الرجوع للعمل وحده لا يغني عن الرجوع للمصادر الأساسية

PATHOLOGY
TEAM 436

# Inflammation

**Objectives:**

A) **Be able to identify the cardinal and systemic signs of inflammation and to understand the underlying mechanisms that produce these signs.**
B) **Understands the vascular changes occurring as a response to tissue injury.**
C) **Appreciate the importance of fluid production in inflammation including the difference between exudates and transudates.**
D) **Have some understanding of various chemical mediators of inflammation and their link with the complement system and potentially with coagulation factors.**
E) **Have good knowledge about the types and functions of various inflammatory cells including their role in both acute and chronic inflammation.**
F) **Be aware of the various complication of the inflammatory response, formation of pus and the production and manifestation of chronic inflammation.**
G) **Understands the concept of healing and repair with wounds healing by first and second intention as an example.**
H) **Knows the factors leading to poor healing and inadequate tissue repair.**

Definitions: blue

Examples: green

Doctor's note: red

Extra explanation: grey

Diseases names: Highlight

**A) Be able to identify the cardinal and systemic signs of inflammation and to understand the underlying mechanisms that produce these signs.**

## What is Inflammation?

- Inflammation is a local response of the vascularized living tissue to infection and damaged tissue that brings cells and molecules of host defense from the circulation to the sites where they are needed. It's considered "Innate immunity"

## Aim of Inflammation?

eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult. (تتخلص من المسبب للمرض و الضرر الناتج عنه)

- Although inflammation sometimes causes pain, it gradually disappears leaving little or no damage.
- Inflammation is important for human survival, it's a protective response. It attacks the initial cause of injury and the consequences of such injury.

## When is inflammation terminated?

- Inflammation is terminated when the offending agent is eliminated and the secreted mediators are broken down or dissipated. ينتهي الالتهاب عندما تموت الخلايا المسببة للمرض، و الخلايا التي حاربت المسبب للمرض.. اللي هي خلايا الدم البيضاء و غيرها.
  - There are active anti-inflammatory mechanisms that serve to control the response and prevent it from causing excessive damage to the host.

صحيح ان الالتهاب عملية تدافع عن الجسم و لكن في حال استمرت هذه العملية ستدمر الخلايا السليمة و تهاجمها.

فيوجد **anti-inflammatory mechanisms**

توقف الحرب بعد التخلص من الخلايا الضارة، حتى لا تقضي على الخلايا السليمة.

## Inflammatory reaction development:

1) The offending agent, which is located in extravascular tissues, is recognized by host cells and molecules.
الجسم الممرض يتم تمييزه من قبل الخلايا المستضيفة وخلايا أخرى.
2) Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located. جميع الخلايا التي تدافع يتم نقلها الى مكان الإصابة و تجمع الإجسام المسببة للمرض للقضاء عليها .
3) The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.. تبدآ عملية التدمير و القتل للأجسام المسببة للمرض
4) The reaction is controlled and terminated.ومثل ما قلنا قبل ان الدفاع فقط يقتل الاجسام المسببة للمرض و لا يستمر، فيتم التحكم بالمعادلة و ايقاف الخلايا المدافعة حتى لا تقضي على الخلايا السليمة.
5) The damaged tissue is repaired.

## Can inflammation be harmful?

It can sometime cause harm, such as:

- Anaphylactic reaction "allergic reactions"
- Rheumatoid arthritis "inflammation in the joints"
- Atherosclerosis.

**Note:**

- **Sometime inflammation can cause cell injury.**
- **The suffix ( itis) means inflamed tissue or organ , such as ( pancreatitis ,appendicitis).**

# Signs of inflammation

**Local signs (cardinal) :** (at location of illness, injury, or infection) are restricted to a specific area.

1- Redness (Rubor)

2- Swelling (tumor)

3- Warmth (Calor): local heat.

4- Pain (dolor)

5- Loss of function (Functio laesa)
if someone has an acute inflammation in his right arm and the doctor asks him to move it away and he can't move it because it is very painful and he has lost the function of that organ because of the inflammation.

**Systemic manifestations (generalized signs):** affect the entire body or present all over the body and aren't restricted to a specific area.

1- Fever:
usually caused by chemical mediators of inflammation which act on the thermo regulator centers in the thalamus and call the fever to raise.

2- vomiting:
It can be seen even if the inflammation is not in GIT.
It's usually seen in children.

3- anorexic: lack of appetite

4- Malaise: tiredness or weakness.

**NOTE:**
**These signs can be seen in the external organs like the skin or in the internal organs.**

# C-reactive protein:

It is a type of acute phase proteins (non-specific) that is secreted by the liver in response to cellular stress or inflammation.

(يعني الجسم لما يحدث له انفلاميشن بتفرز الليفر هذا النوع من البروتين فلما نسوي تحليل نعرف ان فيه مشكله.)

# erythrocytes sedimentation rate (ESR):

it is the rate at which red blood cells sediment in a period of one hour.

If there is inflammation the ESR will increase because of the exudate of the fluids from the blood vessels to interstitial tissue which will cause viscosity (لزوجة), and also it is non-specific test.

# systemic effects of inflammation (acute-phase reaction):

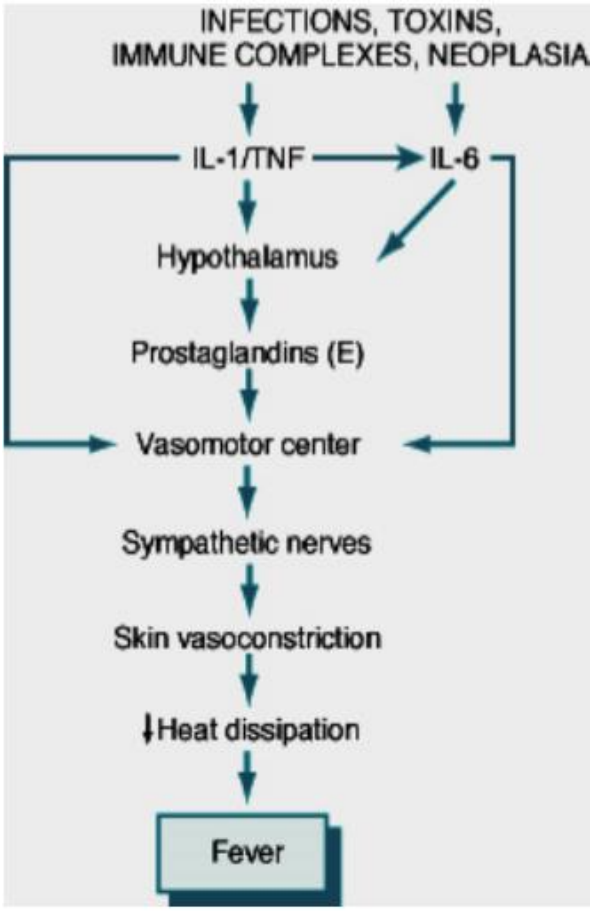
the cytokines **TNF** (Tumor Necrosis Factor), **IL 1**(interleukin 1), **IL 6** (interleukin 6) are the most important mediators of the acute-phase reaction. These cytokines are produced by leukocytes (and other cell types: macrophages, mast cells and endothelial cells) in response to infection or in immune reactions and are released systemically.

The acute-phase consist of several clinical and pathologic changes:

## 1-Fever:

- It's an elevation of body temperature.
- produced in response to substances called pyrogens (a substance that produces fever when released into the blood).
- pyrogens act by stimulating prostaglandin synthesis in the hypothalamus.
- In the hypothalamus, the prostaglandins, especially $PGE_2$, stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level (instead of 37 it will be 38,39,40°c).

NSAID, including aspirin, reduce fever by inhibiting cyclooxgygenase and thus blocking prostaglandin synthesis.




Types of pyrogens:

**-exogenous pyrogens:**

bacterial products

Stimulate leukocytes to release cytokines (IL1 & TNF) that increases the enzymes (cyclooxygenase) which will convert AA into prostaglandin

**-endogenous pyrogens:**

IL 1 AND TNF

## 2-Elevated plasma levels of acute-phase proteins:

These proteins are mostly synthesized in the liver, and in the place of acute inflammation. their synthesis is stimulated by cytokines especially IL 6 (interleukin 6).

These proteins include:

- C-reactive protein (CRP)
- Serum amyloid A (SAA)
- Lipopolysaccharide binding protein
- a-2 macroglobulin
- Haptoglobin
- Ceruloplasmin
- Fibrinogen (increases Sedimentation, which will cause erythrocytes to form stacks “rouleaux”)

Detection of elevated levels of acute phase proteins is an indication of an inflammatory response.

## 3-Leukocytosis:

- Leukocytosis occurs because of accelerated release of cells (under the influence of cytokines, including TNF & IL1) from the bone marrow.
- WBC climbs to 15,000 to 20,000 cells/ml
- both mature and immature neutrophils may be seen in the blood.
- the presence of immature cells is referred to as “shift to the left”.

| | |
|---|---|
| **Neutrophilia** (increased neutrophil count) | **Bacterial Infection** |
| **Lymphocytosis** (increased lymphocytes count) | **Viral infection (mononucleosis, mumps, and german measles)** |
| **Eosinophilia** (increased eosinophil count) | **Bronchial asthma, hay fever, and parasite infections** |
| **Leukopenia** (decreased number of WBC) | **Typhoid fever, infection caused by some viruses, rickettsiae, and certain protozoa** |

## 4-other manifestations of the acute-phase response:

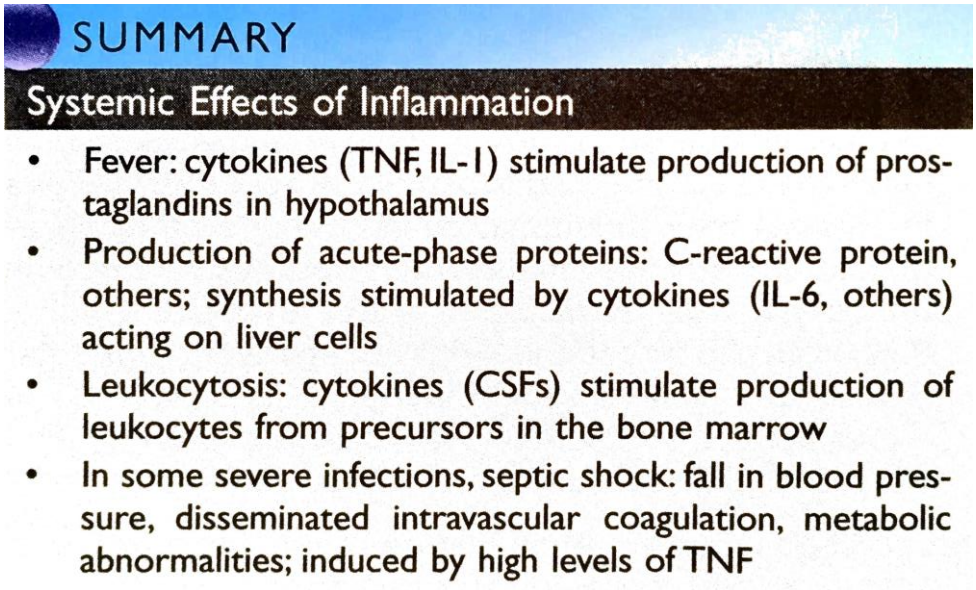
- Increased heart rate and blood pressure
- decreased sweating
- chills
- anorexia
- malaise

# Summary:

**1. Chronic inflammation is different from acute inflammation with respect to causes, nature of the inflammatory response, and tissue changes.**

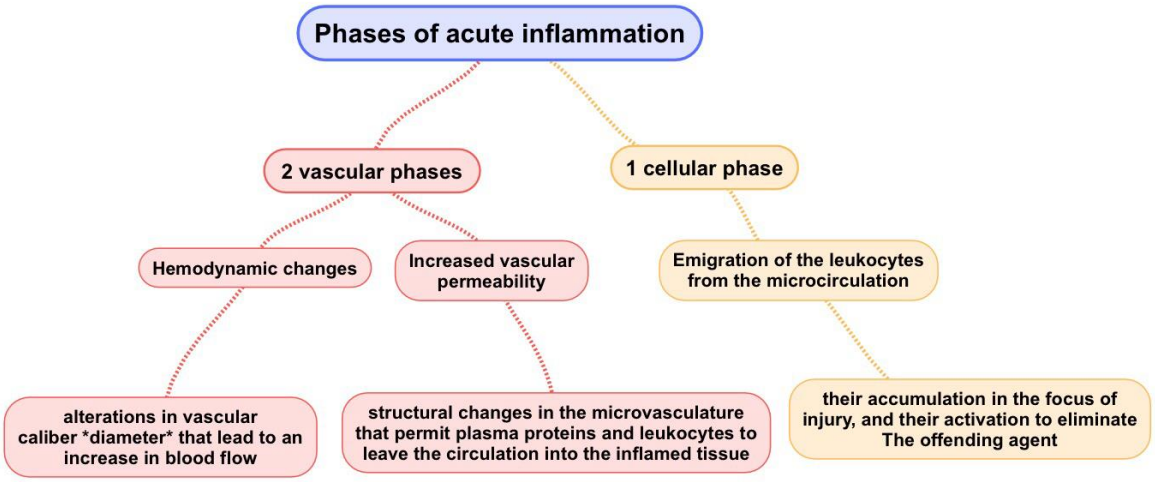
**2. Different clinical settings associated with different types of inflammatory cells (e.g. eosinophils, monocyte-macrophages, and lymphocytes) accumulate in the tissues.**

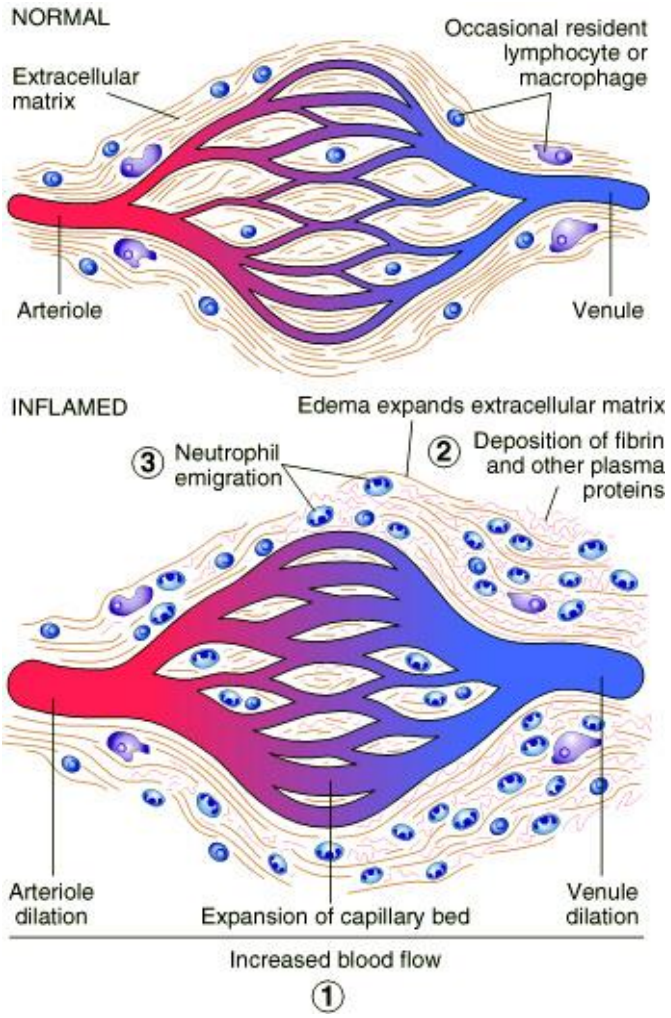
**3. The systemic manifestations of inflammation include fever, leukocyte left shift, and acute phase reactants.**



**B)Understands the vascular changes occurring as a response to tissue injury.**

# Phases of acute inflammation




Vasodilation (hemodynamic chnages )

THE FIGURES:

Vascular and cellular reactions of acute inflammation. The major local manifestations of acute inflammation. compared with normal are :

(1) vascular dilation and increased blood flow (causing erythema and warmth).

(2) extravasation of plasma fluid and proteins (edema) .

(3) Leukocyte (mainly neutrophil) emigration and accumulation.

# Phases of changes in vascular caliber and flow

**Vasoconstriction**
Transient (temporary) of arterioles Which lasts for 3-5 seconds

**Vasodilatation**
It involves the arterioles (or venules or vessels )

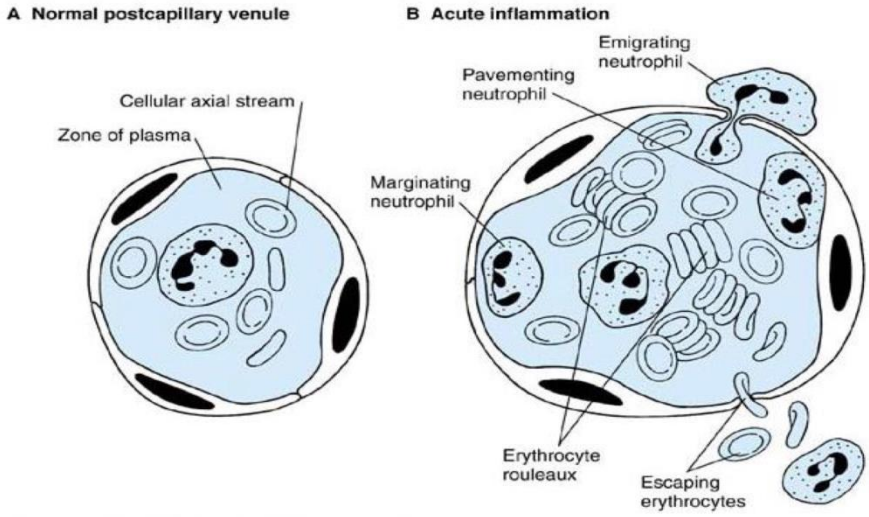
Leading to increase the blood flow by histamine

( which produced in mast cells ) .

**Increase permeability**
Slowing of the circulation due to increase permeability of the microvasculature, this leads to outpouring of protein-rich fluid in the extravascular in tissues.

It will make the area warm and red

**Stasis**
Slow circulation due to dilated small vessels packed with red cells




Increased vascular permeability

A hallmark of acute inflammation (escape of a protein- rich fluid) induced by :

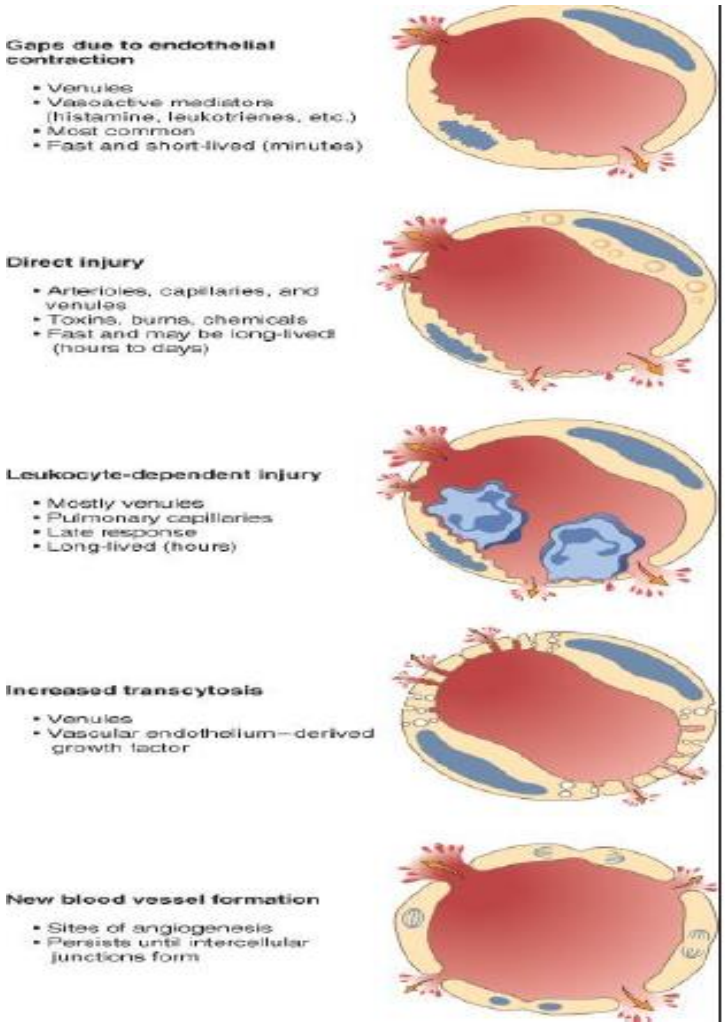
- histamine
- Kinins , and other mediator

It affects through the gaps between endothelial cells the :

- Small and medium size venules.

## Mechanisms lead to increased vascular permeability

- Endothelial cell contraction 15-30 min
- Endothelial injury
- *immediate sustained response* 6-24 hours
- *delayed prolonged leakage 12* hours-days
- *Leukocyte-mediated endothelial injury*
- *Transcytosis (occurs via channels formed by fusion of intracellular vesicles)*
- Leakage from new blood vessels




**Mechanisms lead to vascular permeability**

## Cellular events:

## steps involved in extravasation of Leukocytes from the blood to the tissue:

- An important function of inflammation is Leukocyte Extravasation.
- Leukocyte Extravasation: delivering Leukocytes to the site of injury and activate them to perform their normal functions in host defense.

## Leukocytes Functions

| | | |
|---|---|---|
| ingest offending agents | Kill bacteria and microbes | get rid of necrotic tissue and foreign substances |

- Because Leukocytes' function is to defend the host, once they are activated they might cause harm to healthy tissue (tissue damage and inflammation).

## Removal of offending agents mechanism:

Recognize the microbe through the receptors → **Activate Leukocytes** by increase in cytosolic Ca2+ and activation of enzymes(Protein kinase C and phospholipase A2 → Destroying microbes through:
1. phagocytosis
2. intracellular killing

## Recruitment of Leukocytes:

Margination → Rolling and Tumbline → Adhesion → Diapedesis → Migration

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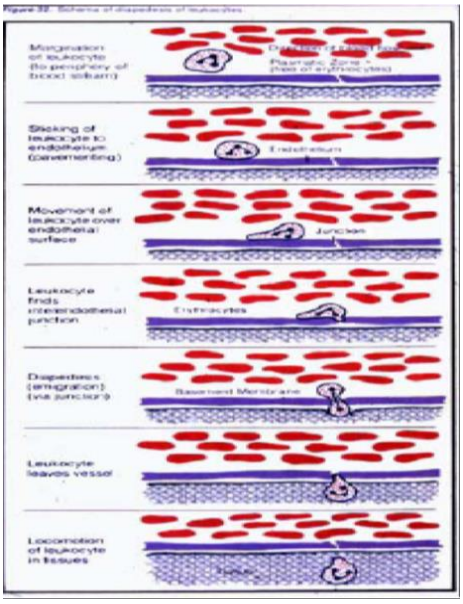
**Leukocyte exudation**



**Margination**

**Sticking**

**Migration**

**Insertion into jct.**

**Diapedesis**

### 1- Margination:

- Leukocytes usually travel in the middle of the blood stream but when an injury happens they go to the margin. (هامش)
- because blood flow slows early in inflammation (stasis), the endothelium can be lined by white cells (pavementation).

### 2- Rolling and Tumbling: تتدحرج

### 3- Adhesion:التصاق

- They adhere to the endothelial cells due to the action of adhesion molecules.
- Adhesion molecules:

  Selectin: outer surface of endothelial cells.

  Integrin: outer surface of Leukocytes.

### 4- Diapedesis (Transmigration):

- ↑ Vascular permeability
- cells (leukocytes) travel from the vessels to the tissue
- occurs in postcapillary venules.

### 5- Migration (هجرة)

- Cells move towards the site of injury.
- They are directed through chemotaxis
- Chemotaxis: movement of organism in response to a chemical stimulus.
- Neutrophils, monocytes, lymphocytes, eosinophils and basophils all use the same pathway to migrate from blood to tissue.

**Note:** Differentiate between **migration** and **margination.**

## Inflammasome:

- is a protein complex that recognizes products of dead cells and microbes.
- Induce secretion of active IL1
- Consists of a sensor protein (leucine rich protein called NLRP3) and enzyme Caspase 1 , which is converted from inactive to an active form.

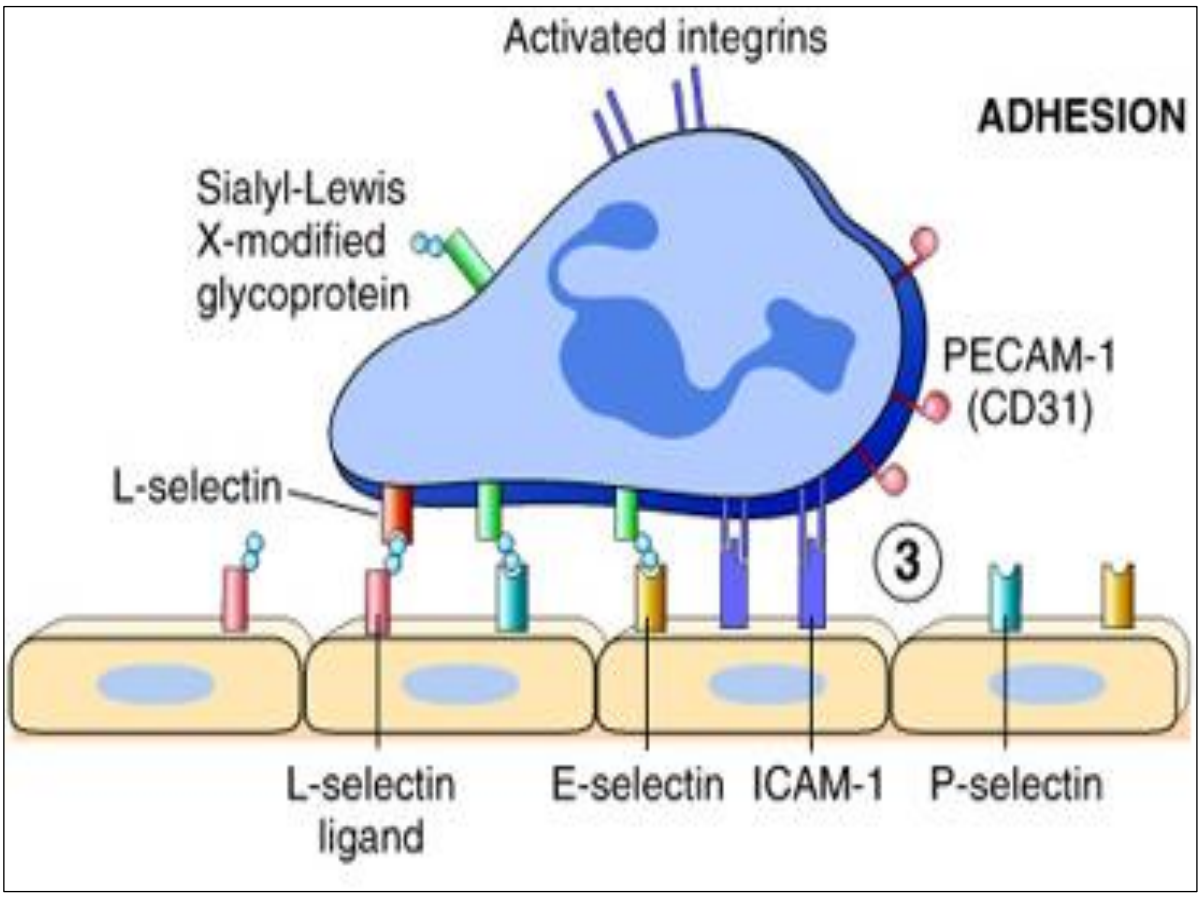
## Leukocyte Adhesion:

mediators such as histamine, thrombin, and platelet activating factor (PAF) stimulate the redistribution of P-selectin from its normal intracellular stores in granules (Weibel-Palade bodies) to the cell surface.

Weibel-Palade bodies are the "glue factory" of endothelial cells, because they synthesize P-selectin, an adhesion molecule for leukocytes, and von Willebrand factor, the adhesion molecule of the platelet

### Adhesion molecules and receptors:

| 1-selectins | 2- Integrin |
|---|---|
| • **E- selectin**: confined to endothelium, induced by TNF & IL1.<br>• **P- selectin**: present in endothelium and platelets from Weibel-Palade bodies.<br>• **L-selectin:** expressed on most leukocyte and endothelium.<br>NOTE: E-selectin and P-selectin bind to Sialyl-Lewis X glycoprotein and slow the leukocytes. | • are transmembrane heterodimeric glycoproteins, made up of **α and β chains** expressed on leukocytes and bind to ligands on endothelial cells.<br>• up regulated on leukocytes by: C5a & LTB4 resulting in firm adhesion with vessel wall. |
| **3- immunoglobulin molecules** | **4- Mucin-link glycoproteins (PECAM 1)** |
| • **ICAM-1:** (intercellular adhesion molecule 1)<br>• **VCAM-1:** (vascular cell adhesion molecule 1)<br>IL-1 and TNF activate (ICAM) and (VCAM) on venular endothelial cells. | these glycoproteins are found in the extracellular matrix and on cell surfaces.<br>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. |

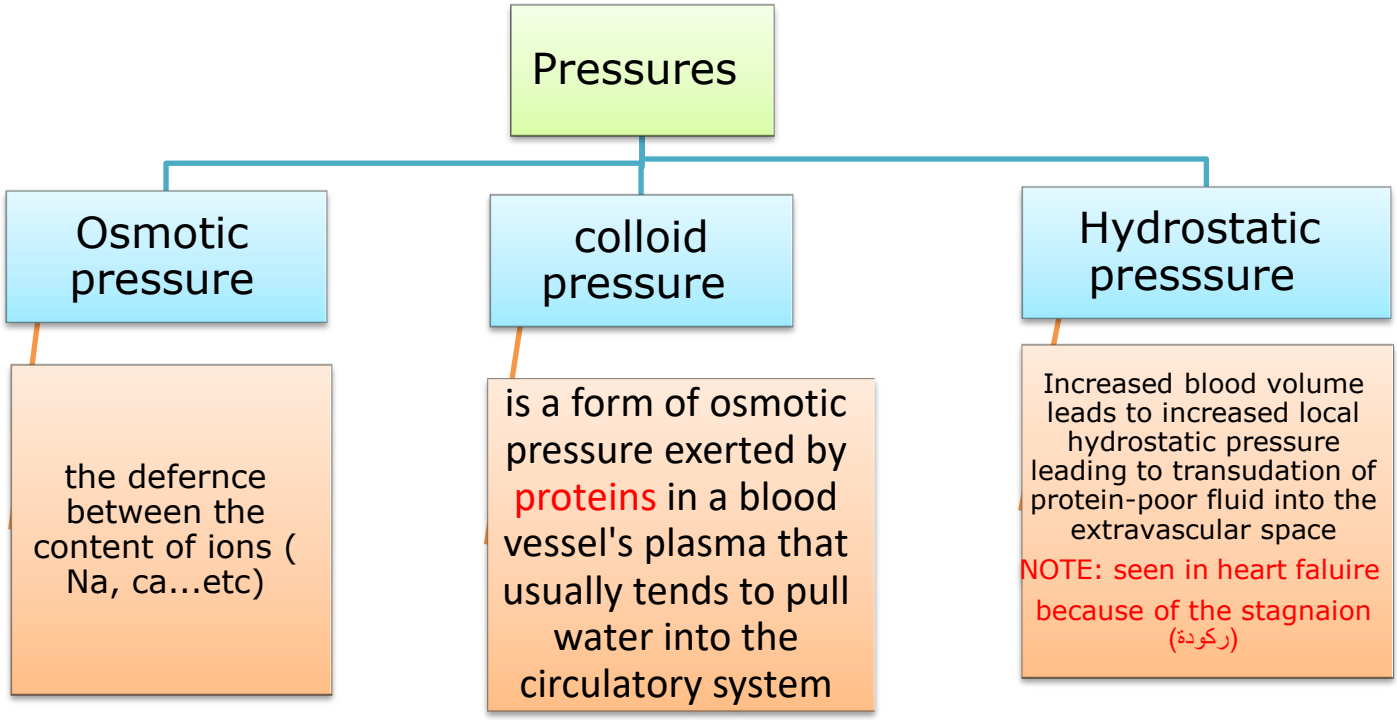



## Leukocyte Adhesion Deficiency:

- **Autosomal recessive defect of integrins, there are two types:**
  - LAD type 1 is a deficiency of $\beta_2$-integrin.
  - LAD type 2 is a deficiency of an endothelial cell selectin that normally binds neutrophils.
- **Clinical findings:**
  - Delayed separation of umbilical cord.
  - Increased circulating neutrophils (leukocytosis due to loss of the marginating pool).
  - Recurrent bacterial infection that lack pus formation.
  - Poor wound healing.

**C- Appreciate the importance of fluid production in inflammation including the difference between exudates and transudates.**

**There are three types of pressures that control the fluids inside the vessels**




**NOTE:**

**Colloid pressure** is seen in Renal and Liver diseases which shows a transudate edema. (protein is produced by the live, so if there is a problem with the liver there will be decrease in colloid pressure).

Edema

Excess of fluid in the interstitial space.

**Transudate**

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

**- Low inflammatory cells**

-It is essentially an ultra filtrate of blood plasma that results from osmatic or hydrostatic imbalance across the vessel wall Without an increase in vascular permeability

**Exudate**

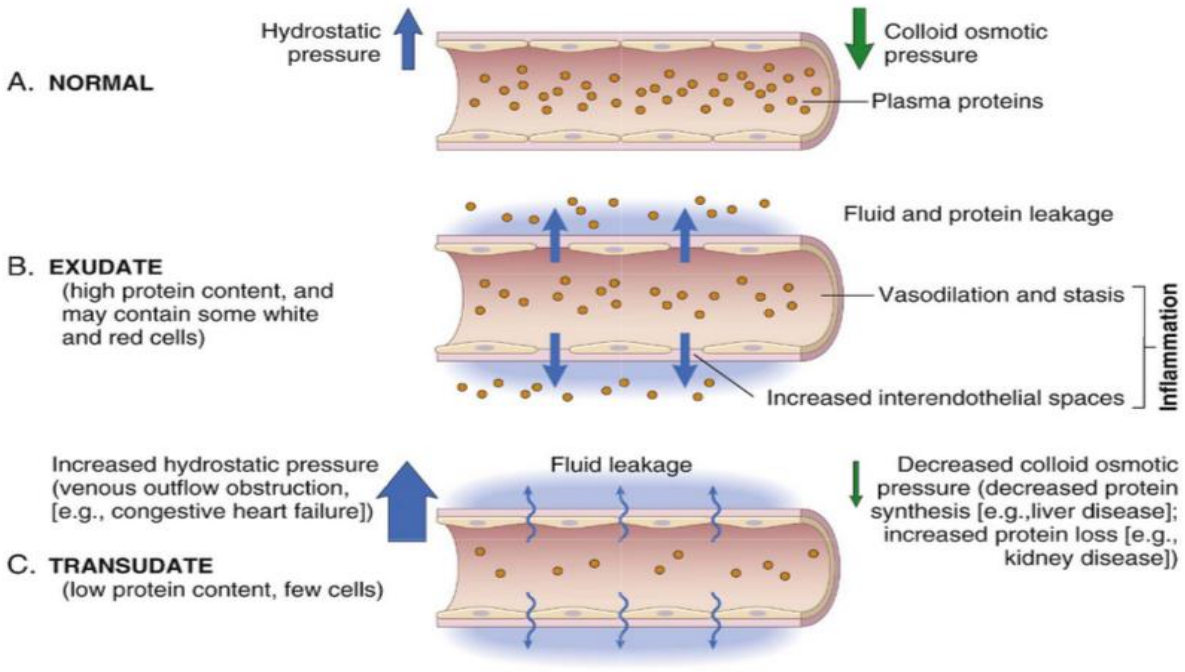
an inflammatory extravascular fluid that has **a high protein** concentration, cellular debris, and a **specific gravity above 1.020**

**- large number of inflammatory cells.**

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

**Note:**

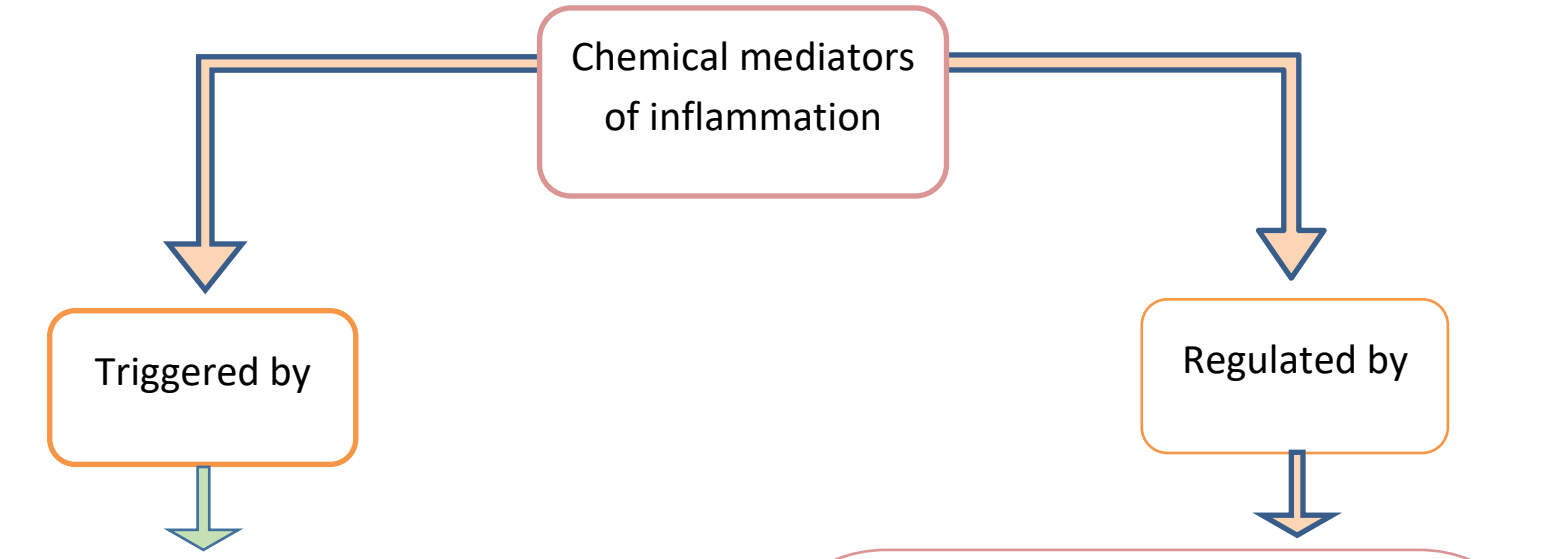
- **Exudate happens because of:**
  1- **Gaps between endothelial cells (which lining the blood vessels)**
  2- **Inflammation cells destroy endothelial cells.**



**C) Have some understanding of various chemical mediators of inflammation and their link with the complement system and potentially with coagulation factors.**

## Chemical mediators of inflammation

-Chemical mediators of inflammation are substances produced during inflammation inducing specific events in acute inflammation, responsible for the vascular and cellular events in acute inflammation.




1-microbial products

2-host proteins, such as the proteins of the complement, kinin and coagulation systems.

( these are themselves activated by microbes and damaged tissues)

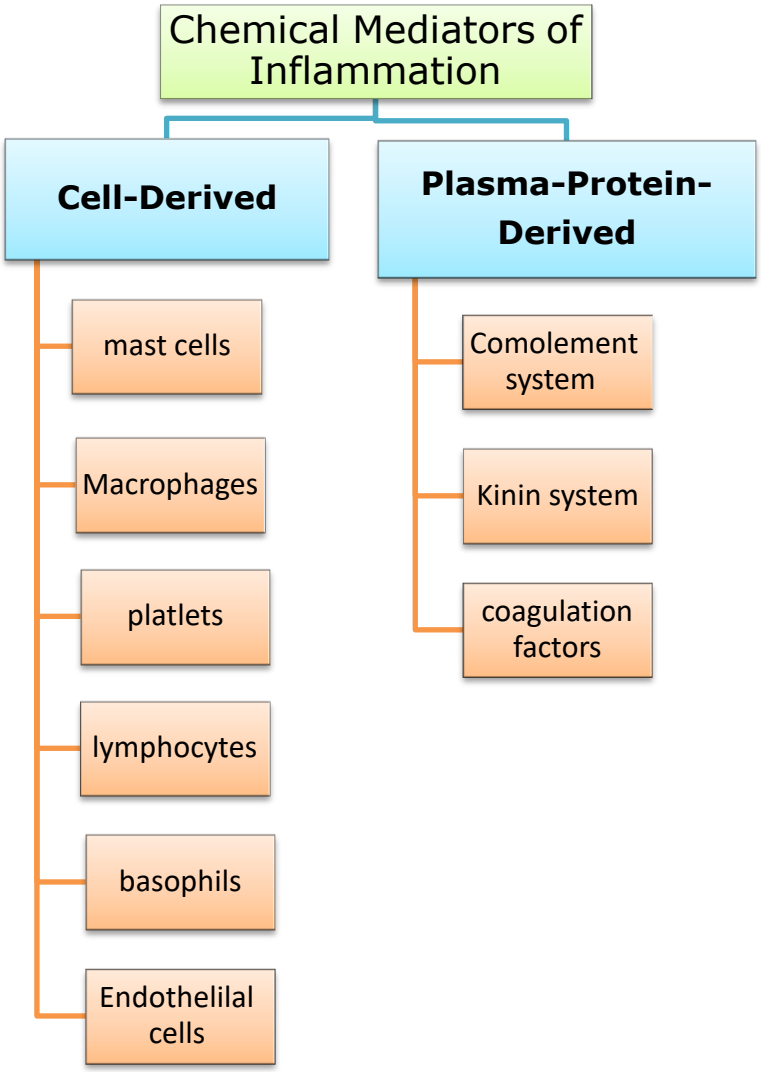
Most mediators have the potential to cause harmful effects.

(كل شيء اذا زاد عن الطبيعي يصبح مضر)

Therefore, there should be a mechanism to check and balance their action.

Mediator function is tightly regulated by:

1) decay (e.g. AA metabolites) اختصار لـ (Arachidonic acid)
2) inactivated by enzymes (e.g. kininase inactivates bradykinin)
3) eliminated (e.g. antioxidants scavenge toxic oxygen metabolites)



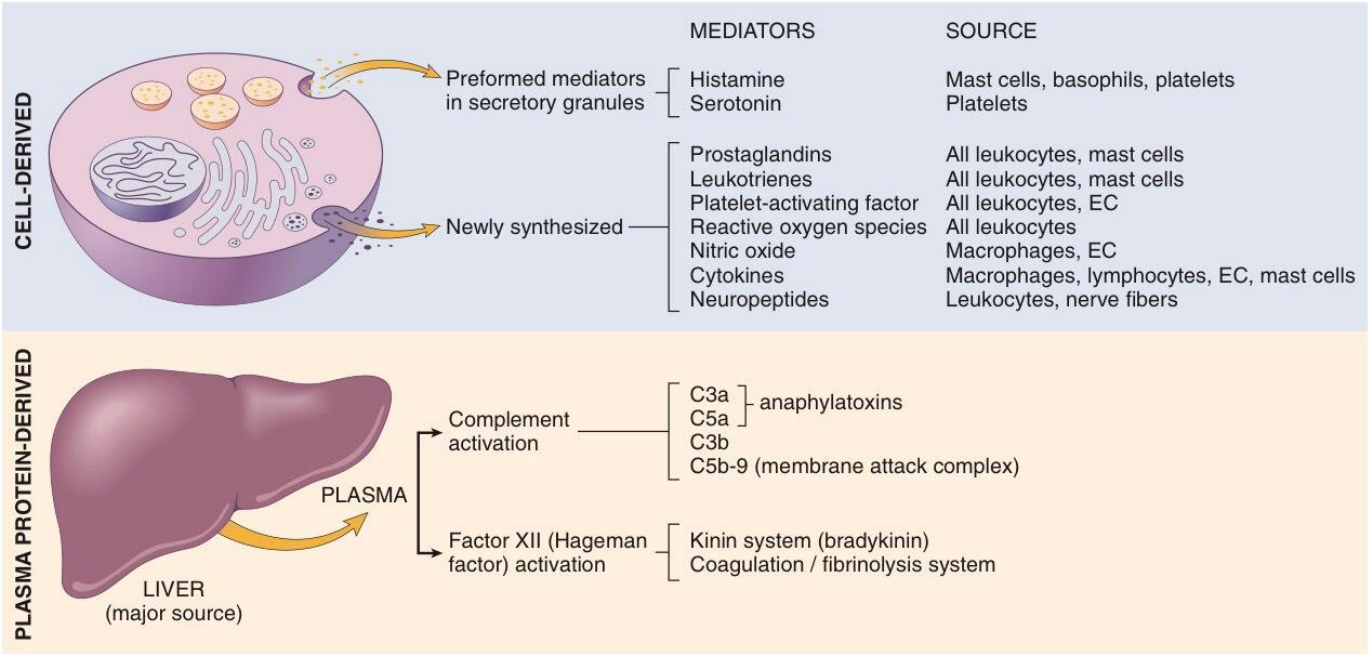




**Figure 2–15** Mediators of inflammation. The principal cell-derived and plasma protein mediators are shown. EC, endothelial cells.

# 1-Cell derived

مقتبس من 434 &435

| Histamine | Serotonin (5-hydroxytryptamine) (5-HT) | Platelet activating factor (PAF) |
|---|---|---|
| • Secreted by mast cells, basophils and platelets.<br><br>**It Causes**:<br>• Vasodilation.<br>• Increased vascular permeability (venular gaps)<br>• Endothelial activation<br>**E.g.:**<br>When there is a physical injury, such as trauma or heat, immune reactions involving binding of IgE antibodies to their receptors on mast cells. After this binding, mast cells will release histamine from its granules. 17 When a bee stings you, its antigen will cause a hypersensitivity reaction in the body. This will lead to increased production of IgE, which will bind to mast cells and make it produce histamine. This explains how the bee sting leads to the production of all these effects on the body. | • Secreted by platelets<br><br>**It causes:**<br>• Vasoconstriction.<br><br>• it comes from metabolized amino acid called tryptophan. | Secreted by leukocytes, endothelial cells, mast cells, Platelets, -Neutrophils ,Eosinophils .<br><br>**It causes:**<br>• Vasodilation.<br>• Increase vascular permeability<br>• Leukocytes adhesion. |

| Prostaglandins | Leukotrienes |
|---|---|
| Are metabolites of Arachidonic Acid (found in cytoplasmic membranes of inflammatory cells (cell membrane phospholipids)<br>they both are secreted by : mast cells and leukocytes. | |
| It Causes:<br>❖ Vasodilation.<br>❖ Pain.<br>❖ fever.<br><br>• all medicines (المضادة للألم والحرارة) are (antiprostaglandin)<br><br>• when the phospholipids in the cell membrane is metabolized by (phospholipase) of inflammatory cell neutrophils, macrophages and others, arachidonic acid will be produced, then **Cyclooxygenase** enzymes act on it and produce thromboxane A2 and **Prostaglandins**. | It causes:<br>❖ increased vascular permeability.<br>❖ chemotaxis.<br>❖ leukocyte adhesion and activation.<br><br>It has 4 types: D4 - B4-C4-E4<br><br>• **D4-C4-E4:** -increase vascular permeability.<br>-bronchospasm.<br><br>• **B4:** Chemotaxis→ (directional migration of inflammatory cells from blood vessels to site of injury (site of antigen).<br><br>It is produced when arachidonic acid is metabolized by **5-lipoxegenase** |

| Reactive Oxygen Species (ROS) | Nitric oxide (NO) | Cytokines |
|---|---|---|
| • Secreted by leukocytes.<br>• ROS causes damage of tissue and killing of microbes.<br><br>ROS types:<br>$H_2O_2$<br>OH<br>$O_2$- | • Secreted by endothelial cells, macrophages.<br><br>**Causes:**<br>Vasodilation which cause relaxation of the smooth muscles in the blood vessels.<br>Killing of the microbe. | Secreted by macrophages, lymphocytes and endothelial cells.<br><br>**Function:**<br>• They activate endothelial cells<br>• Increase integrin and selectin[1].<br>• Shock and fever.<br>• induce the activation of T Lymphocytes and B lymphocytes<br>• induce formation of active macrophages<br><br>Acute inflammation cytokines:<br>• Interleukin 1 (IL-1) and Tumor necrosis factor (TNF)<br>Chronic inflammation cytokines:<br>• Interferon Gamma (INF- γ) and Interleukin 12 (IL-12).<br><br>**IL1 & TNF stimulate**<br>-expression of L-selectin on the surface on neutrophils.<br><br>-the expression of E-selectin and P-selectin on the surface of venular endothelial cells. |

**Chemokines**

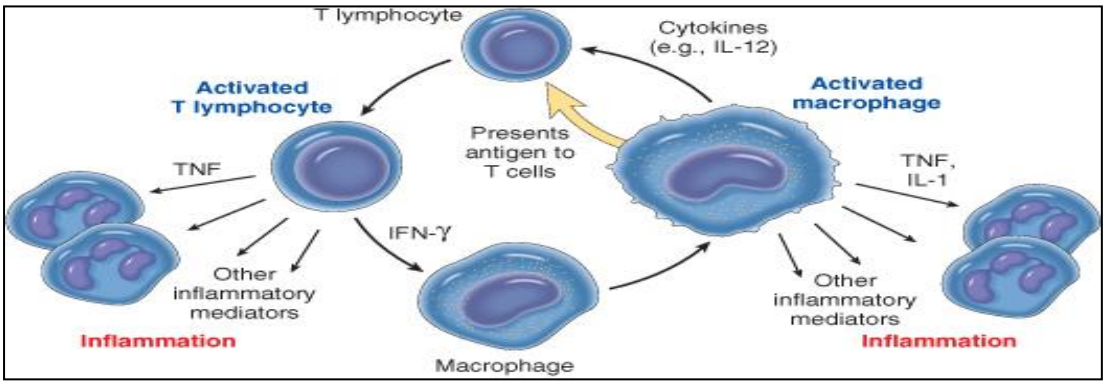
- Small proteins.
- Secreted by leukocytes and activated macrophages.

Main functions:
- - Leukocyte recruitment & activation in inflammation
- - Normal anatomic organization of cells in lymphoid and other tissues
- They activate the movement of the neutrophils.
- Chemotaxis.

**Lysosomal Enzymes of Leukocytes**

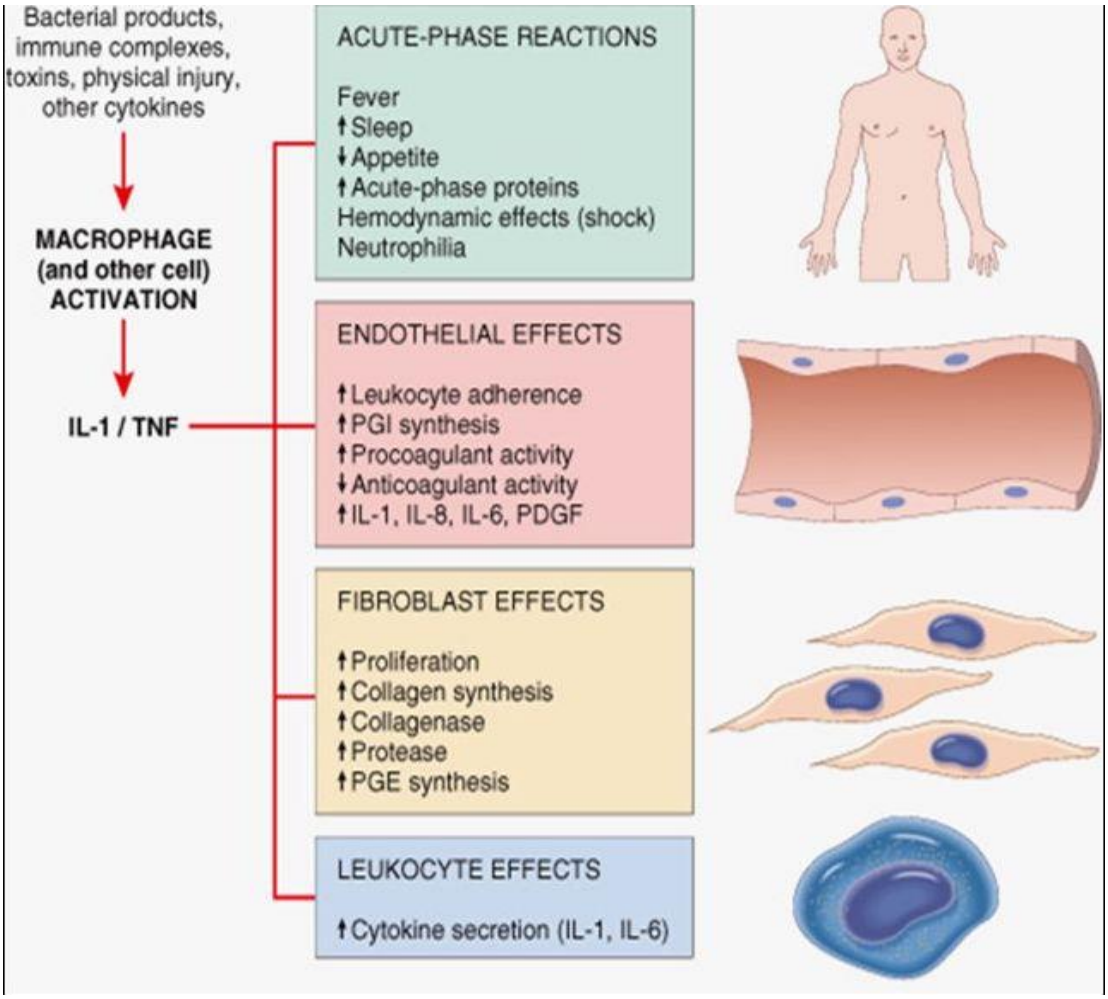
- Secreted by Neutrophils & Monocytes granules.

Enzymes:
- Acid proteases
- Neutral proteases (e.g. elastase, collagenase, & cathepsin)
- **All of these lead to killing the microbe.
- Their action is checked by:
- Serum anti-proteases (e.g. α1-antitrypsin)

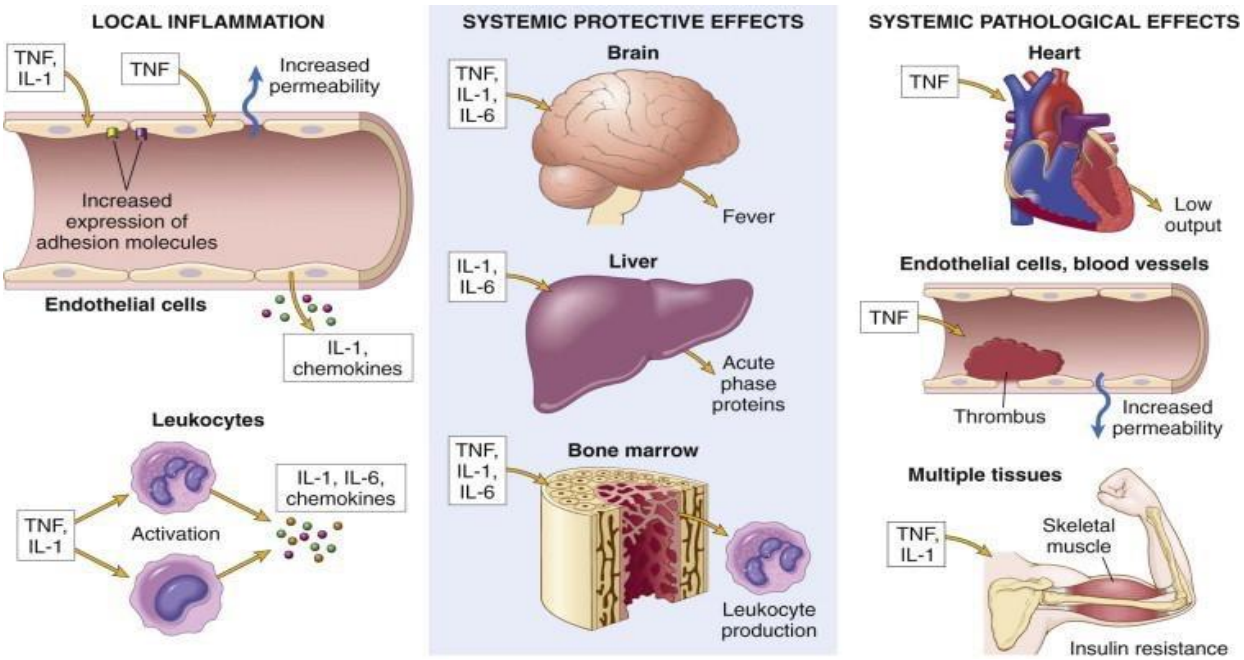



[1]1- selectin and integrin are two adhesion molecules and they cause activation and adhesion of leukocytes.

## This picture shows the function of Cytokines:




***Major roles of cytokines in acute inflammation:**



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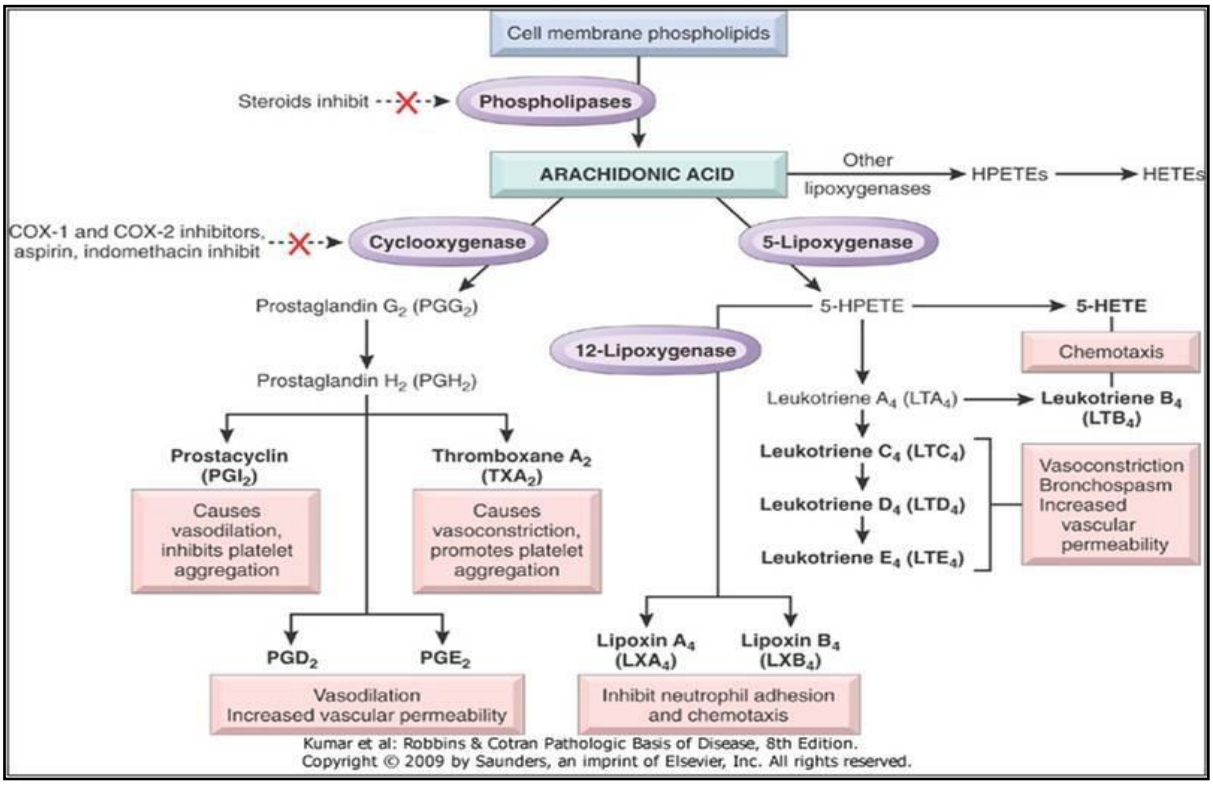
| Arachidonic acid | | | |
|---|---|---|---|
| **Cyclooxygenase** | | **Lipoxygenase** | |
| **COX-1 , COX-2**<br>**=formation of prostaglandin G2 , H2 this will transform into: thromboxane A2 and prostacyclin PGI2** | | ***Formation of lipoxin and leukotriene** | |
| **Thromboxane A2** | **Prostacyclin PGI2** | **Lipoxin** | **Leukotriene** |
| ***vasoconstriction**<br>***aggregation to platelets**<br>**platelets contribute in thrombosis (coagulation)*<br>**platelets are different from coagulation factor; because : platelets are **cells** coagulation factor is a **substance*** | ***vasodilation**<br>***inhibits platelet-aggregation** | **antagonize the prostaglandins**<br>**"anti-prostaglandins"**<br>**inhibit neutrophil adhesion and chemotaxis* | *** C4, D4, E4, B4**<br>**C4, D4, E4 :**<br>***bronchospasm** *(major symptom in asthma)*<br>***increased vascular permeability**<br>**B4 :**<br>***chemotaxis** |

**If this metabolic pathway CONTINUED we will have ...**

**Prostaglandins E2 , D2 ; which cause vasodilation, increase vascular permeability that we see in inflammation..**

**TO STOP THE FORMATION OF PROSTAGLANDINS**

**I may give the patient steroids cortisone and this is one of the actions of cortisone; as it inhibits the action of phospholipase and stop the formation of arachidonic acid.** **steroids are very important in inhibiting action of phospholipase.*



| Source | Major inflammatory action |
|---|---|
| **Mast cells/Basophils** | **Increased vascular permeability** |
| **Neutrophils** | **Leukocytes aggregation** |
| **Monocytes/Macrophages** | **Leukocytes adhesion** |
| **Endothelium** | **Leukocyte priming/chemotaxis** |
| **Platelets** | **Platelets activation** |
| **Other** | **Stimulation of other mediators (LT,O2-)** |

## 2-Plasma Derived mediators:

A variety of phenomena in the inflammatory response are mediated by plasma proteins that belong to three interrelated systems:

1) complement system: (is an important part of immunological reactions, they are proteins found in the plasma and their function is to control inflammation, they are 9: C1, C2, C3, …etc.)

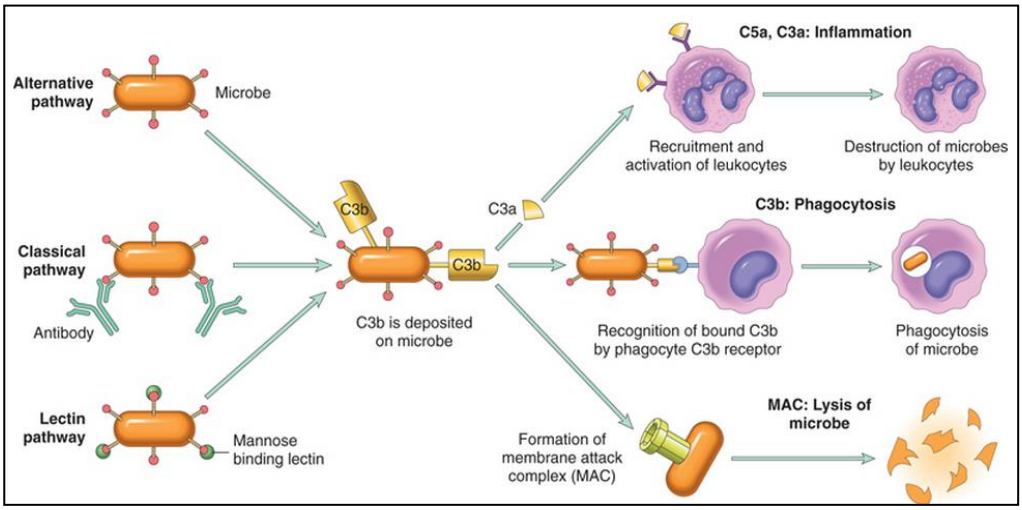
2) Kinin: (activated by clotting factors, important in hemodynamic and in the control of the blood pressure).

3) clotting system.

## • 1) Complement system:

- Are proteins that are secreted by the liver and released to the circulation (plasma) when there is cell injury, damage or inflammation.
- Usually found inactive in the blood, inflammation leads to cleavage and activation.

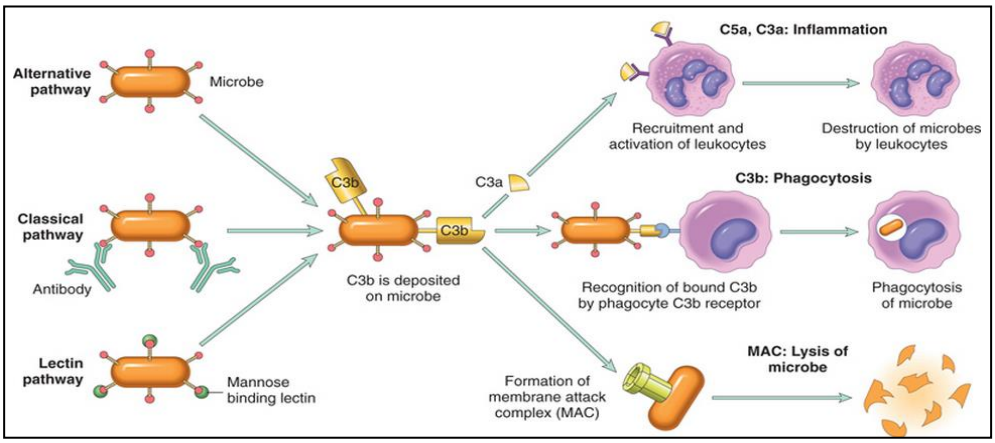
**C reactive protein: Is released and activated in inflammation and cell injury, it is not specific but gives you a brief idea.



## Complement system is activated by two ways:

1) Classical pathway: Antibodies formed and then attach to the surface of the bacteria, the attachment leads to the cleavage of the complement 3 to C3a and C3b.

2) Alternative pathway: The bacteria directly attack the complement C3 and converts it to C3a and C3b.




The components of the complement that have a role in inflammation: C3a, C5a, C3b and C5ab, they increase and activate leukocytes chemotaxis and cause opsonization, they are opsonins.

- Opsonin (C3b): Is a substance which when it coats the antigen or any foreign material it will make it susceptible for phagocytosis by the lysosomal enzymes and by reactive oxygen species (ROS).

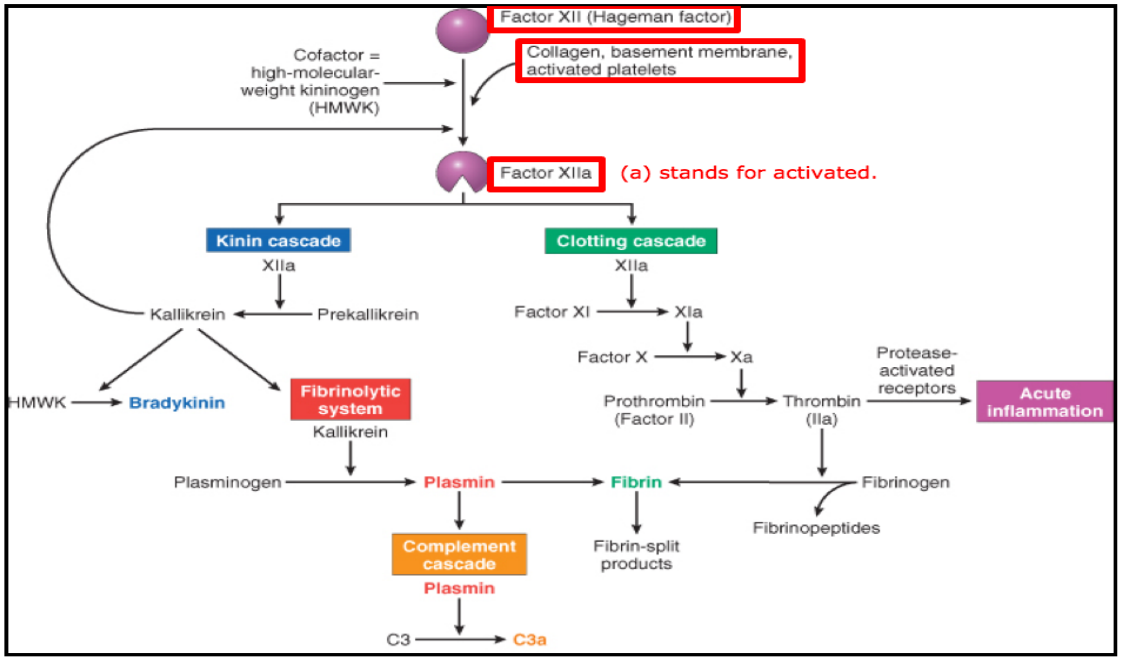
- Immunoglobulin: Are also opsonins, they help in opsonization.

Q: What are the substances that will predispose and prepare those particles for phagocytosis?

Answer: Opsonins.

| | Complement components functions: |
|---|---|
| C3a & C5a | - Increase vascular permeability (*anaphylatoxins*), causes vasodilation<br>- Chemotaxis (mainly C5a), killing of bacteria, inflammatory reaction, vasodilation and activation of the vessels and inflammatory cells. |
| C3a | - Leads to recruitment and activation of leukocytes, then destruction of the microbe. |
| C3b | - Opsonization and phagocytosis. |
| C5 to C9 | - Membrane attack complex (MAC) and kill the bacteria. |

## 2- Kinin & clotting system:




**please pay attention to the red notes written on the mind maps they are very important.

- Kinin has multiple factors.

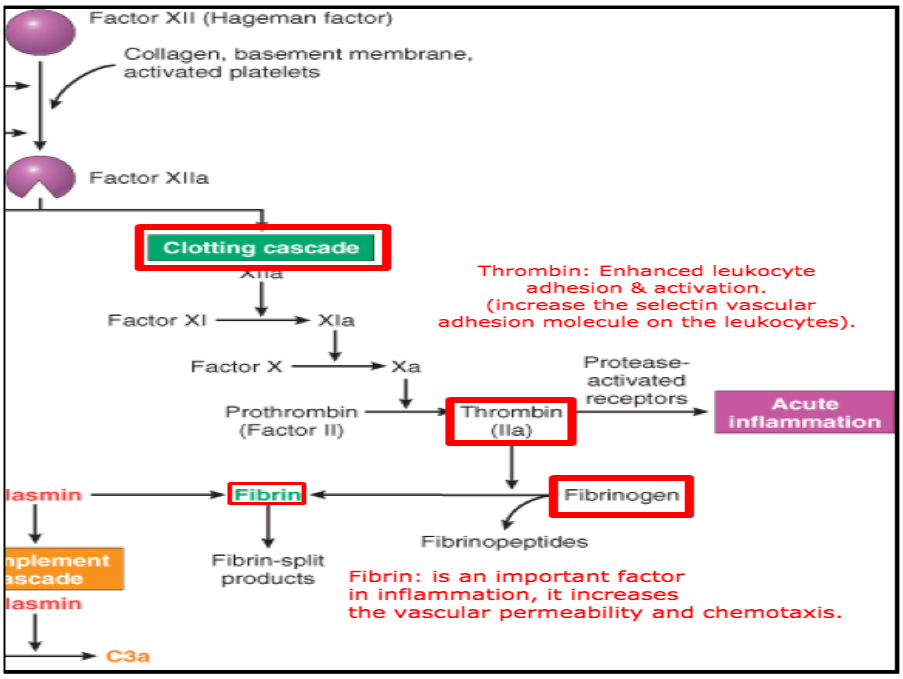
- Factor XII = Factor 12 = Hageman factor.

- The factors are soluble Proteins found in plasma and they are inactive, they're activated whenever needed.

- Activation of factor 12 (Hageman factor):

- After injury.
- After bacterial infection.
- After cut of the basement membrane of the blood vessels.
- After exposure to collagen fiber.
- After activation of platelets.

## A) Clotting cascade(pathway):

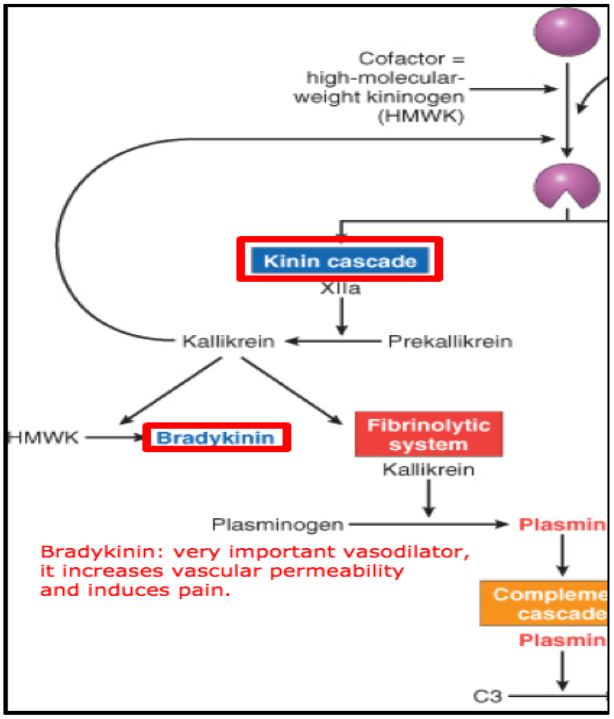



- **Factor 12 (Hageman Factor)** stimulates two systems: clotting system and Kinin system.
- Clotting system: F11 stimulates f10, F10 stimulates F8 … until Fibrinogen > Fibrin.
- Among the clotting cascade, thrombin is formed which is an important mediator in acute inflammation.
- During the inflammation, the coagulation factors are activated (when checking an inflamed area, you can see a small thrombi and fibrin in the blood vessel )
- When factor 8 is efficient it causes hemophilia, which is a hereditary disease affecting males.

## B) Kinin cascade (pathway):

- Kinins are produced by **the liver**

1) Prekallikrein is activated by F XIIa to form Kallikrein.
2) Kallikrein converts HMWK into Bradykinin.

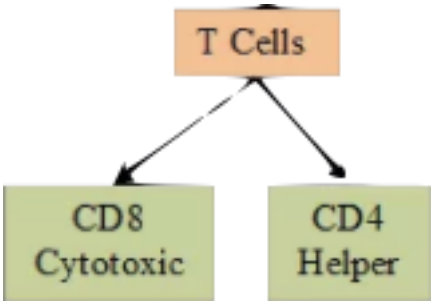



**Pain: Prostaglandin E2 and Bradykinin.

# Summary of Plasma-protein derived chemical mediators

| Complement | Kinin | Clotting |
|---|---|---|
| - Is an important part of immunological reactions, they are proteins **found in the plasma** and their function is to control inflammation, they are 9: C1, C2, C3, …etc.)<br><br>- Are proteins that are secreted by **the liver** and released to the circulation (plasma) when there is cell injury, damage or inflammation.<br><br>- Usually found inactive in the blood, inflammation leads to **cleavage** and activation.<br><br>- activated by two ways:<br>1) Classical pathway.<br>2) Alternative pathway.<br><br>- The components of the complement that have a role in inflammation: C3a, C5a, C3b and C5ab, they increase and activate leukocytes chemotaxis and cause opsonization, they are opsonins.<br><br>- C3a: Leads to recruitment and activation of leukocytes, then destruction of the microbe. | - Kinins are produced by **the liver**.<br><br>- activated by clotting factors, important in hemodynamic and in the control of the blood pressure).<br><br>1) Prekallikrein is activated by FXIIa to form Kallikrein.<br>2) Kallikrein converts HMWK into Bradykinin.<br><br>Bradykinin: Very important vasodilator, it increases vascular permeability and induces pain.<br><br>**Pain: Prostaglandin E2 and Bradykinin. | - stimulated by Factor XIIa.<br><br>- When factor 8 is efficient it causes hemophilia, which is a hereditary disease affecting males.<br><br>- During the inflammation the coagulation factors are activated (when checking an inflamed area, you can see a small thrombi and fibrin in the blood vessel).<br><br>- Among the clotting cascade, thrombin is formed which is an important mediator in acute inflammation.<br><br>- Thrombin: Enhanced leukocytes adhesion & activation. (increase the selectin vascular adhesion molecule on the leukocytes).<br><br>- Fibrin: Is an important factor in inflammation, it increases the vascular permeability and chemotaxis. |

# Cell-mediated Immunity:

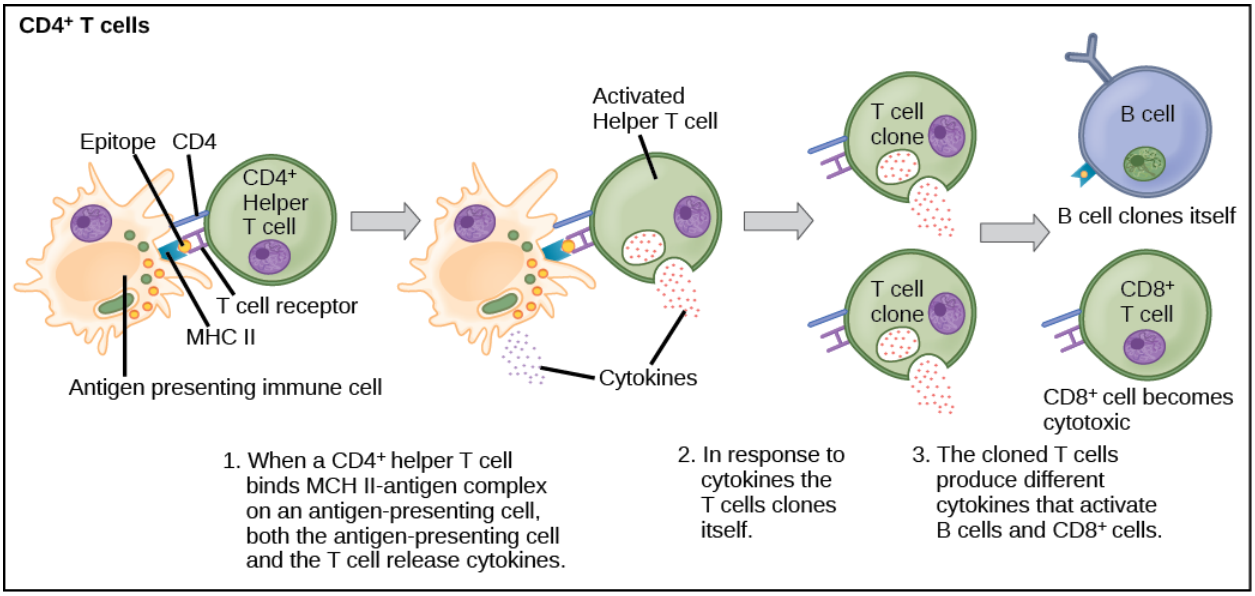


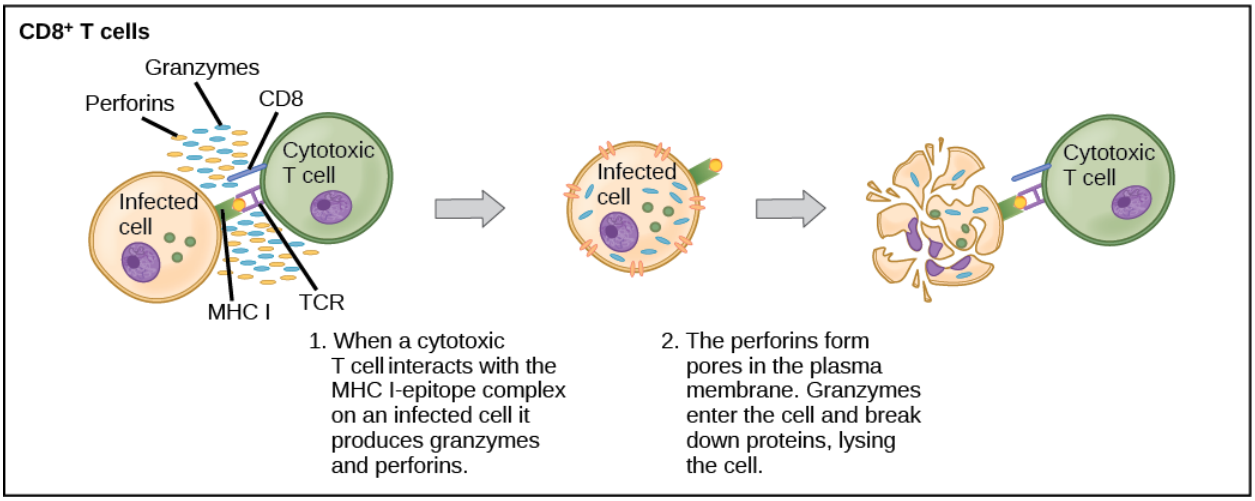

- Dendritic cells (DCs) capture microbial antigens from epithelia and tissues and transport the antigens to lymph nodes.
- During this process, the DCs mature, and express high levels of **MHC**[1] molecules and co-stimulators.
- **Naive**[3] T cells recognize MHC-associated peptide antigens displayed on DCs.
- The T cells are activated to proliferate and to differentiate into effector and memory cells, which migrate to sites of infection and serve various functions in cell-mediated immunity.
- CD4+ effector T cells of the **TH1**[2] subset recognize the antigens of microbes ingested by phagocytes, and activate the phagocytes to kill the microbes; other subsets of effector cells enhance leukocyte recruitment and stimulate different types of immune responses.
- CD8+ cytotoxic T lymphocytes (CTLs) kill infected cells harboring microbes in the cytoplasm.
- Some activated T cells remain in the lymphoid organs and help B cells to produce antibodies, and some T cells differentiate into long-lived memory cells.

1- MHC: Major Histocompatibility Complex is a set of cell surface proteins essential for the acquired immune system to recognize foreign molecules. it has 2 types: MCH I & MCH II

2- **There are two main types of helper T cells: Th1 cells and Th2 cells. Th1 cells work to eliminate invaders that occur inside our cells (viruses and some intracellular bacteria). Th2 cells aim to destroy pathogens that occur outside our cells (bacteria and parasites).**

3- Naive: natural and unaffected or haven't encountered any antigens yet.




## For further understanding:

**D) Have good knowledge about the types and functions of various inflammatory cells including their role in both acute and chronic inflammation.**

## Cells involved in both acute and chronic inflammation:

### Neutrophils:

- Cell that has 3-5 lobess of nucleus.
- rich of lysosomes.
- Rich of lysosomal enzymes and has a role in phagocytosis.
- seen in bacterial inflammation and acute inflammation.
- (neutrophilia) means increase in neutrophils.

### Lymphocytes:

- seen in viral infection and chronic inflammation.
- (lymphocytosis) means increase in lymphocytes.

### Eosinophils:

- It has two lobes.
- It has eosinophilic granules (reddish, acidophilic)
- Weak phagocytosis
- Seen in both chronic and acute inflammation.
- Increased in patients with parasitic and allergic (asthma).

### Plasma cells:

- They produce immunoglobulin E (IgE) which plays a major role in chronic inflammation.
- Seen in the bone marrow and tissue.
- Plasma cells shouldn't be seen in blood, if it's seen in a patient's blood that means he has leukemia.
- Progenitor (خلايا مولدة للخلايا).

### Mast cells:

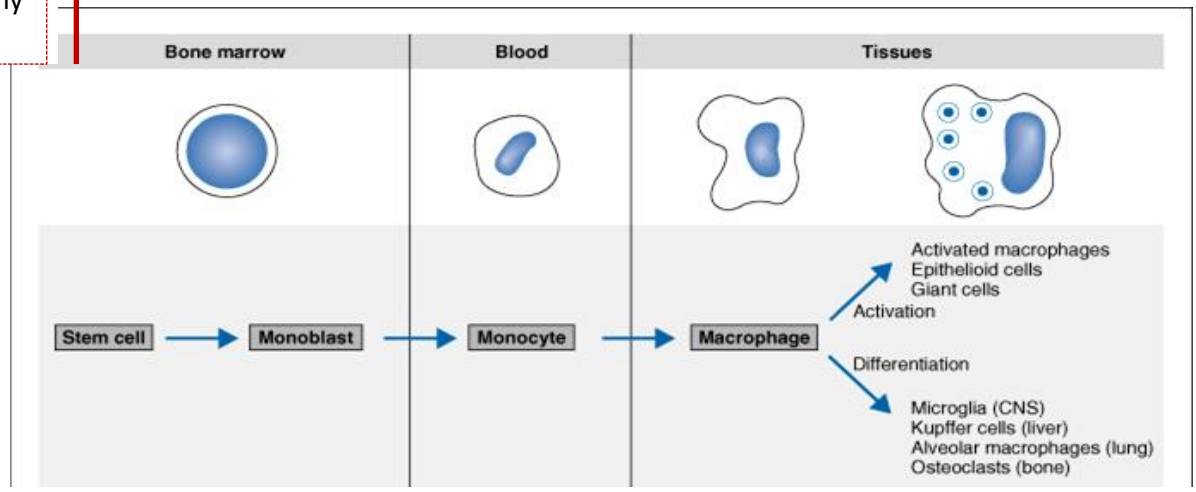
- Seen in bone marrow and tissue
- Never seen in blood.
- Their granules contain histamine, products of AA oxidative and serotonin.
- When there is an allergic reaction, IGE will bind on receptor on the surface of the mast cells and then the mast cell will release its granules.

## Macrophages and monocytes:

يختلف اسمها إذا تغير مكانها ...

Under the influence of adhesion molecules and chemokines, they begin to emigrate into extravascular tissues (to a site of injury) quite early in acute

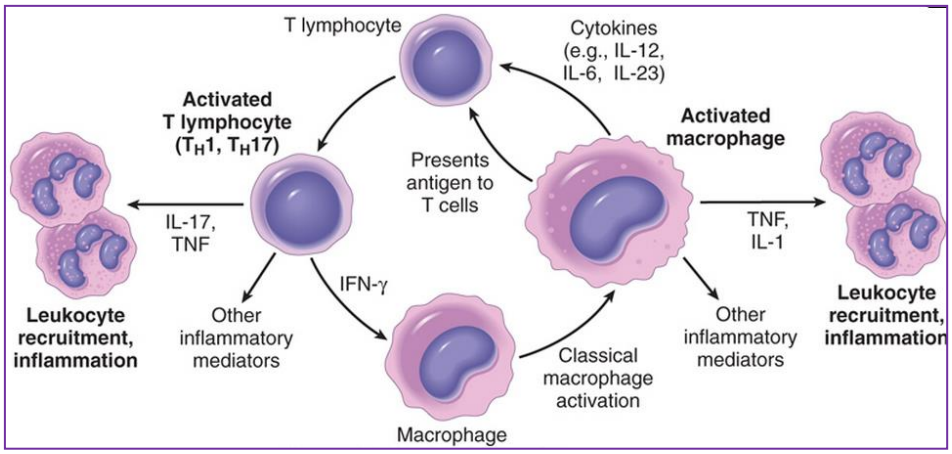
| Location | name | Spesific Location | name |
|---|---|---|---|
| Blood | monocytes | | |
| Tissue | Macrophages | liver | Kupffer cells |
| | | spleen & lymph nodes | sinus histiocytes |
| | | CNS | microglial cells |
| | | lungs | alveolar macrophages |

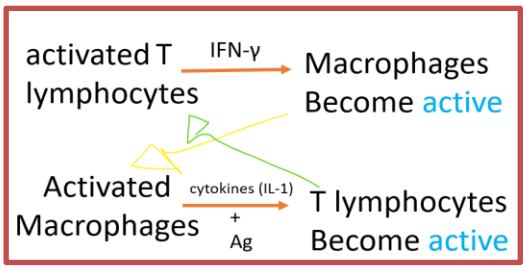



### ❖ Macrophages may be activated by a variety of stimuli, including:

A- cytokines (e.g., IFN-γ) secreted by $T_h1$ lymphocytes and by NK cells.

B- bacterial endotoxins.




الرسمة هذي توضح الصورة اللي فوق (سوو سكيب لو فاهمينها ☺ )

## ❖ The roles of activated macrophages in chronic inflammation:

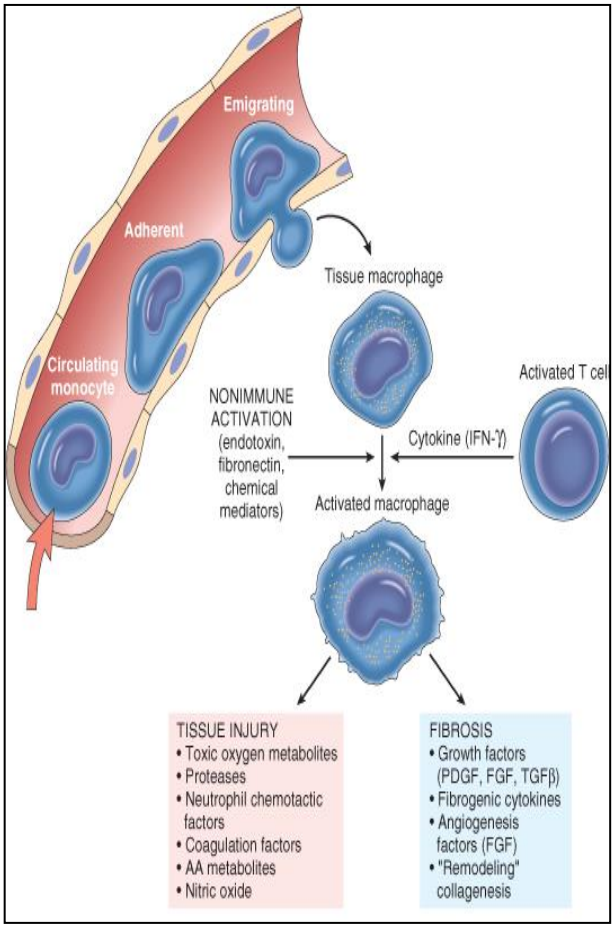
**A- display antigens to T lymphocytes and respond to signals from T cells, thus setting up a feedback loop.**

**B- secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and eicosanoids).**

**C- to eliminate injurious agents such as microbes (by phagocytosis).**

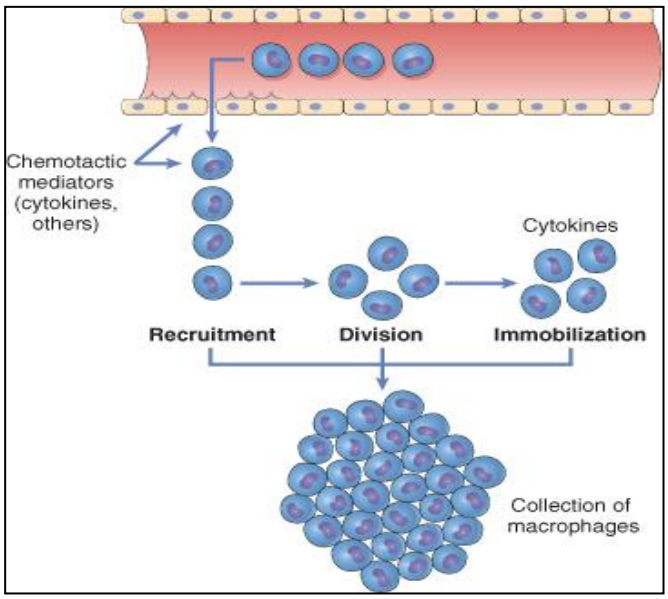
**D- It is responsible for much of the tissue injury in chronic inflammation (by producing ROS & others free radicals)**

**E- to initiate the process of repair.**
Fibrosis: **increase in extracellular matrix (ECM) → formed of collagen.**
Angiogenesis: **formation of new blood vessels from old blood vessels. This can be seen in connective tissue to increase the blood supply and help in the healing process. and they are mediated by some chemical mediators (vascular proliferation factor / vascular derived proliferation factor) (VPF/VDPF)**




## ❖ macrophage accumulation (in tissue) persists by:

A- Recruitment of monocytes from the circulation
B- Local proliferation of macrophages
C- Immobilization of macrophages



## Lymphocytes

*T- lymphocytes function is cell mediated immunity .

*CD4+T lymphocytes promote inflammation and influence the nature of the inflammatory reaction.

*B – lymphocytes function in humoral immunity .

*B – lymphocytes transferred to plasma cells ( when it is activated).

*plasma cells found in tissue.

**They are characterized chronic inflammation**

---

## Subsets of helper T (TH) cells(cell mediated immunity )

*In response to stimuli (mostly cytokines ) CD4+T cells will differentiate to*

### $T_H1$

*TH1 cells produce the cytokine IFN-γ*

Function: *activates macrophages in the classical pathway*

### $T_H2$

*TH2 cells secrete IL-4, IL-5, and IL-13*

Function: *recruit and activate eosinophils and responsible for macrophage activation.*

### $T_H17$

*TH17 cells secrete IL-17 and other cytokines*

Function: *induce the secretion of chemokines responsible for recruiting neutrophils and monocytes into the reaction.*

# Activating and inhibitory receptors of natural killer (NK) cells

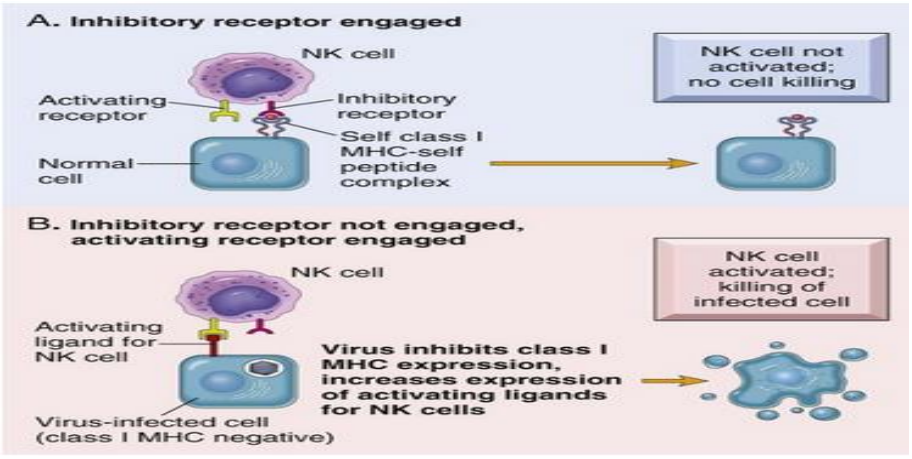
**Healthy** cells express self class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells

(الخلايا السليمة تتميز بإنه يتواجد على سطحها MHC بالتالي تتعرف عليه على (inhibitory receptors ) سطح NK وبكذا نضمن إن الخلية ما تتحل بفعل NK

**In infected** and stressed cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged, and ligands for activating receptors are expressed

The result is that NK cells are activated and the infected cells are killed.

( على العكس من الخلية السليمة ، الخلية المصابة يكون على سطحها ( ligand) اللي بدورها يتم التعرف عليها بواسطة (activating receptors ) وبالتالي NK تتنشط والخلية المصابة تتحل




**Natural killer cells (NK)**

# Humoral immunity ( B – lymphocytes )

B – lymphocytes recognize antigens

under the influence of TH cells and other stimuli they transfer to

Plasma cells (anti-body secreting cells )

Activated B – cells undergo

long-lived memory cells

heavy-chain class switching

affinity maturation

## IgE

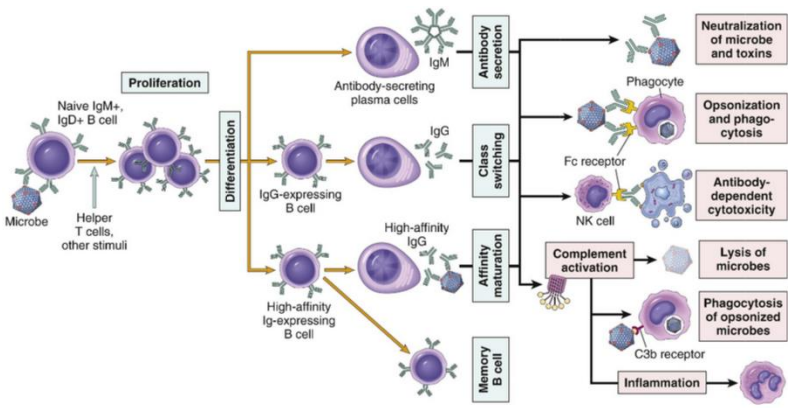
Function : mast cell and eosinophil activation

## IgG- IgM

Function : activate complement

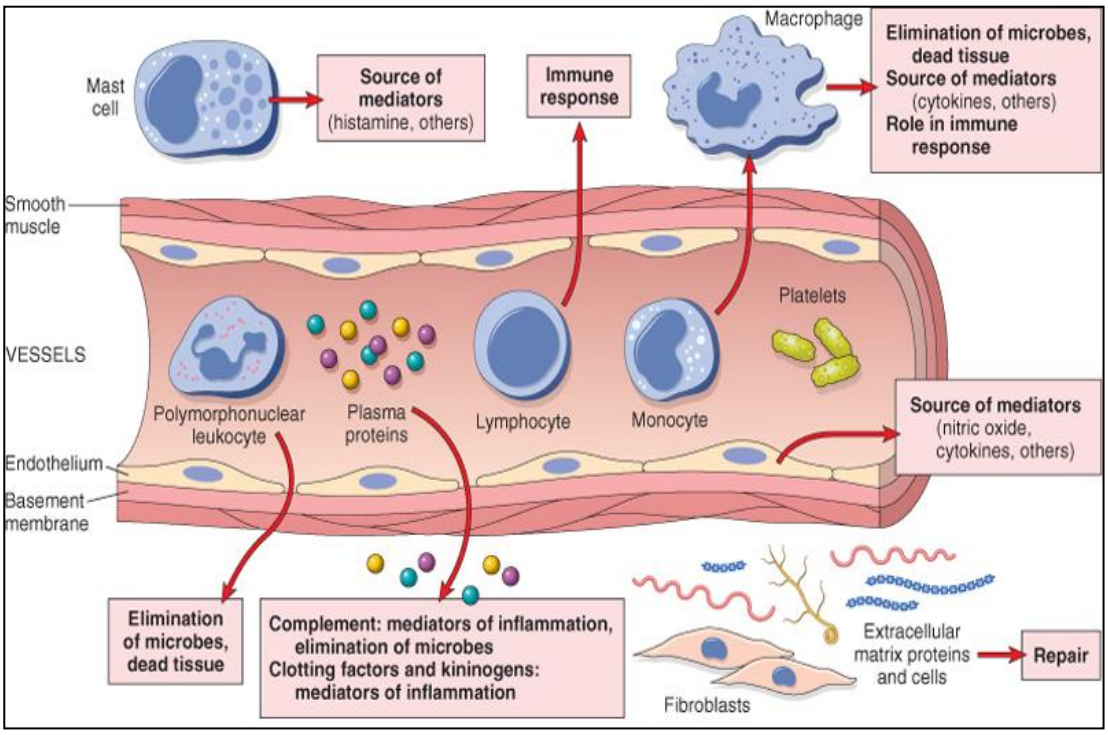
## IgA

Function : mucosal immunity




Humoral immunity

the picture shows the cells and their functions




# Phagocytosis :

**(هي عملية ابتلاع الجراثيم والأجسام الغريبة)**

ukocyte Activation: (العمليات إلي تنشط فيها خلايا الدم البيض

1-Phagocytosis
2-Intracellular destruction
3-Liberation of substances that destroy extracellular microbes and dead tissues (تطلق مواد عشان تدمر الميكروبات والانسجة الميتة).
4-Production of mediators.

**The phagocytic cells are :**

1- Neutrophils.
2- Macrophages (histiocytes). إذا كانت نشطة للفاجوسايوسز يسير اسمها ماكروفيج أما إذا كانت راكدة ما تسوي شيء يسير اسمها هيستوسايت
3- Eosinophil (weakly phagocytic).

Note : In some diseases we check the blood for complement system protein. If they were low, this means that they have been used, and this means that I am dealing with an inflammatory process or inflammation. If it was normal it means that the immunologic system is not activated and I am not dealing with an inflammatory process.(434 team)

## Phagocytosis occur in three steps:

1- Recognition and Attachment of the particle to be ingested by the leukocyte.

This step occur by **opsonins :** which are substances that coating particle , such as a microbe, to target it for phagocytosis.

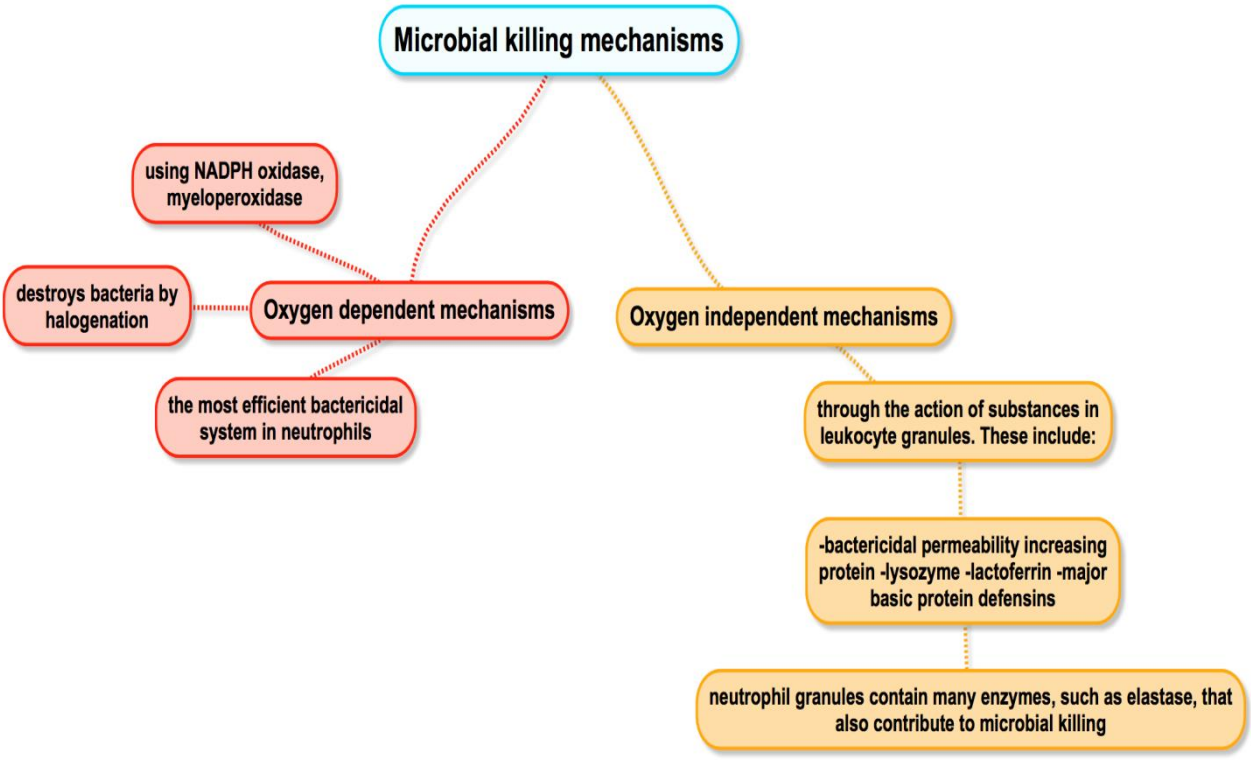
Important **opsonins** are :

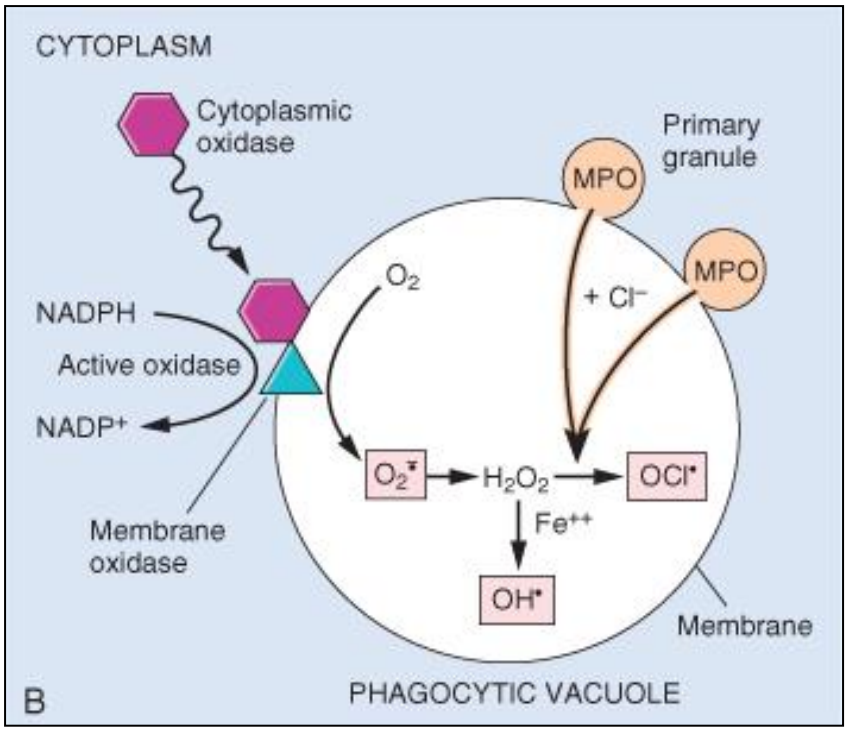
1) C3b "complement protein" : It is an opsonin, it prepares the microorganism for phagocytosis. It will coat the antigen and prepare it for phagocytosis.
2) Immunoglobulins : it is "Fc proteins" of "IGg antibodies. When immunoglobulins coat the bacteria or antigen they make them amenable.
3) Plasma proteins : such as collectins and lectins (mannose-binding lectin).

Note: **C3b & Fc proteins , act as a receptors in phagocytosis.**

2- Engulfment by the cytoplasm (pseudopods) resulting in vacuole called **phagosome**.
3- The **phagosome** fuses with **lysosomal granule** resulting in **phagolysosome,** than the ingested material is killed.

*Phagocytosis*
**Killing and Degradation**





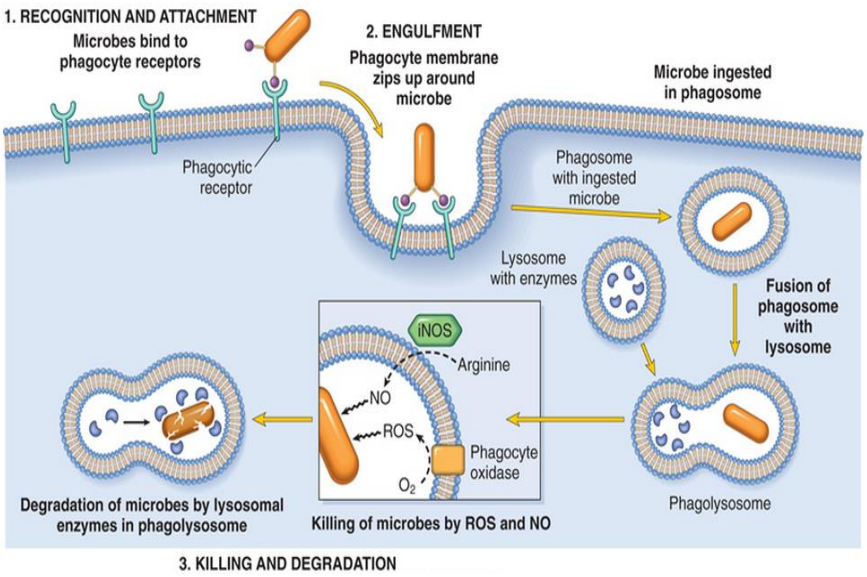

$O2 \xrightarrow{\text{NADPH Oxidase}} O_2^-$

$O_2^- \xrightarrow[\text{(SuperOxide Dismutase)}]{\text{SOD}} H_2O_2$

$H_2O_2 \xrightarrow{\text{MPO in presence of } Cl^-} HOCL$

*This picture is for the O-dependent

## Summary of phagocytosis:



## Defects in Leukocyte Function and Associated Diseases:

Defects in leukocyte function, both genetic and acquired, lead to increased vulnerability to infections:

- Defects in leukocyte *adhesion*.
- Defects in *phagolysosome function*.
- Defects in *microbicidal activity*.

### 1) Genetic:

***Defects in Adhesion:*** Leukocyte adhesion deficiency type 1 and 2.

***Defects in Phagocytosis:*** Chédiak-Higashi syndrome. (Protein involved in organelle membrane fusion)

***Defects in Microbicidal Activity:*** Chronic granulomatous disease. (Decreased oxidative burst).

---

### 2) Acquired

***Chemotaxis:*** Thermal injury, diabetes, malignancy, sepsis, immunodeficiencies.

***Adhesion:*** Hemodialysis, diabetes mellitus.

***Phagocytosis and microbicidal activity:*** Leukemia, anemia, sepsis, diabetes, neonates, malnutrition.

## Chediak-Higashi syndrome

-a defect in phagolysosome formations.

-an autosomal recessive disease that results from disordered intracellular trafficking of organelles, ultimately impairing the fusion of lysosomes with phagosomes. (no phagolysosomes)

Clinical feature:

- Increased risk of pyogenic infection.
- Neutropenia (defect in generation from BM).
- Giant granule formation (granules formed cannot move in cytoplasm).
- Defective primary hemostasis ( platelet granule are not secreted).
- Albinism.
- Peripheral neuropathy.

## Chronic granulomatous (CGD)

2 types:
A. X-linked: NADPH oxidase (membrane component)

B. Autosomal recessive:
1. NADPH oxidase (cytoplasmic components)
2. Myeloperoxidase deficiency: (absent MPO-H2O2 system) pt. have increased risk of candida infection.

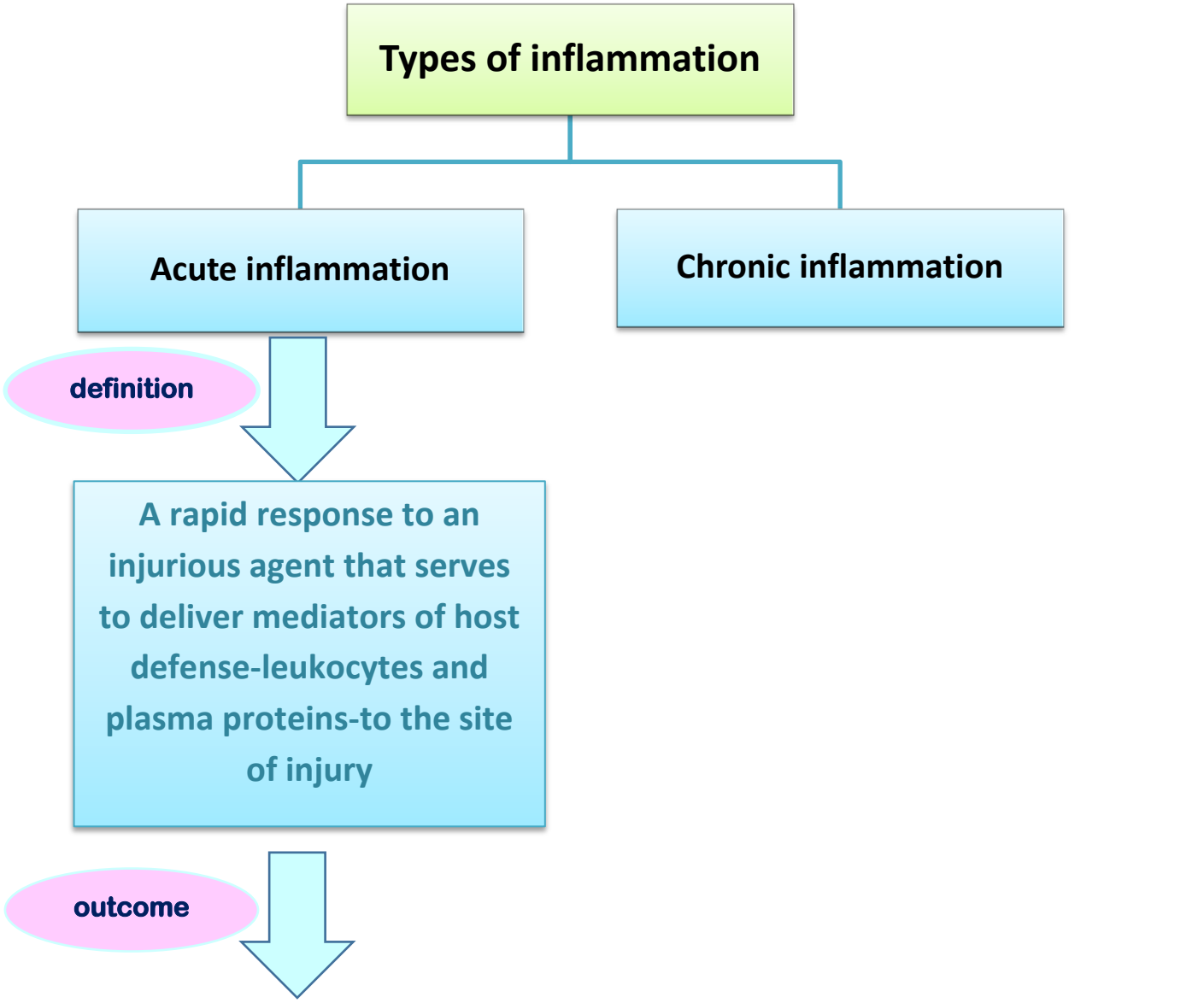
-Due to NADPH oxidase defect (X-linked or autosomal recessive)
-Leads to infection and granuloma formation with catalase-positive organisms, particularly staphylococcus aureus, pseudomonas cepacia, serratia marcescens, nocardia and aspergillus.
-Nitroblue tetrazolium test (NBT): is used to screen for CGD. Leucocytes are incubated with NBT dye, which turns blue if NADPH oxidase can convert O2 to O2-, but remain colorless if NADPH oxidase is defected.

-NBT test is normal in Myeloperoxidase deficiency type.

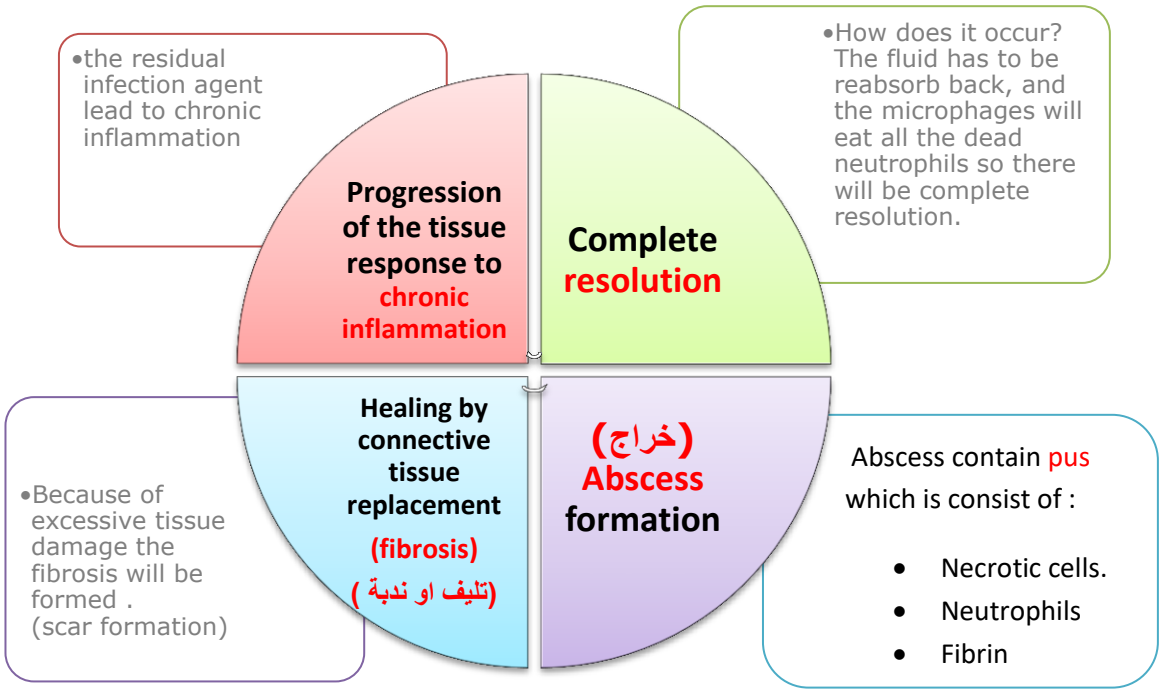
## Comparison of Chronic Granulomatous Disease and Myeloperoxidase Deficiency

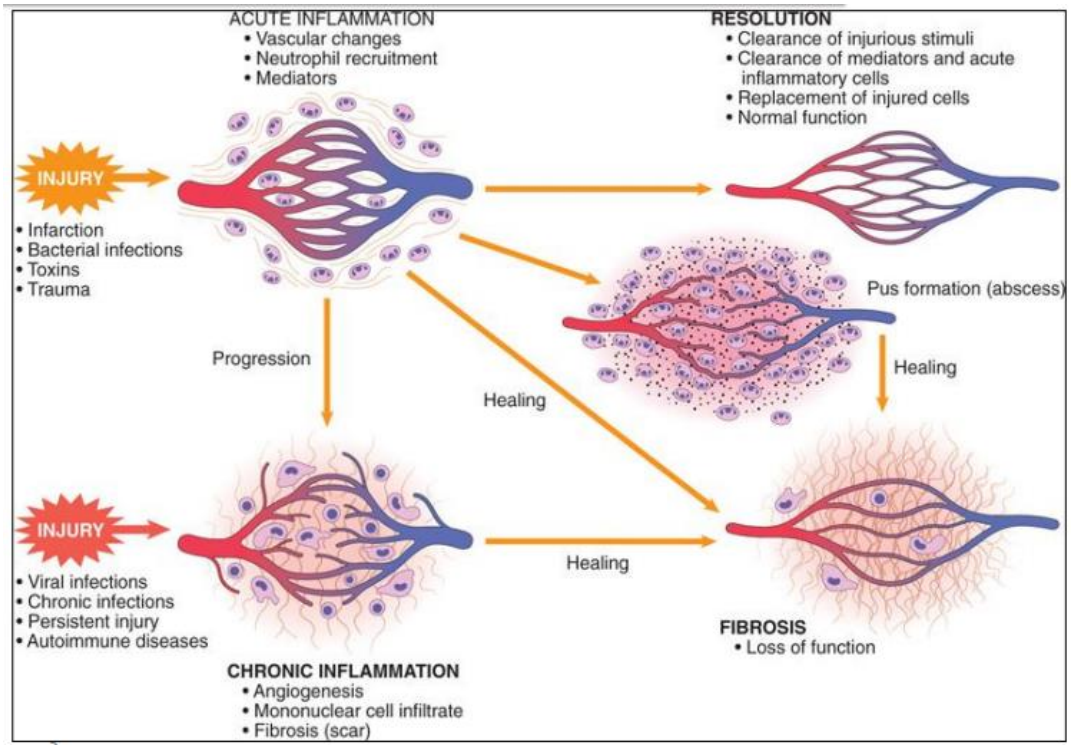
| | CHRONIC GRANULOMATOUS DISEASE | MYELOPEROXIDASE DEFICIENCY |
|---|---|---|
| Inheritance pattern | X-linked recessive | Autosomal recessive |
| NADPH oxidase | Absent | Present |
| Myeloperoxidase | Present | Absent |
| Respiratory burst | Absent | Present |
| Peroxide ($H_2O_2$) | Absent | Present |
| Bleach (HOCl) | Absent | Absent |

E) Be aware of the various complication of the inflammatory response, formation of pus and the production and manifestation of chronic inflammation.



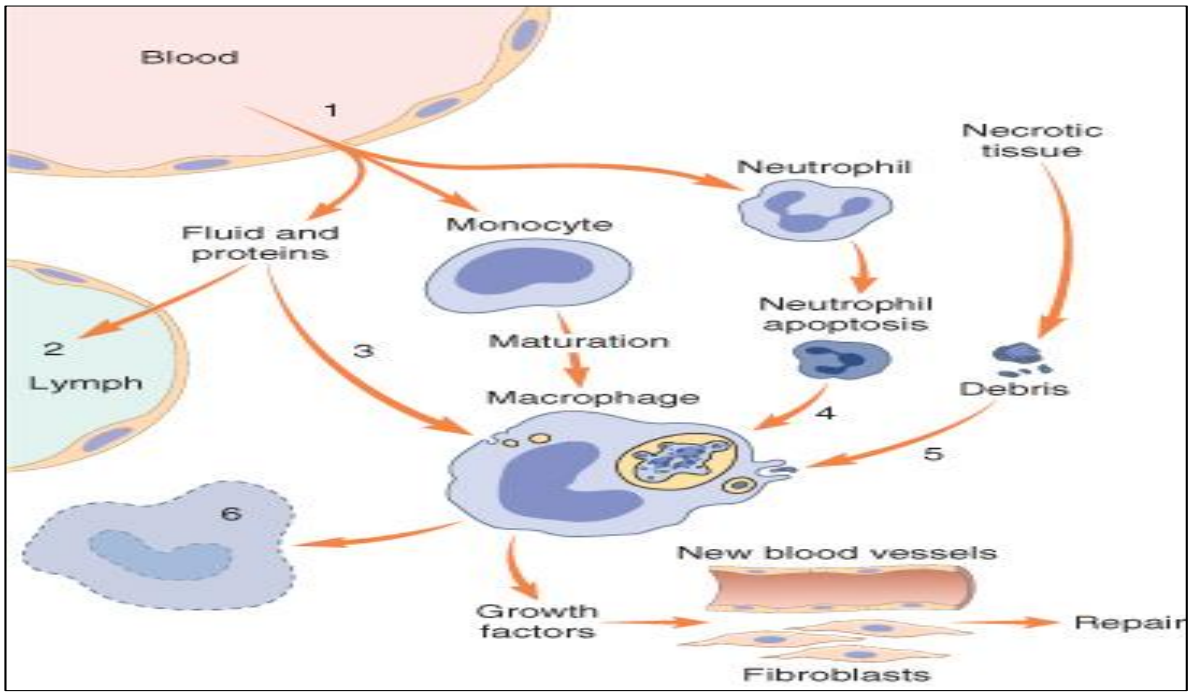
## Acute inflammation may have one of the four outcomes:



## Events in the resolution of inflammation:

- **This involves neutralization, decay, or enzymatic degradation of the various chemical mediators; normalization of vascular permeability; and cessation توقف of leukocyte emigration نزوح and apoptosis**
- **The necrotic debris, edema fluid, and inflammatory cells are cleared by phagocytes and lymphatic drainage**



# chronic inflammation

it is Inflammation of prolonged duration (weeks to years) in which continuing inflammation,tissue injury, and healing, often by fibrosis,proceed simultaneously

## essensial changes in chronic inflammation

Absence of polymorphs (natural life span of 1–3 days); the appearance of:
macrophages,lymphocytes and often plasma cells

Proliferation of vascular endothelium by 'budding'
– formation of new capillaries (angiogenesis).

Proliferation of fibroblasts with collagen production leading to Fibrosis

## causes of chronic inflammation

Persistent infections by microbes that are difficult to eradicate These include :

- Mycobacterium tuberculosis
- Treponema pallidum (the causative organism of **syphilis**)
- certain viruses and fungi

– All of which tend to establish persistent infections and elicit (يثير) a T lymphocyte-mediated immune response called delayed-type hypersensitivity.

Immune-mediated inflammatory diseases (hypersensitivity diseases):

Diseases that are caused by excessive and inappropriate activation of the immune system leading to autoimmune diseases.

e.g.
**– Rheumatoid arthritis**
**– inflammatory bowel disease**
**– psoriasis** (صدفية)
– Immune responses against common environmental substances that cause allergic diseases, such as **bronchial asthma**.

Prolonged exposure to potentially toxic agents:

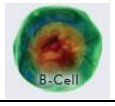
- Examples are non-degradable **exogenous** materials such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (**silicosis**)

- **Endogenous** agents such as cholesterol crystals, which may contribute to **atherosclerosis**

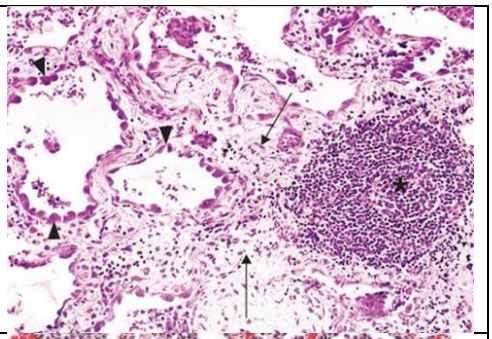
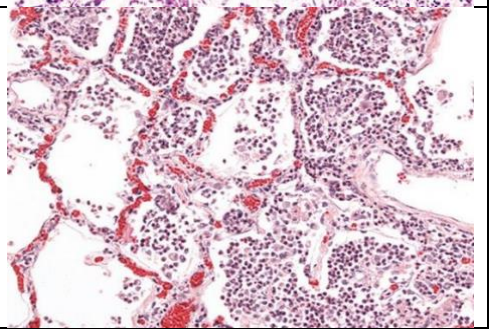
Mild forms of chronic inflammation may be important in the pathogenesis

of many diseases that includes:

- neurodegenerative disorders such as **Alzheimer disease**
- **atherosclerosis**
- **metabolic syndrome** and the associated type **2 diabetes**,
- and some forms of cancer in which inflammatory reactions promote tumor development

| Characteristics of chronic inflammation | |
|---|---|
| 1. Infiltration with **mono**nuclear cells: | Macrophages   |
| | Lymphocytes   |
| | Plasma cells   |
| 2. Tissue destruction | induced by the products of the inflammatory cells |
| 3. Repair | vessel proliferation (angiogenesis) and fibrosis |

Remember *Acute inflammation is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate.

| | |
|---|---|
| Lung chronic inflammation |  |
| Lung acute inflammation |  |

## The difference between acute and chronic inflammation:

| Feature | Acute | Chronic |
|---|---|---|
| **Onset** | Fast: minutes or hours | Slow: days, weeks |
| **Cellular infiltrate** | Neutrophils | lymphocytes and macrophages |
| **Tissue injury, fibrosis** | Mild self-limited | Often severe & progressive |
| **Local & systemic signs** | Prominent | Less prominent may be subtle |
| **BOTH** | - Eosinophil.<br>- Macrophages or histiocytes :<br>Histiocytes (inactive during phagocytosis and found in tissue).<br>Macrophages(Active during phagocytosis). | |

**NOTE: some types of inflammation start acute and then develop to chronic and some are chronic from the beginning, such as :**
**Tuberculosis , viral infection (hepatitis B and C), Autoimmune diseases and Brucellosis (حمى المالطية).**

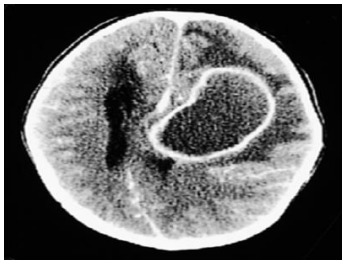
# Morphologic Patterns of Inflammation

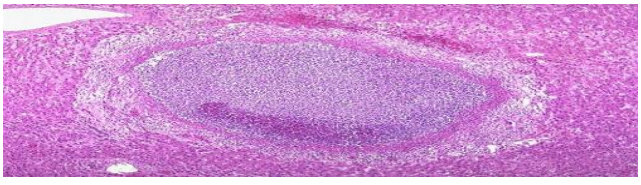
## SUPPURATIVE OR PURULENT INFLAMMATION

- Characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid.
- Caused by pyogenic bacteria (pus-producing) E.g. (Staphylococcus aureus and streptococci).
- **Suppurative abscess:** An enclosed collection of pus consists of a mixture of neutrophils and necrotic debris.

- **Abscesses** : localized collections of purulent inflammatory tissue caused by suppuration تقيح buried in a tissue, an organ, or a confined space.(deep down in organ) , and it contains pus.

NOTE : لو مريض عنده Abscesses,نحلل pus بواسطة cell culture عشان نعرف نوع الباكتيريا .





## FIBRINOUS INFLAMMATION

** bread and butter appearance.

It consists of fibrin which comes from activation of coagulative cascade by factor 12 (Hageman).

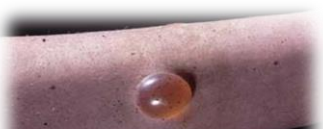
- A fibrinous exudate is characteristic of inflammation in the lining of **body cavities**, such as the meninges, pericardium (membrane closing the heart) and pleura.
(Larger molecules such as fibrinogen –one of the clotting factor- pass the vascular barrier)
- Fibrinous exudates may be removed by fibrinolysis, if not: it may stimulate the ingrowth of granulation tissue (*organization*)

.

## SEROUS INFLAMMATION

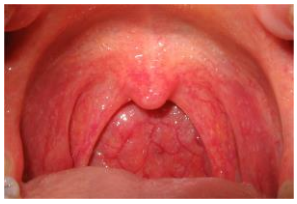
Marked by the accumulation of a thin fluid into subcutaneous tissue or epidermis (Characteristicly occur in burn or physical rubbing)

NOTE: there is no proteins in serous inflammation so it is **Transudate.**



## Catarrhal Inflammation

** increased secretion of mucus
Inflammation affects mucosa-lined surfaces with the outpouring of **watery mucus.**
Eg: (الرشح أو الزكام) common cold
.



## Pseudomembranous Inflammation

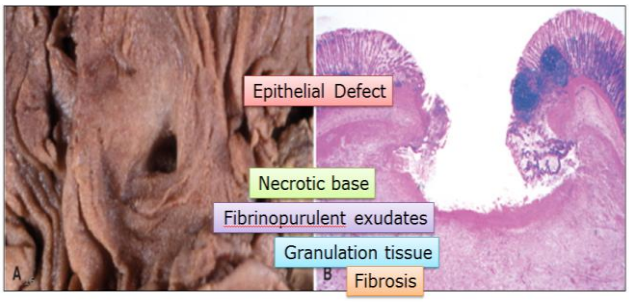
Cause membrane which had been formed by inflammation (caused by fibrin and neutrophils)
More explanation :a form of exudative inflammation that involves mucous and serous membranes; relatively large quantities of fibrin in the exudate result in a rather tenacious membrane-like covering that is fairly adherent to the underlying acutely inflamed tissue.
Eg: colitis and tonsillitis.

## Cellulitis

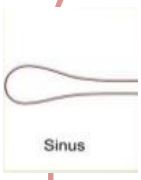
** Widespread infection
Denotes a spreading acute inflammation through interstitial tissue.
Usually caused by staphylococcus and streptococcus.

## ULCERS

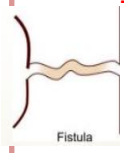
usually is chronic **
An ulcer القرحة is a local defect of the surface of an organ or tissue that is produced by the sloughing انسلاخ (shedding) of inflammatory necrotic .tissue



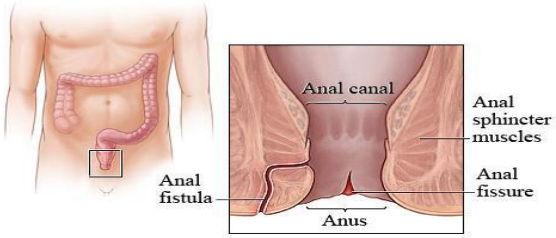
## Sinus and Fistula




- **Sinus**: Blind track lined by granulation tissue leading from epithelial surface down into the surrounding tissues.(has 1 opening ) (مثل الناسور) usually chronic inflammation.




- **Fistula** : is an abnormal communication between the lumen or surface of one organ and the lumen or surface of another, or between vessels.(has 2 opening), usually chronic inflammation.



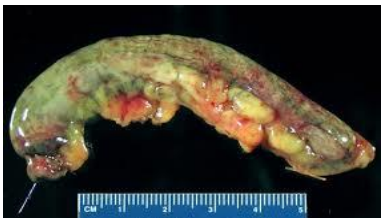

- Anal fistula connects skin surface with the inside of GIT.

## Gangrenous inflammation

435 Team

Sometimes the inflammation becomes
Severe and will activate the coagulation
Cascade, this will result in accumulation
Of platelets, thrombin, and fibrin and will clot the blood vessels.

If inflammation occurs for a long time, local ischemia happens→ gangrene.
e.g. gangrenous appendicitis

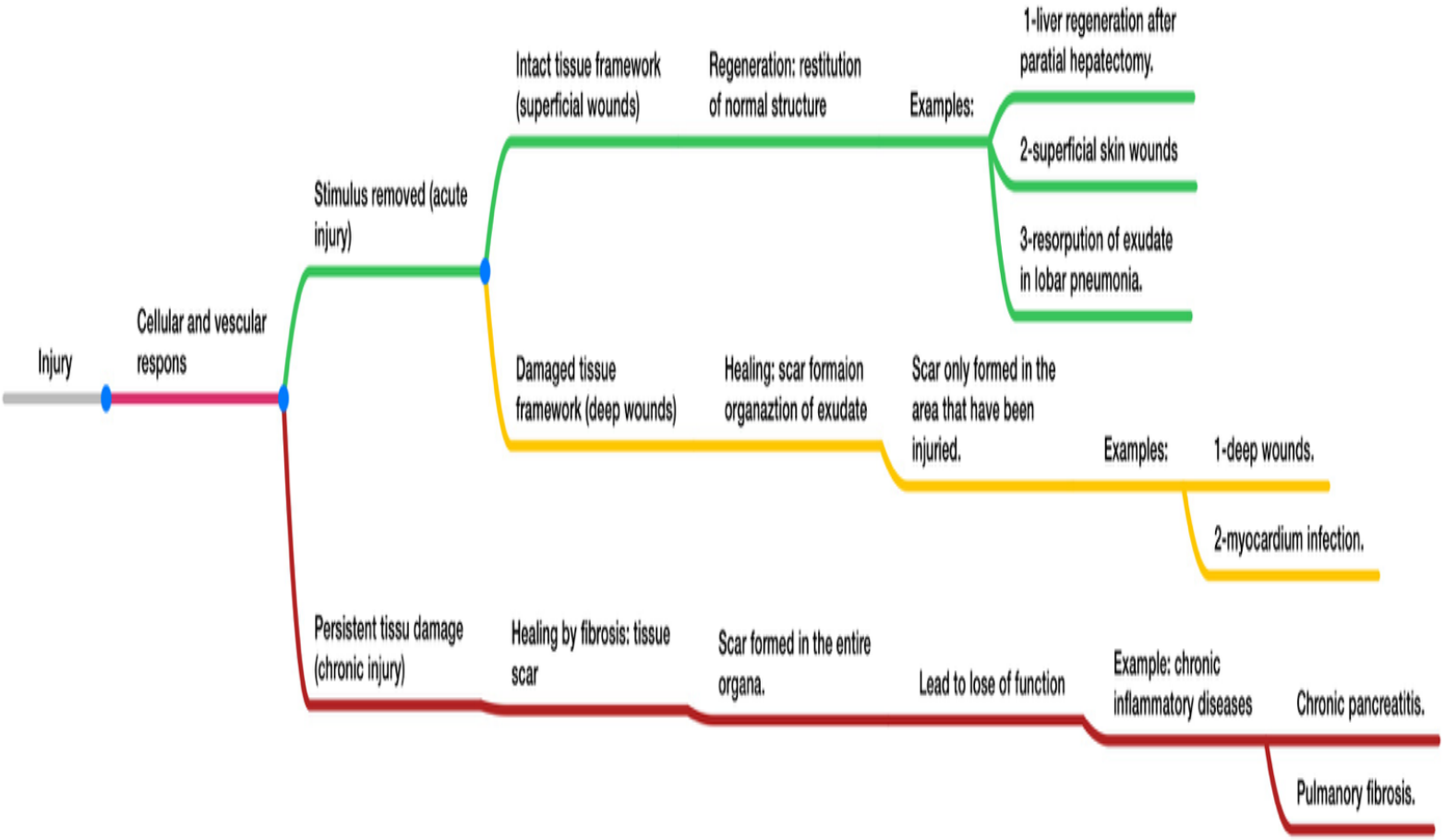


**F) Understands the concept of healing and repair with wounds healing by first and second intention as an example.**

## The aim of repair process:

To restore the tissue to it is original state after inflammatory reaction.

## The repair depends on the type of :



**The repair depending on the type of cells:**

**1- Labile cells:**

- have short live span, rapidly regenerate
- have the power to divide all the time.
- E.g: Squamous, columnar, transitional epithelia, hematopoietic, lymphoid tissue (Epidermis of the skin).

**2-Stable cells:**

- longer living cells than the labile cells
- low mitotic rate (divide whenever needed)
- regenerate under proper condition.
- E.g: liver ( hepatocytes), renal tubular cells, glandular organs and mesenchymal cells.

**3-Permanent cells:**

- have a long live span.
- no mitotic activity (can't reproduce themselves after birth).
- E.g: Neurons, cardiac muscle cells.

**Supporting Tissues**

- Collagens: are supporting tissues secreted by fibroblasts. They are a series of complex polypeptides that bind epithelial tissues and other connective tissues to themselves and to each other providing tensile strength.

- Basement membranes: which lie at the interface of cells and stroma, and they support the overlying cells. They include the following materials:

1- Entactin
2- Heparan sulfate
3- Laminin
4- Proteoglycans and
5- type IV (Four) collagen.

# Healing

As early as 24 hr. after injury fibroblast and vascular endothelial cells begin to form **Granulation tissue** at the site of inflammation (by 3-5 days).

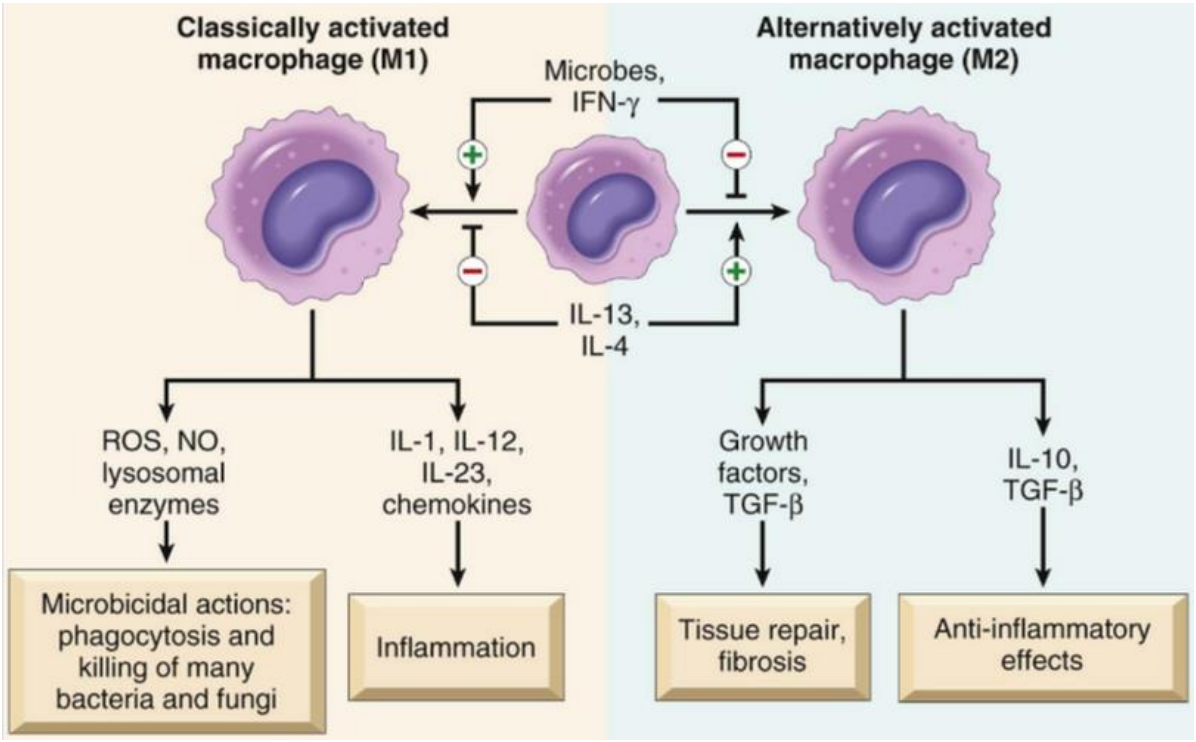
**Granulation tissue** consist of:

1- Fibroblasts surrounded by extracellular matrix.
2- Newly formed blood vessels.
3- Macrophages and some other inflammatory cells.

## The role of macrophages in wound healing:

1- Cleanup of debris, fibrin and other foreign material
2- Induce other cells such as fibroblast and angioblast.
3- Stimulation of matrix production
4- Secrete collagenases enzyme, which causes the scar formation.

## Macrophage has two types as shown in the picture:



### Fibroblast Migration and Proliferation:

— *Migration* of fibroblasts to the site of injury and their subsequent *proliferation* are triggered by multiple growth factors, including mainly TGF-β and others e.g. PDGF, EGF, FGF, and the cytokines IL-1 and TNF

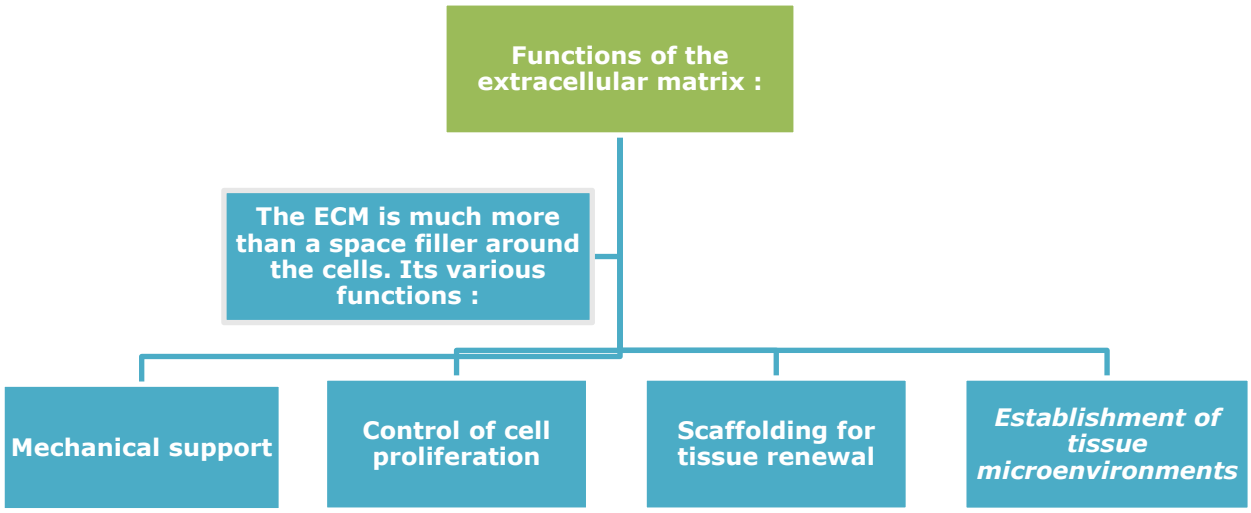
— This lead to:

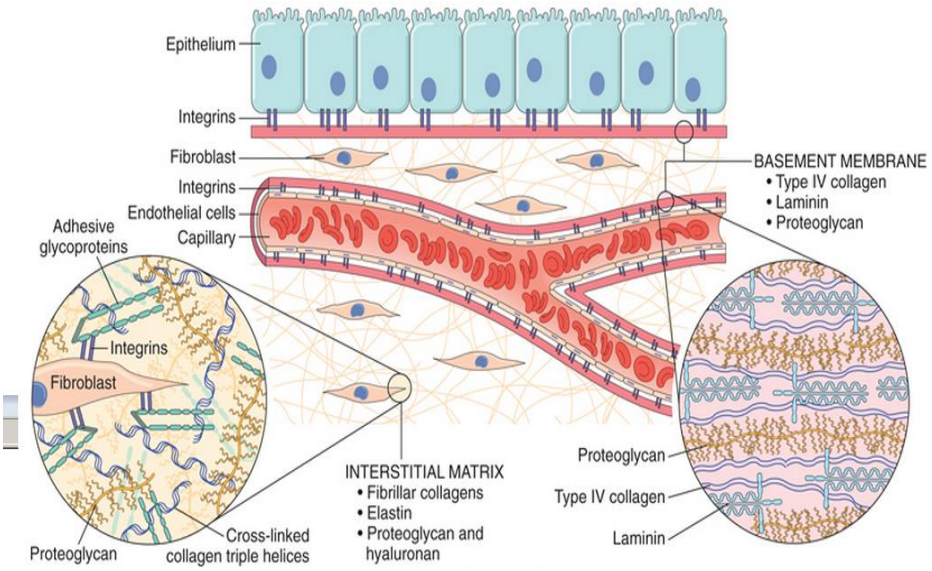
1. *increased synthesis of collagen and fibronectin.*
2. *Decreased degradation of extracellular matrix (ECM) by metalloproteinases.*

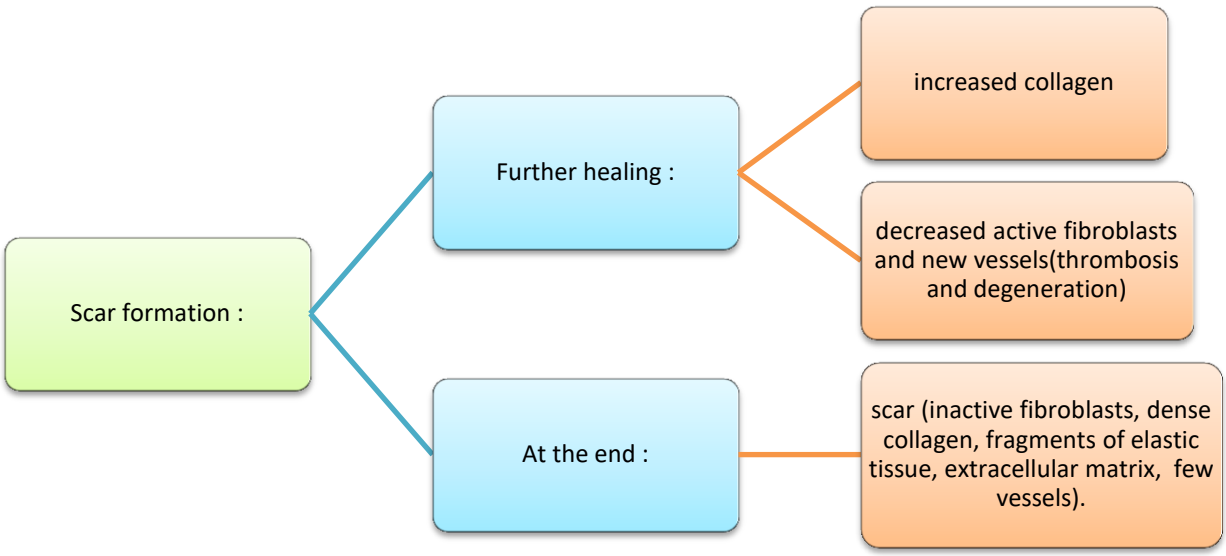
### — Extra Cellular Matrix Deposition and Scar Formation:

— As repair continues, the number of proliferating endothelial cells and fibroblasts decreases.

— *Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation*.





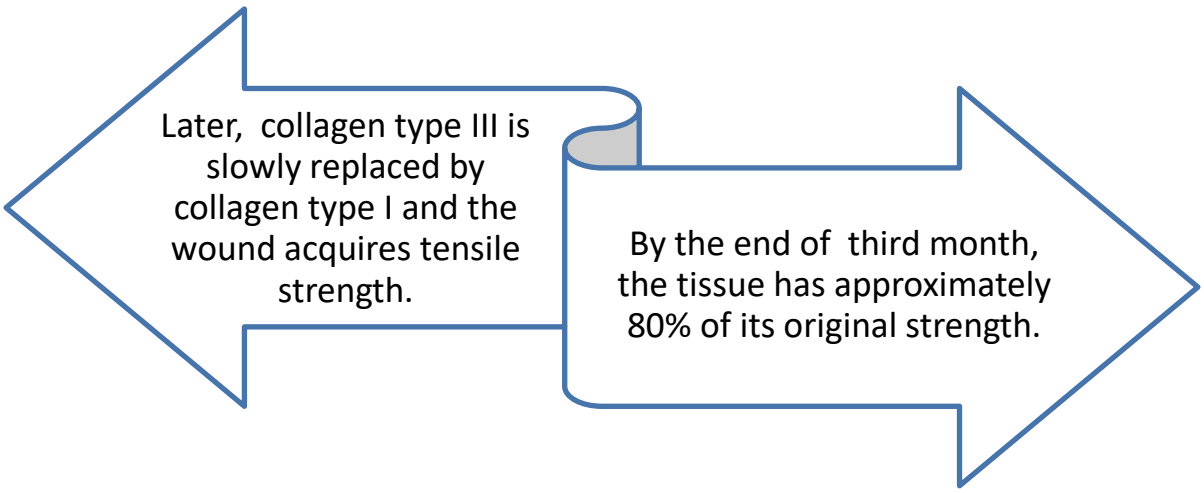

**1\Healing by first intention (Primary union):**

Healing by first intention occurs when edges of the wound are approximated and the wound is quickly covered with epithelium and bound together by collagen. At first, the surface epithelial gap and the opposed connective tissues contain blood clot and debris. The epithelium regenerates, and the Capillaries, Neutrophils, Macrophages and Fibrocytes migrate into the clot. Within a few days, the scab at the surface falls, revealing re-epithelialization and the blood clot is removed by macrophages. Collagen laid down by fibroblasts causing endothelial cells to proliferate, and producing granulation tissue: neutrophils decrease in number,, macrophages increase in number,, collagen in the gap increases,, blood vessels decrease in number,, the scar begins to contract.

Healing by first intention is best exemplified by the healing of an appeased surgical incision.

| | |
|---|---|
| **24 hr.:** | hematoma & neutrophils, mitotic activity of basal layer, thin epithelial layer<br>Hageman factor (factor 12) will activate both the coagulation sequence and the kinin system as an initial response to this injury |
| **day 3:** | macrophages, granulation tissue |
| **day 5:** | collagen bridges the incision, epidermis thickens |
| **2nd week::** | continued collagen and fibroblasts, blanching |
| **End of 1st month:** | scar (cellular connective tissue, intact epidermis, lost appendages). |

## Cont. primary union( healing by first intention):




### 2\Healing by second intention (Secondary Union):

Edges of the wound cannot be opposed in healing by second intention, leaving a defect containing blood clot and debris. The process of wound healing is similar to that in first intention, but takes longer time. The same cells take part in the process, but Granulation tissue is much more pronounced.

*Both types of healing lead to contraction of the wound in later stages due to the presence of myofibroblasts (contractile cells with properties of both fibroblasts and smooth muscle cells) The tensile strength of wounds in both types of healing increases by fibroblasts and the laying down of collagen.

*Healing by First and Second intentions are similar in the Process, the Activity and the Fate of the wound, but they differ in time, as the second intention takes longer period.

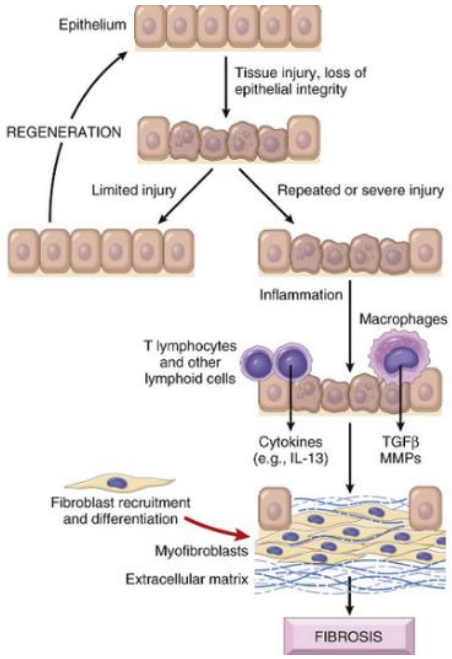
### 3\Abnormal repair:

The wound repair does not go well. The laying down of excessive collagen result in the formation of Keloid and Fibrous adhesions. Retardation of the healing occurs due to: Bacterial infection of the wound,, the presence of foreign bodies,, poor blood supply,, lack of mobility.

Deficient scar formation may result from deficiency of Vitamin C or Severe Protein deficiencies. Retarded wound healing and deficient scar formation may cause wound dehiscence (a wound separation at wound margin). If a large wound cannot be covered by epithelium, the resulting ulcer may require a skin graft. Wound contractures are related due to the action of myofibroblasts. This is seen especially after burns.

## Mechanisms of fibrosis:

- Persistent tissue injury leads to chronic inflammation and loss of tissue architecture.
- Cytokines produced by macrophages and other leukocytes stimulate the migration and proliferation of fibroblasts and myofibroblasts and the deposition of collagen and other extracellular matrix proteins.
- The net result is replacement of normal tissue by fibrosis.



**G) Knows the factors leading to poor healing and inadequate tissue repair.**

# Causes of Delayed Wound Healing

1. Infection → it prolongs inflammation → increase the local tissue injury.

2. Foreign bodies in the wound: inhibit formation of granulation tissue and the wound never heals.

3. Mechanical factors: movement slows healing because it needs stability.الحركة بعد العملية الجراحية ممكن تفتح الجرح او تؤخر اختفاؤه

4. Nutritional deficiencies:

   - Protein deficiency: No collagen fibers formed
   - Vitamin C deficiency: will inhibit collagen synthesis and retard(delay) healing. *collagen fiber consist of 3 peptide chains ,we need vitamin C to bond them.
   - Zinc and Copper deficiency.

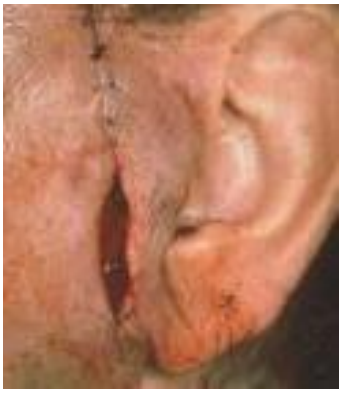
5. Poor perfusion: lack of blood supply due to arteriosclerosis, diabetes or obstructed venous drainage. It may lead to wound ulceration.
6. Chronic diseases: example: diabetes mellitus; it causes abnormal leukocytes function such as weak phagocytosis and weak migration to the site of injury.
7. Excess corticosteroid: steroid drugs can be administered as anti-inflammatory drugs by inhibiting the metabolize of cyclooxygenase and arachidonic acid and delay the formation of inflammatory factors. But this will result in weakness of the scar and delayed wound healing. However, the anti-inflammatory effects of glucocorticoids are sometimes desirable, for example, in corneal infections قرنية العين .

*Note: surgical sutures الخيوط الجراحية help heal the scar faster because they hold body tissues together after an injury or surgery.

## Complications in Cutaneous Wound Healing

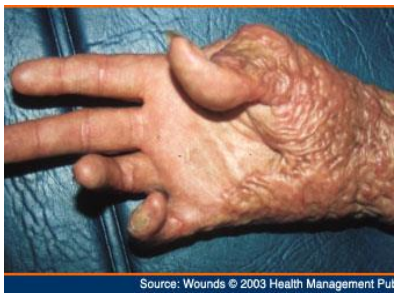
### Deficient scar formation:

- No scar formed.
- Caused by deficiency of Vitamin C or severe protein deficiency,etc. نفس الاسباب اللي قلناها فوق.
- It may cause wound dehiscence الجرح ينفتح بعد العملية الجراحية



### Formation of contractures:

- Most common in large wounds and burns.
- Contraction of the wound is related to myofibroblasts.




### Excessive formation of the repair components

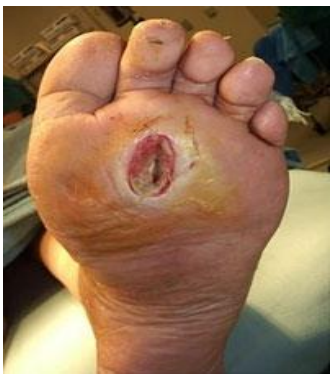
(collagen fibers and scar tissue)

- Keloid.
- Hypertrophic scars
- Fibrous adhesions: associated with Empyema and major abdominal surgeries.

**NOT enough formation of the repair components**

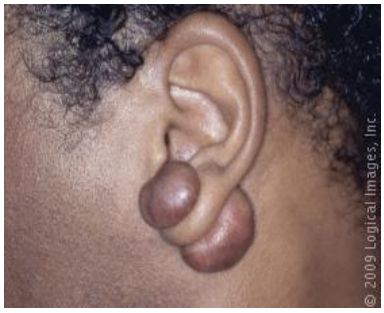
- Atrophic Scars: not enough connective tissue is formed to fill the wound.

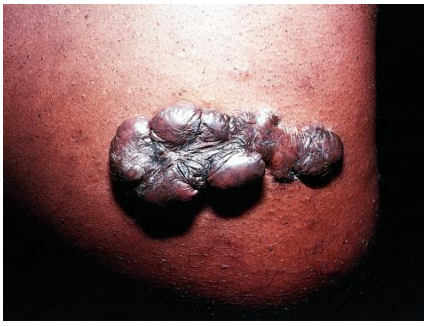
One more example of the complications is wound ulceration. It is caused by poor blood supply that leads to abnormal healing.



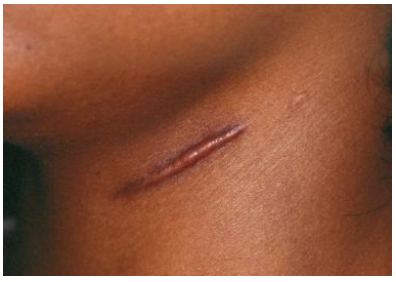
| Keloid | Both | Hypertrophic scar |
|---|---|---|
| Definition: Excessive scars composed of irregularly deposited hyalinized collagen bands. They may appear as bulging masses.<br>• The tissue extends beyond the borders of original wound.<br>• Does not regress with time, and tends to recur after excision.<br>• It is hypertrophic and hyperplastic C.T.<br>• It is more common in people with very dark skin (black)<br>• May appear after ear piercing تخريم الاذن | • Overgrowth Of dense fibrous tissue.<br>• Appear after burns or surgical wounds. | • The tissue does NOT expand beyond the boundaries of the initial injury.(take the same shape of injury)<br>• Characterized by erythematous and pruritic(itch).<br>• May undergo partial spontaneous resolution. |

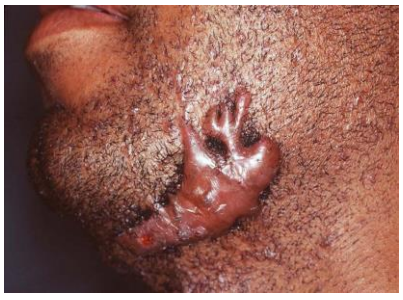
**keloid**

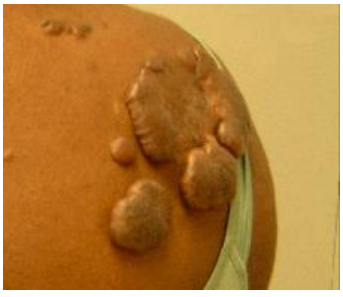


**Hypertrophic scar**







# References


- Doctor's slides.
- Doctors' notes.
- Robbins.
- 434 & 435 teams.

# Best Wishes and Good Luck

## Team Leaders

Ashwaq Almajed – Fahad Alzahrani

### Team members:

**Girls**

Nehal Beyari

Najd AlTheeb

Muneerah Alzayed

Atikah Kadi

Ghada AlHadlaq

Atheer AlRsheed

Amal AlShaibi

Haneen Alsubki

Doaa Walid

Rania Alessa

Raneem Alghamdi

Reema Alshayie

Ghadah Almazrou

Fatimah AlTassan

Lama AlTamimi

Njoud Alenezy

Aldanah Almutib

Ghadah AlMuhana

Deena AlNowiser

**Boys:**

Abdulaziz Al-Hussainy

Faisal Algharbi

Abdulaziz AlMohammed

Abdullah Altwiraqi

Abdullah Al-Aseri

Abdullah Bassam

Essam Alshahrani

Fahad Alaskar

Faris Aljaafar

Mohammed Hakami

Mohammed Almania

Moayed Ahmed

Moataz Altokhais

Sultan Almalki

Turki Alobathani

Waleed Almajlad

Waleed Al-askah

### Online Quiz:

For any suggestions or questions

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