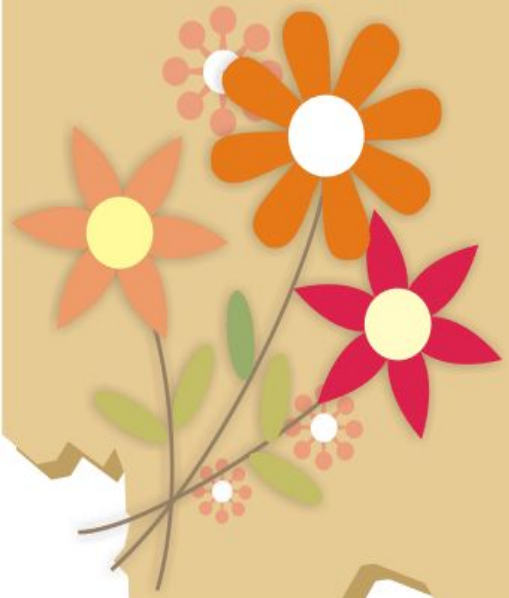
INFLAMMATION

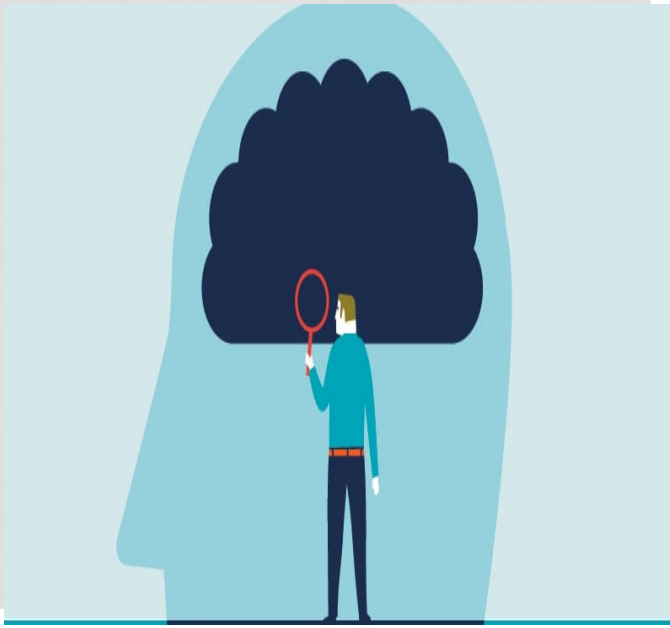
Dr. Dina Saleh

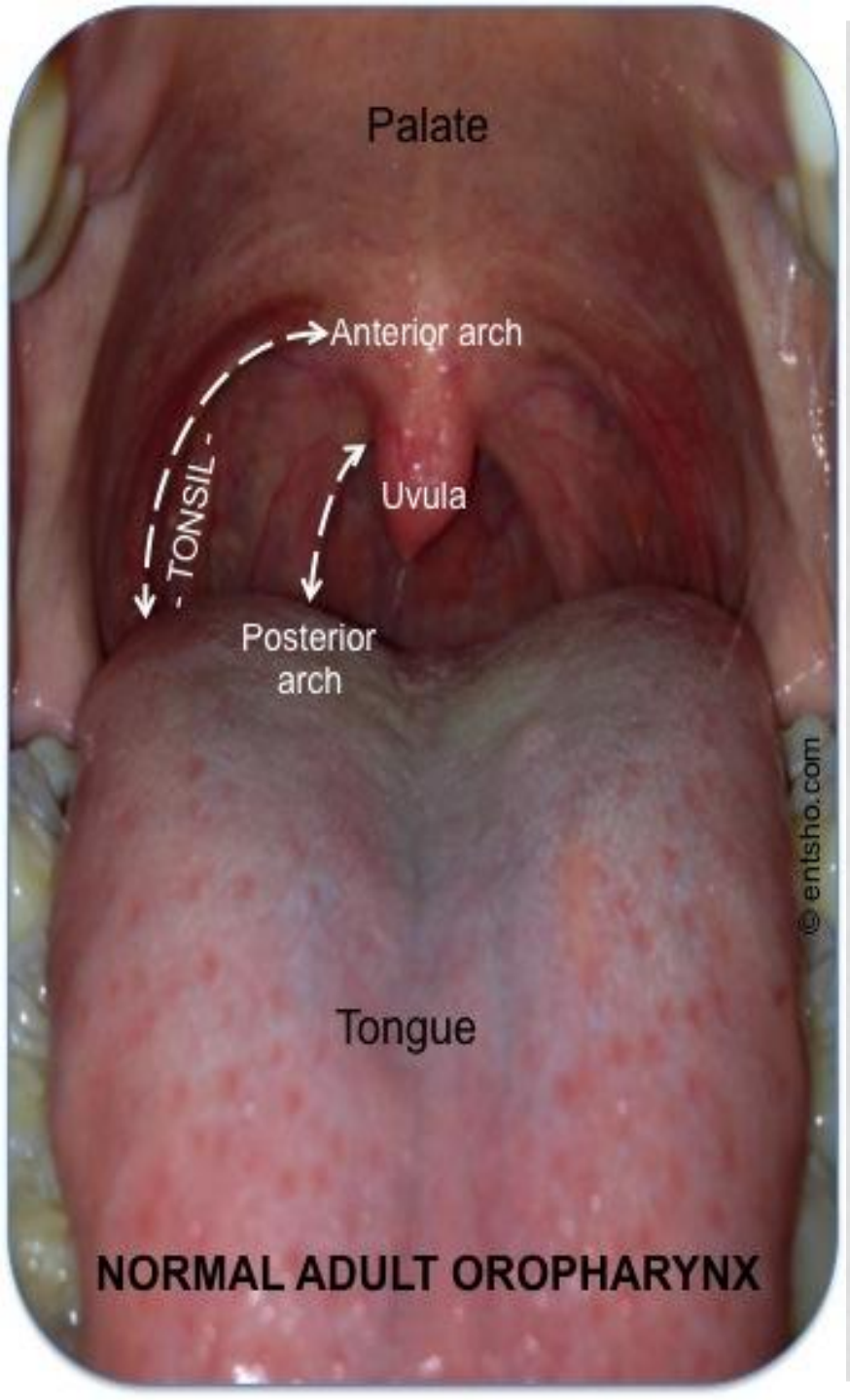


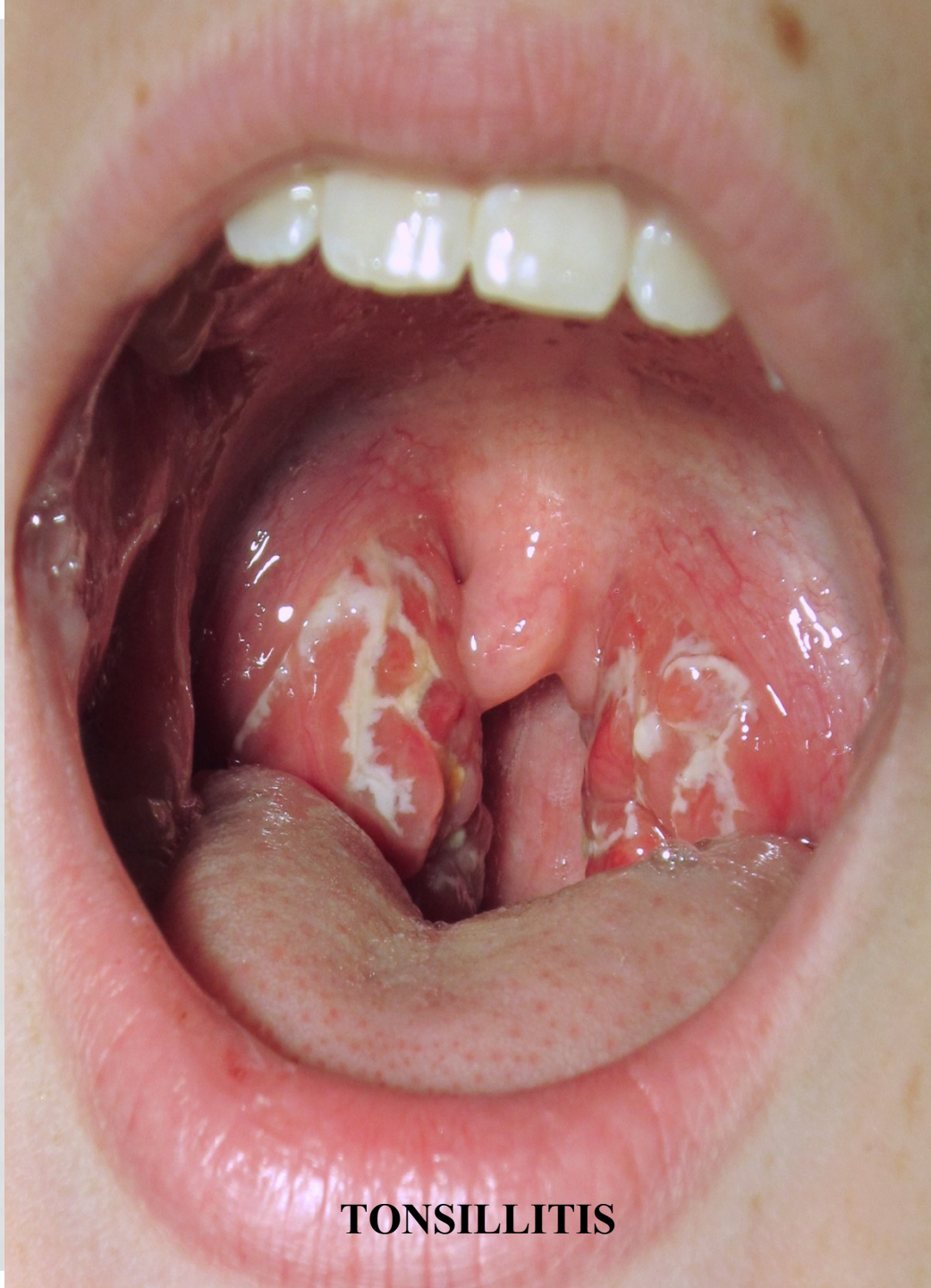
- Define Inflammation.
- Recognize the cardinal signs of inflammation
- Compare between acute & chronic inflammation.
- Describe the sequence of vascular changes in acute inflammation & their purpose.
- List cells & molecules that plays important roles in inflammation
- Recognize morphological patterns of acute inflammation.
- Describe systemic manifestation of acute inflammation.

A clinical study of patients with tonsillar infections is performed. The most typical clinical course averages 3 days from the time of onset until the patient sees physician. Most of these patients experience fever & chills. On physical examination, the most common findings include swelling, erythema, and tonsillar purulent exudate. Which of the following changes did these patients most likely have?

a. **Granulomatous inflammation**
b. **Acute inflammation**
c. **Chronic inflammation**
d. **Necrosis**







TONSILLITIS


What is
Inflammation?

INFLAMMATION

- Inflammation is a protective response of living, vascularized tissues to eliminate the cause of cell injury, and to initiate the process of repair.
- It is induced by chemical mediators that are produced by host cells in response to injurious stimuli.
- Inflammation normally is controlled and self-limited .

- Although inflammation helps clear infections and other noxious stimuli, can themselves cause considerable harm.(*How ??)
- Therefore, injury may accompany entirely normal inflammatory reaction, and the damage may even become the dominant feature if the reaction is very strong, prolonged or inappropriate .

Types of inflammation

According to the defense capacity of the host and duration of response, inflammation can be classified into

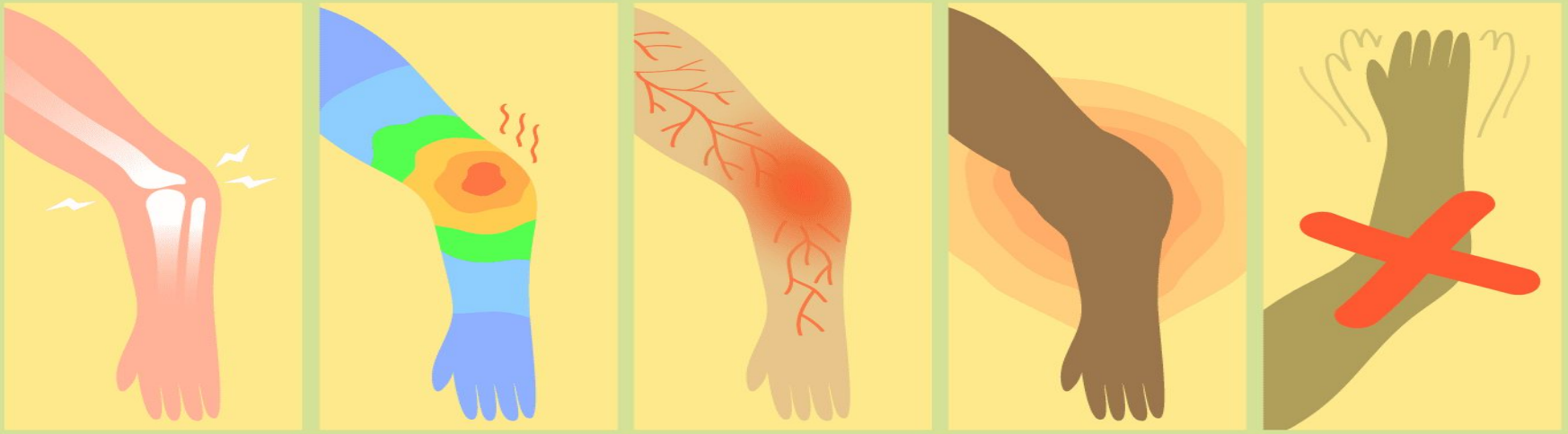
Acute inflammation.1

Chronic inflammation.2

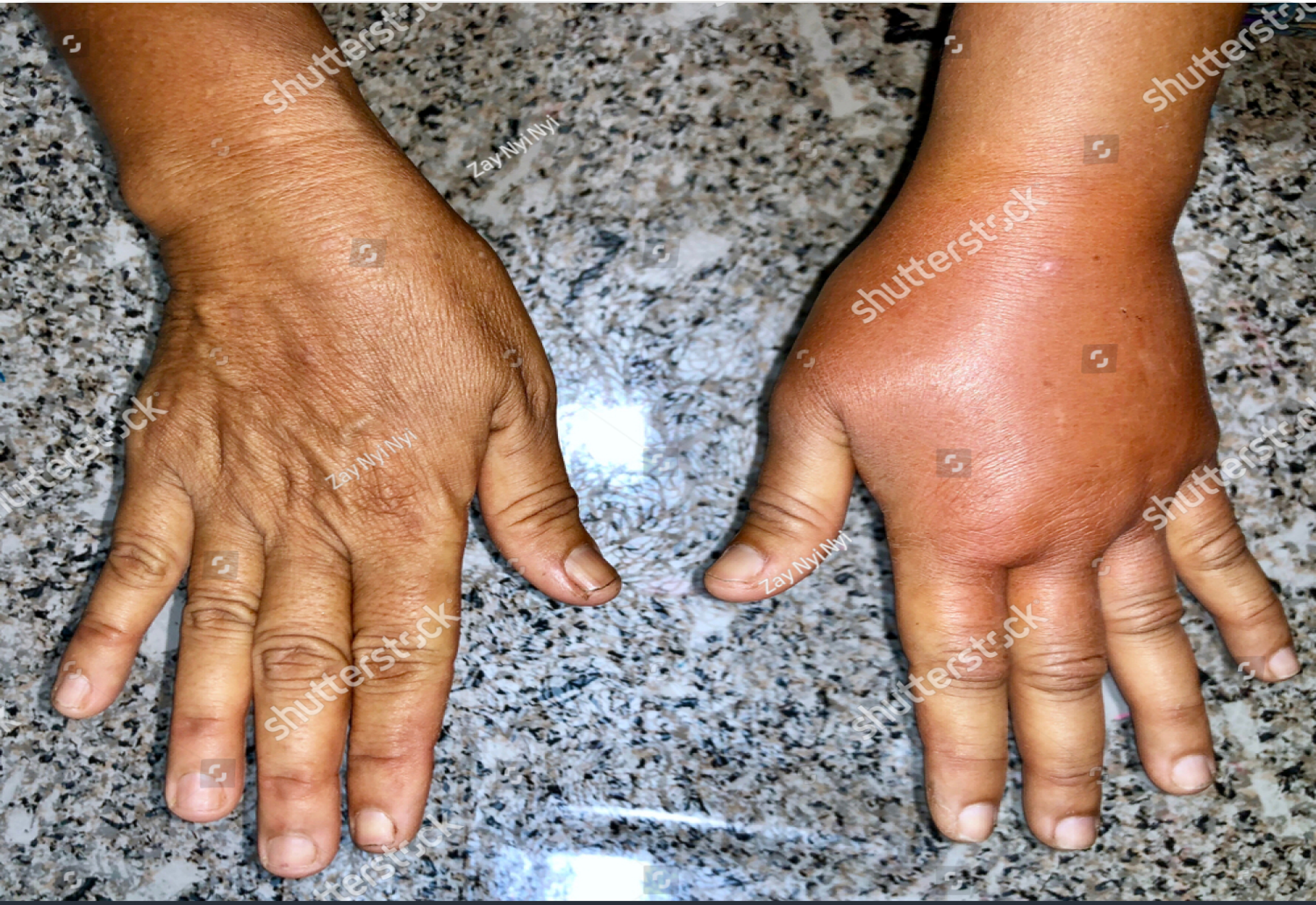
Acute versus chronic inflammation

feature	acute	chronic
onset	Fast: Minutes to hours	Slow: days
cells	neutrophils	Lymphocytes & macrophages
Tissue injury and fibrosis	Mild and self limited	Severe, progressive
Local and systemic signs	prominent	May be subtle

5 Cardinal Signs of Inflammation



verywell



- In general, steps of inflammatory response can be remembered as the 5Rs ;

Recognition of the injurious agent
Recruitment of leukocytes
Removal of the agent
Regulation (control) of the response
Resolution (repair)

Recognition of microbes , necrotic cells and foreign substances

- Phagocytes, Dendritic cells , Epithelial cells and many other cells ,express receptors that are designed to sense the presence of infectious pathogens and substances released from dead cells.
- These receptors are called " pattern recognition receptors " ?*
- The two most important families of these receptors are:
  - **Toll like receptors (TLRs);** recognize products of bacteria , viruses and other pathogens. TLRs are located in plasma membranes and endosomes, so they are able to detect extracellular and ingested pathogens.
  - **Inflammasome** is a multi-protein cytoplasmic complex that recognizes products of dead cells, such as uric acid and extracellular ATP, as well as crystals .

Innate vs. Adaptive

First line of germ defense

Second layer germ defense



Skin Gut Mucous

Lymphatic system: lymph nodes, spleen, thymus, etc.

Fast acting

Slow to respond

White blood cells – neutrophils and macrophages

White blood cells – B and T cells. Create **antibodies** for "repeat" offenders

Response is nontargeted and broad acting

Antibodies act against specific targets

No memory of germs killed in the past

Antibodies remember and hold a grudge for "repeat" offenders

Components of Acute Inflammation

Vascular changes.1

There will be increase in blood flow

Aims to bring cells and proteins to the site of injury

Cellular events .2

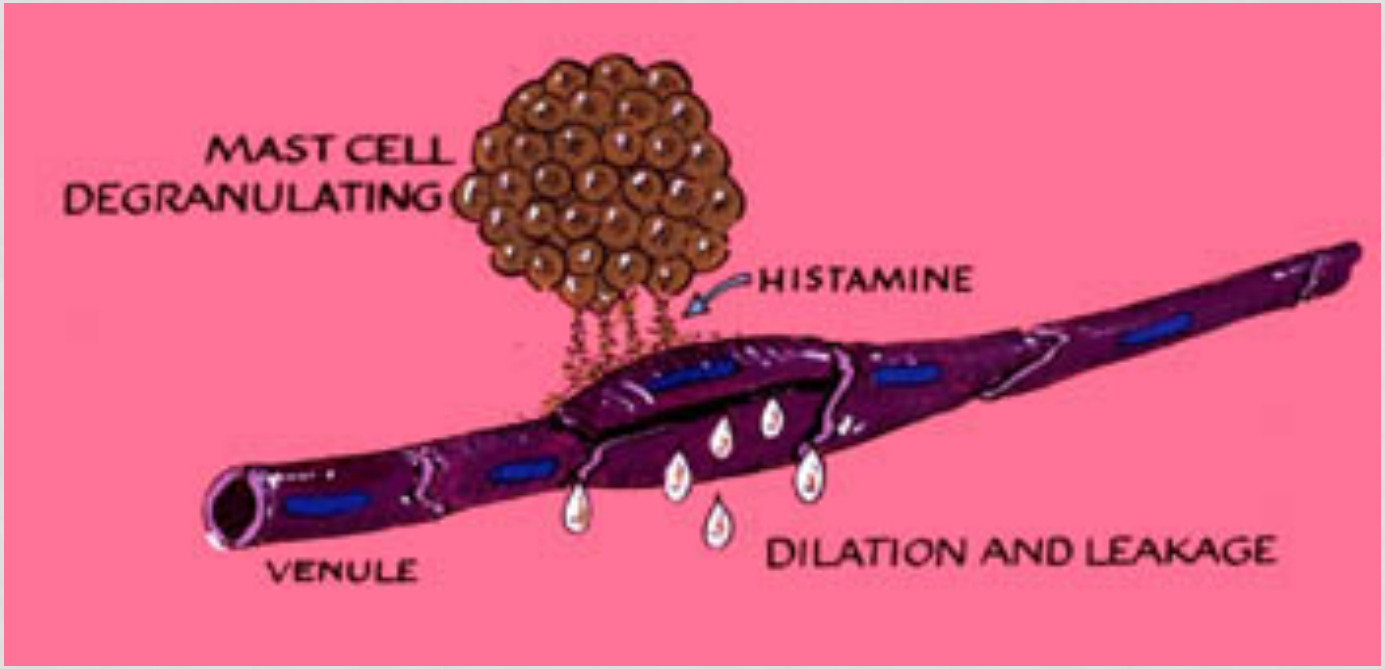
Recruitment of leukocytes

Aims to activate the leukocytes leading to the process of destruction of invaders

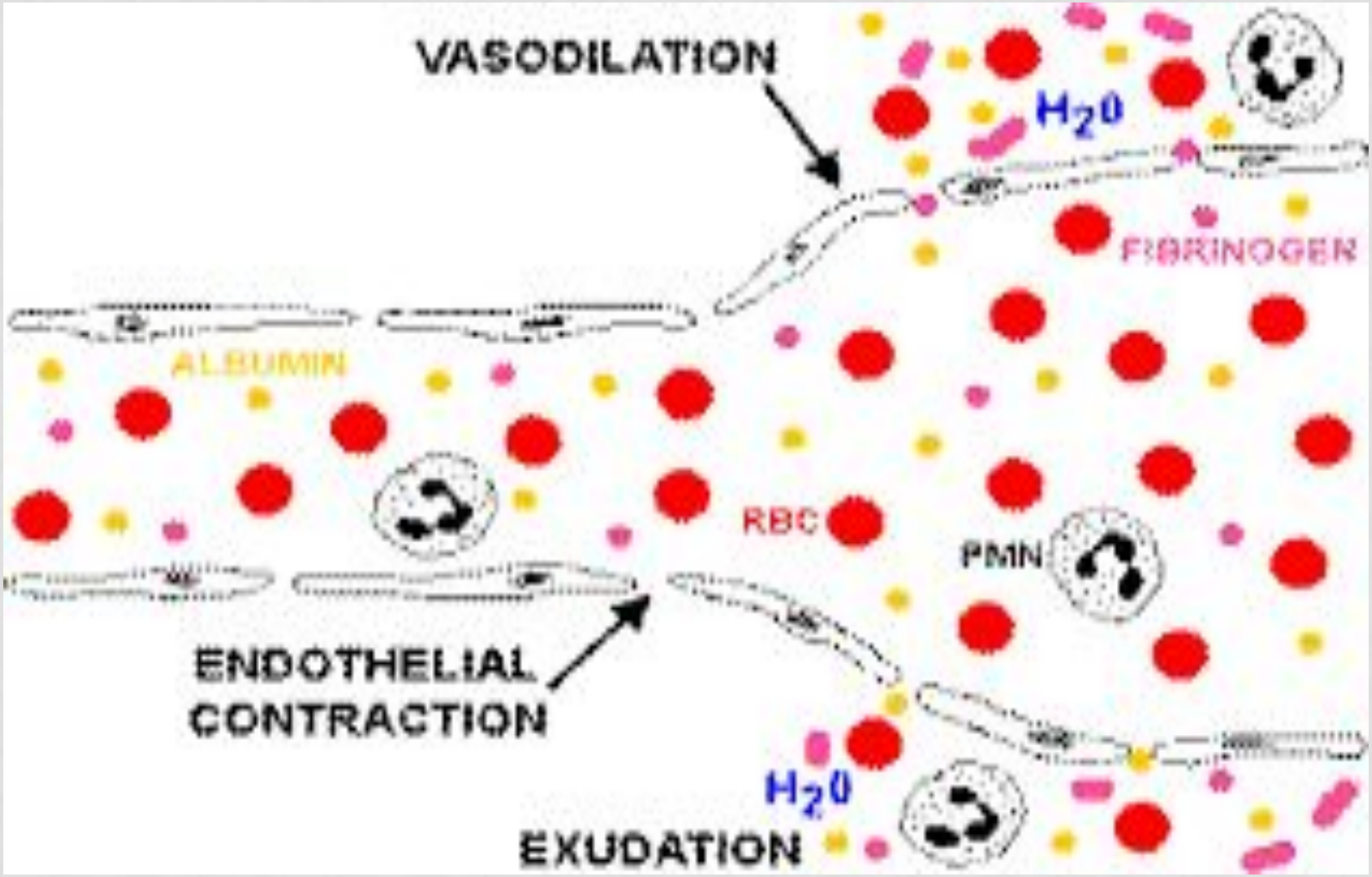
Vascular changes

a . Changes in vascular caliber and flow

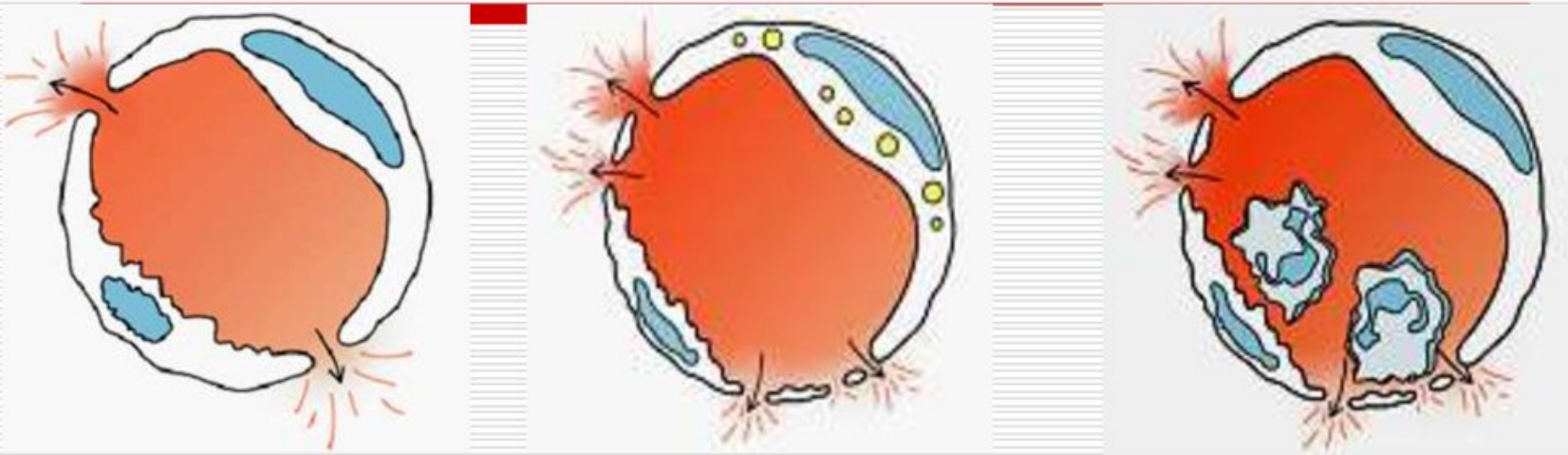
* Initial transient vasoconstriction.
*Massive vasodilation mediated by histamine.
*These changes explain the clinically noted heat and redness.



b. Increased Vascular Permeability



Increase of vascular permeability



Endothelial cells contraction

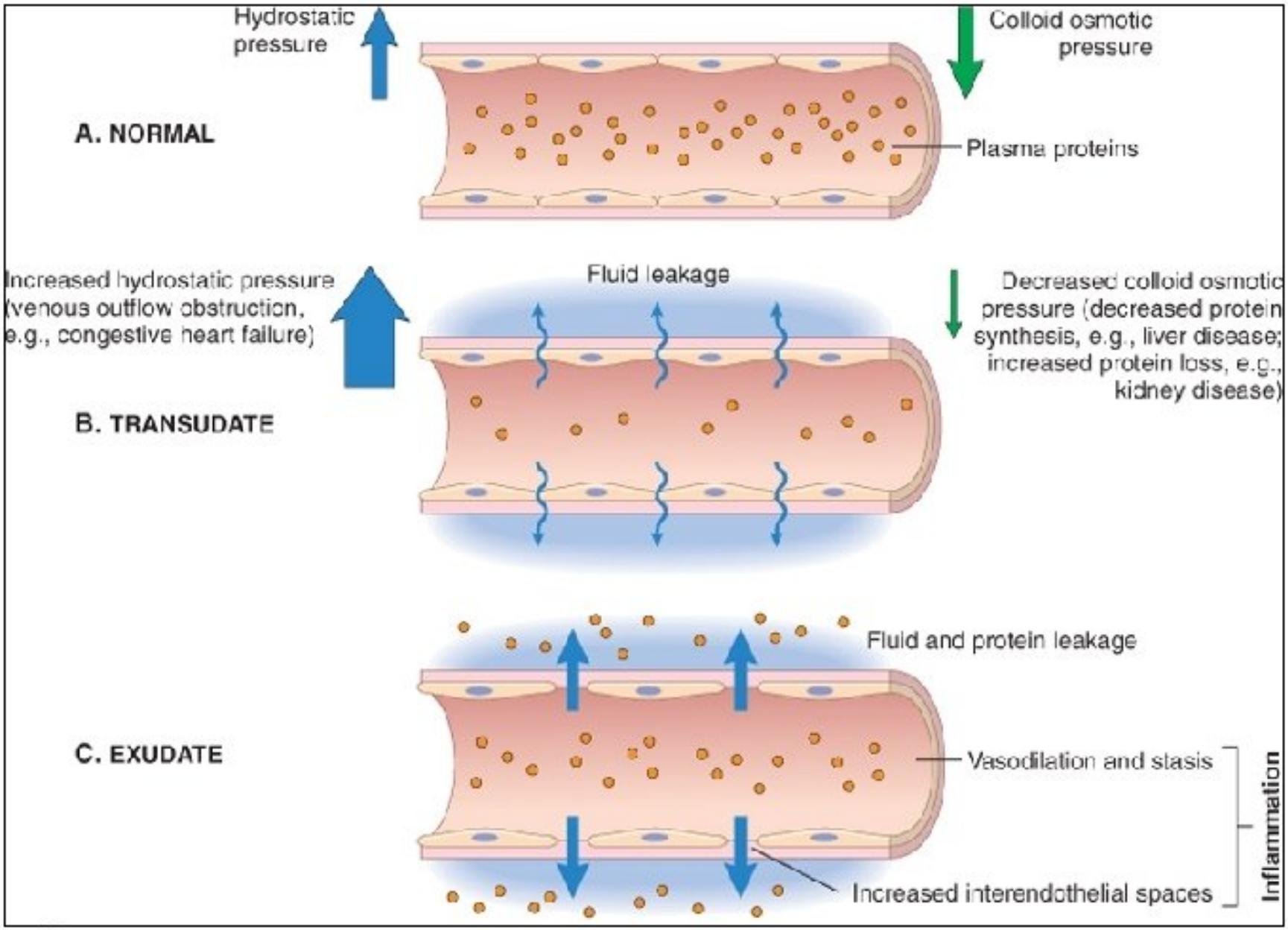
- **histamine, bradykinin**
- **occurs rapidly after exposure to mediator**
- **reversible**

Direct endothelial injury

- **severe non-specific injuries (burns or bacterial infection)**
- **leakage lasts until vessels are thrombosed or repaired**

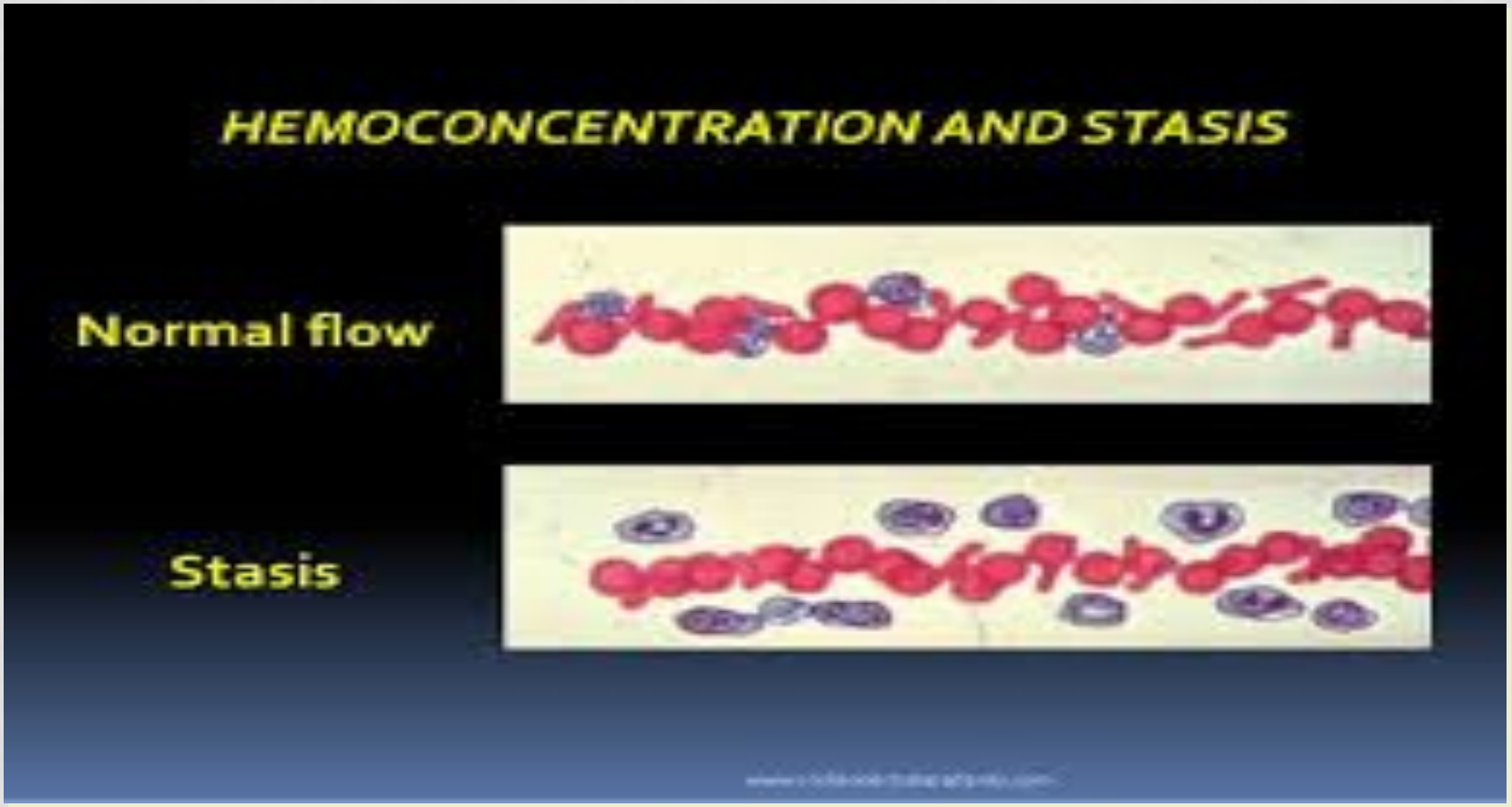
Leukocyte-dependent endothelial injury

- **toxic oxygen radicals and proteolytic enzymes**


Hydrostatic pressure
Colloid osmotic pressure
A. NORMAL
Plasma proteins
Increased hydrostatic pressure (venous outflow obstruction, e.g., congestive heart failure)
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis, e.g., liver disease; increased protein loss, e.g., kidney disease)
B. TRANSUDATE
Fluid and protein leakage
C. EXUDATE
Vasodilation and stasis
Increased interendothelial spaces
Inflammation

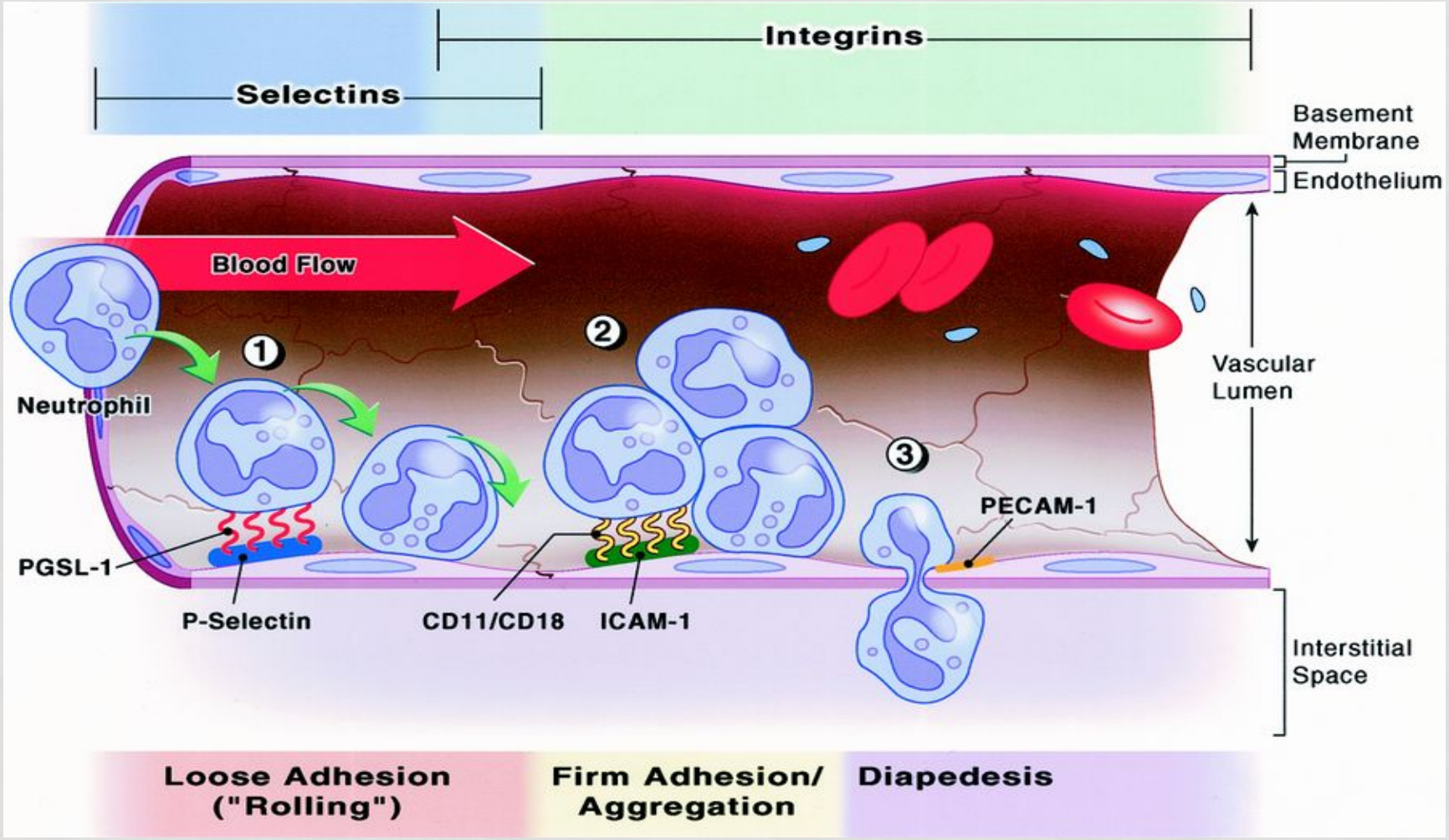
Increased permeability leads to:-

- Edema
- Stasis → Margination



Cellular events

a. Leukocyte recruitment



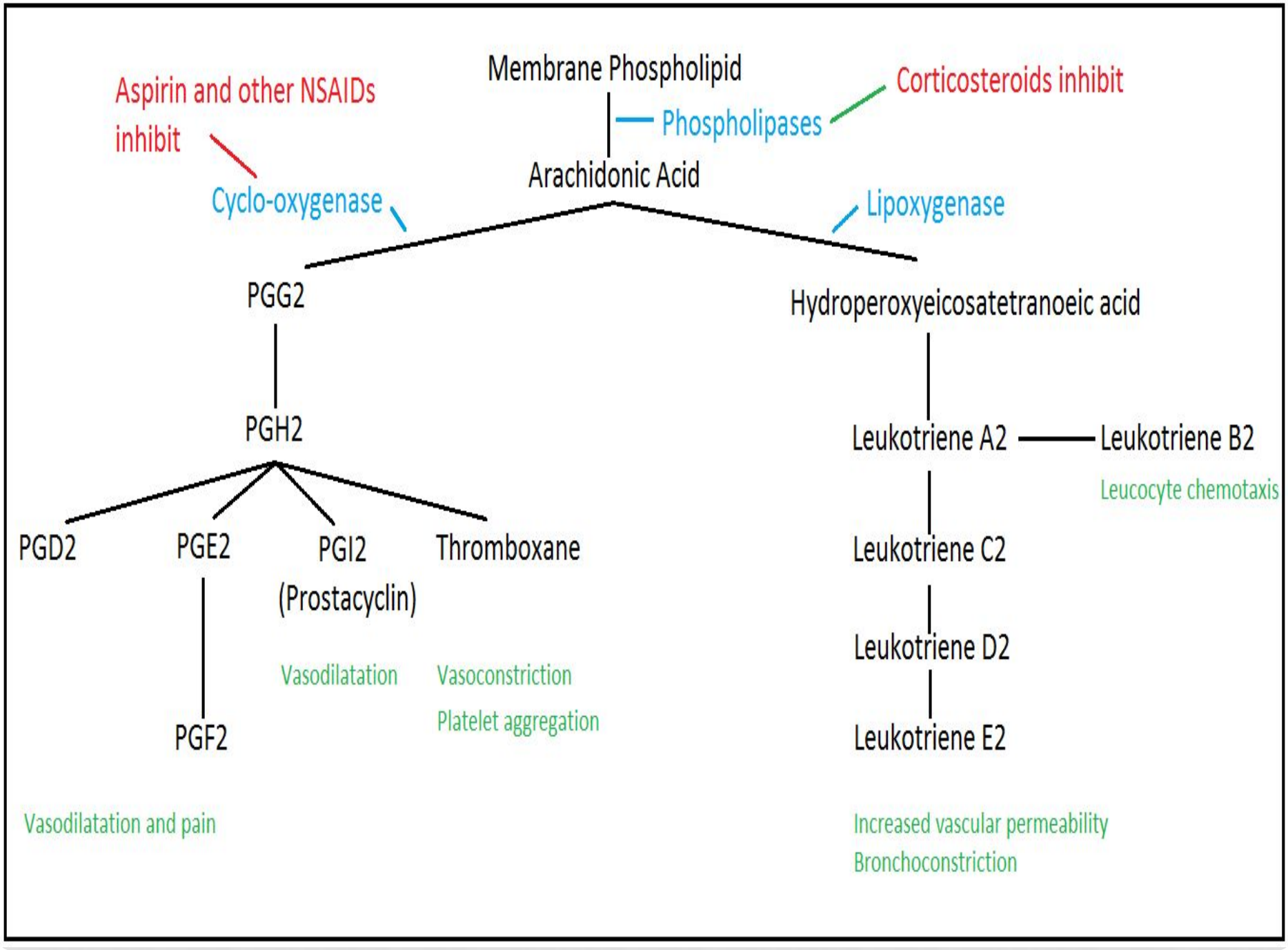
Defects in adhesion can be seen in :

- Diabetes mellitus
- Corticosteroid use
- Acute alcohol intoxication
- Leukocyte adhesion deficiency (autosomal recessive condition with recurrent bacterial infection & delay in umbilical cord sloughing

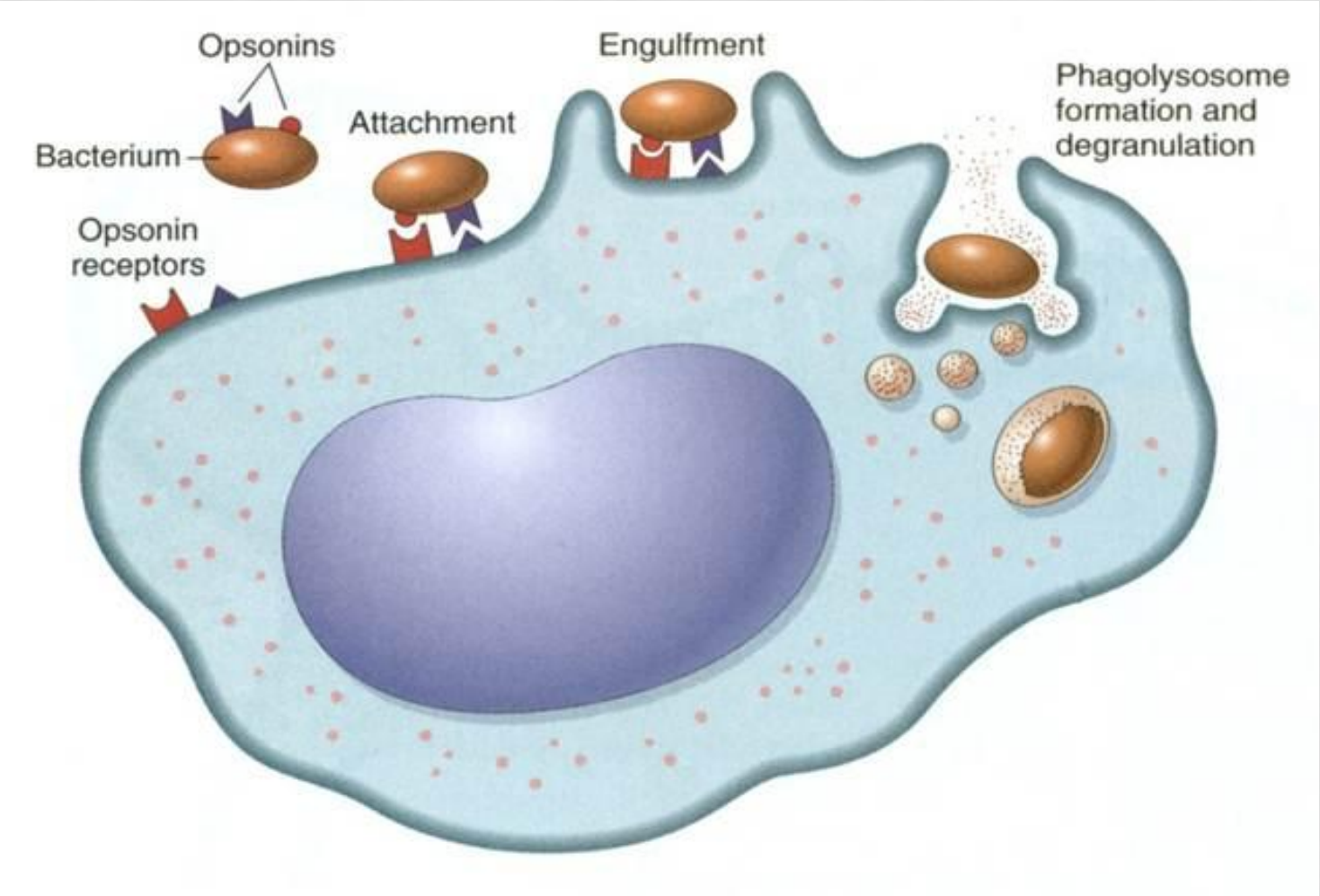
:b. Leukocyte activation

Induction of a number of responses within leukocytes, which are mediated by microbes, products of necrotic cells, antigen-antibody complexes, and cytokines. **The activation of leukocytes is reflected functionally as follows:**

1. Production of arachidonic acid (AA) metabolites
2. Secretion of lysosomal enzymes and other microbicidal substances
3. Activation of macrophages: through the release of IFN-γ
4. Activation of phagocytosis through stimulation of opsonins-receptors.


Membrane Phospholipid
Aspirin and other NSAIDs inhibit
Phospholipases
Corticosteroids inhibit
Arachidonic Acid
Cyclo-oxygenase
Lipoxygenase
PGG2
Hydroperoxyeicosatetranoeic acid
PGH2
Leukotriene A2
Leukotriene B2
Leucocyte chemotaxis
PGD2
PGE2
PGI2
(Prostacyclin)
Thromboxane
Leukotriene C2
Vasodilatation
Vasoconstriction
Platelet aggregation
Leukotriene D2
PGF2
Leukotriene E2
Vasodilatation and pain
Increased vascular permeability
Bronchoconstriction

Phagocytosis

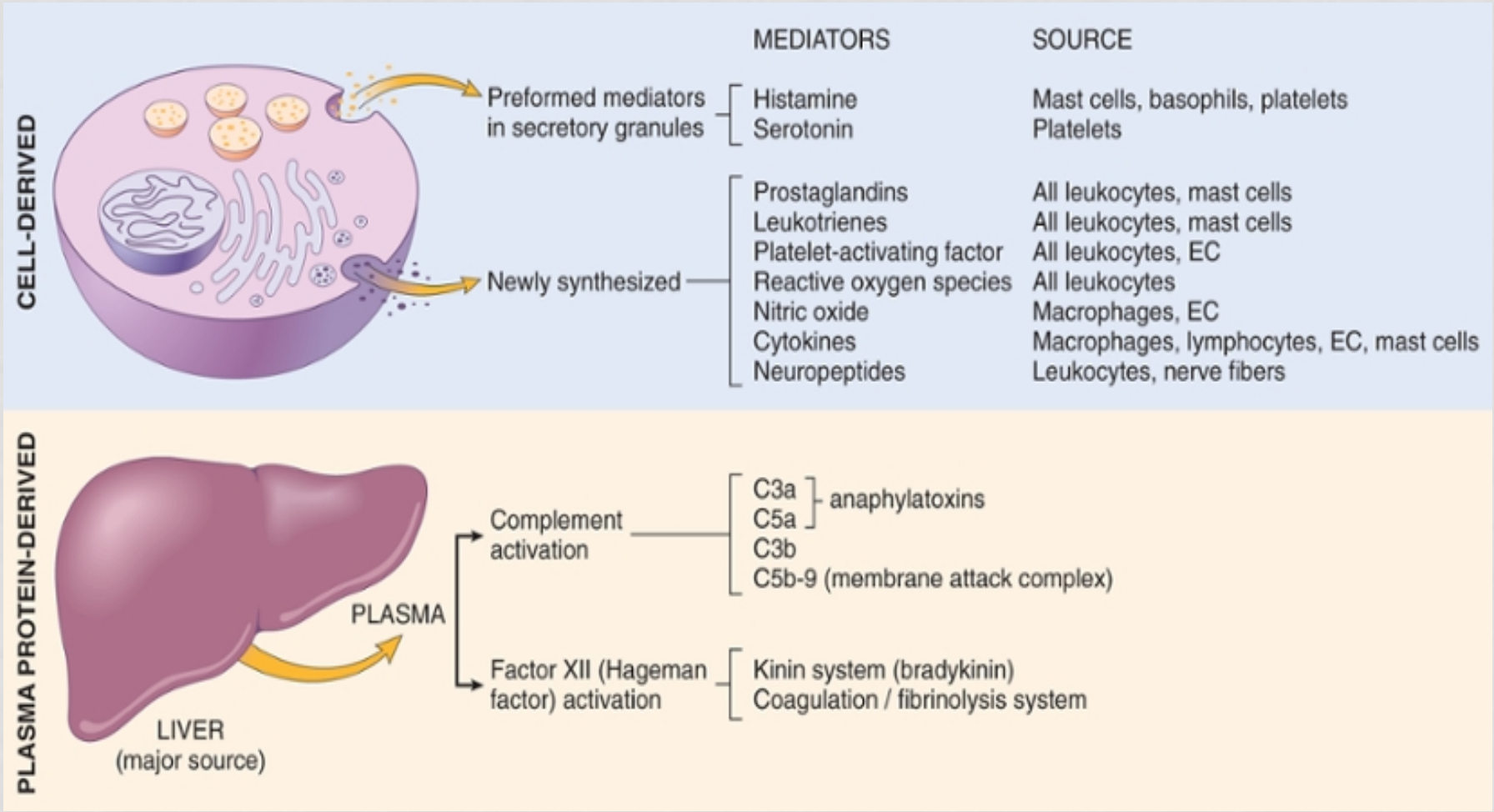


**The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of stimulus. In most forms of acute inflammation, neutrophils predominate during the first 6 to 24 hours, and then are replaced by monocytes in 24 to 48 hours.

** There are, however, exceptions to this pattern of cellular exudation :

- Pseudomonas organisms—**neutrophils** predominate over 2 to 4 days
- Viral infections, **lymphocytes** may be the first cells to arrive
- Some hypersensitivity reactions and parasitic infestations, **eosinophils** may be the main cell type.

CHEMICAL MEDIATORS OF INFLAMMATION

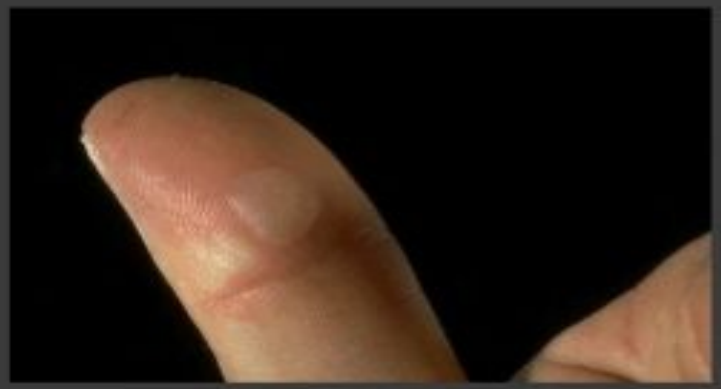


Role of mediators in different reactions of inflammation	
Histamine, PGs , NO	Vasodilation
Histamine, serotonin, ,substance P LTs C4, D4, E4 Bradykinin	Increased vascular permeability
C3a, C5a bacterial products, , LTB4, IL-1	Leukocyte recruitment and activation
IL-1, TNF, PGs	Fever
PGs& Bradykinin	Pain
Lysosomal enzymes, ROS, NO	Tissue damage

- The action of most mediators are tightly regulated; once activated and released from cells , mediators quickly **decay**(e.g. A.A. metabolites), are **inactivated by enzymes**(e.g. kininase inactivates bradykinin), are **eliminated**(e.g. antioxidants scavenge toxic oxygen metabolites) or are **inhibited**(complement regulatory proteins block complement activation).

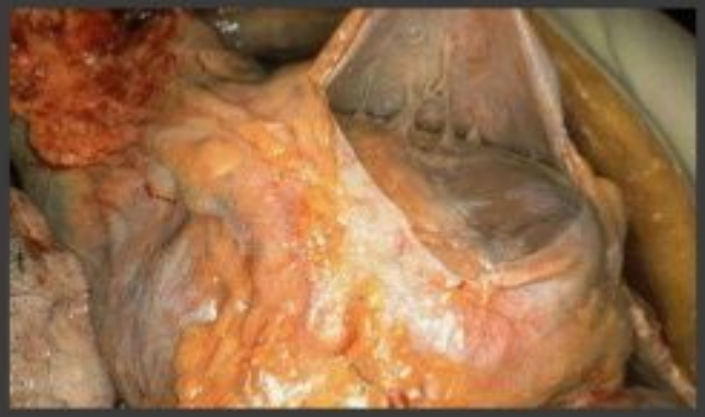
MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

Different morphological patterns of acute inflammation can be found depending on the cause and extend of injury and site of inflammation

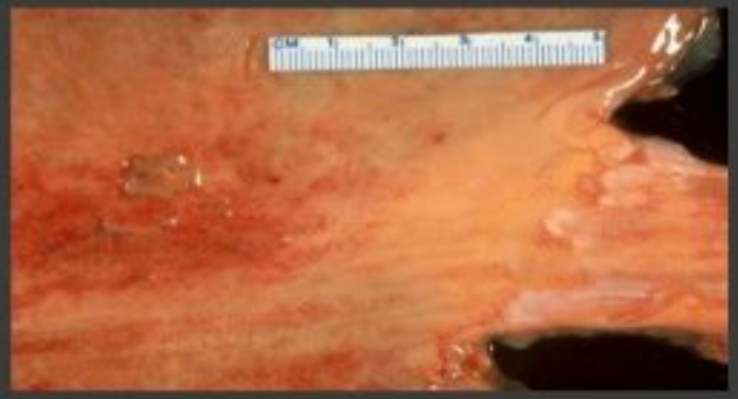


Serous inflammation

Purulent inflammation

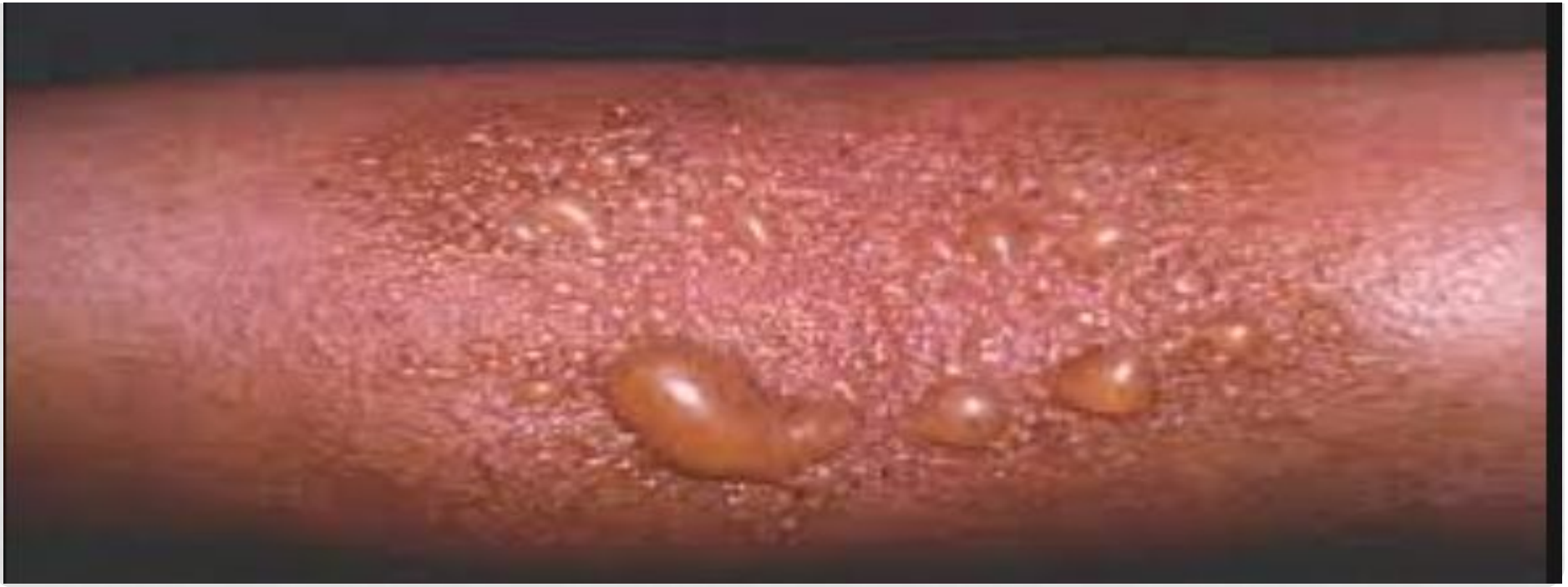


Fibrinous inflammation



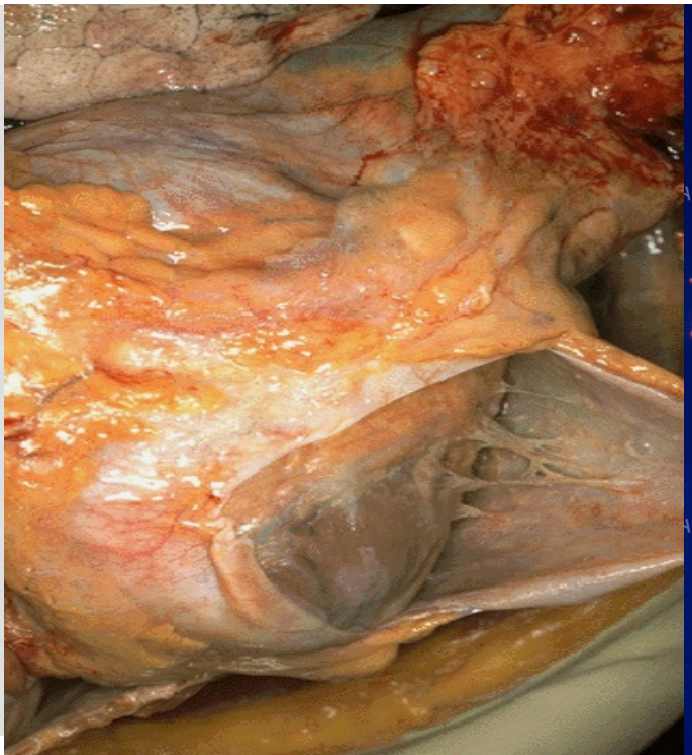
Ulcer

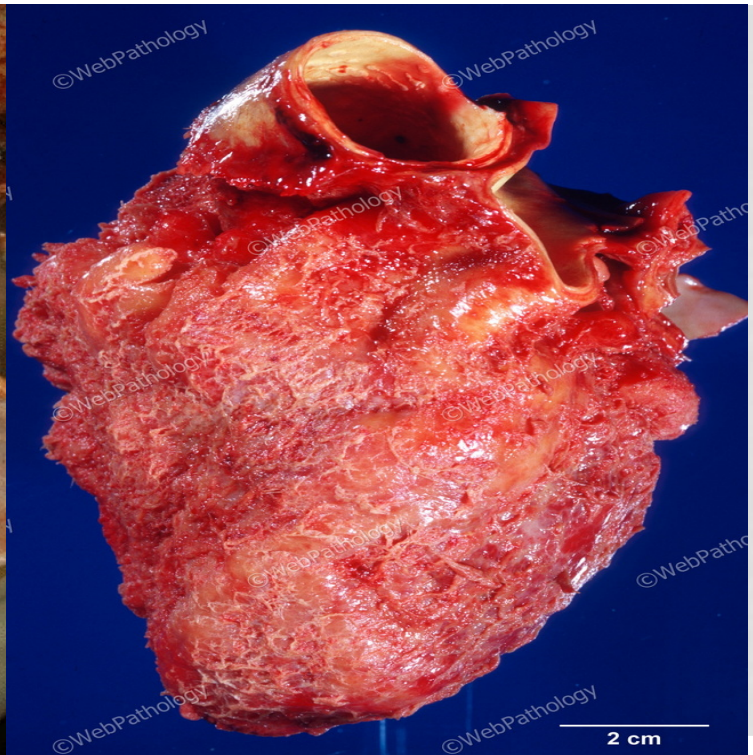
- **SEROUS INFLAMMATION** is marked by the outpouring of a thin fluid that may be derived from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. Accumulation of fluid in these cavities is called an *effusion*.



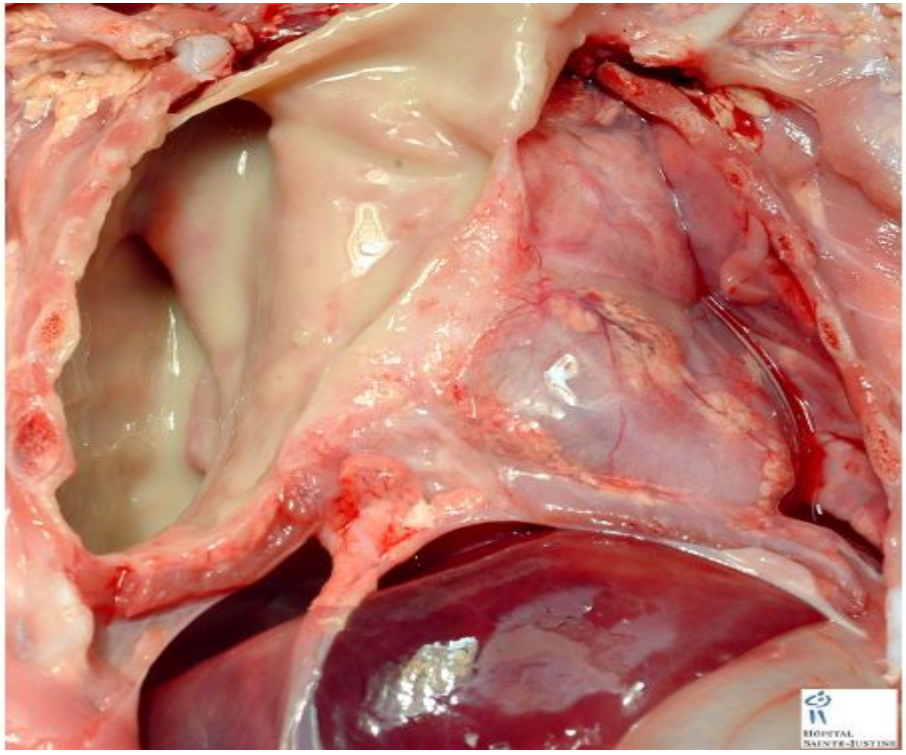
FIBRINOUS INFLAMMATION :

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.



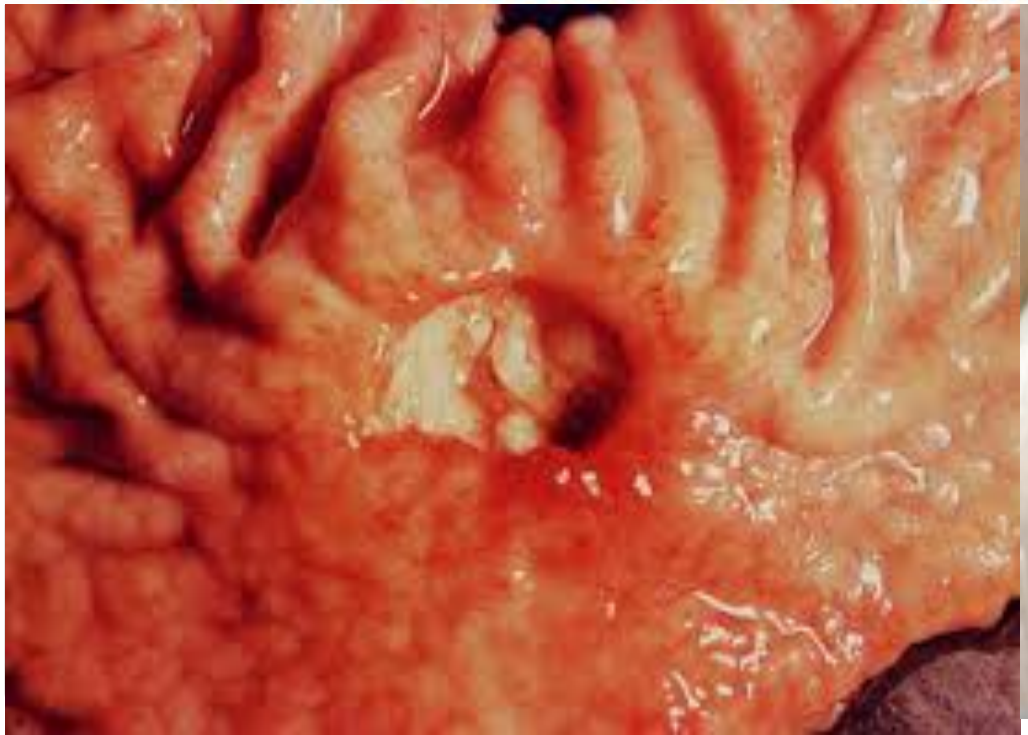


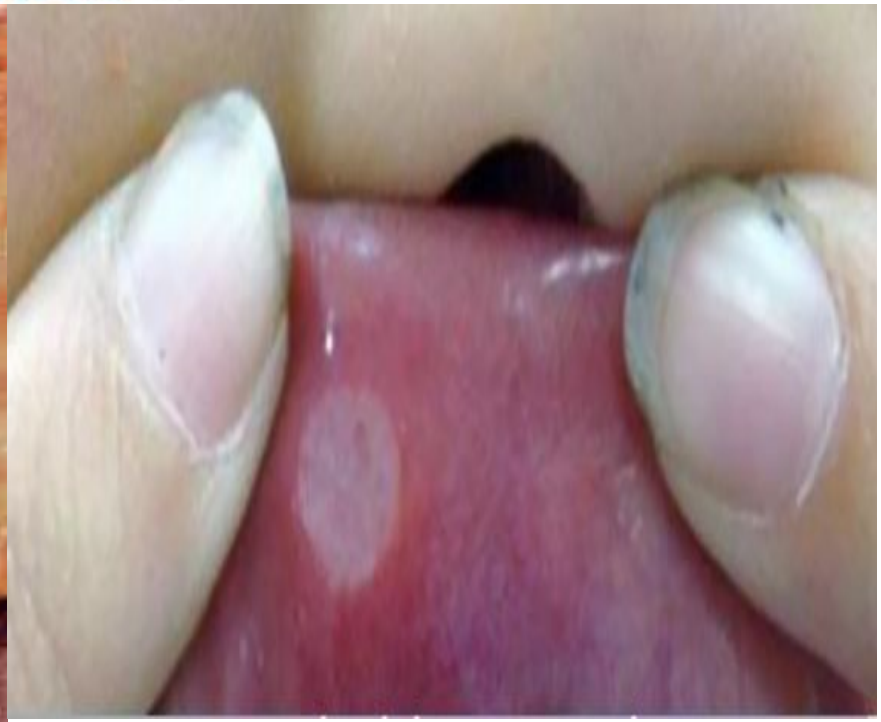
- **SUPPURATIVE / PURULENT INFLAMMATION** is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, liquefactive necrosis, and edema fluid.



- **ULCERATION** :

An ulcer is a local defect, or excavation, of the surface (epidermal or mucosal) of an organ or tissue that is produced by the sloughing of inflamed necrotic tissue .





Systemic effects of acute inflammation

(acute phase reaction)

Cytokines (TNF-a , IL-1 , and IL-6) are the most important mediators of acute phase reaction , which consist of :

1. **Fever (elevation by 1 to 4 C)**
2. **Elevated plasma levels of acute phase protein:**

- C- reactive protein (CRP)
- Fibrenogen
- Serum amyloid A (SAA)

3. Leukocytosis (up to 15000 or 20000 cells/ μl)

occurs initially because of accelerated release of cells from the bone marrow reserve pool (induced by cytokines, including IL-1 and TNF). Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of colony stimulating factors (CSFs).

4. Lymphangitis & lymphadenitis

- In inflammation lymph flow is increased and helps drain the edema fluid. The drainage may transport the offending agent.
- The lymphatics may become secondarily inflamed (**lymphangitis**), as may the draining lymph nodes (**lymphadenitis**).
- In severe infections, the lymph nodes may fail to halt the spread of infection. The organisms gain access to the circulation, thus inducing a **bacteremia**.
- The phagocytic cells of the liver, spleen, and BM constitute the next line of defense.
- In massive infections, bacteria seed distant tissues of the body. The **heart valves**, **meninges**, and **joints** are the favored sites for implantation, leading to ;endocarditis, meningitis, and septic arthritis.

5. Shock : Occur in severe tissue injury or severe bacterial infections which stimulate the production of enormous quantities of cytokines (TNF) leading to :

- Profuse systemic vasodilation and increased vascular permeability which result in hypotension and shock.
- Activation of coagulation pathway leading to DIC?** .

6. Other manifestations of acute phase reaction include

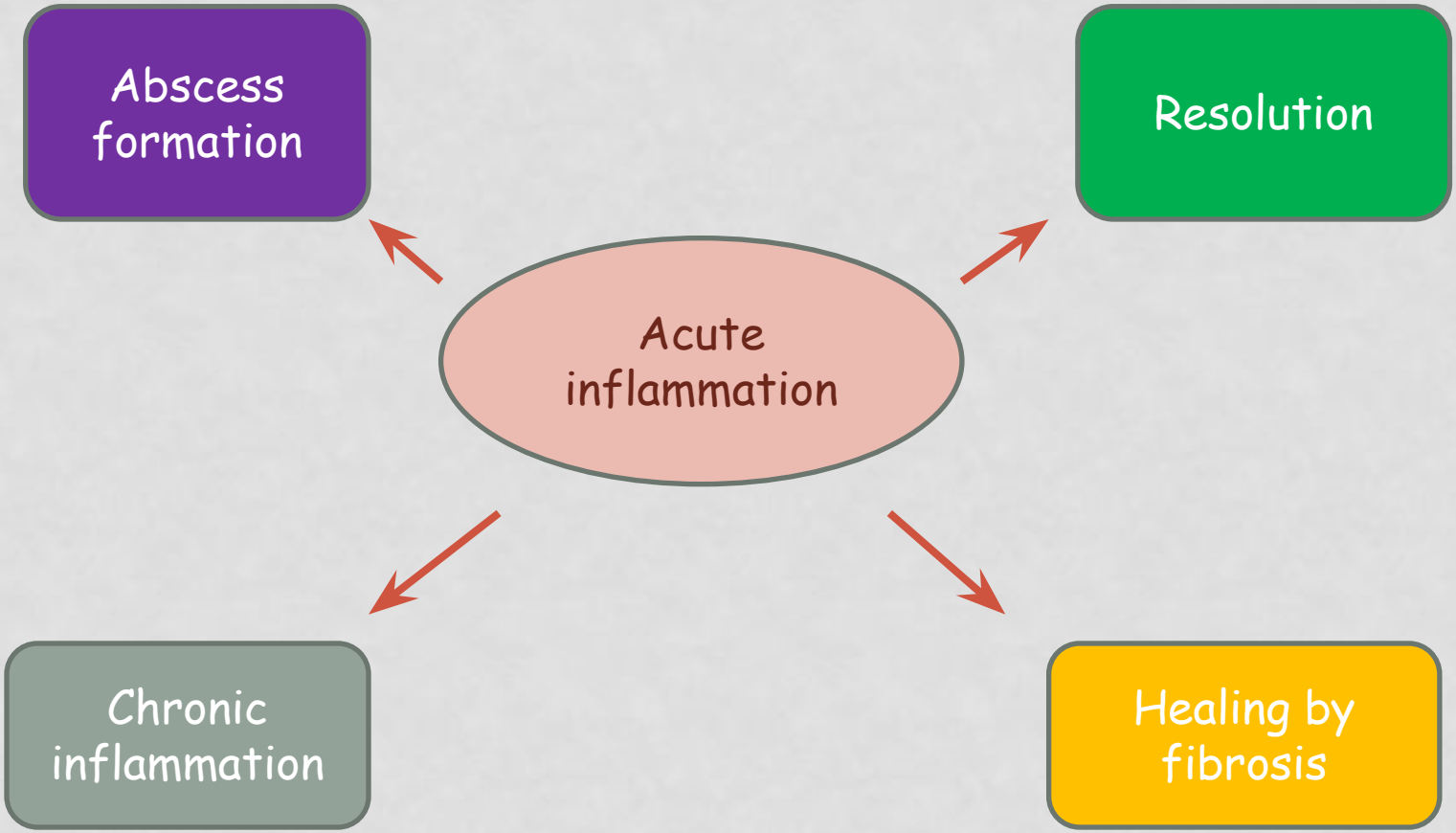
- Increased HR , BP .
-Rigors (shivering) , chills (the perception of being cold) .
-anorexia , drowsiness and malaise .

Anti-inflammatory mechanisms

Inflammatory reactions subsides because many of the mediators are short-lived and are destroyed by degradative enzymes. In addition, there are several mechanisms that counteract inflammatory mediators such as:

- Lipoxins & complement regulatory proteins.
- Activated MQs secrete IL-10 which down-regulate the responses of activated MQs (negative feedback loop).
- TGF-B mediator of fibrosis in tissue repair after inflammation.

OUTCOME OF ACUTE INFLAMMATION




THANK
YOU!