CHS 2413
Pathology and Physiopathology

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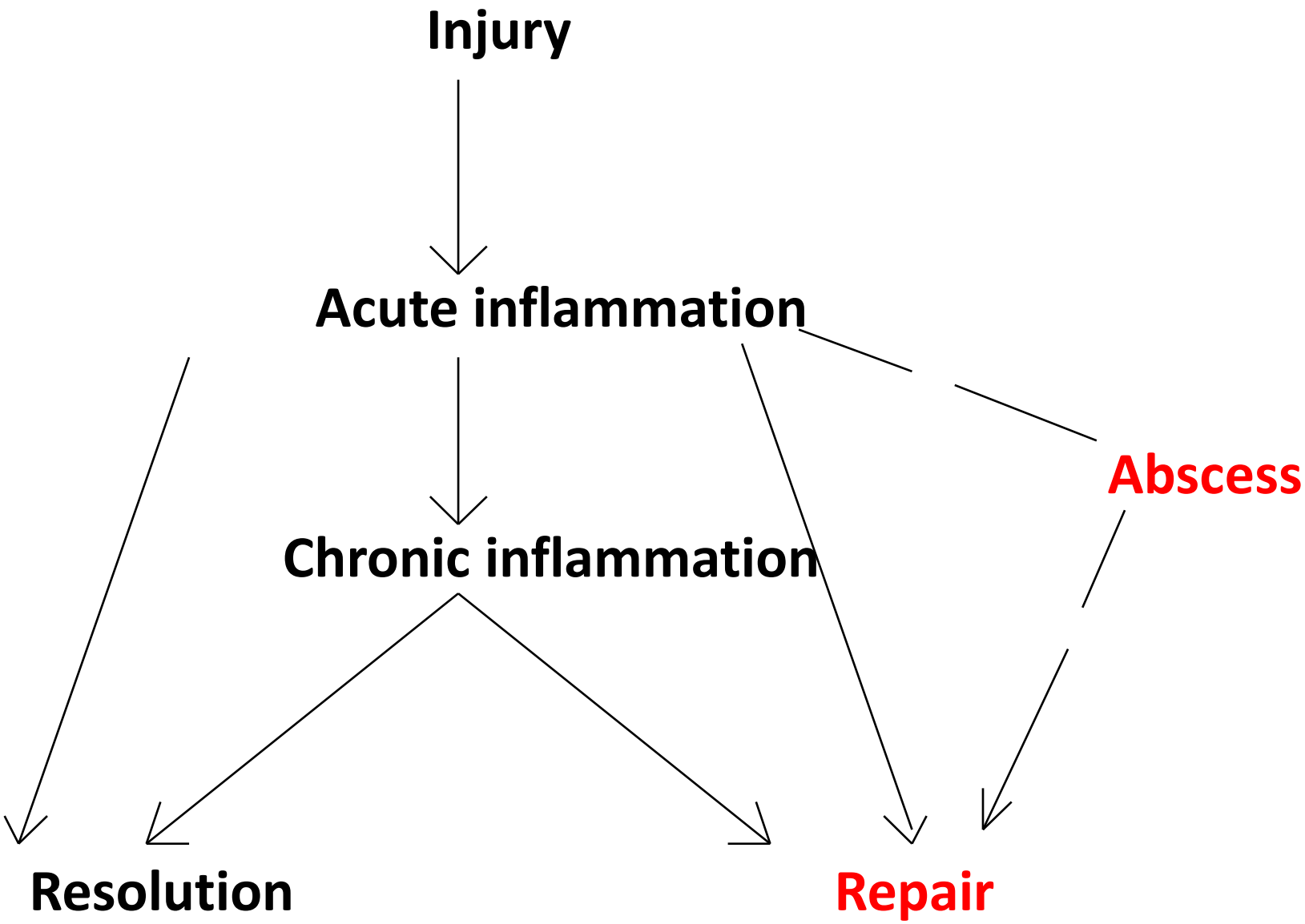
Inflammation

What is Inflammation?

- A reaction of a living tissue & its micro-circulation to a pathogenic insult.
- A defense mechanism for survival .
- Reaction of tissues to injury, characterized clinically by: heat, swelling, redness, pain, and loss of function.
- Pathologically by : vasoconstriction followed by vasodilatation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, and deposition of fibrin

Inflamatory Diagram



Etiology

Force and duration of any agent influence should be stronger, than adaptive possibilities of a tissue

Exogen

Physical injury **(alien bodies, hard pressure on a tissue, high and low temperature, ionizing and ultra-violet rays, high and low barometric pressure, electrical current)**

Chemical **(acids, alkalis, salts of heavy metals, drugs, toxins, or caustic substances like battery acid.)**

Biological infection
(microorganisms - bacterias, viruses, mycotic agents; animal organisms - worms, insects).

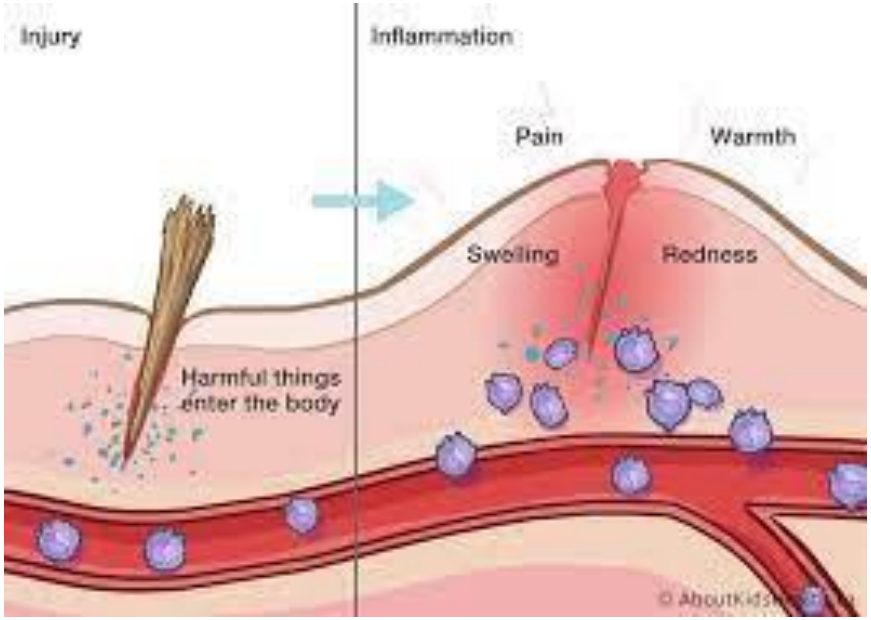
Endogen

- **Chemical:Cholic acids**
- **Immunologic (Complex antigen-antibody)**

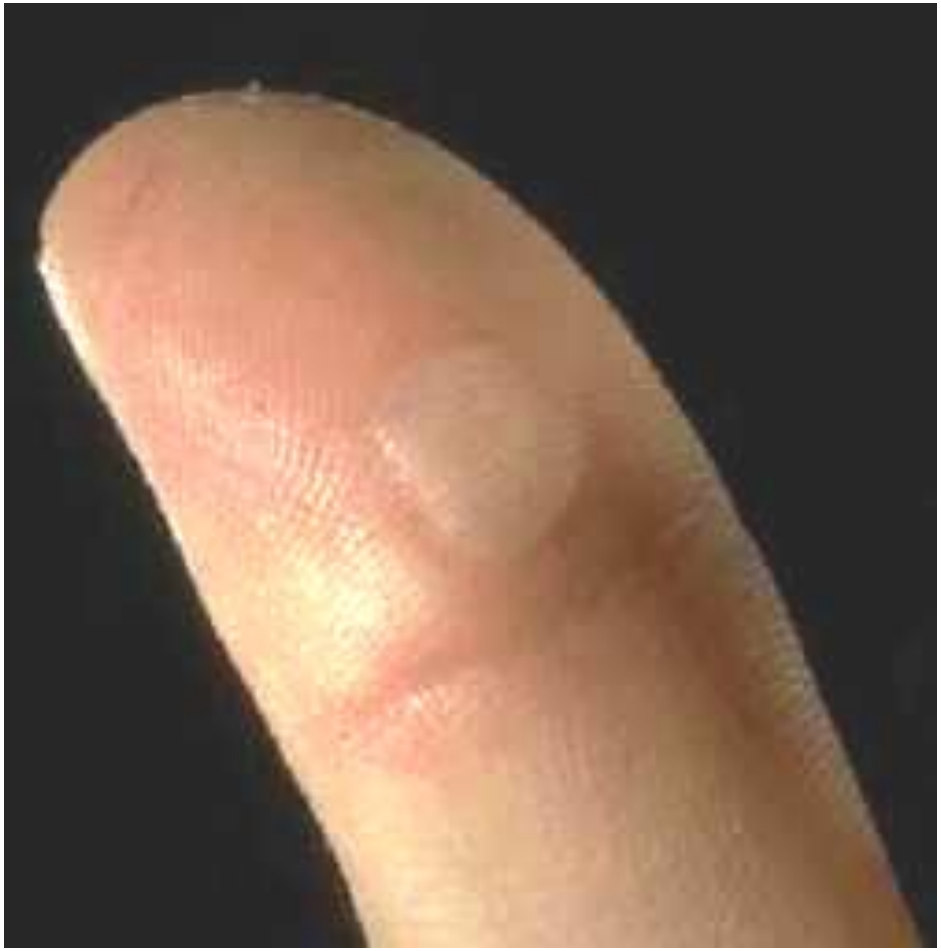
How Does It Occur?

The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.

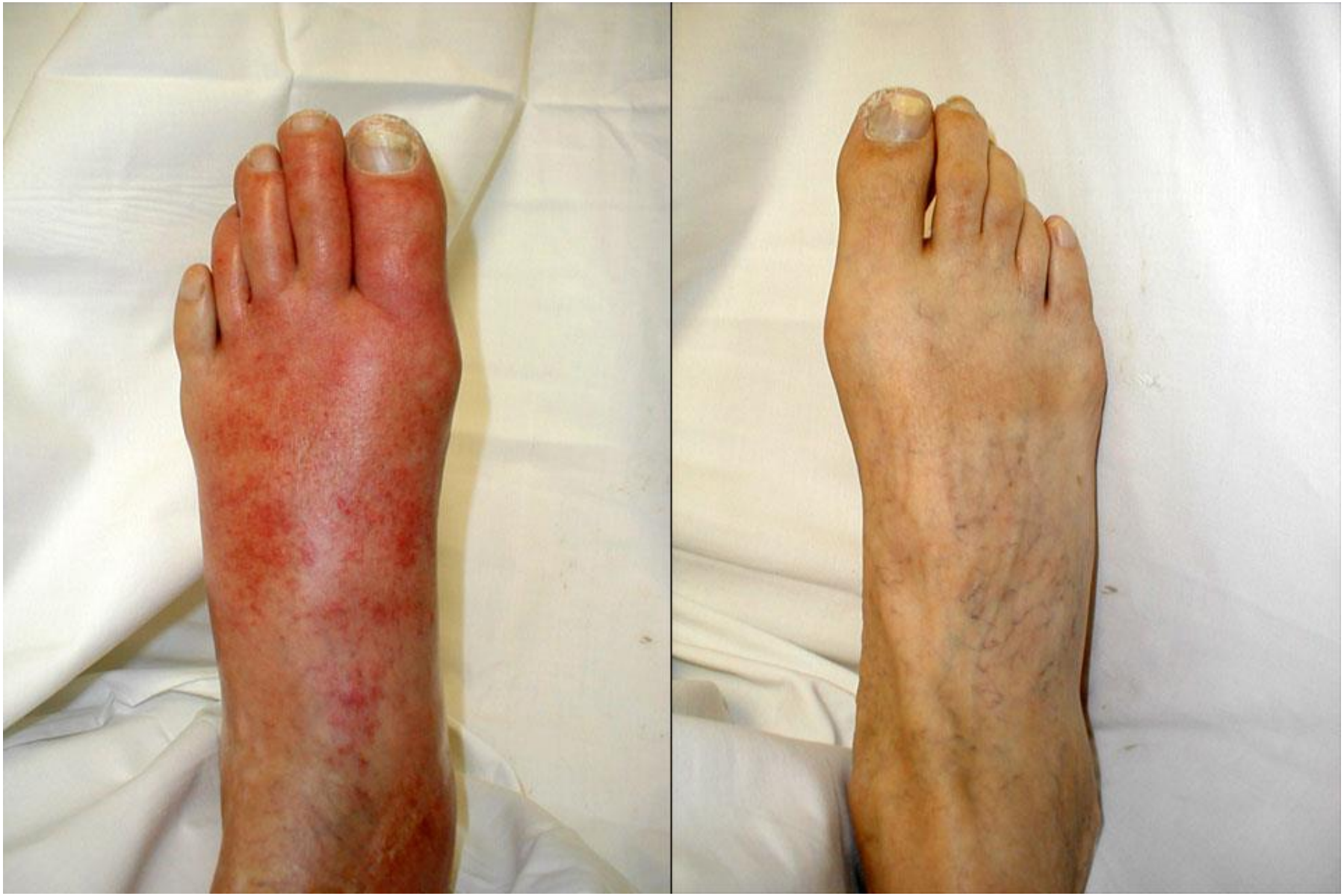
- Tissue injury or death ---> Release mediators



Cardinal Signs of Inflammation

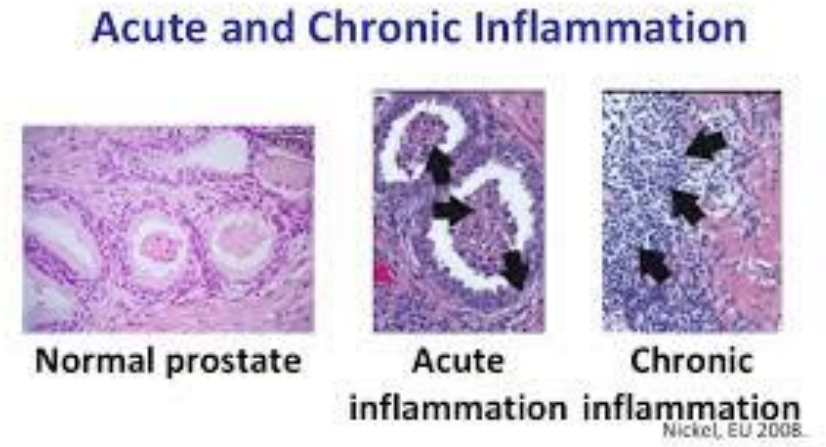


- Redness : Hyperaemia.
- Warm : Hyperaemia.
- Pain : Nerve, Chemical mediators.
- Swelling : Exudation
- Loss of Function: Pain

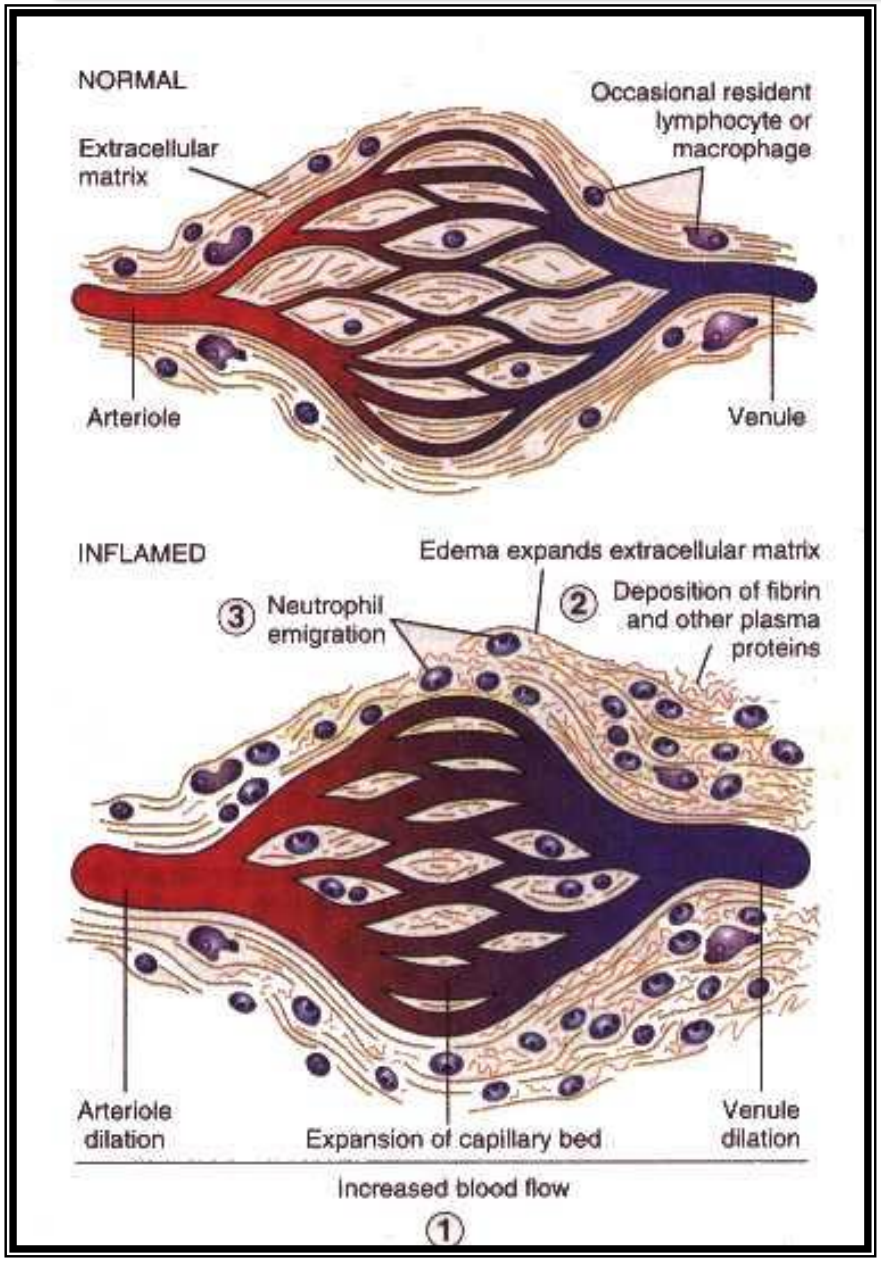


Classification

- Time course
  - Acute inflammation: Less than 48 hours
  - Chronic inflammation: Greater than 48 hours (weeks, months, years)
- Cell type
  - Acute inflammation: Neutrophils
  - Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).



Mechanism of Inflammation



- **Pathogenesis: Three main processes occur at the site of inflammation, due to the release of chemical mediators.**

(1) Increased blood flow Vascular dilation and (causing erythema and warmth).

(2) Increased vascular permeability (pain, swelling & loss of function) Extravasation and deposition of plasma fluid and proteins (edema)

(3) leukocyte emigration and accumulation in the site of injury.

INFLAMMATION
(definition of the notion)

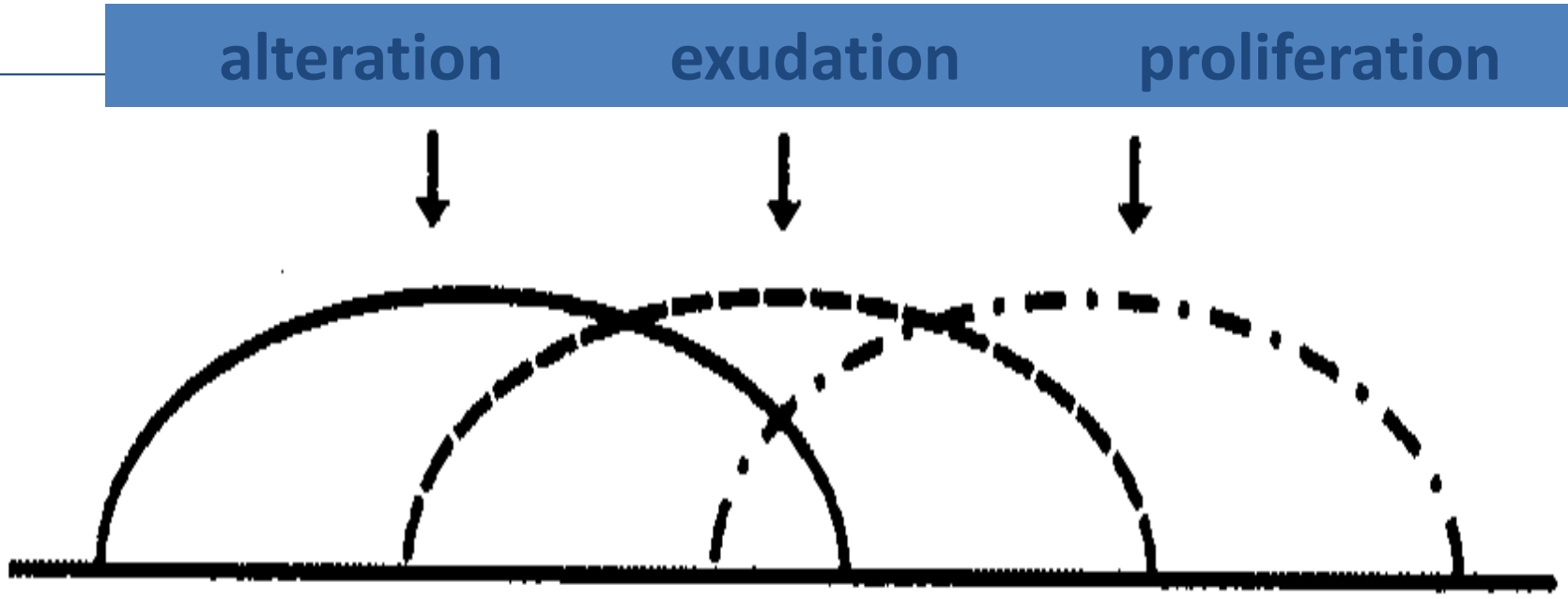
It is a typical pathological process, which arises after damage of tissue and consists of three main vessel-tissue components

1. **Alteration**
2. **violation of microcirculation, exudation and migration of leucocytes;**
3. **Proliferation**

Inflammation, as a typical pathological process has common regularities, which always are present and don't depend on the cause, localization, species of an organism and it's individual features

STAGES

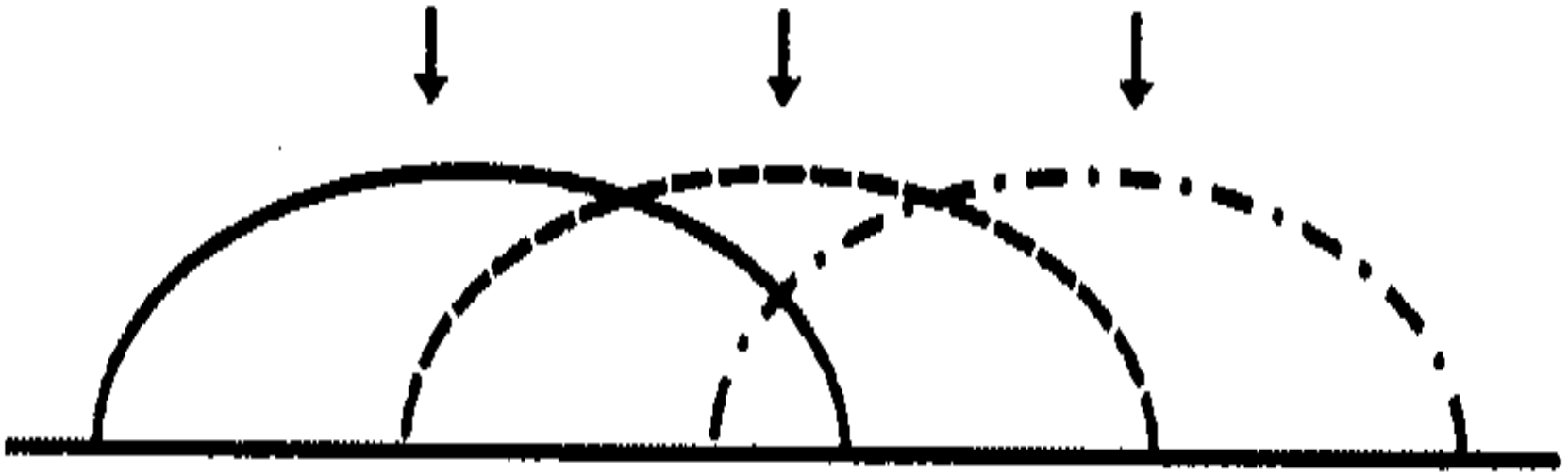
1 – alteration
2 – exudation
3 - proliferation



STAGES

1 – alteration

alteration exudation proliferation



Pathogenesis

- ***Primary alteration*** **is the result of pathological agent influence on a tissue**
- ***Secondary alteration*** **is the consequence of the primary alteration and that arises even at the absence of the damaging agent. Metabolism disorder (local acidosis, hyperosmia, hyperoncia), violation of microcirculation, free radicals formation, biological active substances action, lysosomal enzymes (damaged cells origin) conduce its development**

Thus!!!

Damage of the tissue and formation of the biological active substances are the main effects of the alteration

The Inflammatory Response

- **Key purposes = DEFENSE**
    1. **To hunt & kill invaders**
    2. **To limit their spread**
    3. **To prepare tissue for repair**

- **Key events**
    1. **Increase of vascular permeability**
    2. **Recruitment (margination) & emigration (diapedesis) of WBC's**
    3. **Phagocytosis**

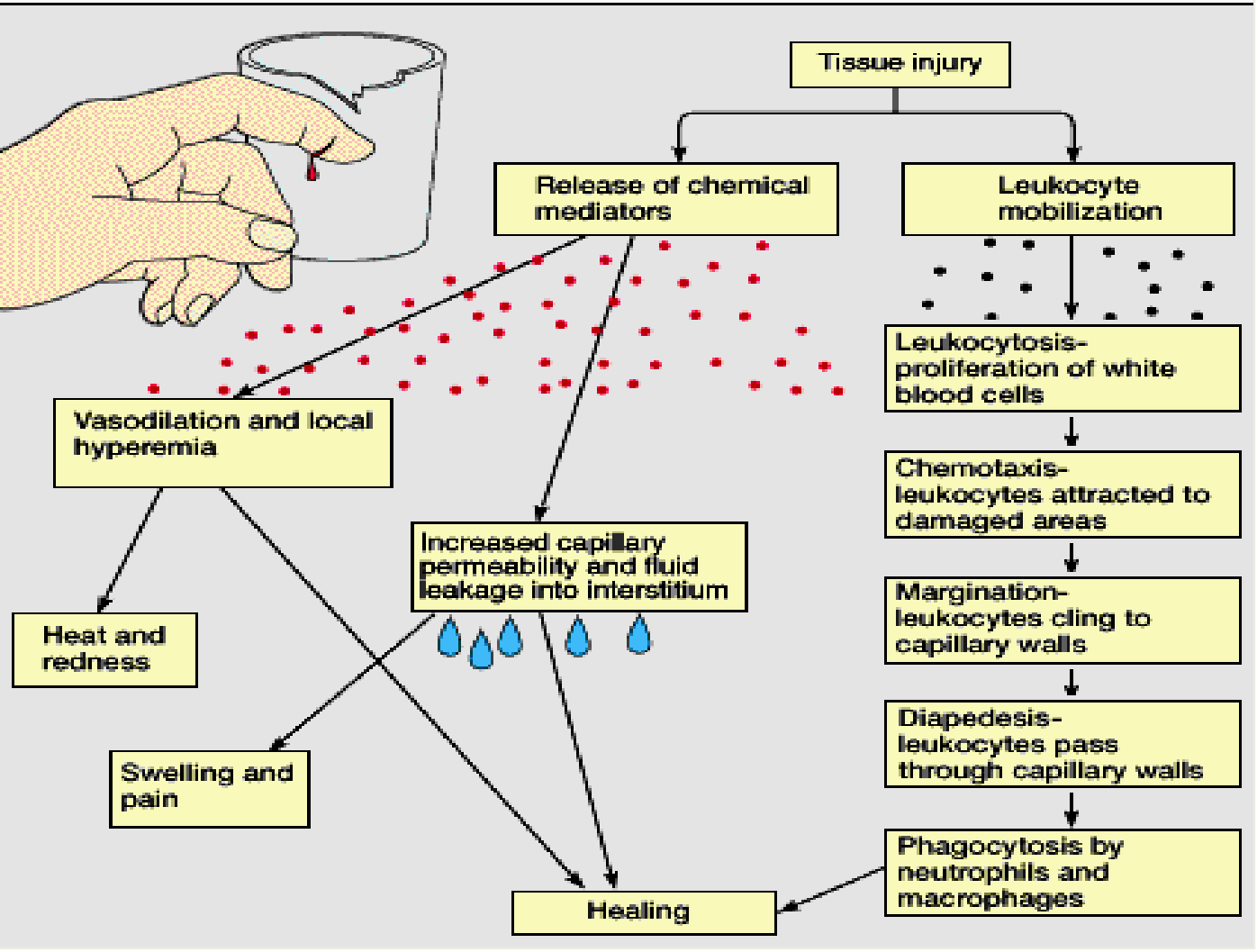
The Inflammatory Response

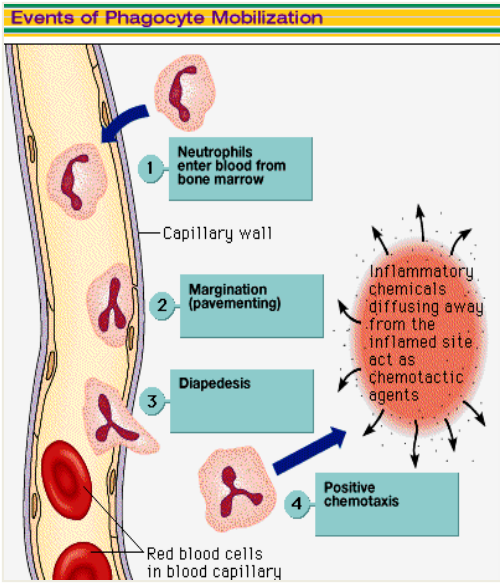
- **Inflammatory response = normal body defense mechanism to tissue injury**
  - » **Note: Inflammation is NOT infection**

- **Cells of the inflammatory response when get tissue injury**
  - **Main groups;**
    - **Phagocytes --- "the eaters"**
      - **Macrophages --- become active as APC's (antigen presenting cell)**
      - **Neutrophils --- "little eaters"**
      - **Monocytes --- become tissue macrophages**
    - **T- lymphocytes (helper-T) ---- produce cytokines which " call all to action"**
    - **Platelets ---- release PAF (platelet activating factor) which in turn begins call to action and release of chemical mediators**
    - **Mast cells --- release chemical mediators that begin inflammation**

- **Local effects of inflammation**
  - 4 cardinal signs of inflammation
    - Redness (rubor) – from increased blood supply
    - Heat (calor) – from increased blood supply
    - Swelling (tumor) – from increased permeability & increased proteins in interstitial fluid
    - Pain (dolar) – from chemical mediators
  - Also get inflammatory exudate
    - Serous – from allergic reactions & burns
    - Purulent – from infections
      - May lead to abscess
- **Systemic effects of inflammation**
  - General malaise
  - Fatigue
  - Headache
  - Fever
    - Caused by pyrogens (chemicals released from phagocytes)
    - Beneficial
      - Inhibits growth of pathogens
      - Enhances repair process via increased metabolic rate

Events of Inflammation





- Leukocytosis
- Chemotaxis
- Margination
- Diapedesis

Local symptomatology

- classical 5 symptoms

  (Celsus 1st c. B.C., Virchow 19th c. A.D.)

  1. calor - heat
  2. rubor - redness
  3. tumor - swelling
  4. dolor - pain
  5. functio laesa - loss (or impairment) of function

LOCAL SIGNS (by Cels and Gallen)

SWELLING (lat. - tumor) – is the result of exudation

REDNESS (lat. - rubor) - is the result of arterial hyperemia

HEAT (lat. - calor) - is the result of arterial hyperemia and impermanent intensification of metabolism in the focus of inflammation.

PAIN (lat. - dolor) - pain is the result of the painful receptors irritation by biological active substances, metabolites, and pressing of painful receptors by exudate

LOSS of a FUNCTION (lat. - functio laesa) is the result of the functional active tissue injury.

Roman physician Celsus described four signs(swelling, redness, heat, and pain. Greek physician Galen added fifth sing - loss of the function.

Systemic symptomatology

- fever (irritation of centre of thermoregulation)
  - TNF, IL-1
  - IL-6 – high erythrocyte sedimentation rate
- leucocytosis - increased number of WBC
  - bacteria – neutrophils
  - parasites – eosinophils
  - viruses - lymphocytosis
- leucopenia - decreased " "
  - viral infections, salmonella infections, rickettsiosis
- immunologic reactions - increased level of some substances (C-reactive protein)

GENERAL SIGNS

FEVER **– results from IL-1 influence on thermoregulative centre (excreted by macrophages and neutrophyles)**

LEUCOCYTOSIS **– is the result of leucocytes outcome from depot, leucocytes proliferation**

PROTEINS OF AQUTE FASE of inflammation **– its content increases in the blood on 50 %, they are synthesized mainly in liver, play protective role (inhibitors of proteinases – antitripsine; antioxidants – haptoglobin, ceruloplasmin; IgG, C-reactive proteine)**

ESR increase **– inflammation couses accumulation of big mass proteins in the blood (globulines, fibrinigen), they adsorb on erythrocytes, decreas surface negative charge and conduce erythrocytes aggregation**

INTOXICATION **– is the result of necrotical substances income in the blood fron area of inflammation**

Changes in vascular flow (hemodynamic changes)

- **Slowing of the circulation**
  - **outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood.**
- **Leukocyte margination**
  - **Neutrophi become oriented at the periphery of vessels and start to stick.**

Lymphatics in inflammation:

- Lymphatics are responsible for draining ***edema***.

Edema: An excess of fluid in the interstitial tissue or serous cavities; either a *transudate* or an *exudate*

Transudate:

An ultrafiltrate of blood plasma permeability of endothelium is usually normal. low protein content (mostly albumin)

Exudate:

A filtrate of blood plasma mixed with inflammatory cells and cellular debris. permeability of endothelium is usually altered high protein content.

Pus:

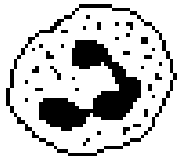
A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.

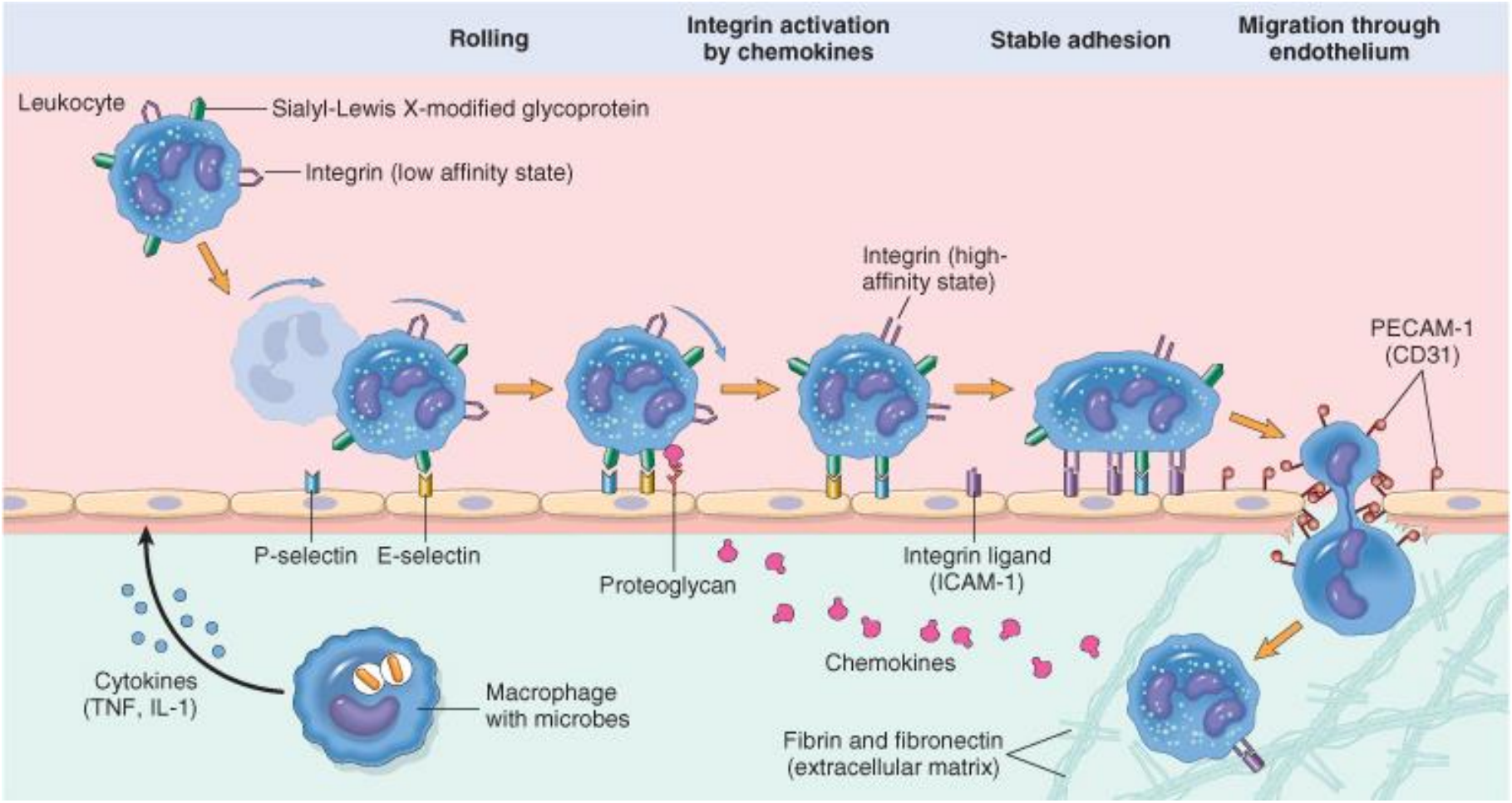
Leukocyte exudation

- Divided into 4 steps

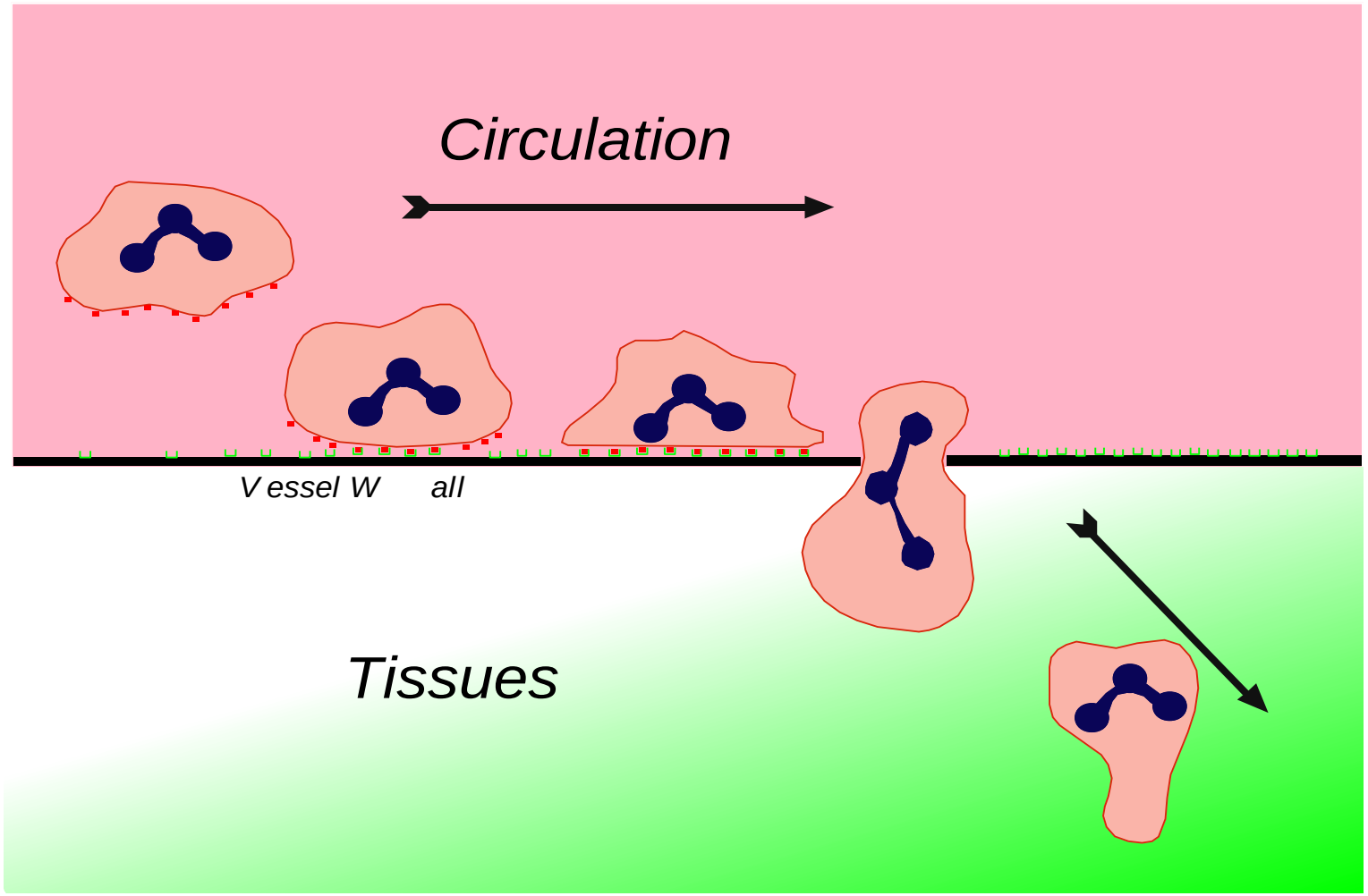
1. Margination, rolling, and adhesion to endothelium
2. Diapedesis (trans-migration across the endothelium)
3. Migration toward a chemotactic stimuli from the source of tissue injury.
4. Phagocytosis

MARGINATION



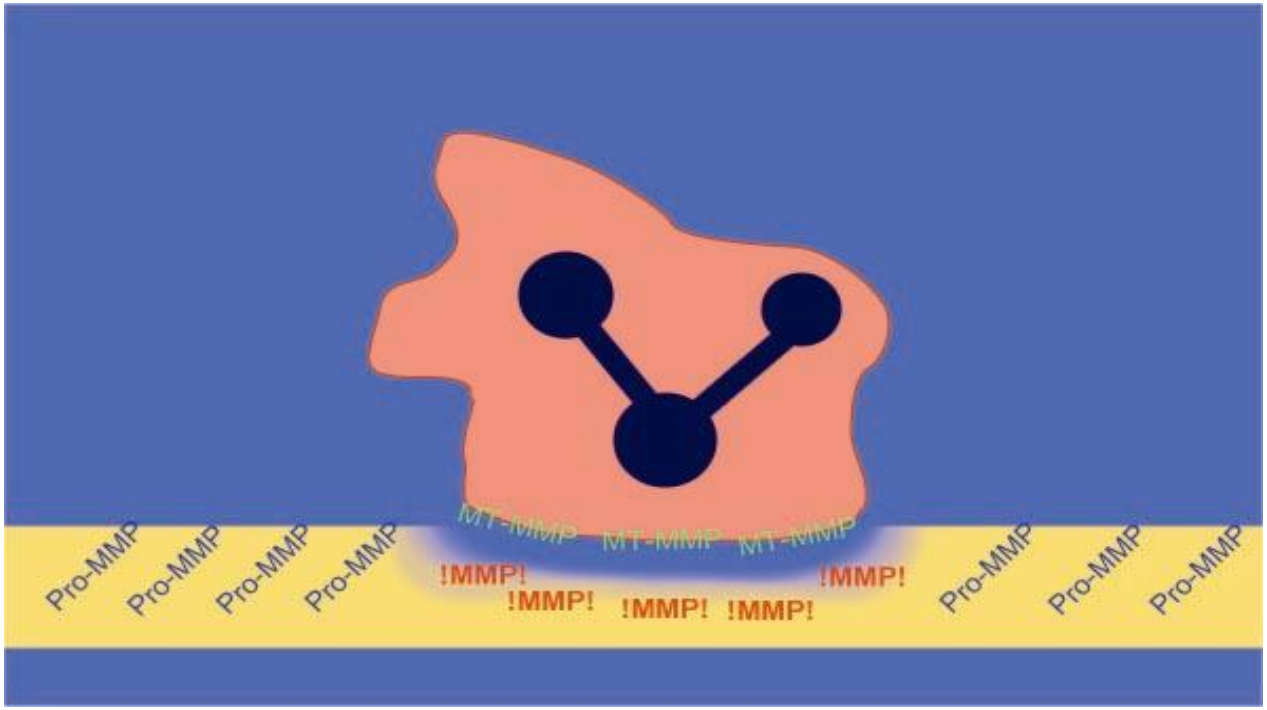

Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
Chemokines
Cytokines (TNF, IL-1)
Macrophage with microbes
Fibrin and fibronectin (extracellular matrix)

Margination, emigration, chemotaxis



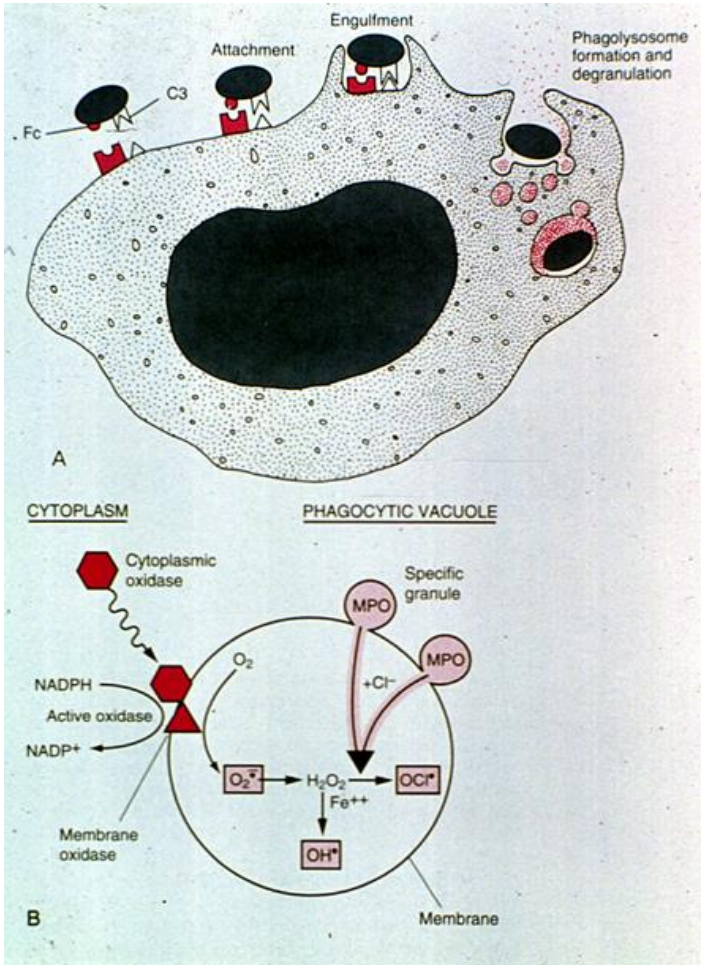
How do neutrophils escape from vessels?

- Relaxation of inter-endothelial cell junctions
- Digestion of vascular basement membrane
- Movement



Phagocytosis

- 3 distinct steps
  - Recognition and attachment
  - Engulfment
  - Killing or degradation



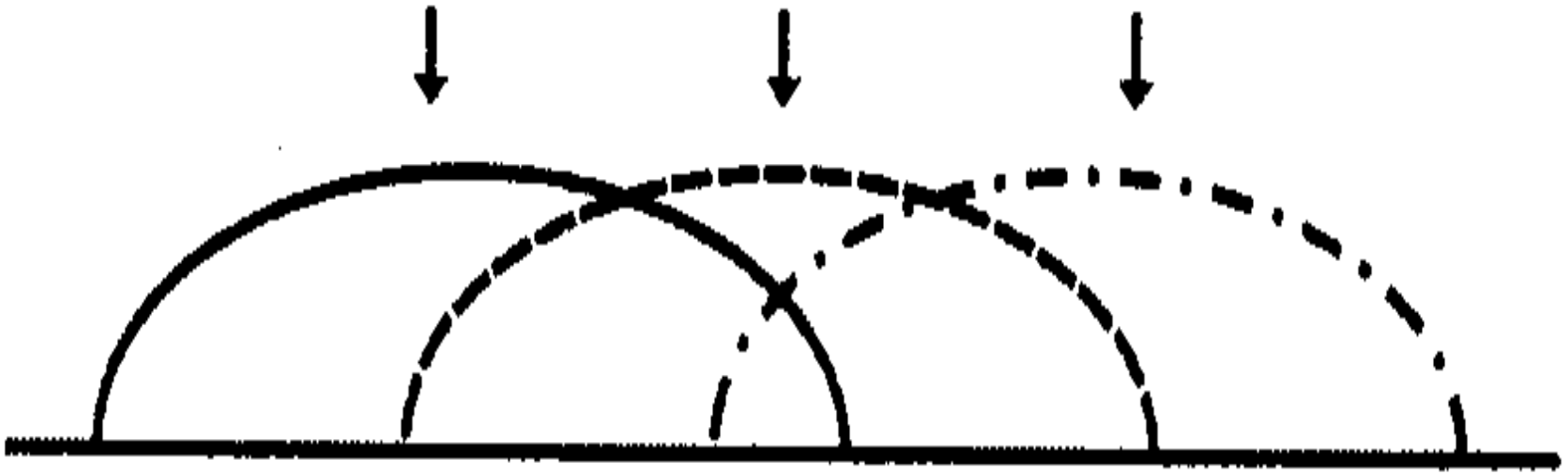
Defects in leukocyte function:

- Margination and adhesion
  - steroids, leukocyte adhesion deficiency
- Emigration toward a chemotactic stimulus
  - drugs
  - chemotaxis inhibitors
- Phagocytosis
  - Chronic granulomatous disease (CGD)

STAGES

2 – exudation

alteration exudation proliferation

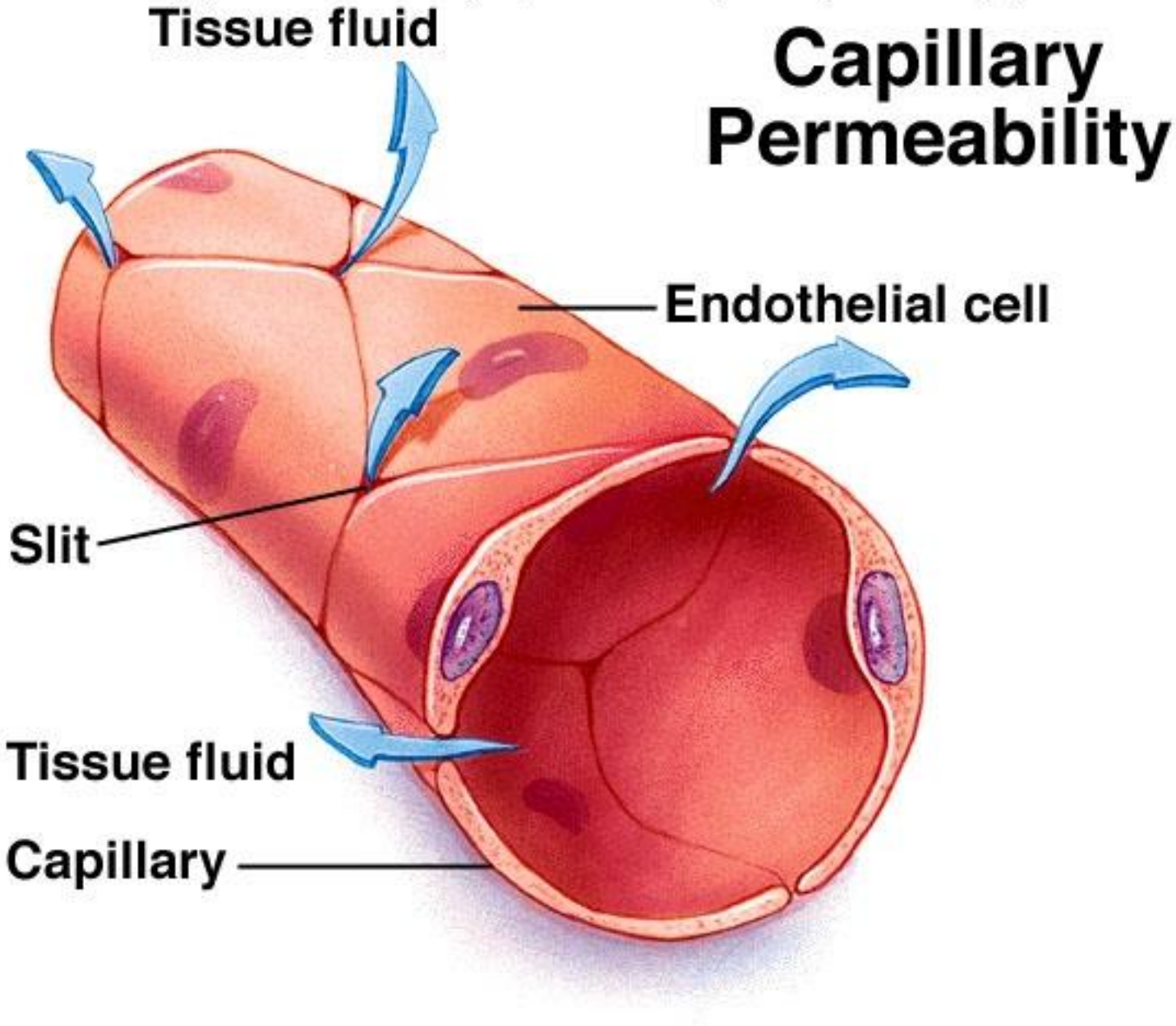


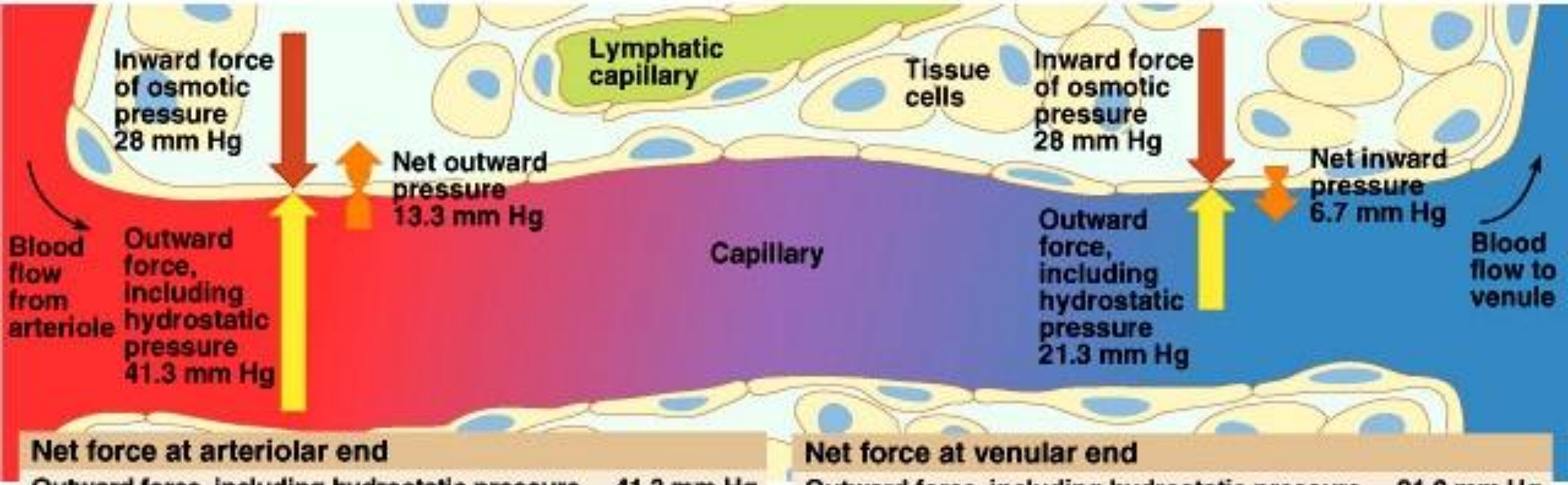
Vascular changes

- vasodilation
  - increased permeability of vessels due to widened intercell. junctions and contraction of endothelial cells (histamin, VEGF, bradykinin)
- protein poor transudate (edema)
- protein rich exsudate

- leukocyte-dependent endothelial injury
  - proteolysis – protein leakage
- $\rightarrow$ platelet adhesion $\rightarrow$ thrombosis

Capillary Permeability

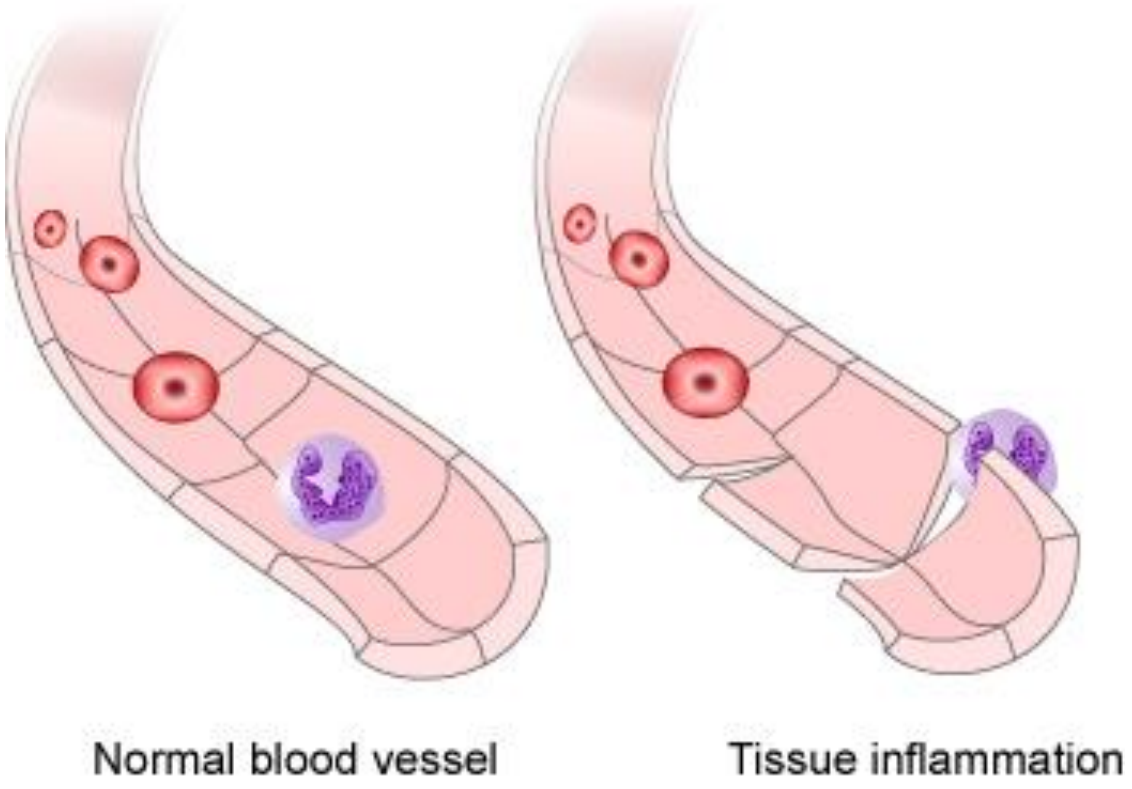




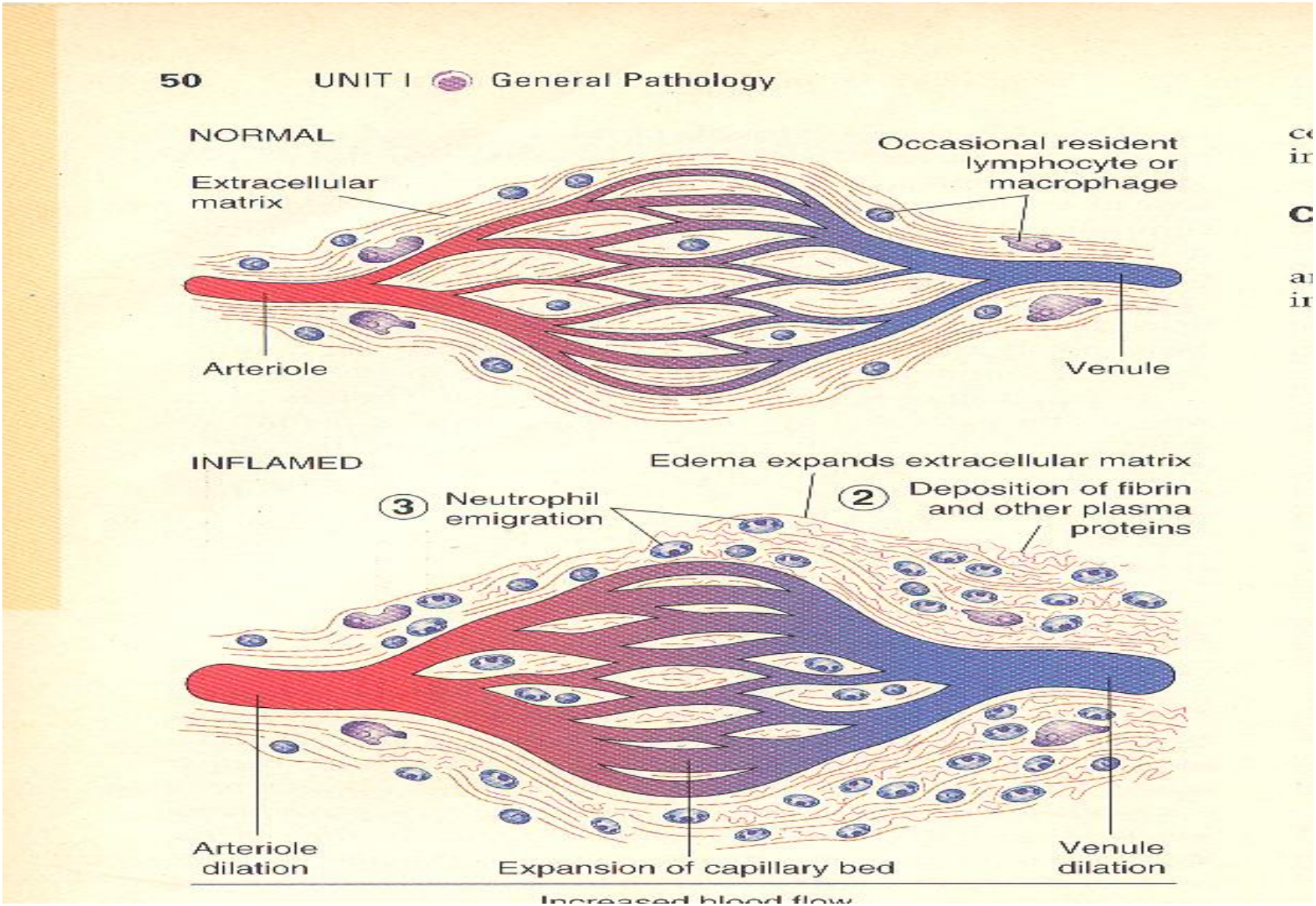
Net force at arteriolar end	
Outward force, including hydrostatic pressure	= 41.3 mm Hg
Inward force of osmotic pressure	= 28 mm Hg
Net outward pressure	= 13.3 mm Hg

Net force at venular end	
Outward force, including hydrostatic pressure	= 21.3 mm Hg
Inward force of osmotic pressure	= 28 mm Hg
Net inward pressure	= 6.7 mm Hg

Acute Inflammation



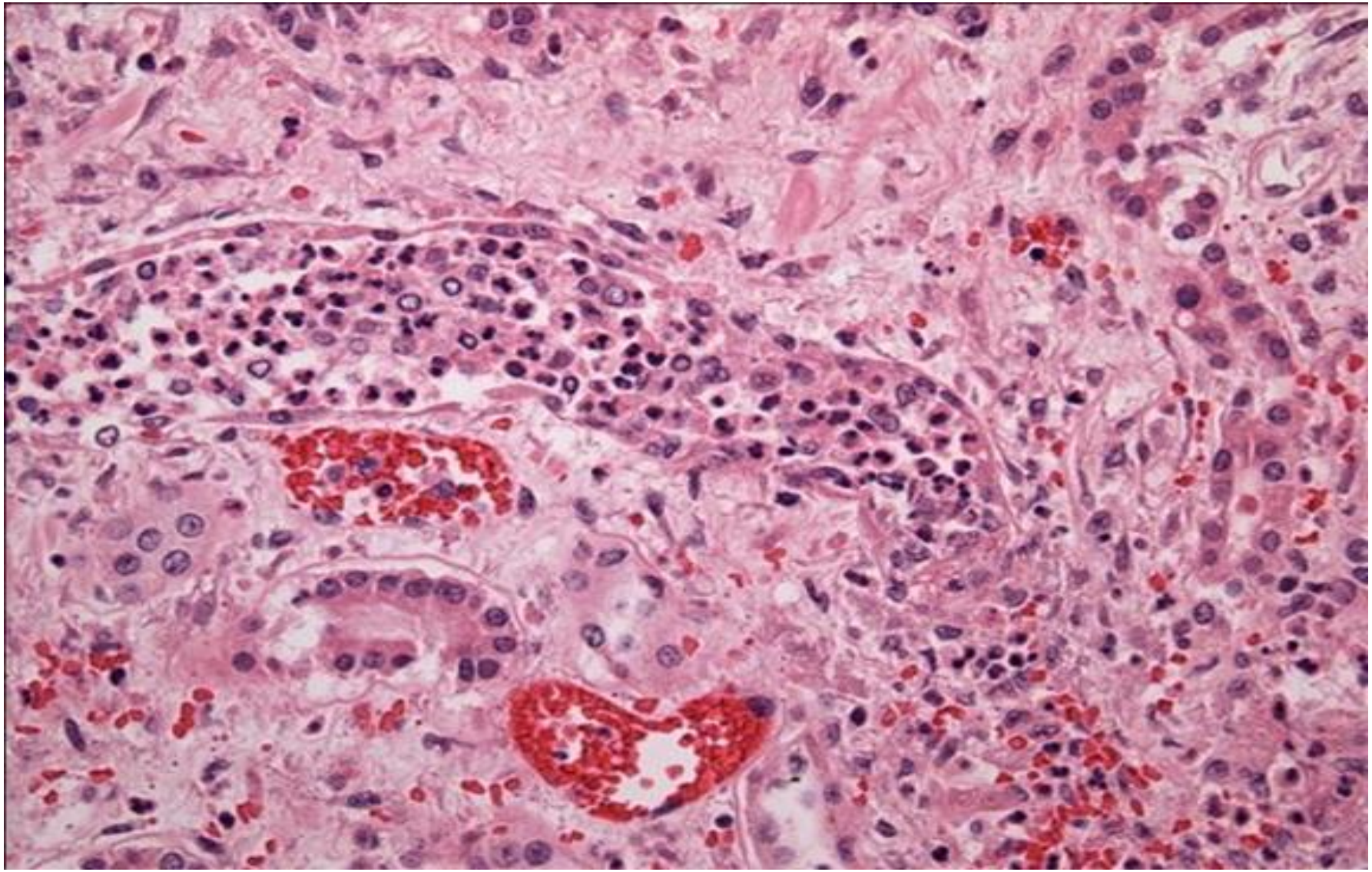
Acute Inflammation



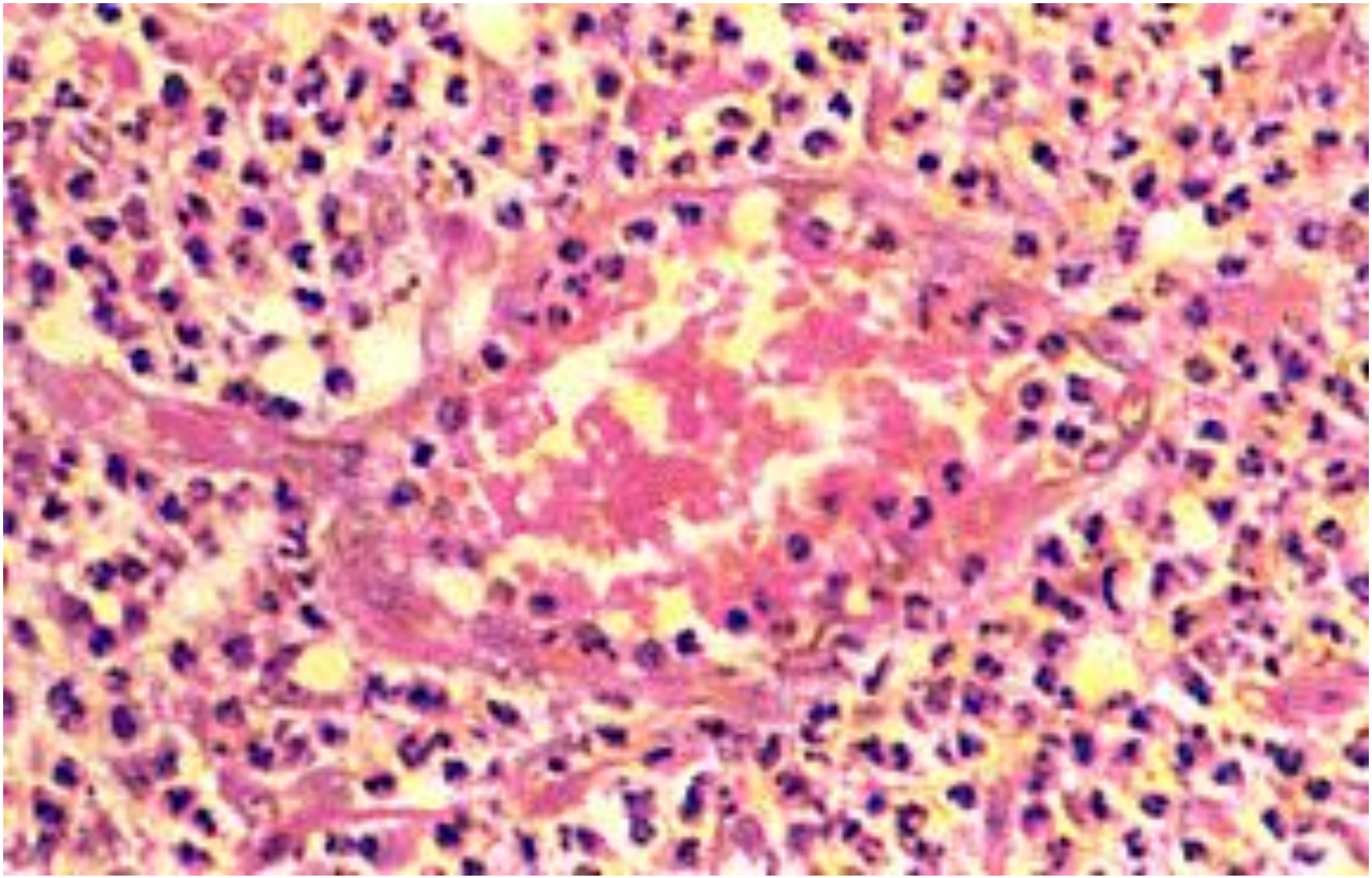
Cellular events

- leukocytes margination → rolling → adhesion → transmigration
- emigration of:
  - neutrophils (1-2 days)
  - monocytes (2-3 days)
- chemotaxis
  - endogenous signaling molecules - lymphokines
  - exogenous - toxins
- phagocytosis - lysosomal enzymes, free radicals, oxidative burst
- passive emigration of RBC - no active role in inflamm. - hemorrhagic inflammation

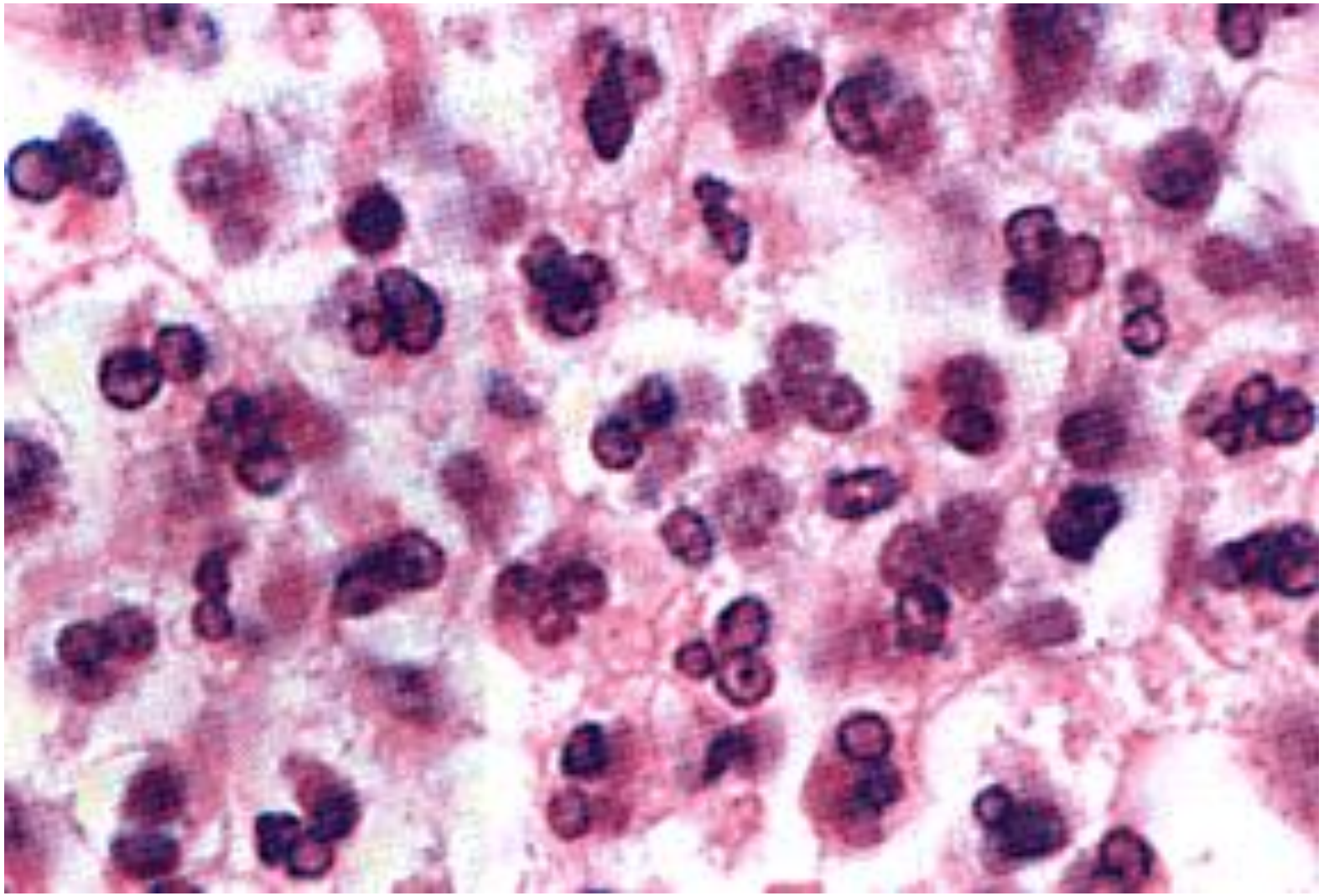
Acute Inflammation



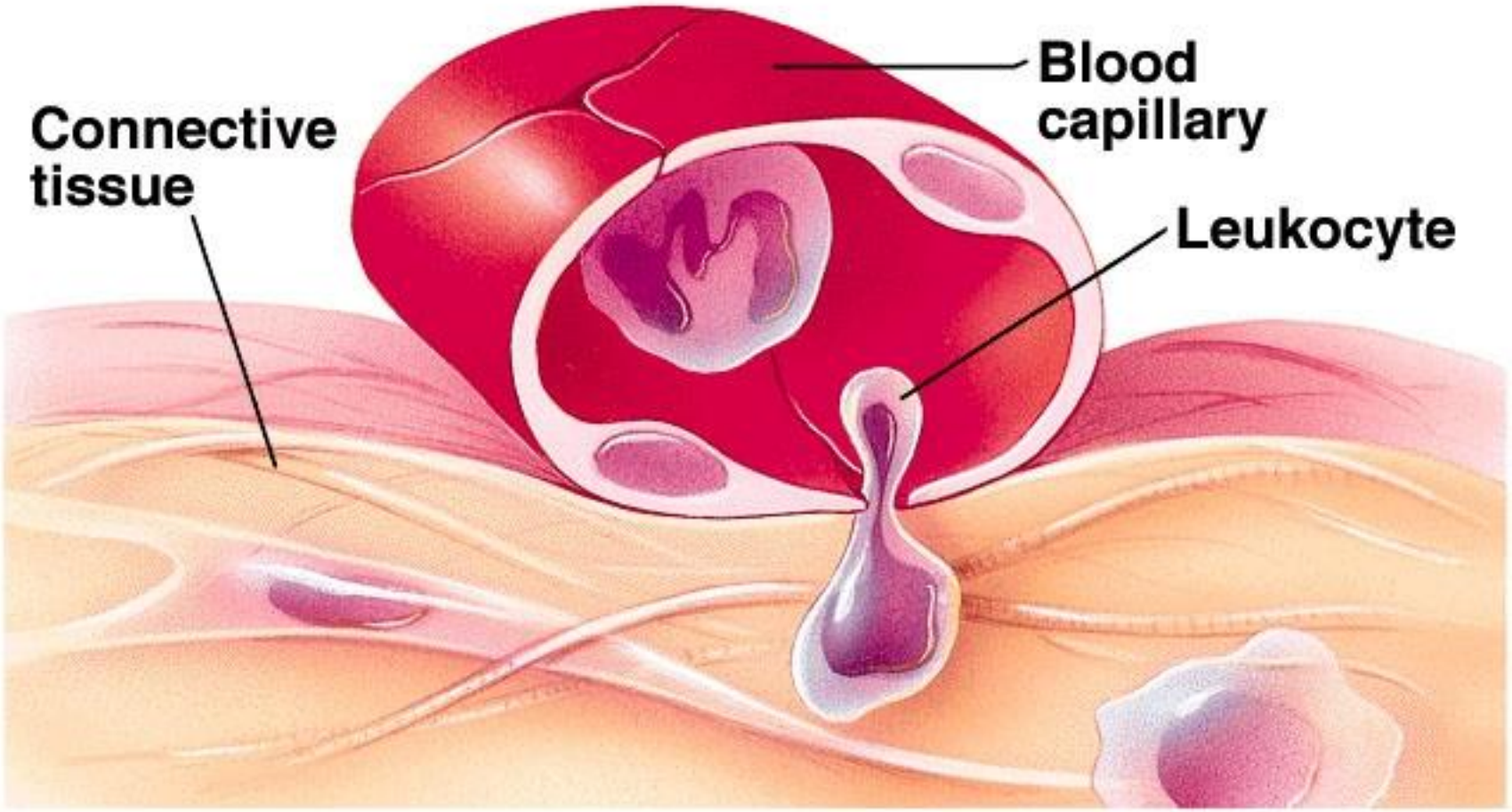
Acute Inflammation



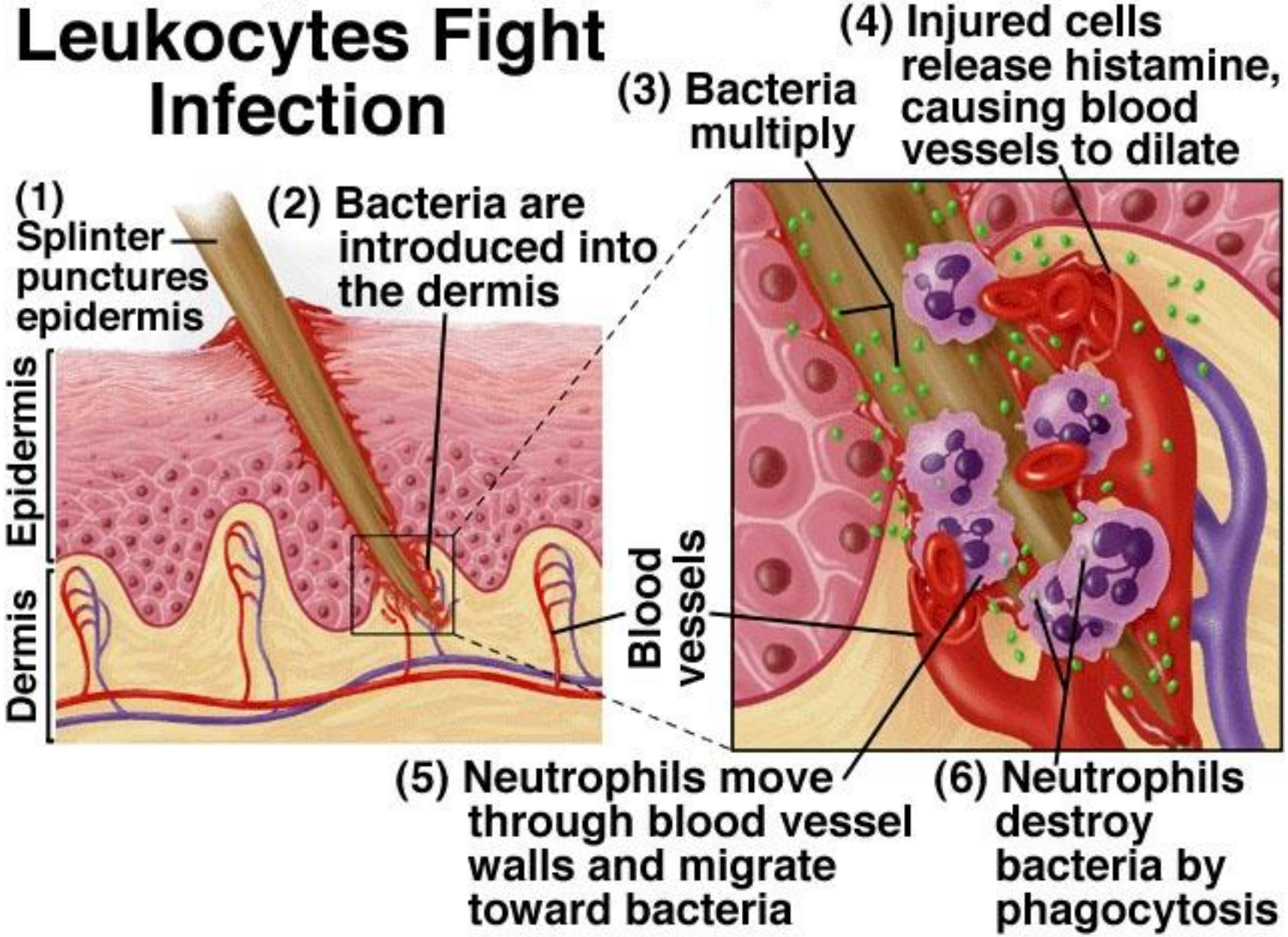
Acute Inflammation
(with pus)



Leukocyte—Diapedesis



Leukocytes Fight Infection



Phagocytosis

- adhesion and invagination into cytoplasm
- engulfment
- lysosomes - destruction
- in highly virulent microorganisms can die leucocyte and not the microbe
- in highly resistant microorganisms - persistence within macrophage - activation after many years

Outcomes of acute inflammation

- 1. resolution - restoration to normal, limited injury
  - chemical substances neutralization
  - normalization of vasc. permeability
  - apoptosis of inflammatory cells
  - lymphatic drainage
- 2. healing by scar
  - tissue destruction
  - fibrinous inflammtion
  - purulent infl. $\rightarrow$ abscess formation (pus, pyogenic membrane, resorption - pseudoxanthoma cells - weeks to months)
- 3. progression into chronic inflammation

Mediators of the inflammation

It is the biological active substances, which synthesized or excreted in area of the inflammation and conduce its proression

HUMORAL

- complement system proteins
- bradykinin
- kallidin
- Coagulative proteins

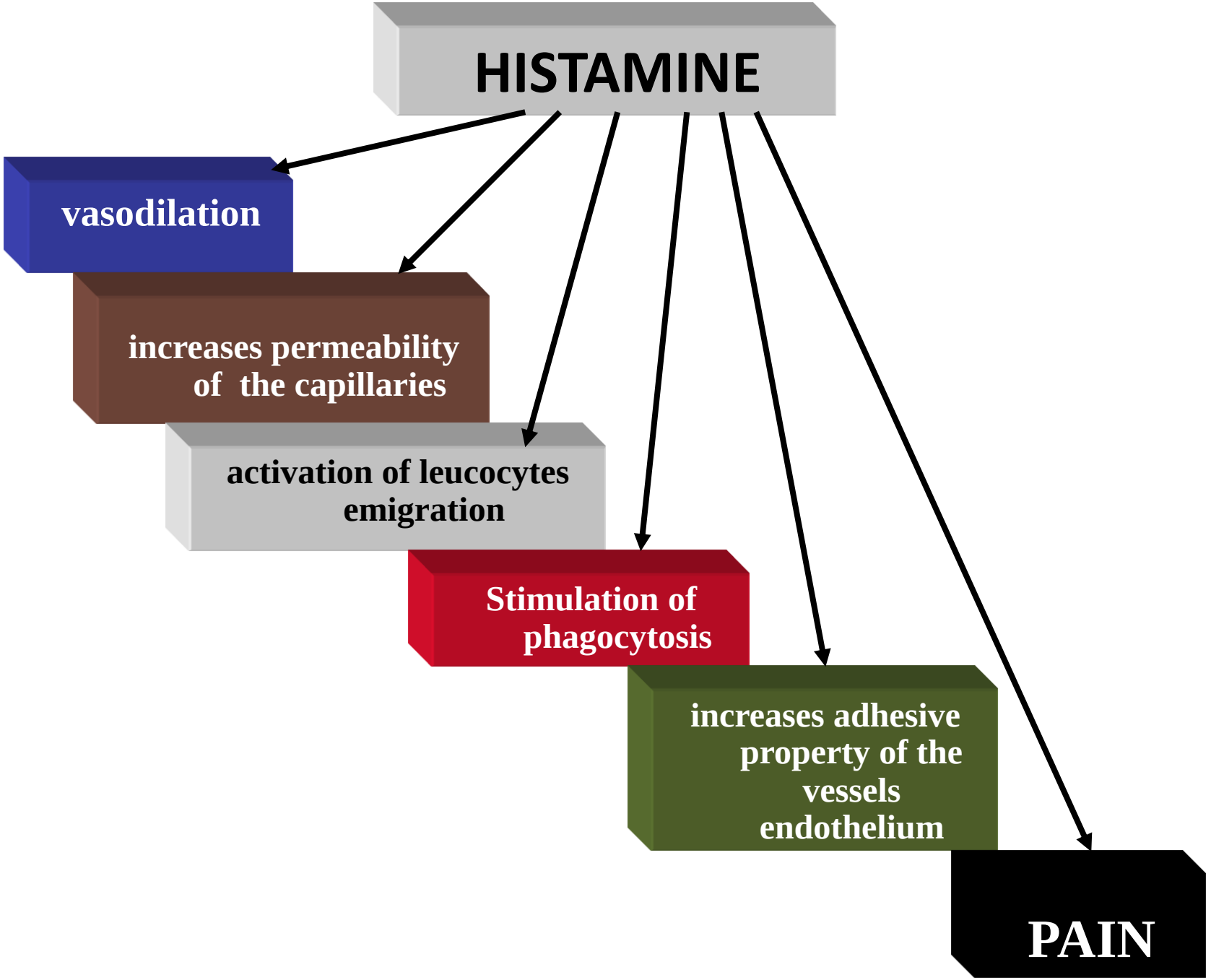
CELLULAR

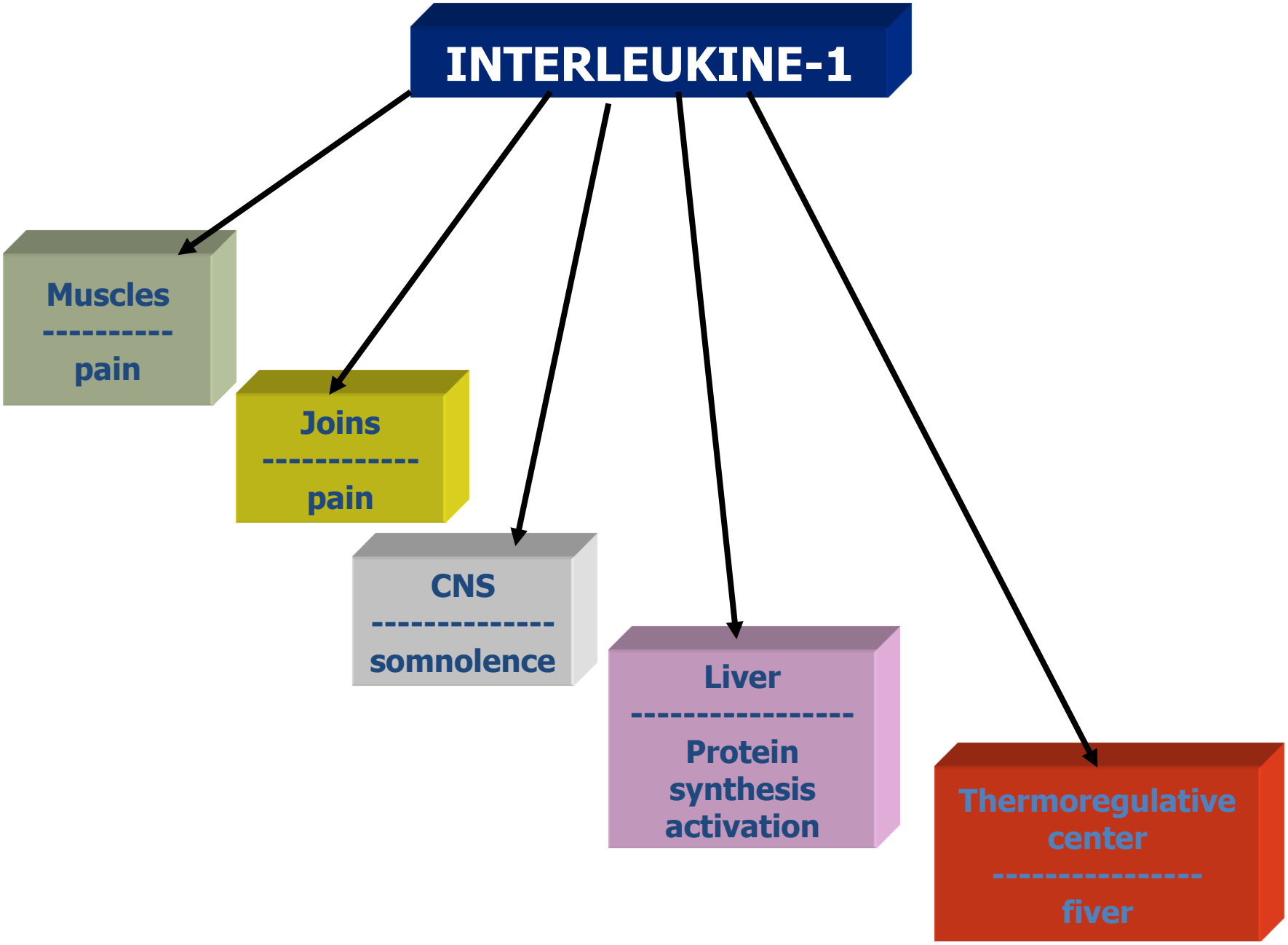
- histamine
- serotonin
- lymphokines (IL-1, IL-6 et all.)
- monokines
- prostaglandines
- leucotriens
- lysosomal enzymes

Chemical Mediators:

Chemical substances synthesised or released and mediate the changes in inflammation.

- *Histamine* by mast cells - vasodilatation.
- *Prostaglandins* – Cause pain & fever.
- *Bradykinin* - Causes pain.


HISTAMINE
vasodilation
increases permeability of the capillaries
activation of leucocytes emigration
Stimulation of phagocytosis
increases adhesive property of the vessels endothelium
PAIN


INTERLEUKINE-1
Muscles
pain
Joins
pain
CNS
somnolence
Liver
Protein synthesis activation
Thermoregulative center
fiver

Chemical Mediators

- **The initial "macrophage (APC cell) – antigen complex" causes chemical mediators to be released:**
  - **Histamine**
    - **From basophils & mast cells**
    - **Cause vasodilation & increased permeability of vessels via release of nitric oxide**
  - **Prostaglandins**
    - **Made in mast cell membrane from fatty acid (arachidonic)**
    - **Cause pain & vasodilation**
  - **Leukotrienes**
    - **"bad" prostaglandins since cause symptoms of inflammation (pain & swelling)**
    - **Cause chemotaxis**
    - **Very important for causing allergies, asthma, & anaphylaxis**

Chemical Mediators

– **Complement**

- Coats bacterial surface; enhances phagocytosis & lyses bacteria
- Inactive plasma proteins become activated by initial An-Ab complex

– **Interferon**

- Proteins that are released by helper T's & kill viruses

– **Bradykinins**

- From inactivated plasma protein
- Cause similar effects like histamine
- Cause pain
- Induce WBC's into area (chemotaxis

EXUDATION

Blood plasma penetration through the vessels wall and accumulation in the area of the injured tissue.

It conduces swelling, pain and loss of function

Thus!!!

Exudation deepens microcirculation violation because haemoconcentration (increased viscosity of the blood), aggregation of the erythrocytes and platelets.

But in this time vital conditions for microorganisms became worse.

Migration of the leucocytes

Stages

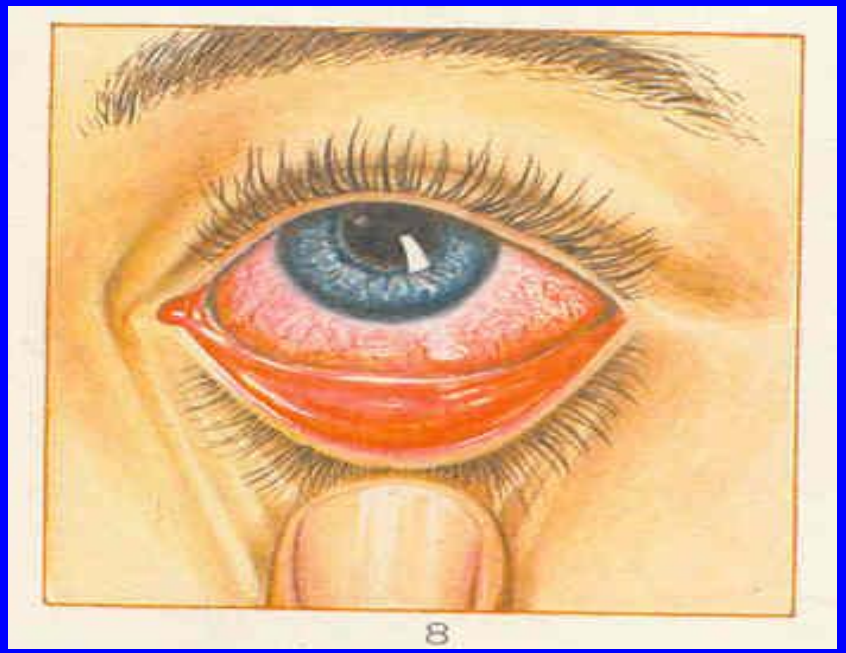
- edge standing
- penetration through the vessels wall
- move in area of inflammation

In most cases of acute inflammation neutrophyles migrate the first (that process lasts 6-24 hours). In 24-48 hours monocytes emigrate most actively. Lymphocytes emigrate a little bit later.

INFLAMMATION TYPES ACCORDING TO EXUDATE KIND

SEROUS INFLAMMATION

develops in mucous and serous membranes, interstitial tissue, skin, and kidneys glomes capsules. The amount of cells in the serous exudate is not large. The serous exudate conduces of microorganisms washing off and their toxins from the damaged surfaces. But the serous exudate in brain coats can squeeze the brain and violate its function. The serous infiltration of the lungs alveolar septs can cause the development of acute respiratory insufficiency syndrome.



INFLAMMATION TYPES ACCORDING TO EXUDATE KIND

FIBRINOUS INFLAMMATION

contains a plenty of fibrinogene, which forms clots of fibrin in tissues (occures when an organism is affected by corinebacterium diphtheriae, pneumococcus, Fridlander's bacillus, Frencel's diplococcus, streotococcus, and mycobacterium of tuberculosis. Such type of an inflammation occurs on mucous or serous coats more often

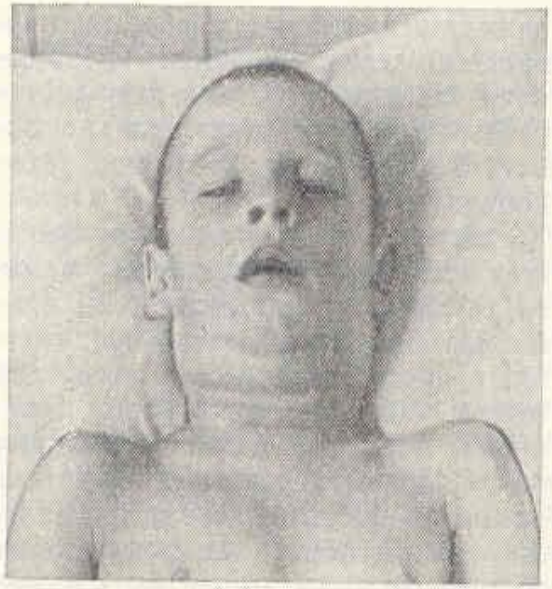
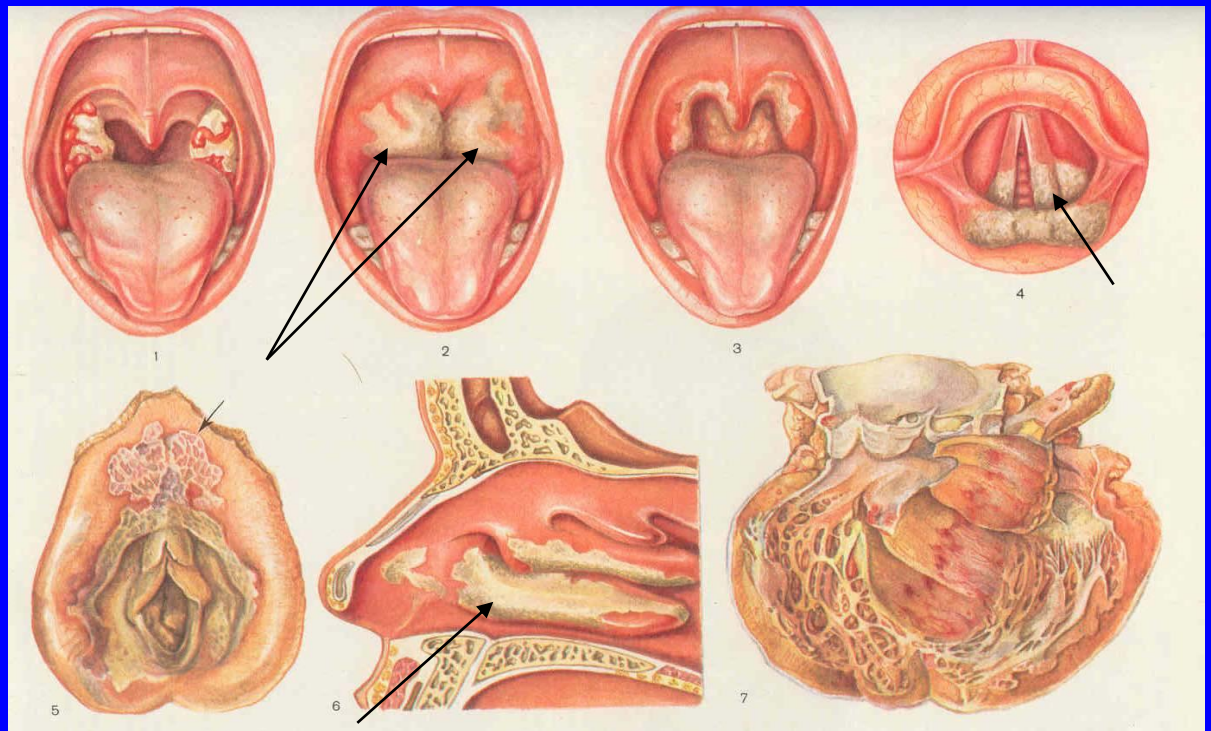


Рис. 4. Больной с отеком шейной клетчатки при токсической форме дифтерии зева.



К ст. Дифтерия. Рис. 1—3. Дифтерия зева (основные формы): рис. 1—локализованная форма (на миндалинах серовато-белые налеты с гладкой поверхностью и четко очерченными краями); рис. 2 — токсическая форма (слизистая оболочка мягкого неба отечна, миндалины резко увеличены и соприкасаются друг с другом, поверхность их покрыта грязно-белыми налетами); рис. 3 — распространенная форма (налеты распространяются за пределы миндалин). Рис. 4. Дифтерия гортани (пленчатые налеты на слизистой оболочке входа в гортань, истинных и преддверных — ложных — голосовых складках). Рис. 5. Дифтерия наружных половых органов девочки (припухлость больших и малых половых губ, грязно-белые налеты на слизистой оболочке, изъязвления на коже — указаны стрелкой). Рис. 6. Дифтерия полости носа (гиперемия слизистой оболочки и пленчатые налеты на ней). Рис. 7. Миокардит при дифтерии (сердце в разрезе): в центре рисунка видны дистрофически-некробиотические изменения (желтоватого цвета) и пятнистые кровоизлияния.

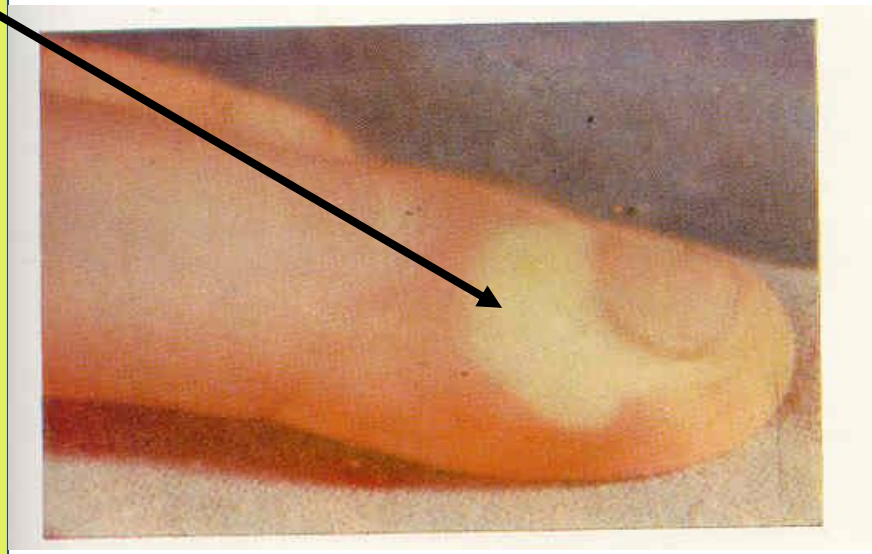
INFLAMMATION TYPES ACCORDING TO EXUDATE KIND

PURULENT INFLAMMATION

Reason - staphylococcus, streptococcus, gonococcus, meningococcus, and Frenkel's diplococcus

Purulent exudate smell bad, consist of of many viable leukocytes and purulent bodies (perishing leukocytes), cells detritus, microorganisms, plenty of proteins (especially globulines)

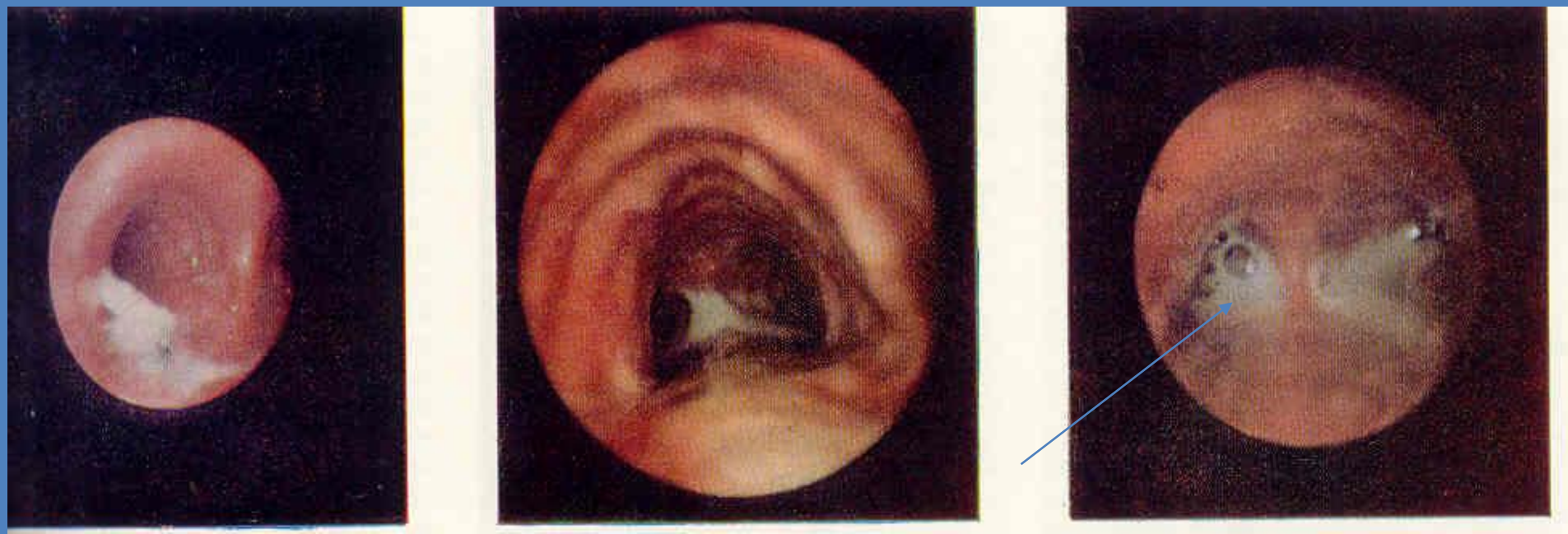
Is characterise by low pH



INFLAMMATION TYPES ACCORDING TO EXUDATE KIND

DECAYING INFLAMMATION

The decaying inflammation develops after the invasion of decaying microorganisms into the purulent inflammation site. During this type of inflammation necrosis of injurious tissues progresses, the inflammation area isn't localized, and this provokes the penetration of alien agent and toxic products into vessels, development of intoxication due to which the patients usually die.



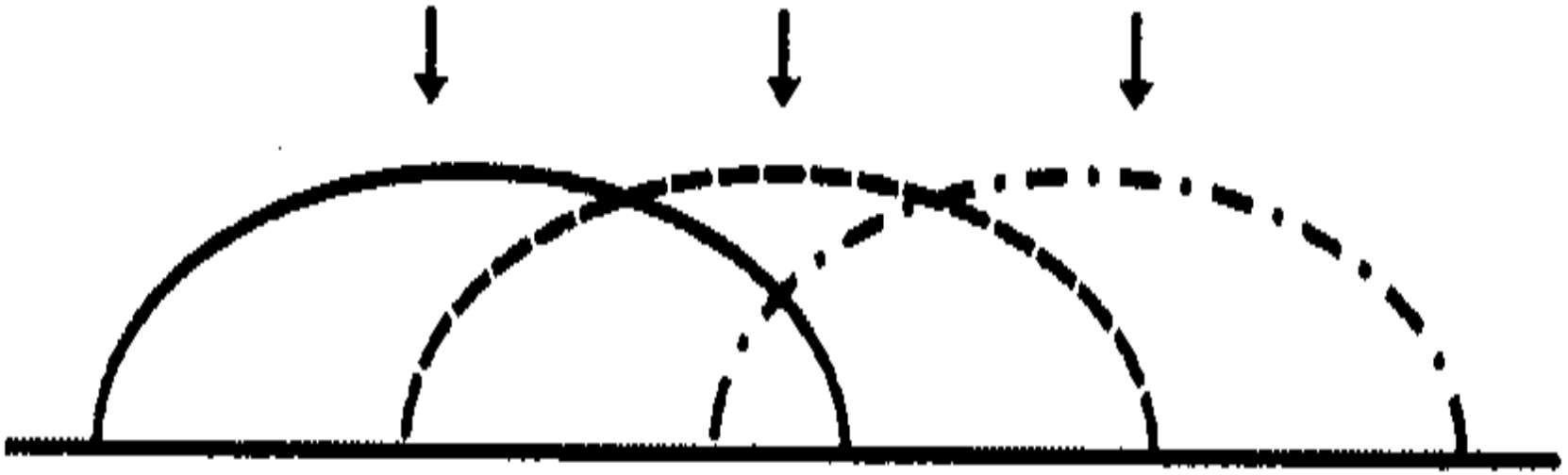
HEMORRHAGIC INFLAMMATION

The hemorrhagic inflammation, as the form of serous inflammation, the fibrinous one or the purulent one, is characterized by erythrocytes impurity to the exudate (Siberian ulcer, natural smallpox, influenza).

STAGES

3 - proliferation

alteration exudation proliferation



PROLIFERATIVE PHASE (tissue regeneration)

IS DEPENDED TO:

- Interaction of the connective tissue cells between each other

(endotheliocytes, fibroblasts, macrophages, lymphocytes)

- Interaction of the connective tissue cells and fibrous elements

(collagen, proteoglicans, fibronectine)

- Interaction of the connective tissue cells, blood cells and parenchymal cells

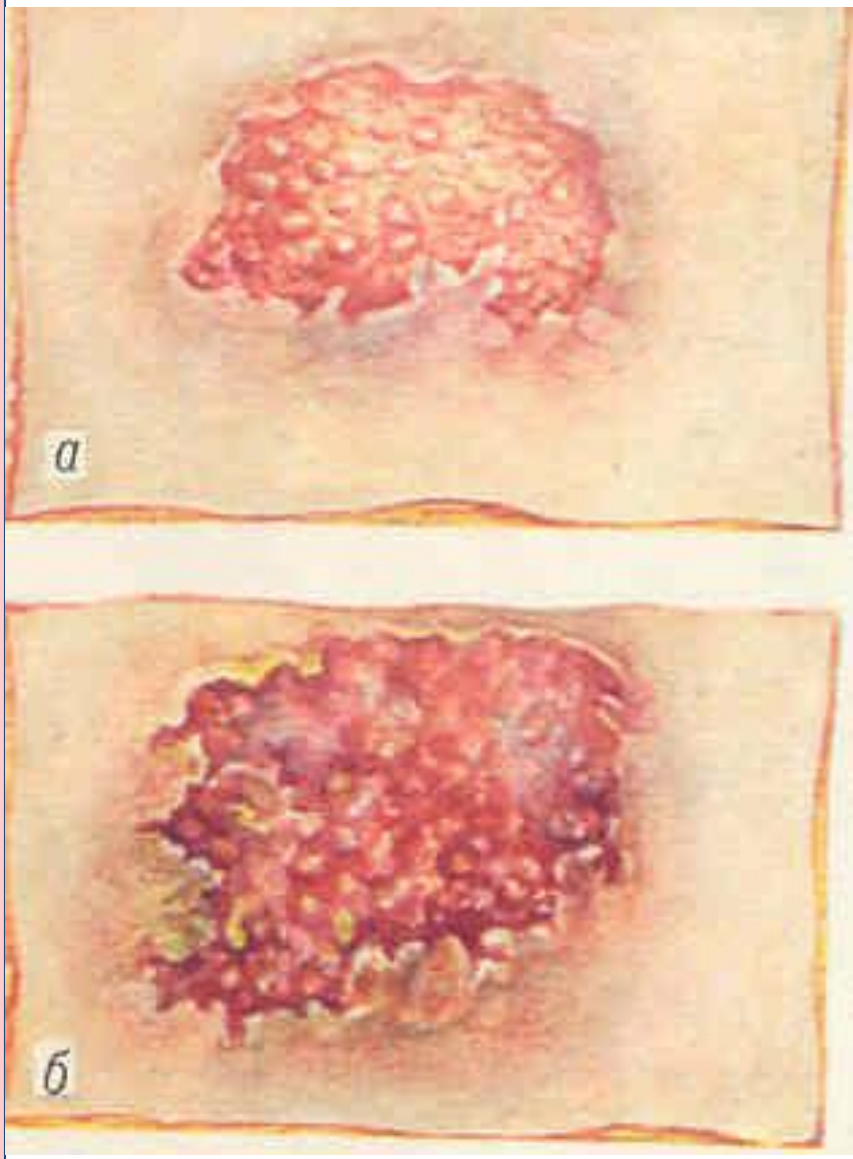
GRANULOUS TISSUE

Young connective tissue with lot of vessels

This tissue covers of wound and ulcer skin defects, it is formed during the damage of mucous membranes and internal organs, during bones fractures, hematoma organization, at necrosis (infarction), and during chronic inflammation.

FUNCTIONS:

1. **covering of defect**
2. **trophy (microcirculation regulation, oxygen and metabolites transport, filtering of substances)**
3. **morphogenetic (influence on epithelium and muscular tissue differentiation).**
4. **incapsulation (closing) of necrosis area and alien bodies**
5. **reconstruction of anatomic and functional structure of injurious tissues**



Granulomatous inflammation

- 1. Bacteria
  - **TBC**
  - leprosy
  - syphilis (3rd stage)
- 2. Parasites + Fungi
- 3. Inorganic metals or dust
  - silicosis
  - berylliosis
- 4. Foreign body
  - suture (Schloffer „tumor“), breast prosthesis
- 5. Unknown - **sarcoidosis**

Chronic Inflammation

- May last for weeks, months or years
  - Recurrent acute inflammation or low-grade responses
- Characteristics:
  - Infiltration by macrophages and lymphocytes
  - Proliferation of fibroblasts instead of exudates
  - Cause may be foreign matter, viruses, bacteria, fungi or larger parasites

Chronic inflammation

- reasons:
  - persisting infection or prolonged exposure to irritants (intracell. surviving of agents - TBC)
  - repeated acute inflamations (otitis, rhinitis)
  - primary chronic inflammation - low virulence, sterile inflammations (silicosis)
  - autoimmune reactions (rheumatoid arthritis, glomerulonephritis, multiple sclerosis)

Chronic inflammation

- chronic inflammatory cells ("round cell" infiltrate)
  - lymphocytes
  - plasma cells
  - monocytes/macrophages activation of macrophages by various mediators - fight against invaders
- lymphocytes $\rightarrow$ plasma cells, cytotoxic (NK) cells, coordination with other parts of immune system
- plasma cells - production of Ig
- monocytes-macrophages-specialized cells (siderophages, gitter cells, mucophages)

- **Chronic Inflammation**
  - The acute inflammatory reaction usually subsides within 48 –72 hours as long as the cause is removed (e.g. touching a hot stove)
  - If the cause persists, you get chronic inflammation
  - Clinically:
    - Increase in connective tissue reaction to the chronicity
      - Get more fibroblasts & more collagen
        - » Thus get more scar tissue
        - » Can get granulomas (collection of chronically inflamed tissue)

- **Treatment of inflammation**
  - Aspirin
  - NSAID's
  - Glucocorticoids
  - Heat & cold
  - Physiotherapy if chronic
    - » Prevents contractures

- **Potential complications of inflammation**
  - Infection
  - Ulceration – from chronic inflammation
    - May lead to:
      - » perforation of viscera
      - » excess scar formation
  - Skeletal muscle spasm
  - Local tissue reactive changes
    - Joints from decreased ROM become stiff
    - Lungs cannot exchange gases
- **Diagnostic tests for inflammation**
  - Leukocytosis
  - Differential WBC count
  - ESR
  - Cell enzymes – may or may not be tissue specific
    - C-reactive protein

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Inflammation is characterized by local

- swelling (edema)
- redness (erythema, vasodilation)
- warmth
- pain

Intermediated by prostaglandins

(G_2, H_2, E_2, $F_{2\acute{\alpha}}$)

NSAIDs Mechanism of Action

Inhibit inflammation and reduce pain by blocking the synthesis of prostaglandins

Stabilize cell membranes to prevent further leakage of substances (edema)

NSAIDs Adverse Effects

- Nausea
- Gastrointestinal distress, ulceration,bleeding
- Vomiting
- CNS stimulation
- Headache
- Vertigo
- Mental confusion
- Hypersensitivity reactions (rash, fever)
- Hepatic damage (elevated serum enzymes)

Immunomodulating Agents

- Immunosuppressive drugs decrease the activity of the immune system and are useful in severe allergic and inflammatory conditions, and in the prevention of organ rejection following transplantation
- Immunostimulant drugs activate the immune system and increase the ability of the body to resist infection and the growth of abnormal cancer cells

Immune Cells

- Macrophages initiate the immune response
- Helper T-cells activate other T- and B-cells
- Killer T-cells attack and kill infectious organisms
- B-cells produce antibodies
- Suppressor cells inhibit the immune system
- Memory cells retain immunogenic information and provide long-term immunity

Immunosuppressant Drugs

Corticosteroid Drugs

- Derivatives of adrenocorticosteroid hormones produced by the adrenal cortex
- Used to suppress the immune system in severe allergy, inflammation, and prevent rejection following organ transplantation
- Prednisone and prednisolone are two widely used corticosteroid drugs
- Corticosteroids are often used in combination with other immunosuppressant drugs

Cytotoxic Immunosuppressant Drugs

- Azathioprine inhibits the synthesis of immune cell DNA and is mainly used to prevent organ transplant rejection
- Cyclophosphamide is an alkylating drug used in immune-based diseases to decrease antibody production by B-cells
- Mycophenolate inhibits T- and B-cell activity and is used to prevent renal organ transplant rejection

Noncytotoxic Immunosuppressant Drugs

- Cyclosporine inhibits the function of interleukin-2 and is widely used to prevent organ rejection following transplantation
- Tacrolimus is similar to cyclosporine in action and clinical usage
- Leflunomide inhibits the synthesis of DNA in T- and B-cells and is indicated for the treatment of rheumatoid arthritis

Immunosuppressive Monoclonal Antibodies

- Muromonab-CD3 binds to and inhibits the action of T-cells involved in organ transplant rejection
- Daclizumab binds to and blocks the interleukin-2 receptor; it is used to prevent renal allograft rejection
- Infliximab inhibits TNF-alpha which is an inflammatory factor active in Crohn's disease

Immunostimulant Drugs

- Alpha-, Beta-, and Gamma-interferon are antiviral factors normally produced by activated immune cells, they are used as drugs to activate the immune system in certain viral infections and cancers
- Interleukin-2 is an immune factor normally produced by lymphocytes, it is used as a drug to activate the immune system in certain cancers