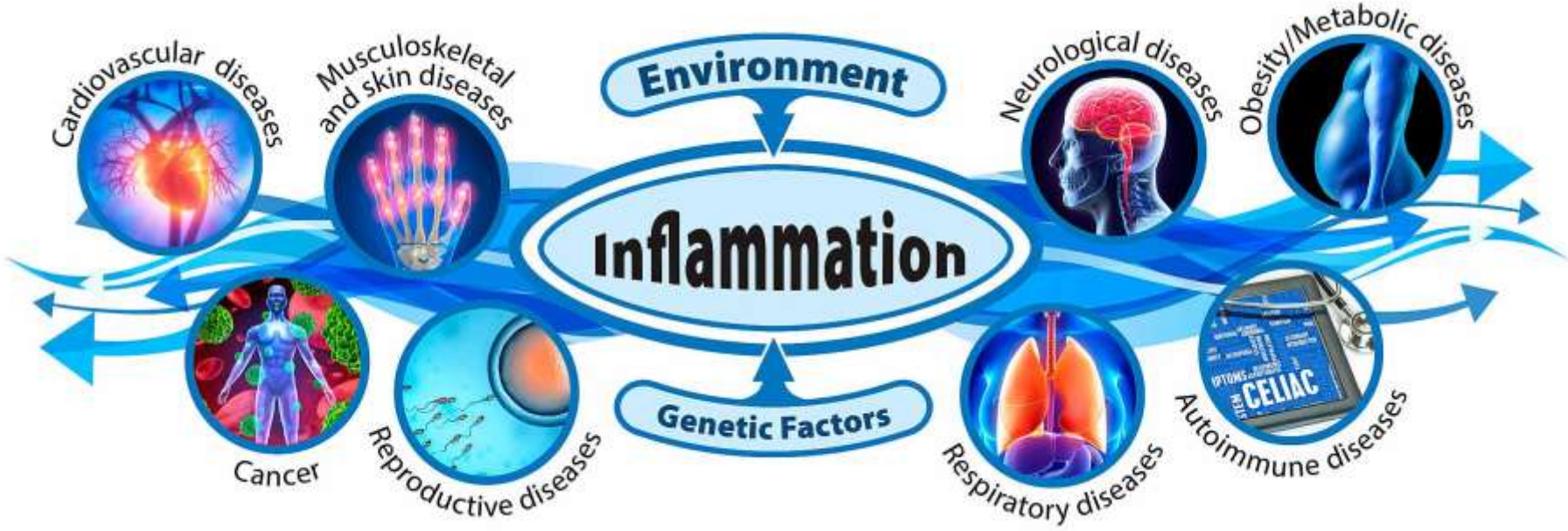
Inflammation 1



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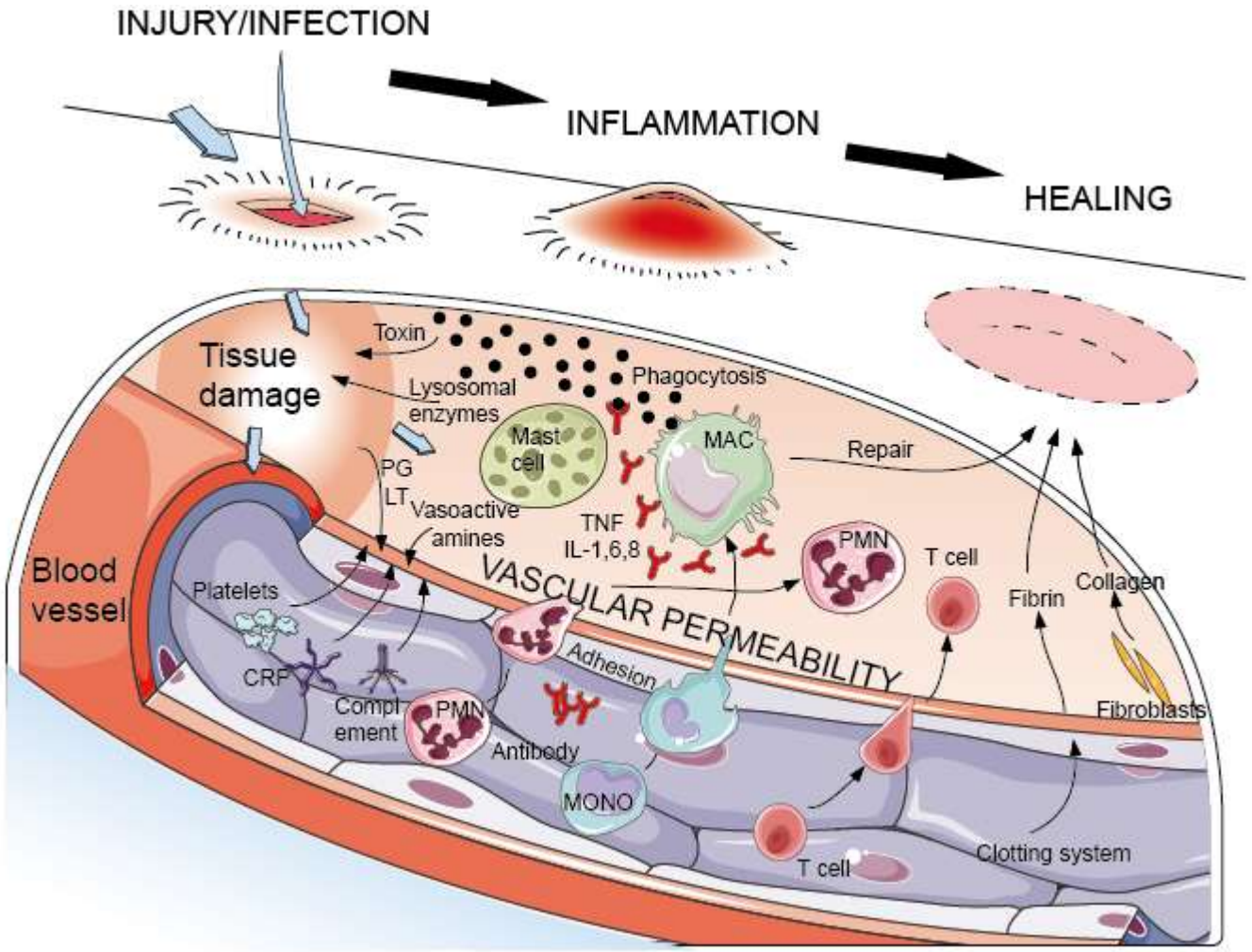
Inflammation

- 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)

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.

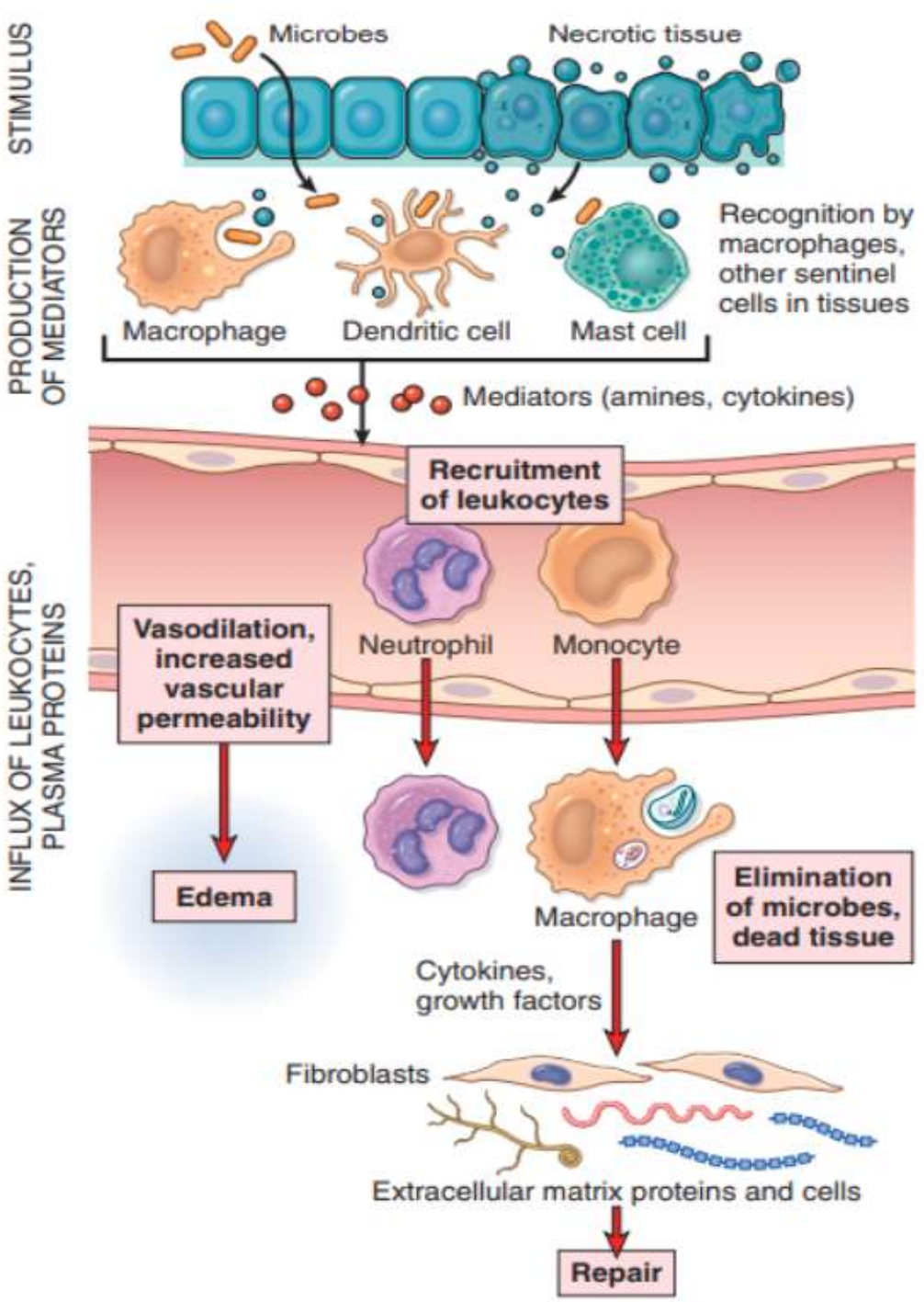

INJURY/INFECTION
INFLAMMATION
HEALING
Tissue damage
Toxin
Lysosomal enzymes
Phagocytosis
Mast cell
MAC
Repair
PG
LT
Vasoactive amines
TNF
IL-1,6,8
PMN
T cell
Blood vessel
Platelets
VASCULAR PERMEABILITY
Fibrin
Collagen
Adhesion
CRP
Compl ement
PMN
Antibody
Fibroblasts
MONO
T cell
Clotting system

Inflammation may be of two types, acute and chronic.

Table 3.1 Features of Acute and Chronic Inflammation

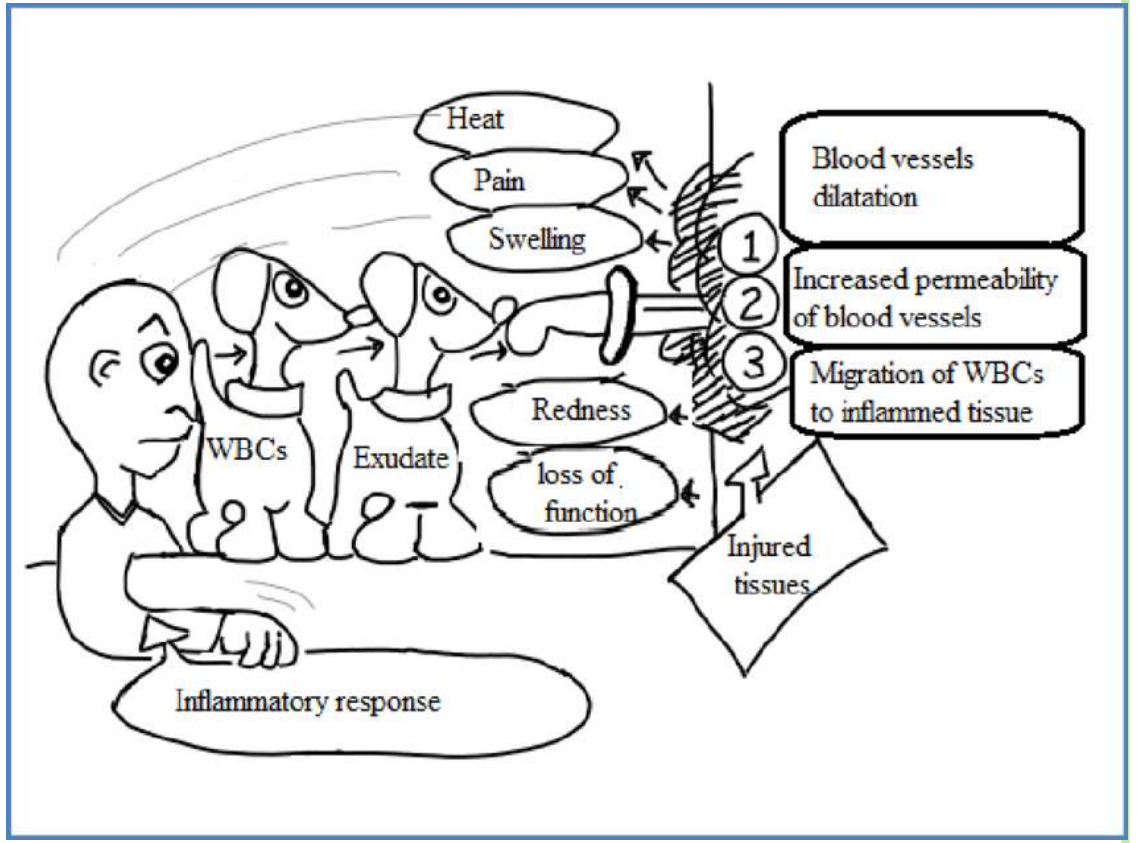
Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

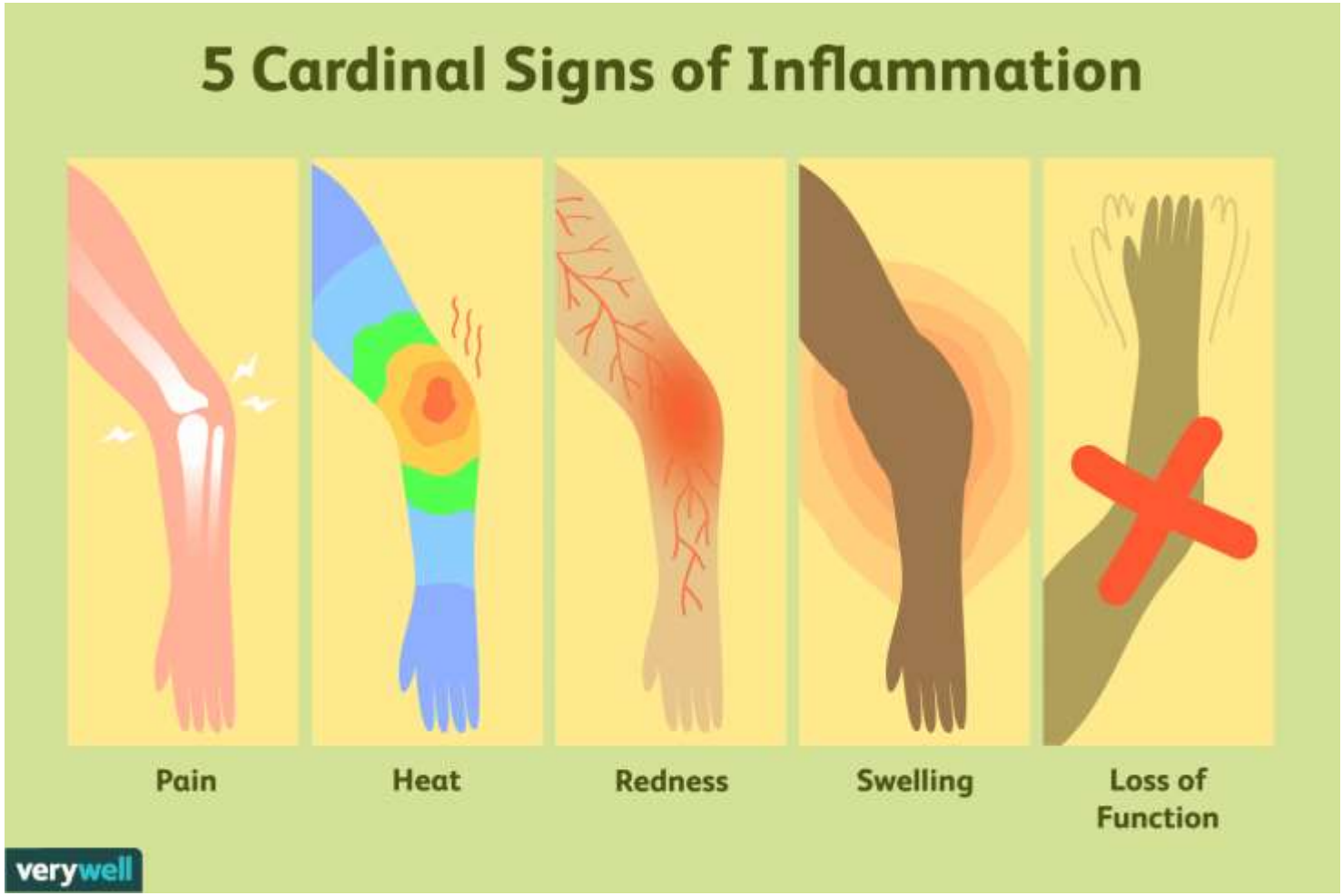
**if the initial response fails to clear the stimulus, the reaction progresses to chronic inflammation


STIMULUS
Microbes
Necrotic tissue
PRODUCTION OF MEDIATORS
Macrophage
Dendritic cell
Mast cell
Recognition by macrophages, other sentinel cells in tissues
Mediators (amines, cytokines)
INFLUX OF LEUKOCYTES, PLASMA PROTEINS
Recruitment of leukocytes
Neutrophil
Monocyte
Vasodilation, increased vascular permeability
Edema
Macrophage
Elimination of microbes, dead tissue
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

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
verywell

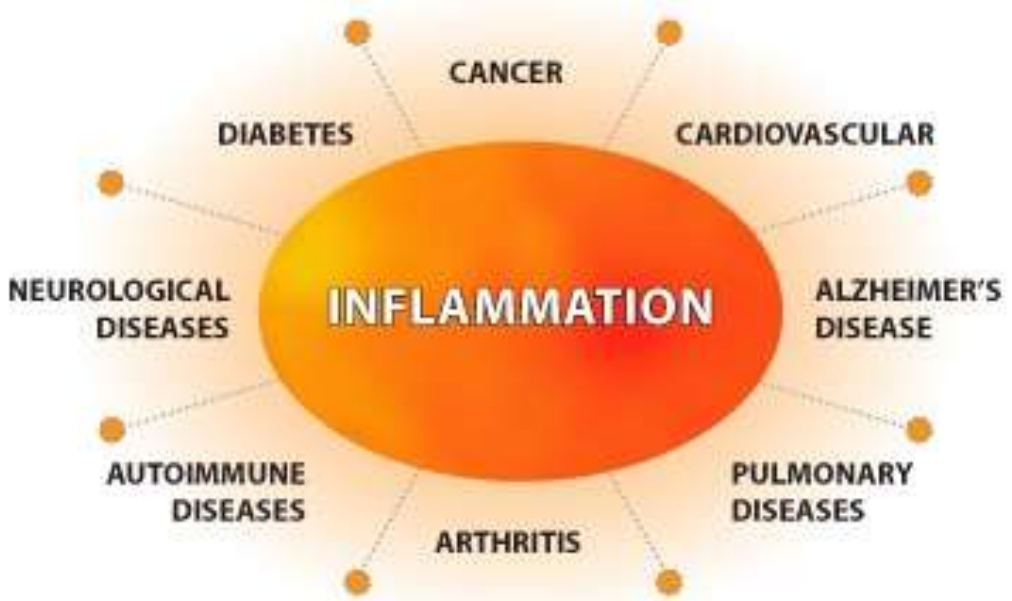
Dose the inflammation always good??

- 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



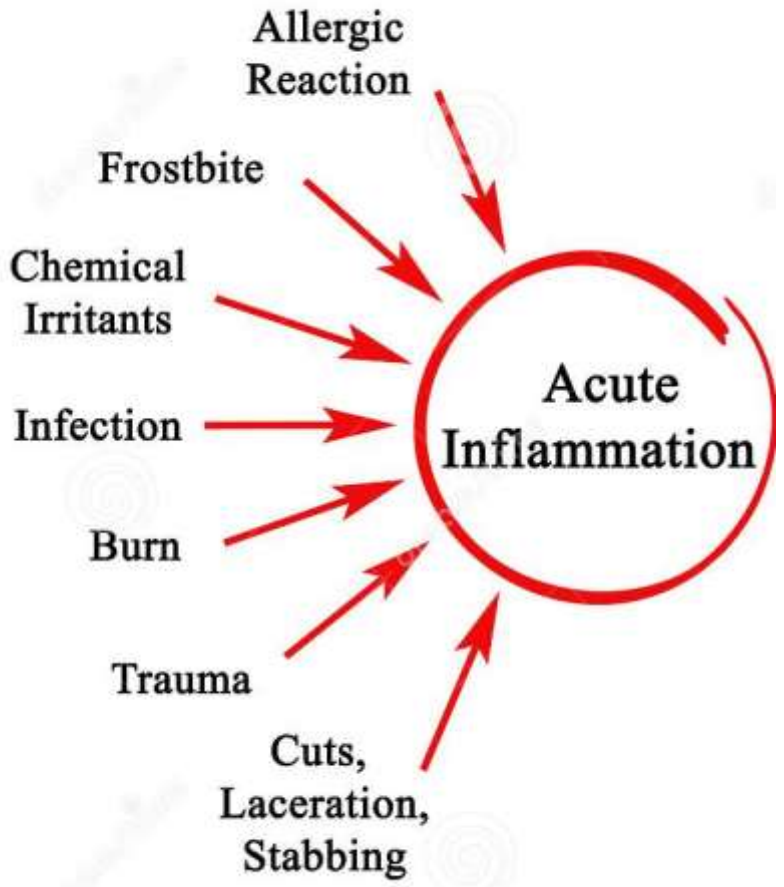
- Not only excessive inflammation but also defective inflammation is responsible for serious illness.
- is most often caused by a reduced number of leukocytes resulting from replacement of the bone marrow by cancers and suppression of the marrow by therapies for cancer and graft rejection

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).

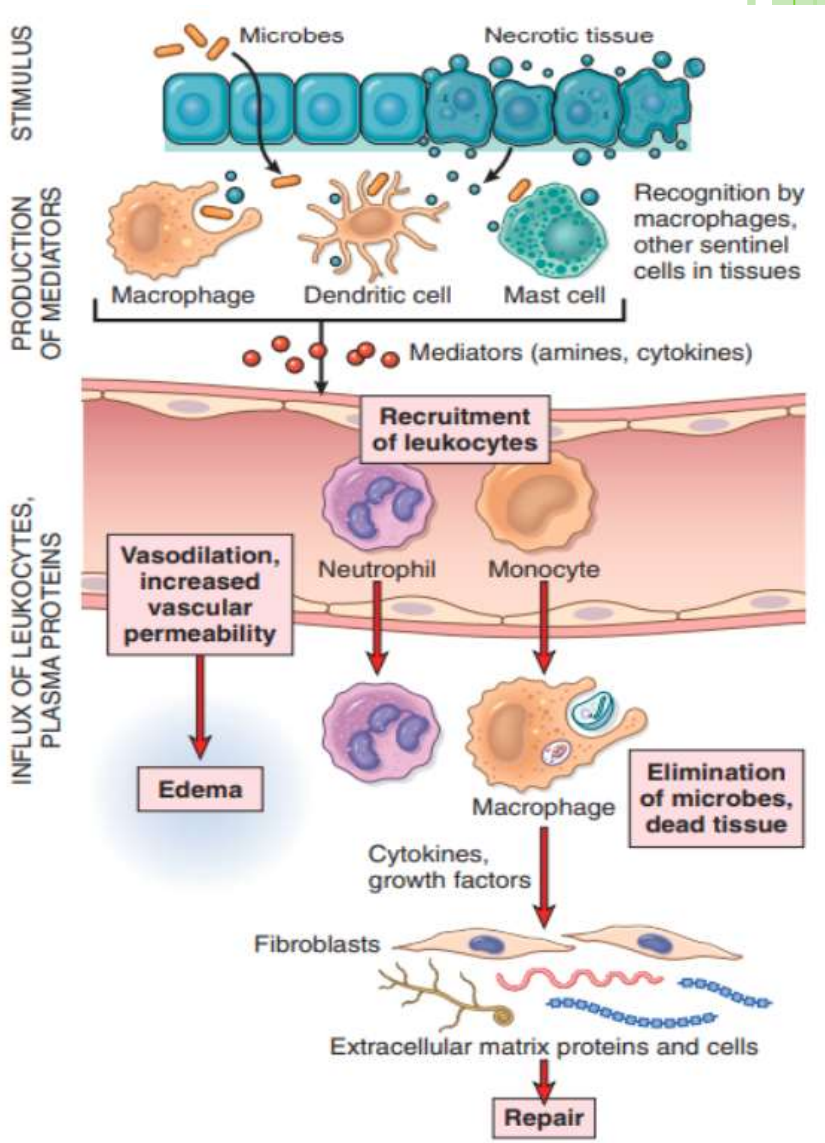
CAUSES OF INFLAMMATION



1.RECOGNITION OF MICROBES AND DAMAGED CELLS

- 1. Cellular receptors for microbes

- The best defined of these receptors belong to the family of T 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, viral cytokines (interferons), and cytokines and membrane proteins that promote lymphocyte activation and even more potent immune responses

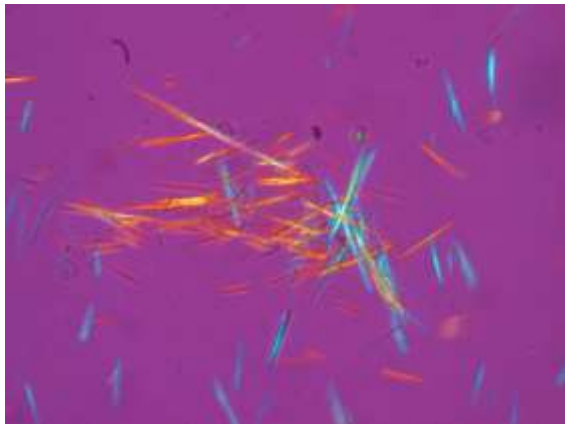
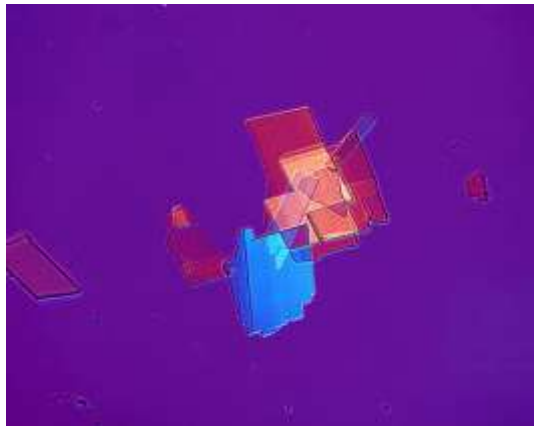
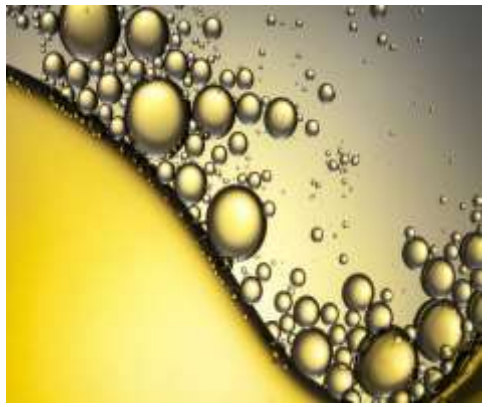
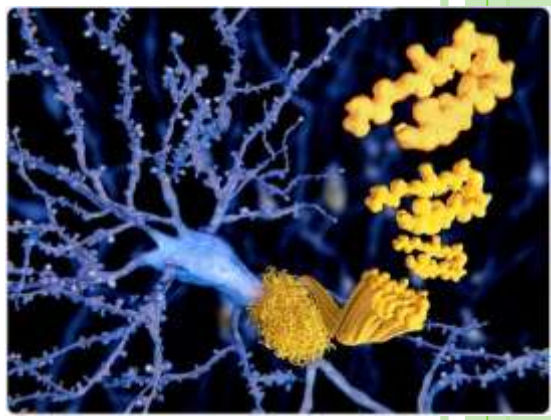


2. Sensors of cell damage

- 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), The receptors activate inflammasome, which induces the production of the cytokine interleukin-1 (IL-1).
- IL-1 recruits leukocytes and thus induces inflammation

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).

AUTOINFLAMMATORY SYNDROMES

- defined as conditions caused by an exaggerated innate immune system response(Gain-of-function mutations in the cytosolic receptors) resulting in episodes of spontaneous inflammation affecting multiple organs.
- IL-1 antagonists are effective treatments for these disorders.

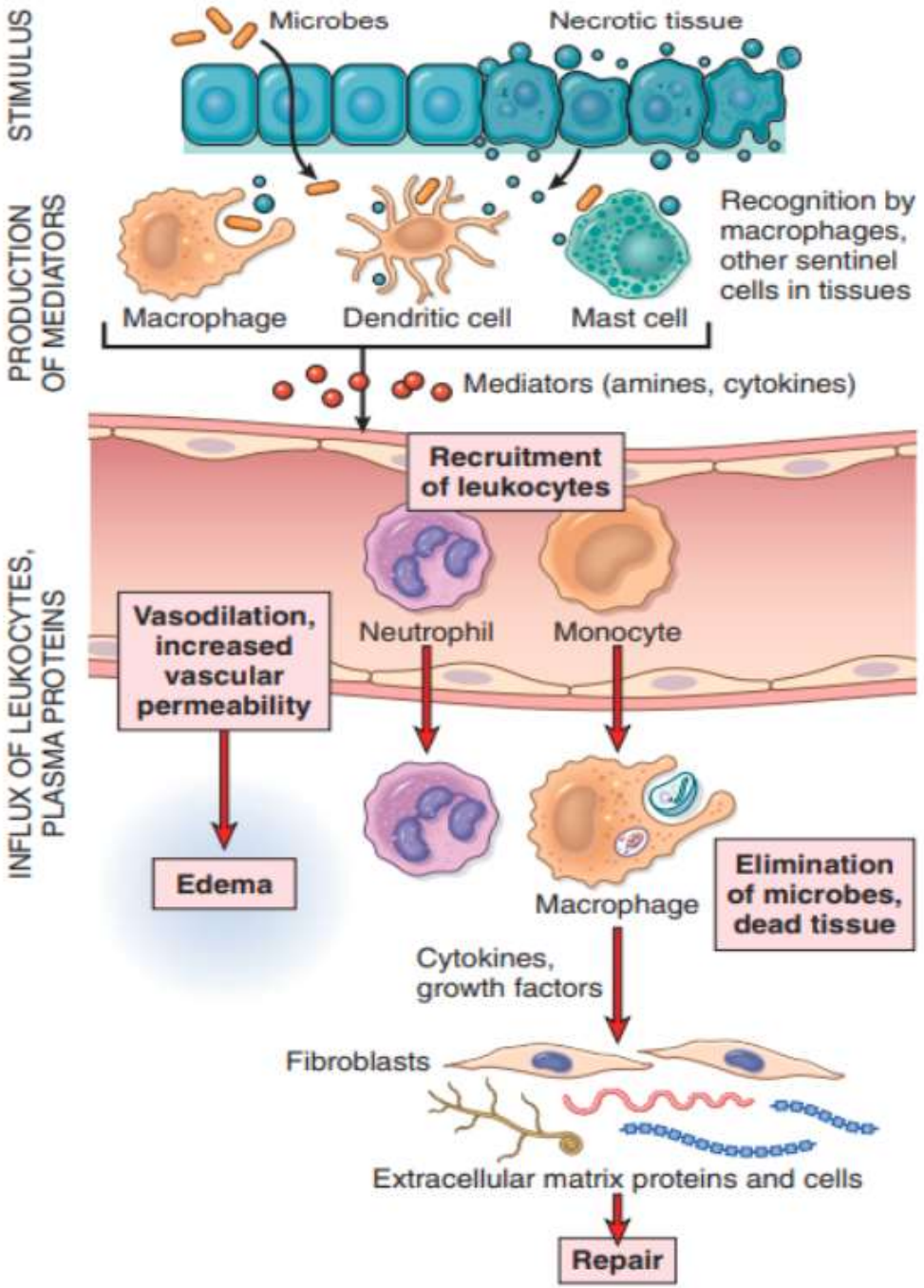
3. Circulating proteins.

- 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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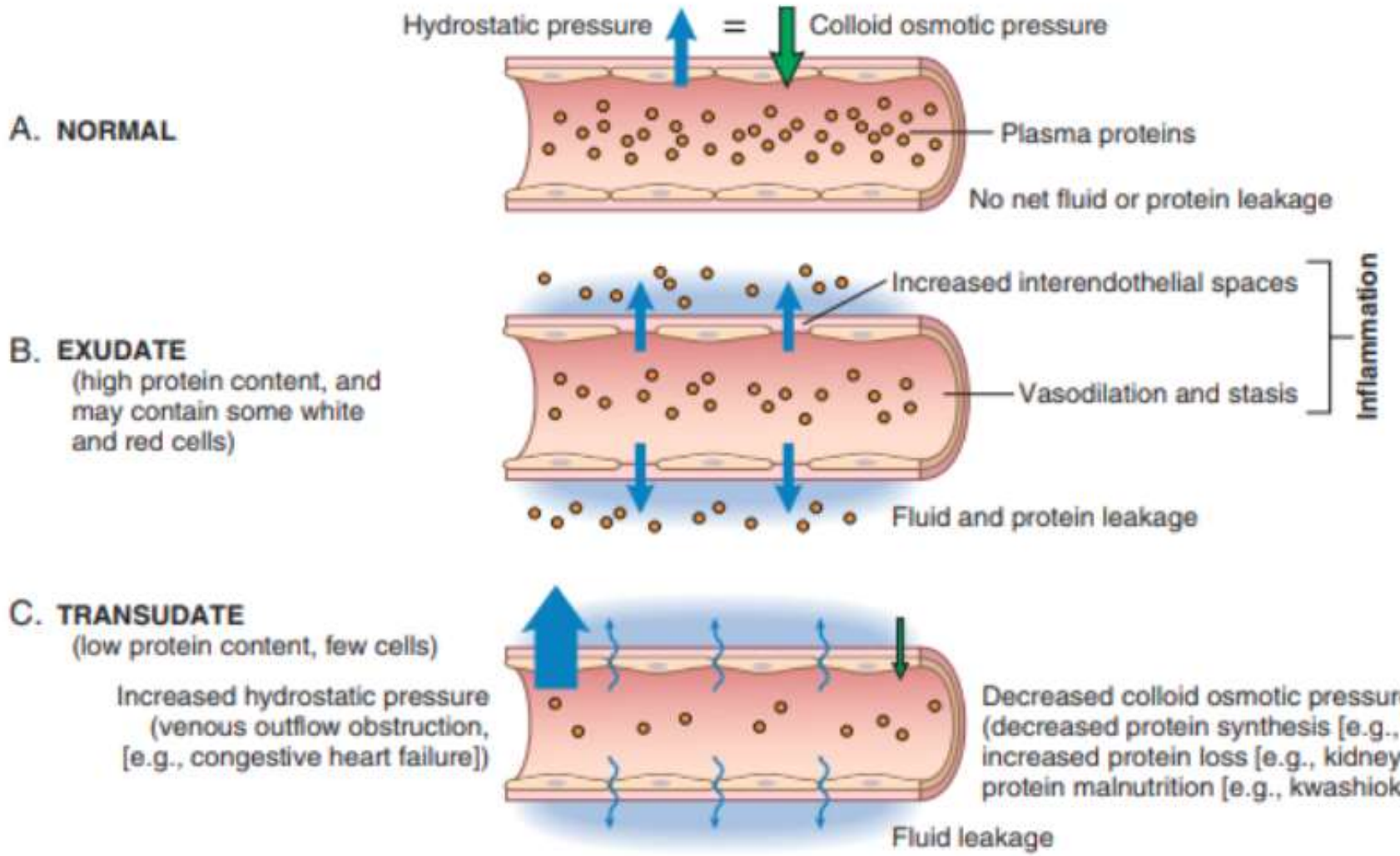
Macrophage
Elimination of microbes, dead tissue
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

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.



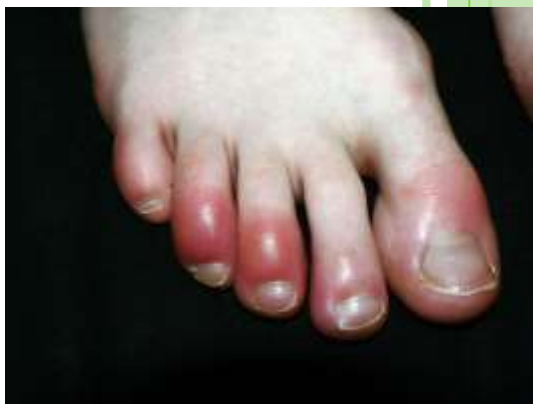
increase in the permeability

normal vascular permeability

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.



- 2. increased permeability of the microvasculature, with the outpouring of protein-rich fluid (an exudate) into the extravascular tissues.

- 3. <u>vascular congestion:</u>
- stasis of blood flow, engorgement of small vessels due to slow blood flow.

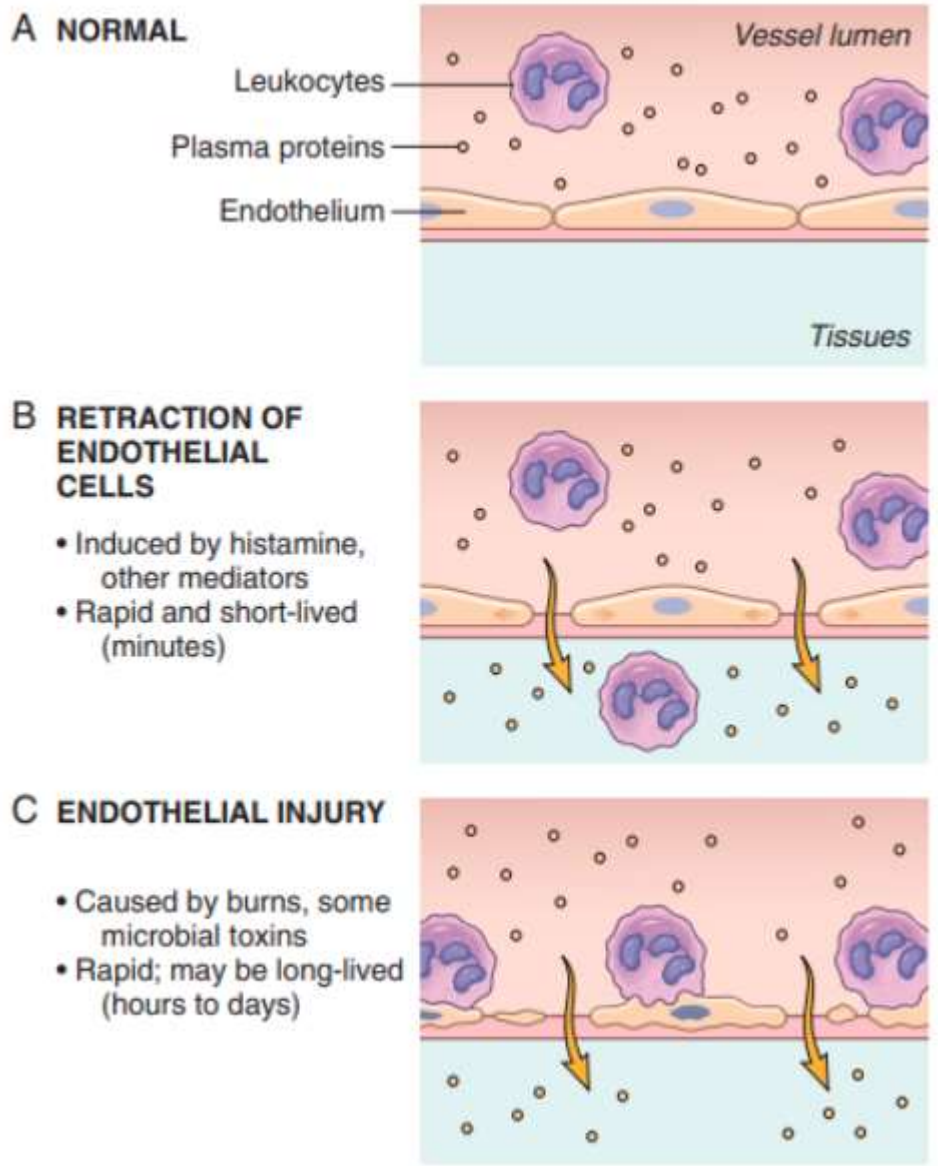
- 4. blood leukocytes, principally neutrophils, accumulate along the vascular endothelium, endothelial cells are activated and leukocytes then migrate through the vascular wall into the interstitial tissue

How dose the vascular permeability increased?

- 1. Retraction of endothelial cells

(immediate transient response):

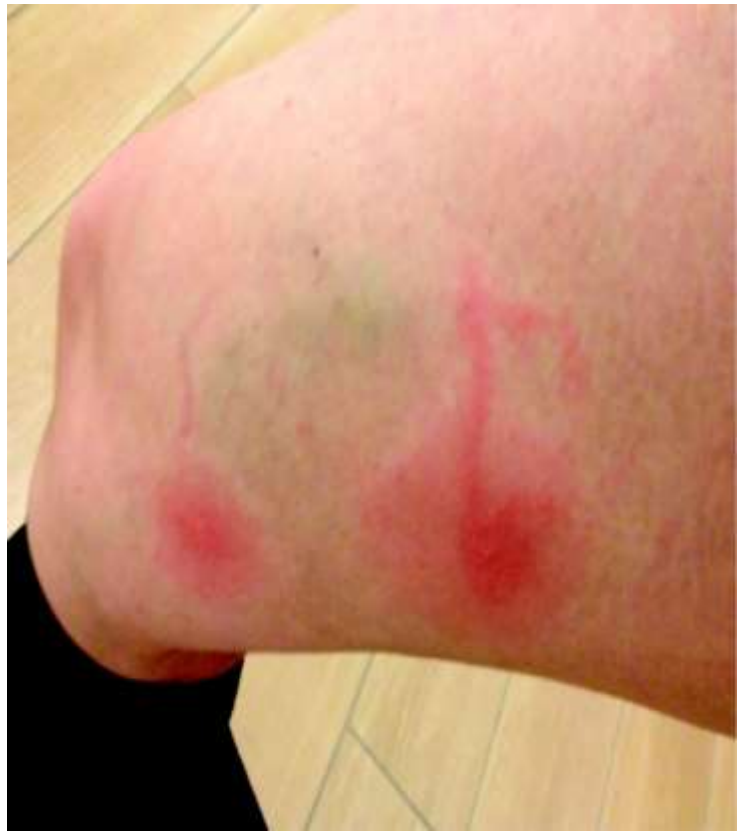
- It is elicited by histamine, bradykinin, leukotrienes.
- 2. Endothelial injury:
- 3. transcytosis:
- Increased transport of fluids and proteins

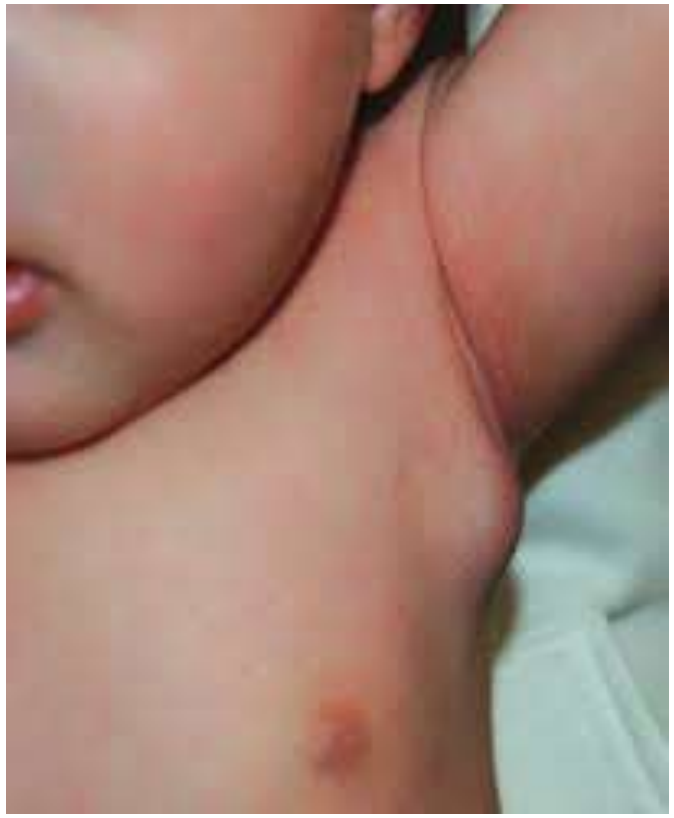


Responses of Lymphatic Vessels and Lymph Nodes

- 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).

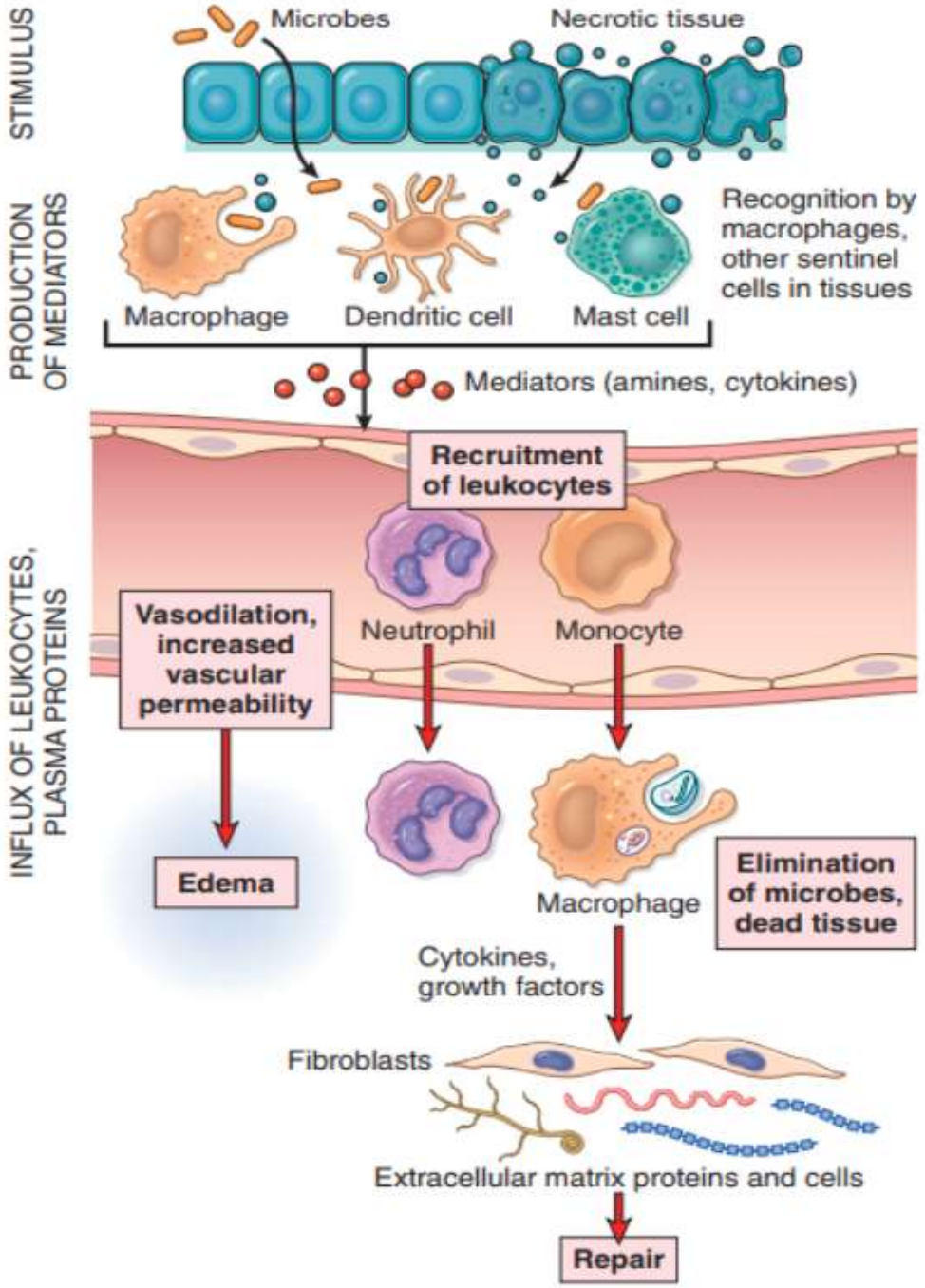




- This streaking follows the course of the lymphatic
- channels and indicates the presence of lymphangitis

painful enlargement of the draining lymph nodes, indicating lymphadenitis.

2.Leukocyte Recruitment to Sites of Inflammation



2.Leukocyte Recruitment to Sites of Inflammation

- Leukocytes that are recruited to sites of inflammation perform the key function of eliminating the offending agents.

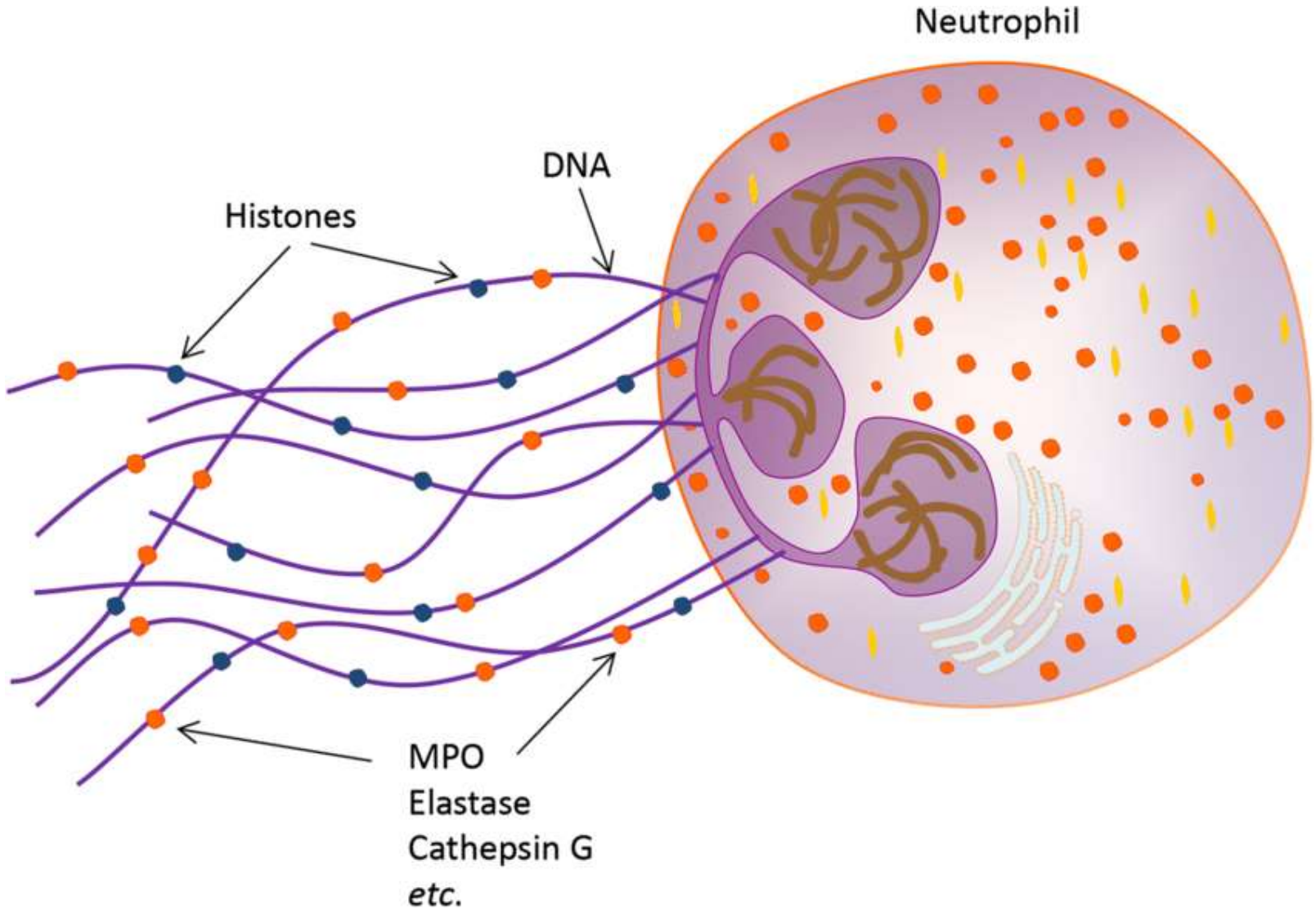
- The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis, namely, neutrophils and macrophages

- These leukocytes ingest and destroy bacteria and other microbes, however, they may induce tissue damage and prolong inflammation.

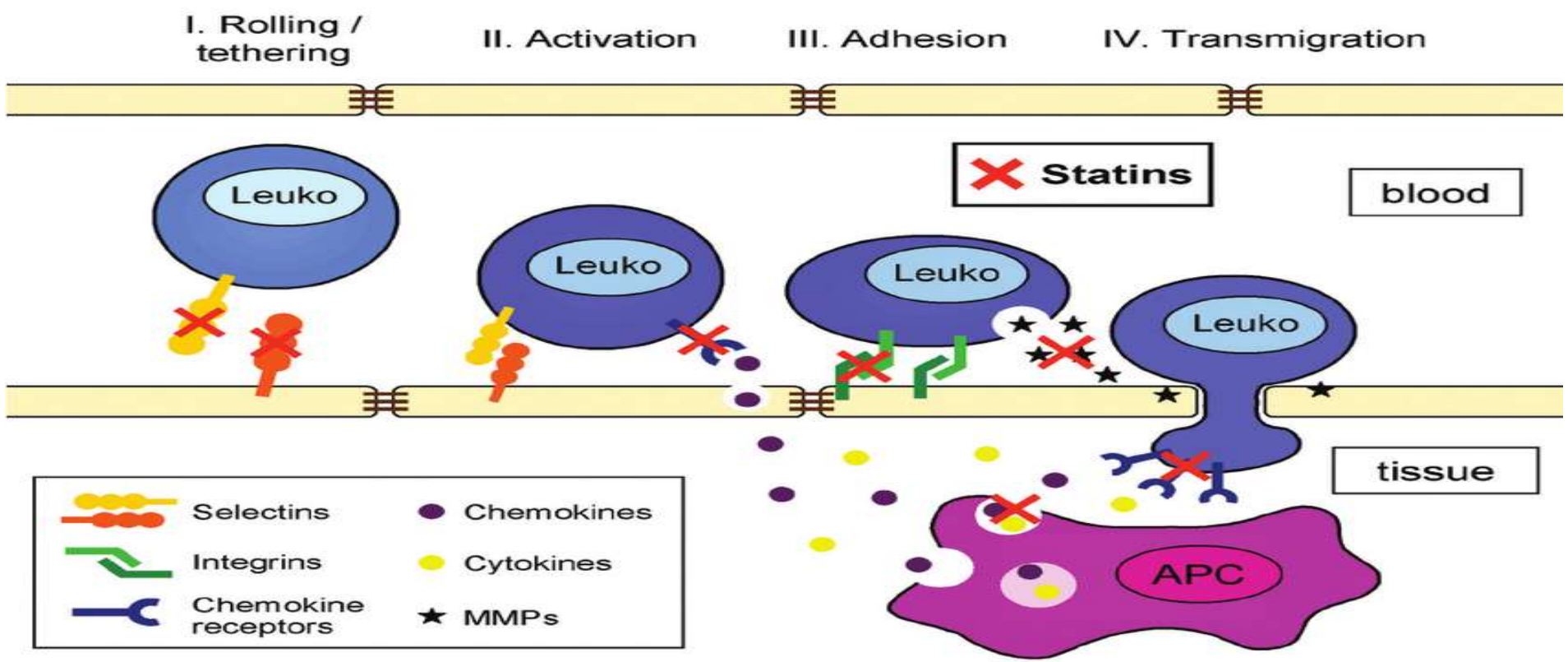
Table 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• 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
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• 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.