Pathology of

INFLAMMATION

CH 2: Lecture II

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Chemical Mediators of Inflammation:

- Direct **vascular** & **cellular** events in inflammation
- **Locally** produced & Plasma-derived mediators (**systemic**).
- **Most mediators** induce their effects by **binding to specific receptors** on target cells.
- **Some have direct enzymatic and/or toxic activities** (e.g., lysosomal proteases or reactive oxygen species).

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Chemical Mediators of Inflammation

- Once activated and released from the cell, most mediators **quickly decay**, are **inactivated** by enzymes, are **eliminated**, or are **inhibited**
- Most mediators have the potential to cause harmful effects.
- **Cytokines:** are polypeptide products of many cell types (but principally activated **lymphocytes and macrophages**) that modulate the function of other cell types, e.g. TNF and IL-1

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Chemical Mediators of Inflammation

- **Vasoactive amines** - Histamine, Serotonin
- **Complement system** – C1 to 9 cytolysis, opsonins.
- **Kinin System** – Kallikreins **à** Bradykinin
- **Clotting system** – FXII, FX, Fibrin, Plasmin
- **Arachidonic acid metabolites:**
  - Prostaglandins - (cyclooxygenase)
  - Leukotrienes – (Lipoxygenase)
  - Lipoxins
- **Others:**
  - Nitric Oxide, Lysozymes, oxygen free radicals

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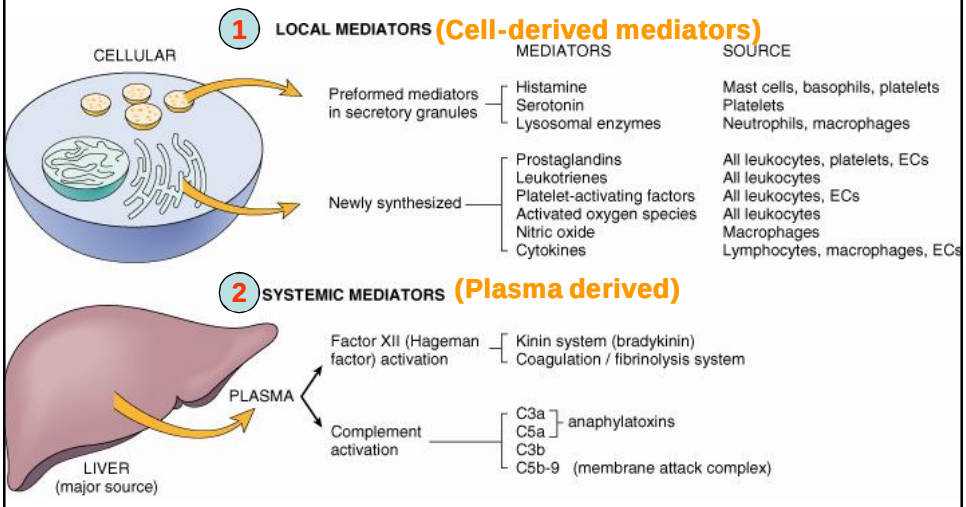
Chemical Mediators of Inflammation



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Chemical Mediators of Inflammation

- **Locally produced:**
- **Histamine**
- **Serotonin / 5HT**
- **Platelet activating factor (PAF)**
- **Prostaglandins**
- **Leukotrienes**
- **Nitric oxide**

- **Plasma derived:**
- **Kinins**
- **Complements**
- **Coagulation system**
- **Plasminolysis system**

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Cell-derived mediators (locally produced):

- **Histamine:**

-synthesized and stored in mast cells, platelets and basophils

-diffuses rapidly through the blood stream

-promotes **vasodilation**, and **increased vascular permeability**

-recognized by specific receptors (H1, H2 and H3)

- **Serotonin:**

-stored in platelets, mast cells and **enterochromaffin cells** of the GI tract

-has **vasoactive** properties

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Cell-derived mediators (locally produced):

- **Platelet activating factor (PAF):**

- it is generated from the membrane phospholipids of neutrophils, monocytes, basophils, endothelium, and platelets (and other cells) by the action of phospholipase A2.

- **platelet stimulation**, **vasoconstriction** and **vasodilation**, **increased vascular permeability** and **bronchoconstriction**, enhances leukocyte adhesion, chemotaxis, leukocyte degranulation, and the oxidative burst

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Cell-derived mediators: Prostaglandins:

- **oxidized derivatives of arachidonic acid produced via cyclooxygenase pathway**
- Products of this pathway include prostaglandin (PGE2), PGD2, PGF2*a*, PGI2 (prostacyclin), and thromboxane A2 (TXA2)
- major sources in the acute inflammatory response include monocytes, macrophages, endothelial cells and platelets
- augmented by a number of stimuli including: bacterial endotoxin, immune complex formation, C3a, bradykinin & IL-1
- promote **pain**, **fever**, **vasodilation** and **increased vascular permeability**

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Cell-derived mediators: Leukotrienes:

- **oxidized derivatives of arachidonic acid produced via lipoxygenase pathway**
- synthesized and released from neutrophils, basophils and mast cells
- LTA4 can be taken up by platelets, RBCs and endothelial cells and converted to LTB4 and LTC4
- lead to vasoconstriction, increased vascular permeability, increased endothelial adhesiveness, bronchoconstriction, neutrophil activation and chemotaxis (LTB4)

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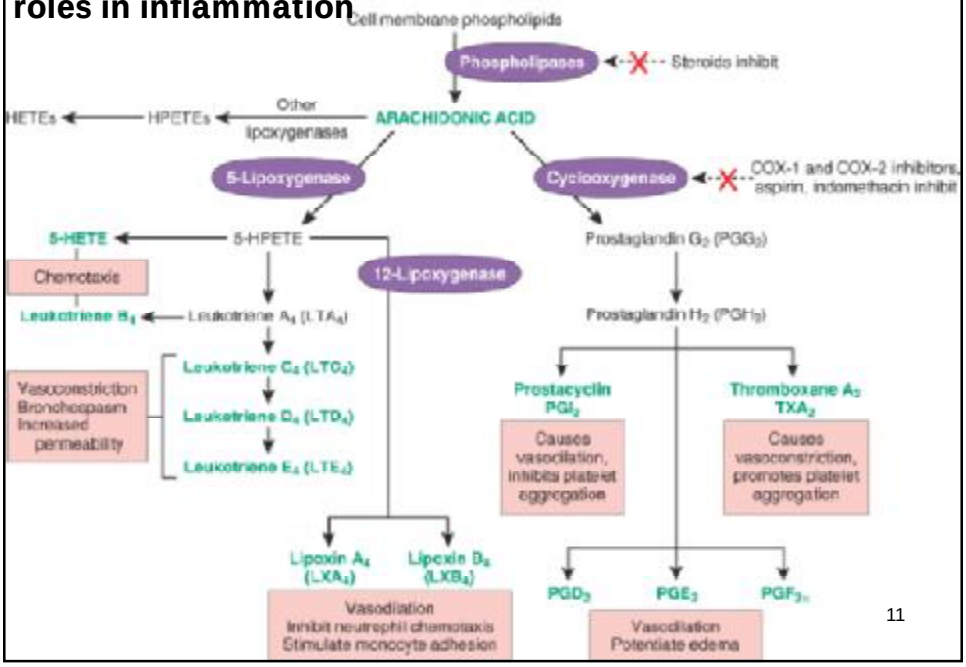
Generation of arachidonic acid metabolites and their roles in inflammation



Cell-derived mediators: Nitric oxide:

- short-acting **soluble free-radical gas** with many functions
- may be **released from endothelial cells** upon stimulation by acetylcholine and bradykinin where it acts as a potent **vasodilator** and **inhibitor of platelet aggregation**
- may also be **released from macrophages** upon stimulation with IFN-g and TNF-a

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More specific mediators: Cytokines

- **Cytokines:** Protein cell products that act as a message to other cells, telling them how to behave & modulate their function
- Products of many cell types (principally activated lymphocytes & macrophages)
- Produced during immune and inflammatory responses
- **IL-1, TNF-α and -b, IFN-γ** are especially important in inflammation.
- Induce **the systemic acute-phase responses**, these include **fever**, **lethargy**, **hepatic synthesis of various proteins**, metabolic wasting (cachexia), neutrophil release into the circulation, and release of adrenocorticotropic hormone (inducing corticosteroid synthesis and release)

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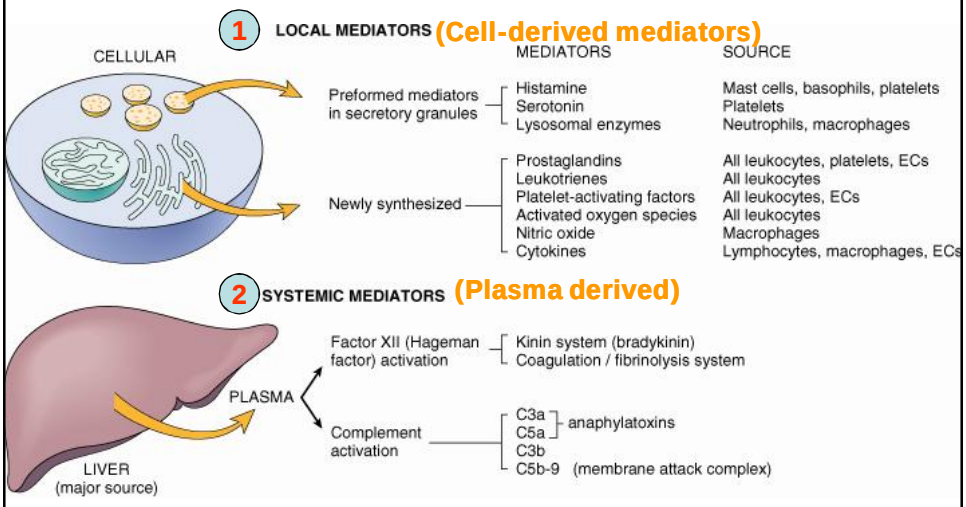
Chemical Mediators of Inflammation



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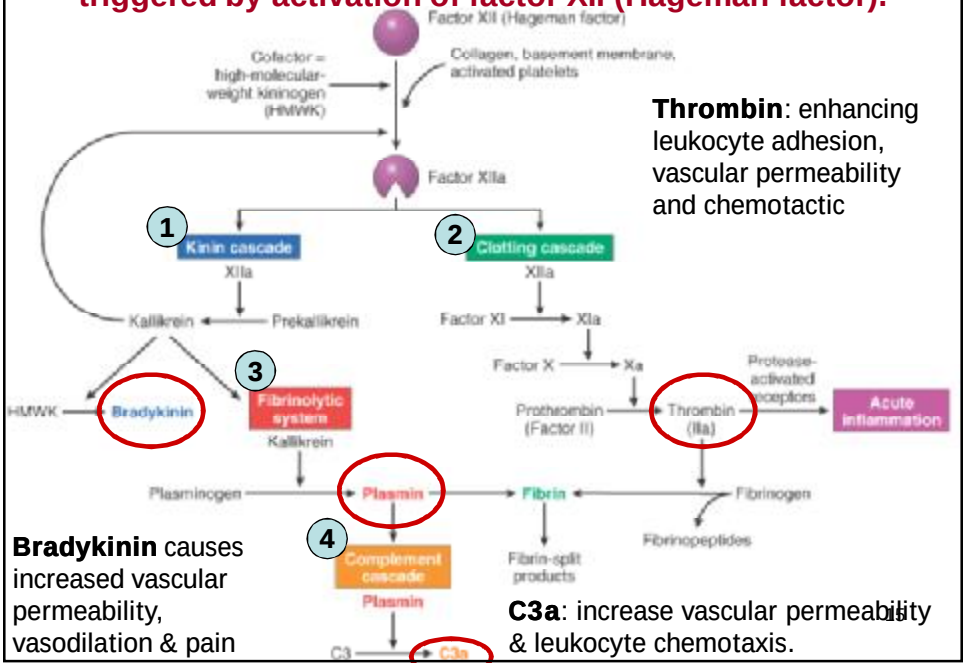
Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor).



Thrombin: enhancing leukocyte adhesion, vascular permeability and chemotactic

Bradykinin causes increased vascular permeability, vasodilation & pain

C3a: increase vascular permeability & leukocyte chemotaxis.

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Plasma-derived mediators: <u>Kinins:</u>

- group of serine proteases, whose **ultimate product is bradykinin**
- **<u>Initiated by</u>** a number of by-products of tissue damage including: collagen, cartilage, basement membranes, endotoxin and plasmin
- activated factor XII (Hageman factor) cleaves prekallikrein to kallikrein which in turn cleaves the proenzyme kininogen to **bradykinin**
- activated factor XII also **generates plasmin** from plasminogen
- induces bronchial **smooth muscle constriction**, **vasodilation, increased vascular permeability, and pain**

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Plasma-derived mediators

Fibrinolytic (Plasminolysis) system:

- activation of factor XII ultimately results in the **cleavage of fibrinogen to fibrin** and smaller fibrinopeptides which serve as inflammatory mediators
- activated factor XII also activates the fibrinolytic system via **plasmin formation**
- **plasmin activates the complement pathway**

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Plasma-derived mediators: Complement system:

- **Components C1-C9 present in inactive form**
  - **Activated via classic (C1) or alternative (C3) pathways** to generate MAC (C5 – C9) that punch holes in microbe membranes
  - **In acute inflammation:**
    - Vasodilation, vascular permeability, mast cell degranulation (C3a, C5a)
    - Leukocyte chemotaxin, increases integrin avidity (C5a)
    - As an opsonin, increases phagocytosis (C3b, C3bi)

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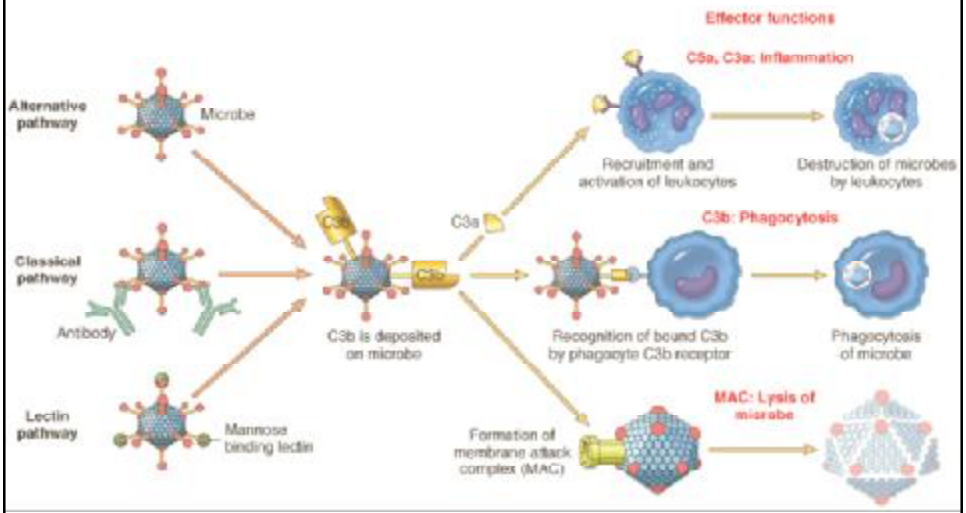
Plasma-derived mediators: Complement system:



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, & by the membrane attack complex (MAC).

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Action of Mediators in Inflammation

- **Vasodilatation:** Histamine, PGI_2, NO
- **Blood vessel permeability:** histamine, C3a, C5a, kinins, PAF, and leukotrienes C, D, and E.
- **Leukocyte adhesion:** IL8, LB4, C5a, TNFα
- **Chemotaxis:** C5a, LTB4, and the chemokines
- **Pain:** Prostaglandins & Bradykinin.

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Outcomes of Acute Inflammation

- The process of acute inflammation is designed to neutralize injurious agents and to restore the tissue to useful function.
- There are four main outcomes of acute inflammation if the patient survives:

1. **resolution**
2. **abscess formation**
3. **healing by fibrosis**
4. **progression to chronic inflammation**

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Outcomes of Acute Inflammation

- **Three factors determine which of these outcomes occurs:**

1) the **severity** of tissue damage

2) the capacity of specialized cells within the damaged tissue to divide and replace themselves, a process termed **regeneration**

3) the **type of agent** which has caused the tissue damage.

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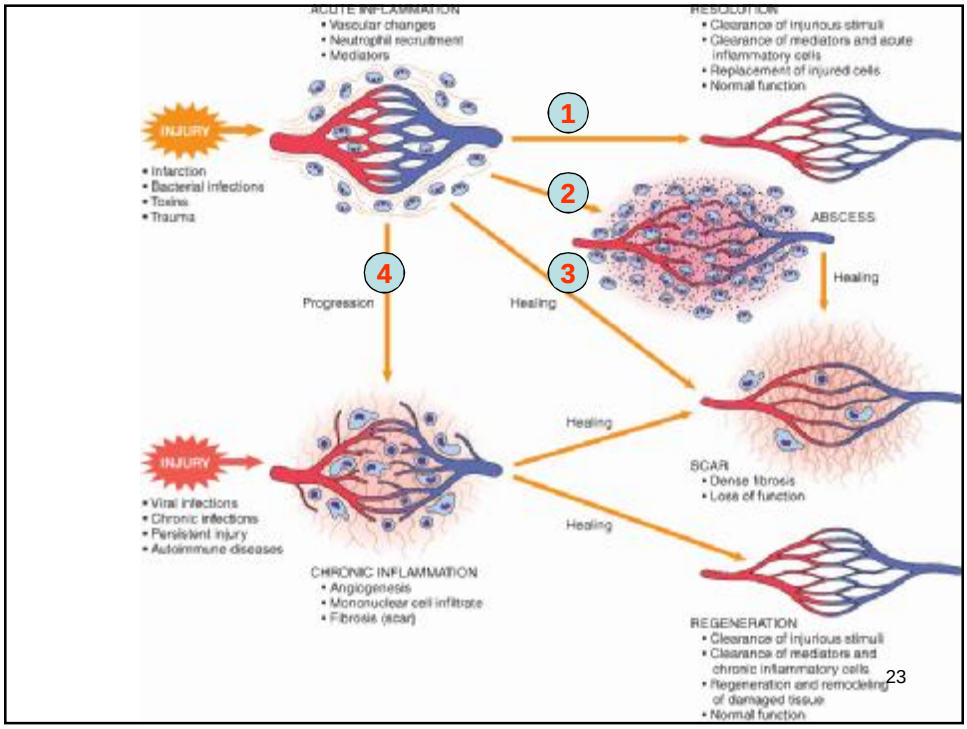

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Outcomes of Acute Inflammation

1) **Resolution:** When the injury is limited or **short-lived**, when there has been no or **minimal tissue damage**, and when the tissue is capable of replacing any irreversibly injured cells.
2) **Abscess formation:** takes place when the acute inflammatory reaction fails to destroy/remove the cause of tissue damage and continues with a component of chronic inflammation. This is most common in the case of infection by pyogenic bacteria. As the acute inflammation progresses, there is liquefaction of the tissue to form **pus. Abscess formation may occur where the only outcome is scarring.**

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Outcomes of Acute Inflammation

3) **Healing by fibrosis (scar formation):** results after substantial tissue destruction or **when inflammation occurs in tissues that do not regenerate**. In addition, extensive fibrinous exudates may not be completely absorbed with resultant fibrosis.

4) **Progression to chronic inflammation** may follow acute inflammation depending on the extent of the initial and ongoing tissue injury, and the capacity of the affected tissues to regrow, chronic inflammation may be followed by regeneration of normal structure and function or may lead to scarring.

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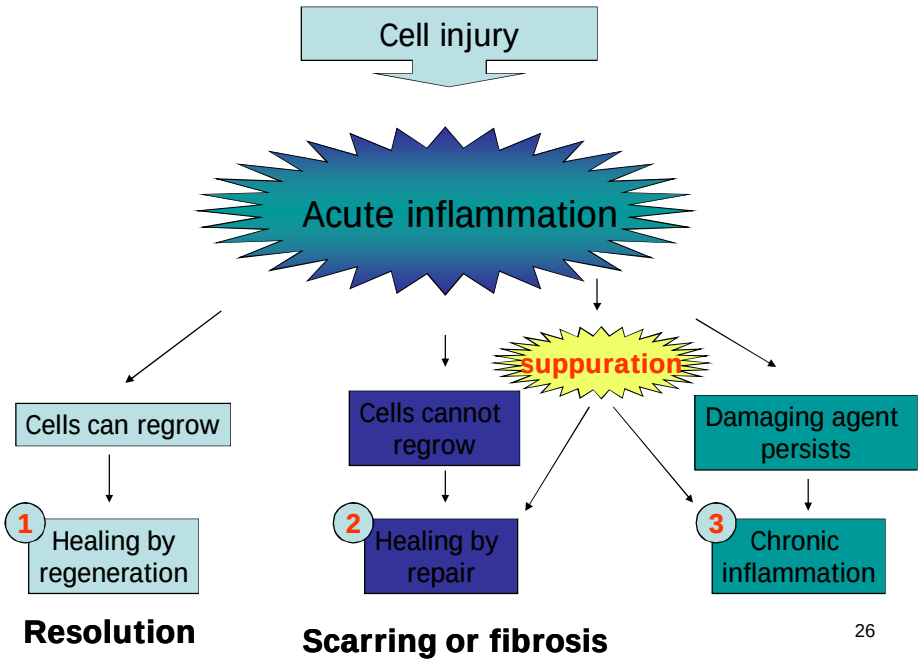

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Morphologic patterns of acute inflammation:

- **Serous inflammation**
- **Fibrinous inflammation**
- **Suppurative "purulent" inflammation**
- **Ulceration**

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1. Serous inflammation:

- describes a pattern of acute inflammation where the main tissue response is an accumulation of fluid with **a low plasma protein and cell content**. This is often called a **transudate.**
- most commonly seen in the skin, e.g. **burn**, or in skin **blisters** resulting from viral infection.
- **inflammation in body cavities, e**.g. pleural effusion, peritoneal effusion "ascites", mainly from bacterial infection.
- **Resolution is the outcome.**

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2. Fibrinous inflammation:

- a pattern of acute inflammation where the acute inflammatory exudate has **a high plasma protein** content.
- **Exudation of fibrinogen**, due to vascular permeability
- **Fibrinogen** derived from plasma is **converted to fibrin**, which is deposited in tissues.
- **Caused by bacterial infection**

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2. Fibrinous inflammation:

- This pattern is particularly **associated with membrane-lined cavities** such as the **pleura**, **pericardium** and **peritoneum** where the fibrin strands form a mat-like sheet **causing adhesion between adjacent surfaces**
- **Outcome:** either **complete resolution** if the fibrin is degraded by fibrinolysis, **or organization** with growth of blood vessels and fibroblasts may occur.

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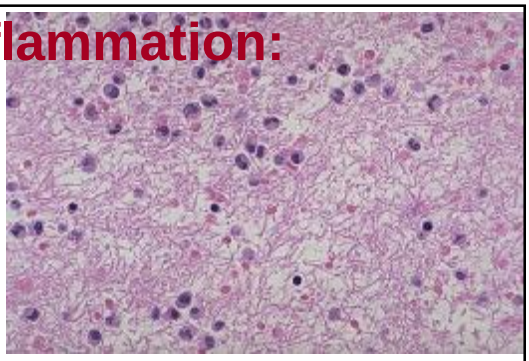
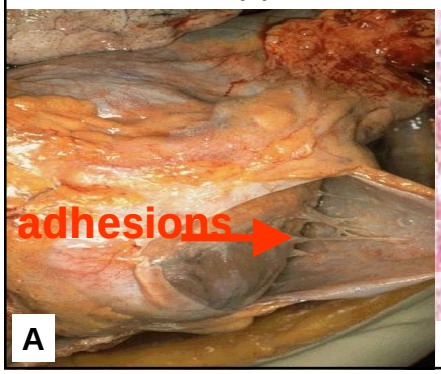
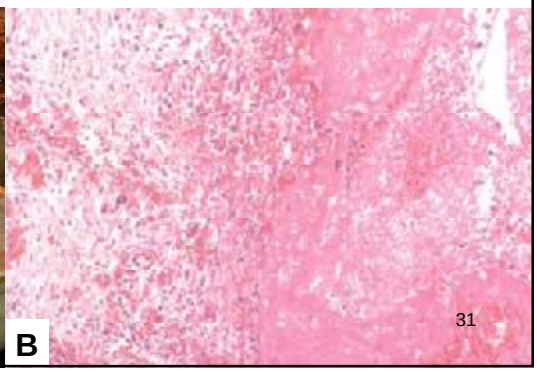
Fibrinous inflammation:

Fibrinous pericarditis:
A) Adhesion between visceral and parietal pericardium.
B) A pink meshwork of fibrin exudate (F) overlies







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3. Suppurative (purulent) inflammation

- refers to acute inflammation in which the acute inflammatory exudate is particularly **rich in neutrophil** leukocytes.
- most commonly seen as a **result of infection by bacteria**.
- **Pus:** a semi-liquid material formed from **a mixture of neutrophils** (viable and dead), **necrotic tissue**, and **edema** fluid in the acute inflammatory exudate.
- **Within cavities, is termed an abscess**.

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3. Suppurative (purulent) inflammation

- **Abscess:** a **circumscribed collection of semi-liquid pus with central area of necrosis surrounded by a zone of viable neutrophils & then a zone of dilated vessels & fibroblastic reaction**
- **Pyogenic bacteria**: Bacteria which produce purulent inflammation, include **Staphylococci**, some Streptococci (**S. pyogenes**, S. pneumoniae), Escherichia coli and the Neisseriae (meningococci and gonococci).
- **Outcome: healing is always by scarring & fibrosis**

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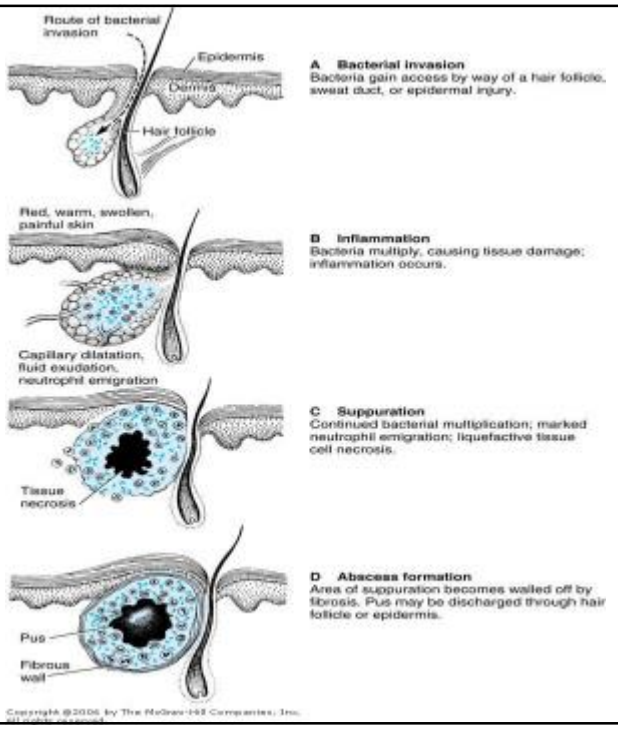

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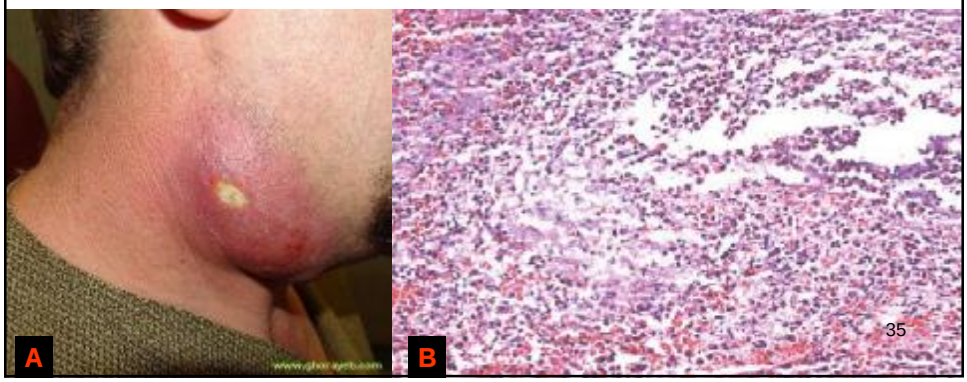
Suppurative (purulent) inflammation

A) Subcutaneous bacterial abscess with collections of pus

B) The abscess contains neutrophils, edema fluid, and cellular debris.



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4. Ulceration:

- A site of inflammation where **the epithelial surface is necrotic and eroded**.
- **Caused** by **toxic or traumatic injury** to the epithelium or due to **vascular** compromise.
- **Has 3 layers:** **neutrophilic** exudates, **vascular** proliferation, & **fibroblastic** proliferating layer
- **Outcome:** Resolution or fibrosis.

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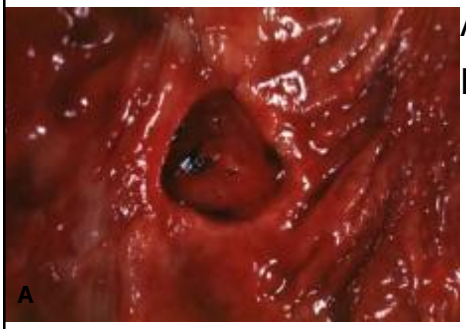
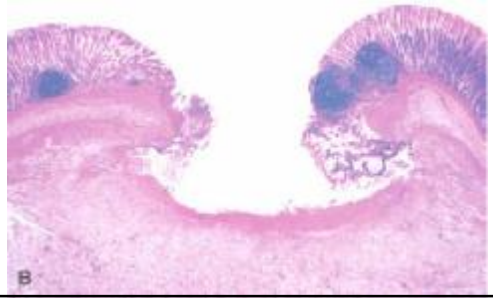
Ulceration:

The morphology of ulcer



A) A chronic duodenal ulcer.

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



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