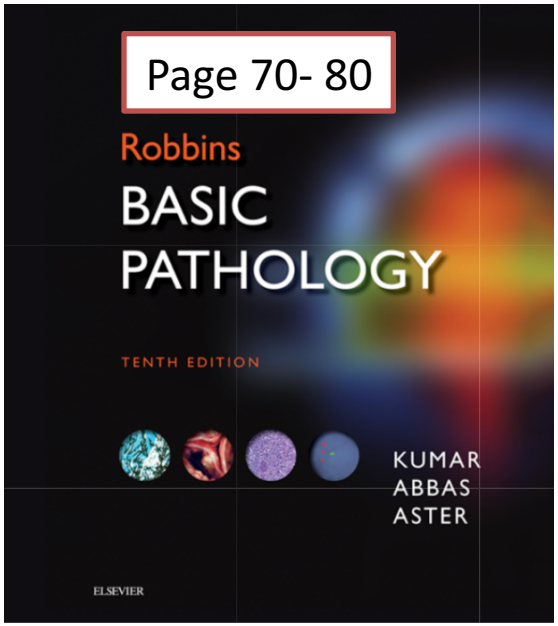
Foundation Block
Pathology
Oct 2019

INFLAMMATION AND REPAIR

Lecture 3

Chemical mediator of inflammation
Different patterns of inflammation
Outcomes of acute inflammation



Lecturer: Dr. Maha Arafah

Objectives

1. **Chemical mediators of inflammation:**
   - I. **Definition**
   - II. **Know the general principles for chemical mediators.**
   - III. **Know the cellular sources and major effects of the mediators.**
   - IV. **List the most likely mediators of each of the steps of inflammation.**

2. **Recognize the different patterns of inflammation.**

3. **List and describe the outcome of acute inflammation.**

What are mediators?

- Chemical mediators of inflammation are substances produced during inflammation inducing a specific events in acute inflammation.

General principles for chemical mediators

The production of active mediators is triggered by:

1. microbial products
2. host proteins, such as the proteins of the complement, kinin and coagulation systems
   - (these are themselves activated by microbes and damaged tissues)

General principles for chemical mediators

Most mediators have the potential to cause harmful effects.

- **Therefore, there should be a mechanism to checks and balances their action.**

- **Mediator function is tightly regulated by:**

1) **decay (e.g. AA metabolites)**
2) **inactivated by enzymes (e.g. kininase inactivates bradykinin)**
3) **eliminated (e.g. antioxidants scavenge toxic oxygen metabolites)**

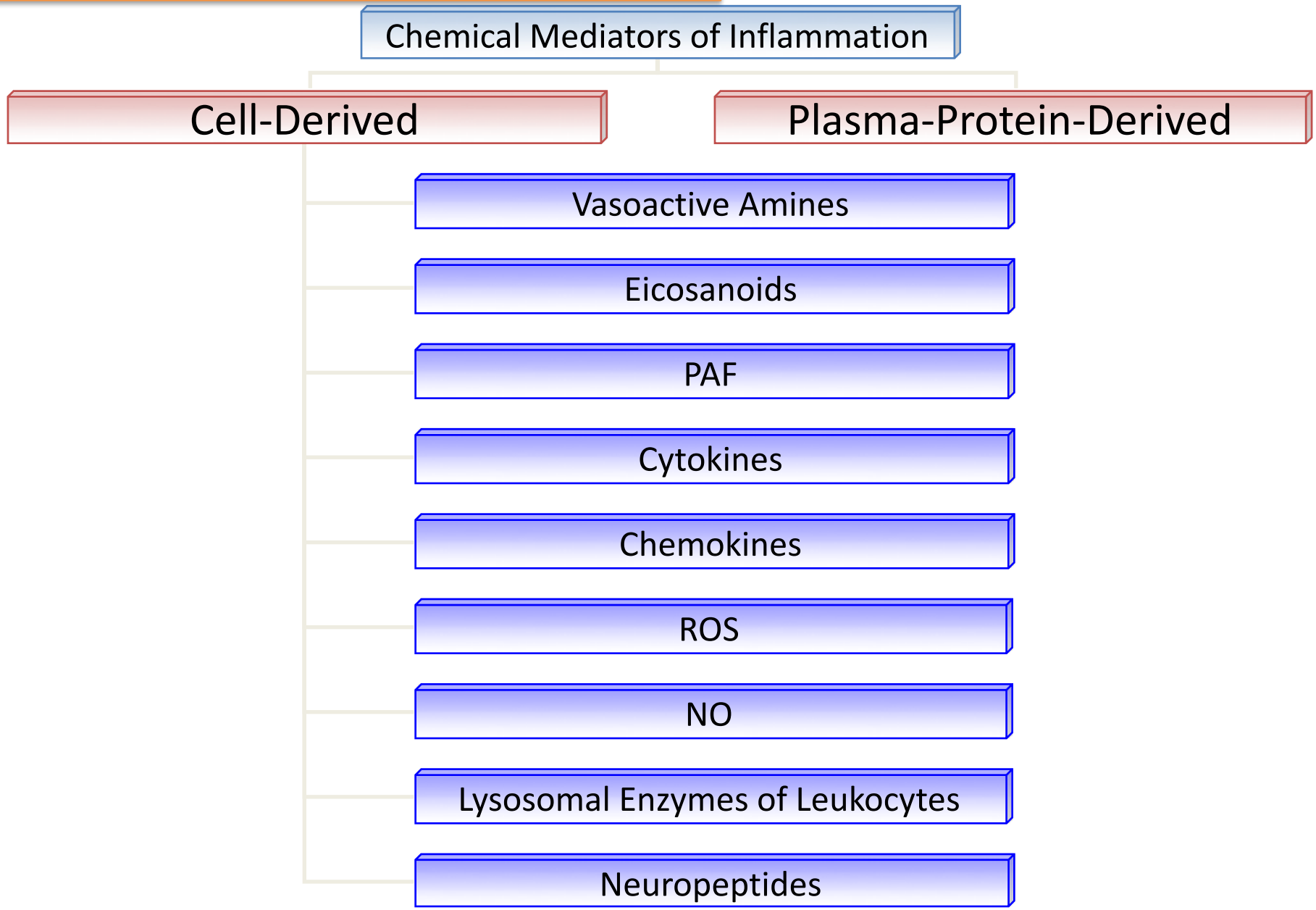
Source of Chemical mediators

- Cell-derived:
  1. Synthesized as needed (prostaglandin)
  2. Preformed, sequestered and released (mast cell histamine)
  3. against offending agents in tissues

- Plasma-derived:
  1. Complement
  2. kinins
  3. coagulation factors

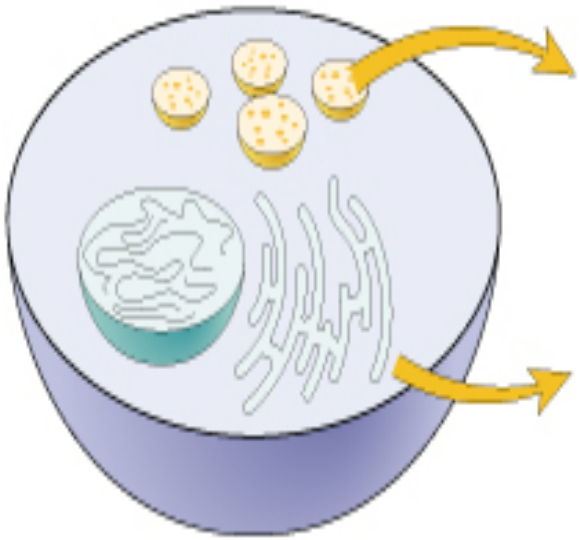
  – Many in “pro-form” requiring activation (enzymatic cleavage)
  – against circulating microbes

Chemical mediators of inflammation



Cell-Derived Mediators

Producing cells:



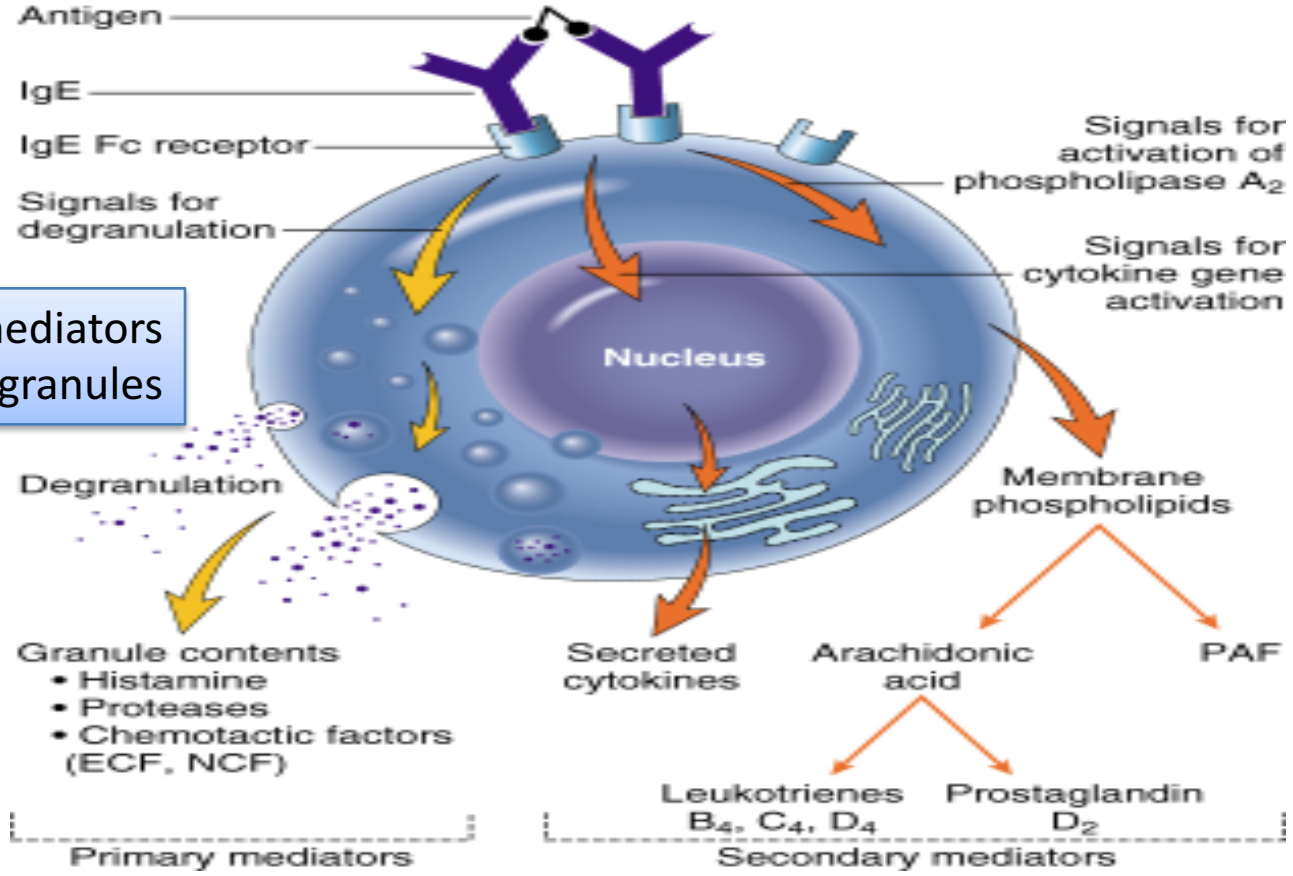
	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC

Vasoactive Amines

Histamine & Serotonin

Among first mediators in acute inflammatory reactions

Preformed mediators in secretory granules



Chemical mediators of inflammation: cell derived- preformed

Histamine

plays a major role in the early phase of acute inflammation and increases vascular permeability

Source:

many cell types, esp. *mast cells*, *circulating basophils*, and *platelets*

Stimuli of Release:

- Physical injury
- Immune reactions (cross-linking of cell-surface IgE by antigen)
- C3a and C5a fragments
- Cytokines (e.g. IL-1 and IL-8)
- Neuropeptides

Actions:

1. ARTERIOLAR DILATION
2. INCREASED VASCULAR PERMEABILITY (venular gaps)
3. ENDOTHELIAL ACTIVATION

Inactivated by:
Histaminase

Serotonin (5-HT)

Source:

Platelets

Action:

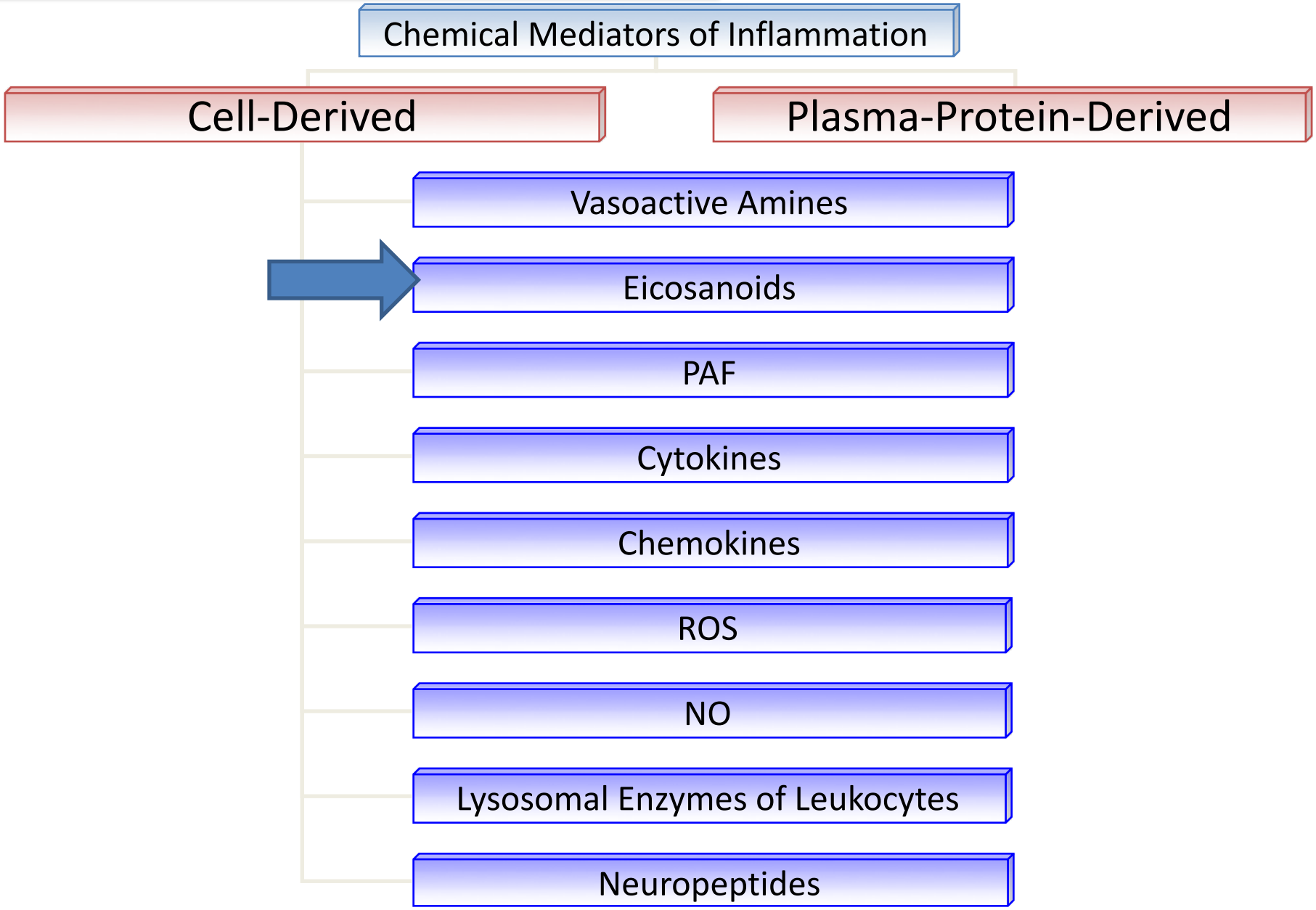
Neurotransmitter in the gastrointestinal tract

A vasoconstrictor (the importance of this action in inflammation is unclear)

Stimulus:

Platelet aggregation

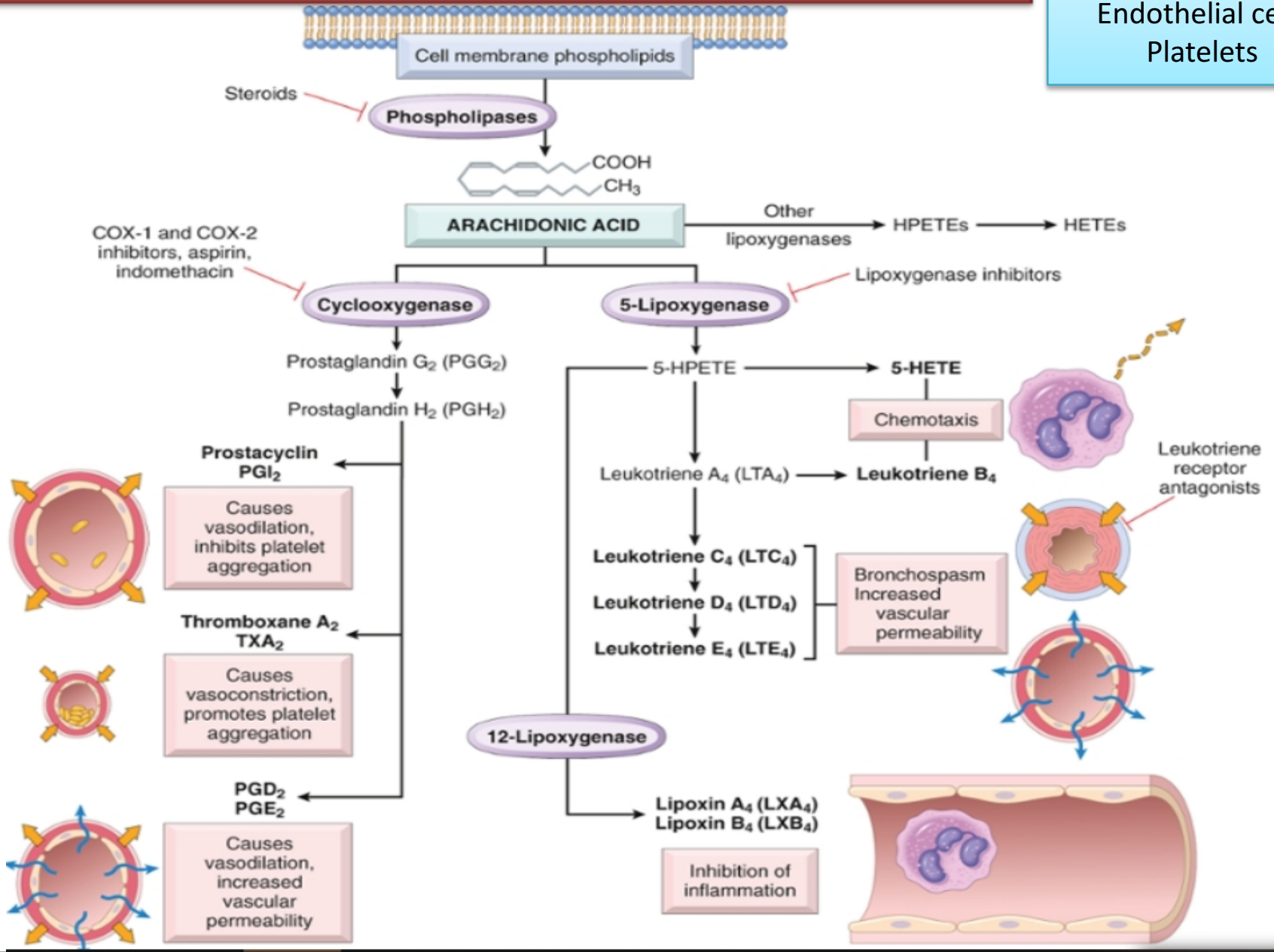
Chemical mediators of inflammation



Chemical mediators of inflammation: cell derived- newly synthesized

Arachidonic Acid Metabolites (*eicosanoids*)

Source:
Leukocytes
Mast cells
Endothelial cells
Platelets

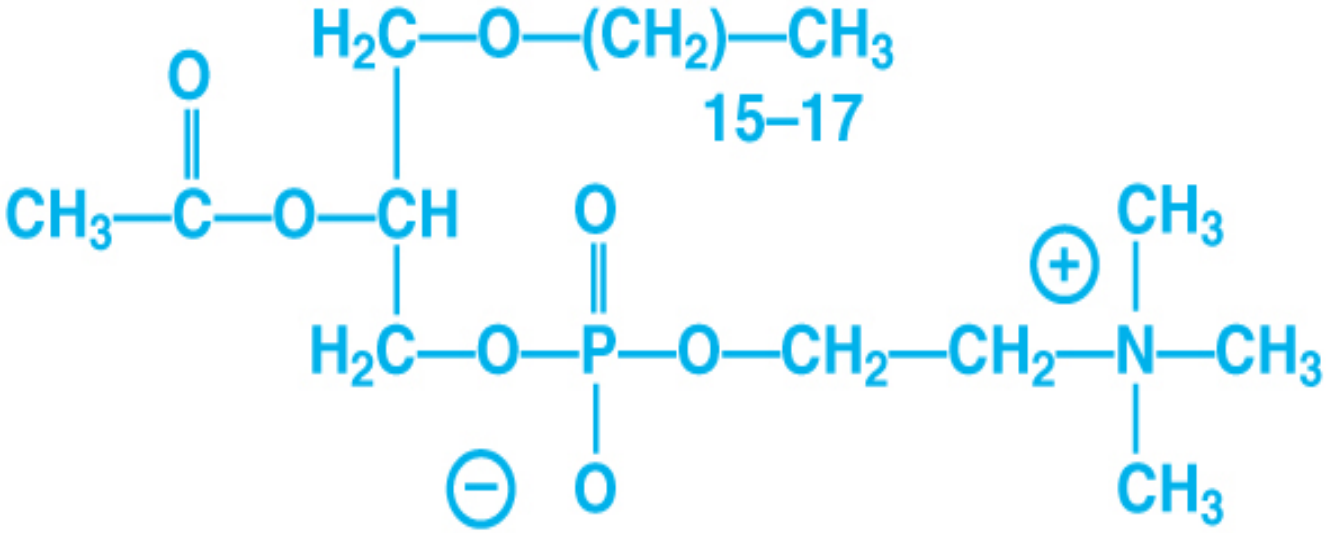


Arachidonic Acid Metabolites (*eicosanoids*)

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

Chemical mediators of inflammation: cell derived- newly synthesized

SOURCES	MAJOR INFLAMMATORY ACTIONS
Mast cells/basophils	Increased vascular permeability
Neutrophils	Leukocyte aggregation
Monocytes/macrophages	Leukocyte adhesion
Endothelium	Leukocyte priming/chemotaxis
Platelets	Platelet activation
Others	Stimulation of other mediators (LT, $O_2^{\bullet-}$)



PLATELET-ACTIVATING FACTOR

Chemical mediators of inflammation: cell derived- newly synthesized

Chemical Mediators of Inflammation

Cytokines

Source:
Lymphocytes
Macrophages
Dendritic cells
Endothelial cells
Epithelial cells

Polypeptides

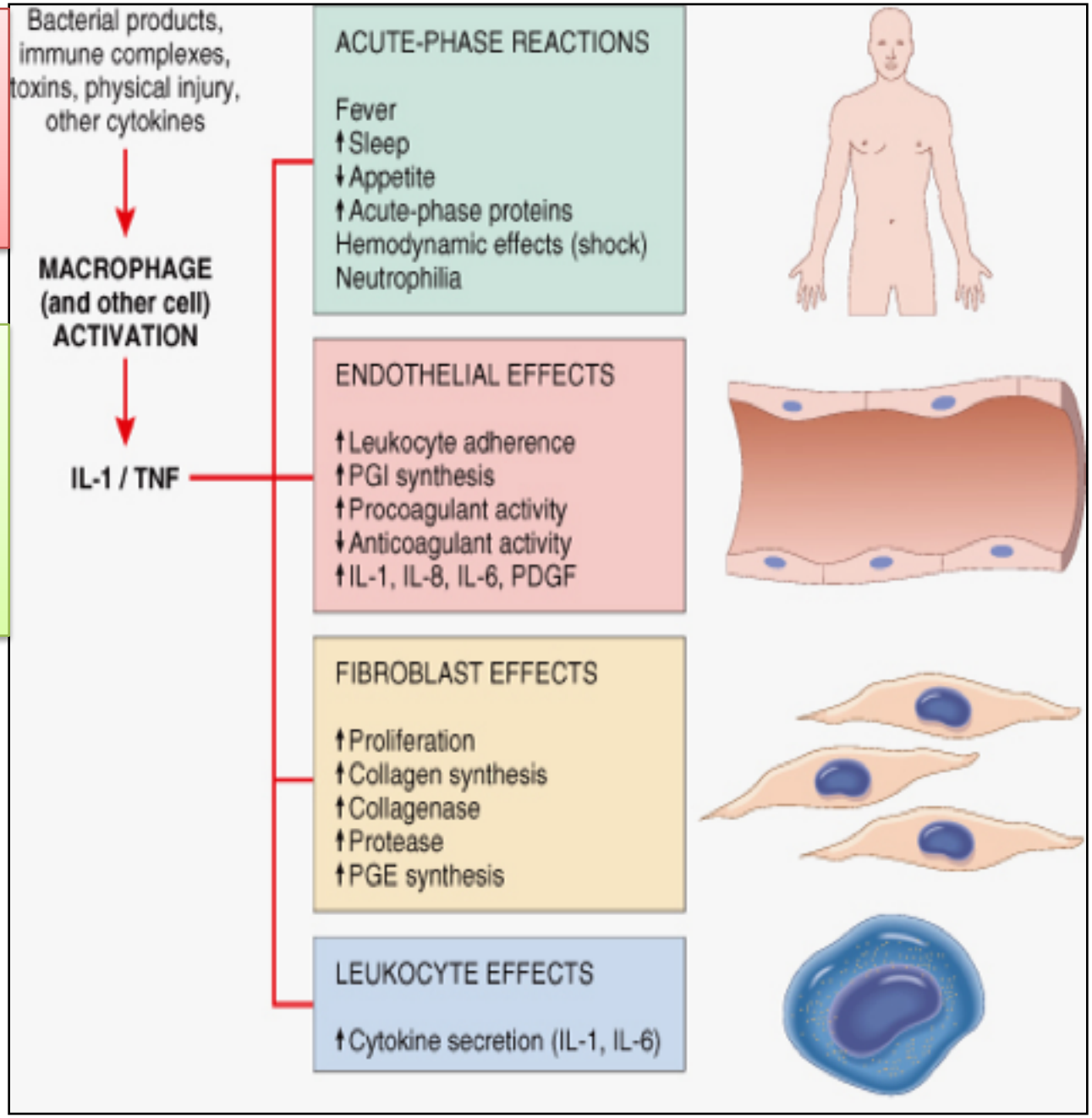
Actions:

- Involved in early immune and inflammatory reactions
- Some stimulate bone marrow precursors to produce more leukocytes
- Have roles in acute and chronic inflammation

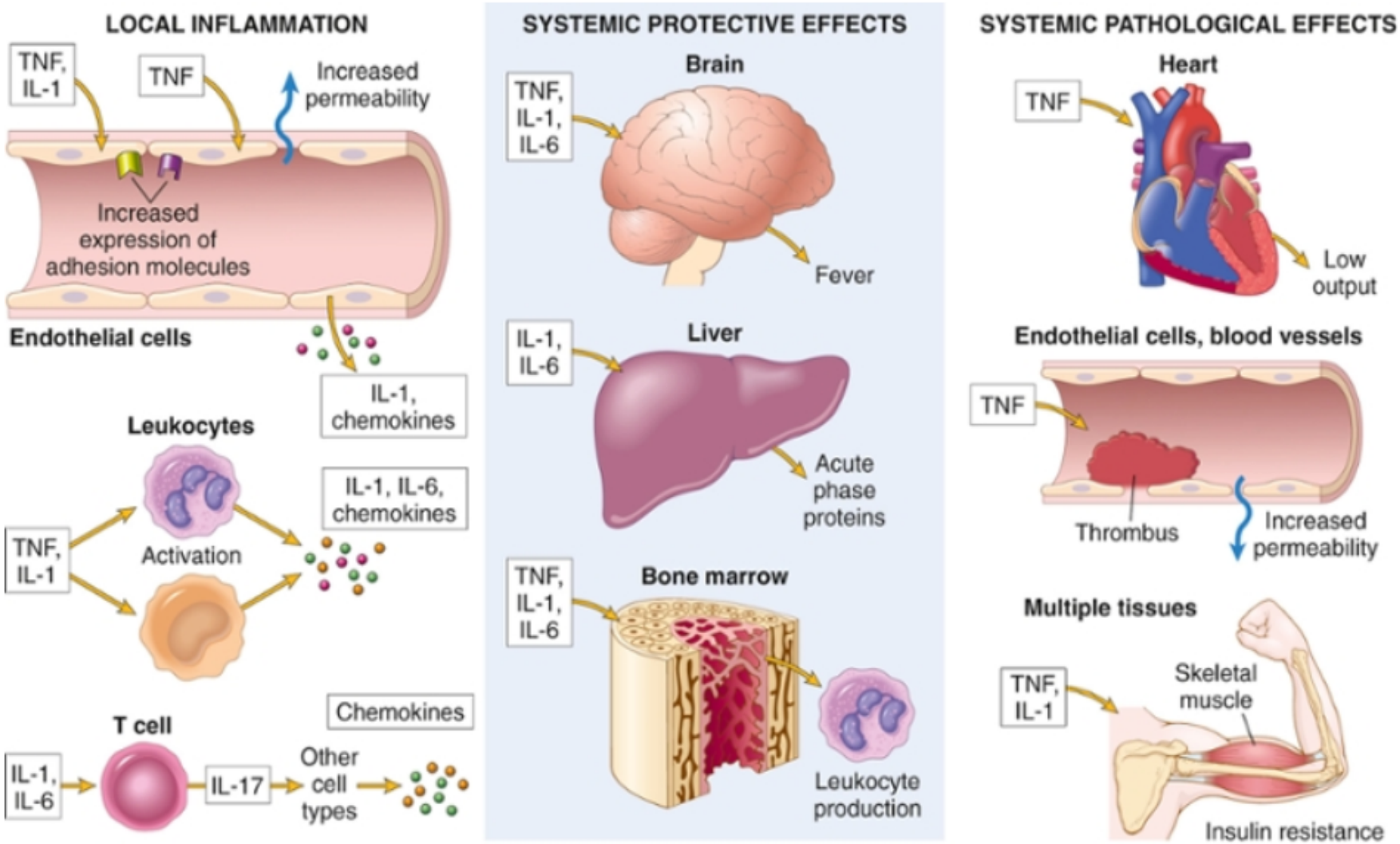
Chemical mediators of inflammation: cell derived- newly synthesized

Cytokine of Acute inflammation:
Interleukin (IL-1) & TNF

:Action
Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects

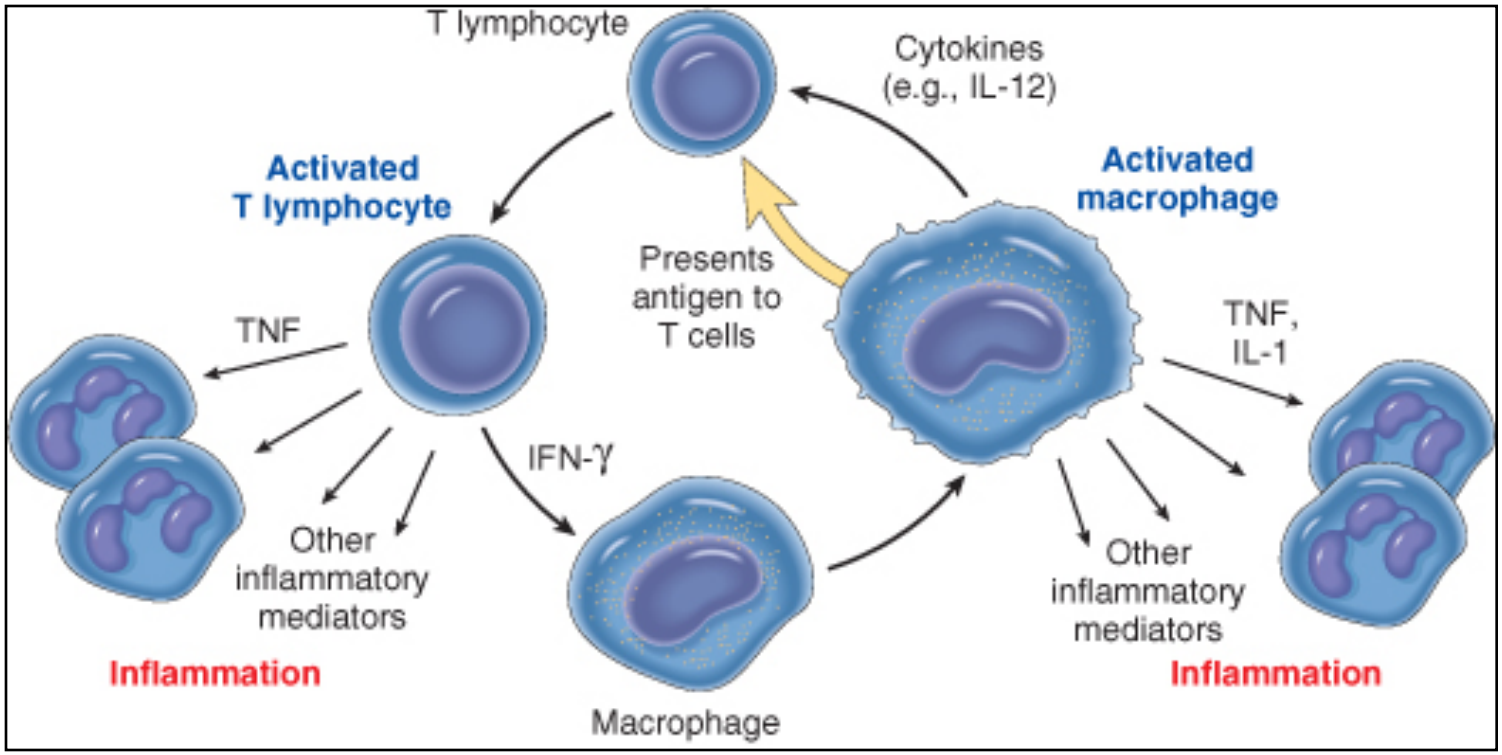


Major roles of cytokines in acute inflammation



TNF antagonists is effective in the treatment of rheumatoid arthritis

Cytokines of Chronic Inflammation:
Interferon-γ (INF- γ) & Interleukin (IL-12)



Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

Chemical Mediators of Inflammation

Chemokines

Small proteins

They are chemoattractants for leukocytes

Main functions:

Leukocyte recruitment & activation in inflammation

Normal anatomic organization of cells in lymphoid and other tissues

Chemical mediators of inflammation: cell derived

Chemical Mediators of Inflammation

Reactive Oxygen Species

Synthesized via

NADPH oxidase pathway

Source:

Neutrophils and Macrophages

Stimuli of release:

Microbes

Immune complexes

Cytokines

Action:

Microbicidial (cytotoxic) agent

Neuropeptides

Chemical Mediators of Inflammation

Nitric Oxide (NO)

Short-lived

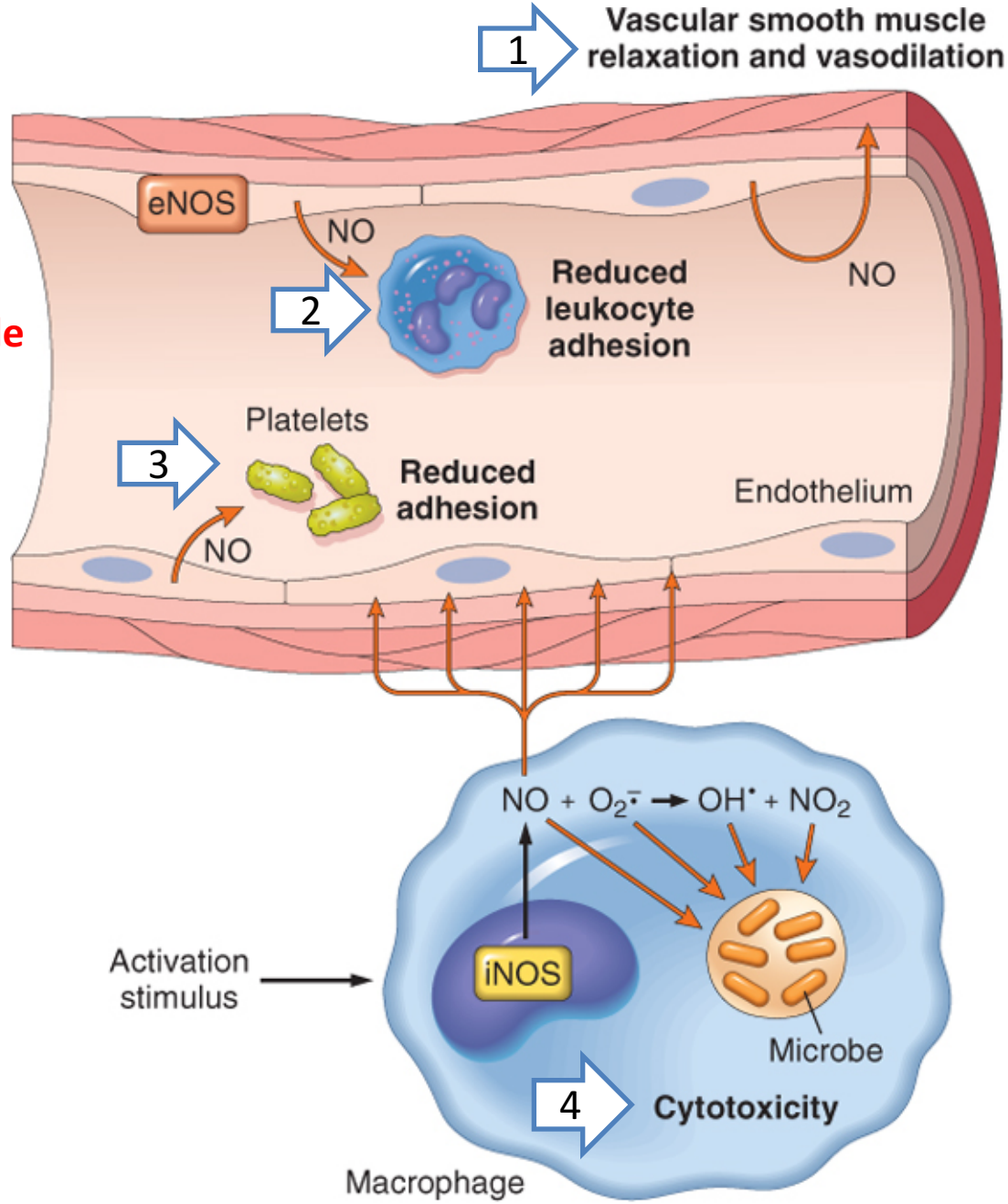
Soluble free-radical gas

Functions:

- Vasodilation
- Antagonism of platelet activation (adhesion, aggregation, & degranulation)
- Reduction of leukocyte recruitment
- Microbicidial (cytotoxic) agent (with or without ROS) in activated macrophages

Chemical mediators of inflammation: cell derived- newly synthesized

Actions of Nitric Oxide



Chemical mediators of inflammation: cell derived- newly synthesized

Chemical Mediators of Inflammation

Lysosomal Enzymes of Leukocytes

Neutrophils & Monocytes

Enzymes:

Acid proteases

Neutral proteases (e.g. elastase, collagenase, & cathepsin)

Their action is checked by:

Serum antiproteases (e.g. α_1-antitrypsin)

Neuropeptides

Chemical Mediators of Inflammation

Neuropeptides

Small proteins

Secreted by nerve fibers mainly in lung & GIT

Initiate inflammatory response

e.g. Substance P :

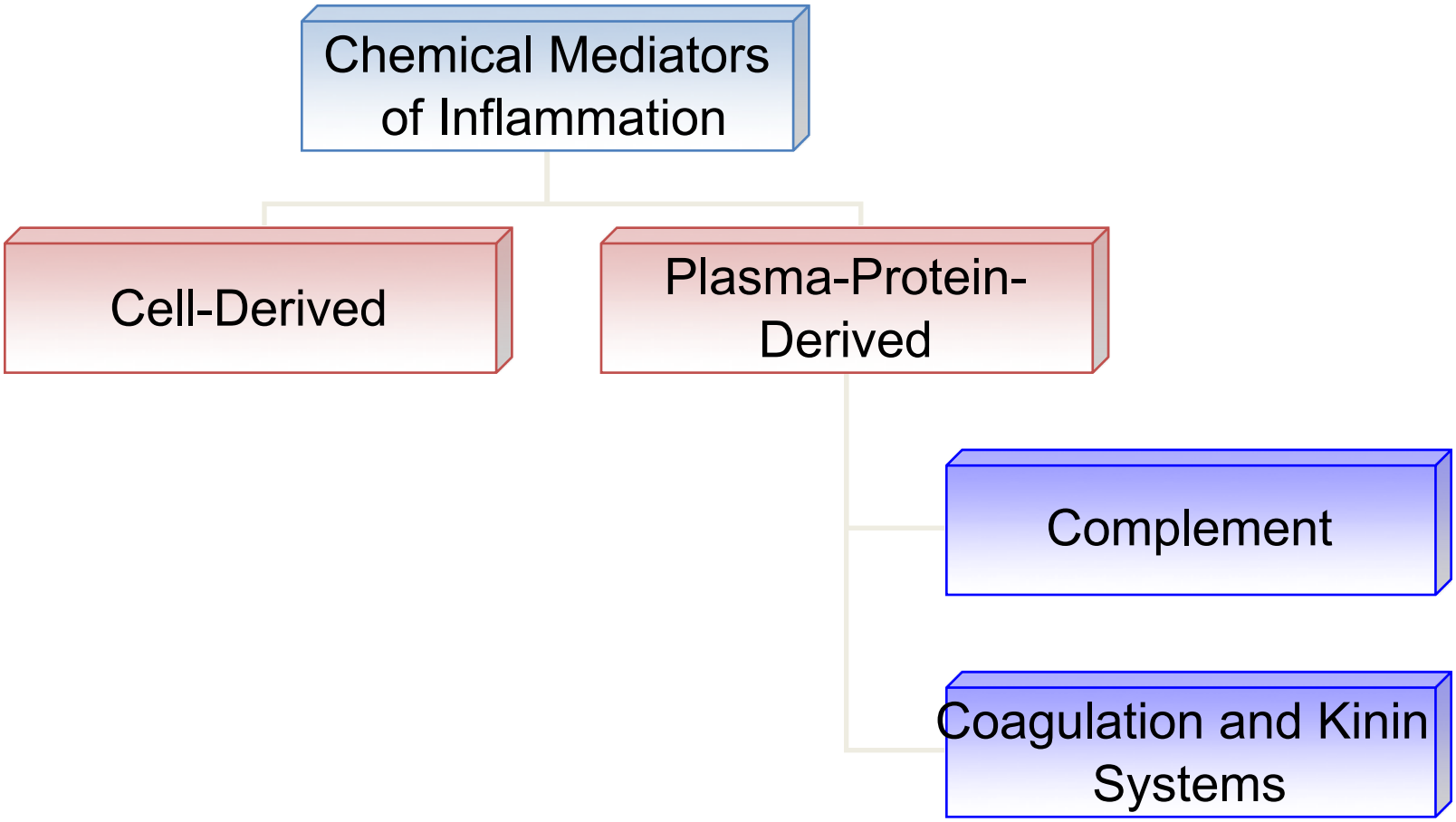
Transmits pain signals

Regulates vessel tone

Modulates vascular permeability

Neuropeptides

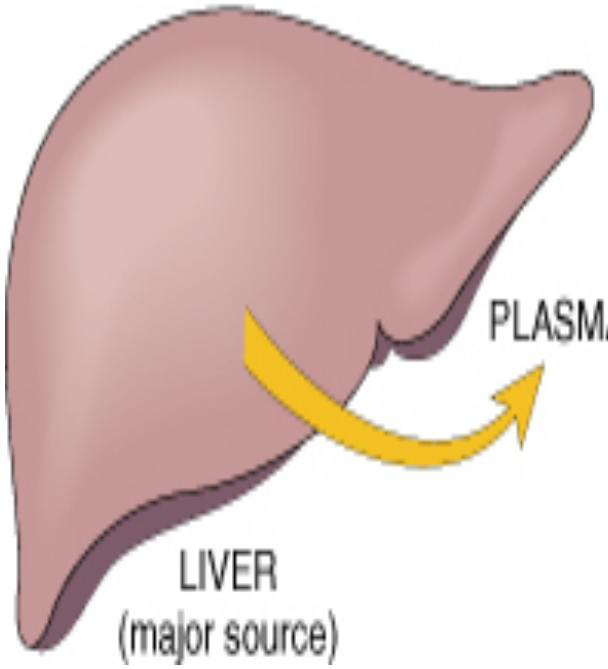
Chemical mediators of inflammation



Chemical mediators of inflammation: Plasma protein derived

Chemical Mediators of Inflammation

- **Cell-Derived**
- **Plasma-Protein-Derived**
  1. Clotting systems
  2. Kinin
  3. Complement

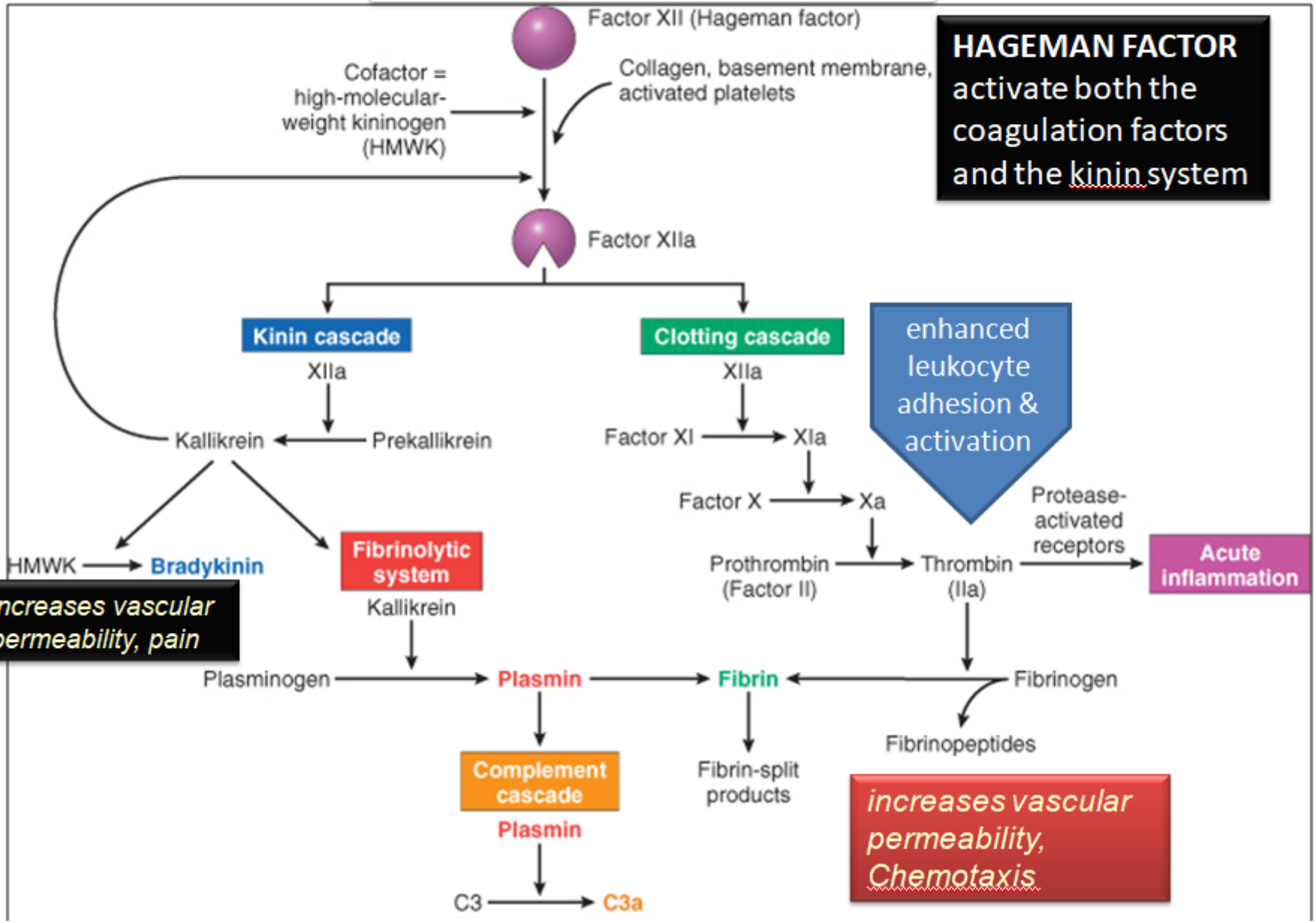


Factor XII (Hageman factor) activation
- Kinin system (bradykinin)
- Coagulation / fibrinolysis system

Complement activation
- C_{3a}, C_{5a} — anaphylatoxins
- C_{3b}
- C_{5b-9} (membrane attack complex)

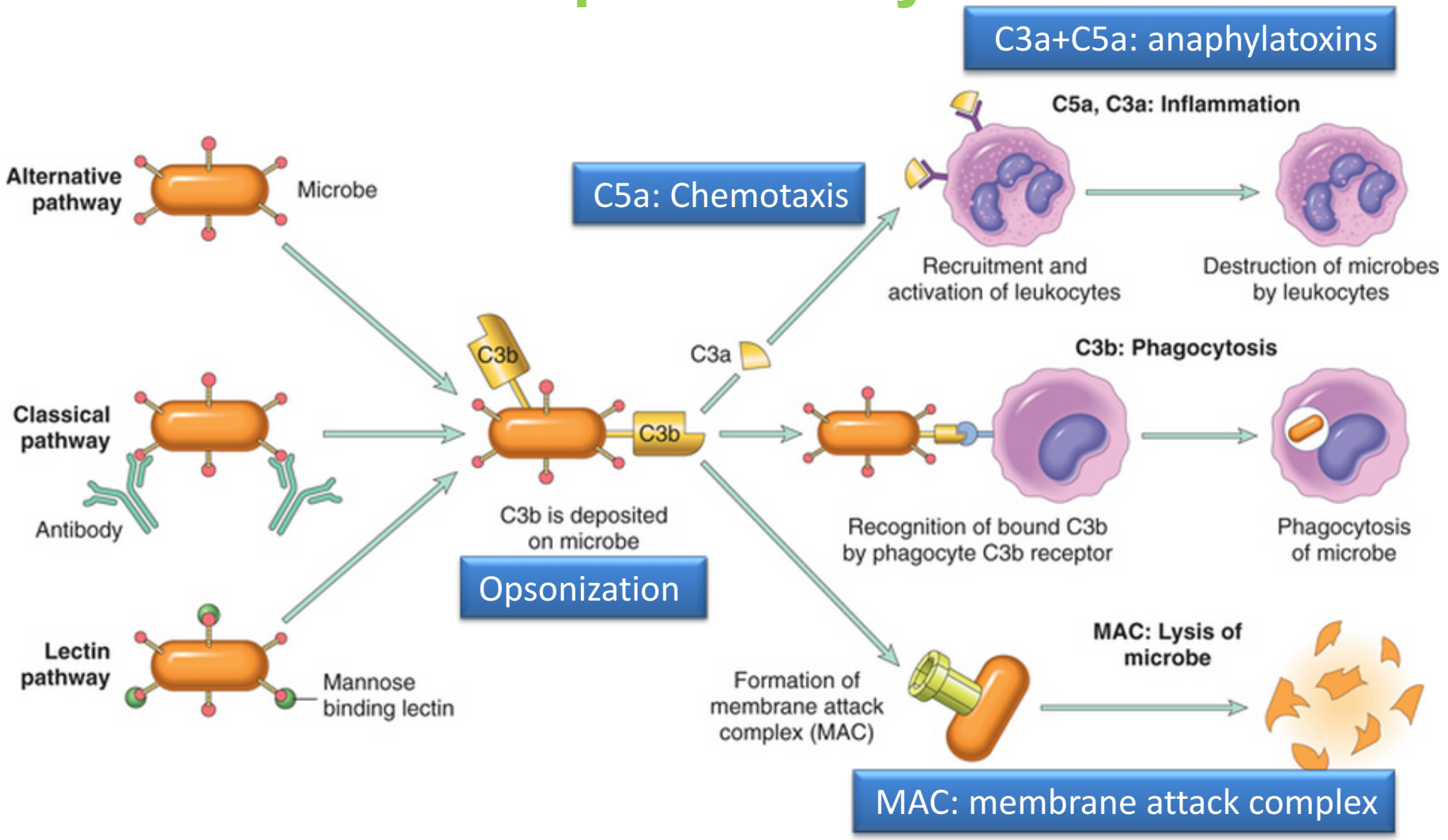
Chemical mediators of inflammation: Plasma protein derived

Kinin & clotting systems



Chemical mediators of inflammation: Plasma protein derived

Complement System



Complement protein: action

C3a & C5a → Increase vascular permeability
(anaphylatoxins)

C5a → Chemotaxis

C3b → Opsonization

C5-9 → membrane attack complex, lead to bacterial lysis

Role of Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins Histamine Nitric oxide
Increased vascular permeability	Vasoactive amines Bradykinin Leukotrienes C4, D4, E4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	C3a, C5a Leukotriene B4 Chemokines IL-1, TNF
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites Nitric oxide

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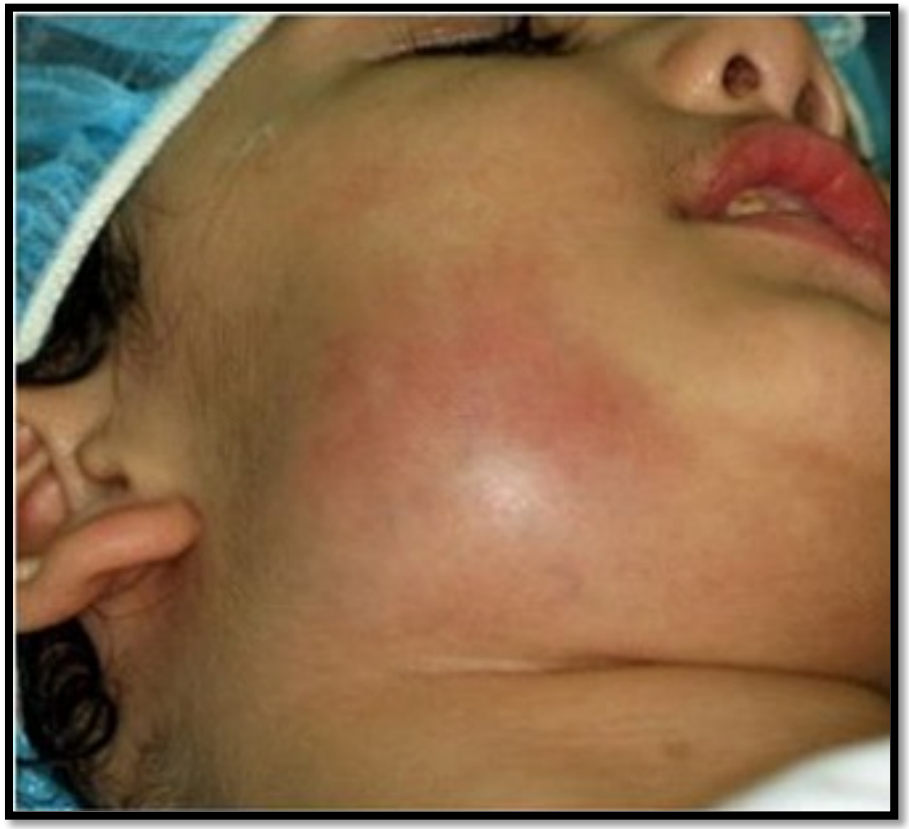
Recognize the different patterns of inflammation

Clinical Features

The 5 ancient cardinal signs of inflammation are



Tumor:-swelling

Due to a histamine-mediated increase in permeability of venules

Rubor :– redness

Calor: – warmth

Rubor and calor are due to histamine-mediated vasodilation of arterioles

Dolor :– pain

mediated by PGE2 and bradykinin

Functio Laesa :– loss of function

The suffix "its" is added to the base word to state the condition as in appendix/appendicitis

Recognize the different patterns of inflammation.

Morphologic Patterns of Acute Inflammation

- Several types of inflammation vary in their morphology and clinical correlates. Why?
  - The severity of the reaction
  - specific cause
  - the particular tissue
  - site involved

Recognize the different patterns of inflammation.

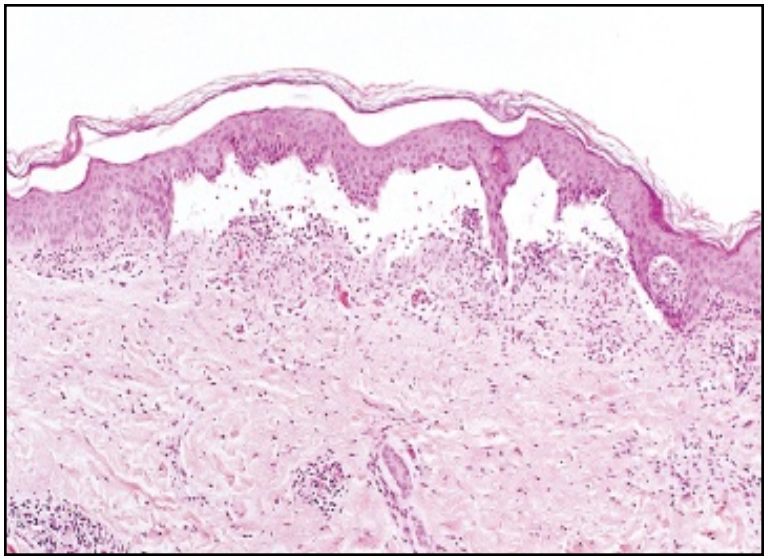
Morphologic Patterns of Acute Inflammation

- **SEROUS INFLAMMATION**
- **FIBRINOUS INFLAMMATION**
- **CATARRHAL INFLAMMATION**
- **SUPPURATIVE OR PURULENT INFLAMMATION**
- **ULCERS**
- **Others**

Recognize the different patterns of inflammation.

SEROUS INFLAMMATION:

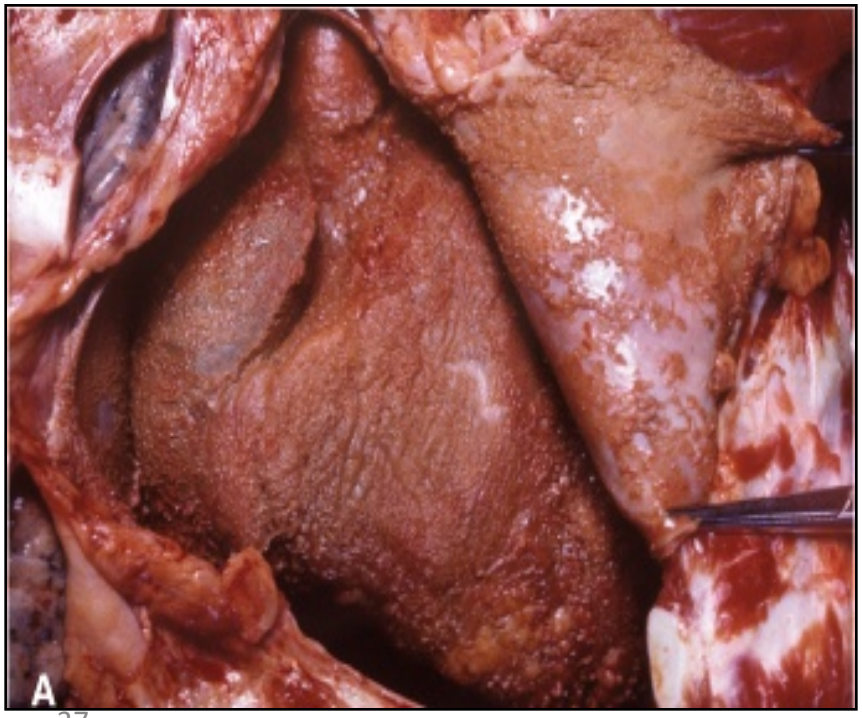
marked by the outpouring of a thin fluid

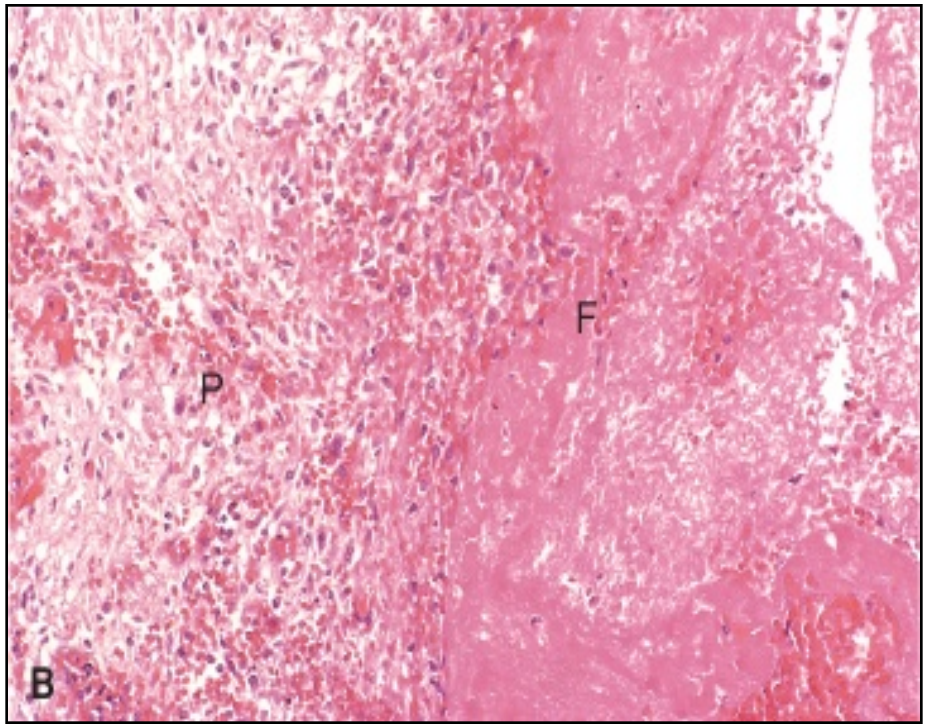


Recognize the different patterns of inflammation.

FIBRINOUS INFLAMMATION

- **A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura (larger molecules such as fibrinogen pass the vascular barrier)**
- **Fibrinous exudates may be removed by fibrinolysis,**
- **if not:** it may stimulate the ingrowth of granulation tissue (*organization*)

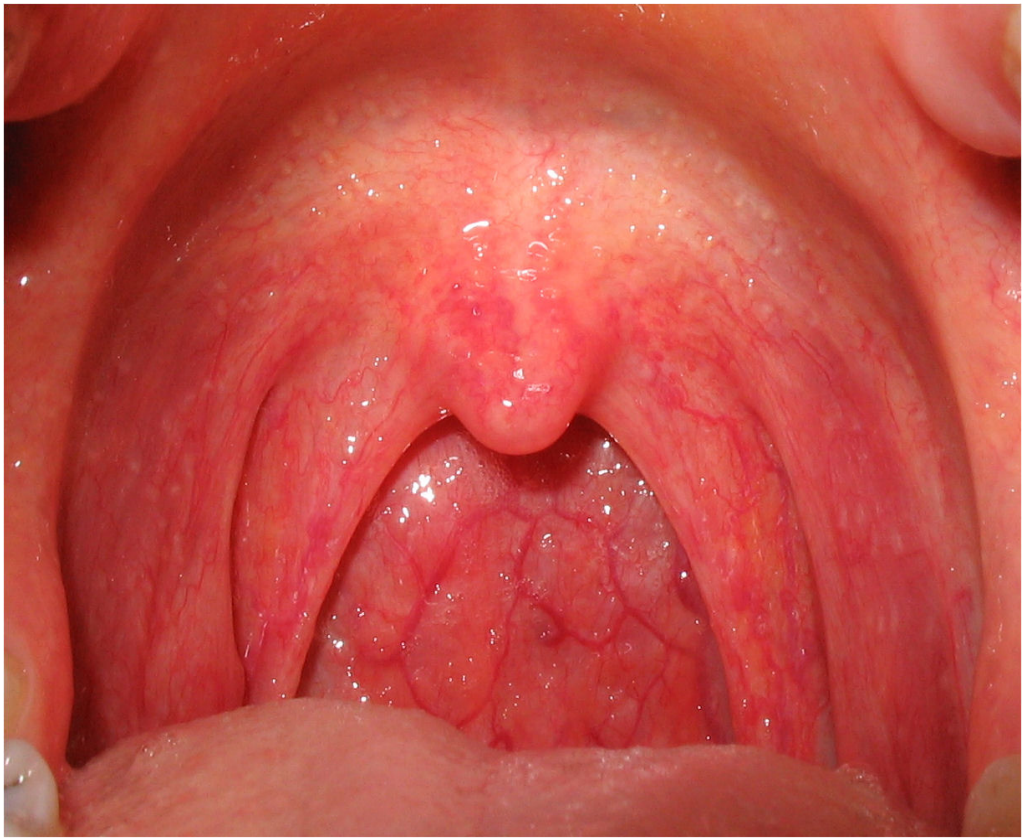




Recognize the different patterns of inflammation.

Catarrhal inflammation

- Inflammation affects mucosa-lined surfaces with the outpouring of **watery mucus**



Recognize the different patterns of inflammation.

SUPPURATIVE OR PURULENT INFLAMMATION

characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid caused by pyogenic (pus-producing) bacteria

Recognize the different patterns of inflammation.

Suppurative abscess

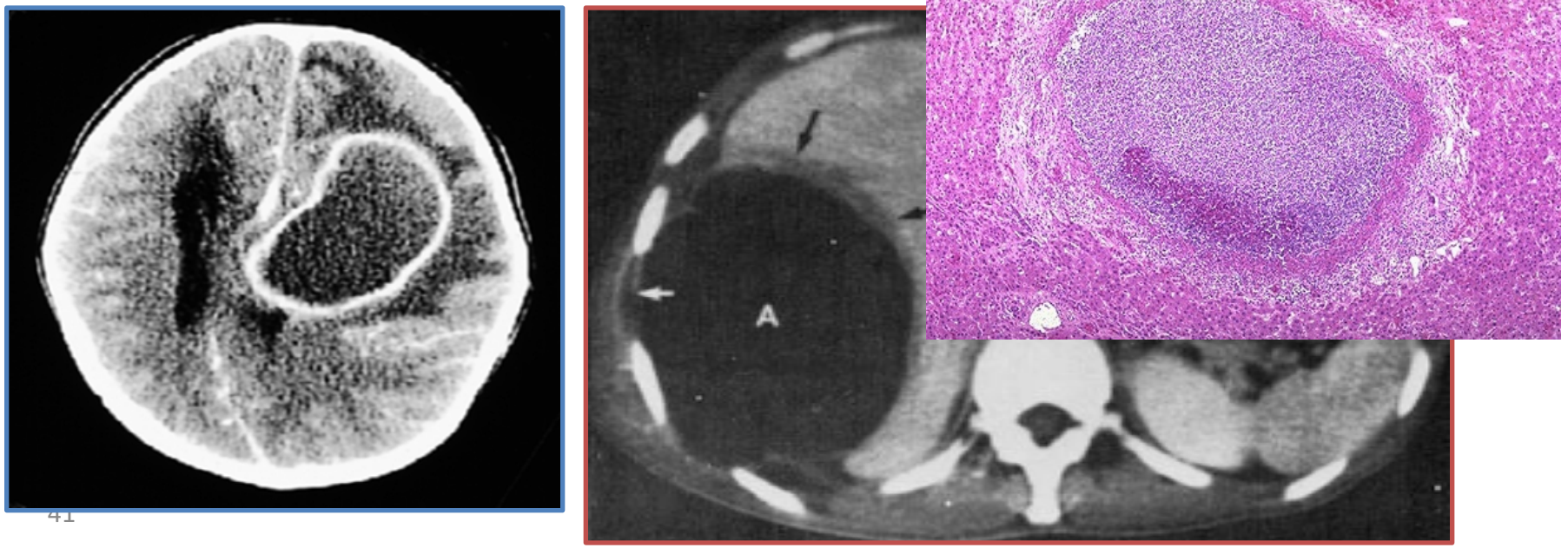
- An abscess is a cavity lined by granulation tissue and containing neutrophils, necrotic cells, bacteria and fibrinous material

Recognize the different patterns of inflammation.

Morphologic Patterns of Acute Inflammation

SUPPURATIVE OR PURULENT INFLAMMATION

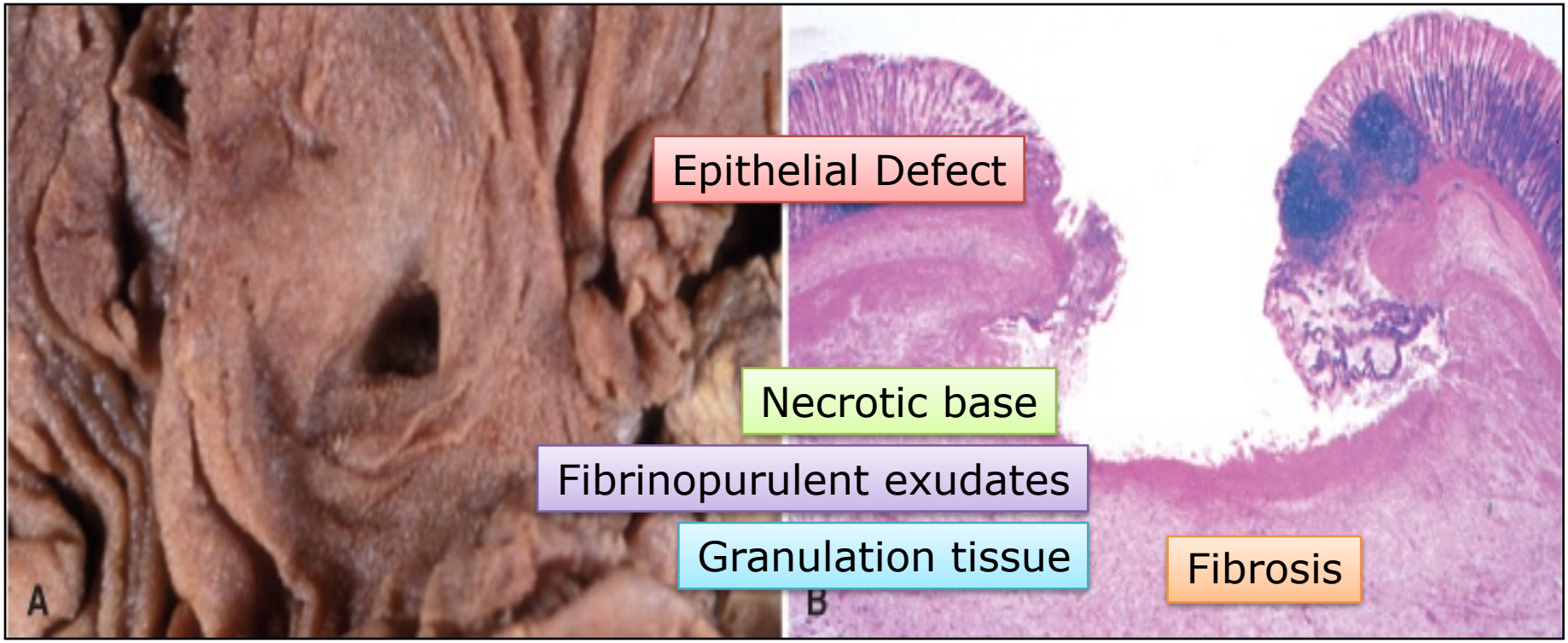
- **Abscesses : A localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space**



Recognize the different patterns of inflammation.

ULCERS

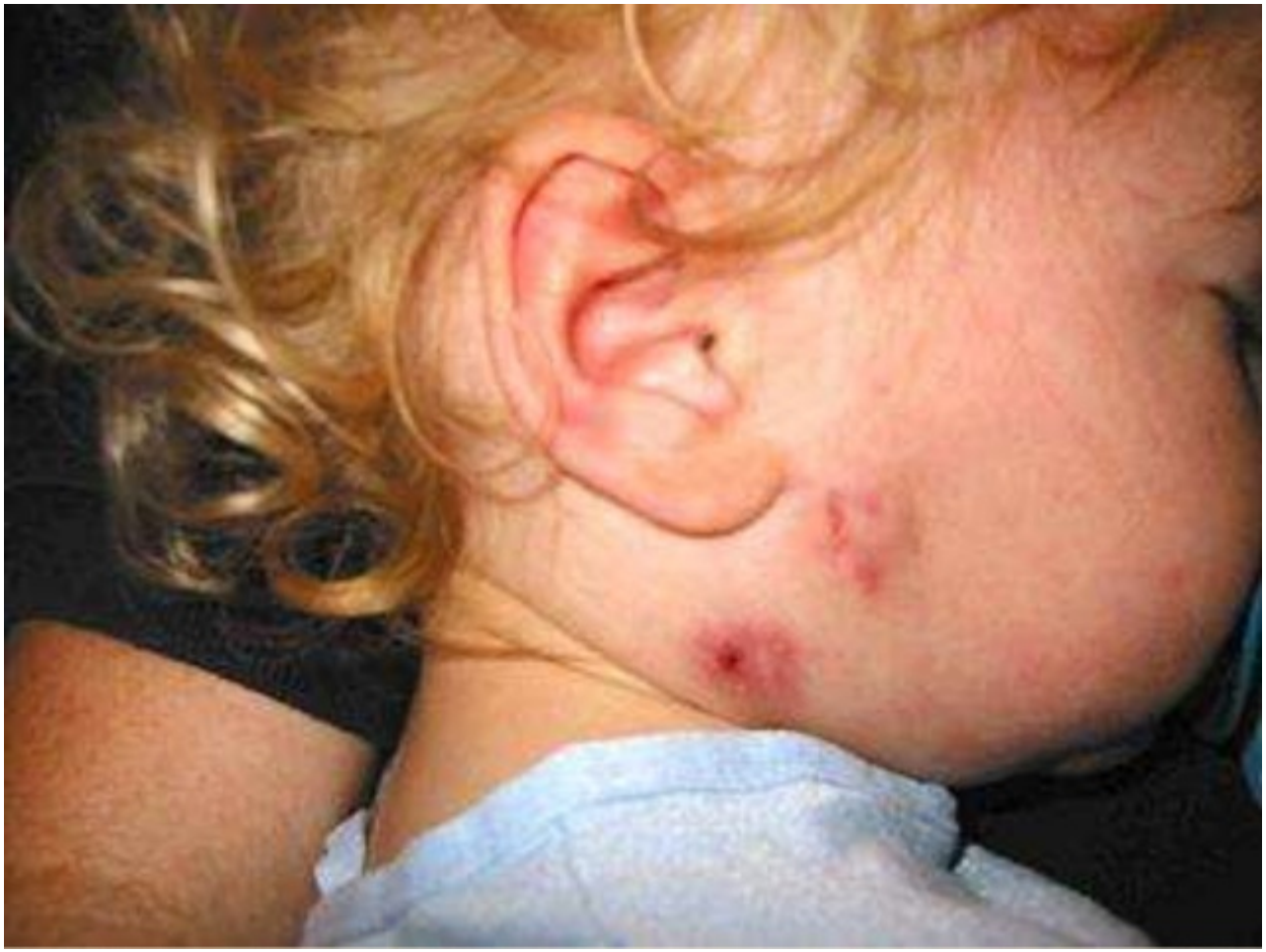
An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue



Recognize the different patterns of inflammation.

Sinus

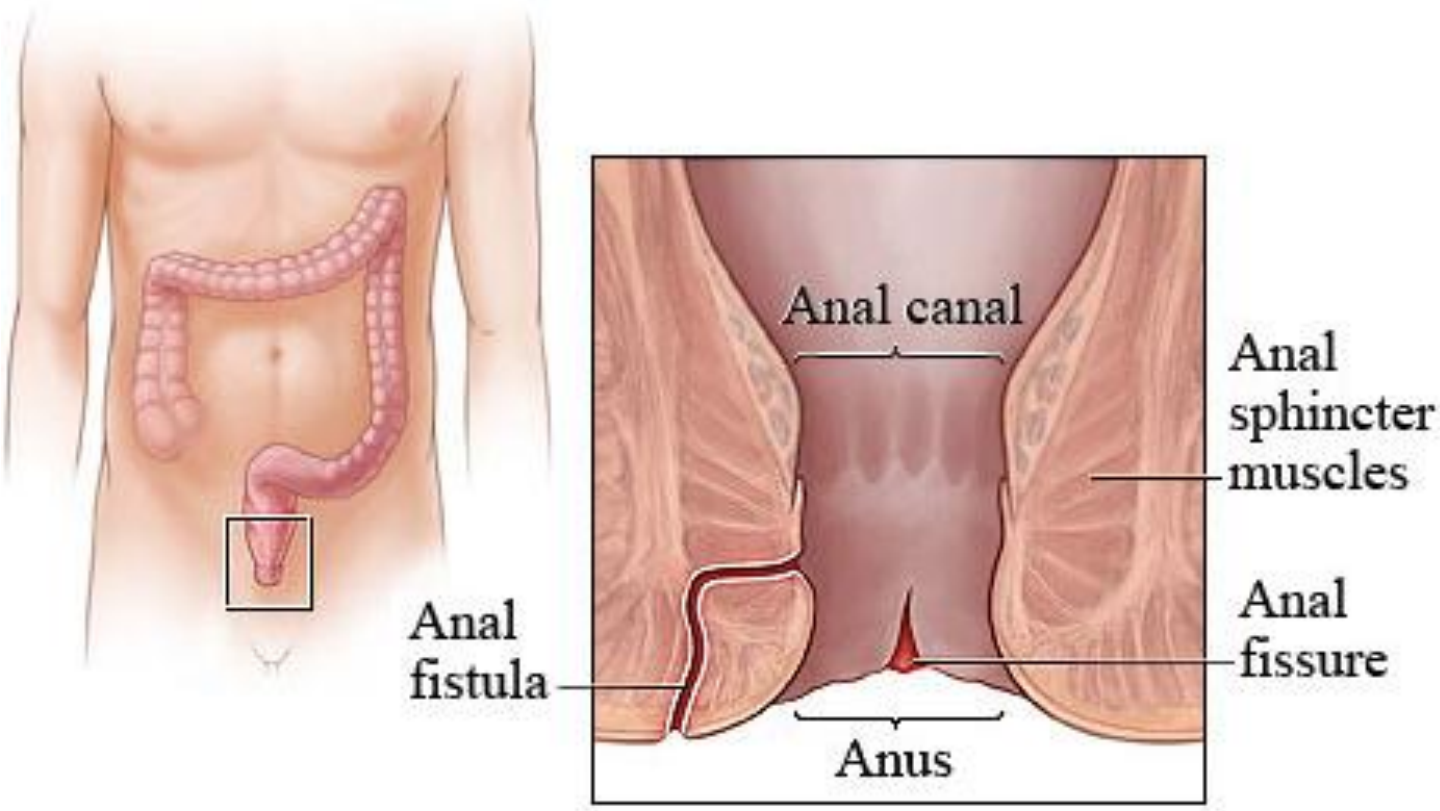
- A tract between the abscess and a surface.



Recognize the different patterns of inflammation.

Fistula

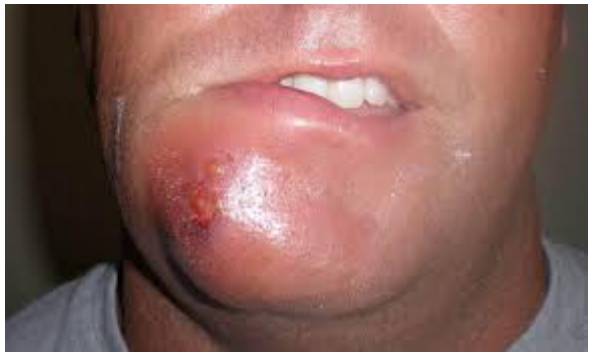
- A tract between two surfaces.

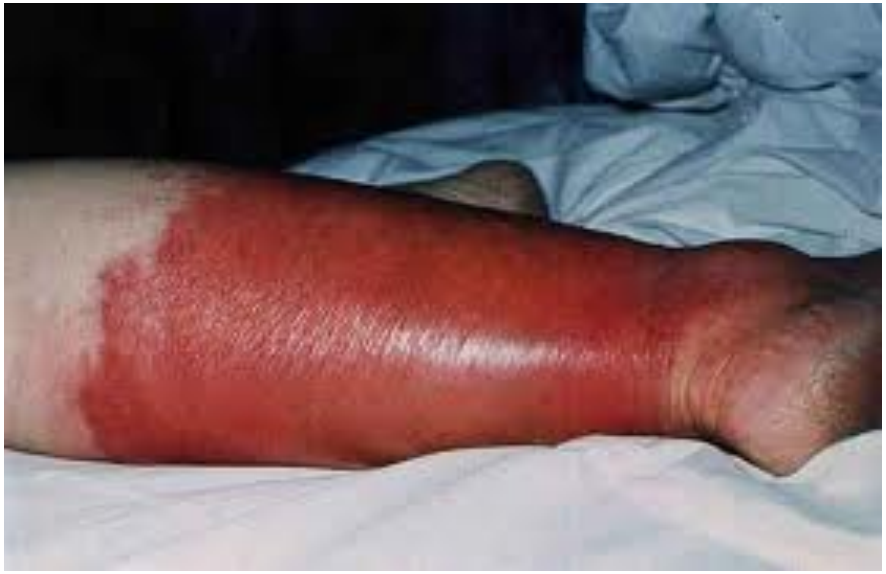


Recognize the different patterns of inflammation.

Cellulitis

- denotes a spreading of acute inflammation through interstitial tissues.





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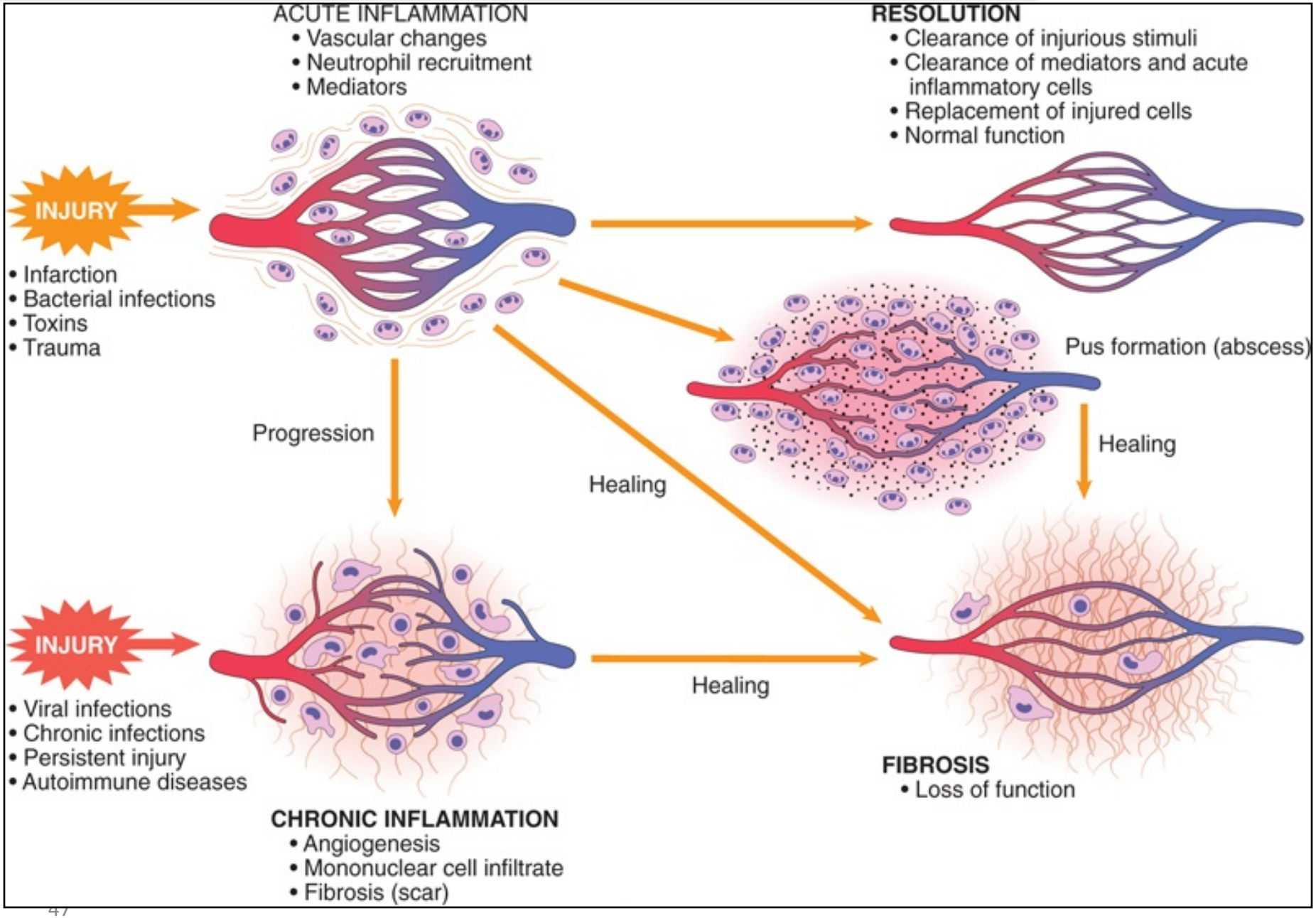


List and describe the outcome of acute inflammation.

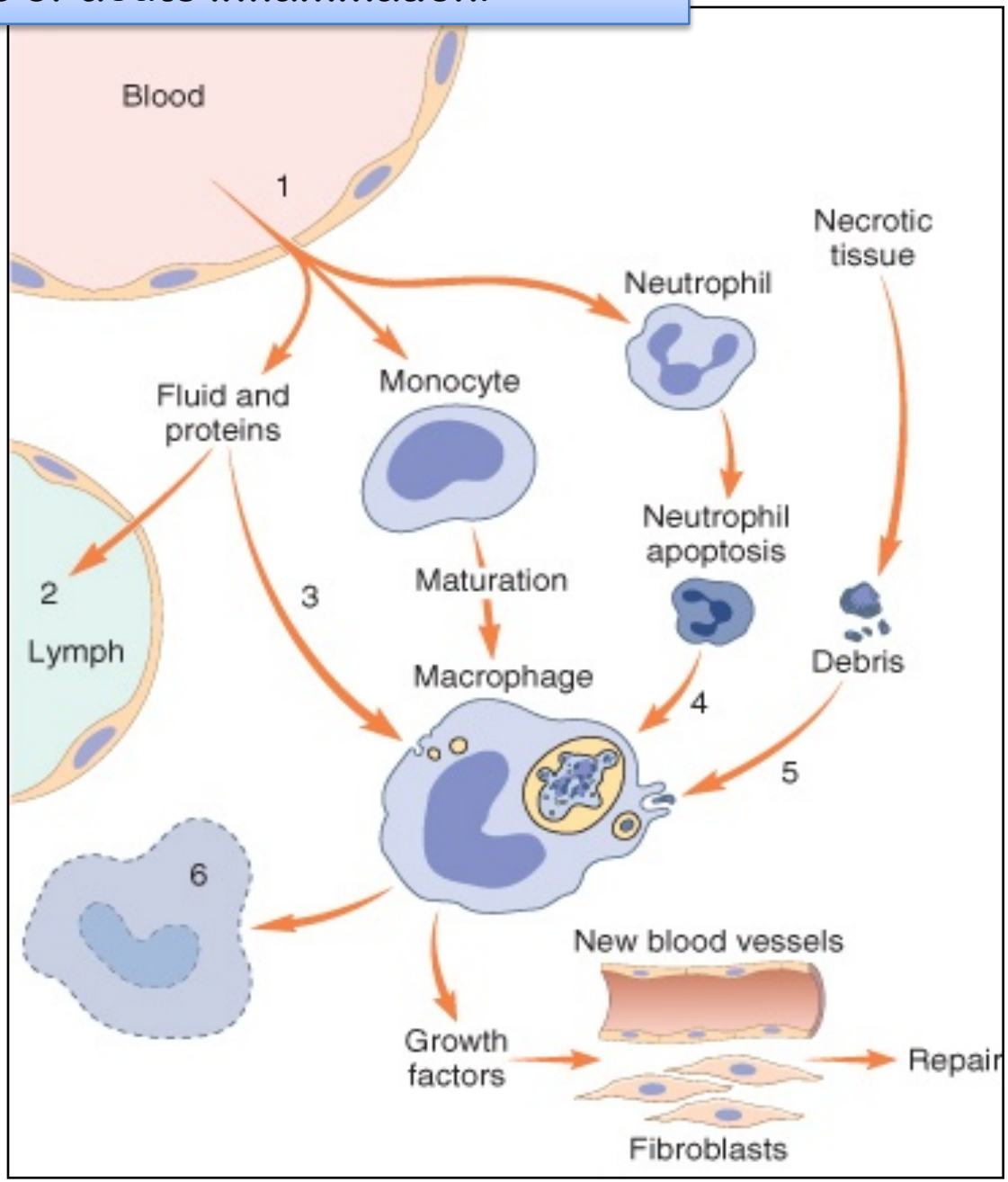
Outcomes of Acute Inflammation

- Acute inflammation may have one of the four outcomes:
  - *Complete resolution*
  - *Healing by connective tissue replacement (fibrosis)*
  - *Progression of the tissue response to chronic inflammation*
  - *Abscess formation*

List and describe the outcome of acute inflammation.

Events in the resolution of inflammation

- This involves neutralization, decay, or enzymatic degradation of the various chemical mediators; normalization of vascular permeability; and cessation of leukocyte emigration and apoptosis
- The necrotic debris, edema fluid, and inflammatory cells are cleared by phagocytes and lymphatic drainage
- Lymph node become enlarged and inflamed



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