جامعة الملك سعود
King Saud University

pathology
MED 439

MED439
KING SAUD UNIVERSITY

Inflammation and Repair: L1 + L2

Objectives:

- Define inflammation.
- List cells & molecules that play important roles in inflammation.
- Types of inflammation: acute and chronic inflammation.
- Recognize the cardinal signs of inflammation.
- Describe the sequence of vascular changes in acute inflammation (vasodilation, increased permeability) and their purpose.
- Compare normal capillary exchanges with exchange during inflammatory response.
- Define the terms edema, transudate and exudate.
- Describe the steps involved in extravasation of leukocytes from the blood to the tissue.
- Know the steps at which selectins and integrins act.
- Describe the meaning and utility of chemotaxis.
- Understand the role that chemokines play in inflammation.
- Describe the steps involved in phagocytosis and the role of igG and Cb3 as opsonins and receptors.
- List the mechanisms of microbial killing.
- Know various defects in leukocyte function.

Color Index:
Girl's Slides
Important
Male's Notes
Female's Notes
Extra information

Inflammation, its causes and steps

When we add the suffix -itis, it means inflammation. E.g. hepatitis means inflammation of the liver, appendix/appendicitis

Inflammation

Is a local response of the vascularized living tissue to Infection and damaged tissue (injury /necrosis) that brings cells and Molecules of host defense to the sites where they are needed.

Aim of inflammation:
1- localize and eliminate the causative agent
2- limit tissue injury
3- restore tissue to normality.

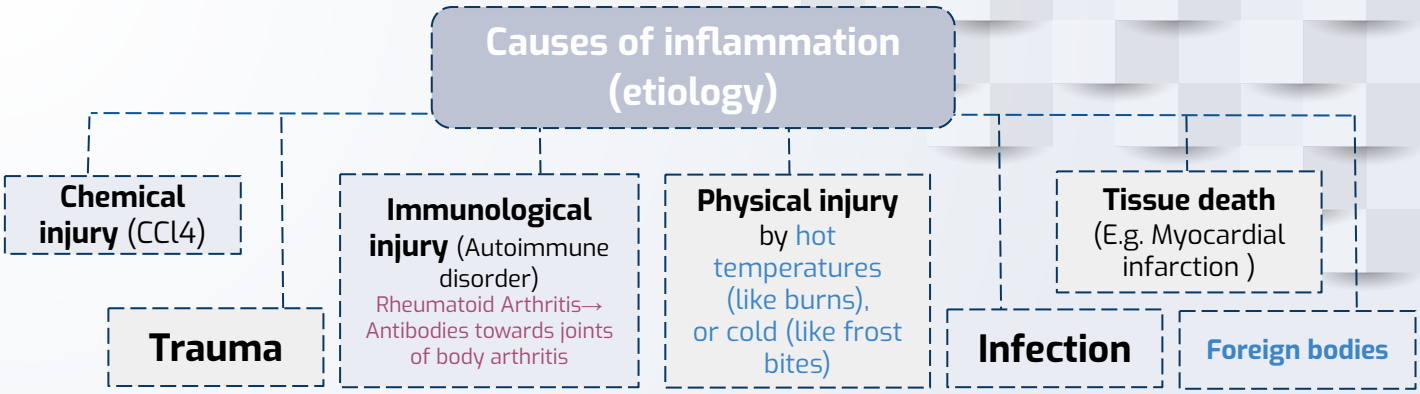
Therefore, inflammation is part of immunity: this is a broad protective response (innate immunity: immunity towards everything)

Acquired: specific to certain organisms

Injury → **Tissue damage** → **Tissue response** → **Eliminates the effect of injury** (pathogen and necrotic tissue) → **Repair** (in case of too much damage, **fibrosis could develop**)

Steps of inflammation

1. The offending agent is recognized by host cells and molecules.
2. Leukocytes and plasma protein are recruited (by chemical mediators) from the circulation to the site of the offending agent
3. The leukocytes and proteins are activated to destroy and eliminate the offending substance
4. The reaction is controlled and terminated (once it's done)
5. The damaged tissue is repaired



Define inflammation

Can inflammation be harmful?

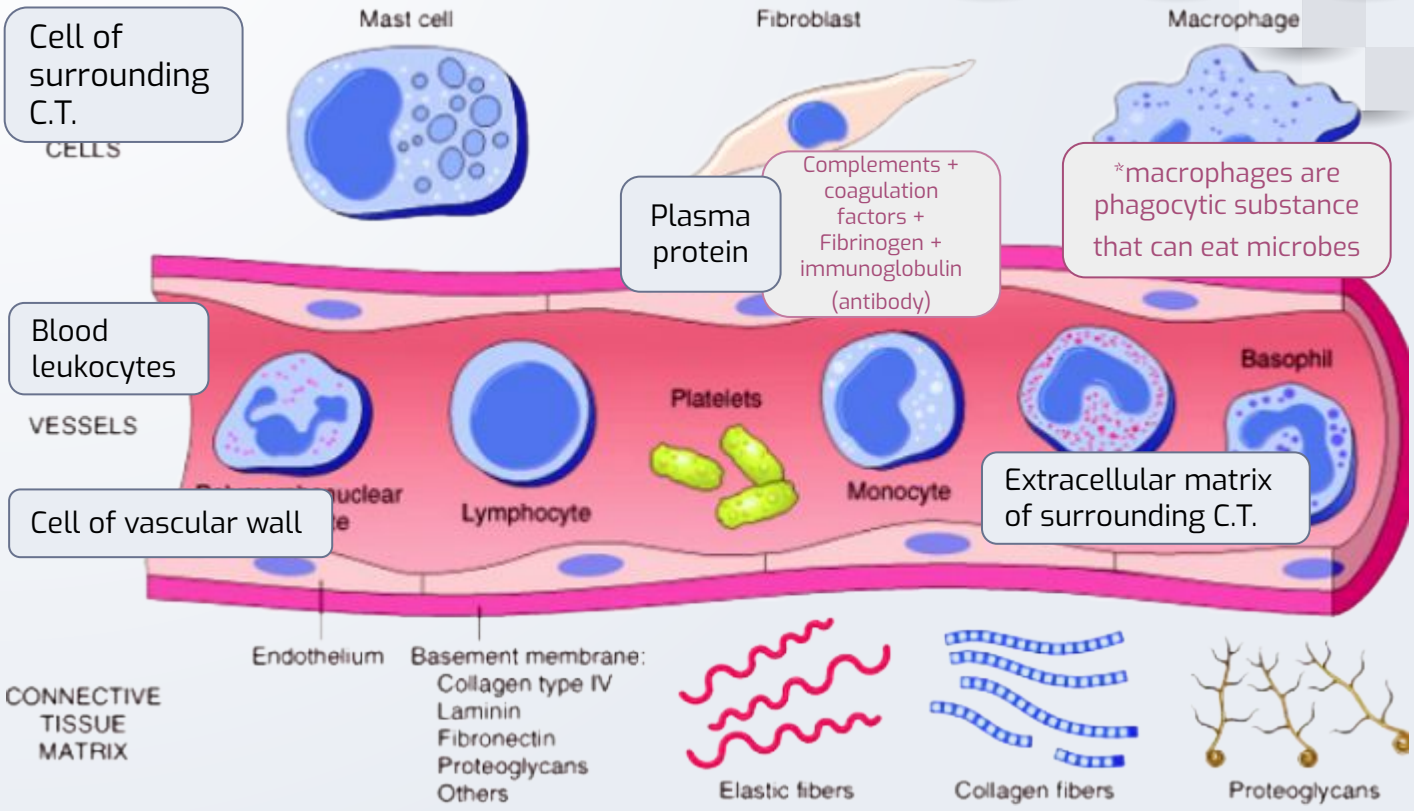
Yes, If it stays for too long (chronic) or produce exaggerated response (acute)

Disorder (Acute)	Cells and molecules involved in injury
Acute respiratory distress syndrome	**Neutrophils**, also called polymorphonuclear lymphocytes
Bronchial **Asthma**/ Bronchoconstriction	**Eosinophils**; IgE antibodies
Glomerulonephritis	**Antibodies and complement**; neutrophils, monocytes
Septic shock	**Cytokines**

Inflammation is terminated when the offending agent is eliminated and the secreted mediators are broken down or dissipated.

There are active anti-inflammation mechanisms that serve to control the response and prevent it from causing excessive damage to the host. (E.g. Enzymatic lysis of protein)

Cells & Molecules that play important roles in inflammation



Inflammation is mediated by chemical substance called <u>chemical mediators.</u>
two types:

1. **Cell derived**, also known as phagocytes and other host cell (leukocyte, Endothelium, Mast cell)
2. **Plasma protein derived**

Types of inflammation

- Acute inflammation
- Chronic inflammation

Compare between acute and chronic inflammation

Feature	Acute	Chronic
Onset	**Fast** : minutes or hour	**Slow** : days or weeks
Cellular infiltrate	**Neutrophils**	**Lymphocytes and macrophages**
Tissue injury, fibrosis	**Mild** , self limited	**Often severe and progressive**
Local & systemic signs	**Prominents**	**Less prominent** may be subtle (Body gets used to it, ongoing destruction of the body)
E.g.	**Hepatitis A** Pneumonia (acute lung inflammation)	**Hepatitis B** Tuberculosis

Acute inflammation

A rapid response to an injurious agent that serves to deliver mediators of host defense-leukocyte and plasma protein- to the site of injury.

The outcome of acute inflammation

Elimination of the noxious stimulus, followed by decline of the reaction and repair of the damaged tissue .

Or

Persistent injury resulting in chronic inflammation .

Clinical features

The 5 ancient cardinal (local) signs (external manifestation) of inflammation are:

*Both latin & english names are required

Tumor: swelling

Due to a histamine mediated increase in permeability of venules. It is released after injury causing edema

Functio laesa: loss of function

Loss of function doesn't necessarily mean complete loss. It can also mean movement constriction

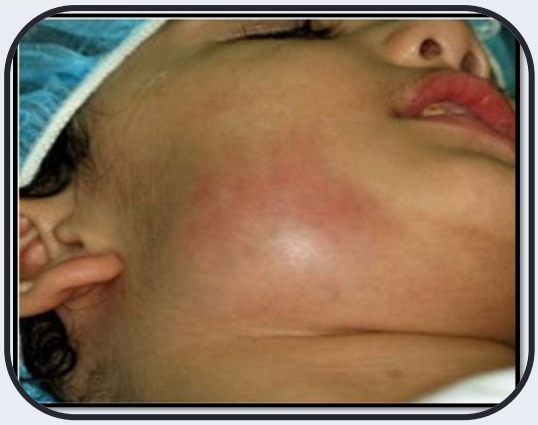
Rubor: redness

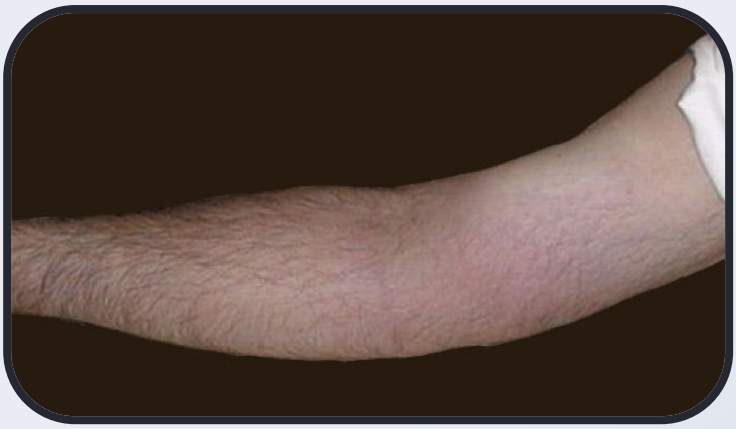
Warmth and redness are caused by the same thing, which is Due to histamine mediated vasodilation of arterioles. Causes Increase blood supply.
Due to vascular congestion caused by the increase of clotting factors

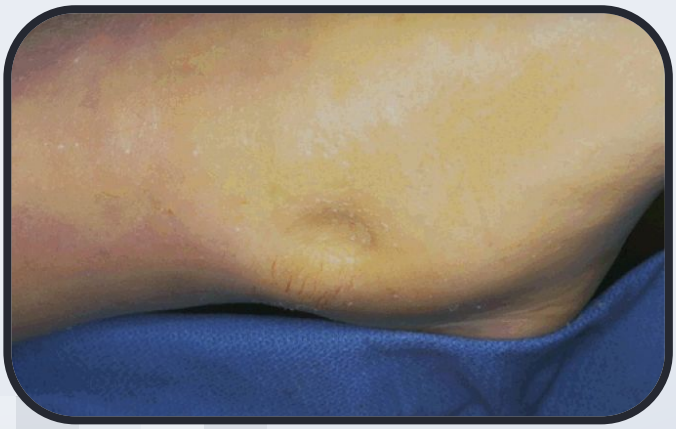
Colar: warmth/Heat

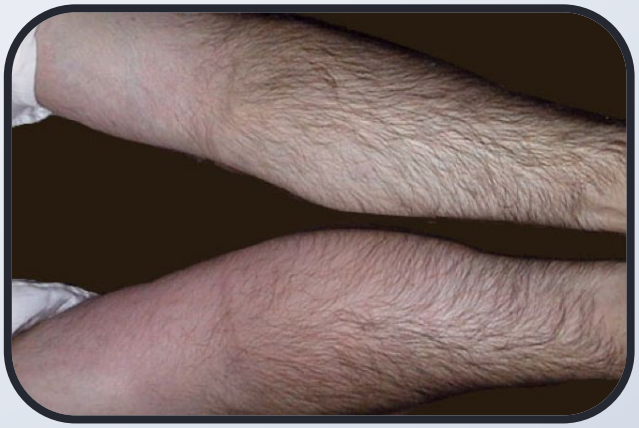
Dolor: pain

Mediated by PGE2 and bradykinin









Events of acute Inflammation

Acute inflammation has three main events:

Vascular

(1) Hemodynamic changes
alterations in vascular caliber (lumen) that lead to an increase in blood flow (vasodilation)

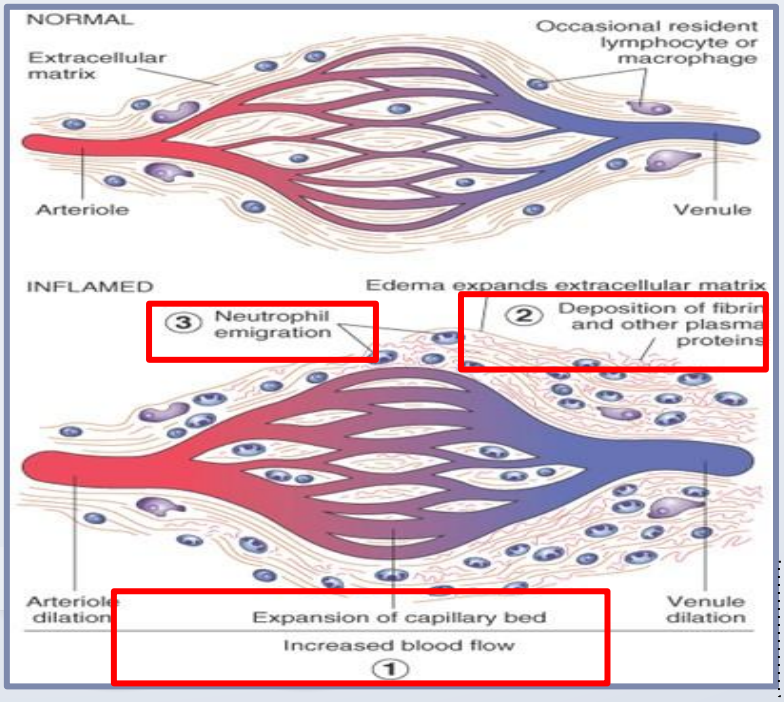
(2) Increased vascular permeability, and exudation of fluids
Structural changes in the microvasculature that permit plasma proteins and leukocytes to leave the circulation

Cellular

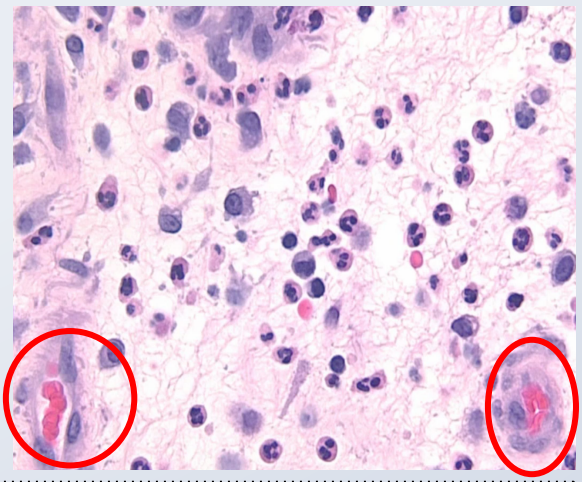
(3) Emigration of the leukocytes from the microcirculation to the site of injury
Their accumulation in the focus of injury, and their activation to eliminate the offending agent

A- Vascular Events

1. Hemodynamic changes (vasodilation*)



*Happens in capillaries (microcirculation)
Involves Change in **Diameter** of blood vessel



Hydrostatic pressure increases with vasodilation (due to more blood in vessels)

A- Vascular Events cont.

1 . Hemodynamic changes
Phases of changes in Vascular Caliber and Flow

1. **Transient vasoconstriction of arteries**
2. **Vasodilation**
3. **Slowing of the circulation** (viscosity Increases)
4. **Stasis** (blood stops at site of injury/Inflammation)

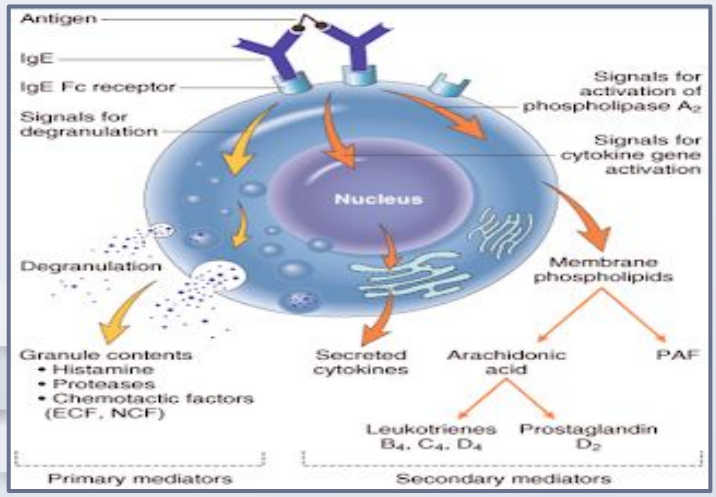
لحظي*

1. Transient* vasoconstriction of arteries

It **disappears within 3-5 seconds in mild injuries**
(Due to a neurogenic reflex that lasts only a few seconds)

2. Vasodilation

It involves the arterioles (firstly) results in **opening of new microvasculature beds in the area leading to increasing blood flow** (of capillaries, Venules and Arterioles) and **cause of redness and hotness in acute inflammation.**
Happens due to histamine effect released from mast cells (stimulated by bacterial product or IgE which leads to degranulation of Histamine carrying granules) located in interstitial tissue around the small vessels



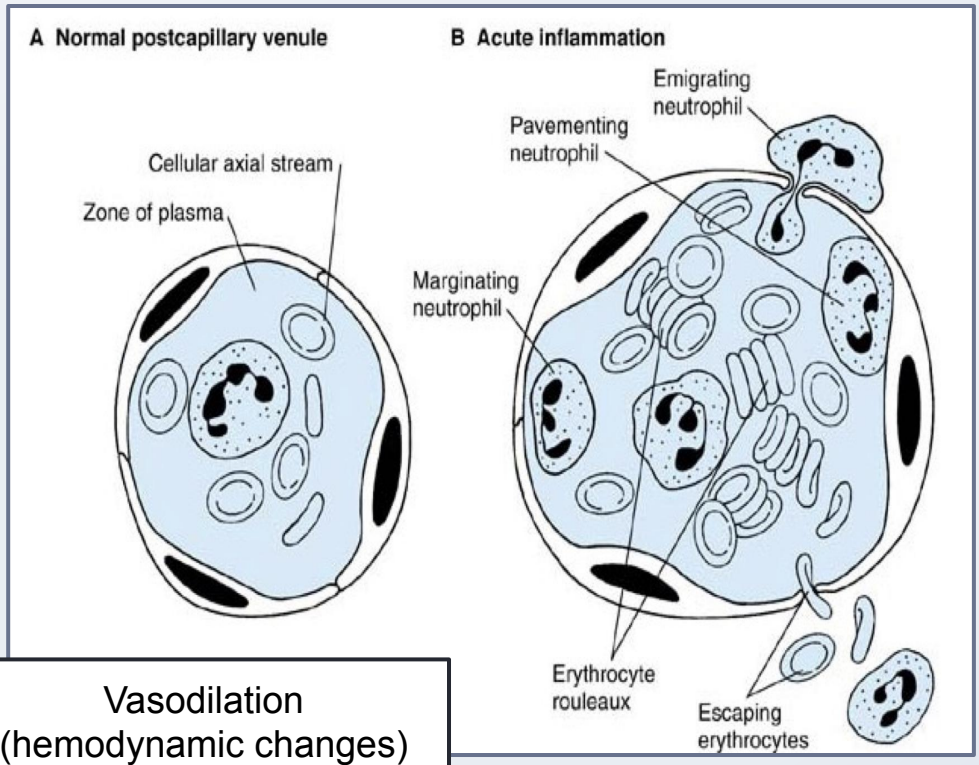
Histamine leads to relaxation of smooth muscle → vasodilation

3. Slowing of circulation

Due to increased permeability of the microvasculature, this leads to outpouring of protein-rich fluid in the extravascular tissues.

4. Stasis

Slow circulation due to dilated small vessels pucked with red cells (increased viscosity)



Vasodilation
(hemodynamic changes)

How does stasis allow <u>cellular events</u> to occur?
(<u>Cellular events:</u> getting neutrophils from blood vessels to site of Injury)
Stasis makes it easier for neutrophils in the middle of the blood vessel to move to the periphery and leave the blood vessels

A- Vascular Events cont.

2. Increased Vascular Permeability

Normally, only watery fluid leaves the blood vessels, but with increased permeability proteins leave too

A hallmark of acute inflammation (**escape of a protein-rich fluid**).
Induced by histamine, kinins, and other mediators.

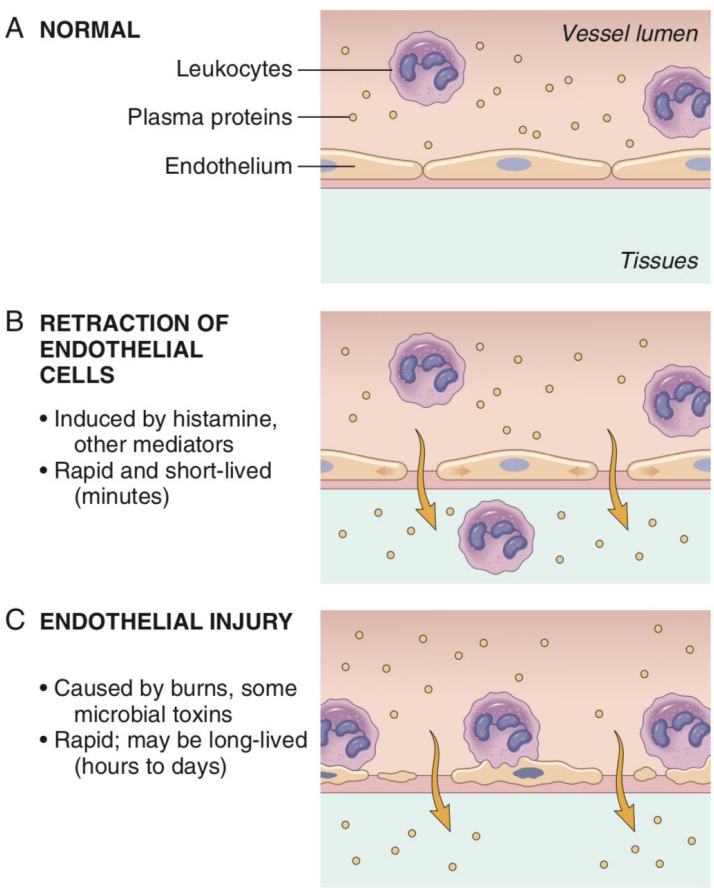
It affects small & medium size <u>venules</u> (unlike hemodynamic which affects arterioles), through gaps between endothelial cells.

It **results in swelling (tumor)** which occurs as a cardinal sign of inflammation.

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

Venules

Arterioles, capillaries and venules



A- Vascular Events Summary

Phases of acute inflammation in vascular caliber

(1) **Vasoconstriction (important)**:

occurs when there's a **cell injury or antigen**. It's temporary and will disappear within 3-5 Seconds

(2) **Vasodilation**:

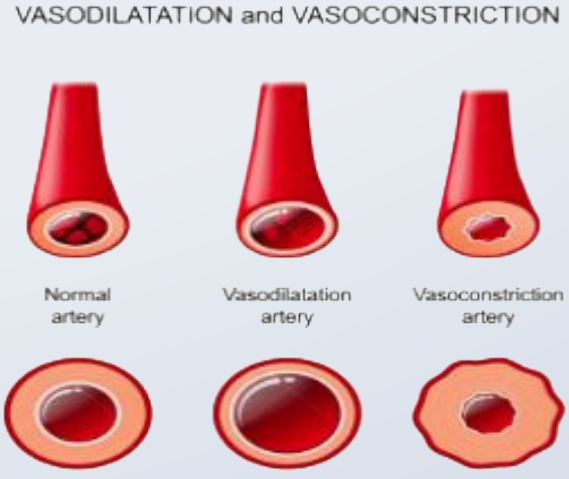
caused by **histamine and serotonin** when the lumen increases (blood vessel diameter increases)

Side note: vasodilation and vasodilatation are the same thing

(3) **Increase in vascular permeability**:

caused by

- Chemical mediators of inflammation, which are **histamine and serotonin**
- **Destruction of blood vessel**, caused by inflammation



What is the edema?

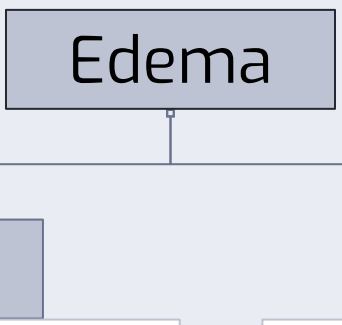
denotes an excess of fluid in the interstitial or serous cavities.

it can be either an **exudate** or a **transudate**

Main difference between them is protein concentration.
Protein content leaks more in inflammation i.e. EXUDATE

Edema is defined as an excess of fluid in the interstitial space.

What is the difference between transudates and exudates?



Transudate

is a fluid with low protein content and a **specific gravity of less than 1.012**

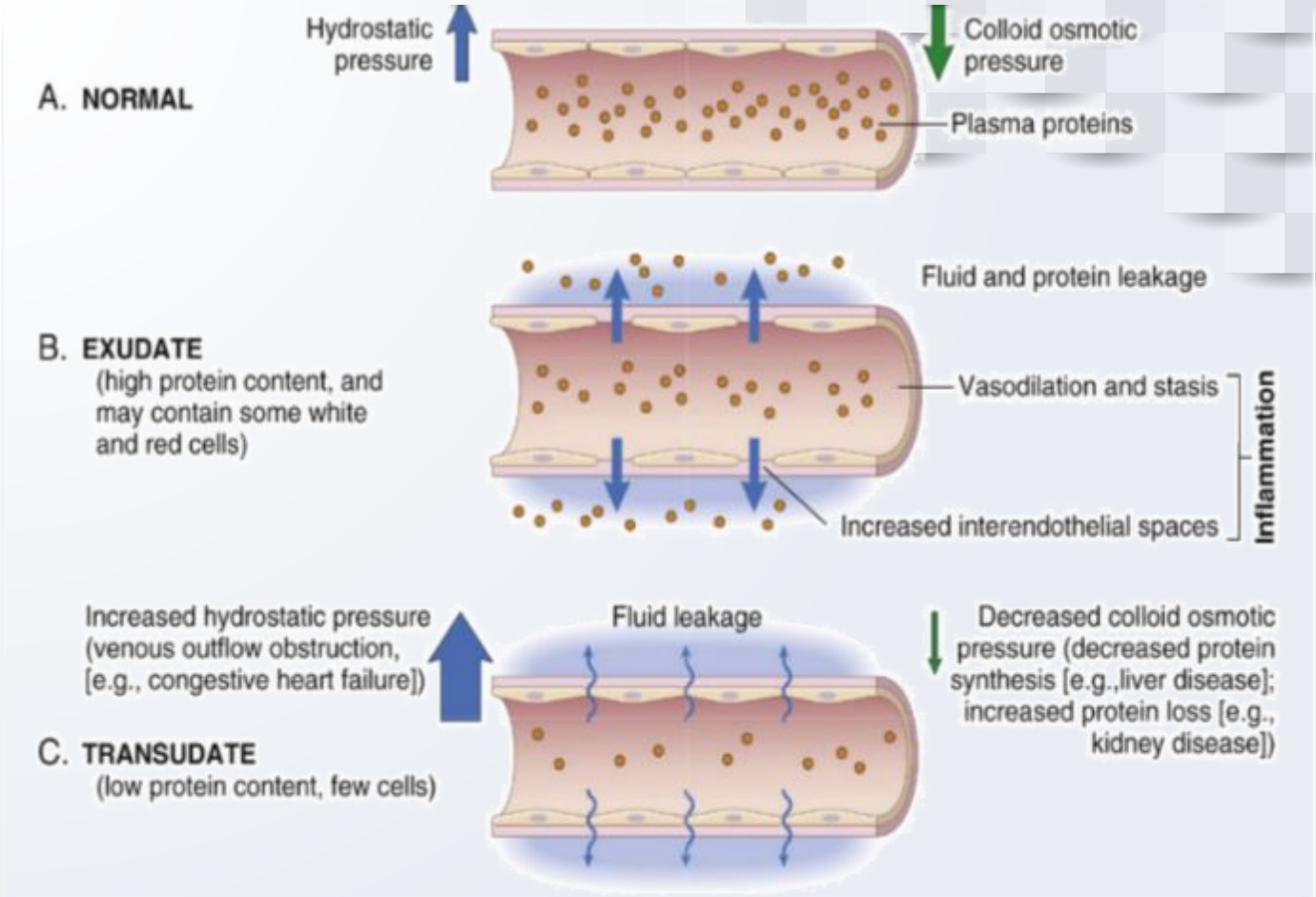
It is **essentially an ultrafiltrate of blood plasma** that results from osmotic or hydrostatic imbalance across the vessel wall.

without an increase in vascular permeability.

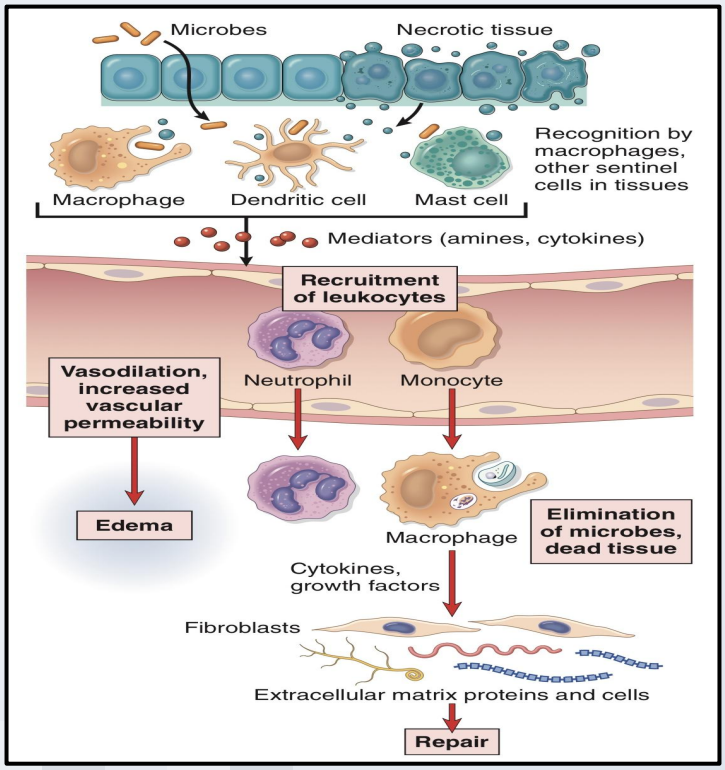
Exudate

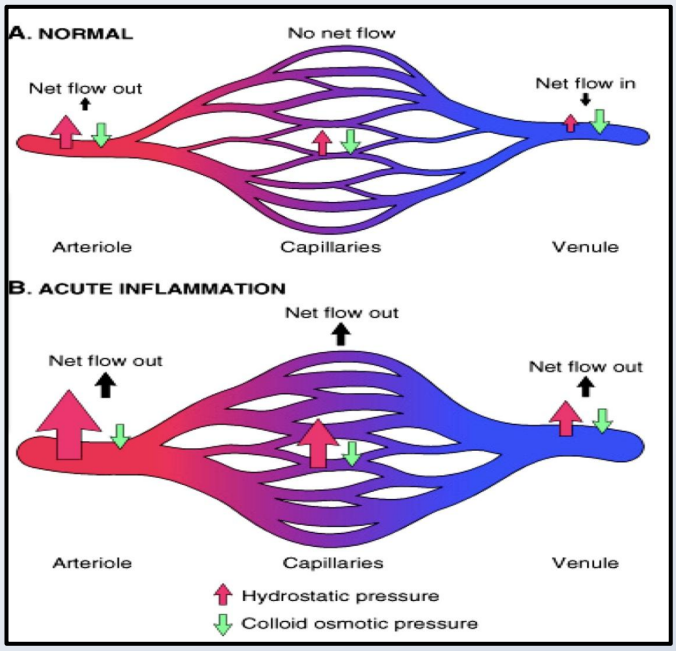
An inflammatory extravascular fluid that has **a high protein concentration**, cellular debris, and a **specific gravity above 1.020**

It **implies significant alteration in the normal permeability** of small blood vessels in the area of injury.
*localized in site of injury



Increased blood volume leads to increased local hydrostatic pressure leading to transudation of protein-poor fluid into the extravascular space.





Acute Inflammation

B- Cellular events

- A critical function of inflammation is to deliver leukocytes to the site of injury. *(LEUKOCYTE EXTRAVASATION)*
- And to activate the leukocytes to perform their normal functions in host defense.

Leukocytes Function:

- Ingest offending agents.
- Kill bacteria and other microbes.
- Get rid of necrotic tissue and foreign substances.

They may induce tissue damage and prolong inflammation, since the leukocyte products that destroy microbes and necrotic tissues can also injure normal host tissues.

the steps involved in extravasation of leukocytes from the blood to the tissues

1. Recruitment of leukocytes

A multistep process involving attachment of circulating leukocytes to endothelial cells and their migration through the endothelium *(extravasation)*

3 Steps :

1- In the lumen:

I. Margination

II. rolling

iii. adhesion to endothelium

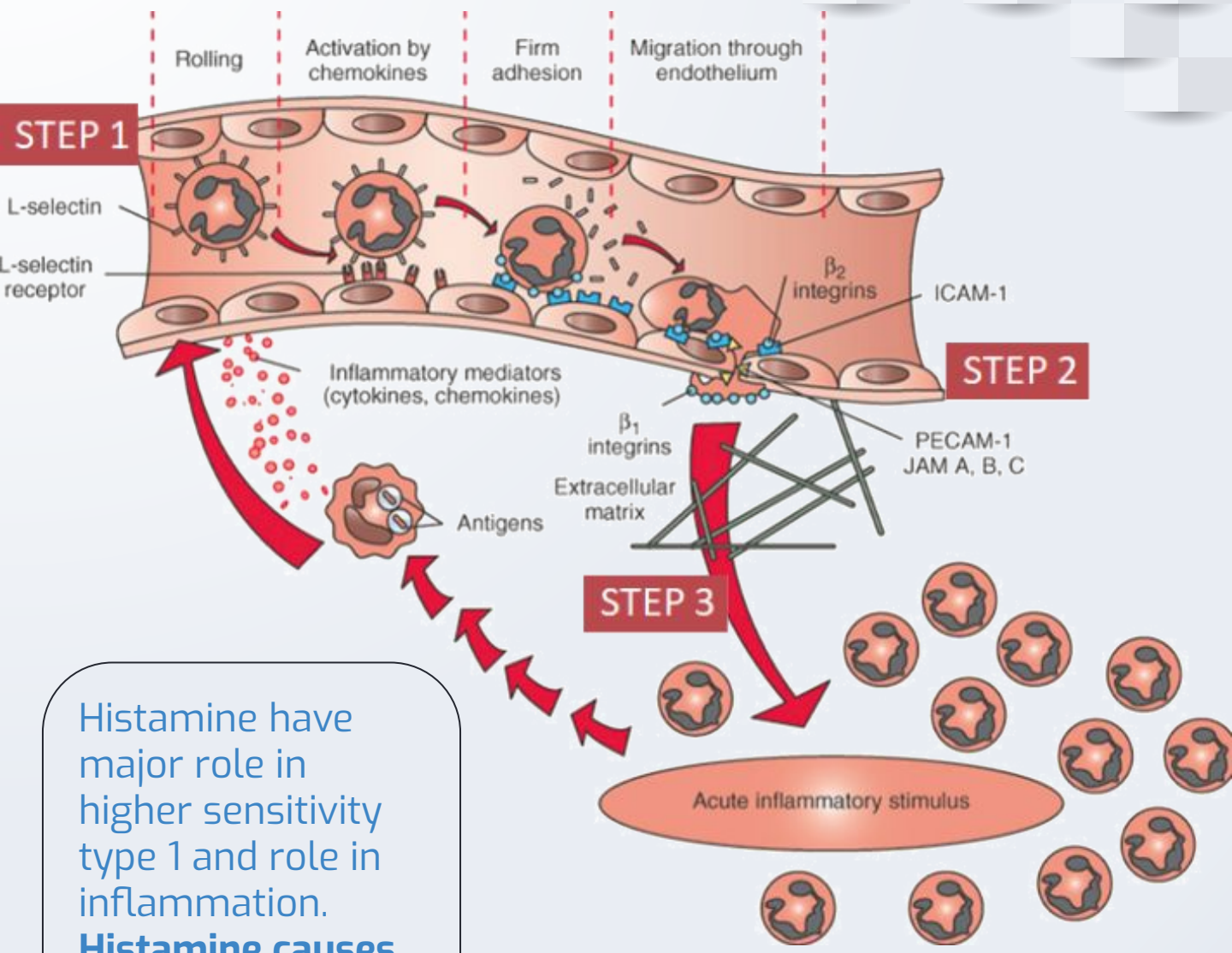
Vascular endothelium normally does not bind circulating cells

2- Transmigration across the endothelium (also called **diapedesis**)

3- Migration in interstitial tissues toward a chemotactic stimulus (injurious agent)

2. Removal of offending agents

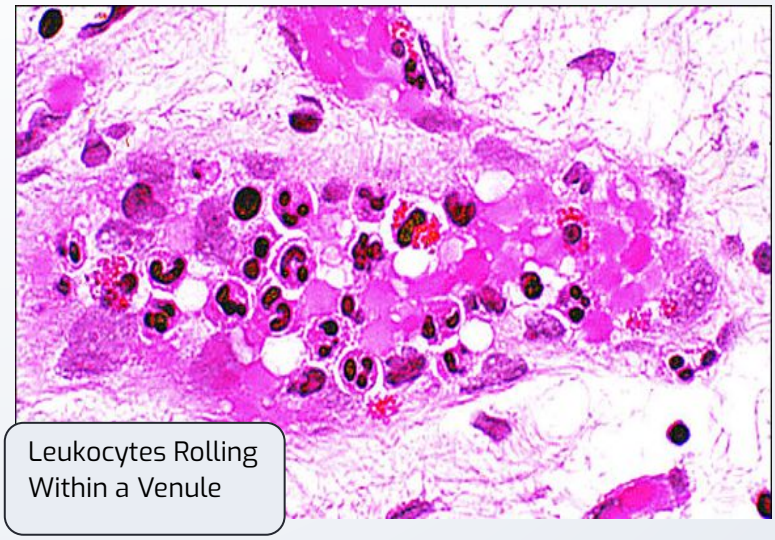
Recruitment of leukocytes



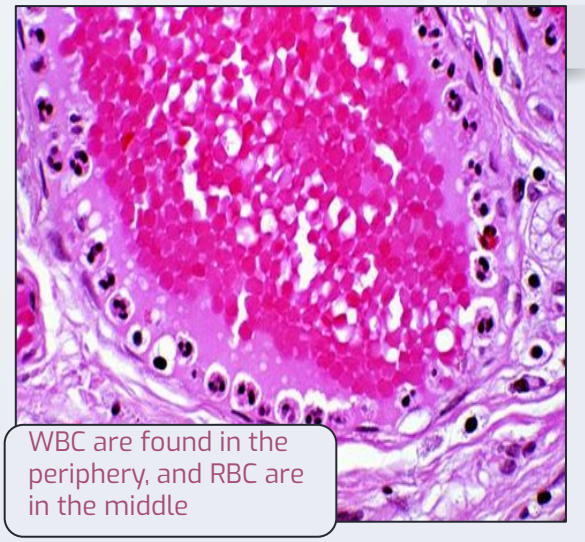
Histamine have major role in higher sensitivity type 1 and role in inflammation. **Histamine causes vasodilation and increase vascular permeability.**

Resident tissue **macrophages**, **mast cells**, and **endothelial cells** respond to injury by secreting the cytokines TNF, IL-1, histamine and chemokines: small proteins which stimulate movement of neutrophils
These substances induce changes in blood vessel walls

Recruitment of leukocytes



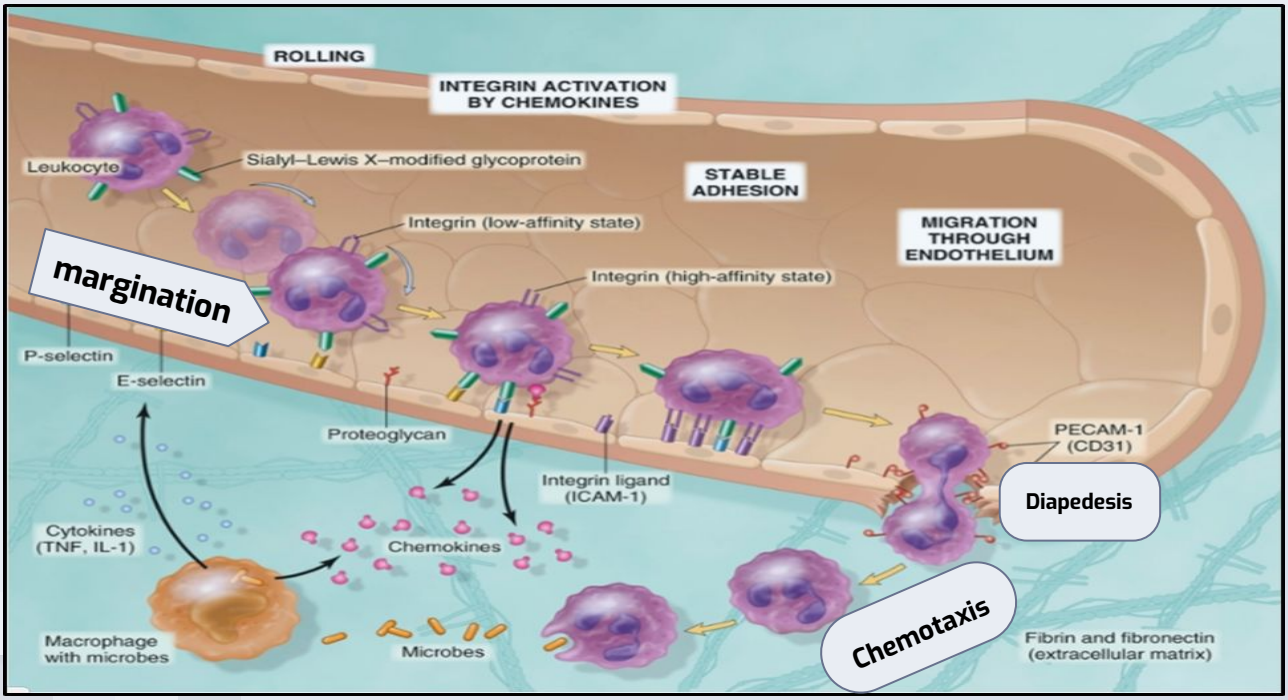
Leukocytes Rolling Within a Venule



WBC are found in the periphery, and RBC are in the middle

Margination

- Because blood flow slows early in inflammation (stasis), the **endothelium can be lined by neutrophils** (**pavementation**)
- **Margination is the first step of leukocytes** action during acute inflammation cells
- The goal is for neutrophils to move to the margin



Adhesion Molecules and Receptors

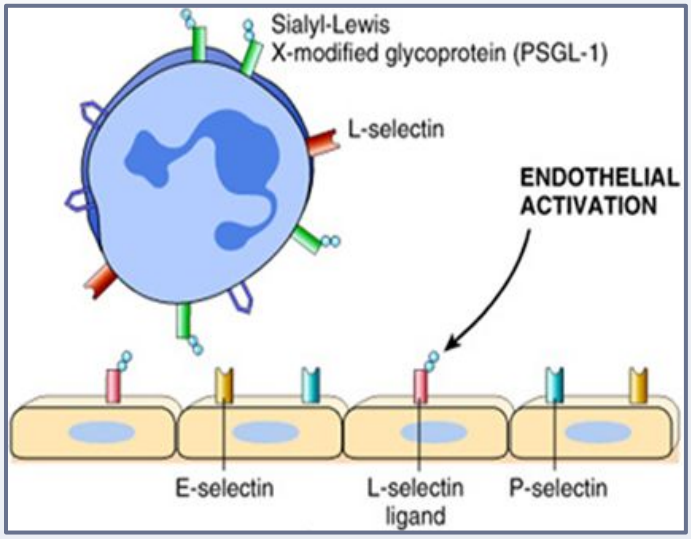
01

Selectins (carbohydrate-binding adhesion molecules) consist of:

E-selectin: confined to endothelium induced by TNF & IL-1

P-selectin: present in endothelium and platelets from Weibel-Palade bodies

L-selectin: expressed on most leukocyte and endothelium



E-selectin & P-selectin **bind to Sialyl-Lewis X glycoprotein** and slow the leukocytes

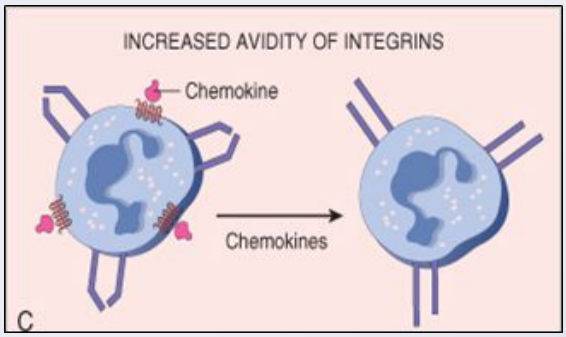
Selectin plays a major role for adhesion

cytokines TNF, IL-1, histamine and chemokines which **stimulate selectin**

Integrins:

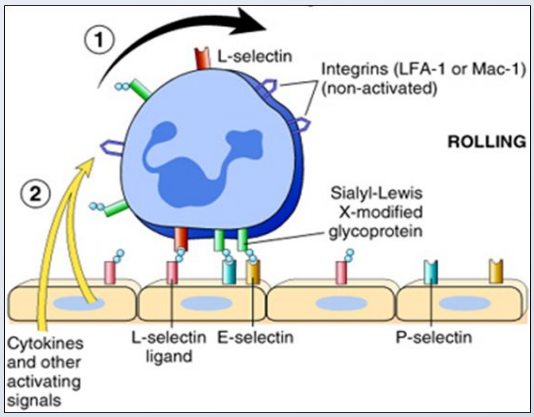
02

An adhesion molecule which is seen mainly located on leukocytes and activated during acute inflammation



·**made up of α and β glycoproteins chains**, expressed on leukocytes and bind to ligands on endothelial cells

· Integrins are up regulated on leukocytes by **C5a & LTB4** resulting in firm adhesion with vessel wall



Adhesion Molecules and Receptors

cause abnormality in inflammation, therefore more severe inflammation

Leukocyte Adhesion Deficiency (LAD) Two types:

–**LAD type 2** is mutations in fucosyl transferase **required for synthesis of sialylated oligosaccharide** (found on surface of leukocytes)

–**LAD type 1** is a deficiency of β_2-integrin

These normally binds **selectins**.

Clinical findings:

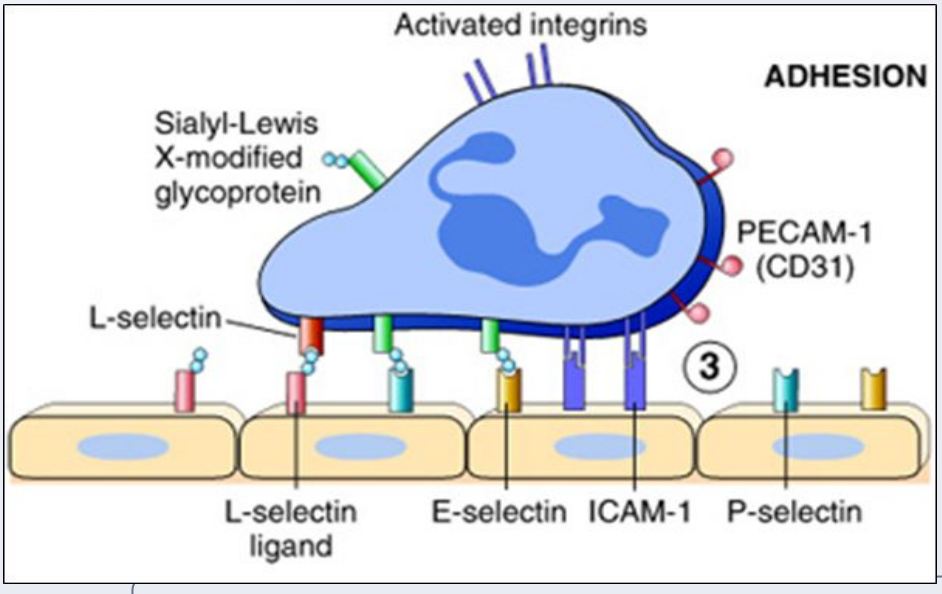
- **Delayed separation of umbilical cord** (depends on lysosomal enzymes released from neutrophils).
- **Increased circulating neutrophils** (leukocytosis due to loss of the marinating pool).
- **Recurrent bacterial infection** that lack pus formation and poor wound healing.

Adhesion Molecules and Receptors

03

The *immunoglobulin family* molecules:

- **ICAM-1** (intercellular adhesion molecule 1)
- **VCAM-1** (vascular cell adhesion molecule 1)



adhesion to endothelium

IL-1 and TNF activate intercellular adhesion molecule (**ICAM**) and vascular cell adhesion molecule (**VCAM**) **on venular endothelial cells.**

Adhesion Molecules and Receptors

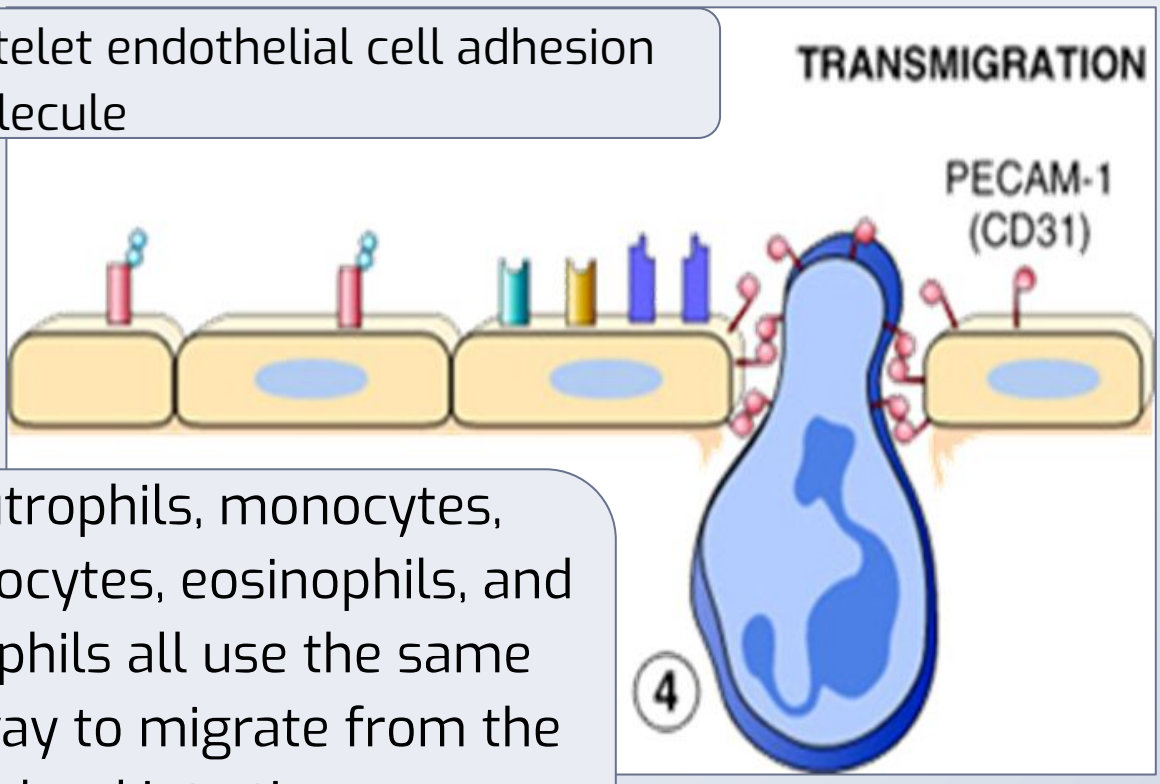
04

Mucin-like glycoproteins: **PECAM-1**

these glycoproteins are found in the extracellular matrix and on cell surfaces

Neutrophils moving along the venular endothelium dissolve the venular basement membrane (**release type IV collagenase**) exposed by previous histamine-mediated endothelial cell contraction and enter the interstitial tissue.

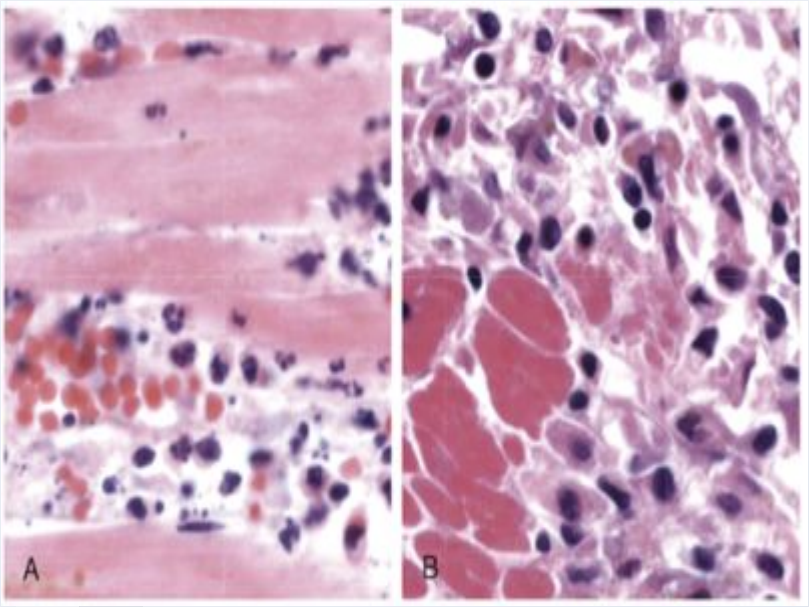
Platelet endothelial cell adhesion molecule

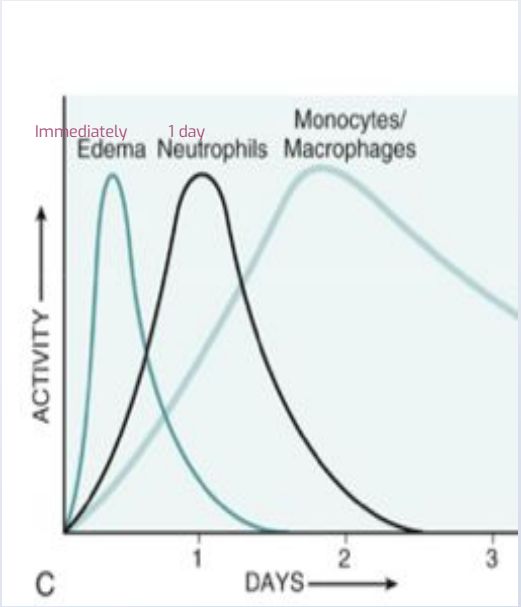


Neutrophils, monocytes, lymphocytes, eosinophils, and basophils all use the same pathway to migrate from the blood into tissues

Leukocyte Adhesion and Transmigration

- Migration of leukocytes through the endothelium is called: **Transmigration** or **Diapedesis**
- Diapedesis occurs predominantly in the post capillary **venules** (stasis & increased permeability)
- The type of emigration of leukocyte **varies with the age of the inflammatory response**
- In most of acute inflammation: **neutrophils** (first responder) **predominate in the inflammatory** infiltrate during the first 6 to 24 hours, **then are replaced by monocytes** (turn to macrophages in tissue) in 24 to 48 hours





Leukocyte Adhesion and Transmigration

Neutrophils are more numerous in the blood,they **respond more rapidly to chemokines**

but are **short-lived**; they undergo apoptosis and disappear after (24 to 48 hours), whereas **monocytes survive longer.**

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 tissue	**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**

HSC: Hematopoietic stem cells

Leukocyte Adhesion and Transmigration

Bacterial infection (Pyogenic) → neutrophils are predominant

The type of emigrating leukocyte varies with the type of stimulus:

In **viral infections**, lymphocytes may be the first cells to arrive

In some **hypersensitivity reactions** and **parasitic infection**, eosinophil may be the main cell type

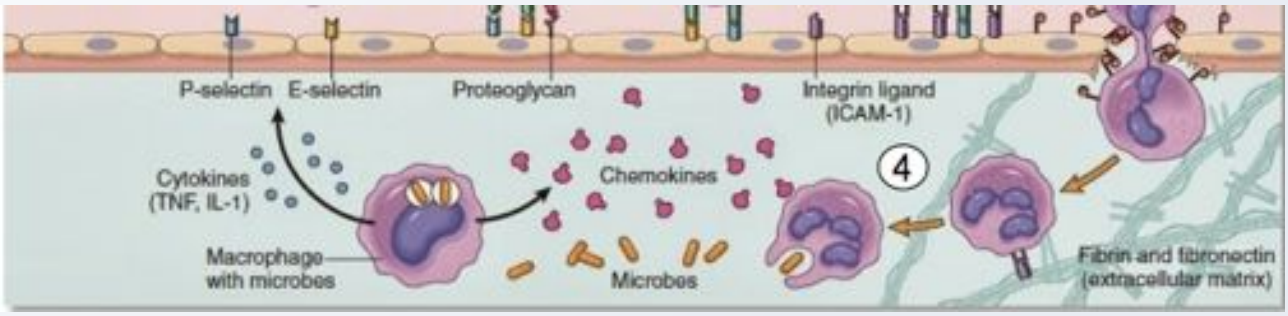
Chronic inflammation: lymphocytes, plasma cells and macrophages are present

Chemotaxis

- After extravasation, leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis, defined as **locomotion oriented along a chemical gradient** (of substances produced at site of injury).

Chemoattraction

Neutrophils are attracted by **bacterial products, IL-8, C5a & LTB4**

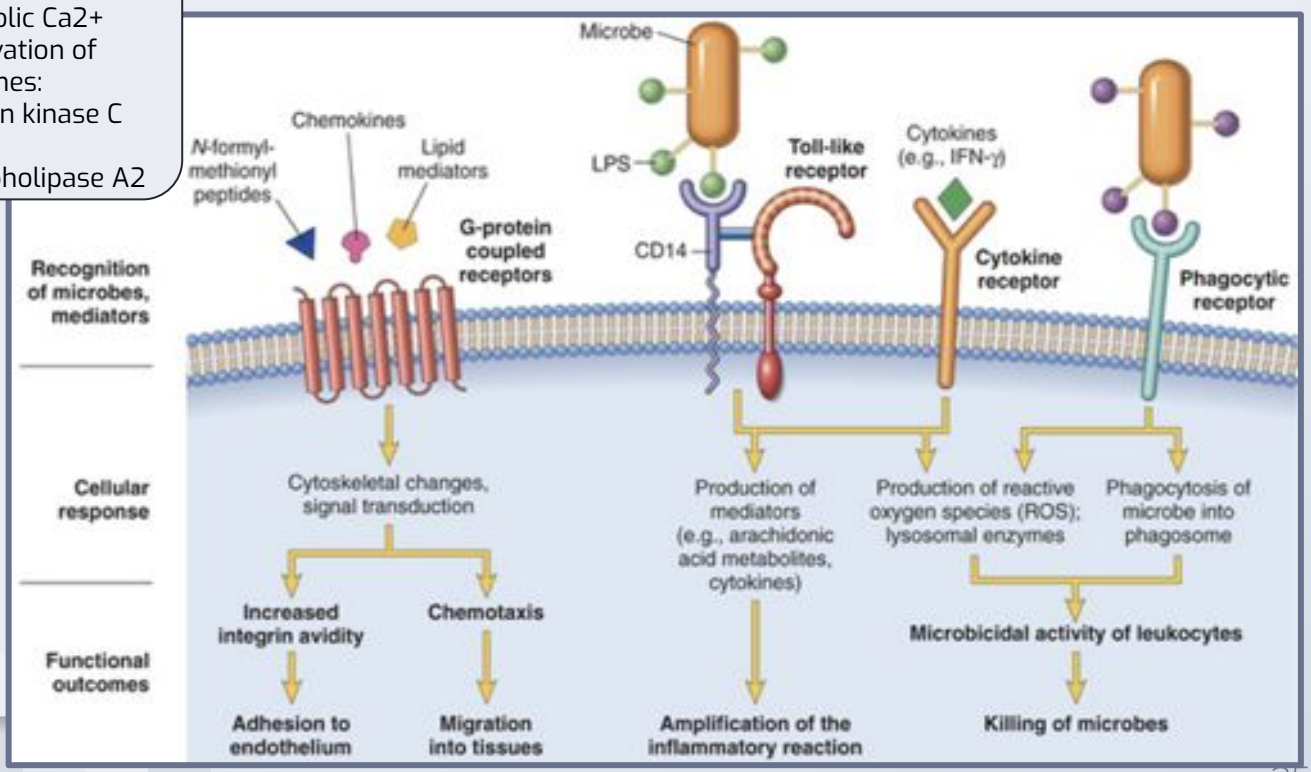


Chemokines act on the adherent leukocytes and stimulate the cells to migrate toward the site of injury or infection

All these chemotactic agents bind to specific seven-transmembrane G-protein-coupled receptors on the surface of leukocytes

- Increase in cytosolic Ca2+
- Activation of enzymes: Protein kinase C and phospholipase A2

المهم تعرفون من الصورة ان في انواع للمستقبلات فقط



Leukocyte Activation

1. **Phagocytosis**
2. **Intracellular destruction**
3. **Liberation of substances that destroy extracellular microbes and dead tissues**
4. **Production of mediators**

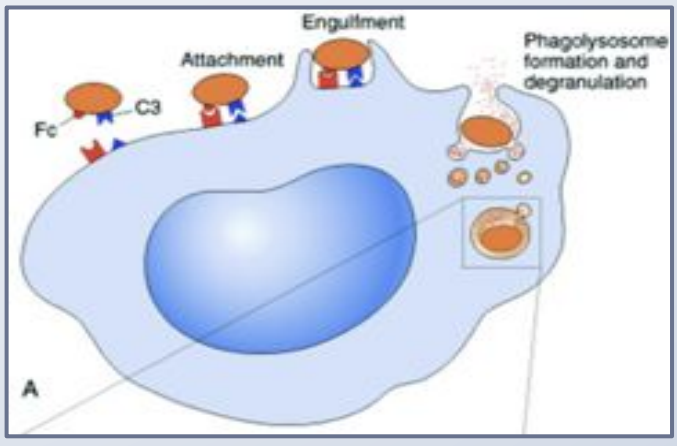
Phagocytosis

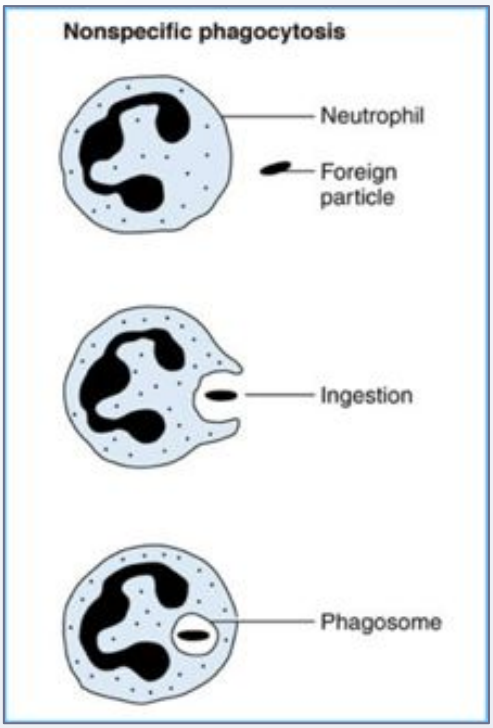
Phagocytosis involves three distinct but interrelated steps

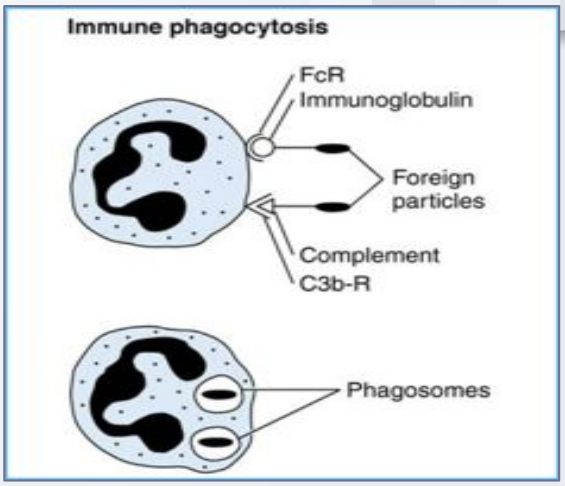
(1) **Recognition and Attachment** of the particle to be ingested by the leukocyte

(2) its **Engulfment**, with subsequent formation of a phagocytic vacuole

(3) **killing or Degradation** of the ingested material.







Immune phagocytosis is much more efficient than non specific phagocytosis
(Stronger + rapid at detection & engulfment)

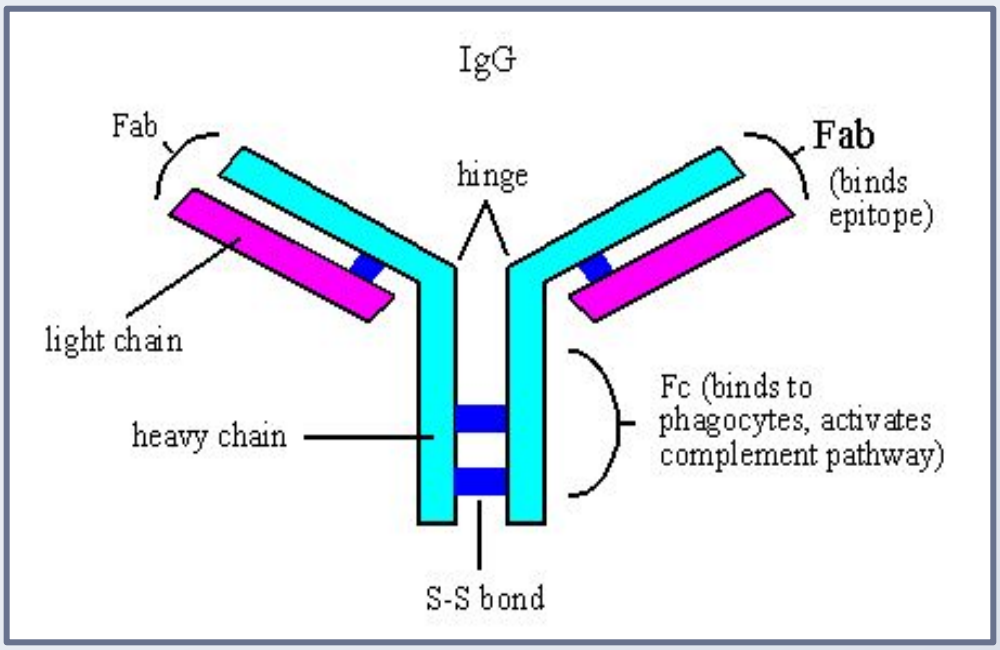
Leukocyte Activation

1. Recognition and Attachment (Opsonization)

- Is the process of coating a particle, such as a microbe, to target it for phagocytosis
- The substances that do this are opsonins.

1. Recognition and Attachment (Opsonization) (cont.)

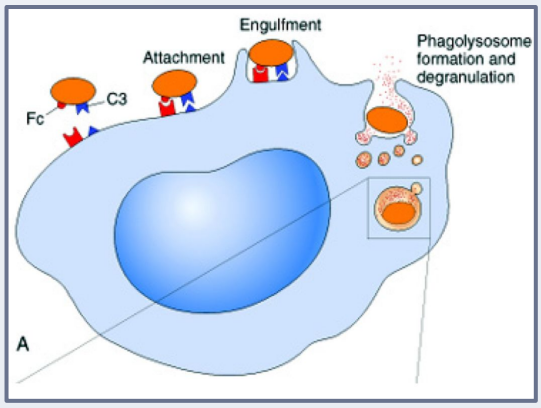
- These substances include:
  – **antibodies** (IgG)
  – **complement proteins** (**C3b**)
  – And others: **lectins** (mannose-binding lectin (MBL), **collectins**, **fibronectin**, **fibrinogen**, and **C-reactive protein**
- These can coat microbes and are recognized by receptors on phagocytes (Fc and C3b receptors).

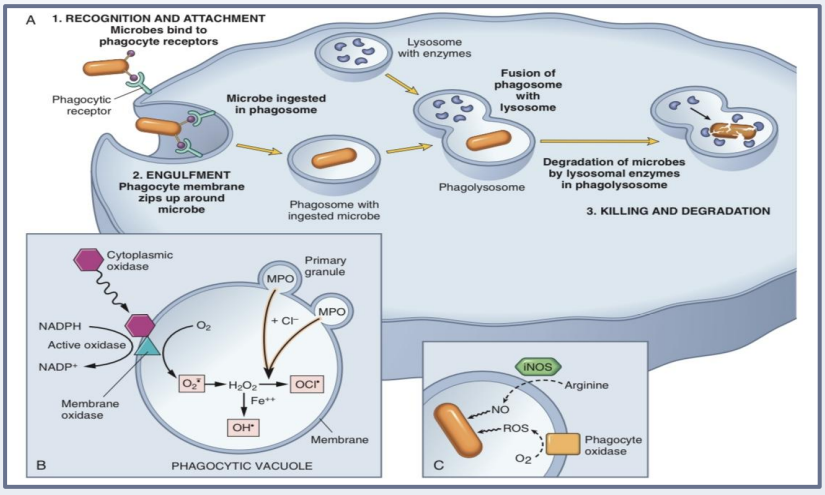


2. Engulfment

During engulfment, extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed, eventually resulting in complete enclosure of the particle within a **phagosome**.

The phagocytic vacuole then fuses with a lysosomal granule, resulting in **phagolysosome**





Defects in leukocyte function:

Protein involved in organelle membrane fusion (**no phagolysosome**)

- **protein trafficking defect**(microtubule defect).

-**Autosomal recessive**.

Chédiak-Higashi syndrome

Clinical features:

-**increased risk of pyogenic infection** (pus producing bacteria)

-**Neutropenia**(defect in generation from BM

-**Giant granule formation** (granules formed can't move in cytoplasm)

-**Defective primary hemostasis** (platelet granules are not secreted)

-**Albinism**

-**peripheral neuropathy**

Phagocytosis: Killing and Degradation

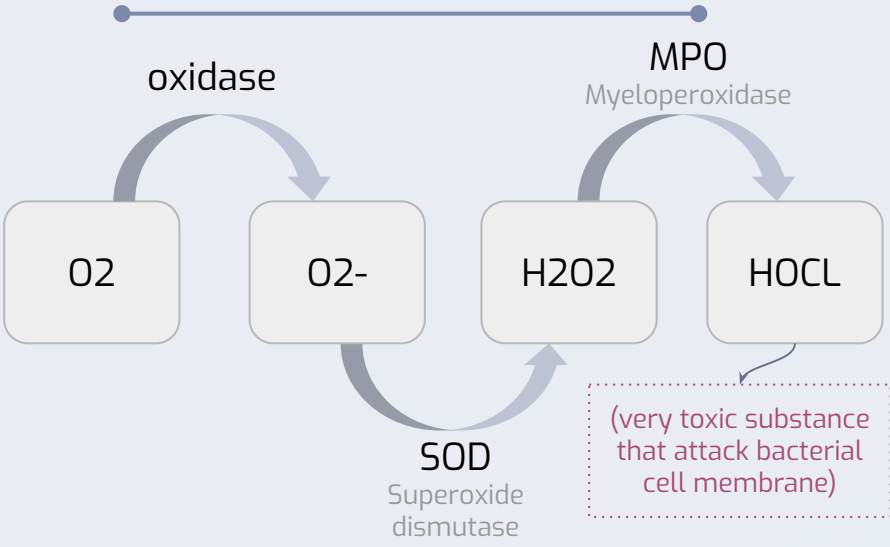
There are 2 mechanisms for Microbial killing:.

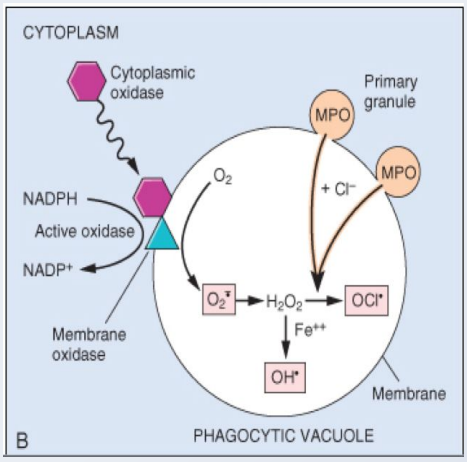
3. Microbial Killing

- Oxygen-independent mechanisms
- Oxygen-dependent mechanisms

1. Oxygen-Dependent Mechanisms

The H2O2-MPO-halide system is the most efficient bactericidal system in neutrophils.





Chronic granulomatous disease:
Decreased oxidative burst.
it has 2 types: (discussed in the next slide)

ما ركزت عليها الدكتورة

Chronic granulomatous disease

X-linked: **NADPH oxidase** (membrane component)

Autosomal recessive

- **NADPH oxidase** (cytoplasmic components)
- **Myeloperoxidase deficiency:** (absent MPO-H2O2 system) pt. have increased risk of candida infection.

Infection and granuloma formation with catalase positive organisms e.g. S aureus, Nocardia and Aspergillus.

2. Oxygen-independent mechanisms

through the action of substances in leukocyte granules. These include:

- **Defensins**
- **Bactericidal permeability increasing protein (BPI)**
  - · Can potentiate further inflammation by damaging tissues.
  - ·These harmful proteases are **controlled by a system of anti proteases in the serum**.
- **Lysozyme**
- **Lactoferrin**
- **Major basic protein**

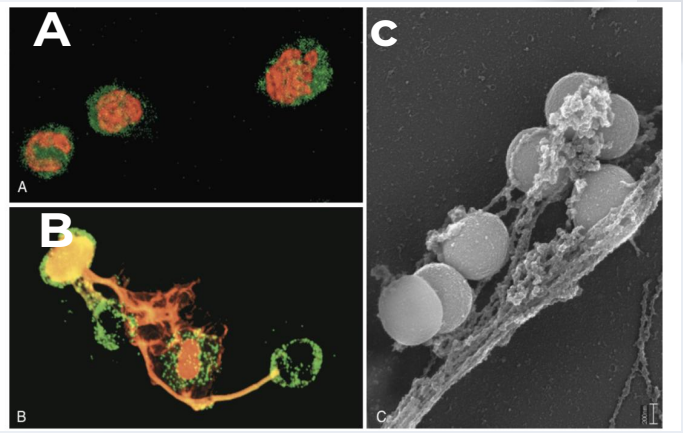
Neutrophil granules contain other enzymes, such as elastase, that also **contribute to microbial killing**

Neutrophil extracellular traps (NETs)

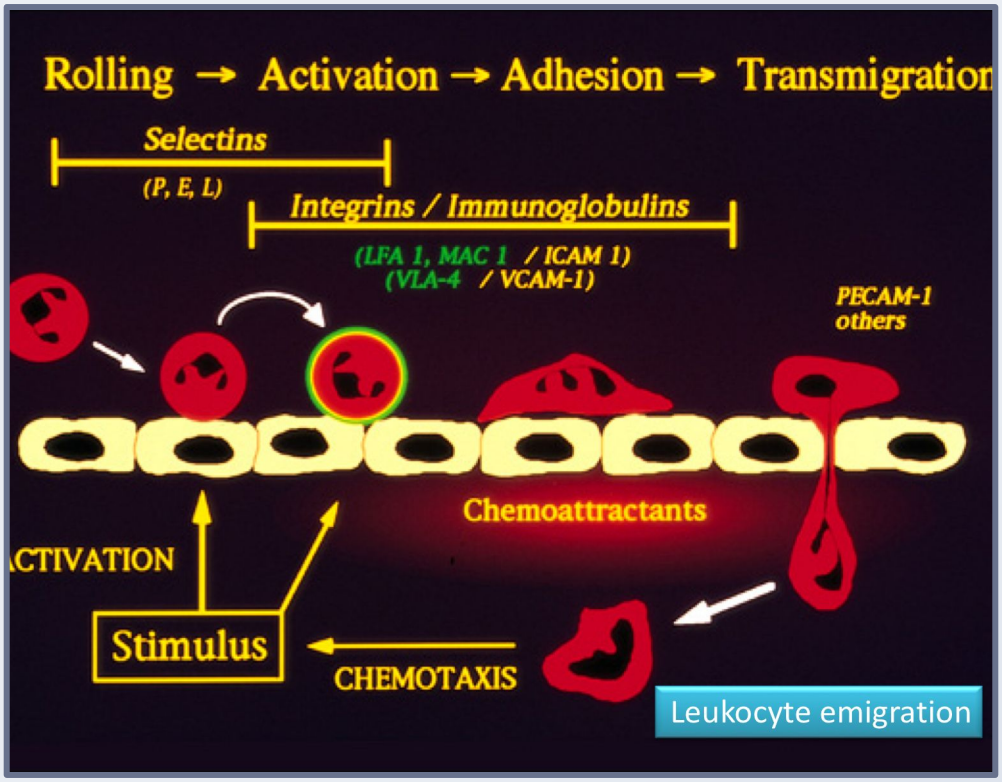
A: Healthy neutrophils with nuclei stained red and cytoplasm green.

B: Release of nuclear material (to trap bacteria) from neutrophils (note that two have lost their nuclei), forming extracellular traps.

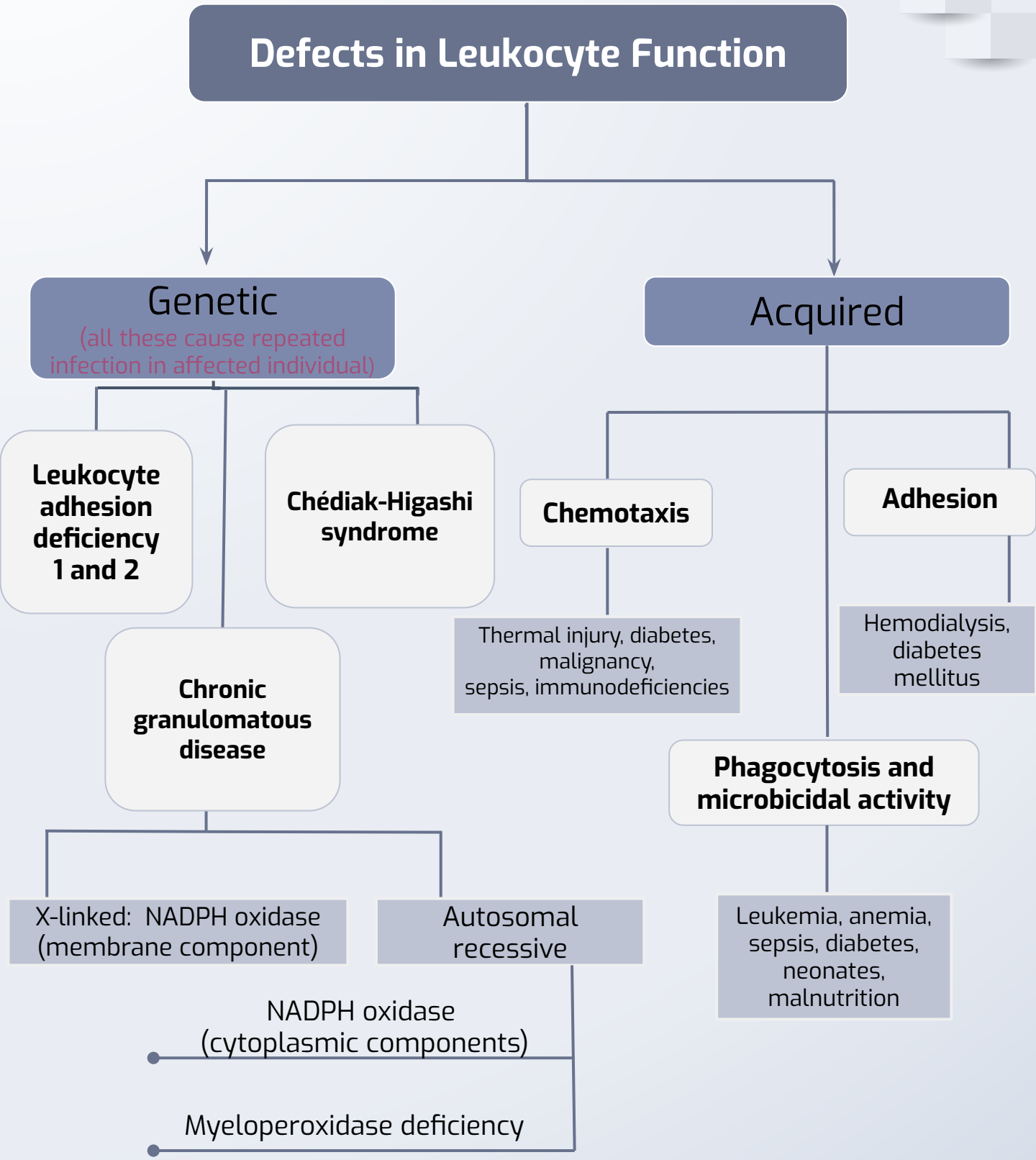
C: An electron micrograph of bacteria (staphylococci) trapped in NETs.



NETs provide an additional mechanism of killing microbes that does not involve phagocytosis



Defects in Leukocyte Function



MCQs

1-Which of the following is a chronic inflammation?			
a- Hepatitis A	b- Hepatitis B	c- Tuberculosis	d- B and C
2-What type of cells are found in acute inflammation			
a- Neutrophils	b- Plasma cells	c- Lymphocytes	d- All of the above
3-Which of the following local/cardinal signs match together?			
a- redness-calor	b- swelling-rubor	c- pain-dolor	d- warmth-tumor
4-Increased vascular permeability results in which of the following ?			
a-rubor	b-calor	C-dolor	d-tumor
5-What is the type of WBC usually found in bronchial asthma ?			
a-Basophil	b-Neutrophil	C-Small lymphocyte	d-Eosinophil
6-excess of high protein fluid in the interstitial space is called			
a-exudate	b-ultra filtration of the plasma	C-rubor	d-transudate

SAQs

1- what is the mechanism (steps) of inflammation?

2- why are leukocytes and plasma proteins activated?

3- what is the aim of inflammation?

1- slide 2
2- to destroy and eliminated offending substance
3- slide 2

MCQs

1- The type of emigrating leukocytes in chronic inflammation?			
A) lymphocytes	B) eosinophil	C) macrophages	D) A & C
2- which of the following is NOT involved in the oxygen-independent mechanism?			
A) lactoferrin	B) MPO	C) defensins	D) bactericidal permeability increasing protein
3- which of the following is an Acquired defect in leukocytes function			
A) Leukocyte adhesion deficiency 1 and 2	B) Chemotaxis	C)Chédiak-Higashi syndrome	D) chronic granulomatous disease
4- In margination neutrophils go to?			
A) Center	B) Margin	C) injured tissue	D) blood stream
5- The first step of leukocytes action during acute inflammation is?			
A) Adhesion	B) Chemotaxis	C) Margination	D) Diapedesis
6- Integrins are up regulated by?			
A) C5a	B) LTB4	C) A & B	D) None

SAQs

1- list three examples of chemoattractant.

2- name the substances that cause opsonization.

3- what are Chédiak-Higashi syndrome clinical features.

4- Integrins made up of.

5- Selectin plays major role in.

6- LAD type 1 is a deficiency of.

1- slide 25
2- slide 28
3- slide 29
4-slide 18
5-slide 18
6-slide 19

- غادة العثمان
- البندري العنزي
- بنان القاضي
- رغد خالد سويعد
- رغد العسيري
- روان باقادر
- ريناد الحميدي
- سارة العبيد
- سارة القحطاني
- ساره المقاطي
- سديم آل زايد
- سمو عبدالرحمن
- شذى الدوسري
- شعاع خضري
- غادة العبدي
- غيداء العسيري
- غيداء المرشود
- فاطمة المعيذر
- فرح السيد
- منال التويم
- مها فهد
- نورة بامرعي

- ماجد العسكر
- هادي الحمصي
- أحمد الخواشكي
- بدر الريس
- حمد الربيعه
- حمود القاضب
- سالم الشهري
- عبد العزيز الكريدا
- عبد اللطيف الشريمي
- فراس القايدي
- فيصل الفضل
- يزيد القحطاني
- أسامة العقل
- بندر الحربي
- حمد الموسى
- سعد الدحيم
- عبد الرحمن الروقي
- عبد الرحمن المبكي
- عبد العزيز العمري
- علي الماطري
- محمد السنيدي
- محمد السياري
- محمد القهيدان
- محمد الوهيبي
- مشعل الثنيان
- نايف آل الشيخ

للتواصل والإقتراحات:
pathology439@gmail.com

Editing File

Helpful videos:

[Arabic video - Inflammation full]
[Arabic video - Cellular phase]
[Dr. Najeeb - Vascular events]
[Inflammation Playlist]
[شرح طالبة]