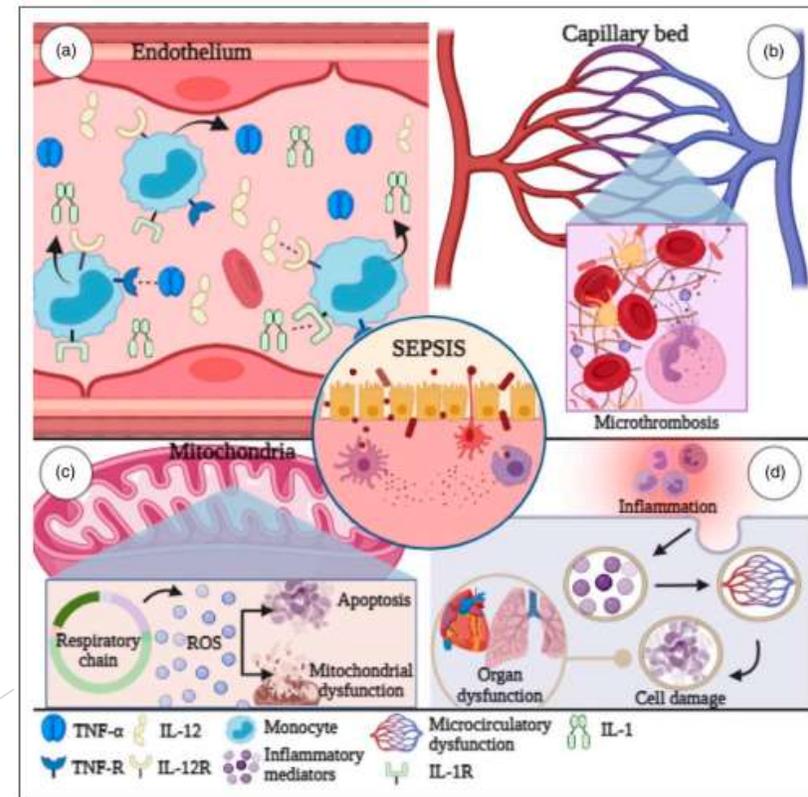


Inflammation 1

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Inflammation

- ▶ Inflammation is a response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites where they are needed, to eliminate the offending agents
- ▶ It serves to rid the host of both the initial cause of cell injury (e.g., microbes, toxins) and the consequences of such injury (e.g., necrotic cells and tissues)

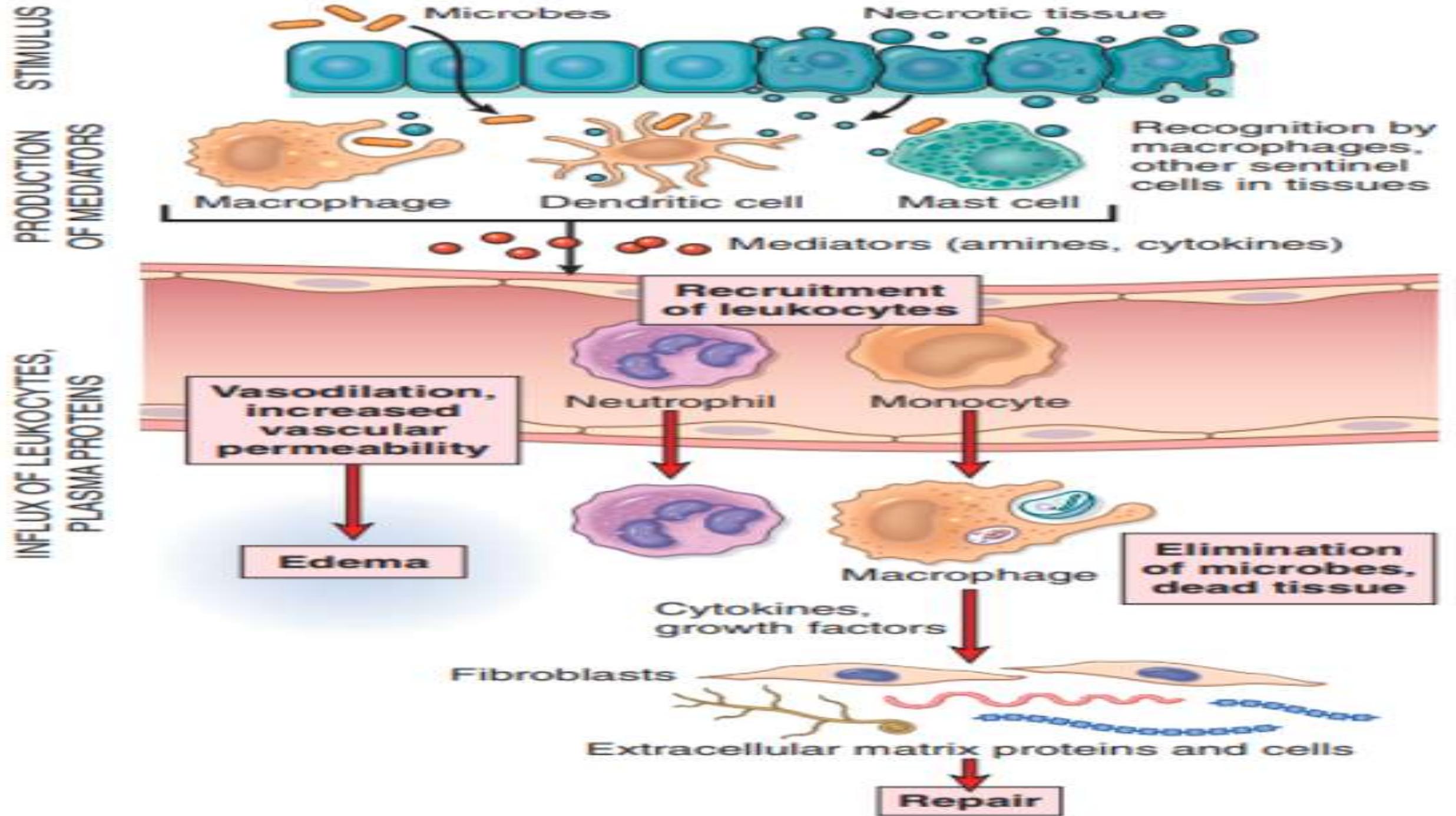


Inflammation

- ▶ **The process of inflammation delivers leukocytes and proteins to foreign invaders, such as microbes, and to damaged or necrotic tissues, and it activates the recruited cells and molecules, which then function to eliminate the harmful or unwanted substances.**
- ▶ **Without inflammation, infections would go unchecked, wounds would never heal, and injured tissues might remain permanent festering sores**

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

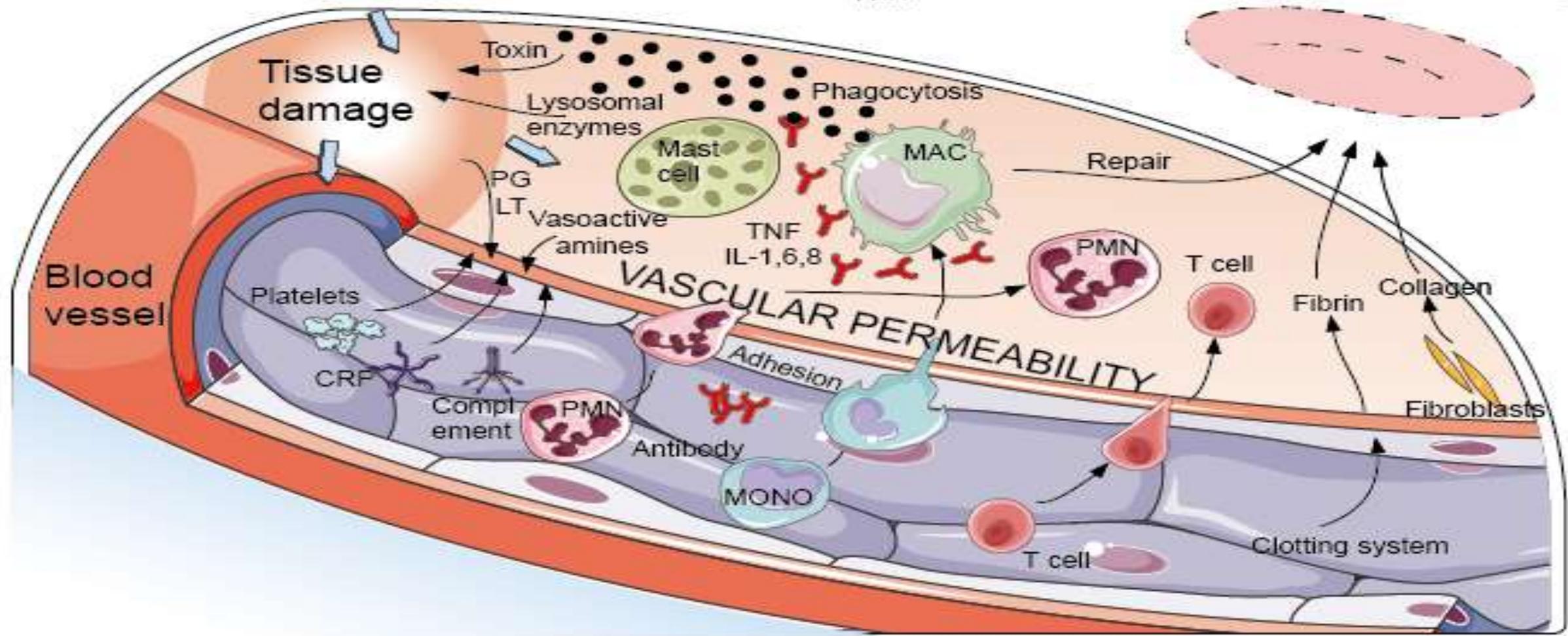
- ▶ Recognition of the offending agent.
- ▶ Recruitment of leukocytes and plasma proteins from the circulation to the site where the offending agent is located.
- ▶ Activation of the leukocytes and proteins to destroy and eliminate the offending substance.
- ▶ Termination.
- ▶ Repair.



INJURY/INFECTION

INFLAMMATION

HEALING



Inflammation may be of two types, acute and chronic.

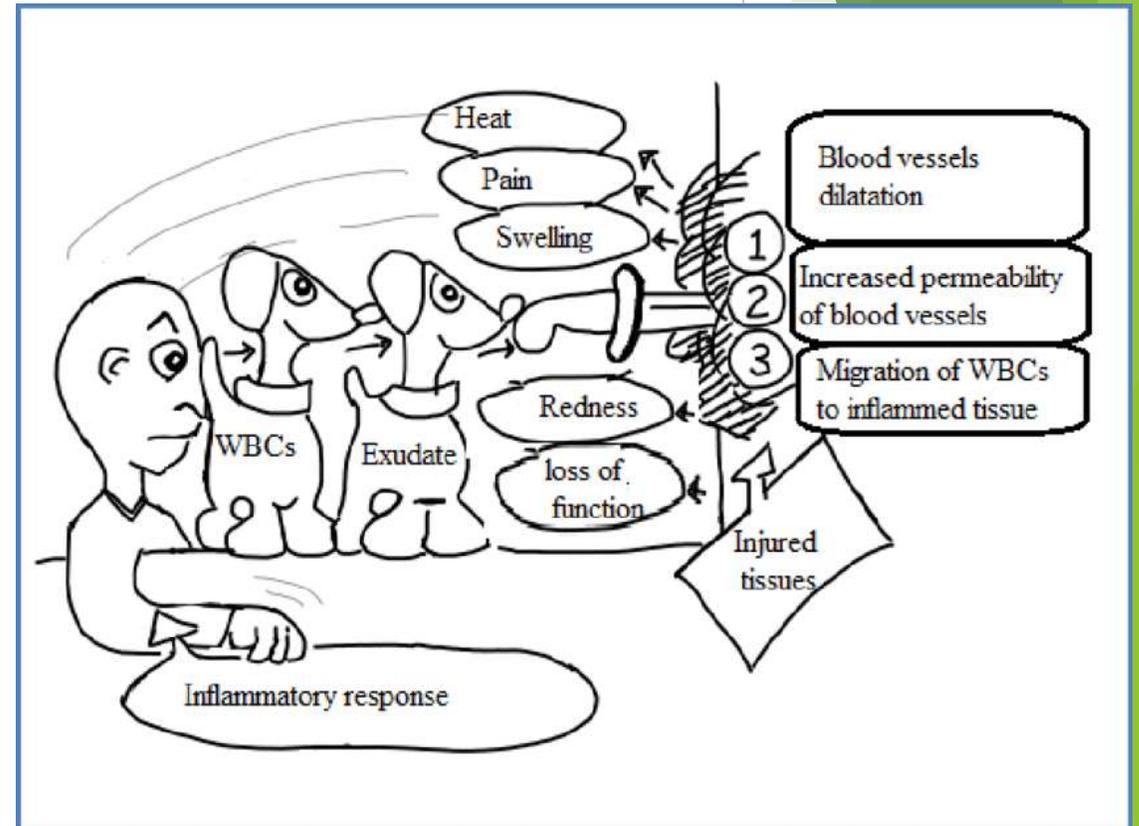
Table 3.1 Features of Acute and Chronic Inflammation

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	May be severe and progressive
Local and systemic signs	Prominent	Less

**if the initial response fails to clear the stimulus, the reaction progresses to chronic inflammation

cardinal signs

- ▶ The external manifestations of inflammation are:
- ▶ Heat (calor in Latin).
- ▶ Redness (rubor)
- ▶ Swelling (tumor),
- ▶ Pain (dolor),
- ▶ Loss of function (functio laesa).



5 Cardinal Signs of Inflammation



Pain



Heat



Redness



Swelling



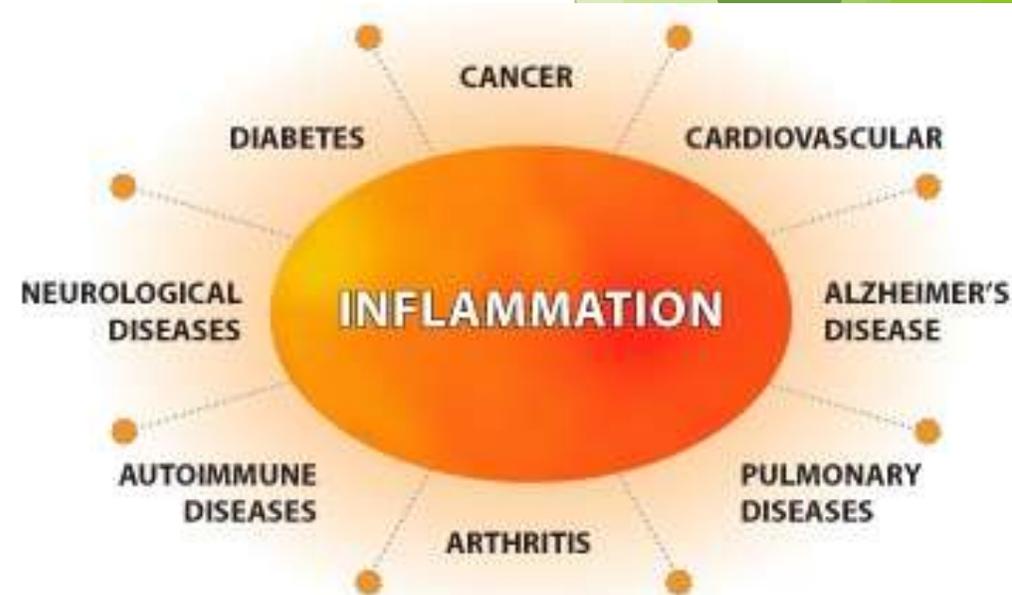
Loss of
Function

Dose the inflammation always good??

- ▶ In some situations, the inflammatory reaction becomes the cause of disease, and the damage it produces is its dominant feature e.g:
 - ▶ 1. Autoimmune diseases: inflammatory reaction is misdirected against self tissues.
 - ▶ 2. Allergies: against normally harmless environmental substances that evoke an immune response.
 - ▶ 3. Common chronic diseases.

Table 3.2 Disorders Caused by Inflammatory Reactions

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts



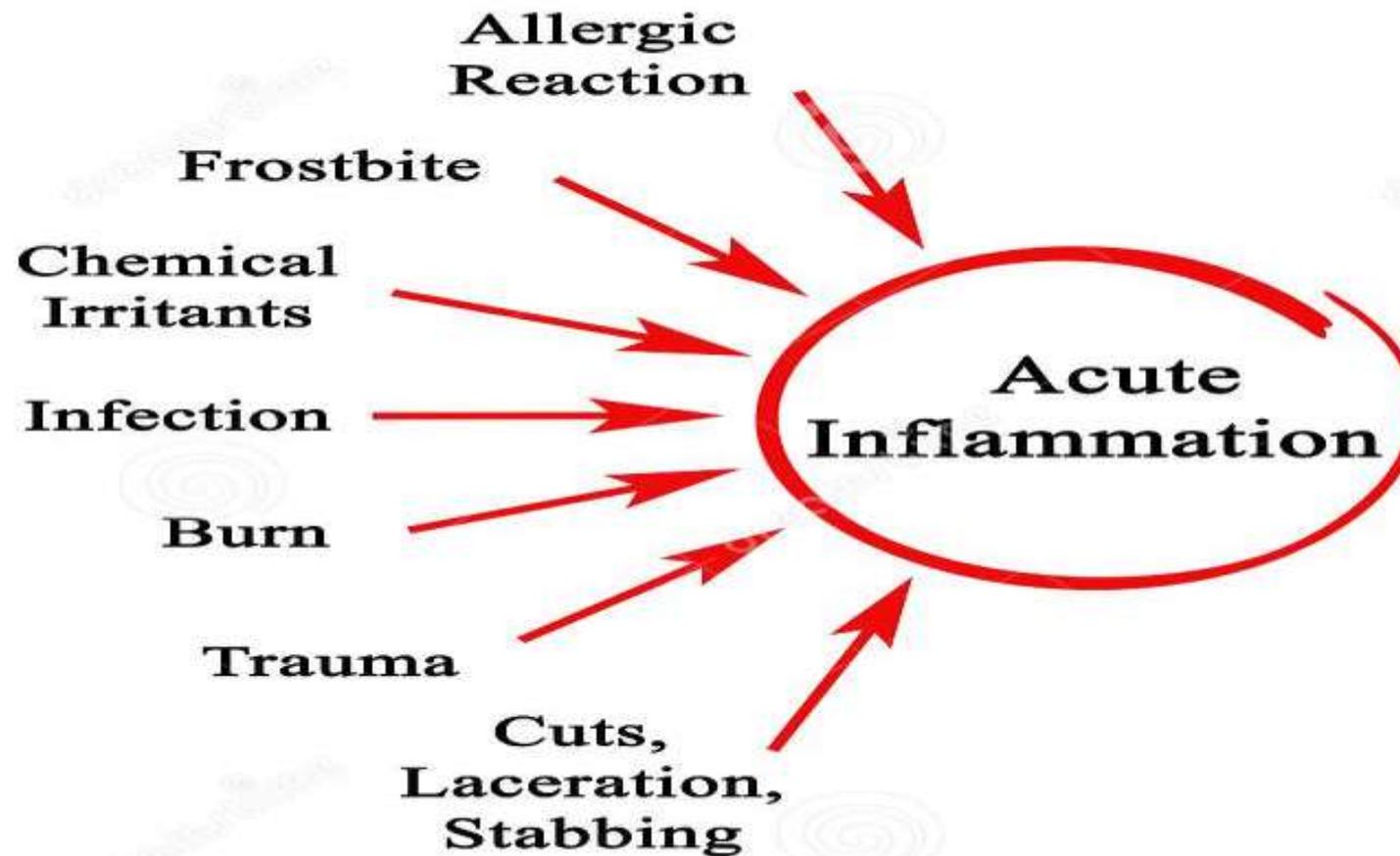
Dose the inflammation always good??

- ▶ **Not only excessive inflammation but also defective inflammation is responsible for serious illness.**
- ▶ **Often caused by a reduced number of leukocytes resulting from replacement of the bone marrow by cancers and suppression of the marrow by therapies for cancer and graft rejection**

Inflammation is terminated when the offending agent is eliminated, how:

- ▶ Mediators are broken down .
- ▶ Leukocytes have short life spans in tissues.
- ▶ Anti-inflammatory mechanisms are activated, serving to control the response and prevent it from causing excessive damage to the host
- ▶ **Tissue repair:**
- ▶ Repair consists of a series of events that heal damaged tissue. In this process, the injured tissue is replaced through regeneration of surviving cells and filling of residual defects with connective tissue (scarring).

CAUSES OF INFLAMMATION



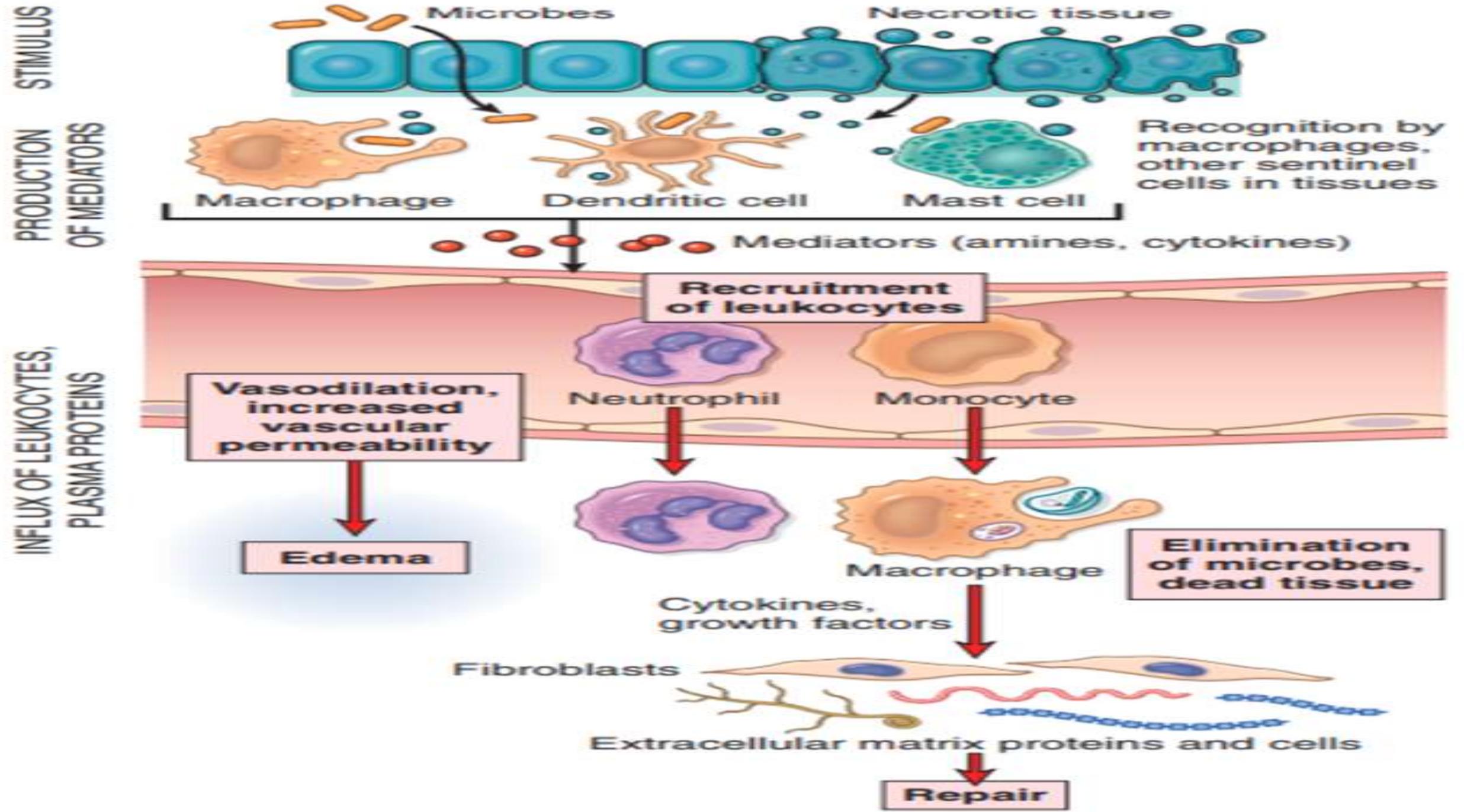
1. RECOGNITION OF MICROBES AND DAMAGED CELLS

▶ 1. Cellular receptors for microbes

▶ The best defined of these receptors belong to the family of Toll-like receptors (TLRs),

▶ Recognition of microbes by these receptors stimulates the production and expression of a number of secreted and membrane proteins.

▶ These proteins include cytokines that induce inflammation, anti-viral cytokines (interferons), and cytokines and membrane proteins that promote lymphocyte activation and even more potent immune responses



2. Sensors of cell damage

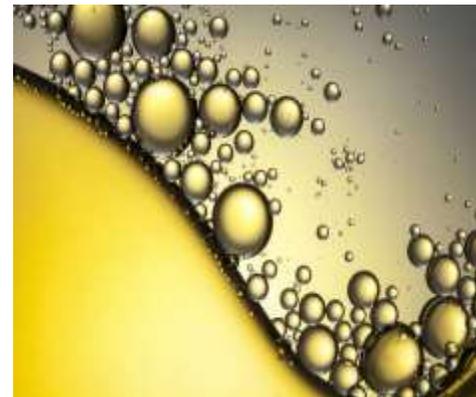
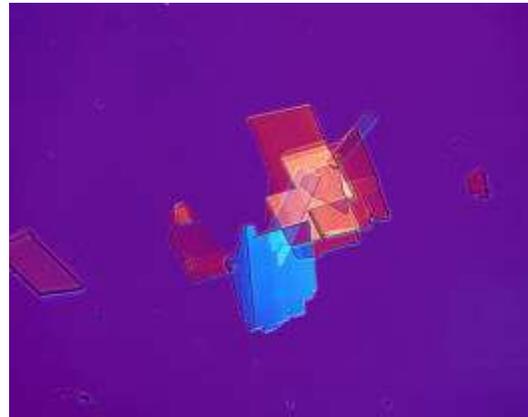
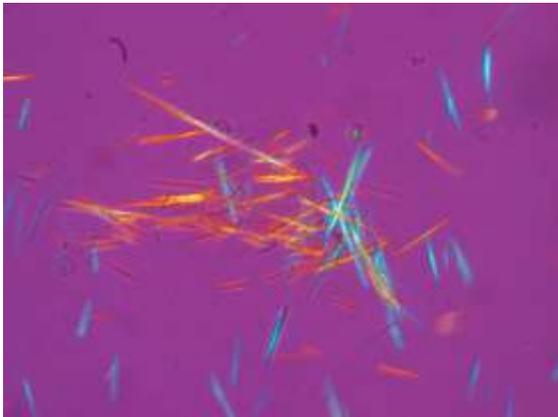
- ▶ All cells have cytosolic receptors that recognize molecules that are liberated or altered as a consequence of cell damage, and are hence appropriately called damage-associated molecular patterns (DAMPs) e.g:
 - ▶ Uric acid (a product of DNA breakdown),
 - ▶ ATP (released from damaged mitochondria),
 - ▶ Reduced intracellular K^+ concentrations (reflecting loss of ions because of plasma membrane injury),
 - ▶ DNA (when it is released into the cytoplasm and not sequestered in nuclei, as it should be normally)

2. Sensors of cell damage

- ▶ The receptors activate a multiprotein cyto-solic complex called the inflammasome, which induces the production of the cytokine interleukin-1 (IL-1)
- ▶ IL-1 recruits leukocytes and thus induces inflammation
- ▶ Gain-of-function mutations in the cyto-solic receptors are the cause of rare diseases known as autoinflammatory syndromes that are characterized by spontaneous inflammation; IL-1 antagonists are effective treatments for these disorders.

The inflammasome also has been implicated in inflammatory reactions to

- ▶ **Urate crystals** (the cause of gout),
- ▶ **Cholesterol crystals** (in atherosclerosis),
- ▶ **Lipids** (in metabolic syndrome and obesity-associated diabetes),
- ▶ **Amyloid deposits** in the brain (in Alzheimer disease).

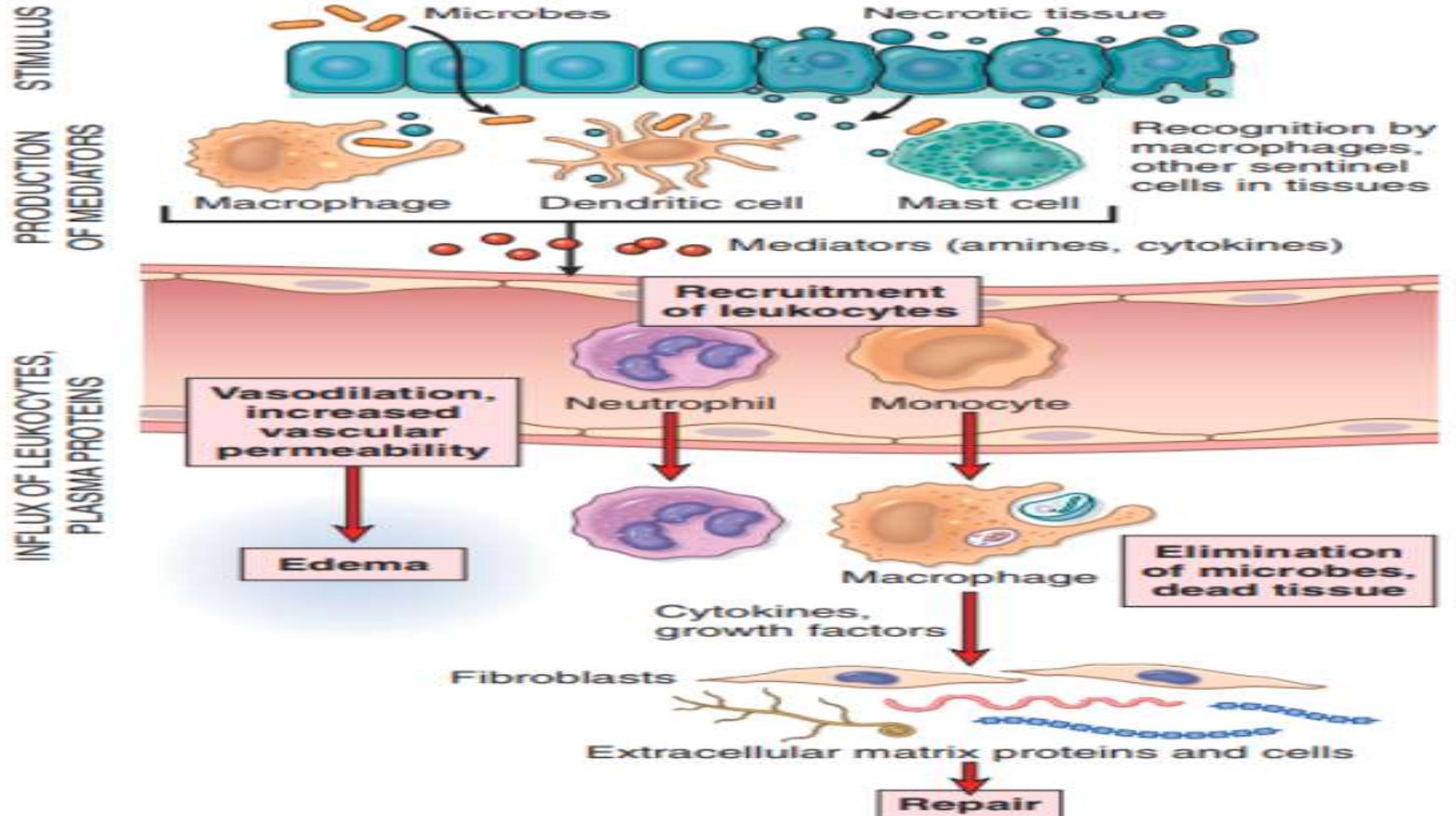


3. Circulating proteins.

- ▶ **Several plasma proteins recognize microbes and function to destroy blood-borne microbes and to stimulate inflammation at tissue sites of infection.**
- ▶ **The complement system reacts against microbes and produces mediators of inflammation**
- ▶ **Mannose-binding lectin recognizes microbial sugars and promotes ingestion of microbes and activation of the complement system.**
- ▶ **Collectins bind to microbes and promote their phagocytosis.**

Acute 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 the leukocytes from the microcirculation, their accumulation in the focus of injury, and their activation to eliminate the offending agent



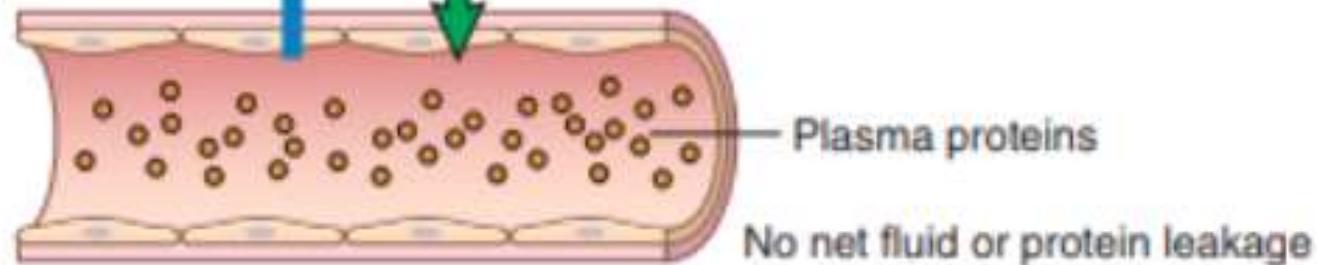
Reactions of Blood Vessels in Acute Inflammation

- ▶ 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
- ▶ Clinically:.... **Edema**
- ▶ Edema denotes an excess of fluid in the interstitial tissue or serous cavities; it can be either an exudate or a transudate.
- ▶ Pus: a purulent exudate, is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes.



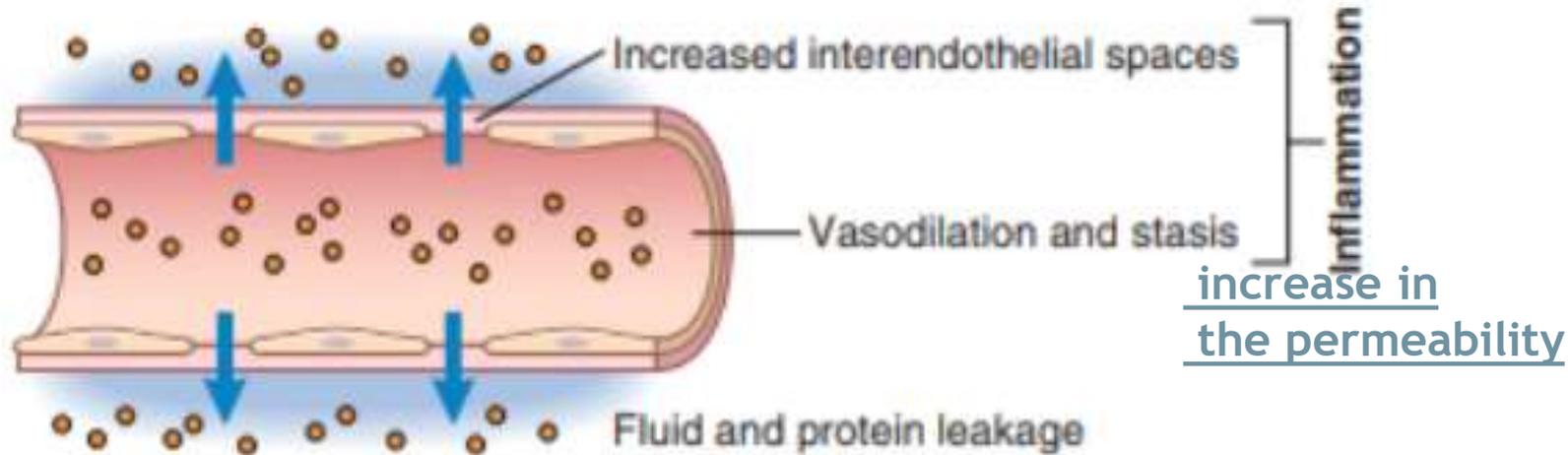
Hydrostatic pressure \uparrow = \downarrow Colloid osmotic pressure

A. NORMAL



B. EXUDATE

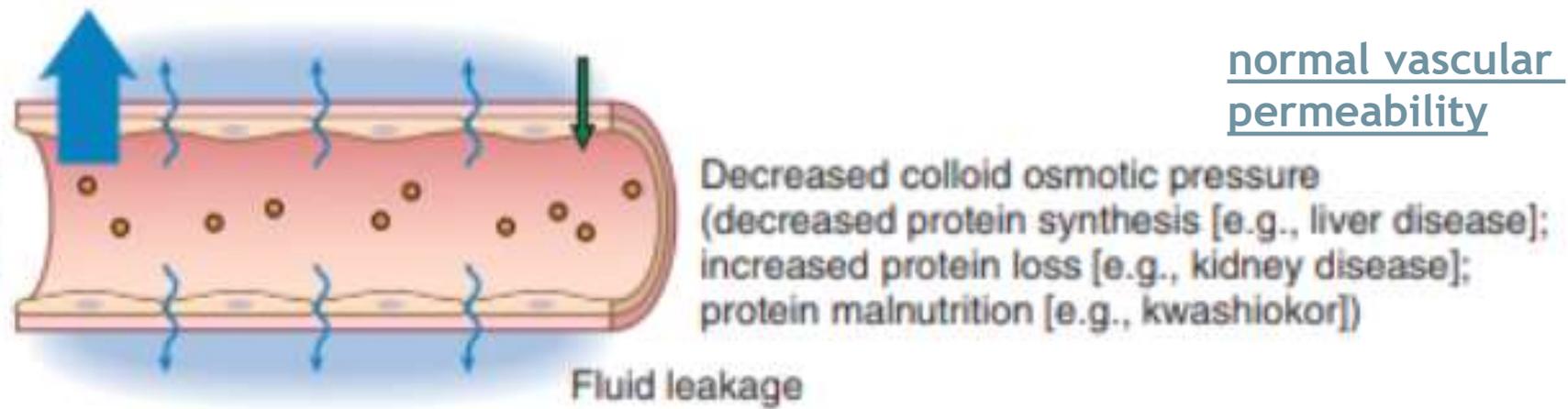
(high protein content, and may contain some white and red cells)



C. TRANSUDATE

(low protein content, few cells)

Increased hydrostatic pressure
(venous outflow obstruction,
[e.g., congestive heart failure])



Changes in Vascular Flow and Caliber

- ▶ Changes in vascular flow and caliber begin early after injury and consist of the following:
 - ▶ 1. Vasodilation:
 - Induced by histamine, acting on vascular smooth muscle
 - First involves the arterioles and then leads to the opening of new capillary beds in the area.
 - The result is increased blood flow, which is the cause of heat and redness (erythema) at the site of inflammation.

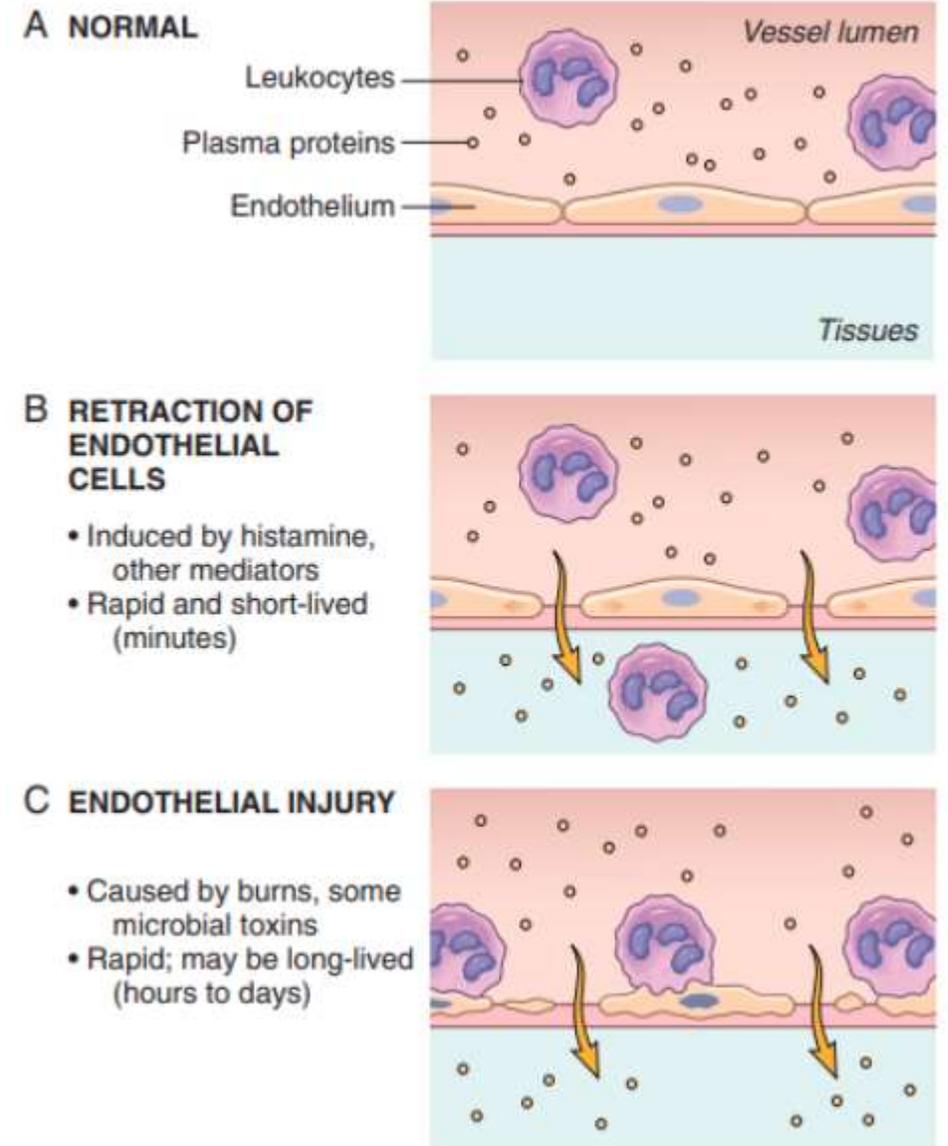


Changes in Vascular Flow and Caliber

- ▶ 2. Increased permeability of the microvasculature, with the outpouring of protein-rich fluid (an exudate) into the extravascular tissues.
- ▶ 3. Vascular congestion:
 - ▶ stasis of blood flow, engorgement of small vessels due to slow blood flow.
- ▶ 4. Blood leukocytes, principally neutrophils, accumulate along the vascular endothelium, endothelial cells are activated and leukocytes then migrate through the vascular wall into the interstitial tissue

How dose the vascular permeability increased?

- ▶ 1. Retraction of endothelial cells (immediate transient response):
 - ▶ It is elicited by histamine, bradykinin, leukotrienes.
- ▶ 2. Endothelial injury
- ▶ 3. Transcytosis
- ▶ Increased transport of fluids and proteins



Responses of Lymphatic Vessels and Lymph Nodes

- ▶ In inflammation, lymph flow is increased to help drain edema fluid that accumulates because of increased vascular permeability. In addition to fluid, leukocytes and cell debris, as well as microbes, may find their way into lymph.
- ▶ The lymphatics may become secondarily inflamed (lymphangitis), as may the draining lymph nodes (lymphadenitis).

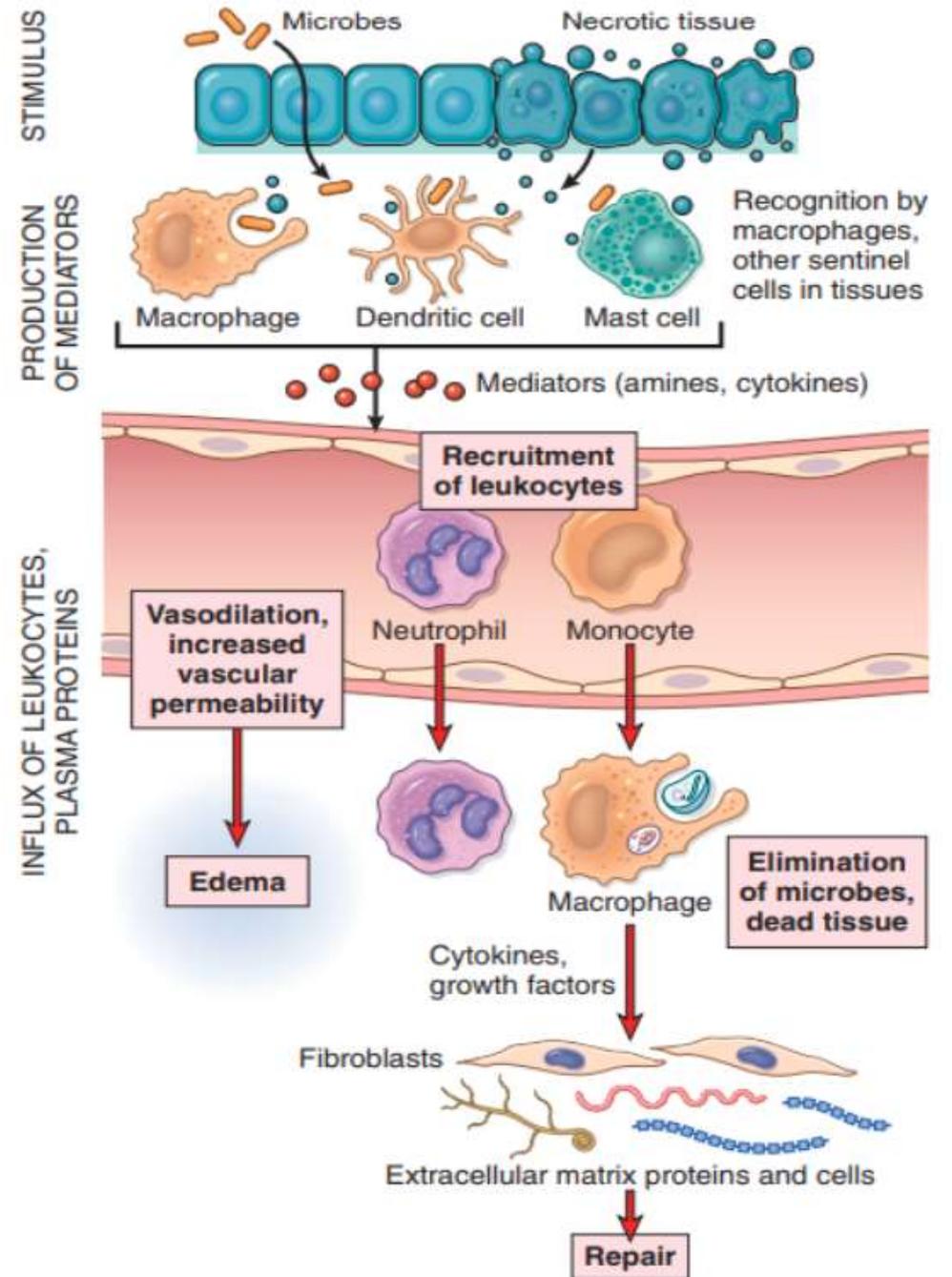


- ▶ This streaking follows the course of the lymphatic channels and indicates the presence of lymphangitis



painful enlargement of the draining lymph nodes, indicating lymphadenitis.

Leukocyte Recruitment to Sites of Inflammation



Leukocyte Recruitment to Sites of Inflammation

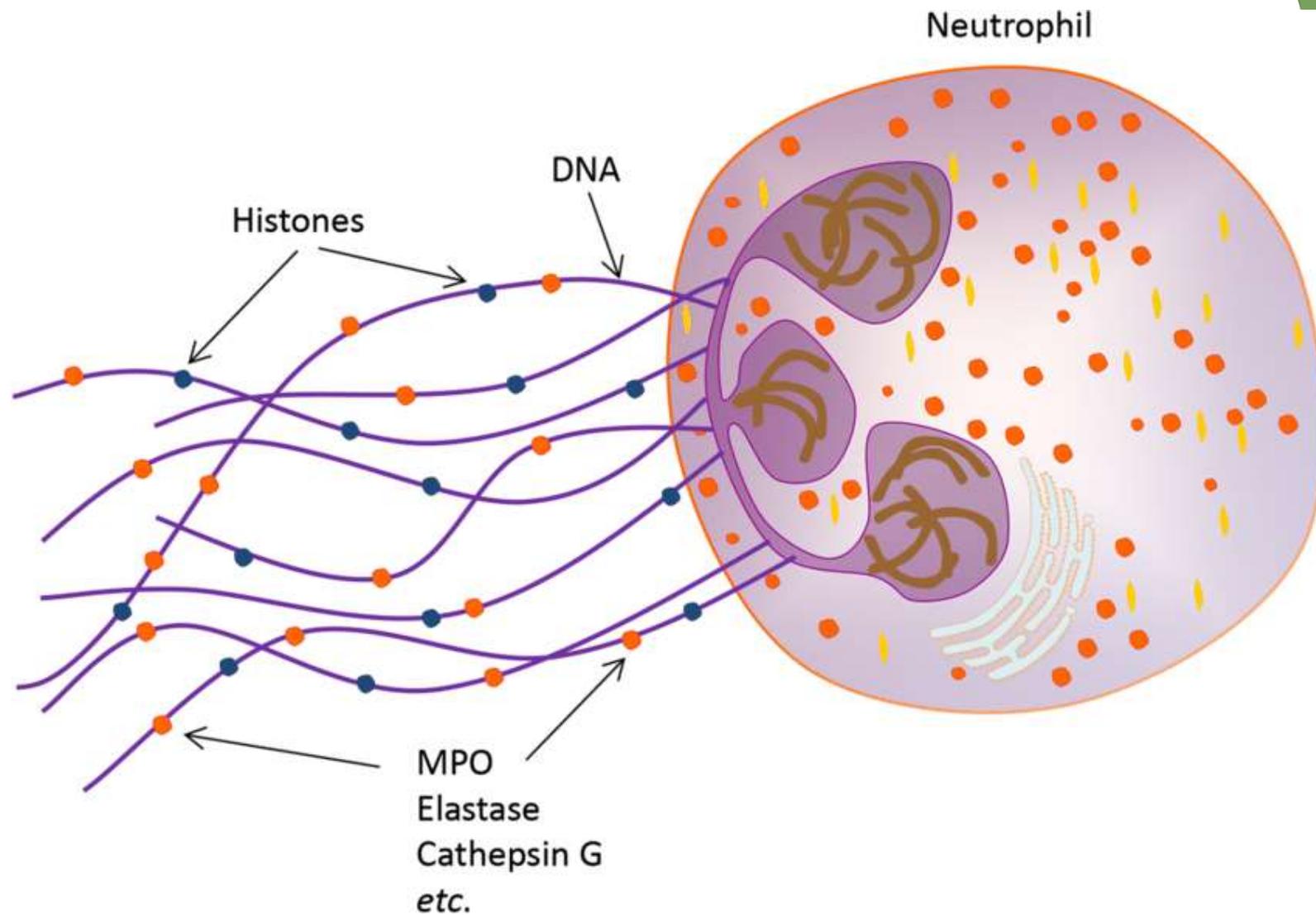
- ▶ **Leukocytes** that are recruited to sites of inflammation perform the key function of eliminating the offending agents.
- ▶ The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis, namely, neutrophils and macrophages
- ▶ These leukocytes ingest and destroy bacteria and other microbes, however, they may induce tissue damage and prolong inflammation.

Table 3.3 Properties of Neutrophils and Macrophages

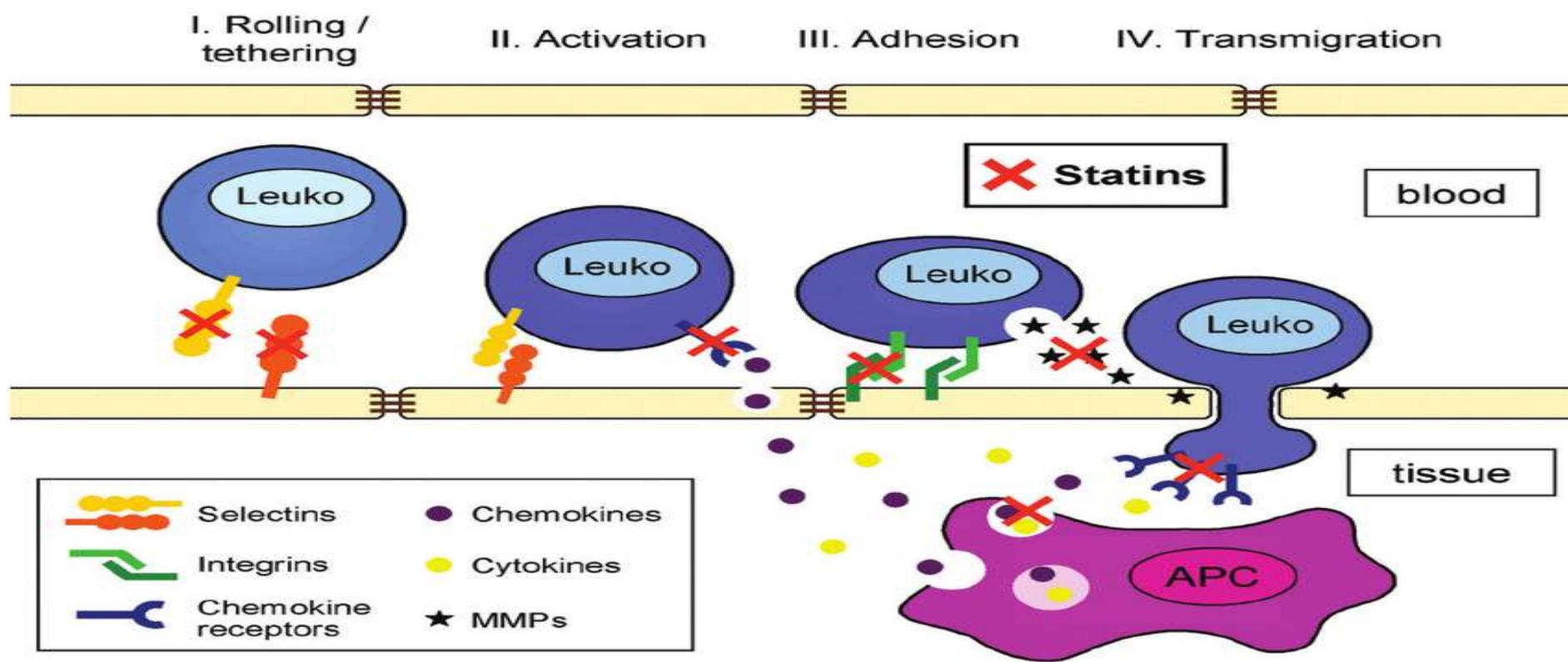
	Neutrophils	Macrophages
Origin	HSCs in bone marrow	<ul style="list-style-type: none"> • HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
<ul style="list-style-type: none"> • Reactive oxygen species 	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
<ul style="list-style-type: none"> • Nitric oxide 	Low levels or none	Induced following transcriptional activation of iNOS
<ul style="list-style-type: none"> • Degranulation 	Major response; induced by cytoskeletal rearrangement	Not prominent
<ul style="list-style-type: none"> • Cytokine production 	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
<ul style="list-style-type: none"> • NET formation 	Rapidly induced, by extrusion of nuclear contents	No
<ul style="list-style-type: none"> • Secretion of lysosomal enzymes 	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular traps.

This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.



The sticky web-like structure of NET is mainly composed of extracellular DNA. These web-like structures are decorated with histones and neutrophil granule proteins such as myeloperoxidase (MPO), elastase, and cathepsin G.



- ▶ 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, and consist of three phases:
 - ▶ 1. Leukocyte Adhesion to Endothelium.
 - ▶ 2. Leukocyte Migration Through Endothelium.
 - ▶ 3. movement of the cells toward the offending agent

THANK YOU.