

Pathology of Inflammation and Repair

LEC.1

Dr. Raghad Hanoon

Objectives

- Define the inflammation
- Explain the causes of inflammation
- Identify the cardinal signs of inflammation and understand their pathogenesis
- Understanding the sequence of vascular and cellular events in acute inflammation.

Overview of Inflammation

- Inflammation is a protective response of vascularized living tissue to infectious organisms and/or tissue damage.
- **Main functions of Inflammation are;**
 1. To contain and isolate injury,
 2. To destroy invading microorganisms and inactivate or dilute toxins
 3. To prepare the tissue for healing and repair.
- However, the benefits of inflammation, **It can also be harmful**, for example, by causing **life-threatening hypersensitivity reactions** (to insect bites, foods, drugs and toxins) or **progressive organ damage** from chronic inflammation and subsequent fibrosis (e.g., rheumatoid arthritis and lung fibrosis).

Causes of inflammation

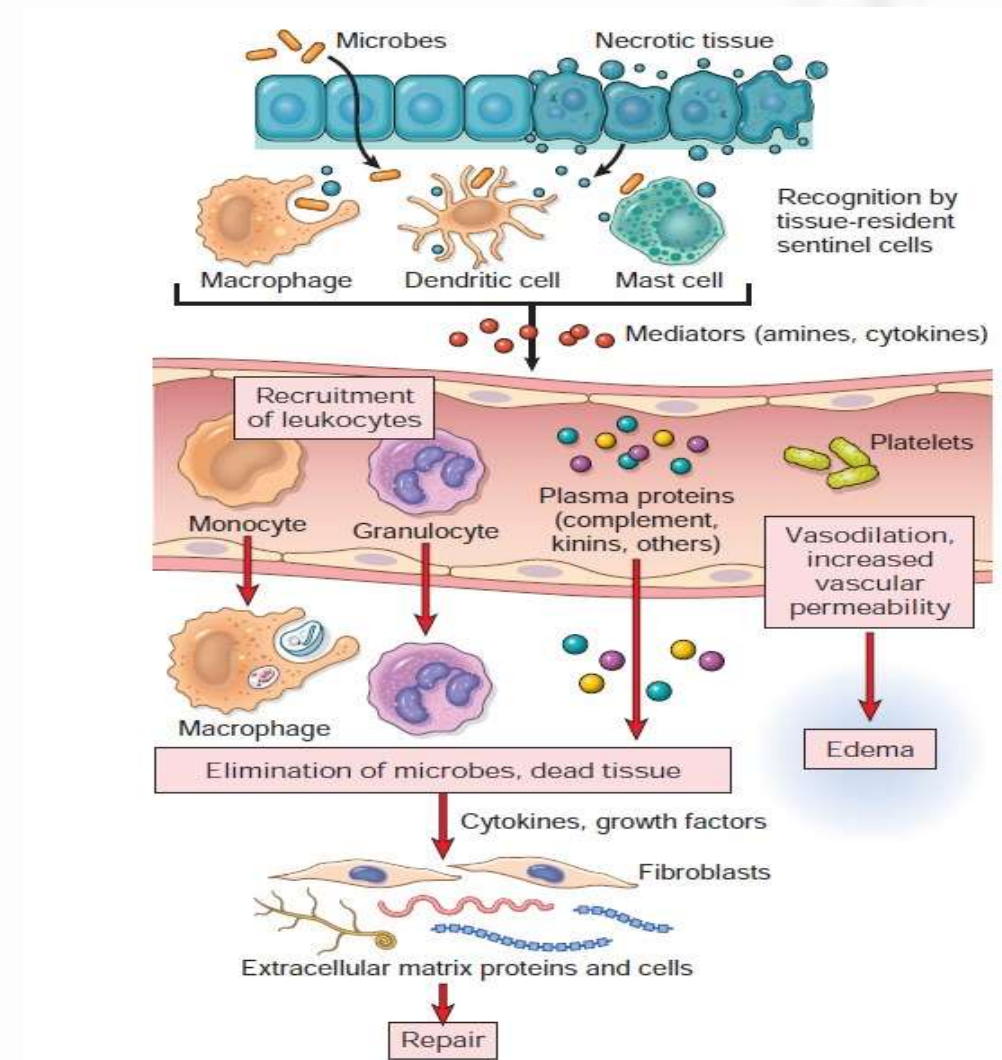
- **Infections:** **Most common cause** , different microbial organisms and toxins elicit varying inflammatory responses from mild to severe or acute to chronic reactions.
- **Tissue necrosis:** Elicits inflammation regardless of the cause of cell death (e.g. ischemia, trauma, thermal/chemical injury).
- **Foreign bodies:** Can be **exogenous**, e.g. splinters, dirt, sutures or **endogenous**, e.g. urate crystal deposits in gout.
- **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 directed **against self antigens, causing autoimmune diseases**, or may be **inappropriate reactions against environmental substances**, as in allergies, or against microbes.
- **Physical:** e.g., thermal injury, as in burns or frostbite; irradiation.
- **Chemical:** acids, alkali, drugs, toxin.

- **Notes:**

- Inflammation is **NOT** a disease in itself, but often a manifestation of a disease.
- It is useful to **differentiate inflammation and infection** because there are typical situations in pathology and medical diagnosis where inflammation is not driven by microbial invasion – for example; atherosclerosis, trauma, ischemia and autoimmune diseases.

➤ The steps of the inflammatory response can be remembered as the five R's:

1. Recognition of the injurious agent
2. Recruitment of leukocytes
3. Removal of the agent
4. Regulation (control) of the response
5. Repair (resolution).



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.**

Inflammation can be divided into two basic types

1. Acute inflammation:

- Early onset (seconds to minutes).
- Short duration (minutes to days).
- Involving fluid exudation (edema) and polymorphonuclear cell (neutrophil) emigration.
- The suffix **(itis)** add to the name of organs signifying acute inflammation, but with some exceptions e.g. colitis, appendicitis , mastitis.
- Systemic signs prominent
- Usually mild and self-limited

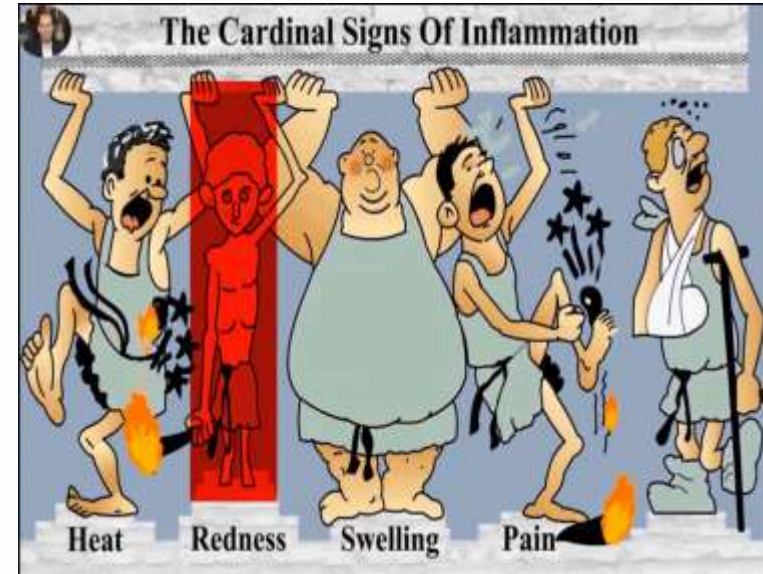
2. Chronic inflammation:

- Later onset (days).
- Longer duration (weeks to years).
- Involving lymphocytes and macrophages, with blood vessel proliferation and fibrosis.
- The suffix **(osis)** add to the name of organs signifying chronic inflammation, e.g. dermatosis.
- Less
- Often severe and progressive

Classical (cardinal) clinical sings of inflammation

➤ There are **five cardinal signs** of inflammation (most prominent in acute inflammation):

1. **Warmth** (Latin: calor) due to vascular dilation
2. **Erythema** (Latin: rubor) due to vascular dilation.
3. **Edema** (Latin: tumor) due to increased vascular permeability
4. **Pain** (Latin: dolor) due to mediator release (bradykinin and PGE2)
5. **Loss of function** (Latin: functio laesa) due to pain, edema, tissue injury, and/or scar.



Inflammations of Skin & adjacent Tissues (cellulitis)

Acute Inflammation

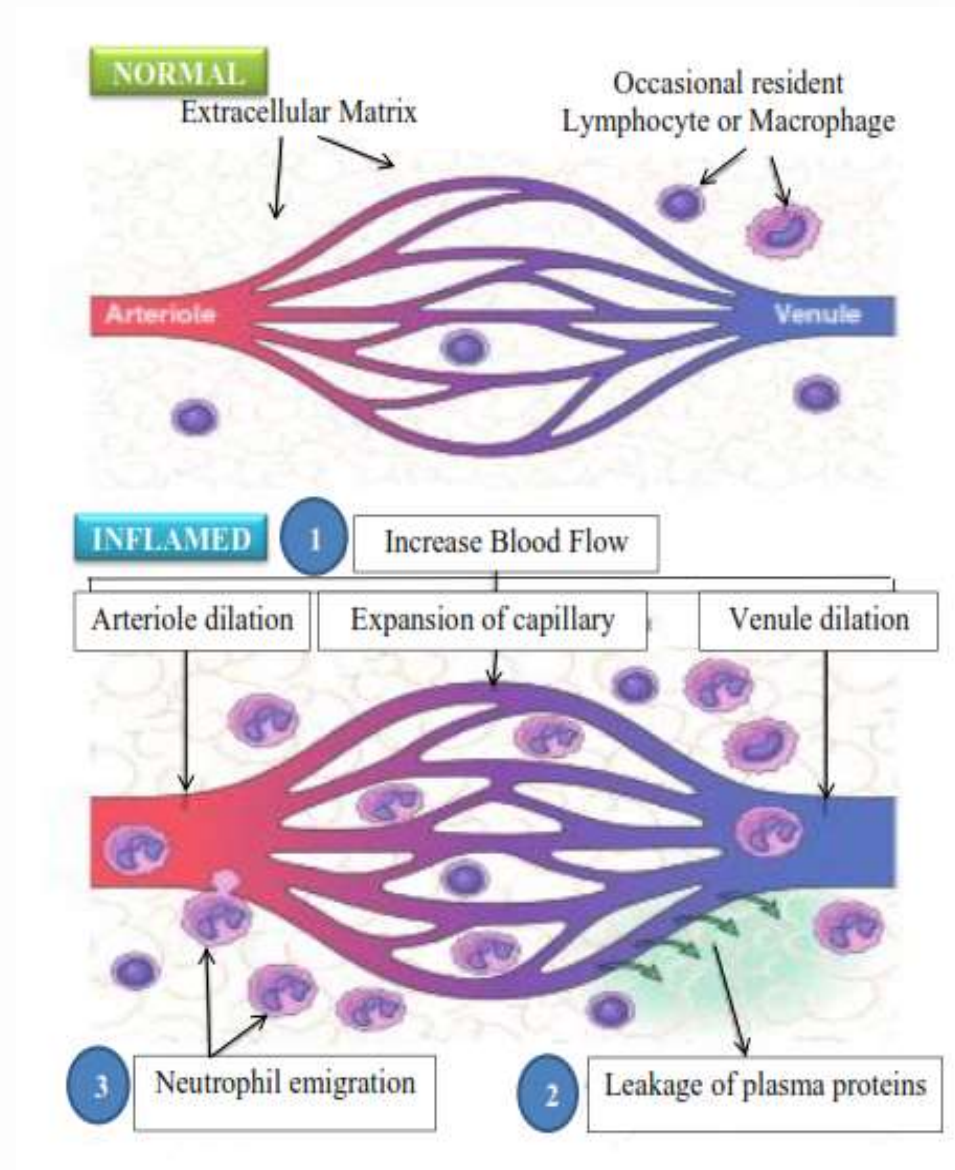
- Acute inflammation is a rapid host response that serves to deliver leukocytes and plasma proteins to sites of tissue injury.
- The sequence of events of acute inflammation is regulated by release of chemical mediators.
- **Acute inflammation has three major components:**
 1. **Dilation of small vessels** 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
- **1 and 2 are vascular changes, while 3 is a cellular changes.**

- The major local manifestations of acute inflammation, compared to normal.

(1) Vascular dilation and increased blood flow (**causing erythema and warmth**)

(2) Extravasation and extravascular deposition of plasma fluid and proteins (**edema**)

(3) Leukocyte emigration and accumulation in the site of injury.



Vascular changes

- The vascular reactions in acute inflammation consist of;
 1. Changes in the vascular flow and caliber
 2. Increased in vascular permeability
- Both designed to maximize the movement of plasma proteins and leukocytes out of the circulation into the site of injury.

1. Changes in vascular flow and caliber; vasodilatation and increased blood flow:

- **Vasodilation** is induced by the action of several mediators, mainly **histamine**, on vascular smooth muscle.
- It is one of the earliest manifestations of acute inflammation, and may be preceded by transient vasoconstriction lasting a few seconds.
- Vasodilation 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 Vascular Permeability (vascular leakage) and decreased blood flow;

- Several mechanisms are responsible for the increased permeability of postcapillary venules, a hallmark of acute inflammation.

1- Contraction of endothelial cells

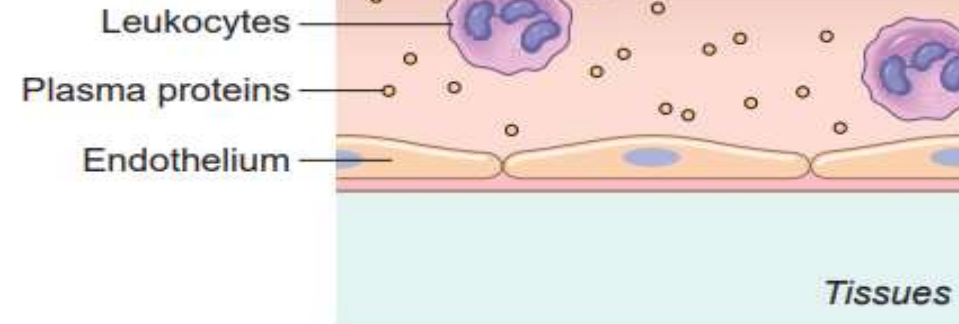
- **Immediate** transient response: occurs rapidly after exposure to the mediator and usually **short-lived** (15-30 minutes.). Can also be delayed (after 2-12 hours) and lasts for several hours or even days; e.g. sunburn.
- Caused by **histamine, bradykinin, leukotrienes** and other chemical mediators.
- Results in opening of inter-endothelial gaps.

2- Endothelial injury

- Caused by **direct physical damage to the endothelium**, for example, in thermal burns or is induced by the actions of microbes and microbial toxins that damage endothelial cells or adhering neutrophils that are recruited and amplify the reaction.
- Resulting in endothelial cell necrosis and detachment.
- In most instances leakage starts immediately after injury and is sustained for several hours until the damaged vessels are thrombosed or repaired.

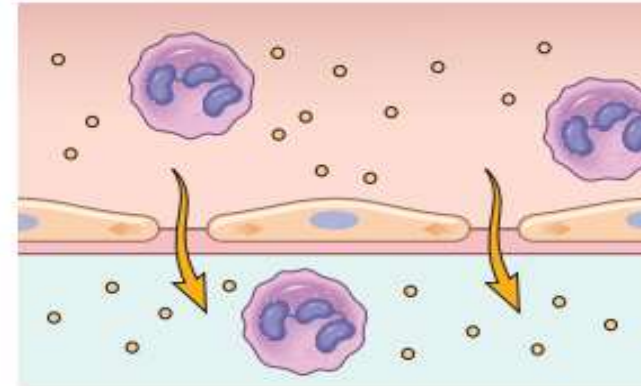
- Principal mechanisms of increased vascular permeability in inflammation and their features and underlying causes.

A. NORMAL



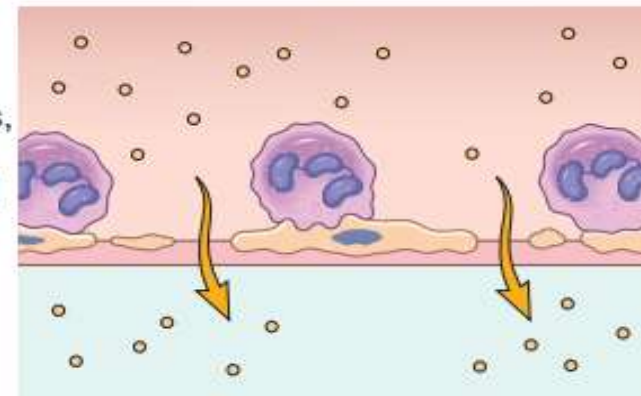
B. RETRACTION OF ENDOTHELIAL CELLS

- Induced by histamine, other mediators
- Rapid and short-lived (minutes)



C. ENDOTHELIAL INJURY

- Caused by thermal burns, some microbial toxins
- Rapid; may be long-lived (hours to days)



- **Increased vascular permeability** leads to the escape of **exudates** into the extravascular tissue (**Exudate** is an inflammatory, extravascular fluid with high protein concentration, specific gravity of 1.020 or more).
- **The loss of fluid and increased vessel diameter** lead to **slower blood flow**, increased concentration of red cells in small vessels, and increased viscosity of the blood.
- These changes result in engorgement of small vessels with slowly moving red cells, a condition termed **stasis**.
- **After stasis leukocytes (Neutrophils) change their normal flow in vessels & begin to accumulate along the vascular endothelial surface** (and then cellular changes developed).

Responses of Lymphatic Vessels and Lymph Nodes

- In acute inflammation, lymphatic vessels participate alongside blood vessels by draining increased extravascular fluid as well leukocytes, cell debris and microbes.
- Lymph flow increases to remove edema fluid caused by increased vascular permeability and lymphatic vessels proliferate to handle the greater load.
- The lymphatic vessels and draining lymph nodes may become secondarily inflamed (lymphangitis and lymphadenitis); inflamed nodes enlarge due to hyperplasia of lymphoid follicles and increased numbers of lymphocytes and macrophages, a change termed reactive (inflammatory) lymphadenitis.



The red streaks represent inflamed lymphatic channels and are diagnostic of lymphangitis



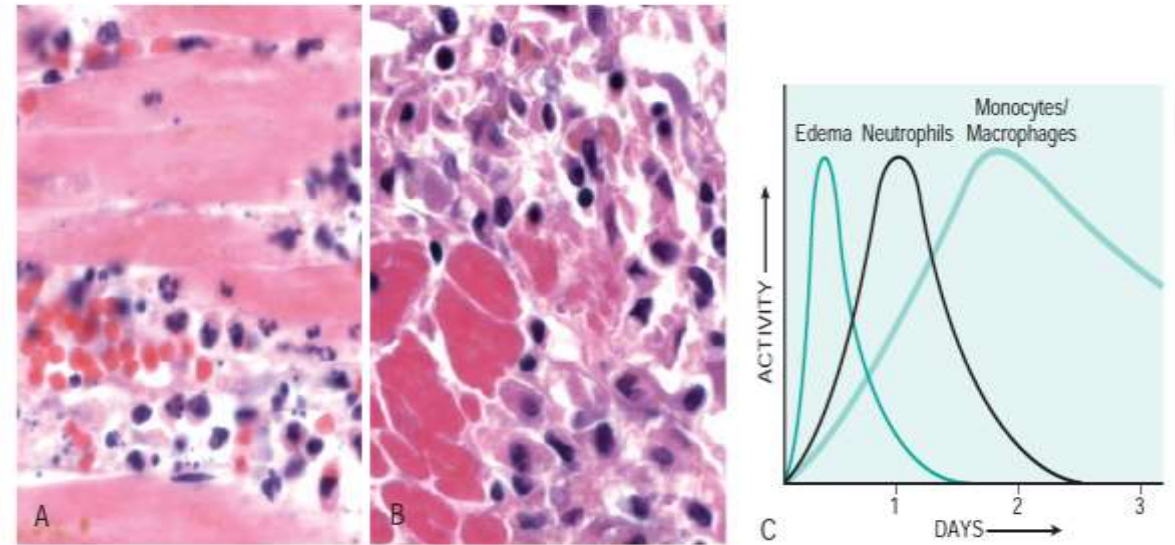
Enlargement of the draining lymph nodes, indicating lymphadenitis

Cellular changes

3. Emigration of leukocytes from the microcirculation, their accumulation in the focus of injury, and their **activation** to **eliminate the offending agent**

- A critical function of inflammation is to deliver leukocytes to sites of injury (**recruitment**), especially those cells capable of phagocytosing microbes and necrotic debris (e.g., neutrophils and macrophages).
- The type of leukocyte that ultimately migrates into a site of injury depends on the **age of the inflammatory response** and the **original stimulus**.

- In most forms of **acute inflammation**, **neutrophils** predominate during the first 6 to 24 hours and are then replaced by **monocytes** after 24 to 48 hours.
- There are several reasons for this sequence:
- Neutrophils are **more numerous** in blood than monocytes, they **respond more rapidly** to chemokines, and they **attach more firmly** to the particular adhesion molecules that are induced on endothelial cells at early time points.
- After migration, neutrophils are **also short-lived**; they undergo apoptosis after 24 to 48 hours, whereas monocytes survive longer.

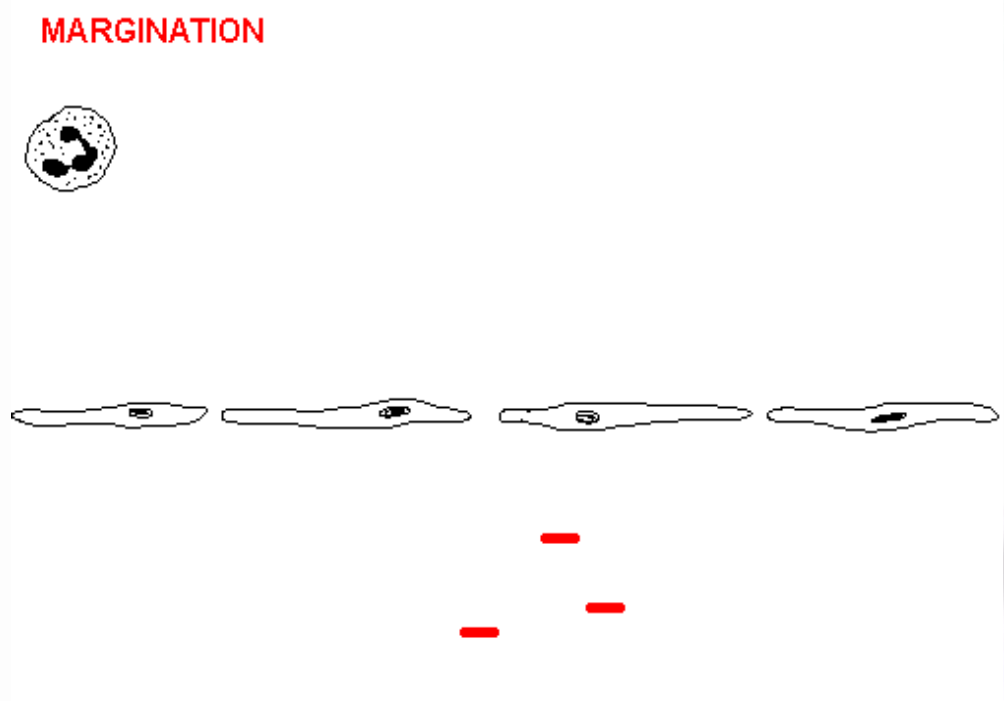


Nature of leukocyte infiltrates in inflammatory reactions.

The photomicrographs show an inflammatory reaction in the myocardium after ischemic necrosis (infarction). (A) Early (neutrophilic) infiltrates and congested blood vessels. (B) Later (mononuclear) cellular infiltrates. (C) The approximate kinetics of edema and cellular infiltration. For simplicity, edema is shown as an acute transient response, although secondary waves of delayed edema and neutrophil infiltration can also occur.

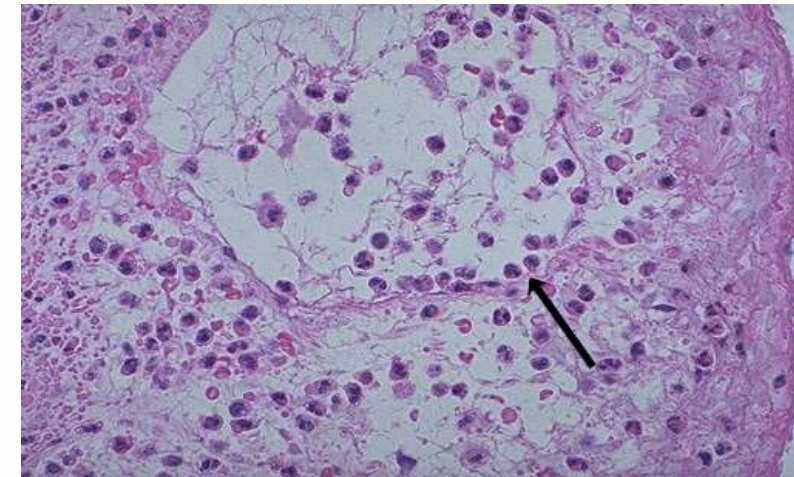
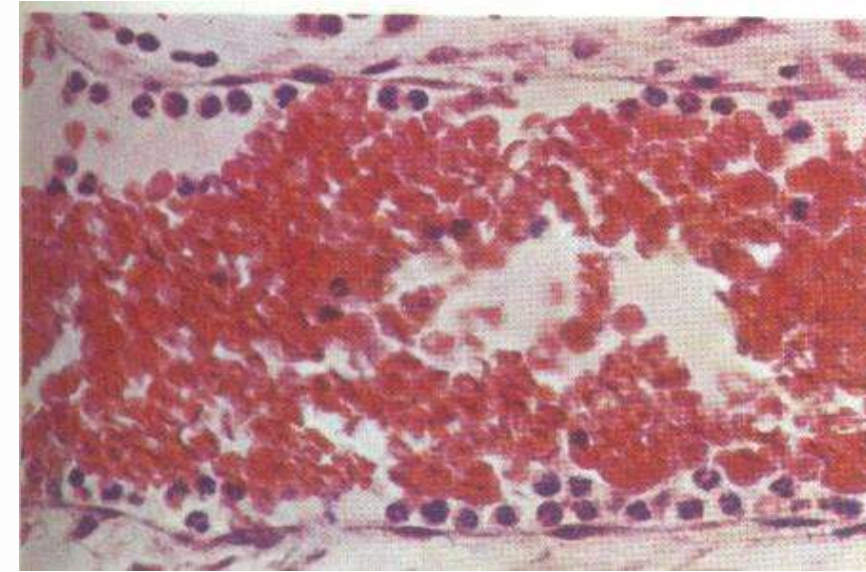
Cellular changes of acute inflammation

- **Emigration (leukocytes recruitment):** The journey of leukocytes from the vessel lumen into the adjacent interstitial tissue. 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**).
 3. Migration in the tissues toward a chemotactic stimulus (**Chemotaxis**).
- **Phagocytosis and Clearance of the Offending Agent**



1. Margination, Rolling and adhesion:

- **Margination;** white cells take a peripheral position along the endothelial surface.
- **Because of dilation** of inflamed postcapillary venules, blood flow slows (**stasis**), and more white cells take a peripheral position along the endothelial surface.
- **Rolling;** Subsequently leukocytes tumble on the endothelial cell surface. Rolling is occurred due to interaction between **selectin** receptors on leukocytes & the endothelial cells.
- **Adhesion;** WBCs stick the surface of endothelial cells, which is achieved **by interaction between integrins on the leukocytes** and **Immunoglobulin family- adhesion molecules on endothelial cells (ICAM-1 and VCAM-1).**



Adhesion molecules

- Adhesion molecules play an important role in acute inflammation.
- Expression of these adhesion molecules is enhanced by secreted proteins called **cytokines (IL-1) and TNF**.
- They are of **three families**: selectins, immunoglobulin family adhesion proteins, and integrins.
- **Selectins**: molecules on leukocytes (L-selectin) and endothelium (E-selectin, P-selectin) act as receptors to provide loose binding for **rolling**.
- **Immunoglobulin family adhesion proteins**: molecules on endothelial cells include intercellular adhesion molecule 1 (**ICAM-1**) and vascular cell adhesion molecule 1 (**VCAM-1**); these bind integrins on leukocytes and mediate **firm adhesion**.
- Platelet- endothelial cell adhesion molecule (**PECAM-1 or CD31**), expressed on leukocytes and endothelial cells, are involved in the **transmigration of leukocytes**.
- **Integrins**: molecules on leukocyte surfaces that bind to members of the immunoglobulin family molecules and to the extracellular matrix.

2. Migration across the endothelium and vessel wall

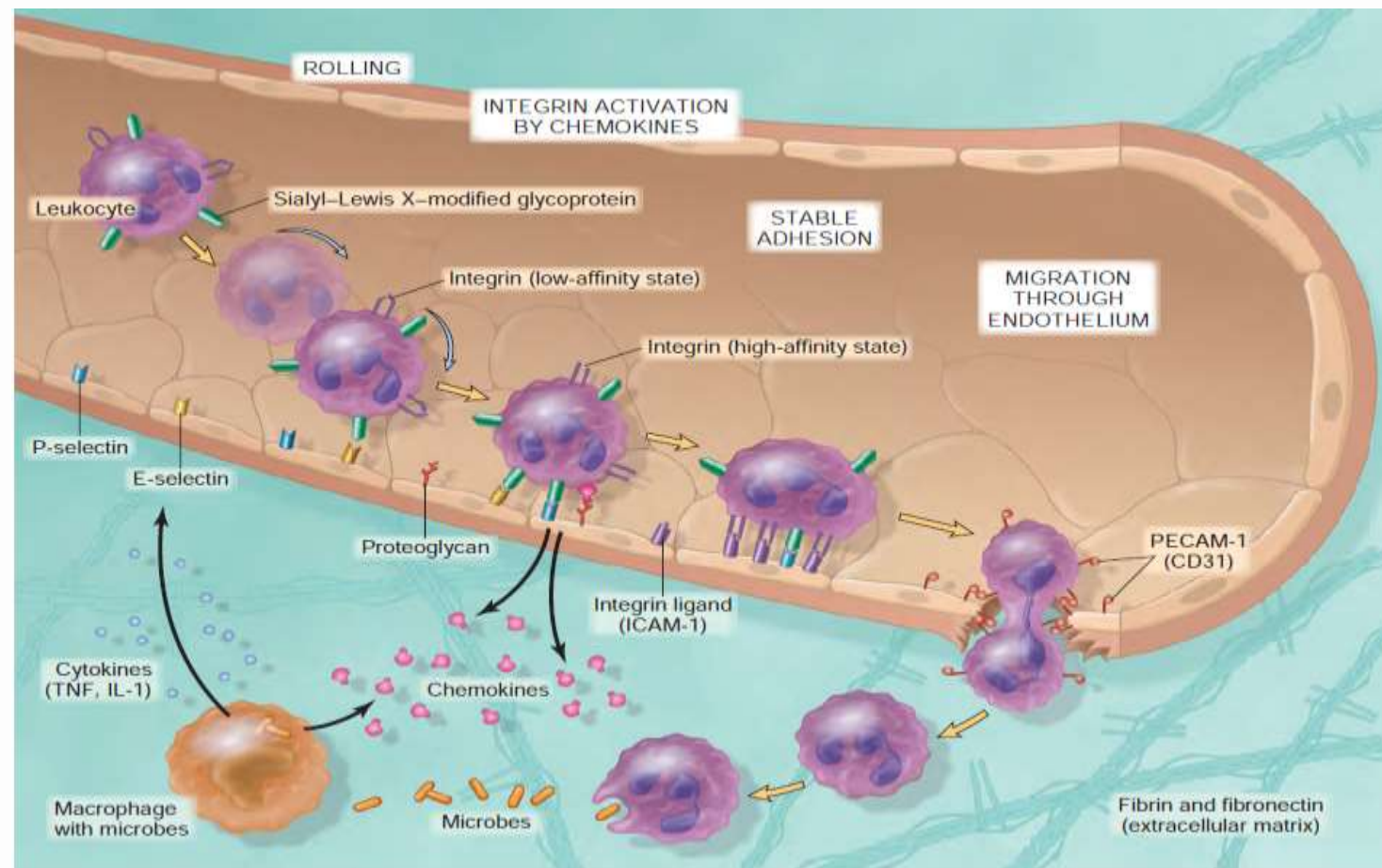
- The movement of leukocytes across the endothelium and through basement membrane into the extravascular space, called **transmigration or diapedesis**.
- Transmigration of leukocytes occurs mainly in **postcapillary venules**.
- **Chemokines** such as **(IL-8)** stimulate adherent leukocytes to migrate through interendothelial gaps toward the site of injury or infection, where the chemokines are being produced.
- Platelet- endothelial cell adhesion molecule **(PECAM-1 or CD31)** at endothelial cells junctions and leukocytes helps this transmigration.
- After traversing the endothelium, leukocytes secrete **collagenases**, to penetrate the basement membrane and enter the extravascular space.

3. Migration in the tissues toward a chemotactic stimulus.

- After extravasation of WBCs, they will migrate toward sites of injury along chemical gradients, this process called **Chemotaxis**.
- Movement of WBC during Chemotaxis toward the sites of injury is achieved by **pseudopodia** (by actin filaments within WBC).
- The chemical gradients (**Chemoattractants**): are proteins present at the site of injury attract WBC to this site. Can be **exogenous** bacterial products and **endogenous mediators**, such as complement components (**C5a**), **Cytokines (IL-8)** and arachidonic acid metabolites, mainly **leukotriene B4 (LTB4)**.

➤ Phagocytosis and Clearance of the Offending Agent

- The two major phagocytes are neutrophils and macrophages.
- Recognition of microbes or dead cells induces several responses in leukocytes that are collectively called **leukocyte activation**.
- The most essential functional consequences of activation are enhanced **phagocytosis and intracellular killing**.
- **Phagocytosis**; is the process by which a cell engulfs a particle and digests it. **which include three steps:**
 - a. Recognition and attachment** of injurious particle to the ingesting leukocytes by **Opsonization** (is the process by which injurious particles are coated by specific plasma particles that are called **opsonins**, to facilitate the recognition & attachment of injurious particles to the killer leukocytes). **These opsonins are included IgG & C₃b**.
 - b. Engulfment** of injurious particle & formation of phagocytic vacuole by Pseudopods of WBCs & then fusion of these vacuoles with the membrane of lysosomes.
 - c. killing & degradation**; The killing of microbes and the destruction of ingested materials are accomplished by **reactive oxygen species** (ROS; superoxide anion(O₂⁻), hydrogen peroxide(H₂O₂) and hydroxyl radical (OH), **reactive nitrogen species** (mainly derived from nitric oxide (NO) and **lysosomal enzymes**.



- **The multistep process of leukocyte migration through blood vessels, shown here for neutrophils.**

The leukocytes 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**, 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 (also known as CD31); *TNF*, tumor necrosis factor.

THANK YOU