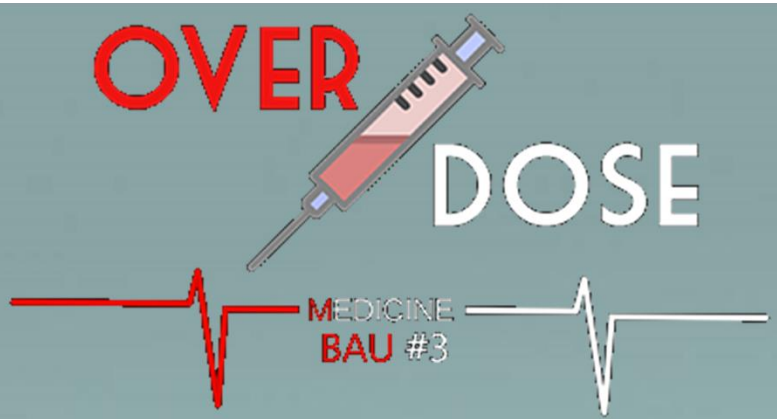

Pathology

Sheet #11

Lecture Title (Acute Inflammation)

Lecture Date : 23-10-2018

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Edited By : Dana Masoud

If you come by any mistake *(whether it be spelling, grammatical or scientific)* while browsing this sheet, kindly report it to the academic team **2023od@gmail.com** **or Facebook account** **الفريق الأكاديمى**

Plasma Protein–Derived Mediators

that belong to three interrelated systems:
the complement, kinin, and clotting systems.

The complement system consists of more than **20** proteins, some of which are numbered **C1** through **C9**. This system functions in both **innate** and **adaptive** immunity for defense against microbial pathogens.

Upon activation, different complement proteins:

(1) coat (**opsonize**) particles, such as micorbes for **phagocytosis & destruction**, **(2)** **increased vascular permeability**, and

(3) induce WBC **chemotaxis.**

These proteins act as antibodies, ,do opsonization and ease the phagocytosis process.

Complement activation ultimately generates a pore like **membrane attack complex (MAC)** that punches holes in the membranes of microbes.

Complement components (numbered C1 to C9), are present in plasma as inactive forms.

Briefly, the most critical step in the elaboration of the biologic functions of complement is the **activation** of the third component, C3 :

(1) via the **classic pathway**, triggered by **fixation of C1** to antibody (IgM or IgG); or

(2) alternative pathway, triggered by microbial surface molecule (e.g., endotoxin), complex polysaccharides, cobra venom, and other substances, in the absence of antibody.

(3) lectin pathway, in which plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1. (classic pathway but in the absence of antibodies).

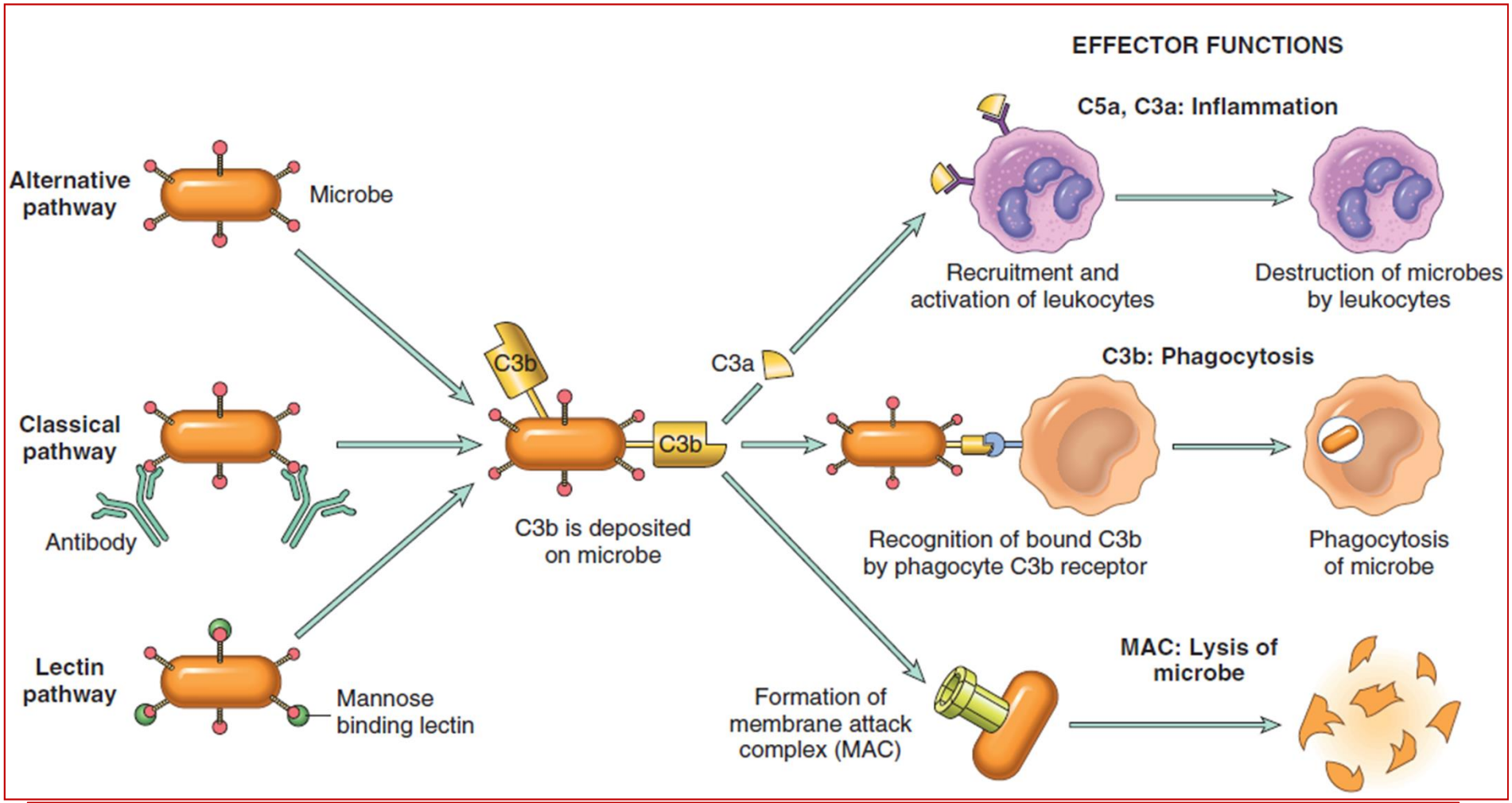


Fig. 3.11 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

The biologic functions of the complement system fall into three general categories:

Inflammation: *(***Vascular effects**) **C3a & C5a** (anaphylatoxins) increase vascular permeability & cause vasodilation **(through what?)**

Phagocytosis: C3b and its cleavage product iC3b (inactive C3b), when fixed to a microbial cell wall, act as opsonins and promote phagocytosis by neutrophils and macrophages, which bear cell surface receptors for the complement fragments.

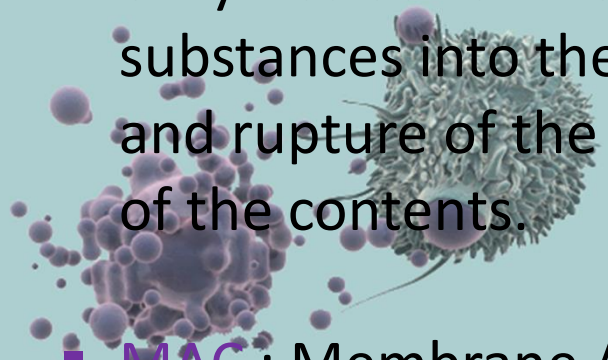
Cell lysis: The deposition of the MAC on cells makes these cells permeable to water and ions and results in death (lysis) of the cells.

Sheet Note: by inducing the production of Histamine by Mast cells.

- To differentiate between the active and inactive forms of complement proteins is that we add an (a) after the name : **C3a, C5a**.

- Remember: in inflammation, the endothelial cells move away from each other causing the formation of large pores and the plasma leaking out.

- Cell Lysis : either happens by leakage of hydrolytic enzymes out of the cell, or by an influx of substances into the cell and therefore swelling and rupture of the membrane and finally leakage of the contents.



- MAC : Membrane Attack Complex.

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The activation of complement is tightly controlled by cell-associated & circulating **regulatory proteins.**

The presence of these inhibitors in cell membranes protects normal cells from inappropriate damage during protective reactions against microbes.

However, inappropriate or excessive complement activation (e.g., in antibody-mediated diseases, such as Glomerulonephritis) can overwhelm the regulatory systems, and this is why complement activation is responsible for serious tissue injury in some immunologic disorders (e.g., GN).

- Whenever there's inflammation there will always be something working on removing it

Coagulation & Kinin Systems

Inflammation and blood clotting are often intertwined, with each promoting the other. The clotting system is divided into two pathways that converge, culminating in the activation of thrombin and the formation of fibrin.

Activation of Hageman factor (**XII**) to activated Hageman factor (**XIIa**) initiates four systems involved in inflammation:

(1) **Kinin system** producing vasoactive kinins (bradykinin);

(2) **Clotting system** including the activation of thrombin, fibrinopeptides, & factor X, **all** with inflammatory properties;

(3) **Fibrinolytic system** producing plasmin & inactivating thrombin; and

(4) **Complement system** producing anaphylatoxins C3a & C5a.

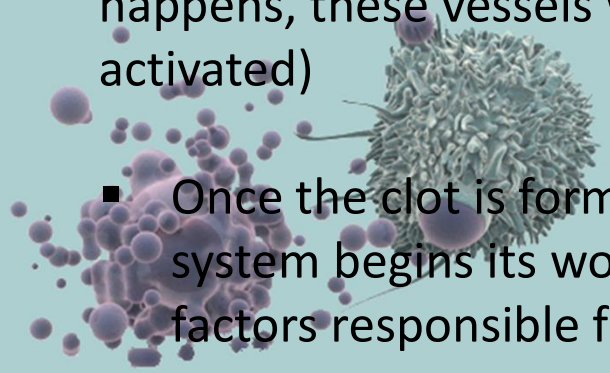
Sheet Note: all these factors are already found in the body, but in the inactive form. When the body needs them, they are **activated** not **synthesized.**

- The numbering system of coagulation factors is not related to their function or the order of their recruitment. (has to do with their discovery)

- **Factor X** is the place where the intrinsic and extrinsic activated coagulation factors converge to form the clot.

- Notice that the Hageman factor activates both clotting (coagulating) and fibrinolytic systems, which is an example of the regulation in our body.

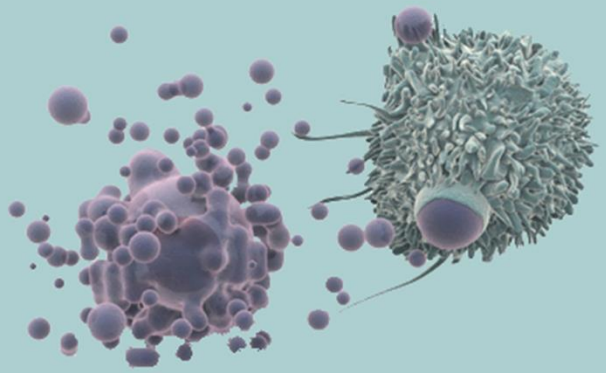
  ex: when the clotting system is activated, the clotted/ fibril blood keeps getting bigger eventually closing the blood vessel (there will be multiple clots of different sizes within these vessels→ so if a wound happens, these vessels would be blocked if the fibrinolytic system is not activated)



- Once the clot is formed and the bleeding is stopped, the fibrinolytic system begins its work by the lysis of the fibrin clot, stopping the factors responsible for clotting.

- **How do fibrin clots form?** by the activation of **Fibrinogen** that forms **fibrin** strands. These fibrin strands wrap around and bond to the already sticky platelets which in turn trap the blood elements, especially RBCs, and the clot forms.

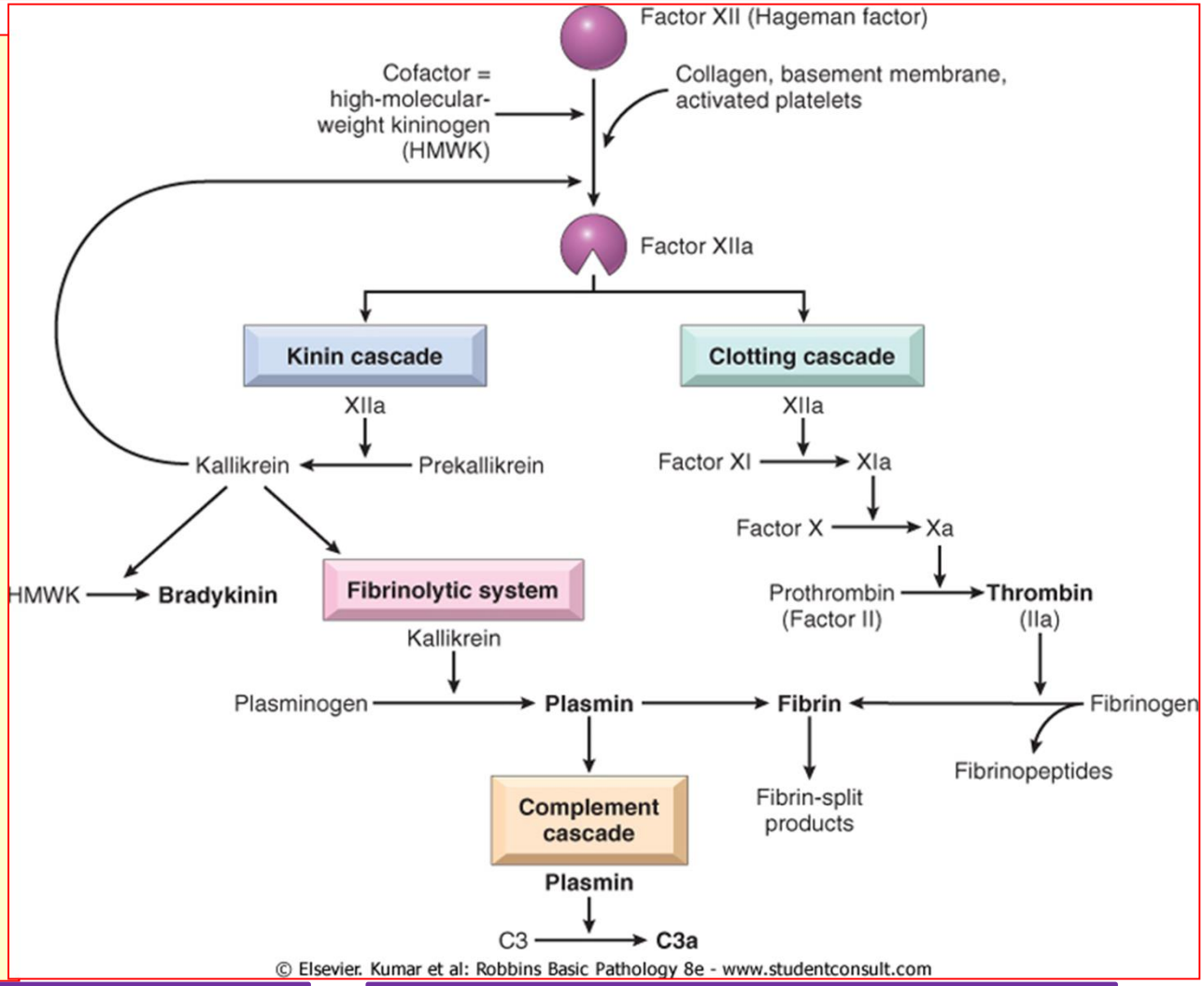
- **Plasminogen** is the inactive form of **plasmin** which is always found in our body. Activating it, causes the plasmin to hydrolyze (eat) the fibrin on the platelets resulting in a dissolved clot.(the stickiness of the platelet is way less)



Interrelationship among the 4 plasma mediator systems triggered by activation of factor XII.

Hageman factor = factor **XII** of the intrinsic coagulation cascade, is a protein synthesized by the **liver,** circulate in an **inactive** form, **until** it encounters (I) **collagen, BM, or activated platelets** (as at a site of EC injury), or (II) **plasmin.**

Each can activate Hageman factor, thereby amplifying the entire set of responses.



Sheet Note: it encounters collagen or BM when there's interruption or any disruption to the vascular wall .

Sheet Note: activated platelets attract substances by degranulation of it's content

With the assistance of a high-molecular-weight kininogens (HMWK) cofactor, factor **XII** then undergo a conformational change (becoming active, **factor XIIa**), exposing an active serine center, that can cleave a number of protein substrates of the kinin & coagulation systems.

In the clotting system , factor **XIIa** activate factor **XI** to **XIa** which in turn convert factor **X** to **Xa** which convert **Prothrombin** into **thrombin** which convert circulating soluble **fibrinogen** to an **insoluble fibrin clot.**

(1) Factor Xa increase vascular permeability & WBC emigration.

(2) Thrombin enhances WBC adhesion to EC.

(3) **Fibrinogen cleavage** results in the generation of **fibrinopeptides** that increase vascular permeability & are chemotactic for WBC.

Fibrinolytic system

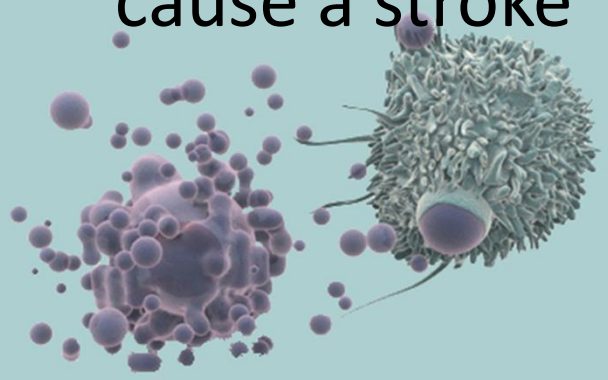
while activated Hageman factor is inducing **clotting,** it is concurrently (at the same time) activating the : **Fibrinolytic system**.

This mechanism exists to counter-regulate clotting by cleaving fibrin, thereby solubilizing the fibrin clot.

Without fibrinolysis, & other regulatory mechanisms, initiation of the coagulation cascade, even by trivial (very mild) injury, would culminate in **continuous & irreversible clotting of the entire vasculature!**

(I) Plasminogen activator {PA} (released from EC, WBC, & other tissues), & **(II) kallikrein,** Both **cleave** **plasminogen**, a plasma protein bound up in the evolving fibrin clot, result in **Plasmin**, a multifunctional protease that cleave fibrin & is therefore important in **lysing clots**.

- The fibrin clot in any wound forms a hard shell around the area, and on the inside it would be wet.
- The fibrin clot is also there on the inside . If this fibrin clot stays there it will turn into thrombus, if the thrombus detaches from its place and into the circulation and into a vessel with a smaller diameter this would block the vessel
- If this blocked vessel was in the brain, this would cause a stroke



However, fibrinolysis also participates in the vascular phenomena of inflammation.

Plasmin, also, cleaves the complement **C3** component to **C3a**, resulting in vasodilation & increase vascular permeability.

Plasmin, also, activate Hageman factor, hereby amplifying the entire set of responses.

Fibrin-split products increase vascular permeability.

Increases the vascular permeability→ To dilute the concentration of toxic substances, and help WBC's and other cells get to the inflammation site

Kinin system activation

Already existing.

in which factor **XIIa** converts plasma **prekallikrein** into **kallkrein**, which act on the circulating High molecular weight Kininogen (HMWK) leads finally to the formation of **bradykinin.**

Bradykinin , ***like Histamine*** causes arteriolar dilatation, increases vascular permeability, & bronchial smooth muscle contraction, causes pain when injected in skin.

+ Edema.

Bradykinin actions are short-lived, because it is rapidly inactivated by degradative **kininases** present in the plasma & tissues.

So, **kallikrein is a:**

1. A potent activator of Hageman factor,
2. Activate plasminogen→ into plasmin,
3. Convert HMWK → to bradykinin.

Again, to dissolve the clot.

Role of Mediators in Different Reactions of Inflammation

- **Vasodilation**: Histamine + NO + PGs
- **Increased Vascular Permeability**: Histamine, serotonin + C3a & C5a {by liberating histamine & serotonin from their cells}+ Bradykinin+LTC4, LTD4, LTE4+PAF+Substance P.
- **Leukocyte recruitment & Activation**: TNF & IL-1 + Chemokines (IL-8) + C3a & C5a + LTB4, + Bacterial products (e.g., N-formyl methyl peptides).
- **Fever**: IL-1, TNF + PG
- **Pain** :PG + Bradykinin + Neuropeptides.
- **Tissue Damage:** lysosomal enzymes of WBC + NO + ROS.

We still do **not fully understand** why some stimuli elicit inflammatory reactions, e.g., necrotic cells are a powerful stimulus for inflammation, but how dead cells trigger this reaction? is not yet established !

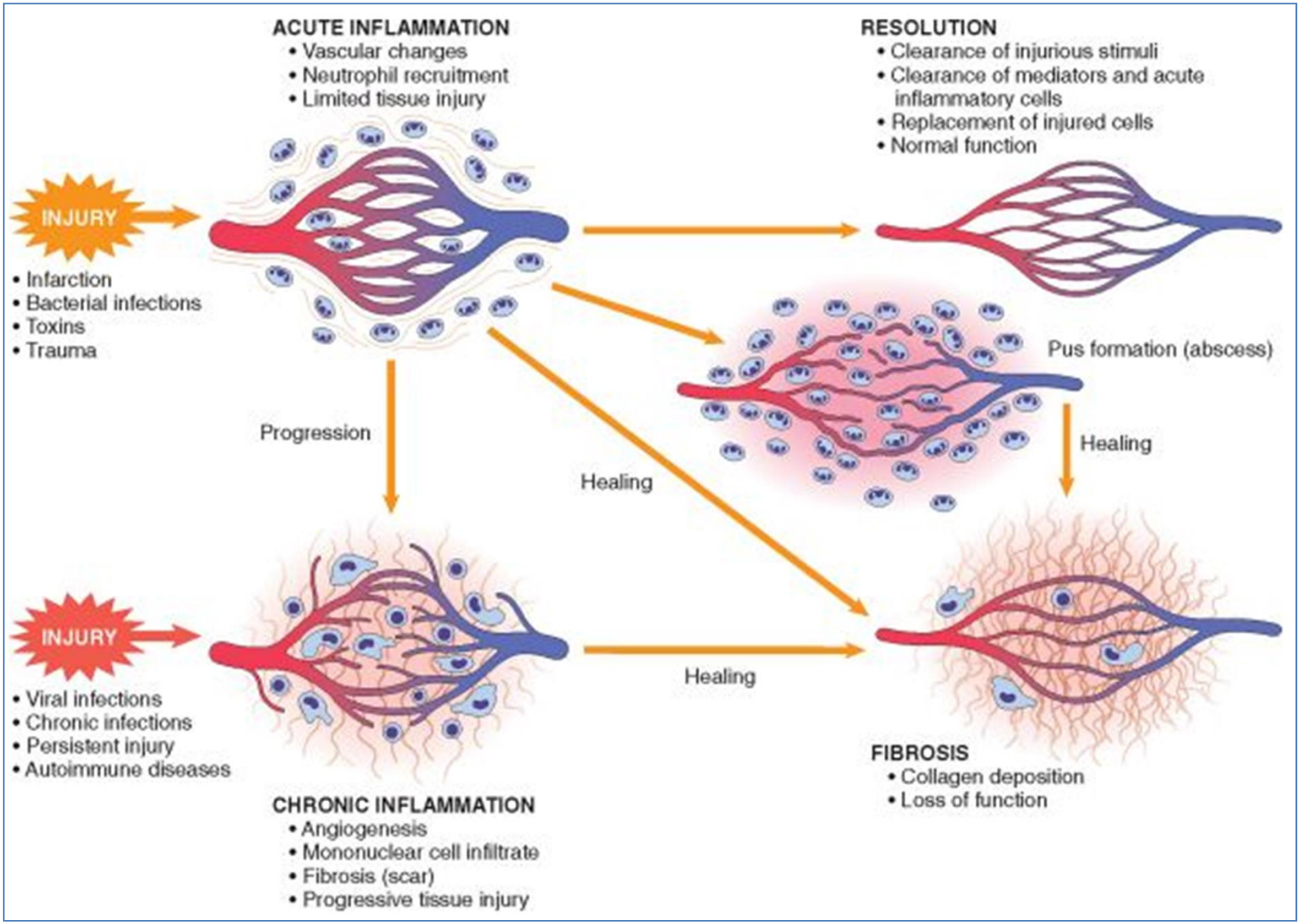
The cell is dead so how can it release the signal??

Hypoxia, itself induces an inflammatory response, partly by stimulating the production of mediators, e.g., VEGF that increases vascular permeability.

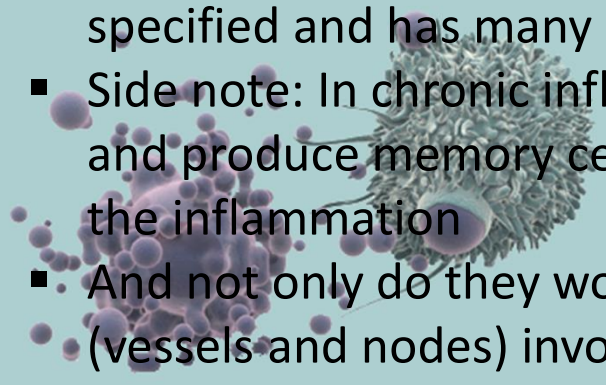
Vascular Endothelial Growth Factor.

Outcomes of Acute Inflammation

all acute inflammatory reactions may have one of three outcomes:



- With infections, toxins, trauma…etc happen, there will always be changes on the capillary bed (the arterioles and post capillary venules)**
- In the pus formation, there is a very large increase in all products and factors of the acute inflammation (microbes and germs) , in the injured cell fibrosis occurs in order for it to support itself . Loss of function happens until it is able to do remodeling
- Progressing of acute inflammation to chronic leads to development of new blood vessels which is called **Angiogenesis**. , also mononuclear cell infiltrate and the rest…
- In the acute inflammation, polymorphonuclear cell infiltration happens unlike in the chronic where it is (mononuclear) and the nucleus is specified and has many shapes.
- Side note: In chronic inflammation lymphocytes stay for a long duration and produce memory cells and anti bodies that persist in trying to resist the inflammation
- And not only do they work, but they also get the whole lymphatic system (vessels and nodes) involved +fibrosis and progressive tissue injury also happen (angiogenesis happens)



Morphologic Patterns of Acute Inflammation

The morphologic hallmarks of all acute inflammatory reactions are dilation of small blood vessels, slowing of blood flow, and accumulation of leukocytes and fluid in the extravascular tissue.

However, special morphologic patterns are often superimposed on these general features, depending on the severity of the reaction, its specific cause, and the particular tissue and site involved.

Serous inflammation is marked by the outpouring of a thin fluid that may be derived from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. Accumulation of fluid in these cavities is called an ***effusion***.

Sheet Note: although in the picture here, there's no cavity, it's called effusion because the inflammation made its own cavity (bubble).

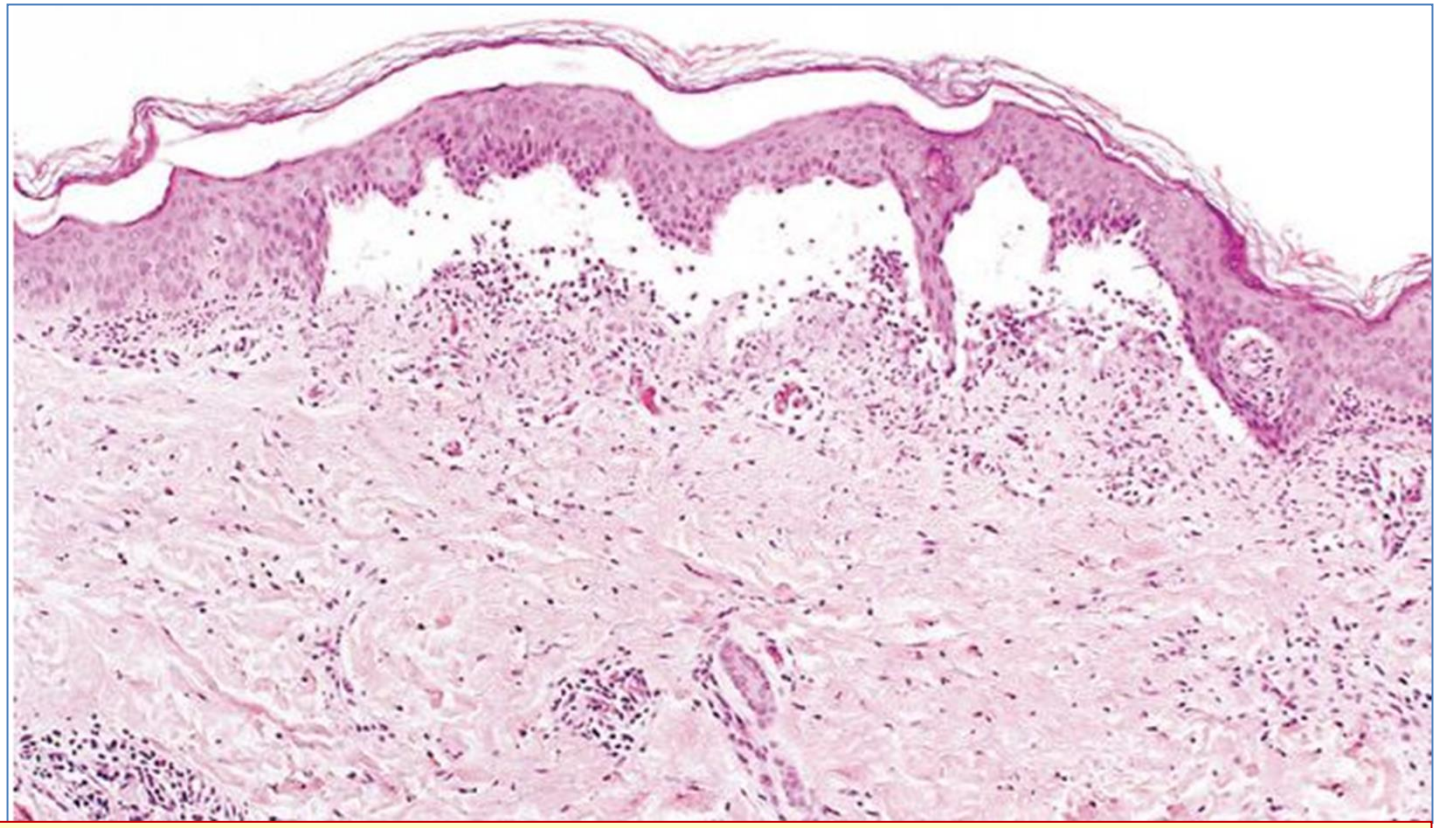
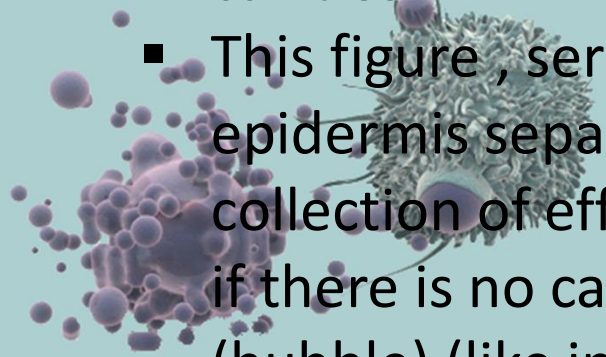


Fig. 3.12 Serous inflammation. Low-power view of a cross section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

- **Remember**:
  Acute inflammation (حاد)
  Severe (شديد)
  Acute inflammation can be severe, moderate, or mild. (chronic too)

- Serous inflammation does not only happen in body cavities, it can happen in any place in the body.

- **Edema** is an accumulation of fluids in interstitial spaces, whereas **Effusion (انصباب)** happens in body cavities.
- This figure , serous inflammation blister shows the epidermis separated from the dermis by a focal collection of effusion , and we still call it effusion even if there is no cavity as it has made it's own one (bubble) (like in burns)



FIBRINOUS INFLAMMATION

With greater increase in vascular permeability, large molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited in the extracellular space. A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus (e.g., cancer cells).

A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura.

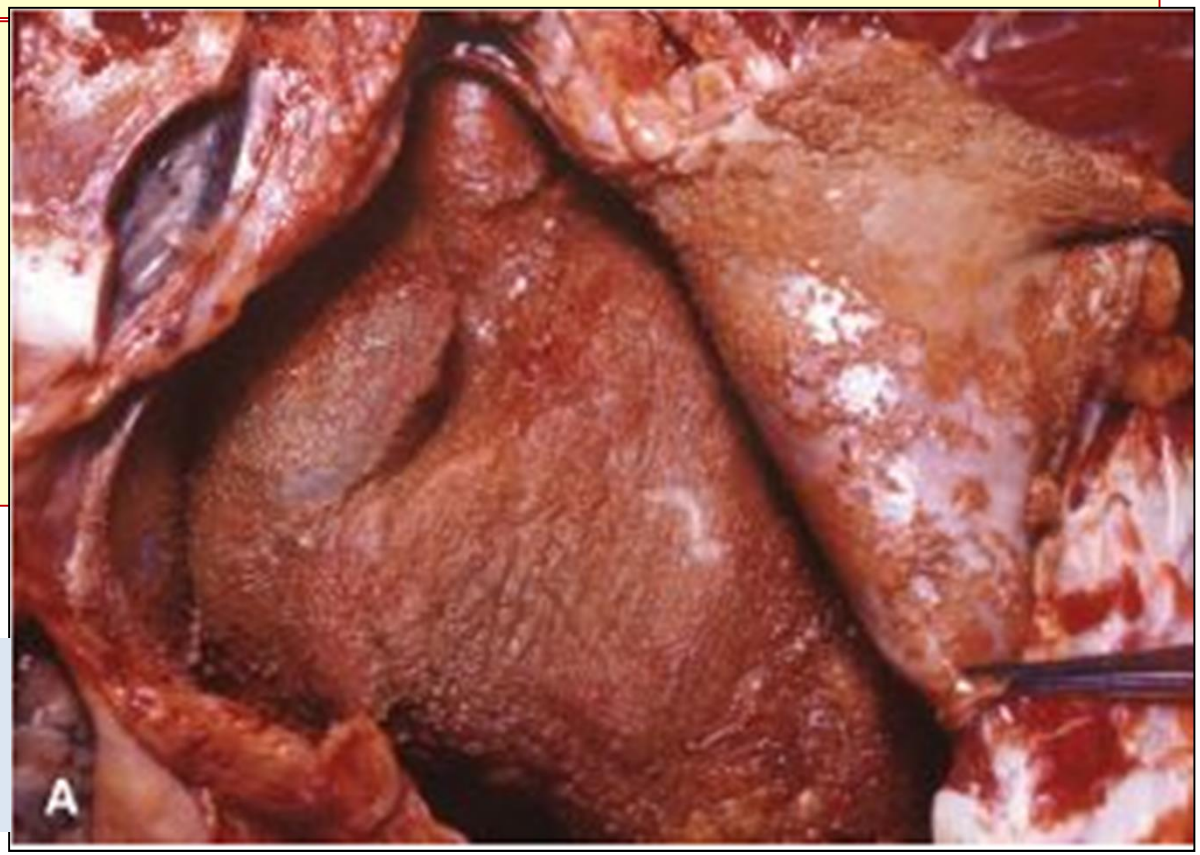
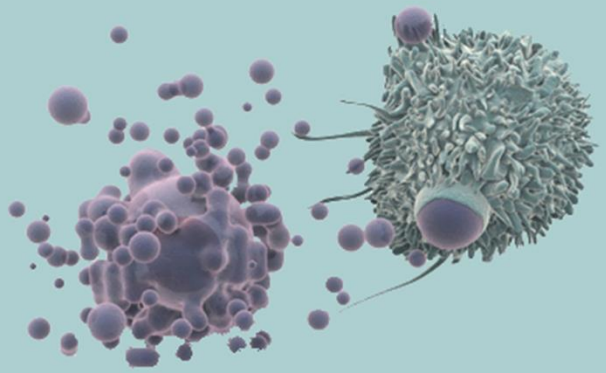


Fig. 3.13 Fibrinous pericarditis. **(A)** Deposits of fibrin on the pericardium.

- These fibers come form Fibrinogens (that already exist in the circulation) turning into fibrin
- When vascular permeably is increased this causes more injury and a longer duration of inflammation



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Histologically, fibrin appears as an eosinophilic meshwork of threads or sometimes as an amorphous coagulum. Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. If the fibrin is not removed, over time it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring (organization).

Fibrinolysis= plasmin is activated
Organization= the matter turn in to an organic one

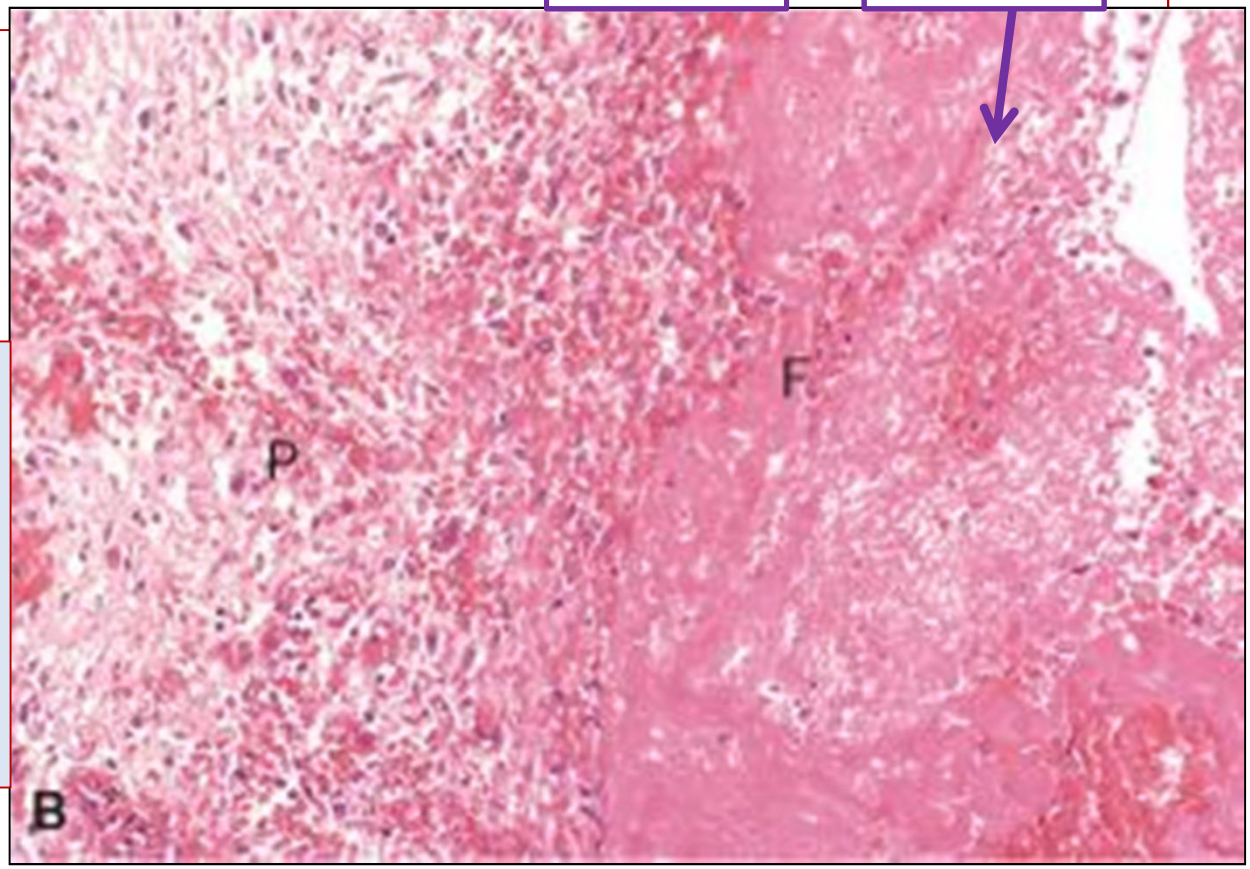


Fig. 3.13
Fibrinous pericarditis. (B) A pink meshwork of fibrin exudate *(F)* overlies the pericardial surface *(P)*.

Suppurative or Purulent Inflammation; ABSCESS

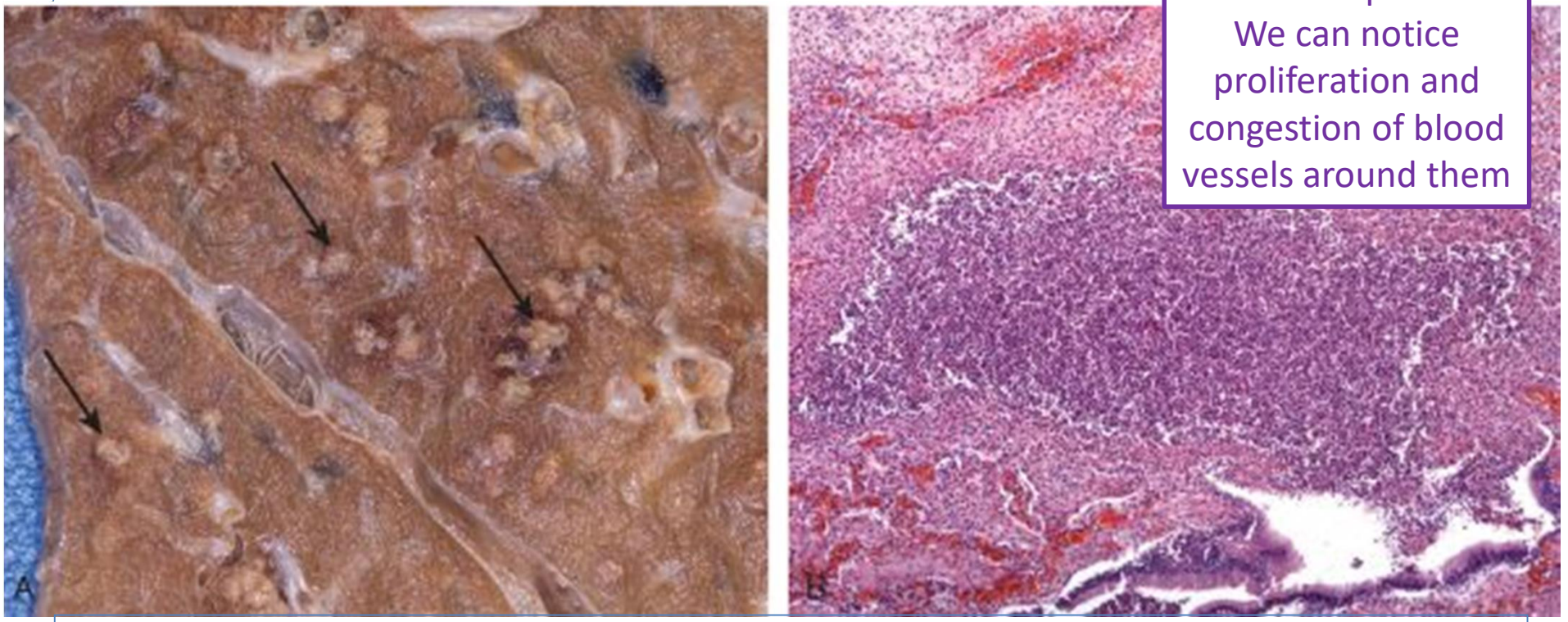
This type of inflammation is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, liquefactive necrosis, and edema fluid.

Certain bacteria (e.g., staphylococci) produce this localized suppuration and are therefore referred to as ***Pyogenic*** (pus-producing) bacteria.

A common example of an acute suppurative inflammation is acute appendicitis.

Abscesses are localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space. They are produced by deep seeding of pyogenic bacteria into a tissue. Abscesses have a central region that appears as a mass of necrotic leukocytes and tissue cells.

Puss filled pockets. We can notice proliferation and congestion of blood vessels around them



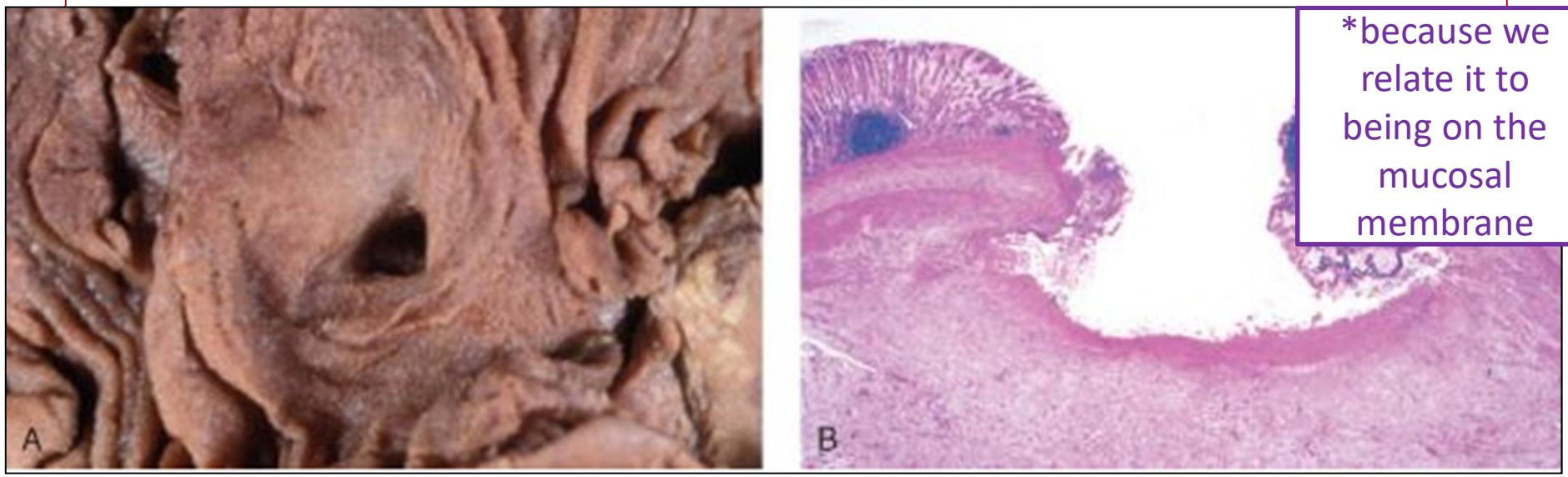
A, Multiple bacterial abscesses in the lung, in a case of bronchopneumonia. B, The abscess contains neutrophils and cellular debris, and is surrounded by congested blood vessels.

+ a fibrous semi-capsule

ULCERS

Sheet Note: it can be seen on any surface in the body, like skin, but mainly in the GIT*.

An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the **sloughing** (shedding) of inflamed necrotic tissue and can occur only when tissue necrosis and resultant inflammation exist on or near a surface.



*because we relate it to being on the mucosal membrane

A- A chronic duodenal ulcer. B- Low-power cross-section of a duodenal ulcer crater with an acute inflammatory exudate in the base.