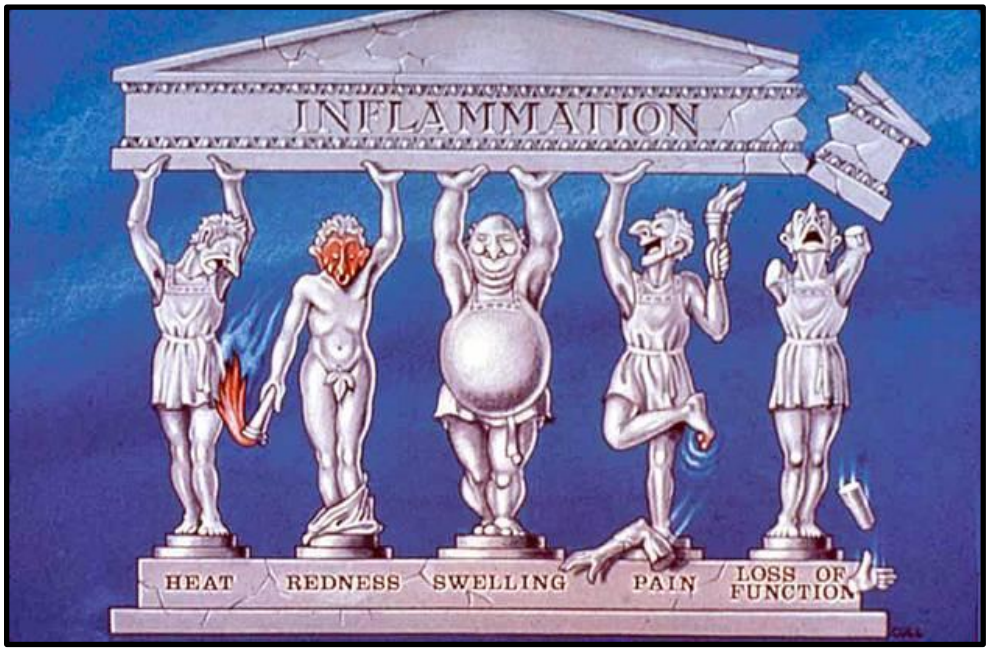
Inflammation & Repair

Team 434



434 Pathology Team

Definitions: Blue.
Examples: Green.
Important: Red.
Extra explanation: Gray. . It is only there to help you understand. If you feel that it didn't add anything to you just skip it.
Diseases names: Underline.

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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 differences between exudates and transudates.
D. Have some understanding of the 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 the various inflammatory cells including their role in both acute and chronic inflammation.
F. Be aware of the various complications of the inflammatory response, formation of pus and the production and manifestations 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.
I. Appreciate the high prevalence of granulomatous diseases in the Kingdom of Saudi Arabia with special emphasis on tuberculosis.
J. Understands the mechanisms and causes of granuloma formation with special emphasis on interaction between T lymphocytes, macrophages and epithelioid histiocytes.

Definition of inflammation

Inflammation: is a local response to tissue injury. Any tissue that reacts to cellular injury or injurious agent will cause inflammation. It is a defense mechanism against any agent that comes from outside the body.

- The use of "**-itis**" in the end of the word mean inflamed tissue or organ.
  - For Example: **Pancreatitis** means inflammation of the pancreas.

Infection: a term used to describe a **biological agent** inside a tissue causing inflammation (bacteria, viruses, parasites and fungi)

- Inflammation is not always a bacterial infection.

مثال واحد لدغته نحلة، دخلت في أيده خشبة، واحد كسرت يده، مافي باكتيريا بس صار عنده كسر biopsy بعد ساعة من مكان الكسر.. لكن لو بتخذ بتلاقي خلايا التهابية كثيرة. وهذا يسمى **physical injury**.

Causes of inflammation:
Bacteria, viruses, parasites, fungi, radiation, physical injury, thermal injury, trauma, frostbite (frostbite happens with very low temperatures in exposed areas such as the ears, tip of the nose, etc.), burns, immunological reactions, fractures, infection after surgeries, and toxic substances.

Signs of inflammation:

Cardinal signs of inflammation:
1- Swelling (**tumor**).
2- Redness (**rubor**).
3- Warmth (**calor**).
4- Pain (**dolor**).
5- Loss of function (**functio laesa**).

- These signs appears in the Surface of the skin and also in the internal organs. Like **acute Appendicitis.** (in the internal organs instead of the **redness** there is **vascular congestion**[1] and it is the cause of the redness that appears in the skin)

Cellulitis: inflammation in the interstitial underneath the skin because of bacteria .

Systemic signs of inflammation:
1. Fever (it is usually caused by the Chemical mediators of inflammation).
2. Chills [2].
3. Malaise[3] (increased fatigue): the patient feels tired.
4. Vomiting (in kids).
5. Increased **erythrocyte sedimentation rate ESR** (will be discussed later).
6. Increased levels of **C-reactive proteins.**

[1] احتقان في الأوعية الدموية
[2] إرتجاف
[3] توعك أو ضيق وتعب.

C-reactive protein: is a type of **acute phase proteins** secreted by the **liver** in response to inflammation.

Function of CRP: The function of CRP is felt to be related to its role in the **innate immune system**. Similar to immunoglobulin (Ig)G, it **activates complement**, binds to Fc [4]receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fc receptors leads to the generation of proinflammatory cytokines that enhance the inflammatory response.

Types of inflammation:

1. Acute inflammation.
2. Chronic inflammation.

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

* Acute inflammation usually associated with cellular changes.
* Chronic inflammation like **Tuberculosis.**

Inflammation process in general consist of :

1. Cellular events.
2. Vascular events.

SUMMARY

General Features of Inflammation

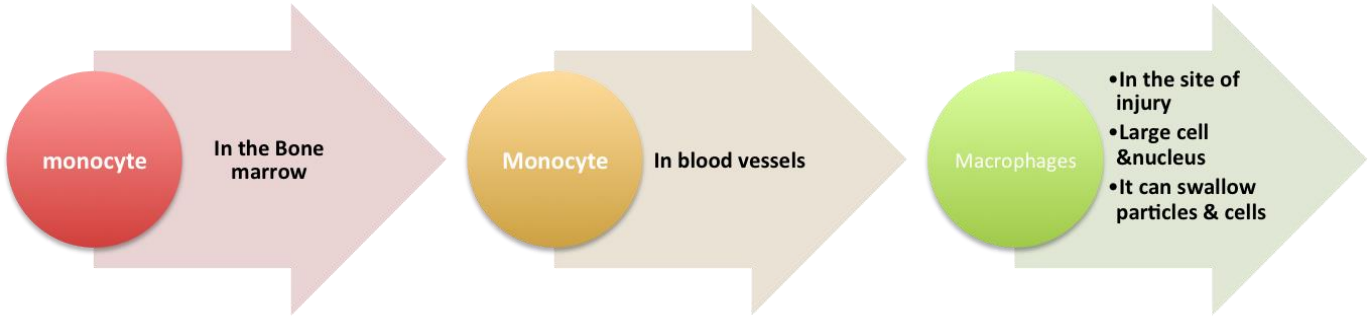
- Inflammation is a defensive host response to foreign invaders and necrotic tissue, but it is itself capable of causing tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five *R*s: (1) *r*ecognition of the injurious agent, (2) *r*ecruitment of leukocytes, (3) *r*emoval of the agent, (4) *r*egulation (control) of the response, and (5) *r*esolution (repair).
- The outcome of acute inflammation is either elimination of the noxious stimulus, followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

[4] receptors present on a variety of cells for the Fc fragment of immunoglobulins. These receptors recognize immunoglobulins of the IgG and IgE class.

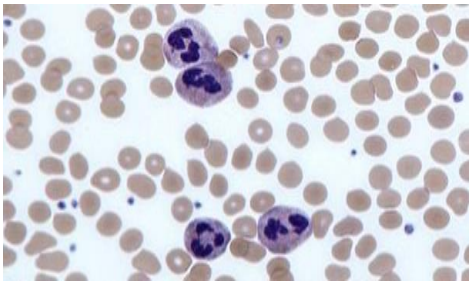
Cells involved in acute and chronic inflammation

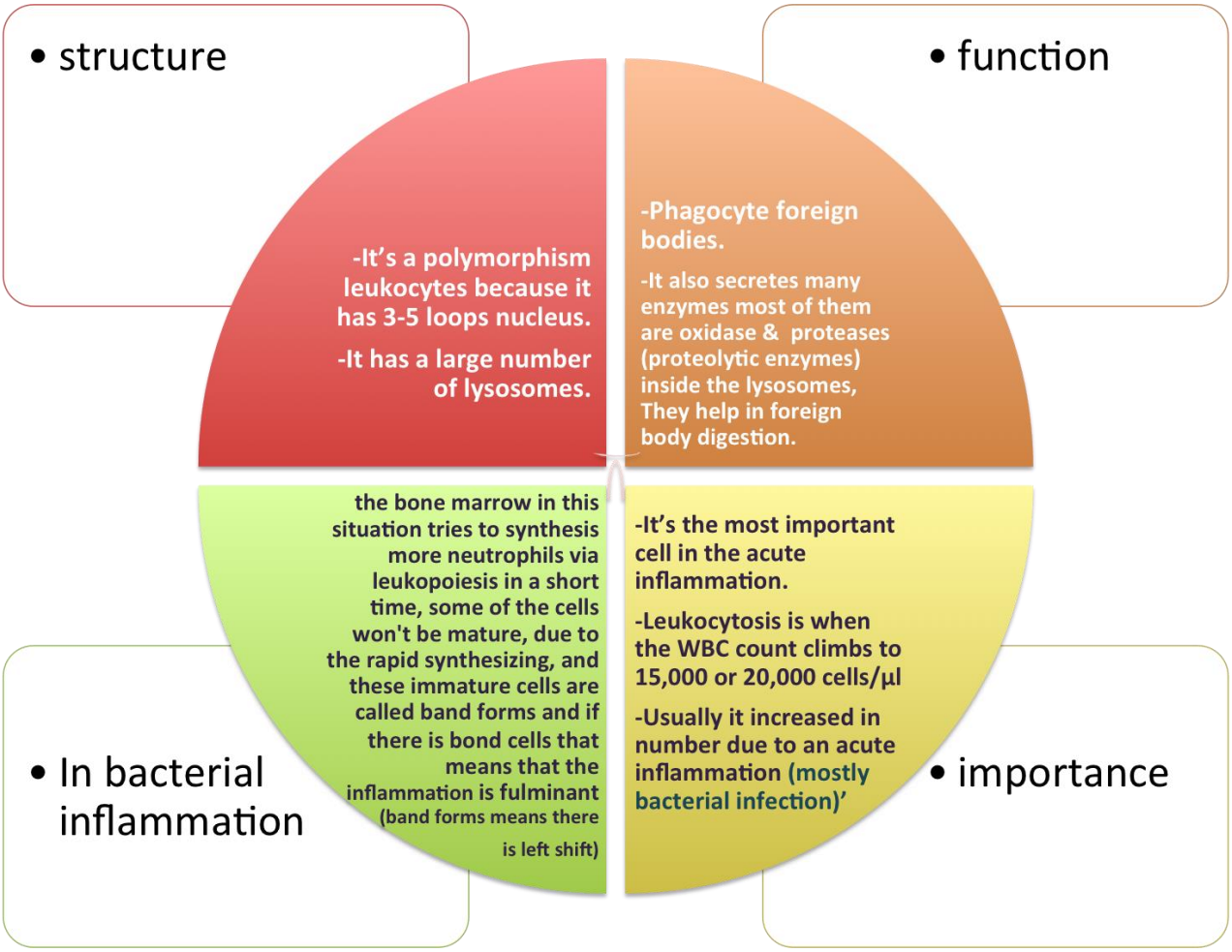
A critical function of inflammation is to deliver leukocytes to the site of injury, and to activate the leukocytes to perform their normal functions in host defense. (Cells will move from the blood circulation to the site of injury in the tissue)

For example :-



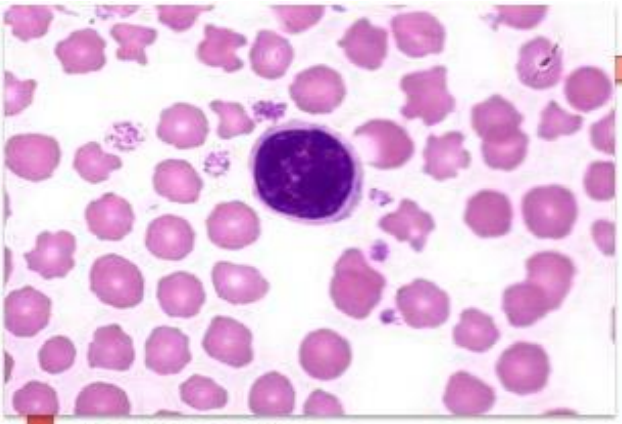
Neutrophils:





Lymphocytes:

Lymphocytes are two types **T lymphocytes** and **B lymphocytes**.



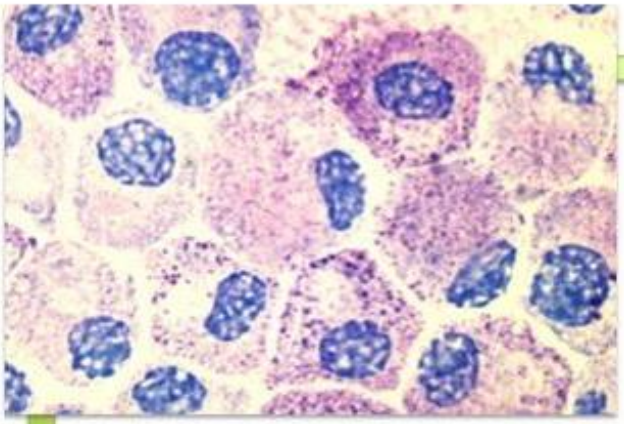
Lymphocytes

-T-lymphocytes function is cell mediated immunity(CMI).

-T-lymphocytes are produce various types of lymphokines, which have local effects.

-Most of the lymphocytes cells in the circulating blood are T-lymphocytes.

-It's characterizes chronic inflammation.



Plasma cells (transferred B-Lymphocytes)

-B-lymphocytes function is humoral immunity.

-B-lymphocytes transferred to plasma cells (when it's activated).

-plasma cells produce immunoglobulins (antibodies)

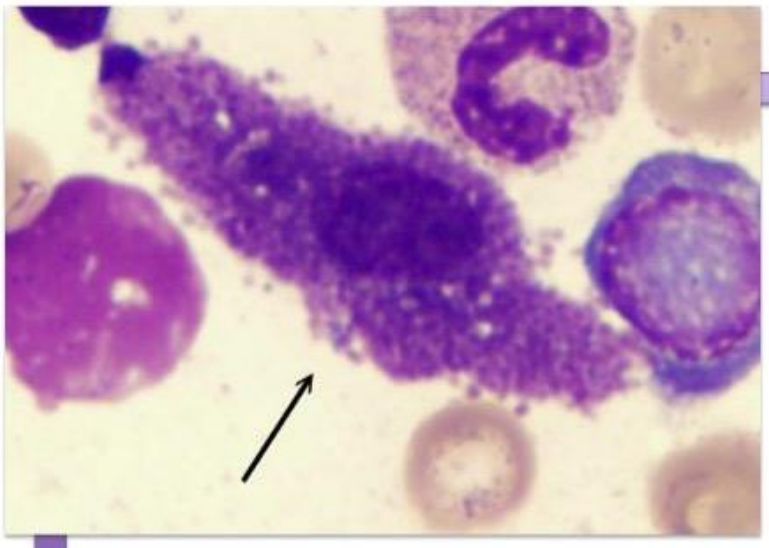
- it's increased in chronic inflammation.

-it's especially prominent in chronic inflammation involving mucosal surfaces.

-Plasma cells are found in tissues.

-Plasma cell has clock-like nucleus and plenty of Rough ER that produce immunoglobulin protein and it modified B-lymphocytes &T-lymphocytes.

Mast Cells:



Mast Cell

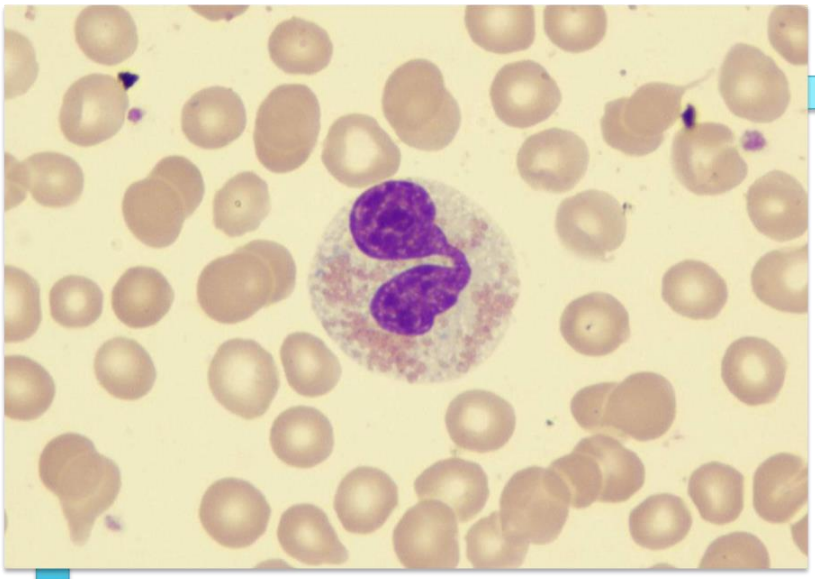
-have a lot of granules.

-plays an important role in allergic reaction especially type one because it has granules which contains histamine.

-When there is allergic the immunoglobulin E (IGE) will bind on the receptor which is on the surface of the mast cell and when this binding occurs, the mast cell will release the granules.

-The histamine which is inside the granules, the serotonin, and the mast cells are found in the tissue and the bone marrow.

Eosinophil:



Eosinophil

-It mostly has two loops.

-It has eosinophilic granules (reddish, or acidophilic).

-Eosinophil can do phagocytosis but it is very weak .

-Eosinophil possess many of the neutrophil enzymes, in addition they can dispense antihistamine in the area of histamine release.

- Normal count in blood 1-2%.

-Abnormal count in blood 20% (tested from stool).

-Its increased in patients with: *parasitic infection. *hypersensitivity infection. *allergic reaction like bronchial asthma.

Eosinophil it can seen in both acute and chronic inflammation.

Cells involved in chronic inflammation:

- Macrophages
- Lymphocytes
- Fibroblasts
- Plasma cells
- Giant cells (formed from the fusion of many macrophages)

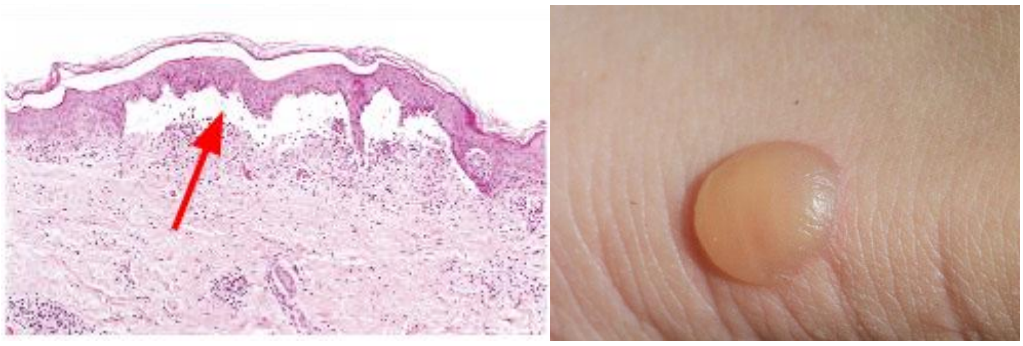
Cells of Inflammation

Cells	Activity	Phagocytosis	Inflammation
Neutrophil	Protease & oxidase	+	Acute
Eosinophil	Major role in parasitic & allergic conditions	+	Acute & chronic
Macrophage (modified monocytes)	Antigen processing & digestion	+	Late acute & chronic
Lymphocytes	Lymphokines	-	chronic
Plasma Cells	Antibodies production	-	Chronic

Morphological Patterns of Acute Inflammation

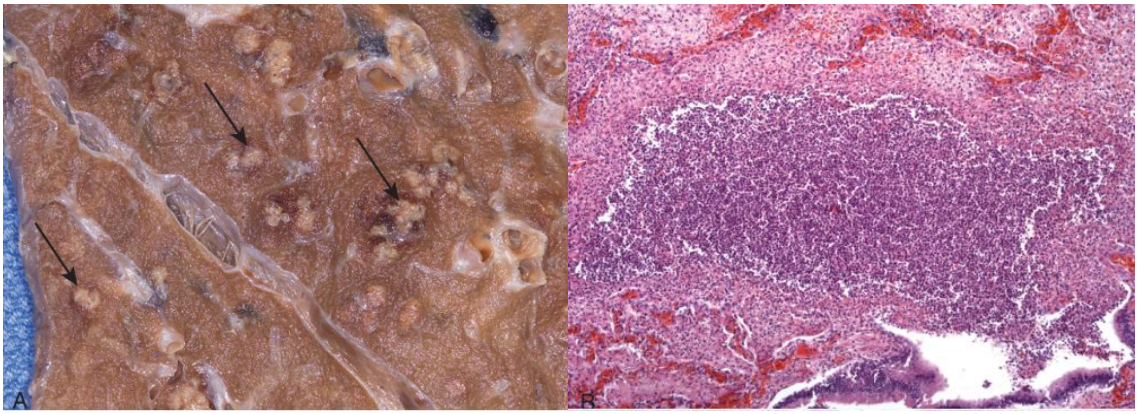
The importance of recognizing these morphologic patterns is that they are often associated with different etiology and clinical situations.

1) Serous inflammation: characterized by the outpouring [5]of a watery, relatively protein-poor fluid. derived either from the **plasma**, or from the **secretions of mesothelial cells** lining the peritoneal[6], pleural, and pericardial cavities. Fluid in a serous cavity is called an **effusion**.
Example: The skin blister [7]resulting from a burn or viral infection.



Serous inflammation. Low-power view of a cross-section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

2) Purulent inflammation: it produces pus.



B: The **abscess**[9] contains **neutrophils** and **cellular debris**[10] and is surrounded by **congested**[11] **blood vessels**. Because of the underlying tissue destruction, the usual outcome with abscess formation is **scarring**.

What does pus contains?

1) Bacteria.
2) Fibrin (end result of the coagulation cascade).
3) Inflammatory cells (neutrophils).

Pyogenic bacteria: Bacteria that produces lots of pus.
Examples: (**Staphylococcus aureus and streptococci**)

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[5] تدفق

[6] the serous membrane lining the abdominal cavity and investing its viscera.

[7] فقاعة

[8] inflammation of the lungs, arising in the bronchi or bronchioles.

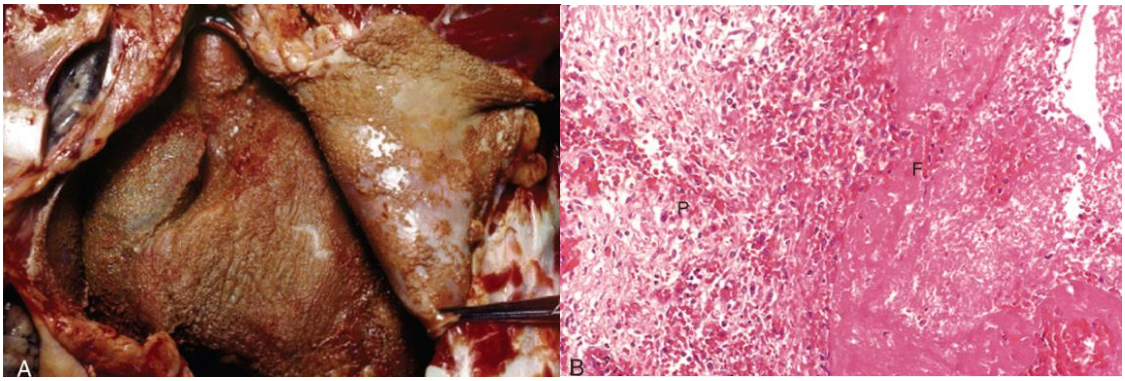
[9] الخراج وهي منطقة منتفخة في الجسم تحتوي على الصديد (pus).

[10] حطام الخلايا

[11] محتقن

3) Pseudomembranous colitis[12]: an inflammation that doesn't produce pus or abscess. occurs in some people who have taken antibiotics. It is most often seen in people who are in the hospital.

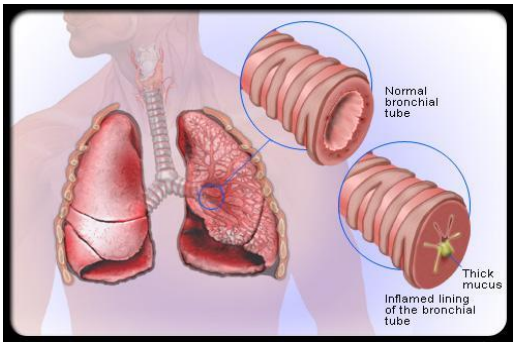
4) Fibrinous inflammation. (Fibrinous pericarditis): caused as a consequence of more (repeated) severe injuries, this result in greater vascular permeability that allows large molecules (i.e. Fibrinogen) to pass the endothelial barrier.
Note: greater vascular permeability → Exudate feature → indicates inflammation.
Note: come back to this after reading the vascular events..



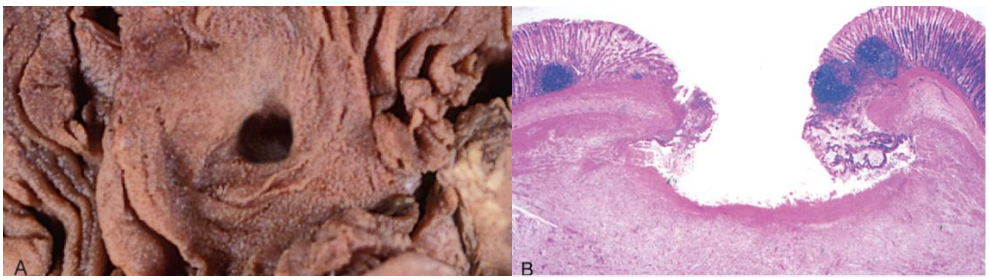
A: Deposits of fibrin on the pericardium.
B: A pink meshwork[13] of fibrin exudate (F) overlies the pericardial surface (P).

5) Gangrenous.

6) Catarrhal inflammation: Regular cold where there is increased secretion of mucus.



6) Ulcer[14]: A local defect (hole) on the surface of an organ or tissue. It produces necrotic cells and sloughing [15](an exclusion of dead layer).



[12] التهاب القولون الغشائي الكاذب
[13] شبكة
[14] قرعة
[15] انسلاخ

Vascular changes

Vascular permeability, Vasodilation

The main vascular reactions of acute inflammation are increased blood flow (secondary to vasodilation) and increased vascular permeability, both designed to bring blood cells and proteins to sites of infection or injury.

Events of acute inflammation (may be accompanied by fever):

1. **Vasodilation**[18] → increased **blood flow** (because of increased **diameter of the blood vessel**) = **Hemodynamic**[19] (**localized**[20]).
2. **Increase in vascular permeability**[21] (caused by **histamine**) → endothelial cells contraction → more neutrophils → edema.

→ Increased vascular permeability happens at the venule because is it is much thinner that the arteriole.
→ Vasodilation (increased diameter of the vessel) happens at the arteriole because it has muscles that contract.

Changes in Vascular Caliber and Flow

1. An **antigen** - is any foreign[22] particle it can be (bacteria, viruses, parasites, suture material) - will enter the body and there will be a temporary **vasoconstriction**[23] (Vascular contraction) that will last for a few seconds to 5 minutes.

2. After vasoconstriction , **arteriolar vasodilation** (by chemical mediators) occurs, resulting in locally increased blood flow and engorgement[24] of the capillary beds. This vascular expansion is the cause of the **redness** (*erythema*), **warmth** and **stasis** of blood flow (slow circulation due to dilated small vessels packed with red blood cells). This lasts as long as the acute inflammation persists.

3. As stasis develops, leukocytes (principally neutrophils) begin to accumulate along the vascular endothelial surface moving from the **center** to the **periphery** of the blood vessel**;** in a process called **margination**.

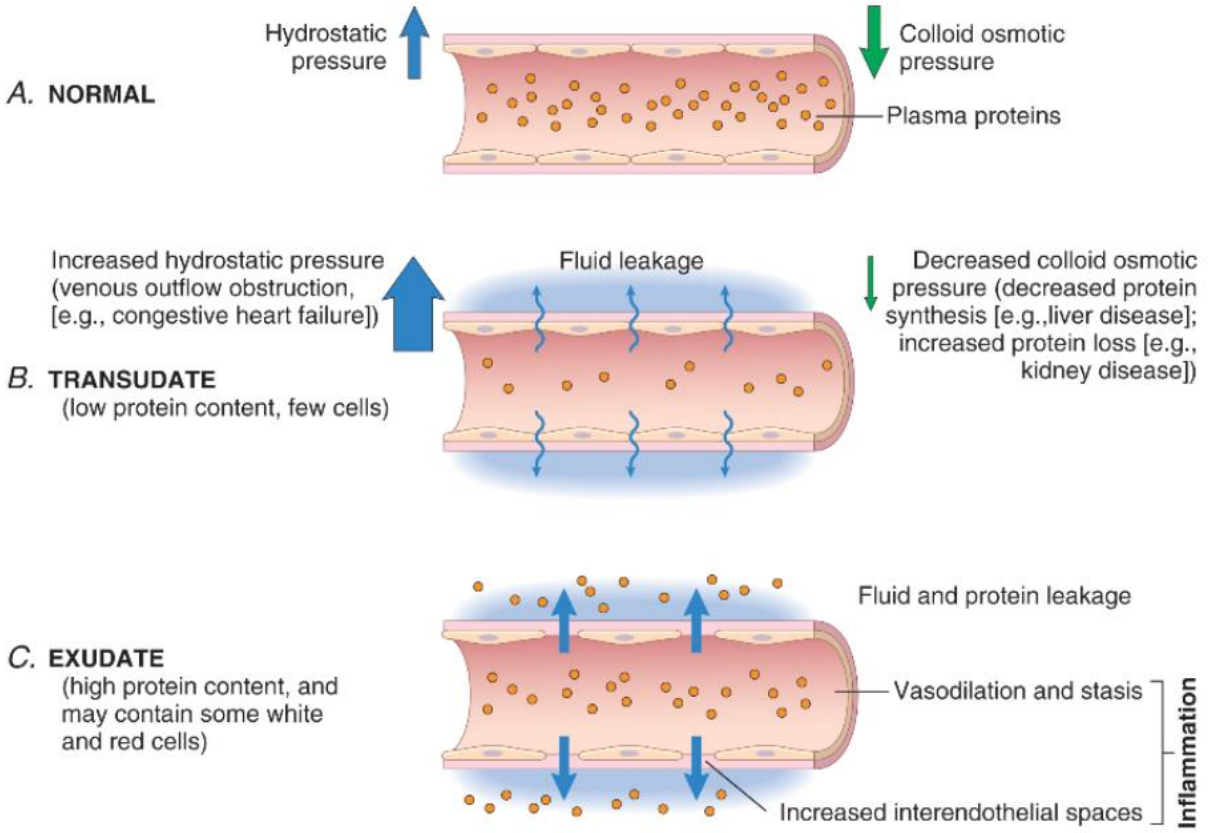
Increased Vascular Permeability

- Increasing vascular permeability leads to the movement of protein-rich fluid ,and even blood cells, to the extravascular tissues. The resulting protein-rich fluid accumulation is called an **exudate**.
- **Endothelial cell contraction** caused by (**histamine**, **bradykinin**, **leukotrienes**). Leading to intercellular gaps in post capillary venules; causing the accumulation of a **exudate**.

[18] توسع الأوعية
[19] relating to the flow of blood within the organs and tissues of the body.
[20] موضعي
[21] زيادة نفاذية الأوعية الدموية .. يعني أن المسافات بين خلايا الوعاء الدموي تكبر لتسمح بمرور السوائل والخلايا من خلالها للأنسجة.
[22] جسم غريب
[23] ضيق في الأوعية الدموية
[24] احتقان

Edema:

1. **Exudate**: rich in protein.
2. **Transudate**: poor in protein.



آحببنا آن نشرح الافكار لهذا القسم عن طريق فديو من انتاجنا:
http://www.youtube.com/watch?v=bAy3I2Ed0q4

Note: when talking about the endothelial cells I said constriction, the correct word is **contraction**. Sorry about that. (min 8:00)

Types of pressure in the capillaries :

1) **Hydrostatic pressure:** due to the **pressure from the blood** to the vessel wall.
2) **Colloid osmotic pressure:** due to the **concentration of proteins** in the vessel.

Please look at our video or look at the figure above to understand how this balance is disturbed. Here is a summary of that:

- Congestive[25] heart failure → high hydrostatic pressure → transudate edema
- Renal disease → low colloid osmotic pressure → transudate edema
- Liver disease → low colloid osmotic pressure → transudate edema

In cases of inflammation, there is increased vascular permeability. **Why?** Because chemical mediators such as **histamine** cause the **CONTRACTION** of the endothelial cells and this will make it very easy for the proteins to pass the vessel. Thus, the type of fluid causing the edema is exudate.

[25] محتقن

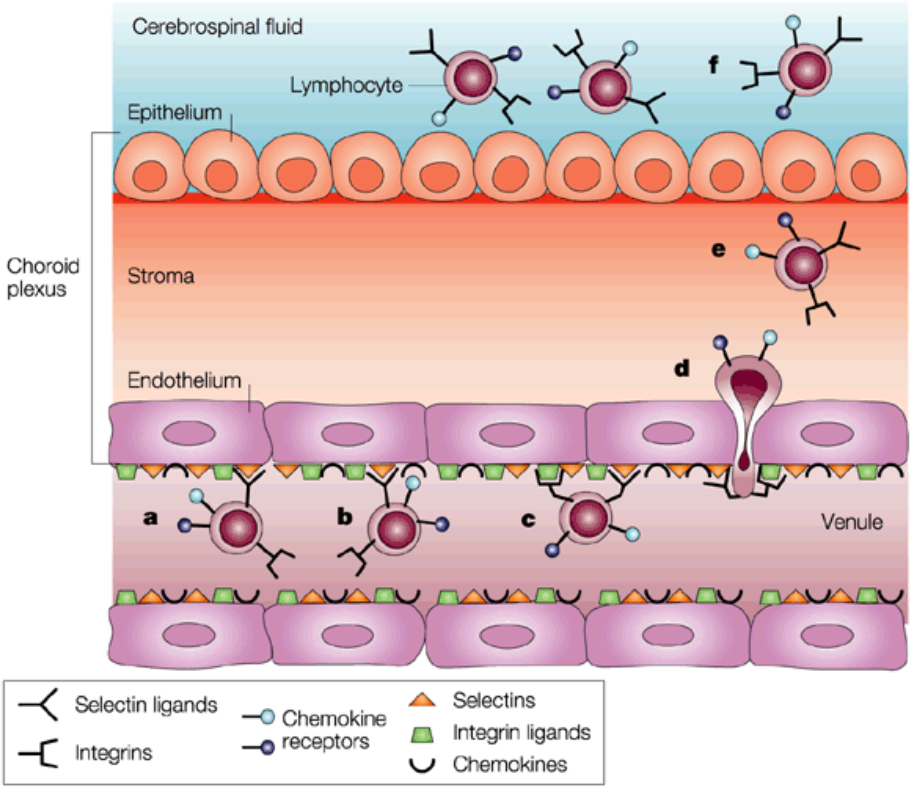
Fluid type	Condition	Content	Specific Gravity
Transudate	Increased Hydrostatic pressure or decreased colloid osmotic pressure	Low protein	<1.020
Exudate	Acute inflammation	High protein	>1.020
Pus	Acute inflammation	High protein & neutrophils	>1.020

SUMMARY

Vascular Reactions in Acute Inflammation

- Vasodilation is induced by chemical mediators such as histamine (described later) and is the cause of erythema and stasis of blood flow.
- Increased vascular permeability is induced by histamine, kinins, and other mediators that produce gaps between endothelial cells; by direct or leukocyte-induced endothelial injury; and by increased passage of fluids through the endothelium. This increased permeability allows plasma proteins and leukocytes to enter sites of infection or tissue damage; fluid leak through blood vessels results in edema.

Cellular Events



Cellular events begin soon after vasodilatation. These cells will adhere to the endothelial cells because there are adhesion molecules called (**selectins** and **integrins**) on the surface of the endothelium and also on the Surface of the inflammatory cells (leukocytes). This will cause the cells to move from the **axial** to the **peripheral** **(the white blood cells move from the center of the blood stream -which is their normal place- to the side of the blood stream (peripheral) ; this makes them become closer to the vessel wall)** this is called **MARGINATION**.
Secondly the inflammatory cells will go between the gaps and between the molecules of the basement membrane and they go out, this action is called **diapedesis** .
Last step is called **CHEMOTAXIS**, chemotaxis will take place. (The directional margination to the site of inflammation)

Selectins: Adhesion molecules cover the endothelial cells.
Integrins: Are the inflammatory cells itself.

مثال عندنا مرض السل مرض تنفسي بالدرجة الأولى ويعتبر من أمراض الالتهاب المزمن، وهو يحدث في الرئة لأن الباكتيريا تحب الأكسجين ولذلك تجدها هناك، وبسبب تراكم البكتيريا ستذهب الخلايا اللمفاوية للصدر، وسيحدث زيادة نفاذية للأوعية الدموية مما يفسر وجود سائل متراكم في الرئة.

Non-specific test: doesn't show the **site or cause** of the inflammation, but it tells me that **there's** an inflammation.

Laboratory tests that indicate inflammation:

1. **Leukocytosis**: is the increasing in number of the leukocytes (white blood cells).
2. **High C reactive protein (acute phase protein):** secreted by the **liver** and it **doesn't** lead you to the **place** of inflammation but it's secreted when there is an inflammation (non-specific).
    - When a patient gets inflammation or necrosis or cell damage this protein is released.
3. **Complement protein**.

4. **Elevated erythrocyte sedimentation[26] rate** (ESR):

When the ESR is increased, the blood which is put in the test tube will go down very quickly.

This is because during inflammation, the **liver** secretes **acute phase proteins.** One of these proteins is **fibrinogen**. We know that erythrocytes have an overall **negative** surface. Fibrinogen is actually **positive** and it will disrupt the negative surface charge of erythrocytes, resulting in an increase in ESR. Remember that this test is non-specific.

This video talks about ESR in general. It is worth watching. However, if you only want more details on how inflammation affects ESR Look at this video min #6

- http://www.youtube.com/watch?v=wkQFXVp9TU0

[26] ترسيب

Chemical Mediators of inflammation

Chemical meditators are responsible for the vascular and cellular events in acute inflammation. Meditators may be produced **locally** by cells at the site of inflammation, or maybe derived from inactive circulating precursors.
So these chemicals were circulating in the blood plasma (produced by the liver) and when they reach the site of inflammation, they become active. Examples: complement system & kinin system.

Chemical meditators are divided into two types :

1. **Cell derived:**
   - Platelets.
   - Lymphocyte.
   - Macrophages.
   - Basophils.
   - Endothelial cells.
   - Mast cell.

2. **Plasma protein derived:** Protein are usually manufacture and the liver and released to the circulation

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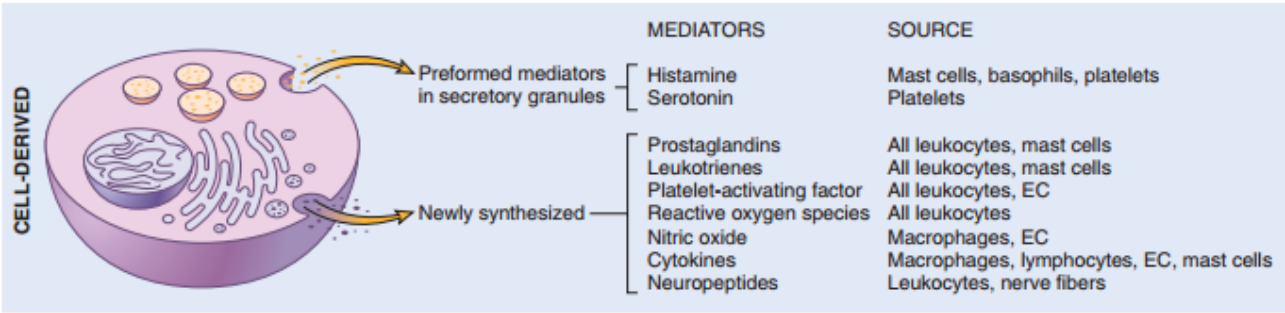
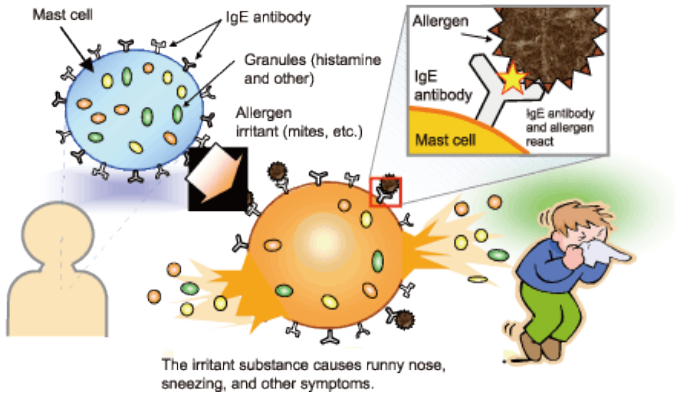
1. Cell derived



Histamine

Secreted by:

1. **Mast cells** (It's a type of inflammatory cells that is found only in the **tissue** and it has granules inside them histamine and serotonin).
2. **Basophils** (Basophils are found in peripheral blood. I usually have multiple granules. And its nuclei have more than one lobe).
3. **Platelets**.



Histamine causes:

- Vasodilatation.
- Increase vascular permeability.
- Endothelial activation.

How is histamine released?
When there is a **physical injury,** such as trauma or heat, immune reactions involving binding of **IgE antibodies** to their receptors on **mast cell**s. After this binding, mast cells will release histamine from its **granules**.

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.

Serotonin (5 hydroxytryptamine)

- Serotonin comes from metabolized amino acid called **tryptophan.**
- Secreted by **platelets**.
- Serotonin causes: **vasoconstriction**.

Platelets play a major role in blood Coagulation[27]. So serotonin is secreted by the platelets to cause vasoconstriction.

Platelet activating factor (PAF)

Secreted by:
1 - mast cell
2 - leukocyte
3 - endothelial cells

PAF causes:
1 - vasodilation
2 - increase vascular permeability
3 - leukocyte adhesion
4 - chemotaxis
5 - degranulation and oxidative burst

Reactive oxygen species (free radical) - ROS

- Secreted by **leukocyte**.
- **ROS** causes damage of tissue and killing of microbes.

Note: in leukocytes there are *different* oxidative enzymes lead to formation of ROS. ROS are **not** stable and have to go into reactions and these reactions damage the cell.

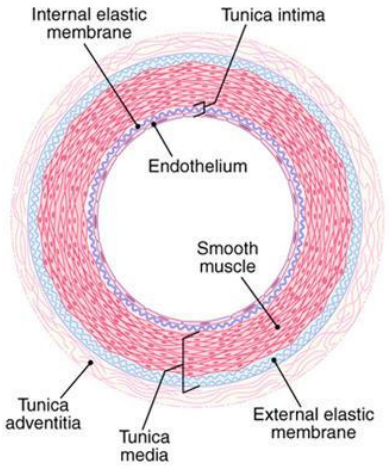
ROS types:
1 - Hydroxyl group (OH).
2 - Superoxide (O_2-).
3 - Hydrogen peroxide (H_2O_2).

NITRIC OXIDE (NO)

Secreted by:
1 - endothelial cells (also called endothelium)
2 - macrophages

Nitric oxide causes:
1 - vasodilation: it relaxes the smooth muscles of the blood vessels.
2 - killing of microbes.

Note:
The structure of blood vessels:
"Inside the vessel" Endothelial cells → basement membrane → smooth muscles → serosa (adventitia) "Outside"



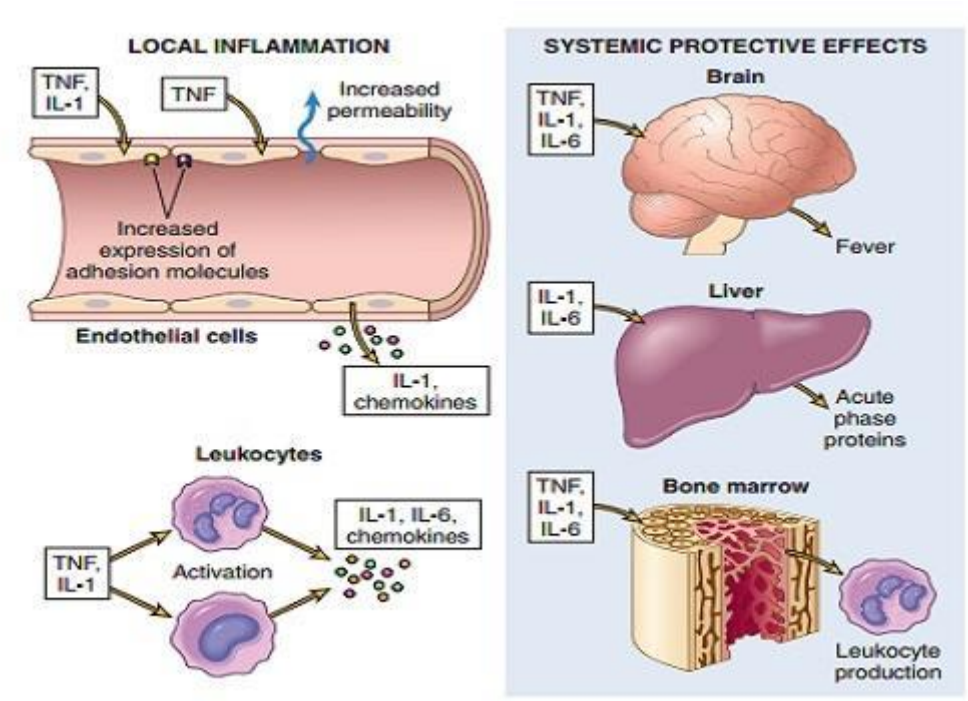
[27] تخثر الدم

Cytokines

- **Cytokines:** are polypeptide products of many cell types that function as **mediators of inflammation** and immune responses and they carry **signals** to neighboring cells.
- Cytokines has different elements such as: **Tumor Necrosis Factor** (TNF) and **Interleukin**.

Secreted by:
1 - macrophagous
2 - endothelial cells
3 - mast cell
4- lymphocyte
TNF and IL-1 cause:
1 - local: stimulate the expression of adhesion molecules on endothelial cells (endothelial activation).
2 - Systemic: fever, metabolic abnormalities and shock (hypothesen).

Notes:
- The major cytokines in **acute inflammation** are **TNF, IL-1, and IL-6**. Other cytokines that is more important in **chronic inflammation** such as **IL-12**.
- Most of modern **anti inflammation** and immunity diseases drugs are **anti TNF.**



Chemokines

Any of a class of cytokines with functions that include attracting white blood cells to sites of infection (chemotaxis).

Secreted by:
1 - leukocytes
2 - activated macrophages

Chemokines causes :
1 - chemotaxis
2 - leukocyte activation

prostaglandins

secreted by:
1 - mast cells
2 - leukocytes

Prostaglandins causes:
1 - pain
2 - vasodilation
3 - Fever

Prostaglandins are very important because a lot of **anti inflammatory drugs**, such as antipyretics[28] and **analgesics**[29] work on blocking prostaglandins (anti-prostaglandins).

Note: when the phospholipid of the cell membrane is metabolized by the action of **phospholipases, arachidonic acid** (fatty acid) is produced. The arachidonic acid is further metabolized by **cyclooxygenase** and gives various **prostaglandins**.

Phospholipid → (via phospho lipases) arachidonic acid → (via cyclooxygenases) prostaglandins

Leukotrienes

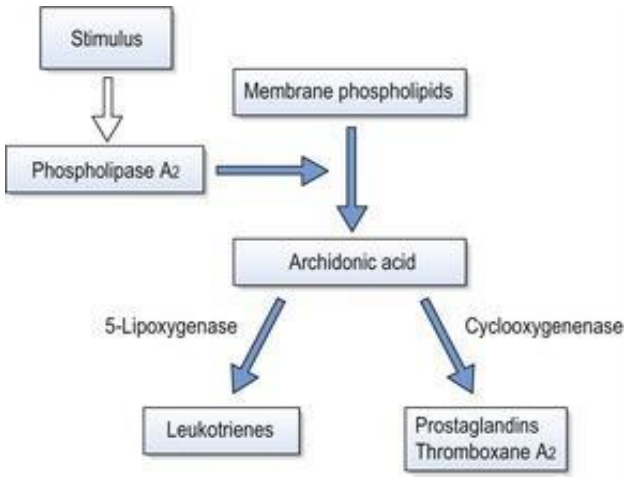
secreted by :
1 - mast cells
2 - leukocytes

leukotriene causes :
1 - increase vascular permeability
2 - chemotaxis
3 - leukocyte adhesion and activation

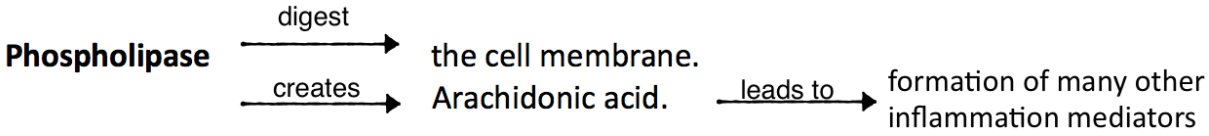
Note: when the phospholipid of the cell membrane is metabolized by the action of **phospholipases, arachidonic acid** (fatty acid) is produced. The arachidonic acid is further metabolized by **5-lipoxygenase** and gives rise to leukotrienes (**B4 , C4 , D4 , E4**)

- **Leukotriene B4** induced chemotaxis.
- **Leukotriene C4 , D4** and **E4** increase vascular permeability and active leukocytes.

phospholipid → (via phospholipase) arachidonic acid → (via 5-lipoxygenase) leukotriene



[28] خافضات الحرارة
[29] مسكنات



So if I want to **stop** the inflammation in the patient, I can **inhibit** the *phospholipase* and make it stop producing arachidonic acid by **STEROIDS**.

Arachidonic acid may be digested by:

1- Cyclooxygenase (COX1 & COX2): these could be inhibited by drugs such as aspirin. *What happens after it is metabolized? *	**2-Lipoxygenase**
-Prostacyclin (PGI2): is causes vasodilation and inhibits platelets aggregation.	-Leukotriene C4 D4 & E4: bronchospasm (ضيق فى التنفس) and increase vascular permeability.
-Thromboxane A2 (TXA2): causes vasoconstriction and promotes (يحفز) platelet aggregation	-Leukotriene B4: Chemotaxis
-PGD2 & PGE2: Vasodilation and increased vascular permeability.	- Lipoxin A4 & B4: inhibit the adhesion and chemotaxis of leukocytes.

Note: PGD2: Prostaglandin D2
PGE2: Prostaglandin E2

2. Plasma protein derived mediators:

Activation of Complement (immune response)

Complement system: The complement system ,which is consisted of a group of **plasma proteins,** is synthesized by the **liver** and is found in the ***plasma.***

- What is the difference between **plasma** and **serum**?

They are the same; but ***plasma*** has coagulation factors and ***serum*** has no coagulation factors (they were used).

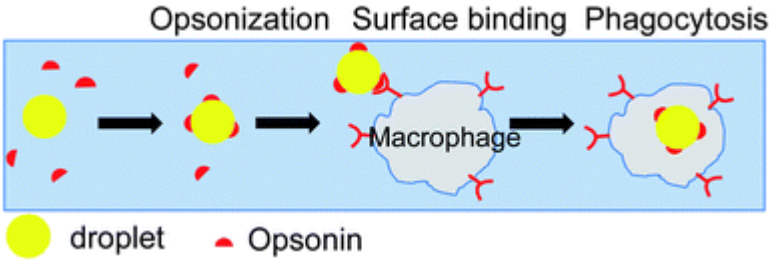
- **The complement system** is made from **20 proteins**.
- **The complement system** can be activated by :
  1- **Classical pathway**; Activated by **Immune Complexes** that contain ***antibodies*** bound to an antigen.
  2- **Alternative pathway**: ***Microbial products*** directly activate complement system.
  3- **Mannose-binding lectin (MBL) pathway**; **MBL** binds to mannose on microorganisms and activates the complement system.

- be careful, ***the classical pathway*** requires **antibody** to activate the pathway, but ***the alternative pathway*** does not require **antibodies** for its activation.

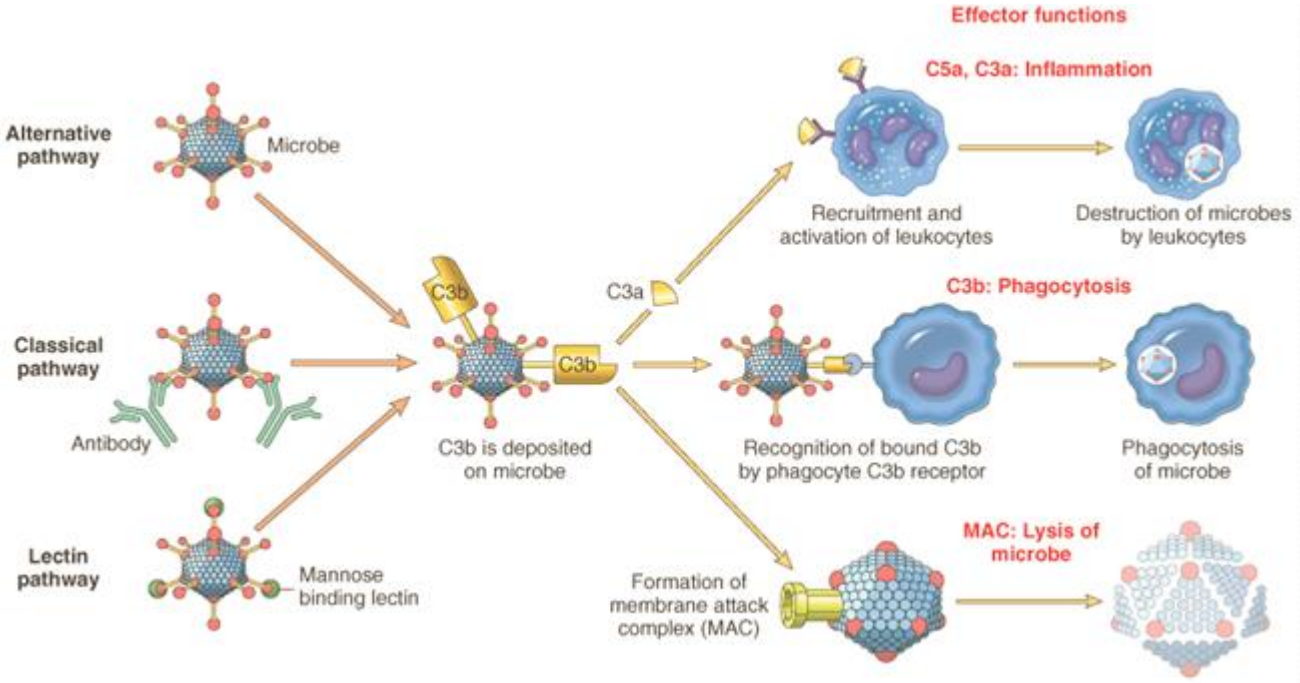
- Immunology talks about the **complement system** in detail, but what is important in pathology and inflammation?

  1- **C3a and C5a** (**anaphylatoxins**)—Stimulate mast cell release of ***histamine*** → inflammation.
  2- **C5a** —Leukocyte ***chemotactic*** factor.
  3- **C3b** —It is an ***opsonin***, it prepares the microorganism for *phagocytosis*. It will coat the antigen and prepare it for ***phagocytosis***.
  4- **C5b-C9** (**M**embrane **A**ttack **C**omplex [**MAC**]) —***Cell lysis.***

- **MAC** ((C5b-9)) is a part of the *complement system*. It will work on the cell membrane of the microorganism and cause their **lysis**. It can ***kill the bacteria***. It may also ***cause cell injury***.



- **Opsonins** enhance *recognition, attachment* and *phagocytosis* of bacteria.
  • Important **opsonins** include **immunoglobulins** (***Fc portion*** of **IgG**), **complement system** product (**C3b**), and **plasma proteins** such as *collectins* (which bind to bacterial cell walls).
  • When **immunoglobulins** coat the bacteria or antigen they make them *amenable*[30].



What are phagocytic cells?

1) **Macrophages** (histiocytes). Histiocytes is less active in phagocytosis, but other than that they are the same.
2) **Neutrophils.**
3) **Eosinophil** (weakly phagocytic).

- 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.

What do we mean by cascade?

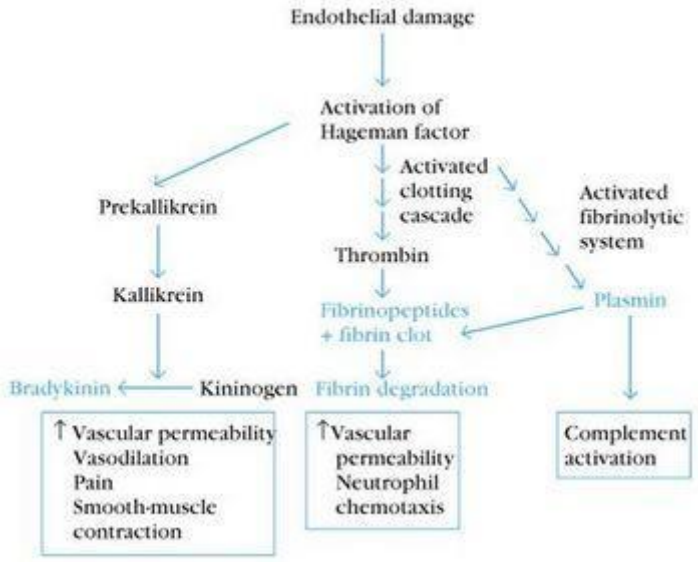
cascade: It is a process where one thing leads to another.

We should know two cascades : **The complement system cascade** and **coagulation cascade**.

Kinin system

The **kinin–kallikrein** system, or simply the kinin system, consists of blood proteins that play a role in *inflammation*, *blood pressure control*, *coagulation* and *pain*. Its important mediators **bradykinin** and **kallidin** are vasodilators and act on many cell types.

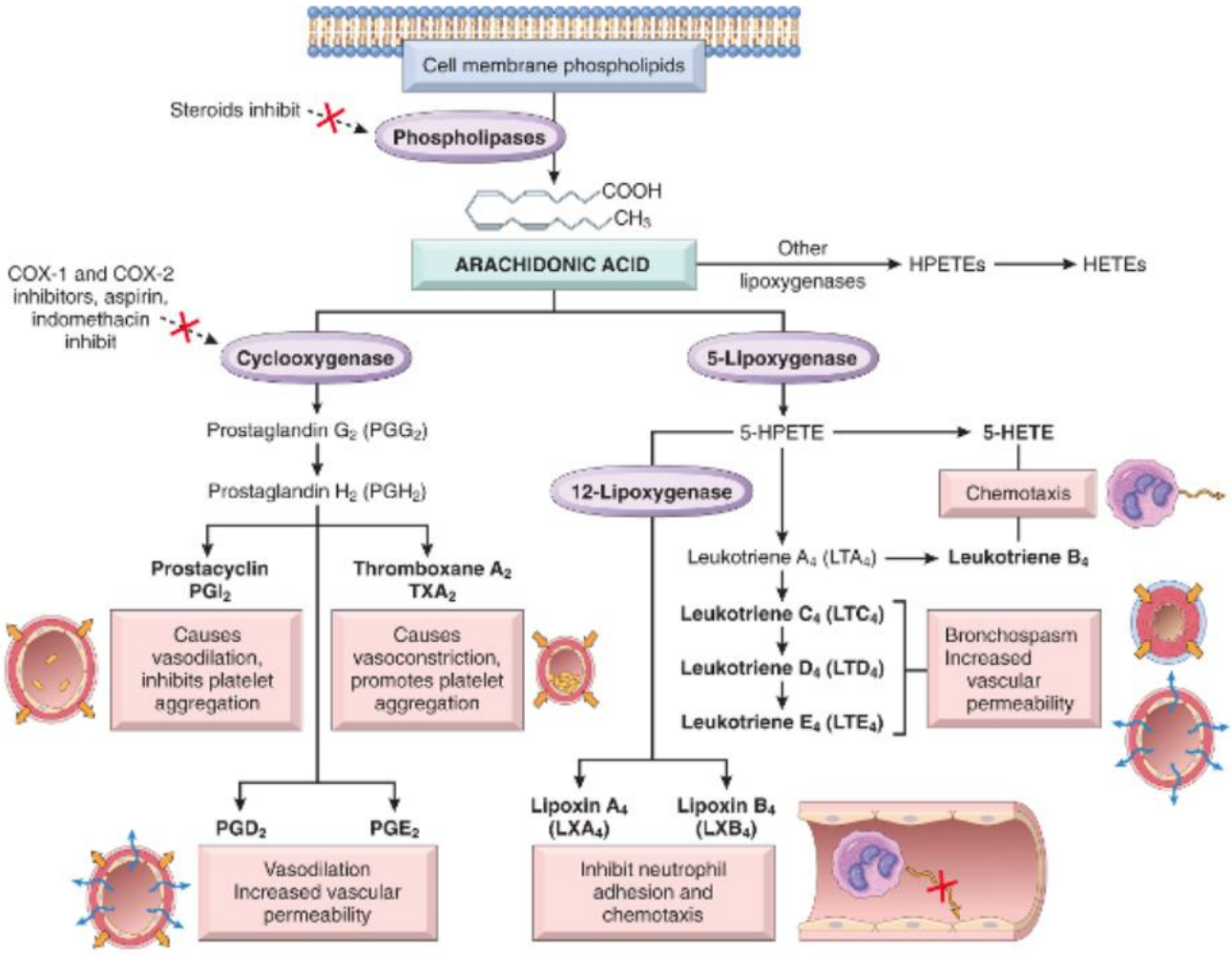
- The Kinin System does not get activated unless the **coagulation cascade** is activated.
- If the **coagulation cascade** was activated (especially **factor 12** which is called the **Hageman factor**) it stimulates the cascade of the kinin system.
- What is important from the kinin system? **Bradykinin**[31].
- **Bradykinin** is a **pain stimulator** and increases the **vascular permeability**.
- The actions of **Bradykinin** are short-lived. **WHY?** Because it is rapidly degraded by **kininases**[32] present in plasma and tissues.
- So when there is **inflammation**, the coagulation system is **activated**.
- Proteases activated during coagulation: NOT IMPORTANT.



- **Complement system**: Leukocyte chemotaxis (**C3a** and **C5a**), opsonization (**C3b**) and cell killing (by **C5b-9** Membrane attack complex).
- **Hageman factor** activation leads to **kinin activation**.
- **Bradykinin** is created after the kinin activation and it causes pain.

[31] a compound released in the blood in some circumstances that causes contraction of smooth muscle and dilation of blood vessels.
[32] an enzyme that catalyzes the transfer of a phosphate group from ATP to a specified molecule.

The chemical mediators effects	
Vasodilation	**By: -prostaglandins: which is Arachidonic acid metabolites, which is made from the cell membrane. -Nitric Oxide: relaxes the muscles and causes vasodilation. -Histamine.**
Increased vascular permeability	**-Histamine and serotonin. -C3a & C5a. -Bradykinin: (formed by the activation of factor 12 (Haegmen factor) it causes pain. -Leukotrines: (C4 D4 & E4): they are formed from metabolizing arachidonic acid by lipooxygenase.**
Chemotaxis, Leukocyte recruitment and activation	**-TNF & IL1: they are formed from the macrophages and endothelial cells. - Chemokines: cause chemotaxis. -Leukotriene B4. - Bacterial products: cause chemotaxis.**
Fever	**-IL1, TNF. -Prostaglandins.**
Pain	**-Prostaglandins. -Bradykinin. -Neuropeptides.**
Tissue damage	**-Because leukocytes proteases are released and may damage healthy tissues.**

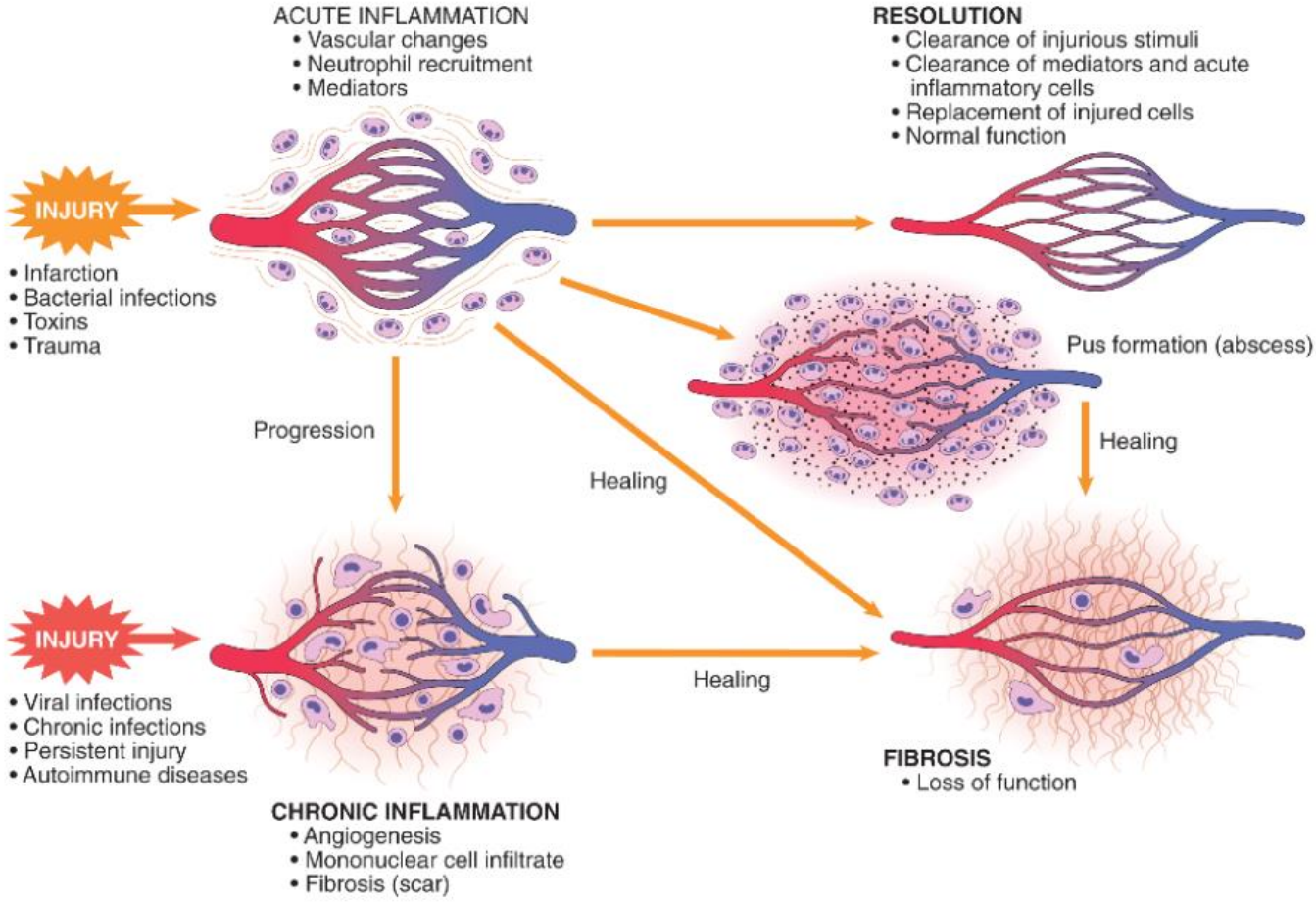


Chronic inflammation

Helpful articule: http://www.wisegeekhealth.com/what-is-a-chronic-inflammatory-disease.htm

Acute inflammation can have one of four outcomes:

1) Abscess formation: the inflammation will be concentrated in an abscess wich is filled with pus.
2) Complete resolution: Clearance of injurious stimuli, and everything is back to normal.
3) Healing: a scar is formed and there will be fibrosis.
4) Acute inflammation will progress to **chronic inflammation.**



What is the difference between chronic and acute inflammation?

	Acute Inflammation	Chronic Inflammation
Duration	Days to weeks	Months to years
Inflammatory Cells	Neutrophils	Lymphocytes & plasma cells.

Note: Eosinophils are found with allergies or parasitic infections, and macrophages are found in both acute and chronic, but are increased at the end of acute inflammation.

An important point: Although the presence of neutrophils is the hallmark of acute inflammation, many forms of chronic inflammation may continue to show extensive neutrophilic infiltrates, as a result of either persistent microbes or necrotic cells, or mediators elaborated by macrophages.

Note:

- Some diseases, such as **hepatitis B&C**, & **tuberculosis (TB),** start as **chronic**. There is no acute hepatitis B or C. Usually the disease starts as acute, and if not treated, it becomes chronic.
- **Staphylococcus aureus bacteria** is always associated with **acute inflammation.**
- Viral hepatitis B & mycobacterium TB are always-chronic.
- Etiological factors determine whether it is acute or chronic.

Features of chronic inflammation:

- Persistent inflammation
- Tissue injur.
- **Scarring**: prominent **fibrosis**.
- Prolonged host response to persistent stimulus.

Angiogenesis: formation of new vessels caused by sprouting[33]; old blood vessels produce new ones. 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**).

Fibrosis: increase in extracellular matrix (ECM) → formed of **collagen** and may have **proteoglycan**[34] but the most important is the collagen (Connective Tissue).

Amyloid: It is a protein secreted by the **liver.** It is secreted in large amounts when there is **chronic inflammation.** It accumulates in the **blood vessels**, and **kidneys** causing problems it's not seen in acute Inflammation. Note that this process requires long periods of time.

What is a granulation tissue and what is a granulomatous inflammation?

Granulation tissue: contains **new small blood vessels**, **fibroblasts**, and **mononuclear cells** in an edematous extracellular matrix; formation of **granulation tissue** is part of the repair response.
A **granulomatous inflammation** is a form of chronic inflammation. When we say **granuloma**, we mean the second one.

- **Granulation tissue**[35] → non specific
- **Granuloma**[36] → specific

A) granulation tissue and chronic inflammation

Granulation tissue is often associated with chronic inflammation (non specific). It represents a healing phase following acute inflammation. Endothelial proliferation is prominent.

How is the granulation tissue formed?

1) At the beginning, the interstitial tissue is edematous (has edema, exudate)which has acute and chronic inflammatory cells.
2) After a while, the acute inflammatory cells go away and it is dominated by chronic inflammatory cells.
3) Finally, fibroblasts dominate the interstitial tissue.

---

[33] تبرعم

[34] a compound consisting of a protein bonded to glycosaminoglycan groups, present especially in connective tissue.

[35] النسيج الحبيبي

[36] الورم الحبيبي

B) Granulomatous inflammation

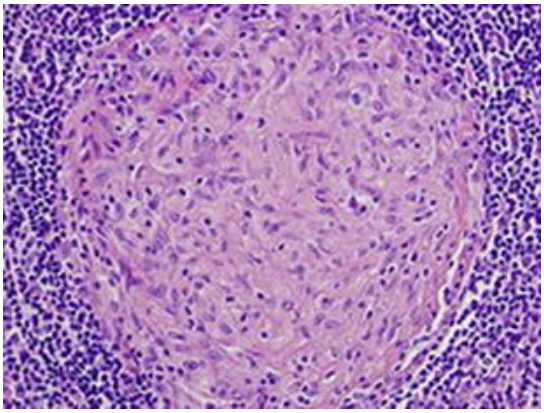
Characteristic of this type of chronic inflammation are granulomas which form **0.5** to **2.0** mm aggregations[37] of epithelioid macrophages surrounded by a rim of lymphocytes. Epithelioid macrophages have an appearance suggestive of squamous epithelial cells due to their abundant[38] pink cytoplasm.

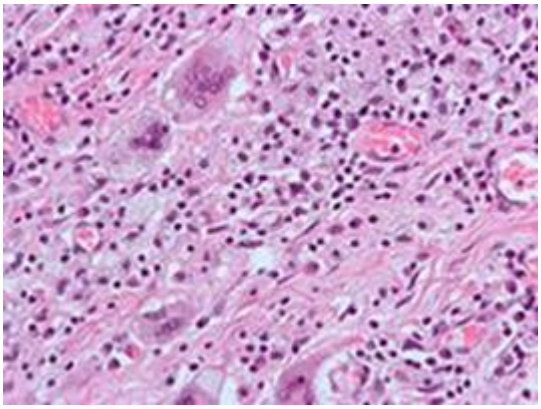
Granulomatous inflammation may be caused by:
foreign bodies , mycobacterial infection for example: **Tuberculosis, leprosy, schistosomiasis, the gamma of tertiary syphilis, cat-scratch disease, lymphogranuloma venereum, tularemia**.

- Sometimes the granuloma contains caseous necrosis as in TB.

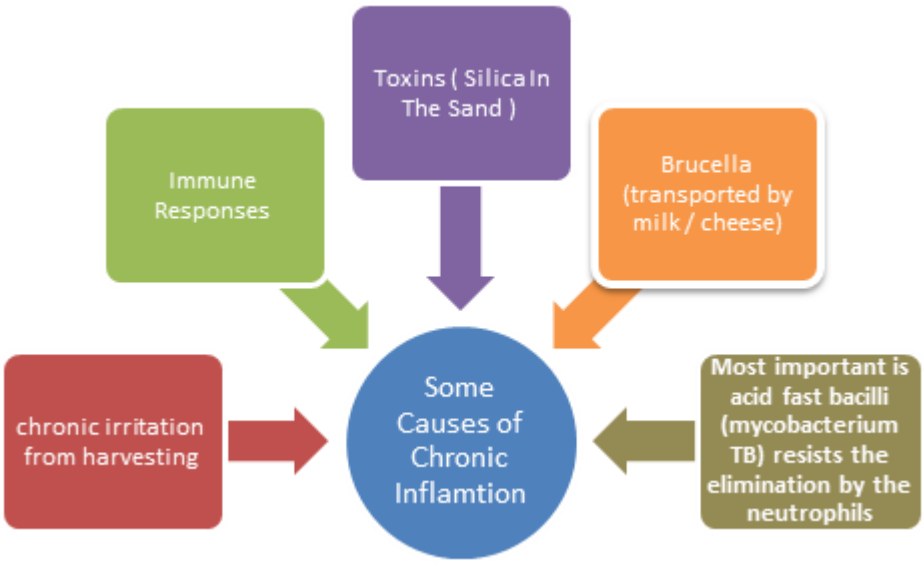
What are multinucleated giant cells?
They form from the cytoplasmic fusion of macrophages.

What are langhans cells?
Langhans giant **cells** are large **cells** found in granulomatous conditions. They are formed by the fusion of epithelioid **cells** (macrophages), and contain nuclei arranged in a horseshoe-shaped pattern in the **cell** periphery.


granuloma


giant cell

- The term **cellulitis** denotes a spreading acute inflammation through interstitial tissue.



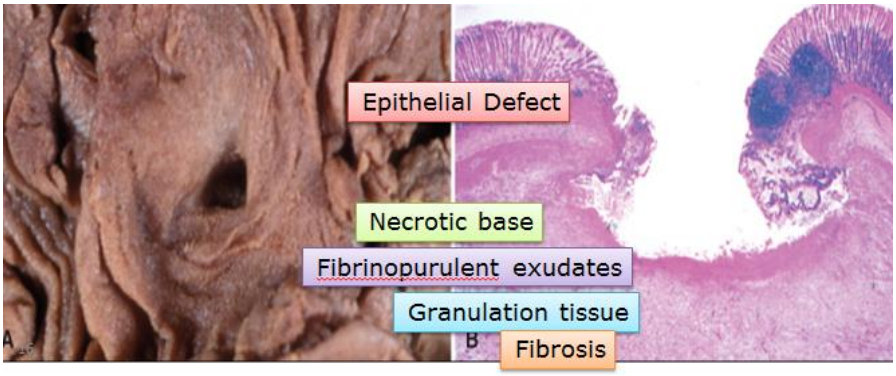
[37] تجمعات
[38] غزيرة

Fibrosis: In chronic inflammation, as a way to repair the damage, our bodies recruit **fibroblasts**, which are normally found in **connective tissue**, to the site of injury and they and they produce **collagen** in these spaces; this is known as fibrosis.
Who is responsible for recruiting fibroblasts?
Macrophages; they produce some growth factors such as (**PDGF, FGF2, & TGF beta**)

Some examples of chronic inflammation:

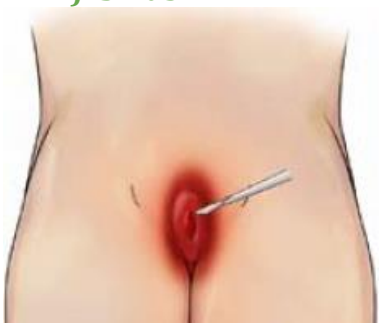
1) **Ulcer**

Note: ulcers have acute and chronic inflammation at the same time; they coexist. An ulcer is a focal loss of the mucosal layer in a part of the GIT (Gastrointestinal Tract), usually in the duodenum or stomach.



Microscopically: we find epithelial necrosis fibrin and some acute inflammatory cells on the surface and under it, a layer of inflammatory vascular granulation tissue.
it is vascular because chronic inflammation is associated with **angiogenesis** (formation of new blood vessels) so he has a vascular growth factor.

2) **Sinus:**



inflammatory tract with one opening (pilonidal sinus in the lower back). It contains pus + ingrown hairs (foreign body) ➡ chronic inflammatory reaction (very common)

3) **Fistula:** ناسور شرجي chronic inflammatory tract that has two openings between two various epithelia (usually starts from the colon and open in the skin (حكة وافرازات تلوث الملابس) (common (nonspecific)

Note: Parasitic infections may be lead to chronic inflammation.
eg: schistosomiasis[39] (associated with a lot of eosinophils)

[39] بلهارسيا

SUMMARY

Features of Chronic Inflammation

- Prolonged host response to persistent stimulus
- Caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many important diseases
- Characterized by persistent inflammation, tissue injury, attempted repair by scarring, and immune response
- Cellular infiltrate consisting of activated macrophages, lymphocytes, and plasma cells, often with prominent fibrosis
- Mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes), with a tendency to an amplified and prolonged inflammatory response owing to bidirectional interactions between these cells

Regeneration and repair

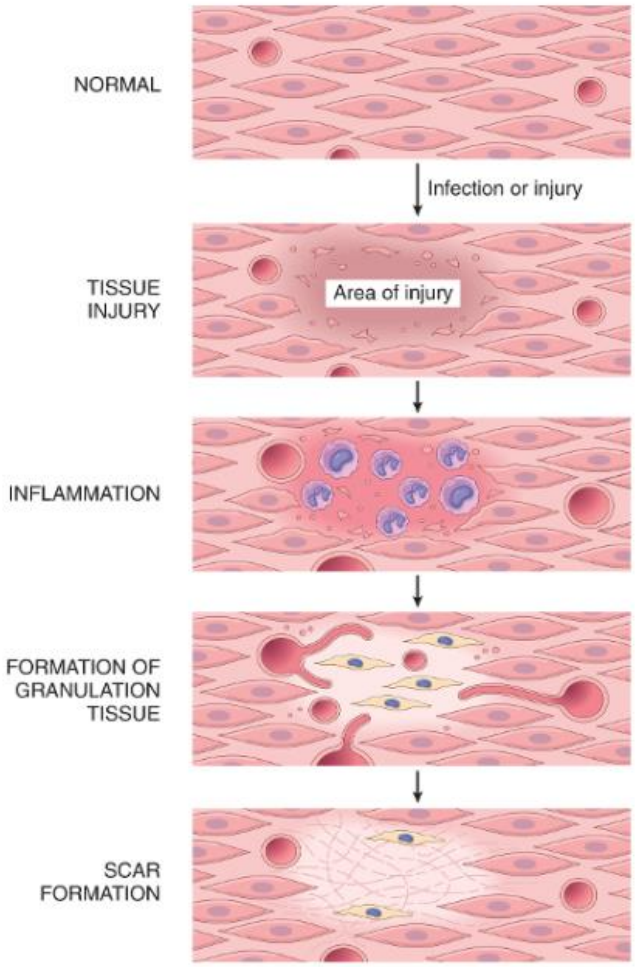
Regeneration and Repair occur through the capacity of the original damaged cell.

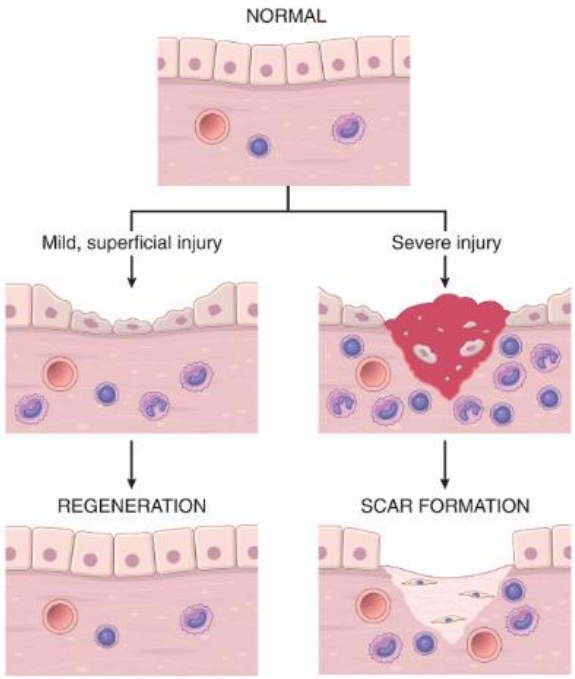
There are 3 Types of cells:

1) **Labile[40] cells:** have a **short life span** and they are **rapidly[41] regenerated** cells. (**Epidermis of the skin**)
2) **Stable cells:** longer-lived cells than the labile cells, they have a **low mitotic rate**, and they can regenerate under proper conditions. (**liver** and **renal tubular cells**)
3) **Permanent cells:** They have **No** mitotic activity. The have a long life span. (**neurons of the central nervous system**)

- **Collagens** are supporting tissues secreted by **Fibroblasts**, They are a series of complex **polypeptides** and they bind epithelial tissues and other connective tissues to themselves and to each other providing tensile strength[42].
- **Basement membranes** lie at the interface of cells and **stroma**, and they support the overlying cells, they include the following materials: **Entactin**, **Heparan sulfate**, **Laminin**, **Proteoglycans** and **type IV collagen**.

Healing:





[40] غير مستقر
[41] بسرعة
[42] قوة الشد

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[43]. 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 lay down by fibroblasts causing *endothelial cells to proliferate*, and producing **granulation tissue**.

1. **Neutrophils** decrease in numbers.
2. **Macrophages** increase in number.
3. **Collagen** in the gap increases.
4. **Blood** vessels decrease in number.
5. The scar begins to contract.

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

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 much longer time.** The **same** cells take part in the process, but **Granulation tissue is much more pronounced[44].**

NOTE: 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**.
Note: 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.

Abnormal repair:

The wound repair does not go well, the **laying down of excessive collagen** result in the formation of **Keloid[45]** and **Fibrous** adhesions.
Retardation[46] of the healing occurs due to:

1. Bacterial infection of the wound.
2. The presence of foreign bodies.
3. The poor blood supply.
4. The 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[47].
- If a large wound **cannot** be covered by epithelium, the resulting ulcer may require a **skin graft**[48].
- **Wound contractures** are related to the action of **myofibroblasts**. This is seen especially following **burns.**

---

[43] حطام
[44] واضح
[45] an area of irregular fibrous tissue formed at the site of a scar or injury.
[46] إعاقة
[47] Wound **dehiscence** is a surgical complication in which a wound ruptures along surgical suture. Risk factors are age, diabetes, obesity, poor knotting or grabbing of stitches, and trauma to the wound after surgery.
[48] زراعة للجلد

Granulomatous inflammation

A form of chronic inflammation characterized by the formation of **granulomas**.

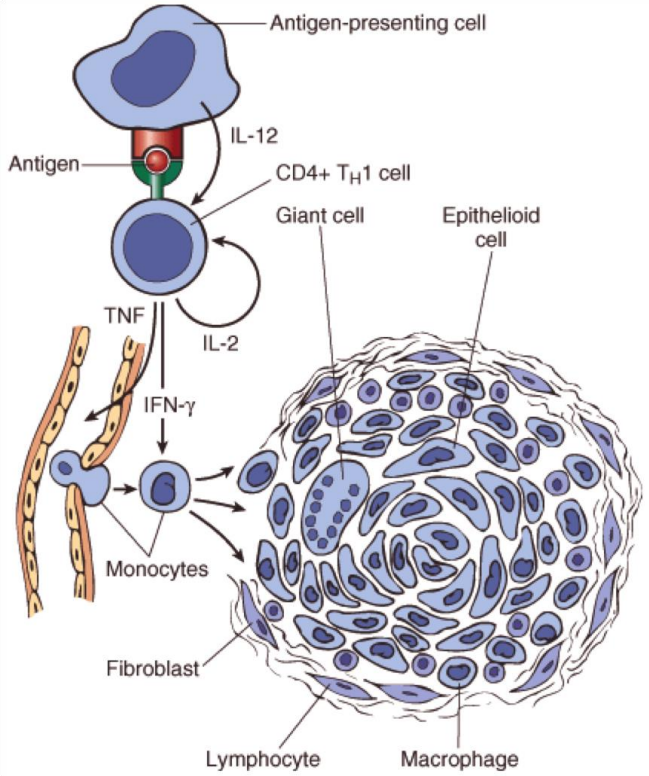
Granuloma: Nodular collection of **epithelioid macrophages** surrounded by a rim of **lymphocytes**.

Epithelioid macrophages: squamous cell-like appearance.

- Recognition of the granulomatous pattern is important. **Why?** Because of the limited number of conditions (some life-threatening) that cause it.

Granulomatous Inflammation pathogenesis:

Neutrophils ordinarily remove agents that incite an acute inflammatory response. However, there are circumstances in which reactive neutrophils **cannot** digest the substances that provoke[49] acute inflammation.



IFN-γ released by the **CD4+ T cells** of the **T_H1** subset is crucial in activating **macrophages**. This is considered as type **IV hypersensitivity**.

1. When macrophages have successfully phagocytosed the injurious agent but it survives inside them.
2. When an active T lymphocyte-mediated cellular immune response occurs. Lymphokines produced by activated T lymphocytes inhibit migration of macrophages and cause them to aggregate in the area of injury and form granulomas.

Types of granulomas:

1. Foreign body granuloma (non immune).
2. Immune granuloma.

[49] إثارة

Foreign body granuloma (non immune)	Immune granuloma
Forms when material such suture are large enough to preclude phagocytosis.	Caused by insoluble particles, typically microbes.
Foreign bodies: ● —Graft material ● —talc (associated with intravenous drug abuse)	**Bacteria** ● —Tuberculosis ● —Leprosy ● —Actinomycosis ● — Cat-scratch disease **Parasites** ● —Schistosomiasis ● —Leishmaniasis **Fungi** ● —Histoplasmosis ● —Blastomycosis **Metal/Dust** ● —Berylliosis
These material don't incite any specific inflammatory immune response.	They're capable of inducing a cell-mediated immune response.
Can be identified in the center of the granuloma, by polarized light (appears refractile).	Diseases with unknown cause: 1. Sarcoidosis 2. Crohn's disease

Examples:

1. **Tuberculosis.**
2. **Schistosomiasis[50].**
3. **Leishmaniasis**
4. **Leprosy[51].**
5. **Sarcoidosis**

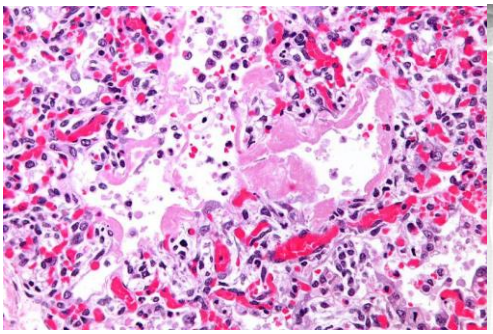
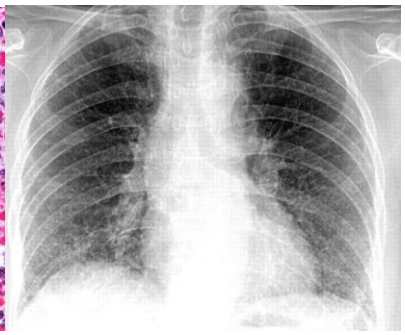
Cord factor: is a glycolipid molecule found in the cell wall of **Mycobacterium tuberculosis** and similar species. It protects M. tuberculosis from the defenses of the host

Cord factor presence increases the production of the **cytokines interleukin-12 (IL-12)**, **IL-1β**, **IL-6** and **TNF** (tumor necrosis factor) which are all **pro-inflammatory cytokines** important for granuloma formation.

[50] البلهارسيا
[51] الجذام

Clinical Cases

Acute Interstitial Pneumonia[52]

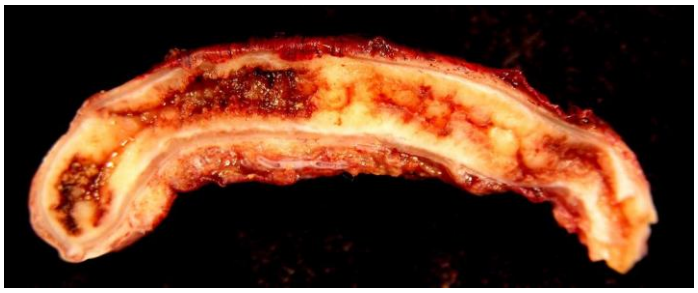



It is an inflammatory condition affecting the alveoli.
You can see that there's a lot of neutrophils.
Symptoms: cough, fever, high ESR, malaise, vomiting, high neutrophil count in the blood.
Diagnoses: bacterial inflammation in the lung. (**acute pneumonia**).
Acute interstitial pneumonitis occurs most frequently among people older than forty years old.

Viral Infection

Symptoms: fever, malaise[53] and weakness.
What is happening? Viral infection are usually associated with leukocytosis (increased number of leukocytes). They could go up to 60%. Neutrophils are usually elevated in bacterial infection, but not viral.
Diagnose: viral infection.

Acute Appendicitis



A 12 years old boy came to the emergency room.
Symptoms: he has a lower abdominal pain in the right side 20 - 30 times a day.
Examination: The surgeon found the his appendix was swollen, with vascular conjunction (cause of redness), and inflammatory exudate.

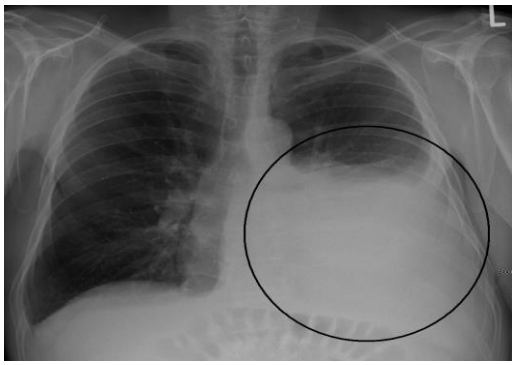
---

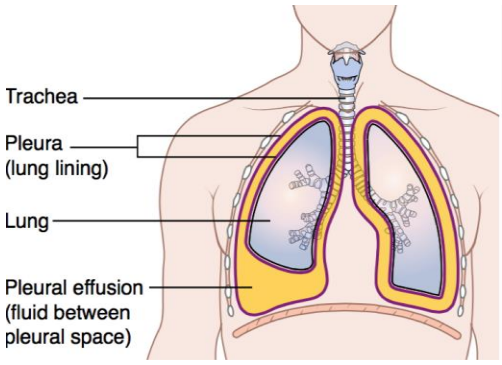
[52] الالتهاب الرئوي

[53] توعك

Diagnose: acute appendicitis[54]

Tuberculosis



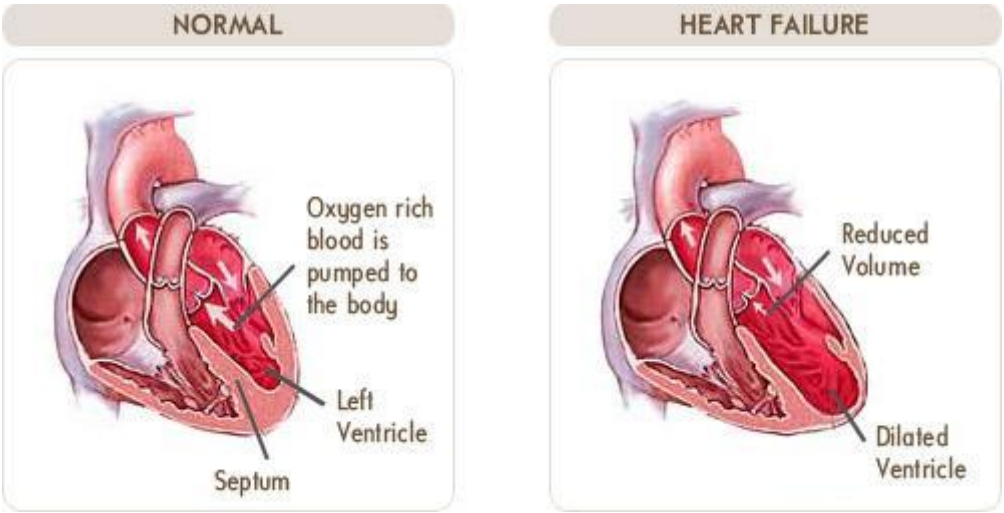


A large left sided pleural effusion as seen on an upright chest X-ray

A 20 year old patient, with exudate in his pleural cavity.
His CBC (Complete blood count) showed increased neutrophils.
Diagnose: We should think of an inflammatory condition, and namely, a bacterial infection. **TB** could be a cause.
If you see an x-ray of a **TB** patient you will find a chronic abscess that has fibrosis.(ندبه)

In acute inflammation of the lung, the alveoli are intact, and the normal architecture of the lung is preserved. There is exudate but the architecture is preserved.
On the other hand, in chronic inflammation of the lungs, we see lots of fibrosis and lymphoid follicles and proliferation of type 3 monocytes to compensate the cells that have been destroyed.
Why are some cells destroyed?
Because fibrosis obstructs the gas exchange and some cells die.
Pathogenesis:
Alveolar fibrosis→ hypoxia→ pulmonary failure → death

Congestive Heart Failure



A 90 year old patient came to the clinic with swollen feet.
Lab results: The fluid had very low protein content (transudate), The CBC showed no elevated leukocytes.

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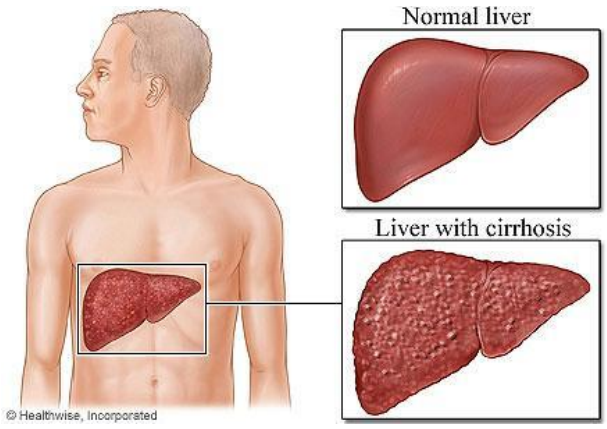
[54] التهاب الزائدة الدودية

Diagnose: you should think of congestive heart failure.

Alcoholic Hepatitis



A 35 year old man يحب السياحه. He had a swelling somewhere in his body and it was transudate. You take a biopsy from his liver (because you suspected liver steatosis) and you find fatty change.

تقول له خفف من الرحلات السياحيه يابو شربل فقد أثر فيك الكحول وعمل لك مشاكل في الكبد

Diagnose: <u>Alcoholic hepatitis.</u> In conclusion, the liver protein synthesis is reduced.

Pathogenesis:

The chronic inflammation leaves fibrosis, and in some cases it causes a disease; eg: alcohol induced liver damage.

(alcohol metabolites → cell injury → formation of free radicals → fibrosis)

At the beginning, there will be fatty change, but after some time, there will be chronic alcoholic hepatitis. As a result, there will be fibrosis, which leads to hepatic cirrhosis.

The liver cells will be in nodules and it will be surrounded by fibrosis and this leads to death

---

Renal Problem

A 52 year old patient came to the clinic with edema in a part of his body.

The patient shows no inflammatory signs and his liver is **OK** and the edema is transudate.

Because you are smart you should think of a **renal problem**.

فتقول له: "أكرِمنا بقطراتٍ من بولِك الثَّمين"

فيقول: "أبْشر يا دكتور... نحنُ في الخدمةِ دائمًا"

The patient's urine has lots of **protein**, his kidneys are abnormally removing the proteins from the blood, causing the edema.

Note: plasma proteins are albumins and globulins.

Questions

One best answer question:

1. Which one of the following substances in the inflammatory exudate[55] is a substrate for thrombin?

a. arachidonic acid

b. fibrinogen

c. kallikrein

d. PGE2

e. serotonin

Answer: B

Substrate: target for the enzyme (we need substance so that this enzyme can act upon).

Example: What's the substrate of amylase? Carbohydrates.

Thrombin: One of the products which occurs as a result of **activation of the coenzyme factor (cascade)**, we know that **coagulation cascade** is activated during the inflammation and it ends with factor 12. The end product will be **clutor thrombus** and **thrombin** is one of these products.

---

2. Which of the following is *not* a "cardinal sign" of inflammation?

a. atrophy

b. heat

c. pain

d. redness

e. swelling

Answer: A

---

3. A 46-year-old man presents with a painful nodule on the skin of his neck. The nodule is inflamed and tender. When incised, it drains sticky yellow fluid that contains large numbers of neutrophils. Which organism is most likely to be responsible?

a. *Clostridium perfringens*

b. Guinea worm (*Dracunculus medinensis)*

c. Louse (*Pediculus* sp.)

d. *Mycobacterium tuberculosis*

e. *Staphylococcus aureus*

Answer: E

Fluids that come with inflammation: exudate, transudate & pus.

Which type of inflammation that gives you transudate? serous inflammation.

a. Clostridium perfringens → Cause of Gangrene.

b. Guinea worm (Dracunculus medinensis) → Parasite → Eosinophil.

c. Louse (Pediculus sp.) → in hair & skin (قمل)

d. Mycobacterium tuberculosis → Causes TB which is a chronic inflammation. Chronic inflammation contains granulomas but not neutrophils (neutrophils are in acute inflammation only).

e. Staphylococcus aureus → Most common pus producing organism.

---

[55] افرازات

4. Which of the following cells is specific for acute inflammation when observed in tissue sections?

a. eosinophil
b. myofibroblast
c. neutrophil
d. plasma cell
e. T lymphocyte

Answer: C

You can see eosinophil in acute inflammation. But it's not the best answer.

---

5. Which of the following represents an essential component of granulation tissue?

a. epithelioid macrophages and giant cells

b. epithelial cells

c. fibroblasts and endothelial cells

d. lymphocytes and plasma cells

e. mast cells and basophils

Answer: C

What's the difference between granulation tissue and granuloma? Granulation is formed of proliferation of blood vessels, chronic inflammatory cells, fibrosis.

---

6. A patient has skin damage due to trauma that heals by fibrosis. Which of the following is mainly responsible for <u>contraction</u> of the wound?

a. endothelial cells.

b. fibroblasts.

c. macrophages.

d. myofibroblasts.

e. smooth muscle cells.

Answer: D

---

7. Which of the following diseases does not cause granulomatous inflammation?

a)Cat-scratch disease

b)Actinomycosis

c)Sarcoidosis

d)Leishmaniasis

e)Staphylococcus infection

Answer: I think it's E because it's a cause of acute inflammation.

True and False:

1. The following are correctly paired:

a. granulomatous inflammation – *Mycobacterium tuberculosis*

b. plasma cells – phagocytosis

c. pus – collection of neutrophils

d. eosinophils – parasitic infection

e. Langerhans' cells – *Mycobacterium tuberculosis*

A. True
B. False
C. True
D. True
E. False

---

2. A deficiency of the following is known to impair wound healing:

a. vitamin C

b. lead

c. vitamin B12

d. zinc

e. corticosteroids

A. True
B. False
C. False
D. True
E. False

---

7. During the <u>acute</u> inflammatory response:

a. histamine causes vasodilation.

b. the exuded fibrin is formed by local fibroblasts.

c. there is upregulation of cell adhesion molecules on endothelial cells.

d. red cell extravasation is a passive phenomenon.

e. complement components may act as chemoattractants.

a. True
b. False → fibrosis is a major end result of chronic inflammation.
c. True → otherwise you will not have diapedesis and adhesion of neutrophils on the cell.
d. True.
e. True.

---

8. The following are characteristic of healing by primary union (healing by first intention) in the skin:

a. large amounts of granulation tissue

b. close apposition of skin edges

c. relatively inconspicuous scarring

d. production of type I and type II collagen

e. proliferation of epidermal cell

a. false → when it's (Large) it's the second intention.
b. true.
c. true.
d. true.
e. true.

Extended matching items (EMIs):

For each of the following, select the most appropriate response from the list:

Theme: inflammatory mediators

A. C-reactive protein
B. Histamine
C. Immunoglobulin
D. IL-1
E. Neutrophil acid hydrolase
F. Nitric oxide

1. An acute-phase reactant.
2. A cytokine.
3. A principal product of mast cells.

---

a.IFN-γ	**1)The most important cell in granulomatous inflammation**
b.Langhans cells	**2)A cytokines that is important in activating macrophages and transforming them into epithelioid cells**
c. Epithelioid histiocytes	**3)Multinucleated cell in TB**
d.Cord factor	**4)Antigen presenting cells**
e.Langerhans cells	**5)pathogenesis of immune type granulomatous inflammation**
f. Type IV hypersensitivity reaction	**6)Microscopic finding of TB**

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Good Luck!

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سهيل الغامدي
محمود تخته
محمد الدماس
محمد الشبانات
ناصر قحطاني
عبدالله الخطاب
وضيف الشرف: معاذ العيسى

مها الربيعة
ريما الناصر
منيرة الدريهم
ريما الرشيد
ريما هزازي
نورة الهلالي
حنان محمد
رزان الصبحي
مشاعل حسين
عهد العنزي
لمياء الذوادي
شهد القحطاني
شيماء الدعيجي