

Pathology of Inflammation and Repair

LEC.2

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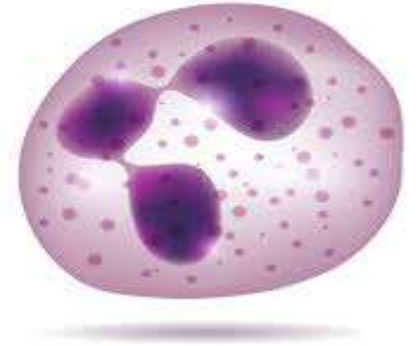
Objectives

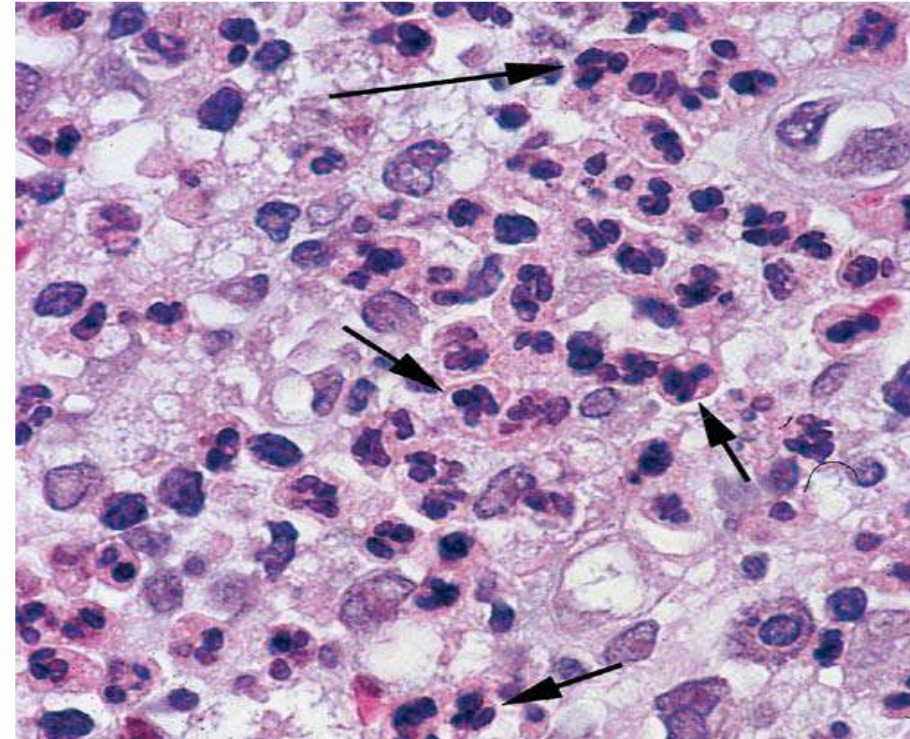
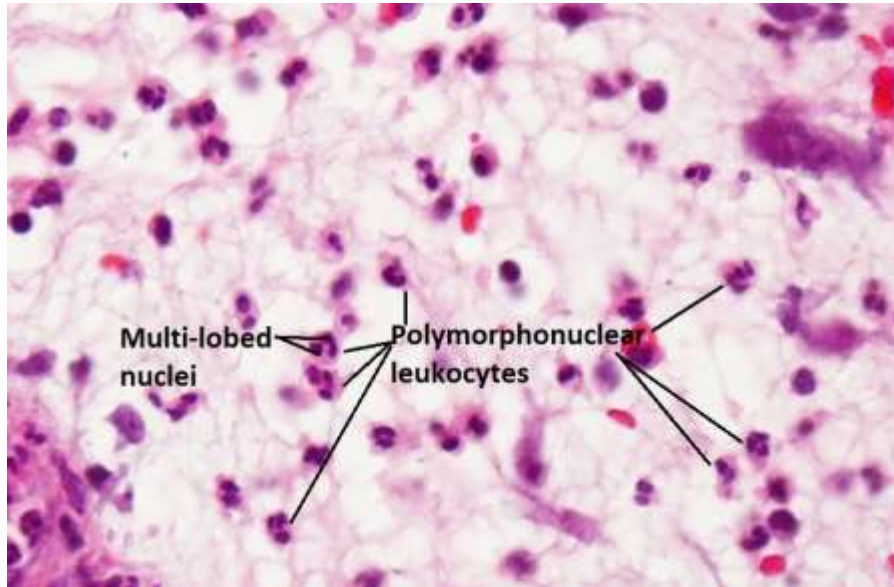
- Explain the role of various chemical mediators of inflammation
- Describe the morphologic patterns of acute inflammation
- Identify the outcomes of acute inflammation

Cells of acute inflammation

- **Neutrophils:** Most prominent cells in acute inflammation during first 6hrs -24hrs.
- **Monocytes-macrophages:** These cells replaced neutrophils in area of acute inflammation **after 2-3days**.
- **Eosinophils:** These cells are prominent in acute inflammatory **allergic diseases & parasitic infestation**.
- **Mast cells & basophils:** they are the main **source of histamine** in acute inflammation.
- **Lymphocytes:** These cells are the **most important cells of chronic inflammation**, but also increased in **acute inflammation due to viral diseases** like influenza, mumps.
- The **main** acute inflammatory cells are: **Neutrophils and macrophages**.

NEUTROPHIL





Acute inflammation with densely packed (PMNs)
with multilobed nuclei

Mediators of acute inflammation

- Inflammatory mediators are the substances that initiate and regulate inflammatory reactions.
- **General properties of Mediators:**
 1. Molecules **derived either from plasma** (synthesized in the liver) **Or** produced locally at the site of inflammation **from cells**
 2. **Produced in response to either microbial products or factors released by necrotic tissues**, thus insuring that inflammation is normally triggered only when and where it is required.
 3. **Most of the mediators are short-lived.** They quickly decay or inactivated by enzymes, or they are otherwise scavenged or inhibited.
 4. **One mediator can stimulate the release of other mediators** and act within amplifying or regulatory cascades to stimulate the release of other downstream factors.
 5. Most mediators **act by binding to specific receptors**, although some have direct enzymatic activity (e.g., proteases) or mediate oxidative damage (e.g., ROS).

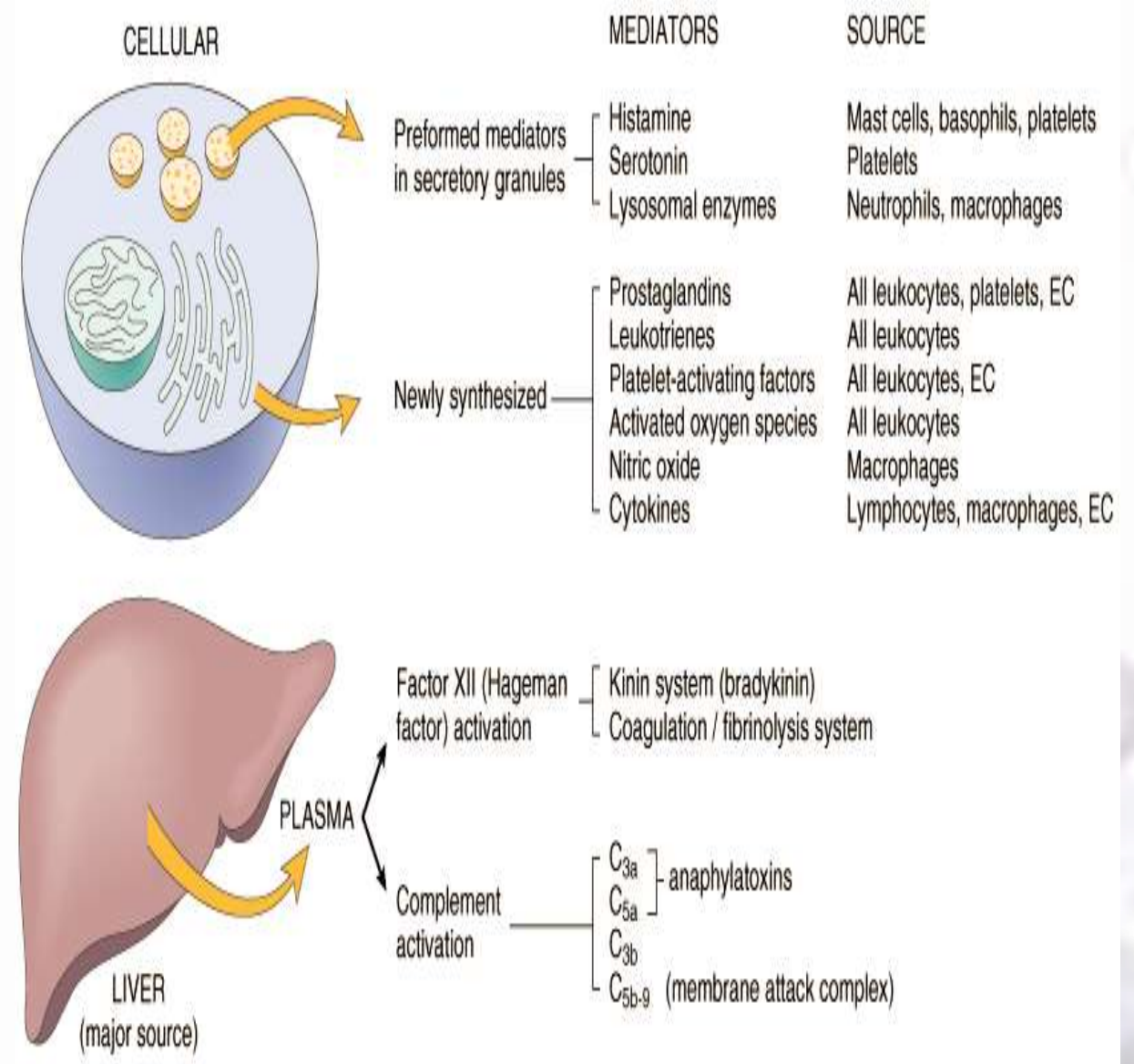
Types of Mediators

A. Cell-derived mediators:

- Produced locally at the site of inflammation, either:
- Ready-made** and rapidly released from intracellular granules (e.g., histamine in mast cell granules) **OR**;
- Synthesized when needed** (e.g., prostaglandins, leukotrienes, cytokines) in response to a stimulus.
- Examples;**
 - Vasoactive amines (Histamine and Serotonin).
 - Arachidonic acid metabolites
 - Cytokines
 - Others (PAF, NO, oxygen derived free radicals, lysosomal enzymes)

B. Plasma-derived mediators

- Synthesized in the liver and circulate in plasma as inactive precursors that are activated by proteolysis, include three systems; **Kinin system**, **Clotting system** and **Complement system**.



A. Cell-derived mediators

- The major cell types that produce mediators of acute inflammation are **macrophages, dendritic cells, and mast cells**, but platelets, neutrophils, endothelial cells and most epithelia can produce some of the mediators.

1. Vasoactive amines (histamine and serotonin)

➤ Histamine.

- **Source:** Mast cell of the tissue & basophils of blood, platelets.
- **Action:** main mediator of immediate transient response, **powerful vasodilator & increased vascular permeability.**
- **Causes of stimulation:**
 1. Physical injury such as trauma, cold or heat.
 2. Allergic immune reactions involving IgE.
 3. Products of complement (C3a and C5a).
 4. Cytokines (IL-1, IL-8).
- Its vasoactive effects are mediated by binding to H1 receptors, on microvascular endothelial cells.

2. Arachidonic acid metabolites:

Arachidonic acid (AA) is a polyunsaturated fatty acid obtained from diet or synthesized from linoleic acid. It is normally esterified in membrane phospholipids, not free.

When cells are activated by stimuli such as microbial products, AA is rapidly metabolized into prostaglandins and leukotrienes—lipid mediators that affect inflammation and hemostasis.

There are two pathways of arachidonic acid metabolites synthesis:

A. Cyclooxygenase (COX): This results in formation of;

- ***Prostacyclin (PGI₂):** cause increased vascular dilatation & inhibit platelets aggregation.

- ***Prostaglandins (PGD₂), (PGE₂):** causes vasodilation, increased vascular permeability. **(PGD₂);** leukocyte chemotaxis. **(PGE₂);** are also responsible initiation of **pain & fever.**

- ***Thromboxane A₂:** cause vasoconstriction & induce platelets aggregation.

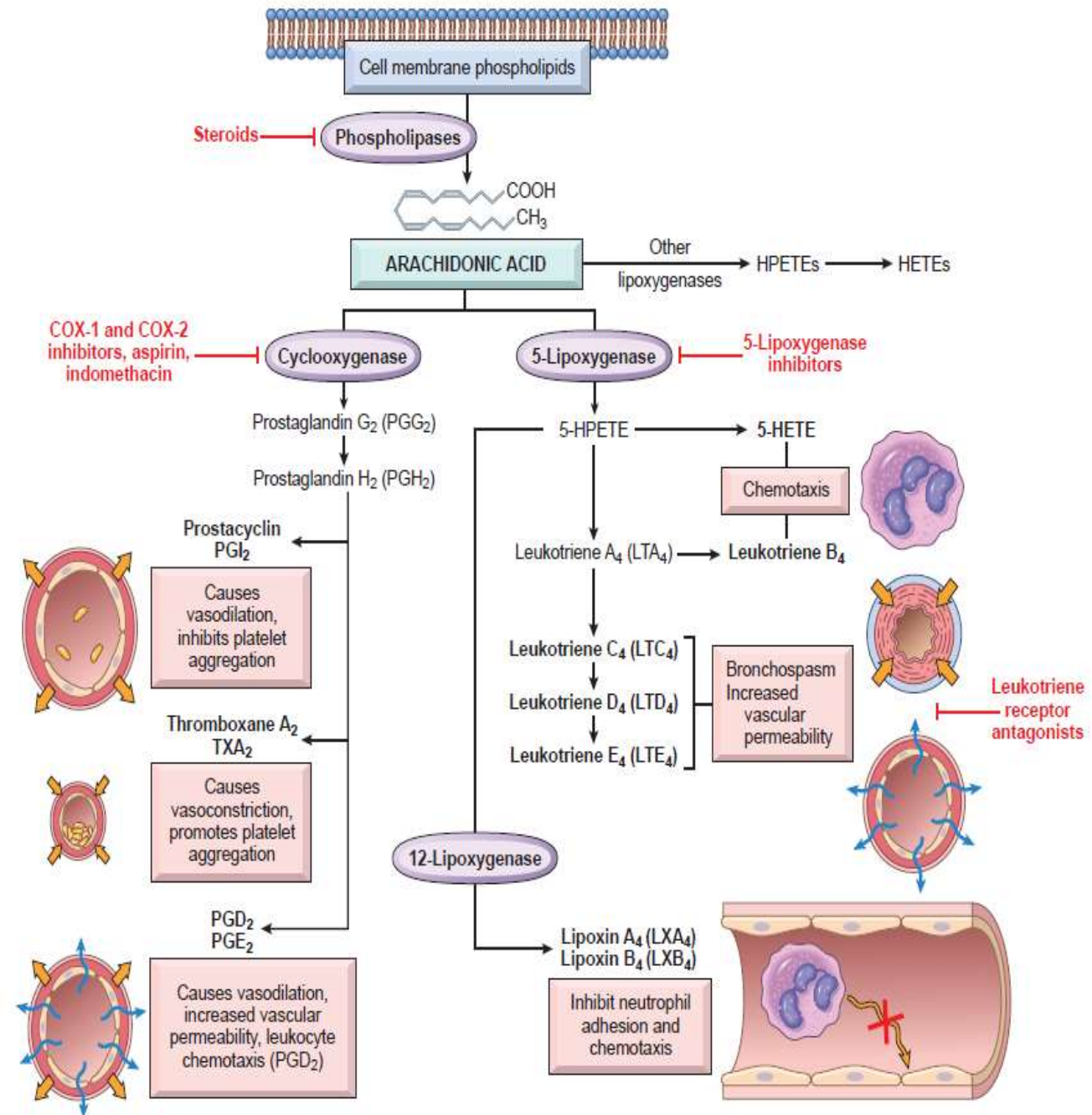
B. Lipoxygenase (LOX): This pathway results in formation of many **leukotrienes;**

- ***(LTB₄),** a potent **chemotactic agent** and activator of neutrophils.

- ***(LTC₄, LTD₄ & LTE₄),** cause vasoconstriction, bronchconstriction & increase vascular permeability.

Production of arachidonic acid metabolites and their roles in inflammation.

Note the enzymatic activities whose inhibition through **pharmacologic intervention** blocks major pathways.



3. Cytokines and Chemokines :

- Cytokines are proteins **produced by** many cell types (principally **activated lymphocytes, macrophages and dendritic cells**) that mediate and regulate immune and inflammatory reactions.
- **TNF and IL-1** are key mediators of inflammation, contributing to both local and systemic reactions:
 - **Local effects:** Promote leukocyte recruitment by enhancing adhesion to endothelium and migration through blood vessels.
 - **Systemic effects:** Induce acute-phase responses to infection or injury, including fever, leukocytosis, anorexia, and lethargy.
- **Chemokines** are a family of small proteins that act primarily as **chemoattractants** for specific types of leukocytes.
- **IL-8;** is typical of this group; it is produced by macrophages and endothelial cells after activation by TNF and IL-1 or microbial products.

4. Others:

➤ Platelets activating factor:

- **Source** :leukocyte, mast cell, basophil and endothelial cells.
- **Action:** Platelets aggregation, Vasodilatation, increased vascular permeability, Chemotaxis, Leukocytes adhesion and Bronchconstriction.

➤ Nitric Oxide (NO):

- **Source:** Endothelial cells, macrophages.
- **Action:** Vasodilation and killing of microbes.

➤ Reactive oxygen species (ROS):

- **Source:** Endothelial cells, macrophages.
- **Action:** killing of microbes, endothelial cell damage, increased vascular permeability.

➤ Lysosomal enzymes: such as myeloperoxidase, acid hydrolases and proteases

- **Source:** neutrophils, macrophages.
- **Action:** destroy bacteria and degrade extracellular components, thereby clearing out pathogens and damaged tissue.

B. Plasma Mediators (proteases)

- Plasma-derived mediators are **produced mainly in the liver** and are **present in the circulation as inactive precursors** that **must be activated**, usually by a series of proteolytic cleavages, to acquire their functional properties
- **Sources:** from three circulating interrelated systems in the plasma, these systems are,

I. Kinin system:

- Activation of this system will result in formation of **Bradykinin**, which is protein has **the same action of histamine**, in addition it causes pain.
- This system is inactivated by **Kinase**.

II. Clotting system:

- There are many proteases within this system that act as mediators of inflammation include;
 1. **XII_a**; causes activation of **thrombin**, which in turn stimulates fibrin clot formation.
 - **Thrombin stimulates leukocyte adhesion during inflammation.**
 2. **X_a**; causes increase **vascular permeability & leukocyte emigration.**
 3. **Fibrinopeptides**; which are synthesized by the action of thrombin, **cause vascular permeability & Chemotaxis of leukocytes.**
 4. **Fibrin degradation products**; They are formed by fibrinolysis (lysis of fibrin), these products cause **increase vascular permeability & vasodilatation.**

III. Complement system:

- This system consists of **cascade of plasma proteins** that play an important role in both immunity & inflammation (C1 - - - C9).
- **C3a, C5a, C4a**; (anaphylatoxin): release of histamine.
- **C3b**: is an opsonin
- **C5a**: chemotactic agent.

Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C ₄ , D ₄ , E ₄
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B ₄
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

Morphologic patterns of acute inflammation

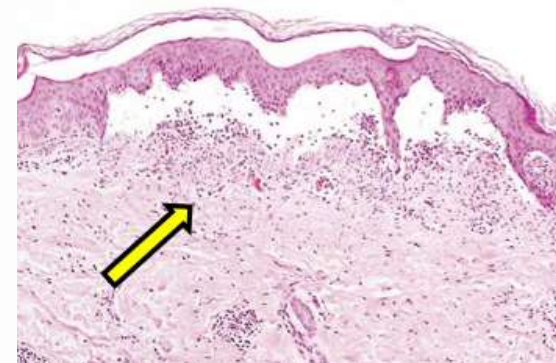
- **General morphologic features:** The morphologic hallmarks of acute inflammatory reactions are dilation of small blood vessels and accumulation of leukocytes and fluid in the extravascular tissue.
- However, special morphologic patterns are often superimposed on these general features, depending on the **severity of the reaction, its specific cause, and the particular tissue involved.**
- **The importance of recognizing the gross and microscopic patterns is that they often provide clues about the underlying cause.**
- Several types of inflammation are recognized, which included:
 - 1- Serous inflammation**
 - 2- Fibrinous inflammation**
 - 3- Suppurative (purulent) inflammation**
 - 4- Ulcerative inflammation**

1- Serous inflammation

- Characterized by outpouring of **watery, cell-poor fluid** (typically not contain microbes or large numbers of leukocytes) into **mesothelial-lined body cavities** (pleural, peritoneal, pericardial cavities) forming an **effusion**, or into **spaces created by cell injury (e.g. in skin blisters)**.
- These fluids derived from either the plasma or the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.
- **Note:** Effusions also occur in non-inflammatory conditions, such as reduced blood outflow in heart failure or reduced plasma protein levels in some kidney and liver diseases.)
- The skin blister resulting from a burn or viral infection represents accumulation of serous fluid within or immediately beneath the damaged epidermis of the skin.



Second-degree burns manifest as erythema with superficial blistering of the skin.



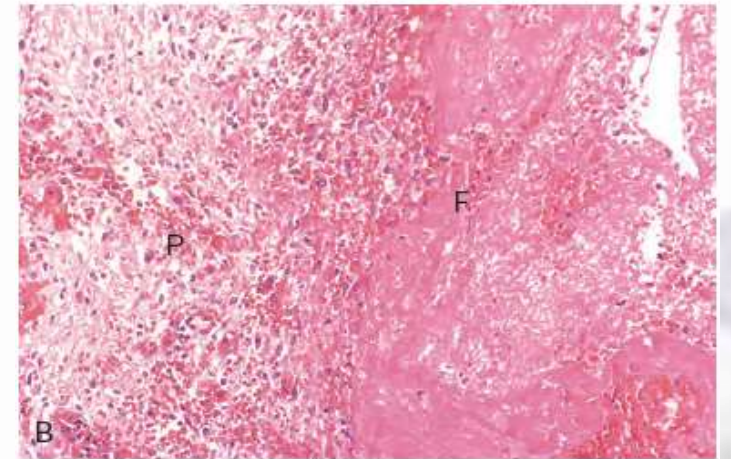
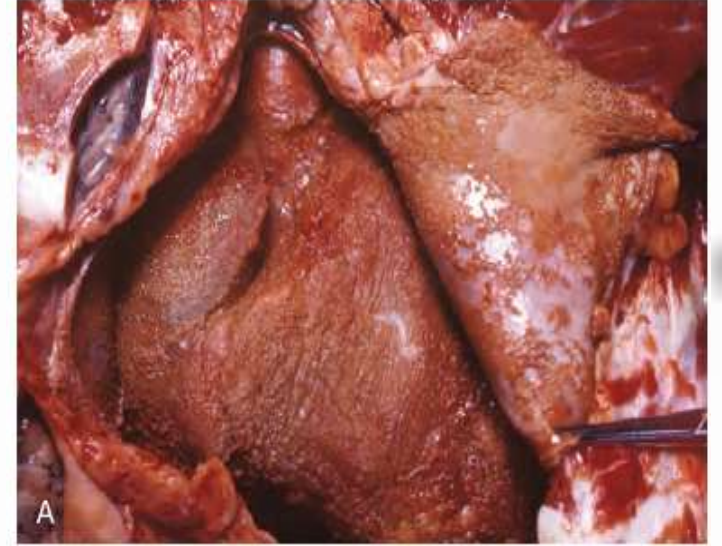
Skin blister
(serous
inflammation)



This is (pleural)
serous effusion
Note the clear,
pale yellow
appearance of
the fluid.

2- Fibrinous inflammation

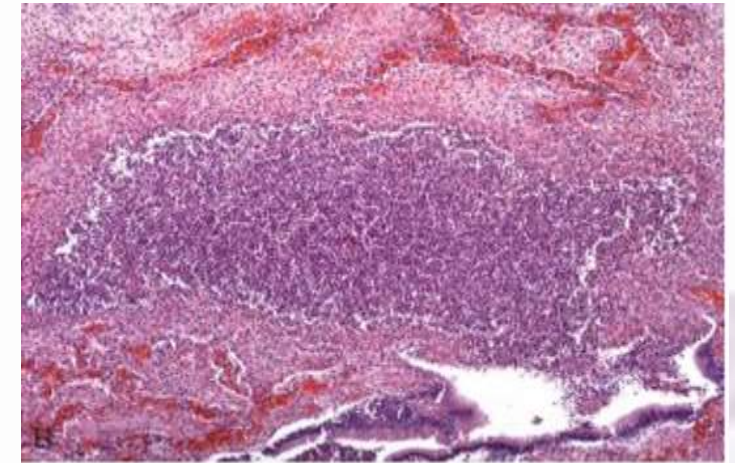
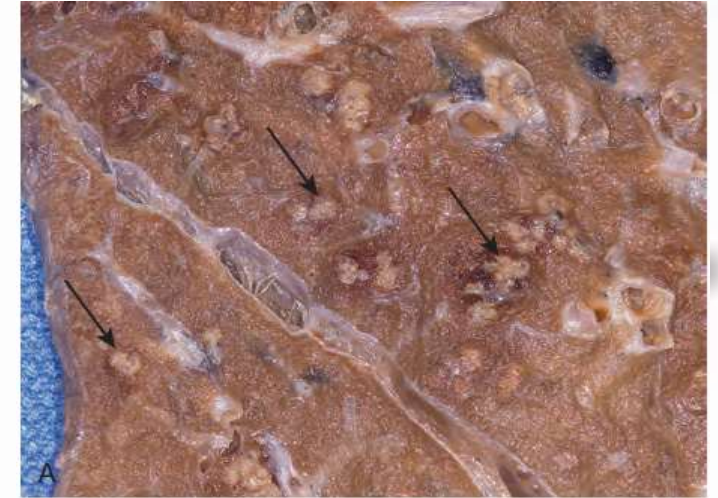
- A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus.
- With more severe injuries and the resulting **greater vascular permeability**, larger molecules such as **fibrinogen** pass the vascular wall, and fibrin is formed and deposited in the extracellular space.
- A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the pericardium and pleura, e.g.: **fibrinous pericarditis**
- **Microscopically**, fibrin appears as an **eosinophilic meshwork of threads or amorphous coagulated mass**.
- Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. However, when the fibrin is not removed, it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring (**organization**). When this occurs within the pericardial sac it leads either to opaque fibrous thickening of the pericardium or, more often, to the development of fibrous strands that reduce and may even obliterate the pericardial space.



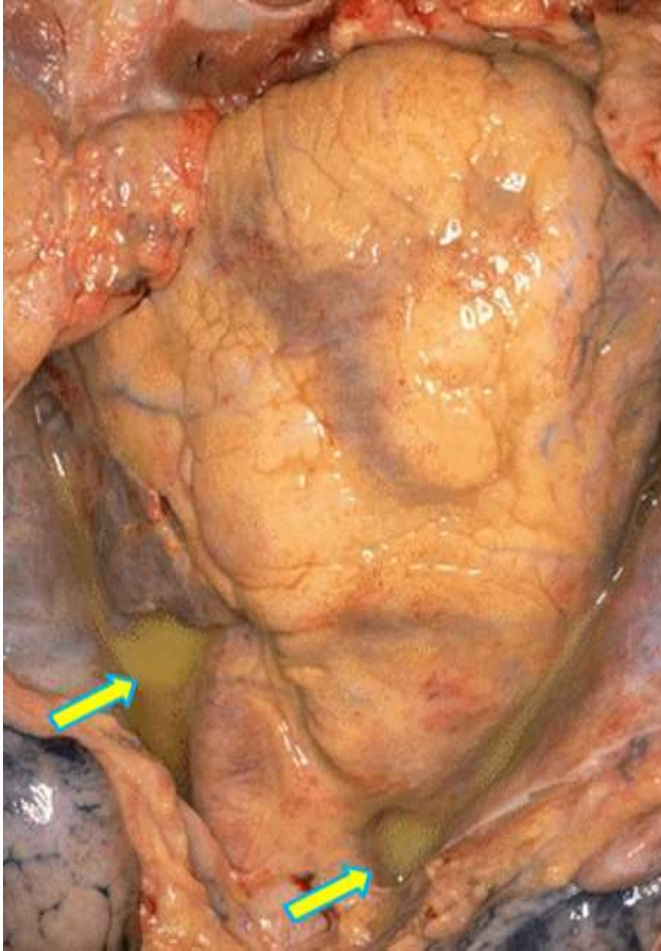
Fibrinous pericarditis. (A) Deposits of fibrin on the pericardium. (B) A pink meshwork of fibrin exudate (F) overlies the pericardial surface (P).

3- Suppurative (purulent) inflammation

- This is characterized by the **production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid.**
- **Certain bacteria** (e.g., staphylococcus aureus, Streptococcus pyogenes, Pneumococci, gonococci, meningococci and E. coli) produce this localized suppuration and are therefore called pyogenic (pus-producing) bacteria.
- A common example of an acute suppurative inflammation is **acute (suppurative) appendicitis.**
- **Pus** is a thick creamy yellow or blood-stained fluid.
- **An abscess** is a localized collection of purulent inflammatory fluid (pus) caused by suppuration buried in a tissue, an organ or a confined space.
- Abscesses are produced by deep seeding of pyogenic bacteria into a tissue.
- A common example of an abscess is the **skin furuncle.**



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



Pus: the yellowish fluid in this opened pericardial cavity is a **purulent exudate**.



abscess is the skin furuncle

4- Ulcerative inflammation

- **Ulcer:** is a local defect of a skin or mucosal surface caused by the sloughing or shedding of inflamed necrotic tissue e.g. gastric/duodenal peptic ulcer
- Ulceration can occur only when tissue necrosis and resultant inflammation exist **on or near a surface**.
- It is most common in (1) the mucosa of the mouth, stomach, intestines or genitourinary tract, and (2) the skin and subcutaneous tissue of the lower extremities, in individuals with disorders that predispose to vascular insufficiency, such as diabetes and sickle cell anemia.
- Ulcerations are best exemplified by **peptic ulcer** of the stomach or duodenum, in which acute and chronic inflammation coexist.
- Ulcers could be simple or malignant ulcers.



(A)



(B)

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



- This patient had diabetes mellitus. This disease leads to marked atherosclerosis with arterial narrowing. When peripheral arteries to the legs are involved, then ischemia of soft tissues and bone occurs. Even minor trauma leads to **ulceration** that heals poorly and often becomes secondarily infected.

Outcomes (Fate) of acute inflammation

- In general, acute inflammation may have one of three outcomes:

1. Complete resolution

2. Healing by fibrosis

3. Progression to chronic inflammation

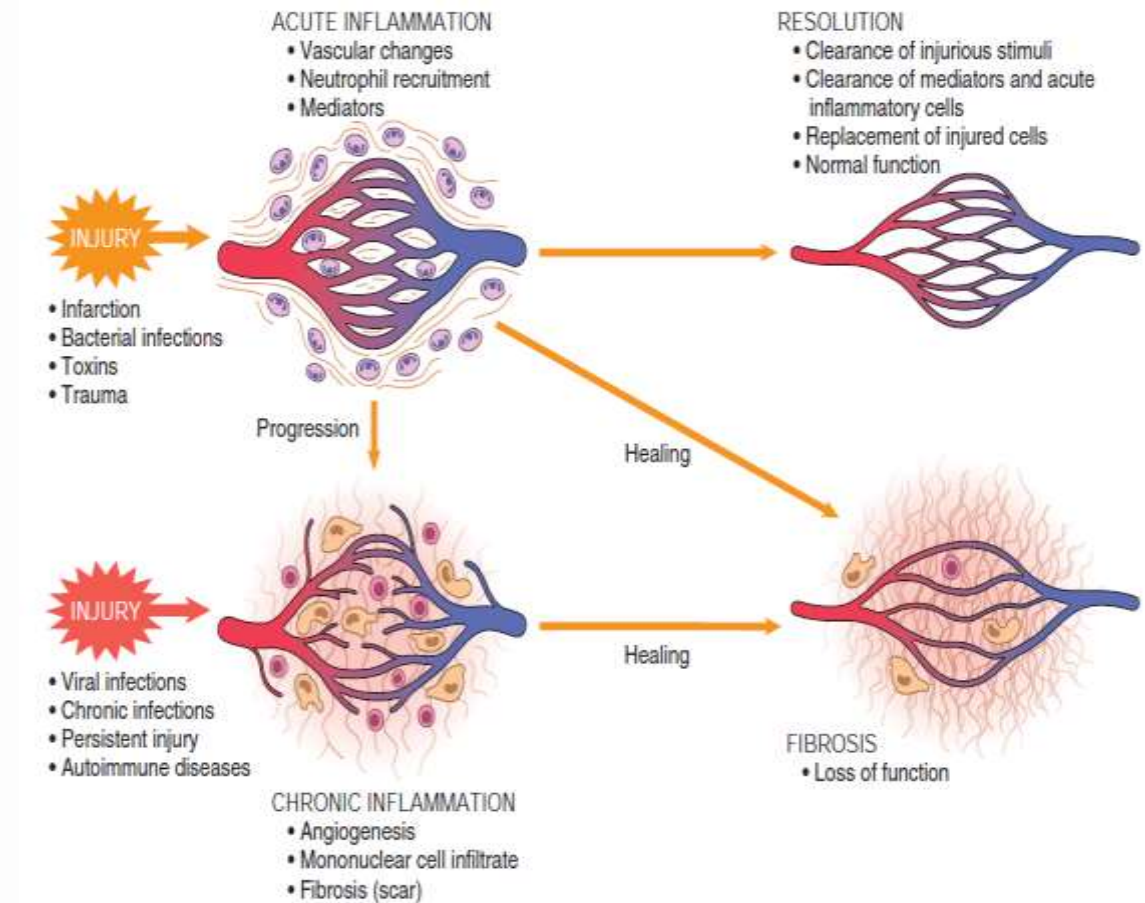
1. **Complete resolution**

- The battle between the injurious agent and the host may end with restoration of the site of acute inflammation to normal. This is called resolution and is the **usual outcome when;**

a. The injury is limited or short-lived

b. There has been little tissue destruction

c. The damaged parenchymal cells can regenerate.



2. Healing by fibrosis : This occurs;

- a. After extensive tissue destruction
- b. When the inflammatory injury involves tissues that are incapable of regeneration
- c. When there is abundant fibrin exudation.
 - When the fibrinous exudate in tissue or serous cavities (pleural, peritoneal, synovial) cannot be adequately cleared, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue—a process also called **organization**.

3. Progression to chronic inflammation

- Acute to chronic transition occurs **when the acute inflammatory response persists**, owing either to the perseverance of the injurious agent or to some interference with the normal process of healing.
- **For example**, failure of acute bacterial pneumonia to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues, leading eventually to a chronic lung abscess.

THANK YOU