

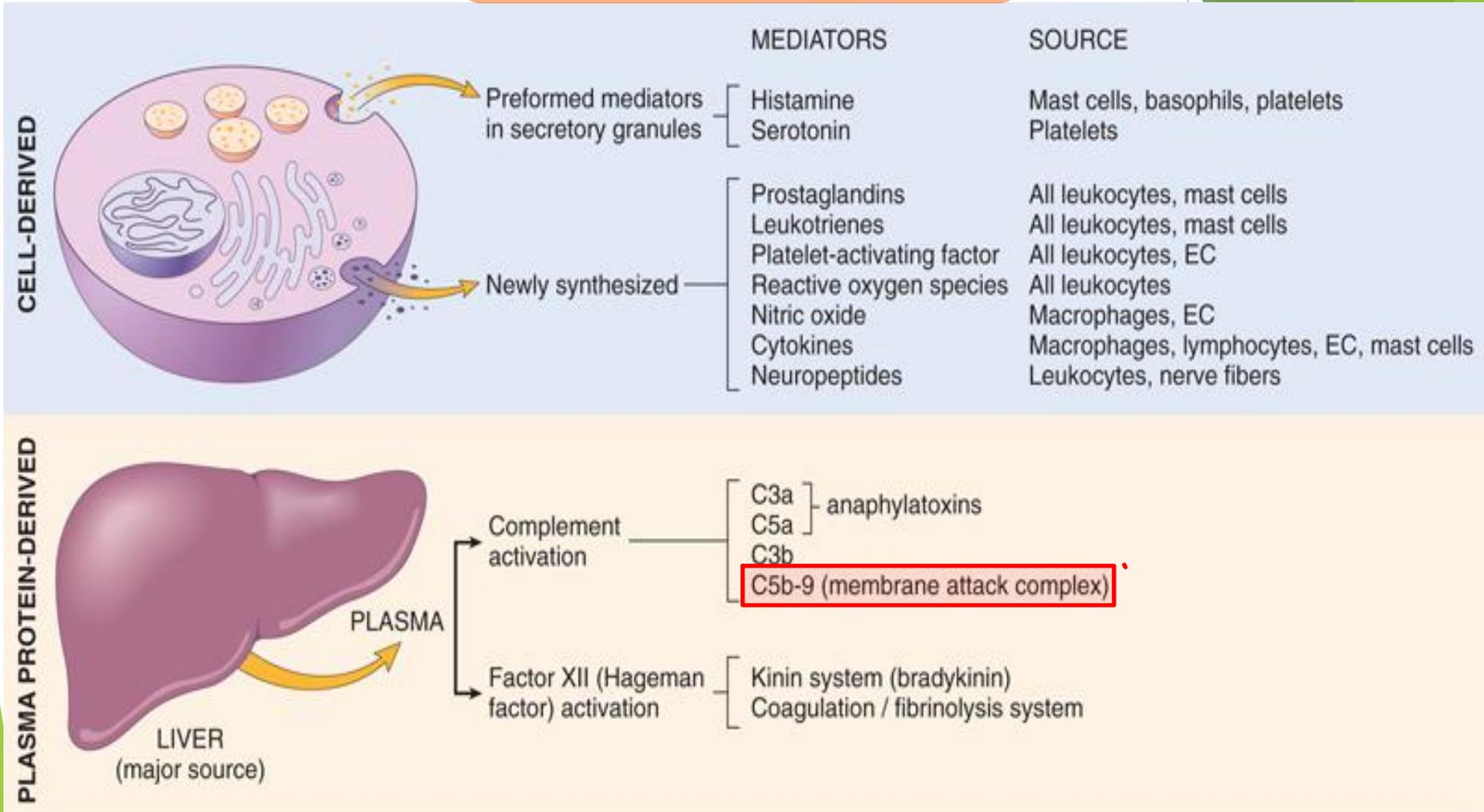
Inflammation IV

Morphology of Inflammation

Dr. Sura Al-Rawabdeh M.D.

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Systemic Mediators of Inflammation

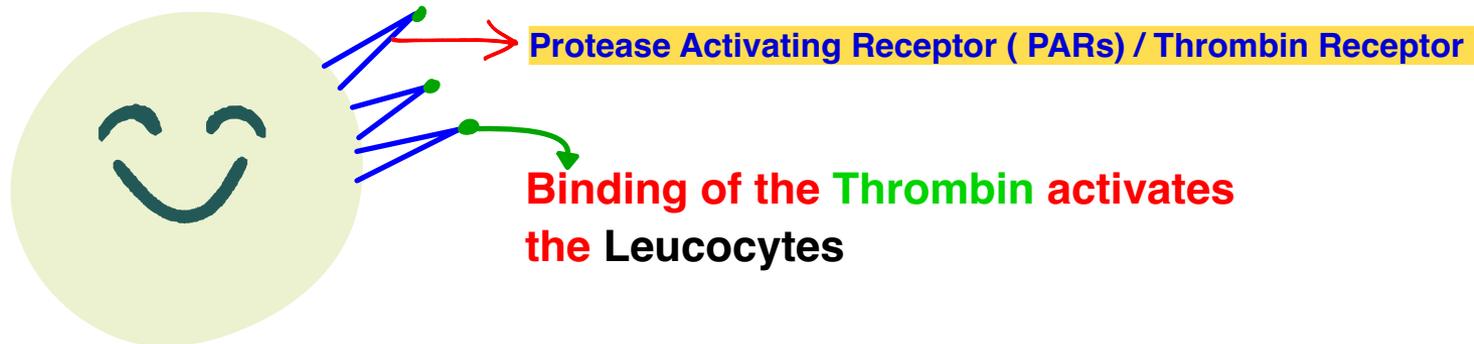
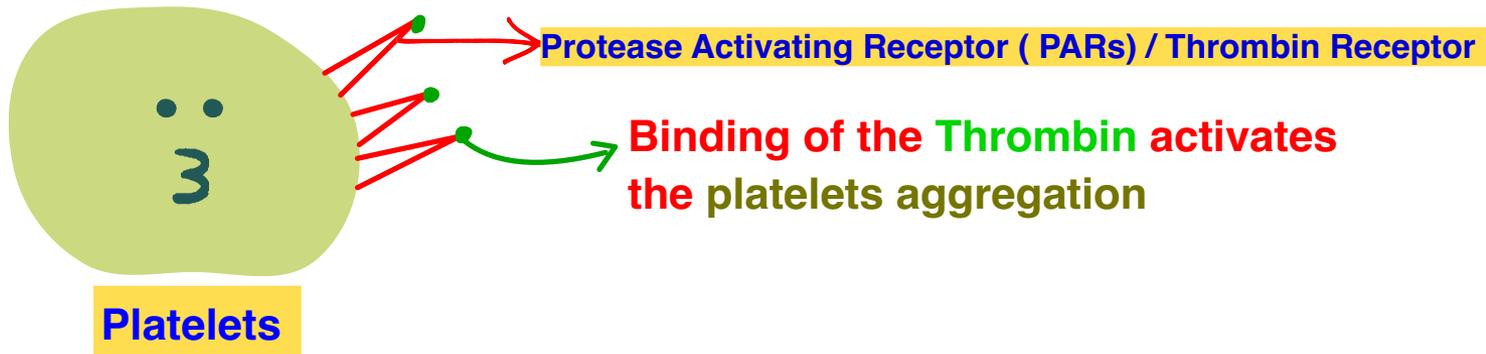
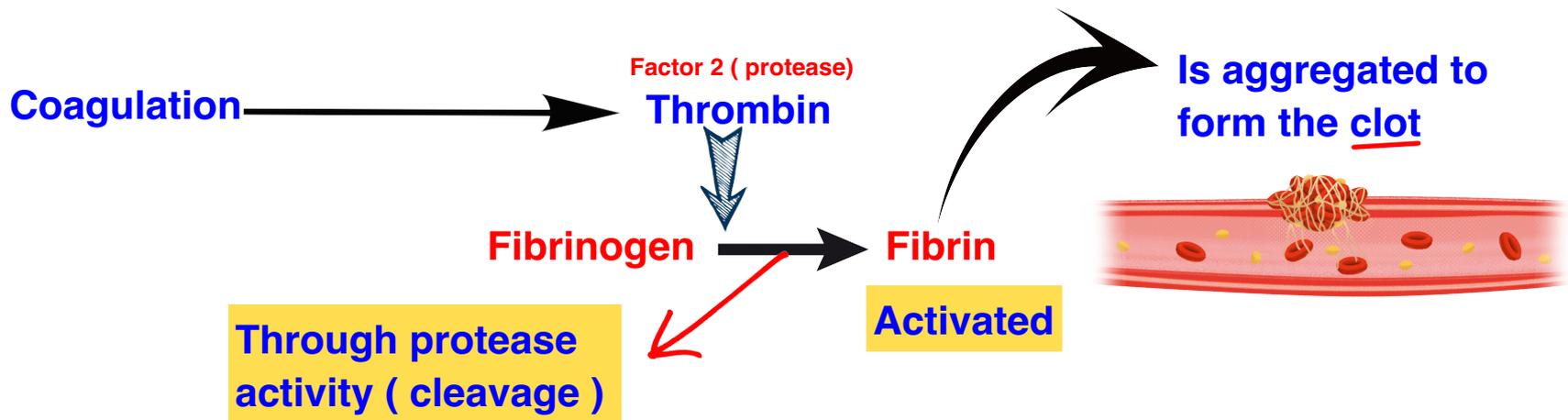


Products of Coagulation

Circulating proteins (clotting factors) and they are inactive
Activated by Injury (inflammation)

▶ Studies performed more than 50 years ago suggested that inhibiting coagulation **reduced the inflammatory reaction** to some microbes, leading to the idea that coagulation and inflammation are linked processes.

▶ This concept was supported by the discovery of protease-activated receptors (PARs), which are activated by thrombin (the protease that cleaves fibrinogen to produce a fibrin clot).



Leucocytes Coagulation causes inflammation by Thrombin (tissue injury)
Inflammation causes Coagulation by breaking of the endothelial cells

Products of Coagulation

▶ **PARs** are expressed on **leukocytes**, suggesting a **role in inflammation** but their **clearest role is in platelets**, in which thrombin activation of a PAR known as the thrombin receptor is a potent **trigger of platelet aggregation** during the process of **clot formation**.

▶ All forms of **tissue injury** that **lead to clotting** also **induce inflammation**, and inflammation causes changes in **endothelial cells that increase the likelihood of abnormal clotting**.

Clotting / Fibrinolytic system

Slow CLOTING IN THE LABORATORY

Intrinsic pathway

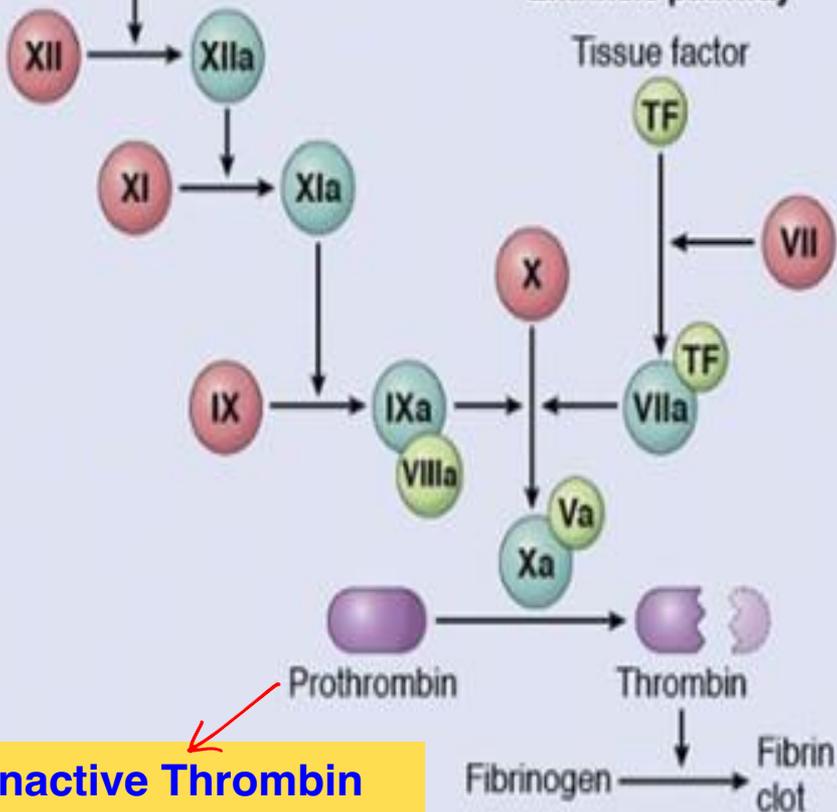
Inside the vascular System

Negatively charged surface (e.g., glass beads)

Fast

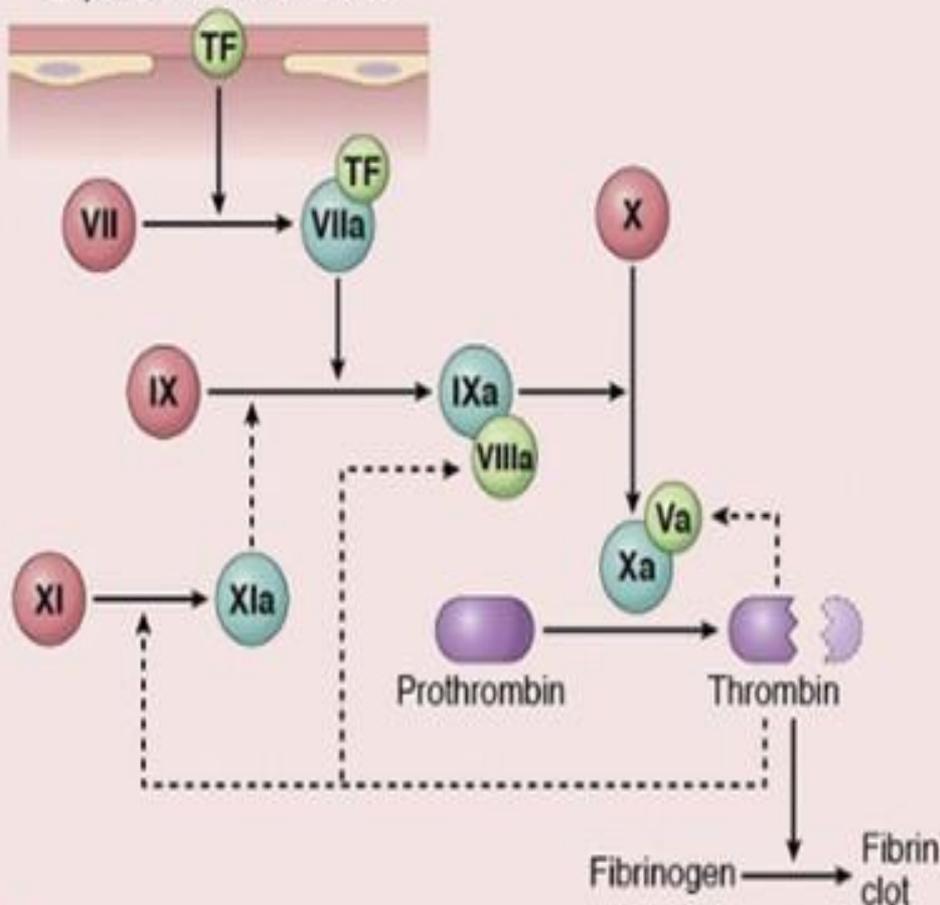
Extrinsic pathway

Tissue factor



CLOTING IN VIVO

Vascular damage
Exposure of tissue factor



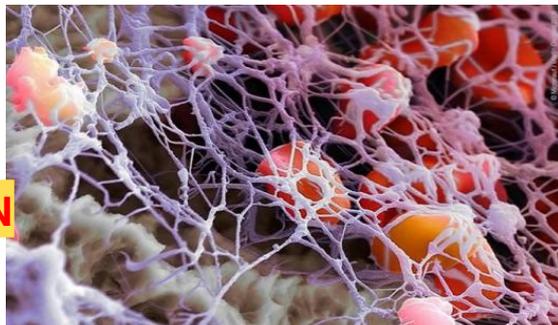
A Inactive Thrombin

B

Clotting / Fibrinolytic system

- ▶ **Fibrin clot** at site of injury helps in **containing the cause**.
- ▶ **Fibrin clot** provides a framework for inflammatory cells.
- ▶ **Xa** causes increased vascular permeability and **leukocytes emigration**.
- ▶ **Thrombin** causes **leukocytes adhesion, platelets aggregation, generation of fibrinopeptides, and is chemotactic.**
- ▶ **Fibrinopeptides** are chemotactic & induce vasopermeability.

Net-like structure of fibrin



Done by the PLASMIN

Clotting / fibrinolytic system

Activated the Anti-coagulation Factors



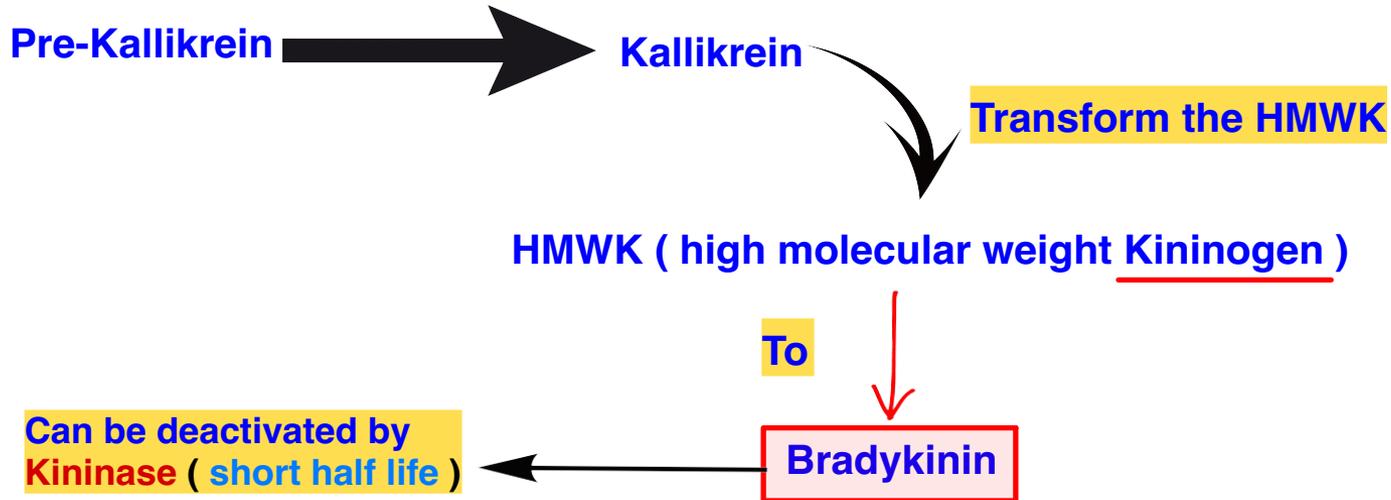
- ▶ **XIIa** also activates the fibrinolytic pathway to prevent widespread thrombosis.
- ▶ **Fibrin split products** increase vascular permeability.
 - ▶ Done by the Anti-coagulation Factors (plasmin)
- ▶ **Plasmin** cleaves **C3** to form **C3a**, leading to dilatation and increased permeability.
 - ▶ Anaphylatoxins
- ▶ **Plasmin** activates **XIIa** amplifying the entire process.

Thrombin as an Inflammatory Mediator

- ▶ Binds to **protease-activated receptors (PARs)** expressed on **platelets, endothelial cells, smooth muscles** leading to:
 - ▶ P-selectin mobilization
 - ▶ Expression of integrin ligands
 - ▶ Chemokine production
 - ▶ **Prostaglandin production** by activating cyclooxygenase-2
 - ▶ Production of **PAF**
 - ▶ Production of **NO**

Kinin System

- ▶ Vasoactive peptides derived from plasma proteins, called kininogens, by the action of specific proteases called kallikreins.
- ▶ Leads to formation of bradykinin from HMWK.
- ▶ Effects of bradykinin
 - ▶ Increased vascular permeability
 - ▶ Arteriolar dilatation
 - ▶ Bronchial smooth muscle contraction
 - ▶ Pain
- ▶ Short half-life (inactivated by kininases)



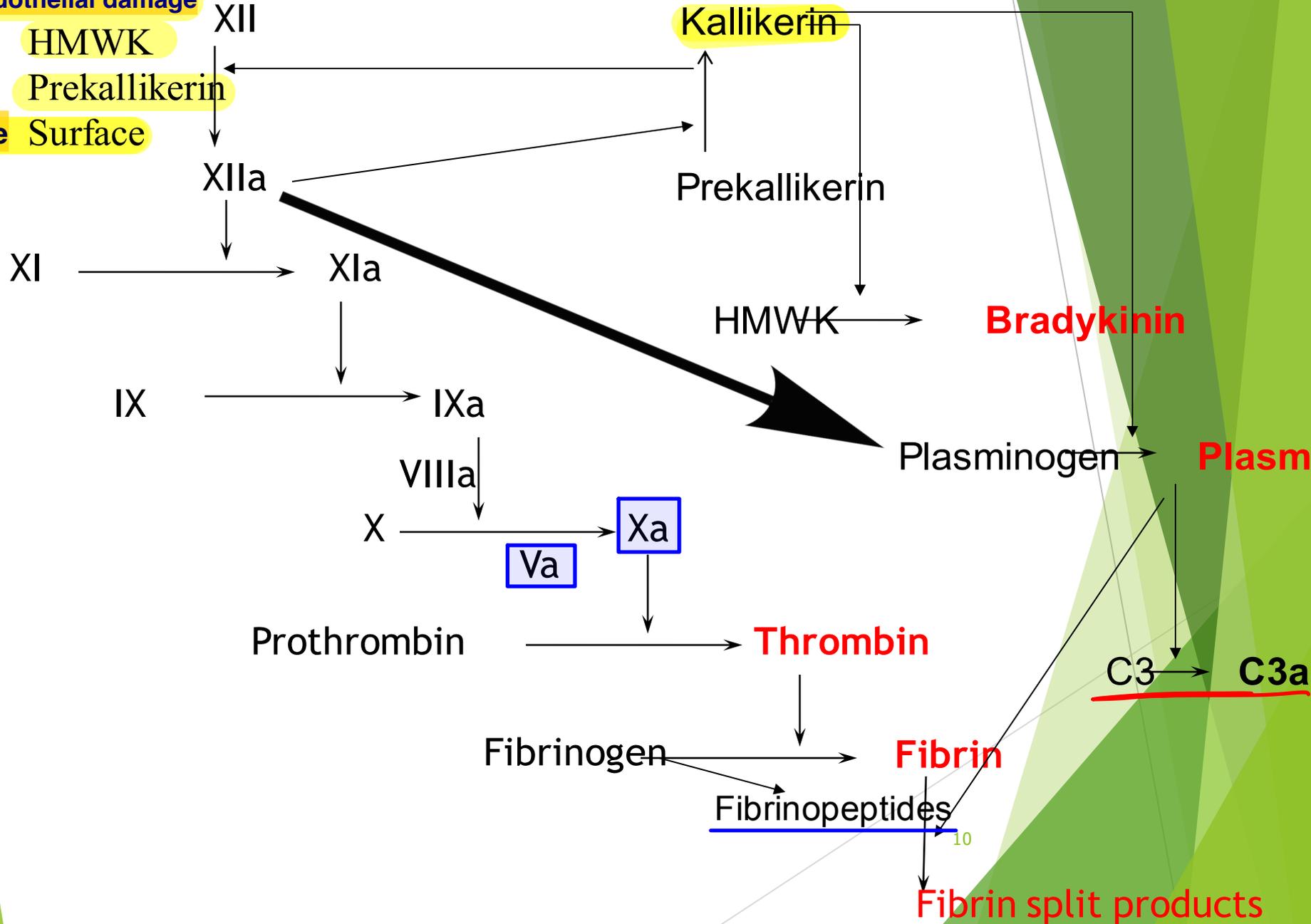
Interaction between the four plasma mediator systems

Endothelial damage

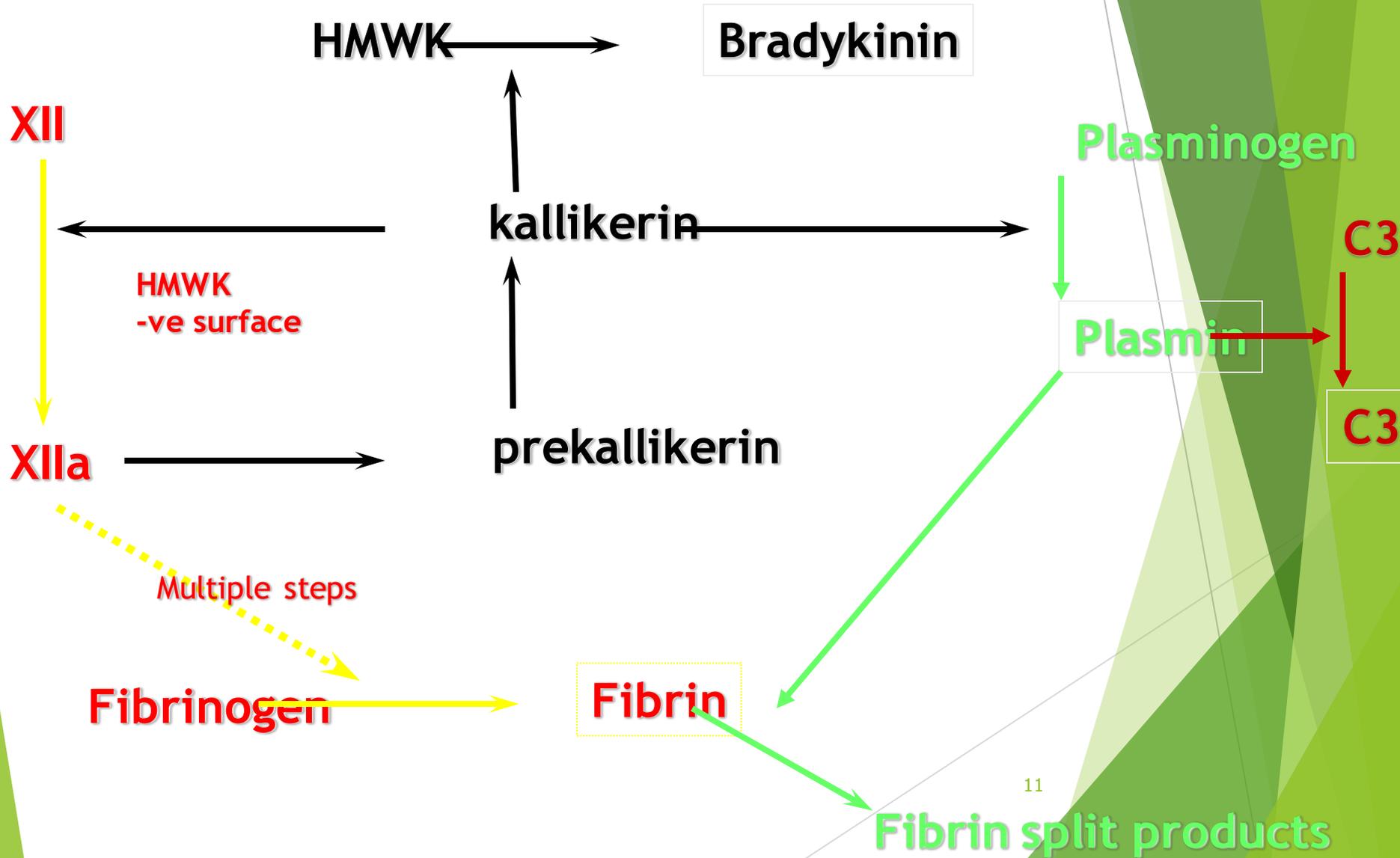
HMWK

Prekallikrein

-ve Surface



Interaction between the four plasma mediator systems



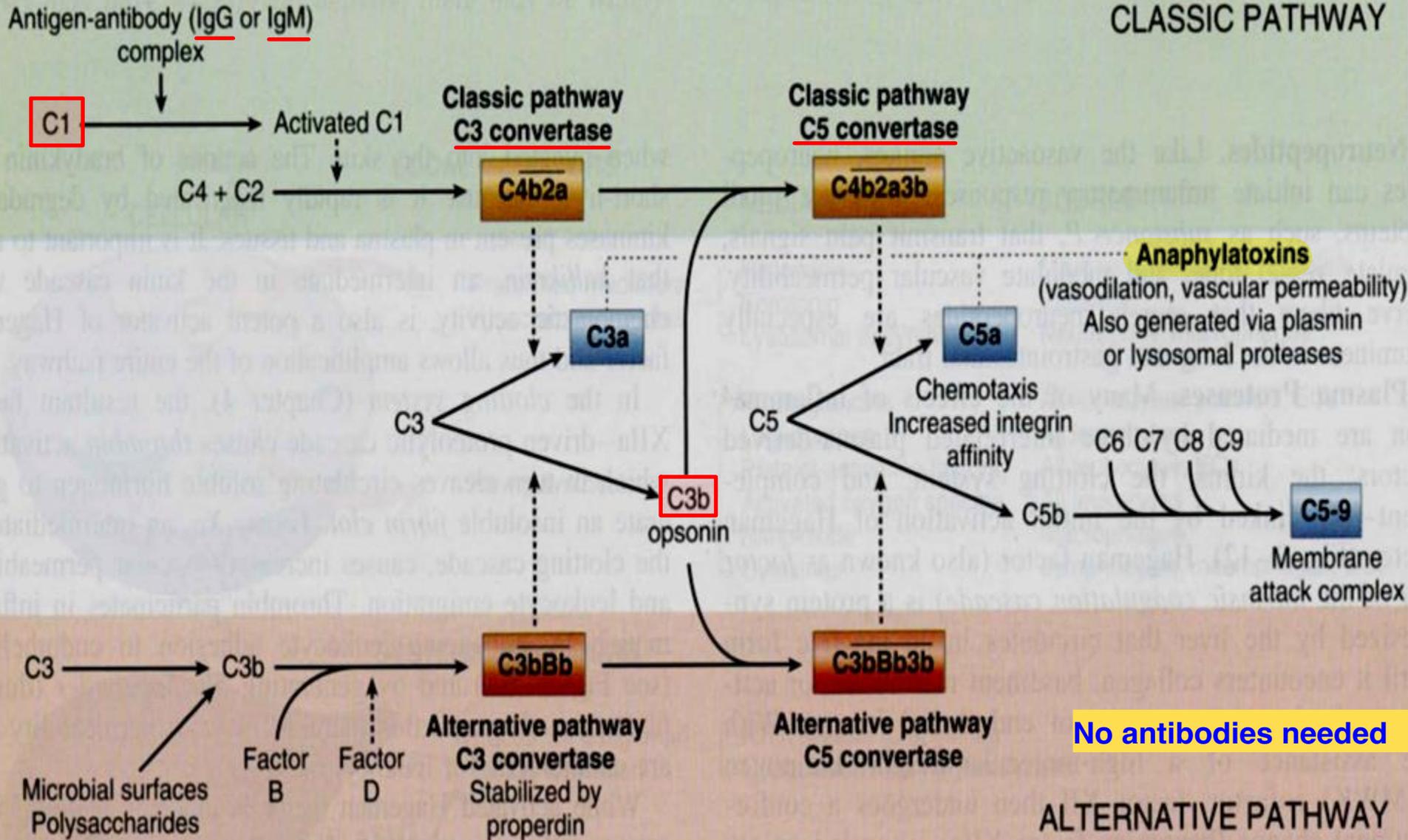
The Complement System in Inflammation

- ▶ The complement system is a collection of soluble proteins and their membrane receptors that function mainly in host defense against microbes and in pathologic inflammatory reactions.
- ▶ More than 20 complement proteins, some of which are numbered C1 through C9.
- ▶ They function in both innate and adaptive immunity for defense against microbial pathogens.
- ▶ Several cleavage products of complement proteins are elaborated that cause increased vascular permeability, chemotaxis, and opsonization.

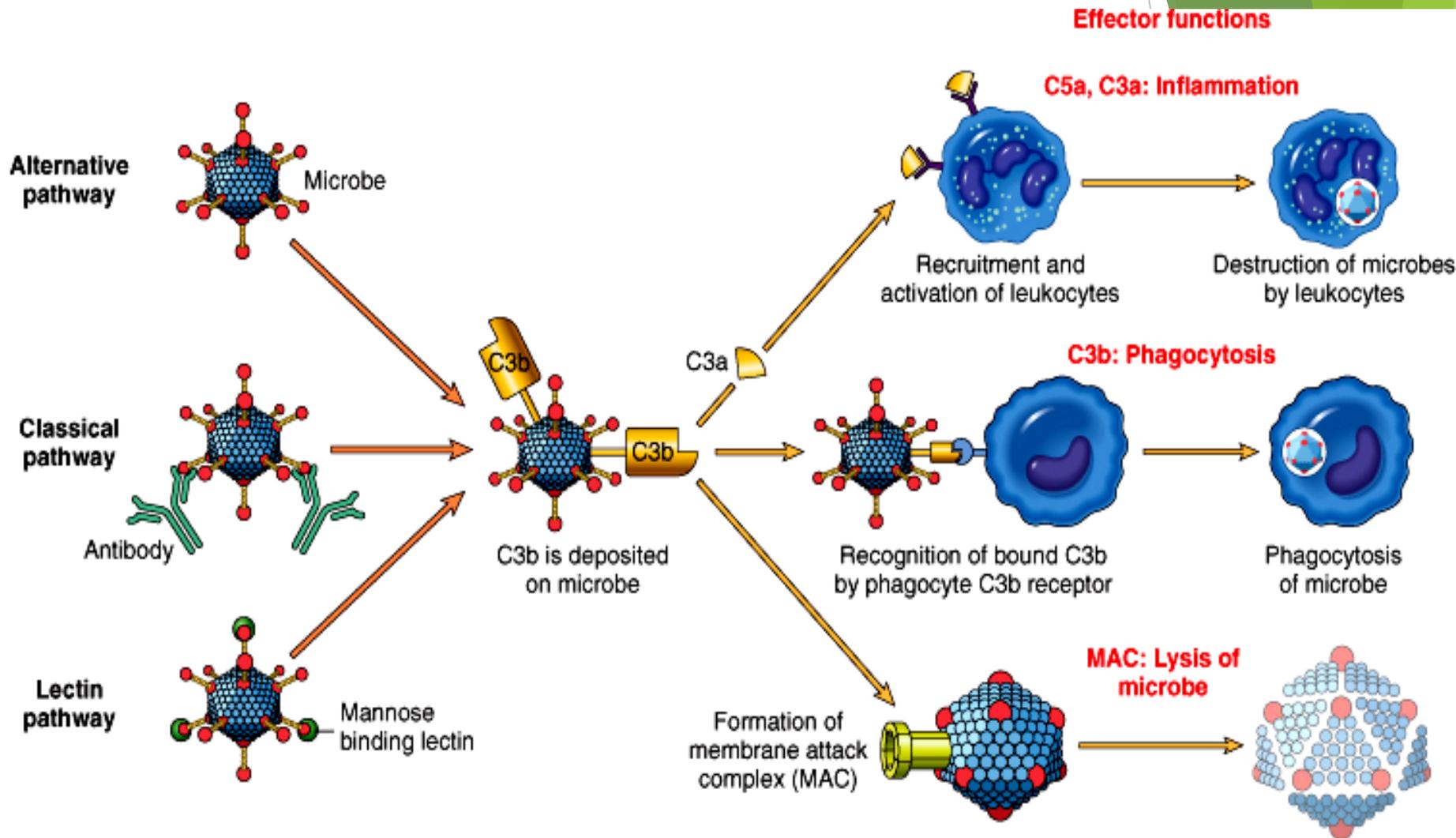
The Complement System in Inflammation

- ▶ C3a and C5a (anaphylatoxins) increased vascular permeability, and cause mast cell to secrete histamine
- ▶ C5a activates lipoxygenase pathway of AA
- ▶ C5a activates leukocytes, increased integrins affinity
- ▶ C5a is chemotactic
- ▶ C3b and iC3b are opsonins
- ▶ Plasmin and proteolytic enzymes split C3 and C5
- ▶ Membrane attack complex (C5-9) lyse bacterial membranes

Complement Activation Pathways



Complement Role in Inflammation



Defects in the Complement System

- ▶ Deficiency of C3 → susceptibility to infections.
- ▶ Deficiency of C2 and C4 → susceptibility to SLE. → systemic lupus erythematosus.
- ▶ Deficiency of late components → low MAC → Neisseria infections.
- ▶ ↓ inhibitors of C3 and C5 convertase (↓ DAF) → hemolytic anemia (PNH)
(Decay-accelerating Factor or CD55)
- ▶ ↓ C1 inhibitor → angioneurotic edema

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

Morphologic Appearance of Acute Inflammation

- ▶ The morphologic hallmarks of acute inflammatory reactions are dilation of small blood vessels and accumulation of leukocytes and fluid in the extravascular tissue.
- ▶ Special morphologic patterns are often superimposed on them, depending on the severity of the reaction, its specific cause, and the particular tissue and site involved
- ▶ The importance of recognizing distinct gross and microscopic patterns of inflammation is that they often provide valuable clues about the underlying cause.

Morphologic Appearance of Acute Inflammation

▶ Catarrhal

- ▶ Acute inflammation + mucous hypersecretion (e.g. common cold).

▶ Serous

- ▶ Abundant protein-poor fluid with low cellular content, e.g. skin blisters and body cavities.

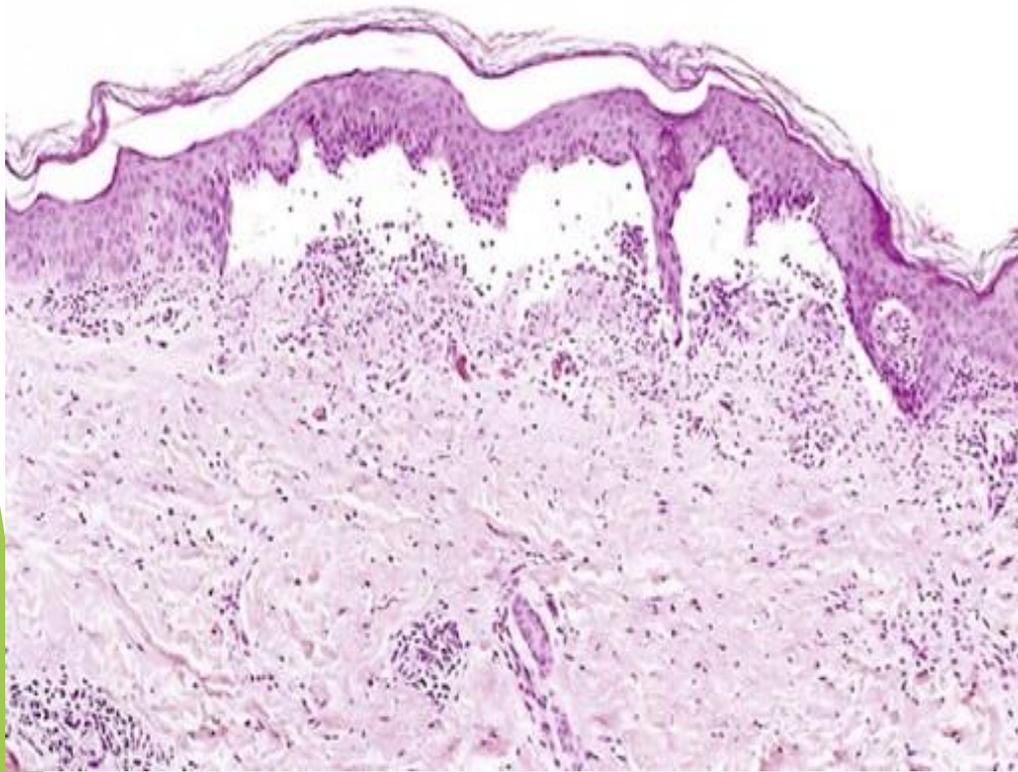
Water bubbles caused by burn

▶ Fibrinous:

- ▶ Accumulation of thick exudate rich in fibrin, may resolve by fibrinolysis or organize into thick fibrous tissue (e.g. acute pericarditis).

Serous inflammation

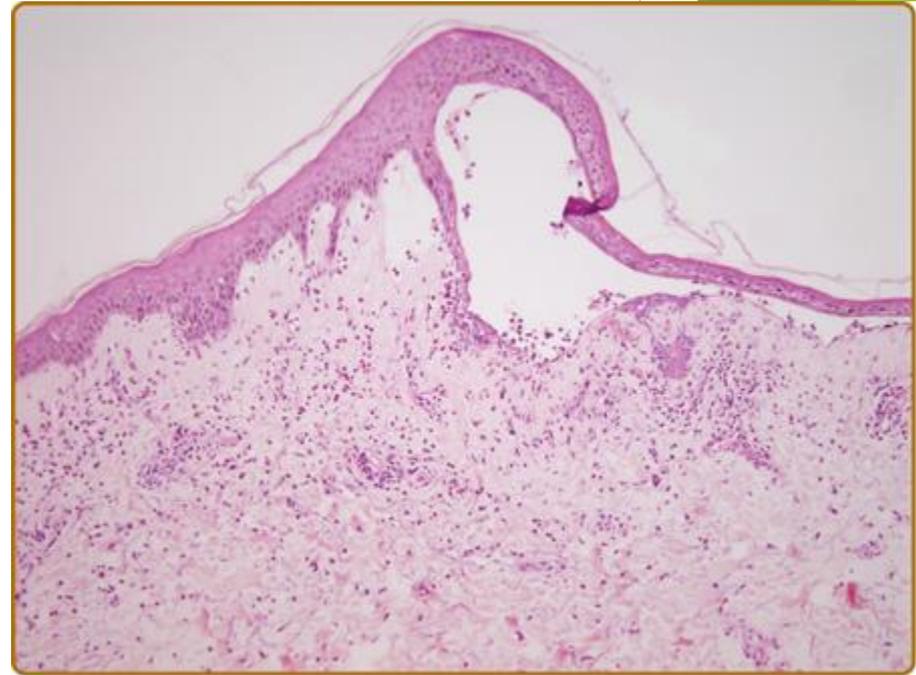
Marked by the **exudation of cell-poor fluid** into spaces created by injury to surface epithelia or into **body cavities** lined by the peritoneum, pleura, or pericardium.



Burn Bister

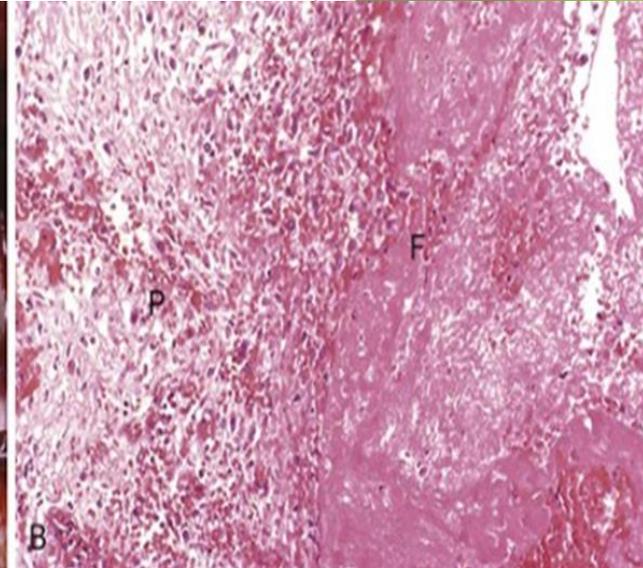
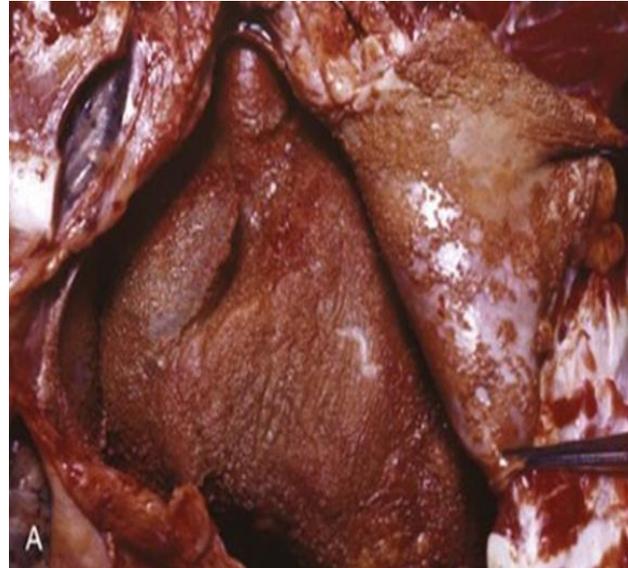
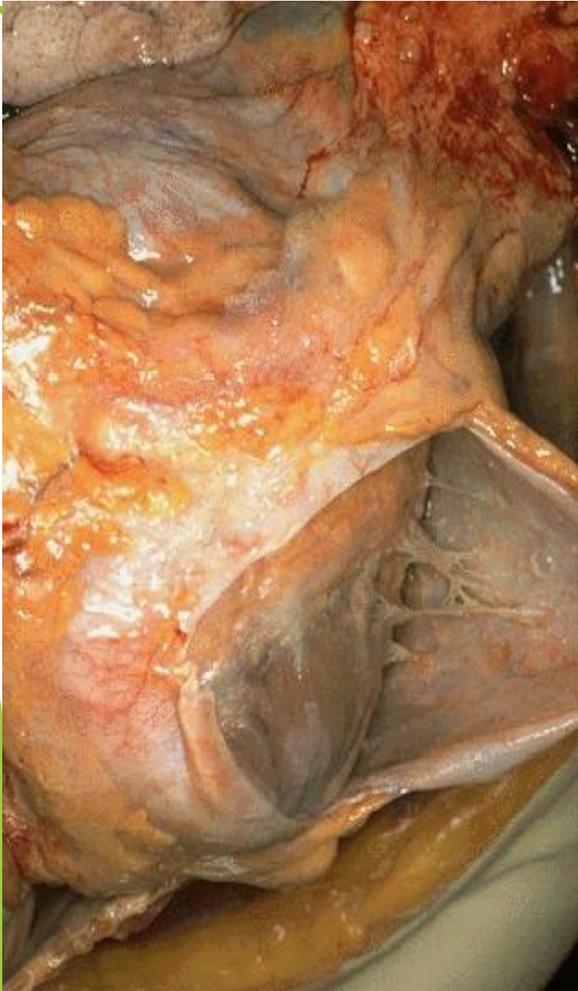
❖ skin blister

- ▶ Resulting from a **burn** or **viral infection**.
- ▶ Represents accumulation of **serous fluid** within or immediately beneath the damaged epidermis of the skin



Fibrinous Pericarditis

- A fibrinous exudate develops when the **vascular leaks** are **large** or there is a local procoagulant stimulus.



Morphologic Appearance of Acute Inflammation

consisting of, containing, or discharging pus

▶ Suppurative (purulent):

▶ Pus: Creamy yellow or blood stained fluid consisting of neutrophils, microorganisms & tissue debris e.g. acute appendicitis

▶ Abscess: Focal localized collection of pus

▶ Empyema: Collection of pus within a hollow organ

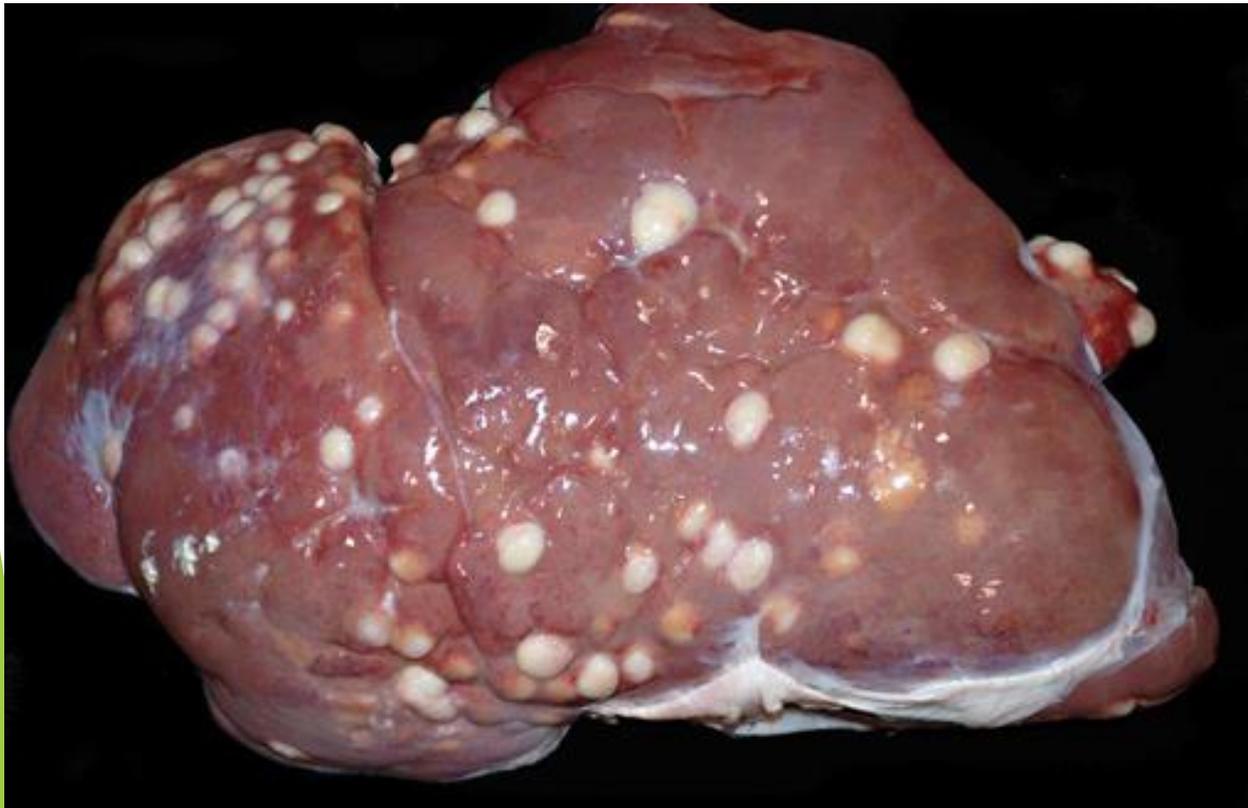
▶ Ulcers:

▶ Defect of the surface lining of an organ or tissue

▶ Mostly GI tract or skin

▶ Abscesses:

- ▶ are localized collections of pus caused by suppuration buried in a tissue, an organ, or a confined space.
- ▶ They are produced by seeding of pyogenic bacteria into a tissue . In time the abscess may become walled off and ultimately replaced by connective tissue

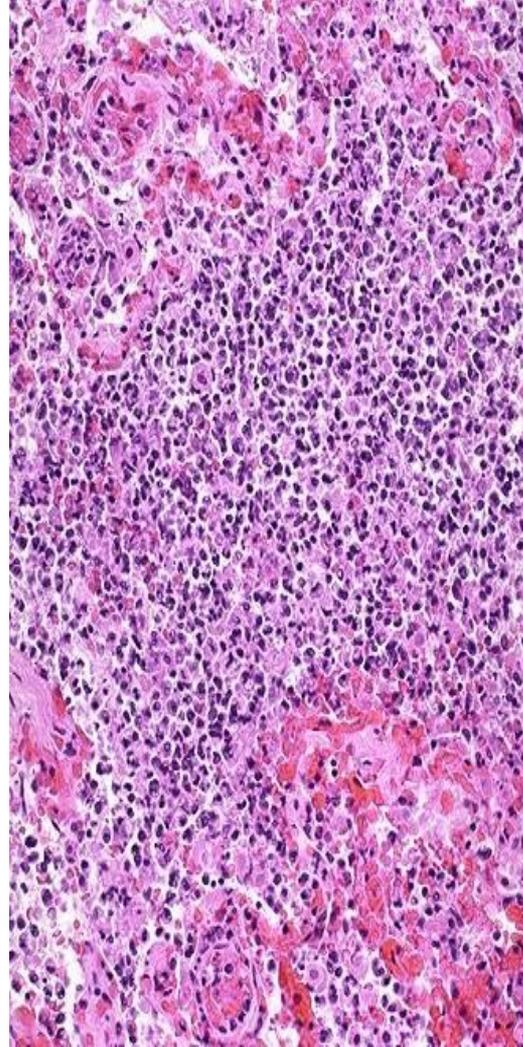
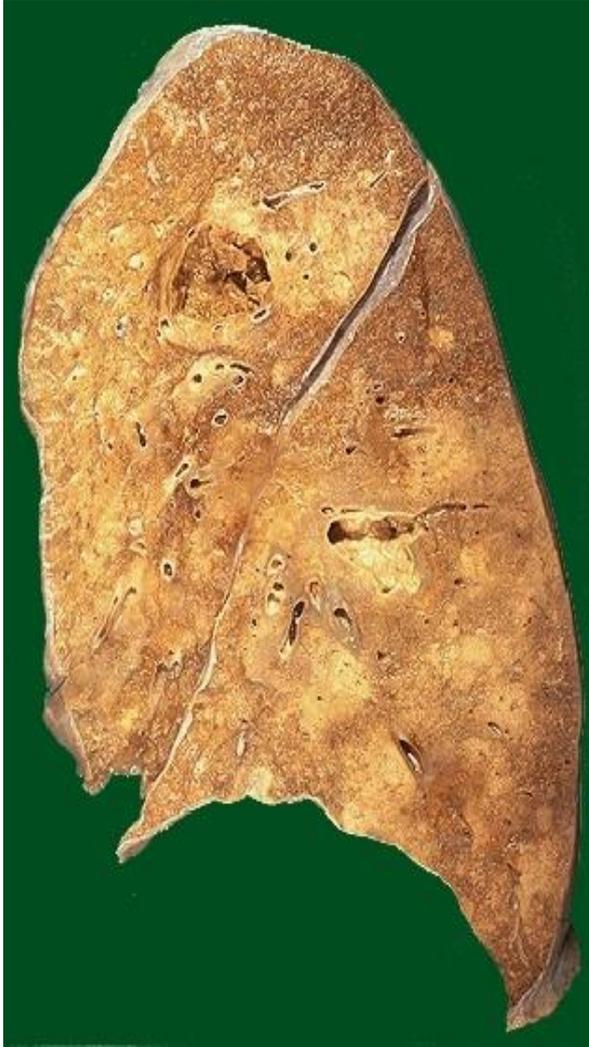


Variably sized abscesses are distributed randomly throughout all lobes of the liver.

Subcutaneous Abscess



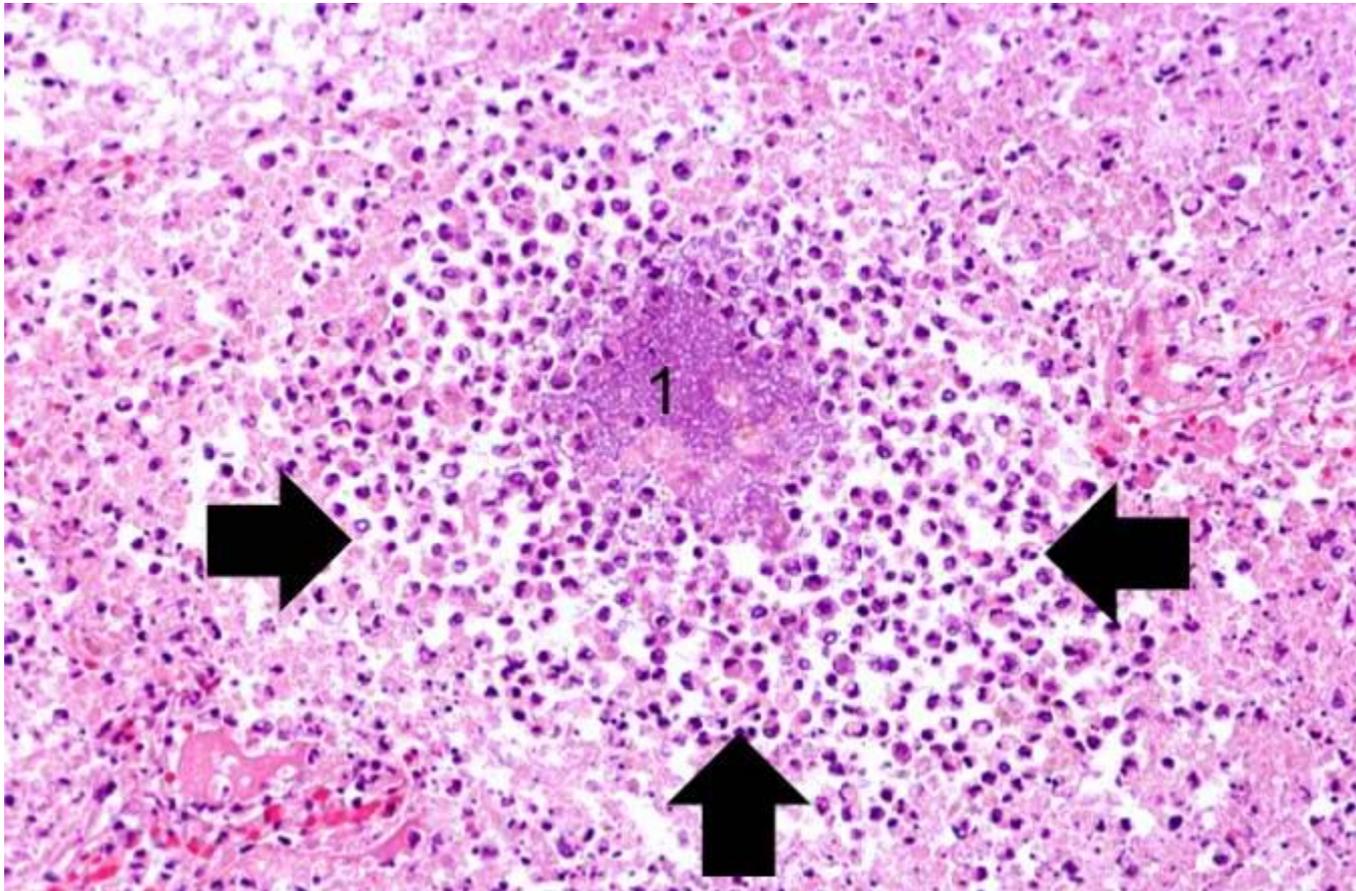
Lung Abscess



Abscesses have a central region that appears as a mass of necrotic leukocytes and tissue cells.

There is usually a zone of preserved neutrophils around this necrotic focus.

outside this region there may be vascular dilation and parenchymal and fibroblastic proliferation, indicating chronic inflammation and repair.

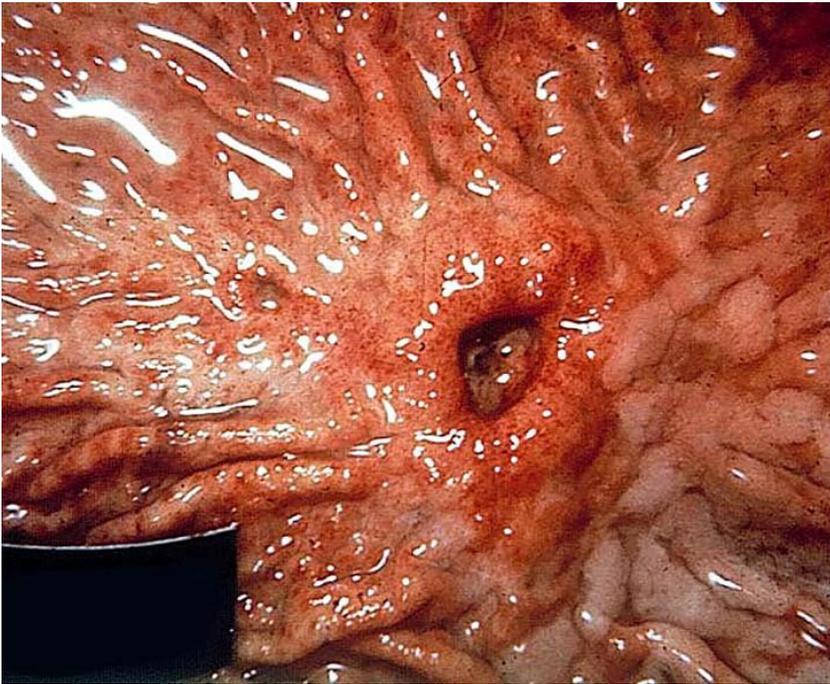


Ulcers

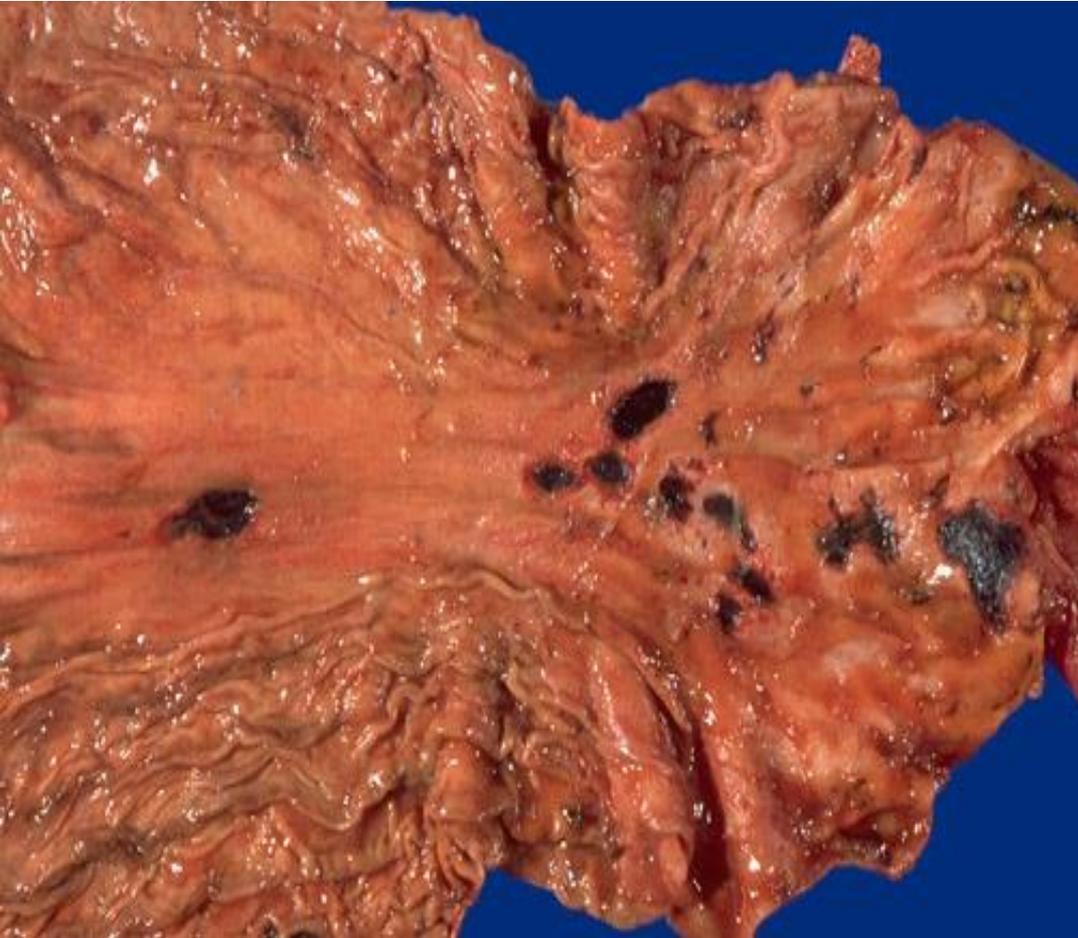


- ▶ An ulcer is a **local defect**, or **excavation**, of the surface of an organ or tissue that is produced by the **sloughing (shedding)** of inflamed necrotic tissue.
- ▶ Ulceration can occur only when tissue **necrosis** and **resultant inflammation** exist on or near a surface

- ▶ It is most commonly encountered in:
- ▶ (1) the **mucosa** of the **mouth, stomach, intestines, or genitourinary tract.**
- ▶ (2) the **skin and subcutaneous tissue** of the **lower extremities** in older persons



Gastric Ulcers



Sub-mucosa is exposed



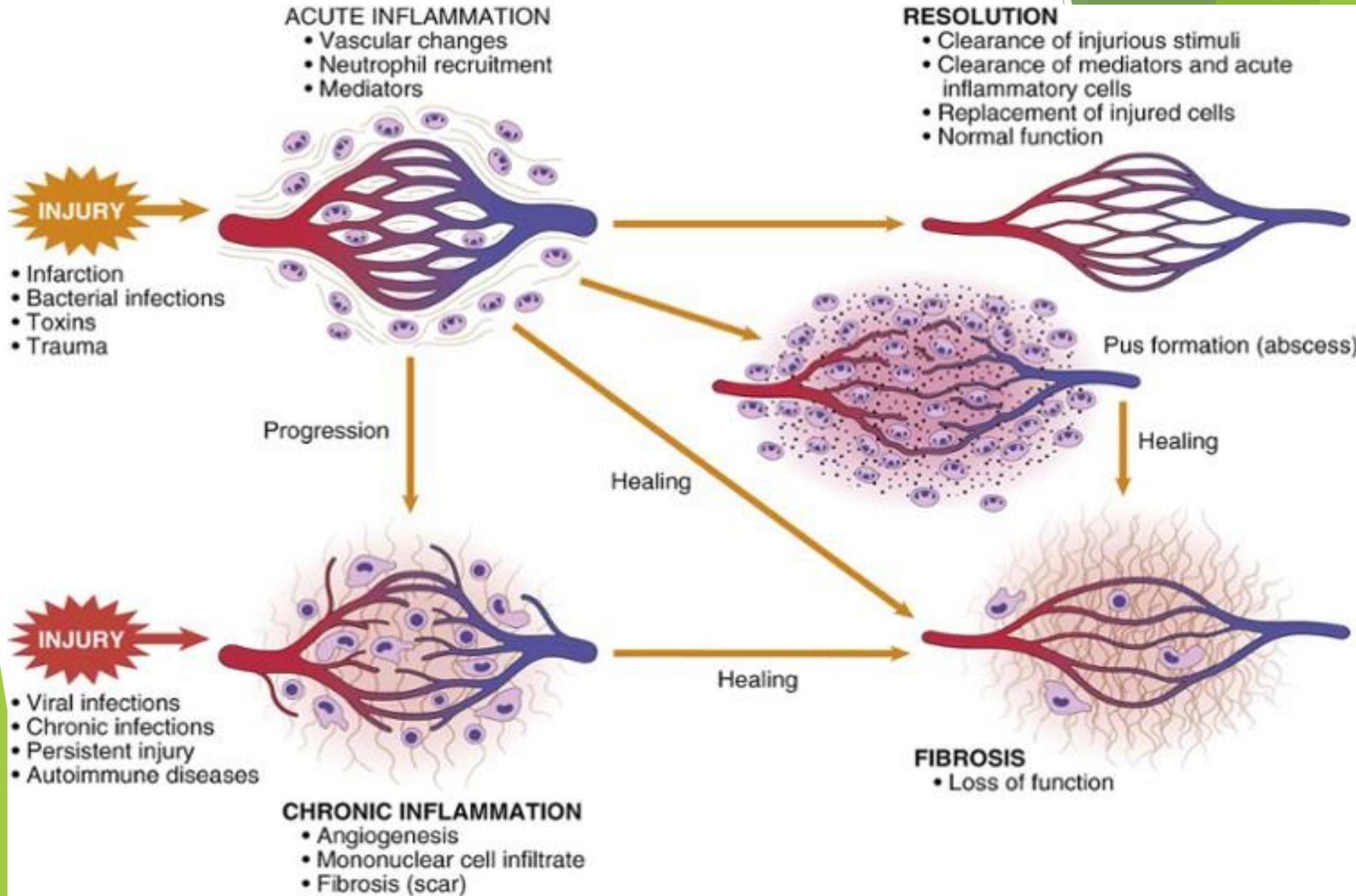
Foot Ulcer



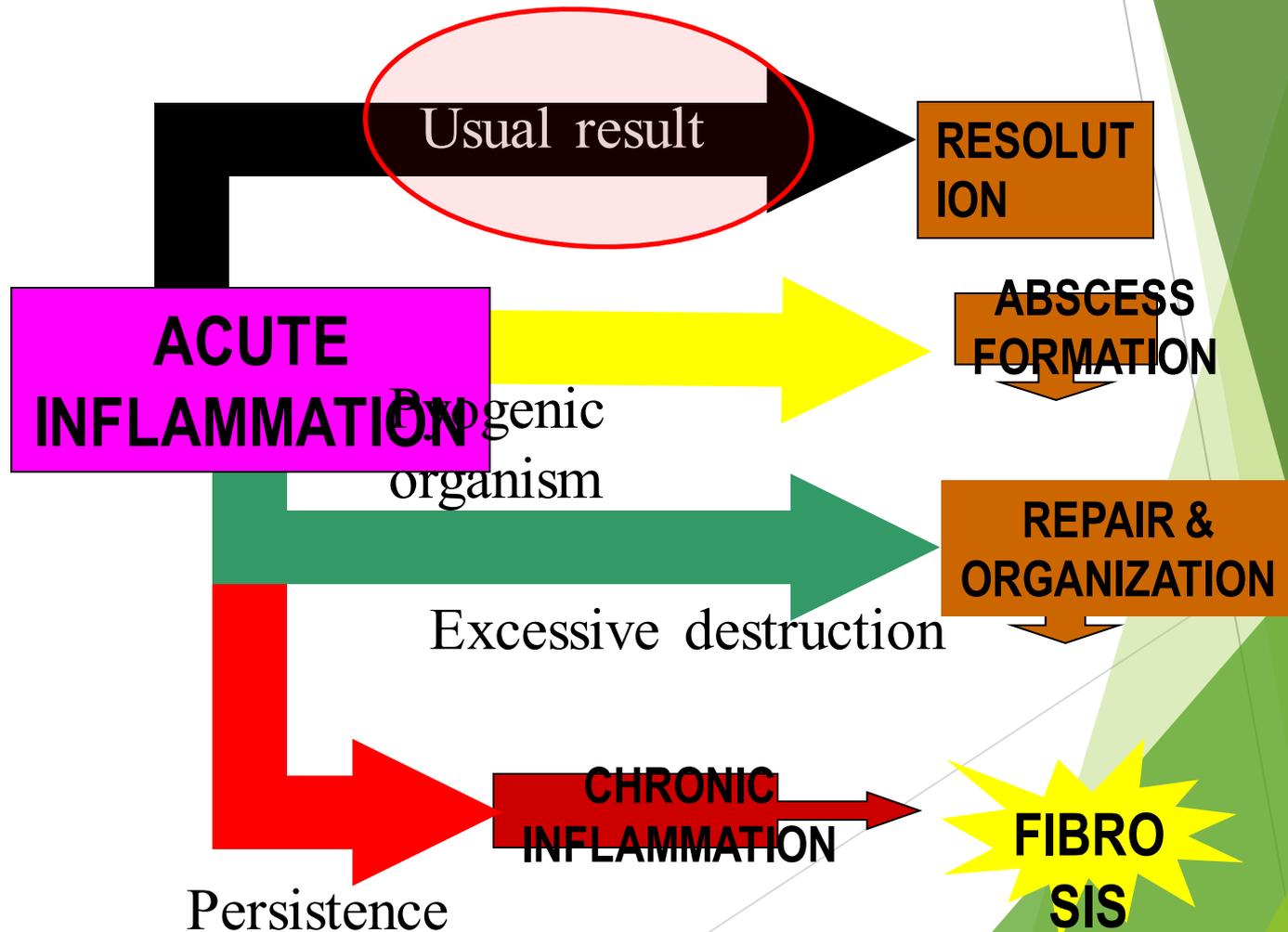
Outcomes of Acute Inflammation

- ▶ **Complete resolution** (back to normal)
 - ▶ Clearance of injurious stimuli
 - ▶ Removal of the exudate, fibrin & debris
 - ▶ Reversal of the changes in the microvasculature
 - ▶ Replacement of lost cells (regeneration)
- ▶ **Healing**
 - ▶ organization by fibrosis through formation of Granulation tissue. Why?
 - ▶ Substantial tissue destruction or
 - ▶ Tissue cannot regenerate or
 - ▶ Extensive fibrinous exudates
- ▶ **Abscess formation**
- ▶ **Progression to** chronic inflammation

Outcomes of Acute Inflammation



Outcomes of Acute Inflammation



Effects of Acute Inflammation

BENEFICIAL:

- ▶ **Elimination of injurious stimulus**
- ▶ **Dilution of toxins**
- ▶ **Entry of antibodies**
- ▶ **Drug transport**
- ▶ **Fibrin formation**
- ▶ **Delivery of nutrients & oxygen**
- ▶ **Stimulation of the immune response**

HARMFUL:

- ▶ **Digestion of normal tissues**
- ▶ **Swelling**
- ▶ **Inappropriate inflammatory response**

The end

Questions