infected area. Once the monocytes are contained in the tissue, they undergo changes in biological properties and become free Macrophages. They are several times more phagocytic than granulocytes and are large enough to phagocytize tissue that has been destroyed. Then they themselves eventually die.

As a result, pus forms, and its formation usually continues until the infection subsides. At times, the pus pushes to the surface of the body or into an internal cavity for dispersal.

As effective as phagocytosis is in contributing to innate resistance, there are times when the mechanism becomes less functional in response to certain conditions. For example,

- with age, there is a progressive decline in the efficiency of phagocytosis. Recipients of heart or kidney transplants have impaired innate defenses as a result of receiving drugs that prevent the rejection of the transplant.
- Radiation treatments can also depress innate immune responses by damaging red bone marrow. Even certain diseases such as AIDS and cancer can cause defective functioning of innate defenses.
- Finally, individuals with certain genetic disorders produce fewer or impaired phagocytes..

Tissue Repair

The final stage of inflammation is tissue repair, the process by which tissues replace dead or damaged cells.

- Repair begins during the active phase of inflammation, but it cannot be completed until all harmful substances have been removed or neutralized at the site of injury. The ability to regenerate, or repair, depends on the **type of tissue**. For example, skin has a high capacity for regeneration, whereas cardiac muscle tissue has a low capacity to regenerate.
- A tissue is repaired when its **stroma or parenchyma produces new cells.** The **stroma** is the supporting connective tissue, and the **parenchyma** is the functioning part of the tissue. The most significant feature of chronic inflammation is the accumulation and activation of macrophages in the infected area.
- Cytokines released by activated macrophages induce **fibroblasts** in the tissue stroma to synthesize collagen fibers. These fibers aggregate to form scar tissue, a process called **fibrosis**. Because **scar tissue** is not specialized to perform the functions of the previously healthy tissue, fibrosis can interfere with the normal function of the tissue .

Fever

While inflammation is a local response of the body to injury, there are also systemic, or overall, responses.

One of the most important is fever, an abnormally high body temperature. The most frequent cause of fever is infection from bacteria (and their toxins) or viruses. The brain's hypothalamus is sometimes called the body's thermostat, and it is normally set at 37°C (98.6°F). It is believed that certain substances affect the hypothalamus by setting it at a higher temperature. Recall from that when phagocytes ingest gram-negative bacteria, the lipopolysaccharides (LPS) of the cell wall are released. LPS causes the phagocytes to release the cytokines interleukin-1 along with TNF-α. These cytokines cause the hypothalamus to release prostaglandins that reset the hypothalamic thermostat at a higher temperature, thereby causing fever .

fever is considered a defense against disease. Interleukin-1 helps step up the production of T cells High body temperature intensifies the effect of antiviral interferons and increases production of transferrins that decrease the iron available to microbes. Also, because the high temperature speeds up the body's reactions, it may help body tissues repair themselves more quickly. The higher temperature may slow the growth rate of some bacteria. Among the complications of fever are tachycardia (rapid heart rate), which may compromise older persons with cardiopulmonary disease; increased metabolic rate, which may produce acidosis; dehydration; electrolyte imbalances; seizures in young children; and delirium and coma. As a rule, death results if body temperature rises above 44° to 46°C (112° to 114°F).

Answer questions

1. What is the definition of inflammation and what are its main functions?
2. What is the difference between acute and chronic inflammation in terms of symptoms and defensive cells?
3. Mention the three stages of the inflammation process.
4. What is the role of TNF-α in the inflammatory response?
5. List the major chemical factors involved in the inflammatory response and their functions.
6. How does fever affect the body's immune response?
7. What is the role of macrophages in the inflammation process?
8. Explain how pus is formed during inflammation and what its components are.
9. How do monoclonal antibodies help treat inflammatory diseases?
10. What are the potential side effects of excessive TNF-α production on the body?
11. What physical and chemical factors may cause inflammation?
12. What is the role of phagocytes in defending the body during inflammation?
13. What is the chemical mechanism that leads to vasodilation and increased vascular permeability during inflammation?
14. What is the difference between fibrosis and normal tissue repair?
15. What are acute-phase proteins and how do they contribute to the inflammatory response?
16. How does the liver contribute to the inflammatory response after an increase in TNF-α levels in the blood?
17. What is the relationship between aging and the decline in the effectiveness of phagocytosis?
18. Give examples of diseases associated with increased TNF-α production.
19. What is the role of cytokines in regulating the inflammatory response?
20. Explain how certain treatments, like radiation therapy, can suppress the innate immune response.
21. What is the role of Toll-like receptors in the response of macrophages?
22. What are the acute-phase proteins involved in the inflammatory response and what are their functions?
23. Describe the process of diapedesis during inflammation and how phagocytes reach the site of damage.
24. What are the three stages of tissue repair after injury?
25. How does chronic inflammation contribute to the development of diseases like rheumatoid arthritis?
26. What is the relationship between elevated body temperature (fever) and the stimulation of T-cell production?
27. How does chemotaxis influence the body's immune response during inflammation?
28. List the chemical substances that attract neutrophils to the site of injury.

29. How can fever lead to serious physical complications, and what temperatures might result in death?

30. What role do cytokines play in promoting healing and the formation of scar tissue?