# Inflammation I.

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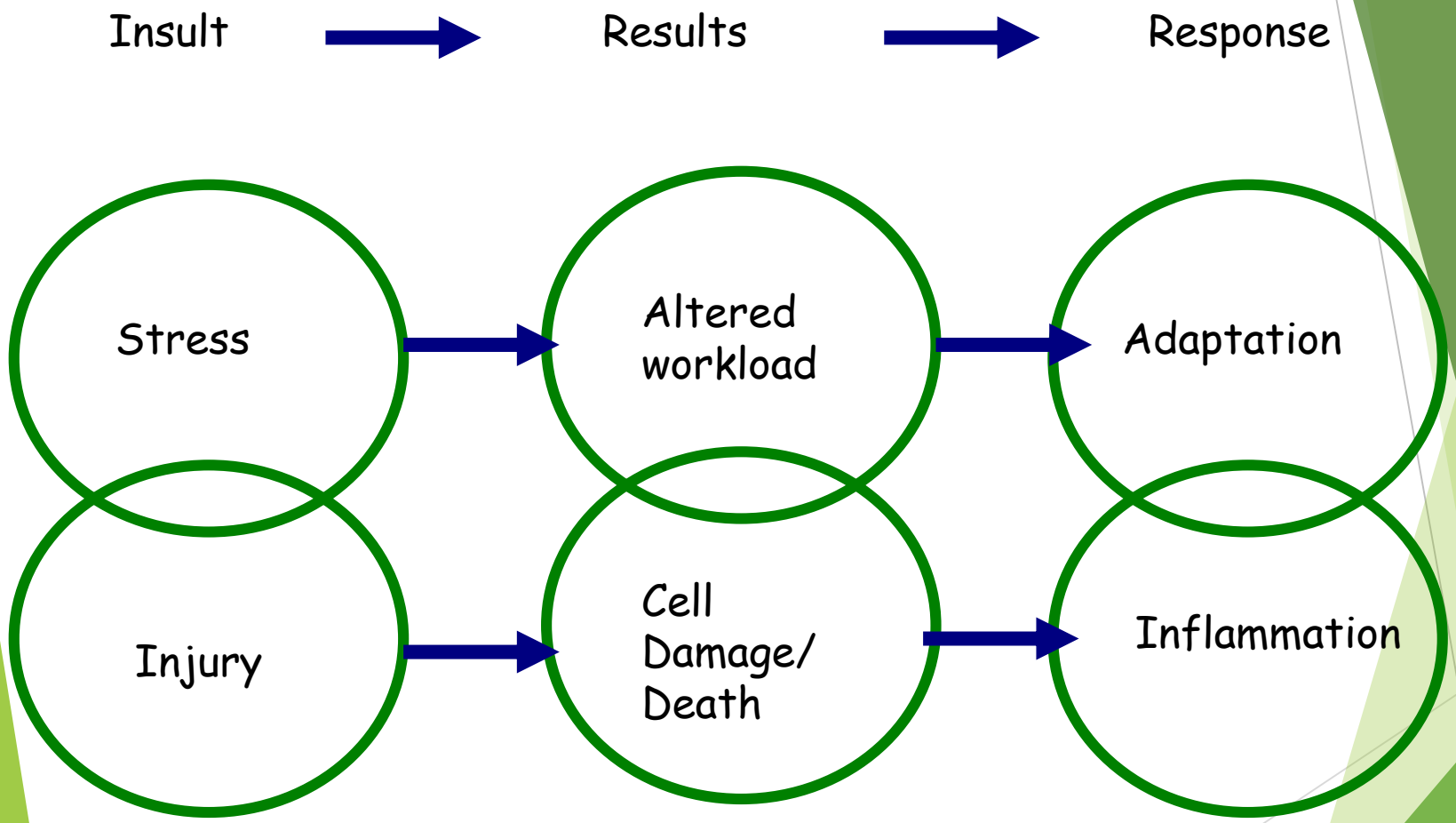
# Facts about inflammation

- High Inflammation Is Tied To Depression
- Inflammation is linked to cardiovascular disease
- Chronic Inflammation increase risk of Alzheimer's
- Chronic Inflammation Is Linked To Cancer
- Exercise Can Reduce Inflammation
- Dark Chocolate reduces inflammation


Insult
Results
Response
Stress
Injury
Altered workload
Cell Damage/ Death
Adaptation
Inflammation

# Definition

- complex protective response to injury
- caused by various endo- and exogenous stimuli
- injurious agents are destroyed, diluted or walled-off
- inflammation is not a disease
- inflammation ≠ infection
- can be potentially harmful (allergies, autoimmunity)

# Causes of inflammation

- Exogenous causes:
  - Physical agents
    - Mechanic agents: fractures, foreign objects, lacerations
    - Thermal agents: burns, freezing
  - Chemical agents: toxic gases, acids, bases
  - Biological agents: bacteria, viruses, parasites
- Endogenous causes:
  - Circulation disorders: thrombosis, infarction, hemorrhage
  - Enzymes activation – e.g. acute pancreatitis
  - Metabolic products deposals – uric acid, urea

# Types of immune response

- Innate (inherited)
  - Fast, uniform response to infection
  - generically coded (same reactions in the population)
  - recogizes conserved antigens: PAMP (LPS, CpG DNA), DAMP
  - linked to Toll-like receptors
  - no memory
  - activates adaptive immunity
  - components: granulocytes, macrophages, complement system

- Adaptive
  - slow response, but highly specific
  - has memory, can be taught
  - not inheritable – different in the members of a population
  - may cause harm: allergies, autoimmunity, tissue rejection
  - components: lymphocytes, plasma cells, antibodies

# Classification
(several points of view)

- according to duration
  - acute - chronic (+ subacute, hyperacute)
- according to histological features
  - non-specific (not possible to trace etiology) - vast majority
  - specific / granulomatous (e.g. TBC)
- according to causative agent
  - non-infectious (sterile) - chemical substances, congelation, radiation - inflammation has a reparative character
  - infectious (caused by living organisms)
    - bacterial, viral, fungal, parasitic, ect.
- according to exent
  - local
  - systemic

# Terminology

- Greek root + -itis
- gastritis
- enteritis
- carditis
- nephritis
- stomatitis

BUT

- pneumonia
- glossitis, not linguitis
- cheilitis, not labiitis

# Acute inflammation

- Rapid onset ( seconds, minutes)
- Short duration ( max. a few days)
- **Exsudation** of fluids and plasma proteins
- Characteristic cells: **neutrophil granulocytes** (PMN cells)
- Orchestered by **chemical mediators**

# Cardinal signs of acute inflammation

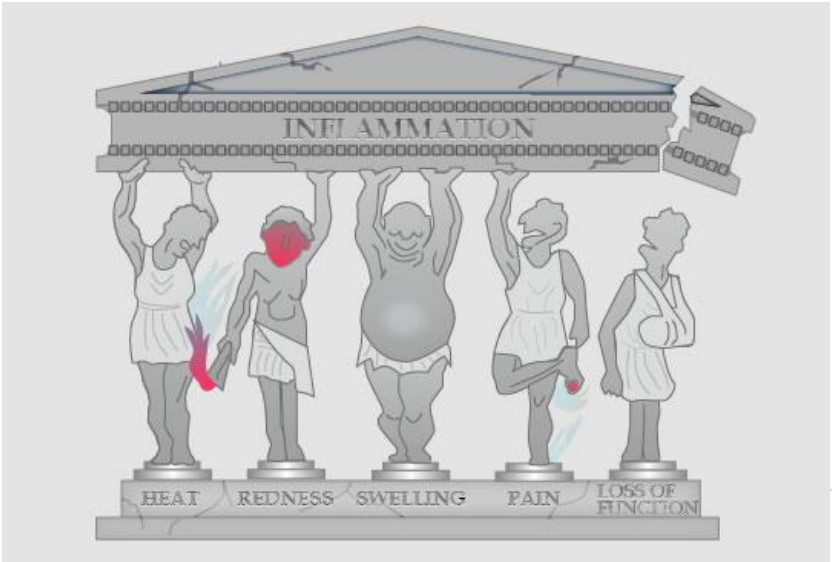
(CELSUS)

**"rubor et tumor cum calore et dolore"**

**(redness and swelling with heat and pain)**

**--Cornelius Celsus in De Medicina, 1st century A.D.**

**later "functio laesa" (disturbance of function) was added by Virchow**



# Components of acute inflammatory reaction

- **vascular** reactions
- **cellular reactions**: migration and activation of leukocytes
- **systemic** reactions (chemical mediators)

# 1. Vascular reactions

Goal: deliver inflammatory cells to the site of injury

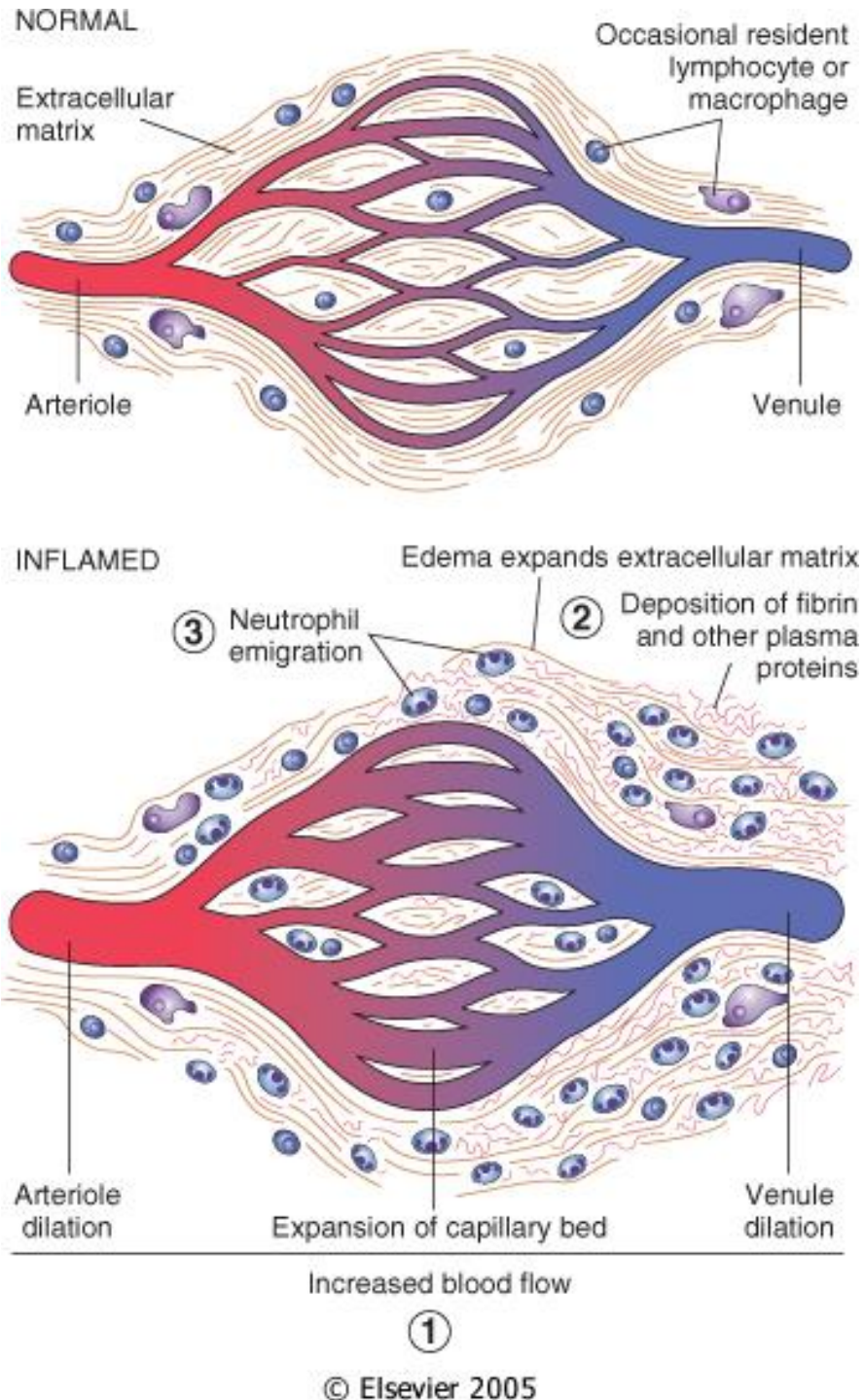
- **1. Vasodilation** (active hyperaemia) arterioles dilate → capillaries open
  - increased blood flow and increased hydrostatic pressure

- **2. Increased vascular permeability**

  Plasma proteins escape→ increased osmotic pressure in the interstitium
  - early phase – histamin, bradykinin (postcapillary venules)
  - late phase – TNFα, INFγ, IL-1 (capillary vall damage)

Result: transudate – fluid with low protein content

exudate - fluid with high protein content

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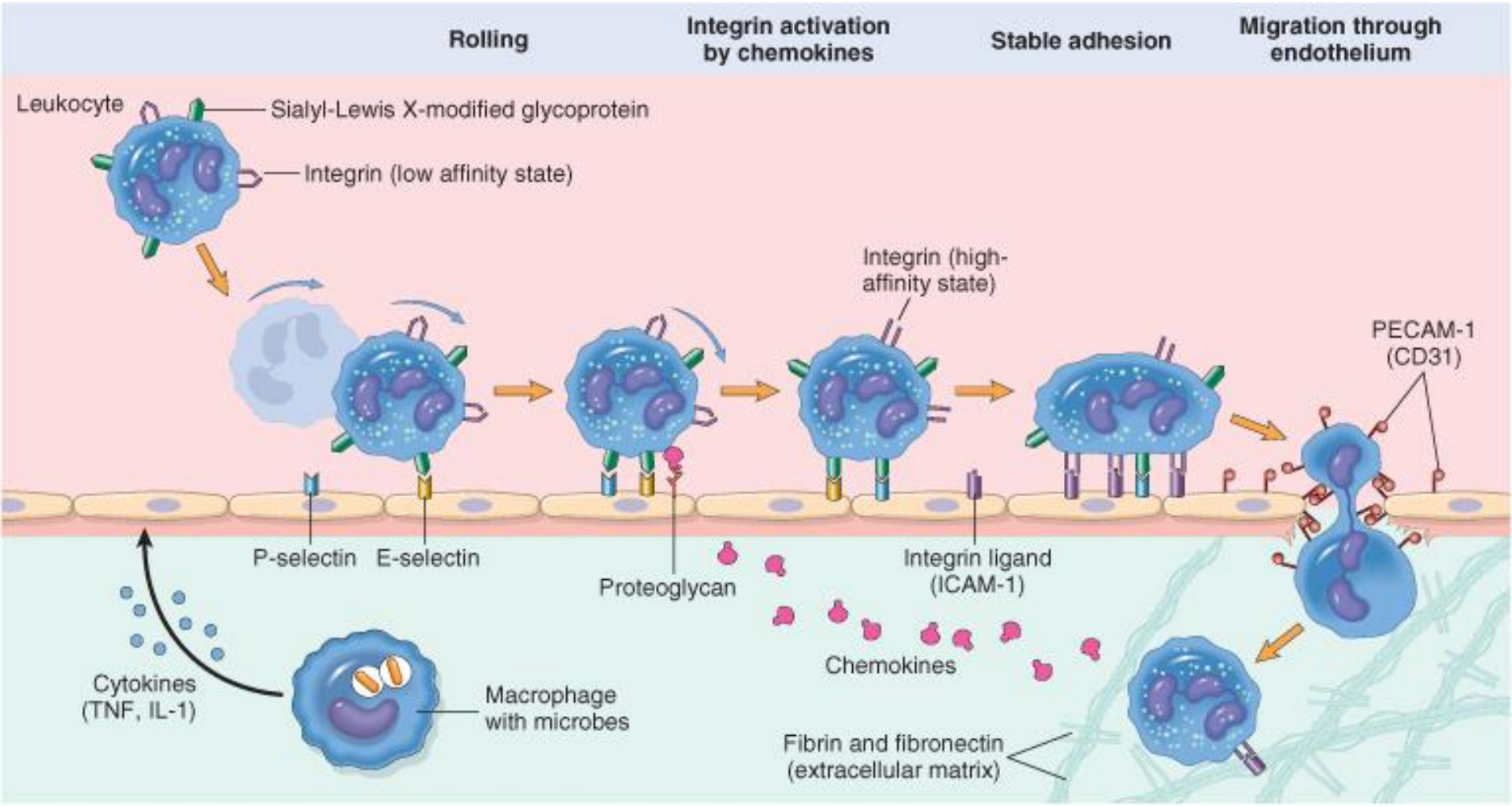
# 2. Cellular events

Goal: **Recruitment** > migration of leukocytes from the microcirculation to site of inflammation

- Steps:
  - **Margination:** fMLP (f-Met-Leu-Phe) complement, thrombin, chemokines
  - **Rolling:** selectins
  - **Adhesion:** integrins, ICAM, VCAM
  - **Transmigration/Diapedesis:** through venules
  - **Activation:** mediators released from macrophages activate leukocytes
  - **Effector mechanisms:** opsonisation (IgG, C3b, CRP), phagocytosis, ROS, proteases

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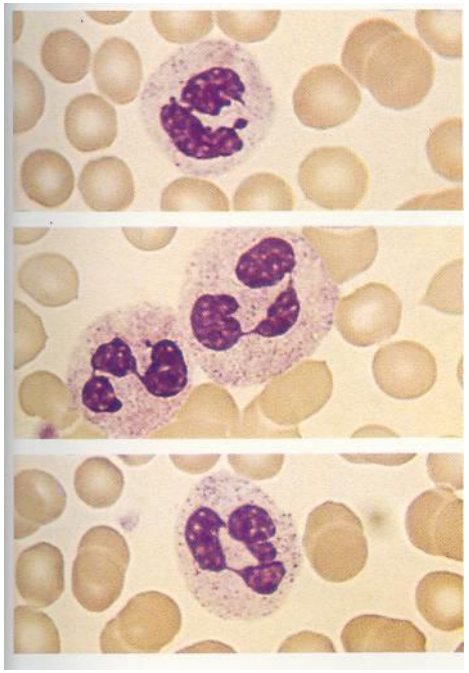
# Cellular components I.

Neutrophil granulocytes

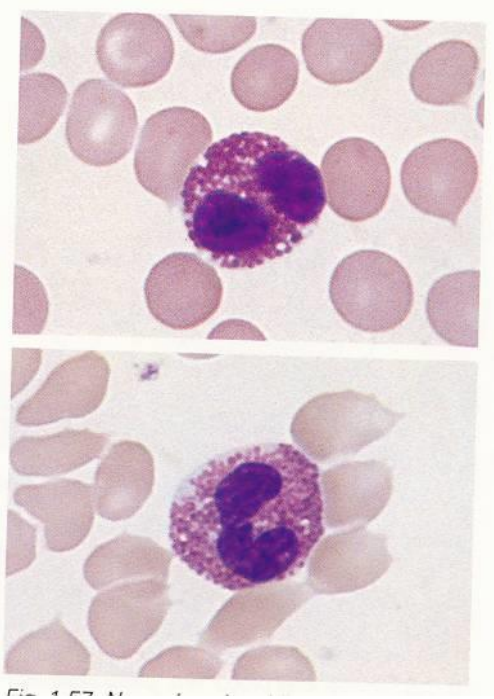
- Major phagocytic granulocyte
- Contain multilobed nucleus
- Neutrophilic granules
- Respond to chemotactic stimuli
- Activated by macrophage and endothelial derived cytokines
- Major cell of acute inflammation
- Primary effector cells in IR to pyogens
- May secrete their enzymes



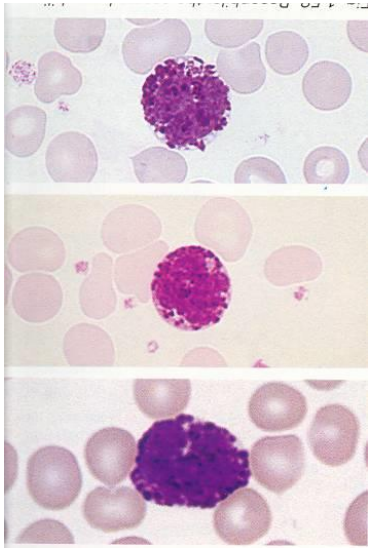
# Cellular components II.

Eosinophil granulocytes

- Contain eosinophilic granules
- Express Fc receptors for IgE
- IgE prevalent in parasitic infections
- IgE mediates activation of eosinophil killing mechanisms
- Role in immediate hypersensitivity to allergens
- Cause tissue injury and inflammation

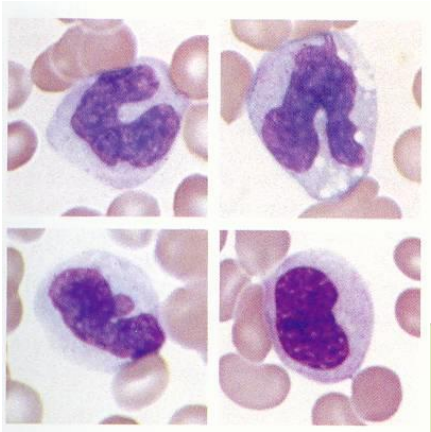


# Cellular components III.



Basophil granulocytes

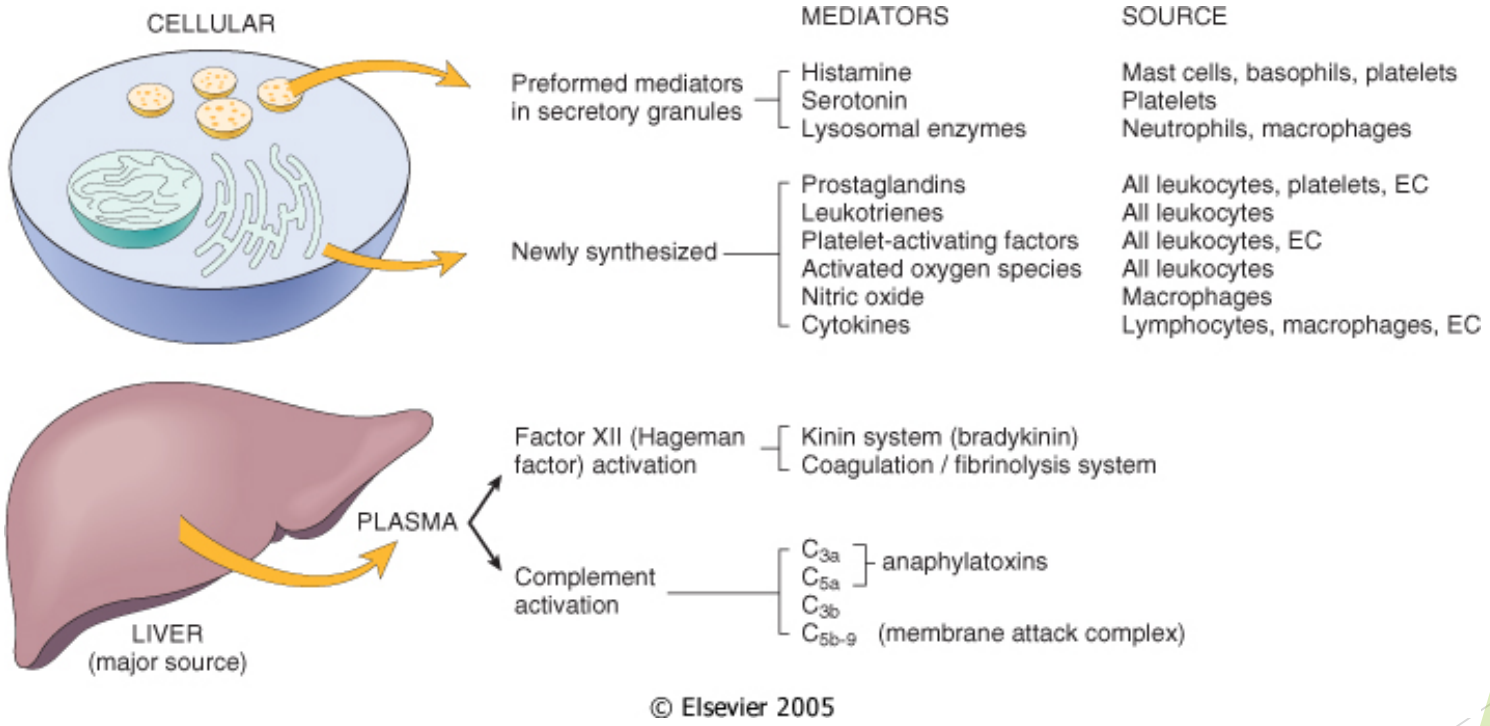
- In circulation –basophils
- In tissue- Mast cells
- Express Fc receptors for IgE
- Release chemical mediators of immediate hypersensitivity



Monocytes/Macrophages

- Regulators of inflammatory response by releasing cytokines
- Major class of phagocytic cells
- Participate in both acute and chronic inflammation
- Provide link between innate and adaptive response (act as APC)
- Phagocytose apoptotic PMN's

# 3. Chemical mediators



# 3. Chemical mediators

- TNF-a and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system), stimulate synthesis of IL-6, IL-8, and interferon gamma.
- Cytokines, especially IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP).

- Complement fragments
  - Stimulate chemotaxis of neutrophils, eosinophils and monocytes;
  - C3a, C5a increase vascular permeability;

- Cytokines
  - Interleukins (IL1, IL 6, IL8)
    - Stimulates the chemotaxis, degranulation of neutrophils and their phagocytic activity
    - Induce extravascularization of granulocytes
    - Fever
  - Tumor necrosis factor (TNF)
    - Leukocytosis
    - Fever
    - Stimulates prostaglandins production

# 3. Chemical mediators

- Prostaglandins
  - Lipid soluble molecules derived from arachidonic acid through the cyclooxygenase pathway.
  - Contribute to vasodilation, capillary permeability, and the pain and fever that accompany inflammation.
  - Cause the dilation of precapillary arterioles (edema), lower the blood pressure, modulates receptors activity and affect the phagocytic activity of leukocytes.
  - The prostaglandin thromboxane A2 promotes platelet aggregation and vasoconstriction

# 3. Chemical mediators

- Leukotrienes
  - From arachidonic acid, but through the lipoxygenase pathway.
  - Histamine and leukotrienes have similar functions.
  - Histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized.
  - Leukotrienes C4 and D4 are recognized as the primary components of the *slow reacting substance of anaphylaxis* (SRS-A) that causes slow and sustained constriction of the bronchioles.
  - Affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and stimulates the chemotaxis and extravascularization of neutrophils, eosinophils, and monocytes.

# 3. Chemical mediators

- Histamine
  - Found in platelets, basophils, and mast cells.
  - Causes dilation and increased permeability of capillaries
- Platelet-activating factor (PAF)
  - Generated from a lipid complex stored in cell membranes;
  - Induces platelet aggregation;
  - Activates neutrophils and is a potent eosinophil chemoattractant;
  - Contributes to extravascularization of plasma proteins
- Plasma Proteases
  - Bradykinin - causes increased capillary permeability (implicated in hyperthermia and redness) and pain;
  - Clotting factors - Contribute to the vascular phase of inflammation, mainly through formation of fibrin peptides

# Summary of chemical mediators

**Vasodilation**

Prostaglandins $E_2$, $D_2$, $F_{2\alpha}$, $I_2$

Nitric Oxide

**Increased Vascular Permeability**

Histamine, Serotonin

Bradykinin

C3a and C5a (through liberating amines)

Leukotrienes $C_4$,$D_4$,$E_4$

PAF (AGEPC)

oxygen free radicals

**Chemotaxis**

C5a

Leukotriene $B_4$

IL-8

Bacterial products

**Pain**

$PGE_2$

Bradykinin

**Fever**

IL-1, IL-6, TNF

$PGE_2$

**Tissue Damage**

Neutrophil and macrophage lysosomal enzymes

Oxygen derived free radicals

Nitric Oxide

# Systemic consequences of inflammation

- **Fever** – caused by pyrogic cytokines (IL-6, TNFα) on hypothalamus
- **Leukocytosis**
- Increased **erythrocyte sedimentation rate** (ESR)
- **Acute phase proteins** (CRP, SAA, fibrinogen)
- Incresed **pulse rate**
- **Chills**

# Outcomes of acute inflammation

1. RESOLUTION - restoration to normal
- in limited injury
- chemical substances neutralization
- normalization of vascular permeability
- apoptosis of inflammatory cells
- increased lymphatic drainage

2. HEALING by granulation tissue / fibrous scar
- tissue destruction
- fibrinous inflammation - adhesions, fibrosis
- purulent inflammation - abscess formation

3. PROGRESSION to chronic inflammation

# Chronic inflammation

Reasons:

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

Cellular component - ("round cell" infiltrate)

- lymphocytes (T and B), plasma cells
- eosinophils – parasites, allergies
- monocytes / macrophages activation by various mediators

# Morphologic patterns of acute inflammation

- Serous inflammation – inflammatio serosa
- Fibrinous inflammation – inflammatio fibrinosa
- Purulent inflammation – inflammatio purulenta
- Hemorrhagic inflammation – inflammatio haemorrhagica
- Gangrenous inflammation – inflammatio ichorosa seu gangraenosa

# Serous inflammation

Exudate: a thin watery fluid, low protein content (transsudate) originating from the plasma or secretions of mesothelial cells lining the body cavities (effusions)

Examples:

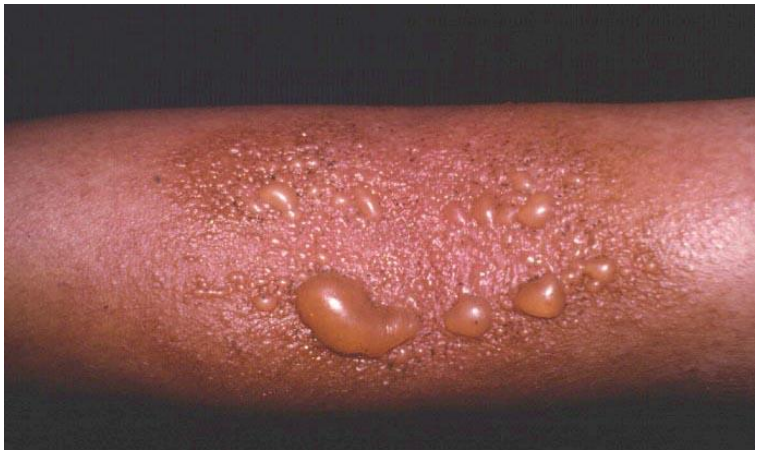
Skin – blisters from trauma or burns

Nasal mucosa - Common cold (rhinitis), allergy

Gut mucosa - cholera

Mesothelial linings - Peritoneal, pleural, pericardial cavities

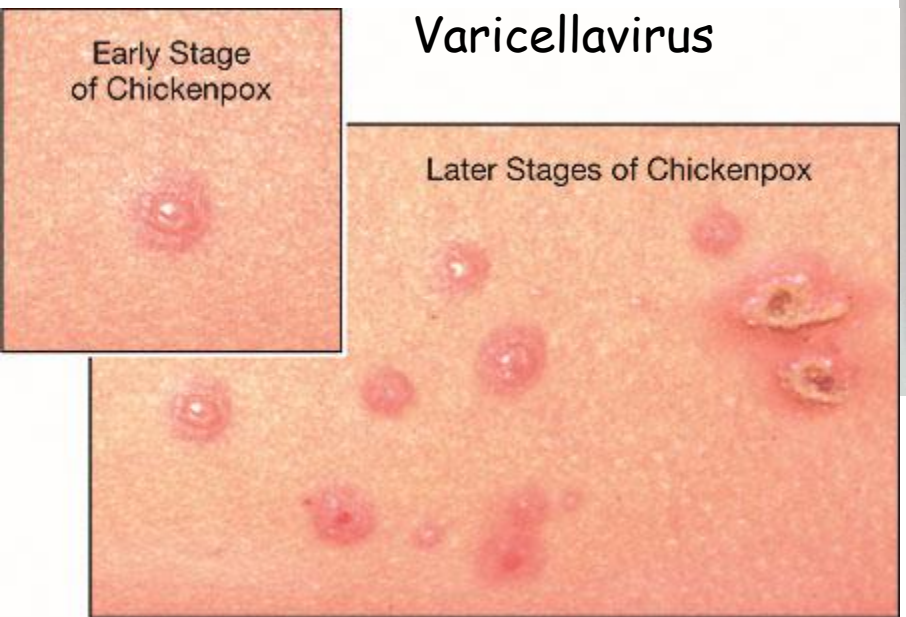
# Blisters



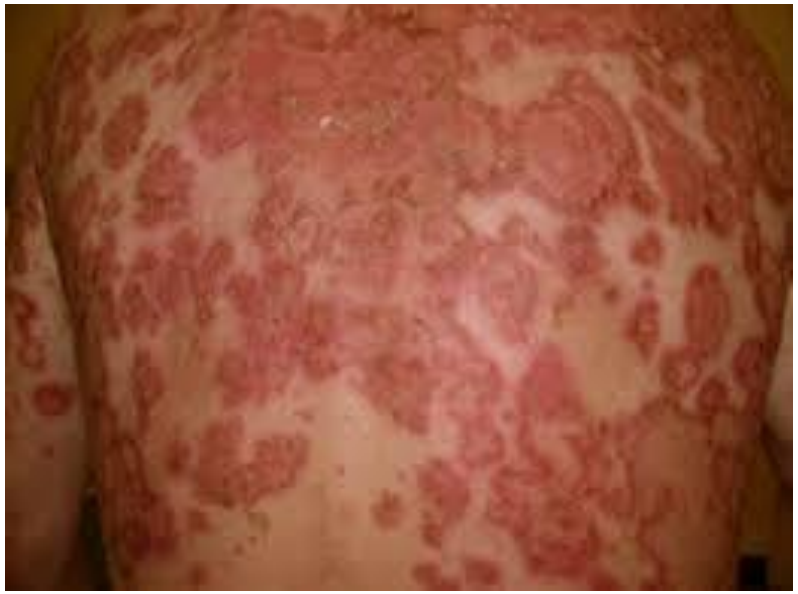
From a burn

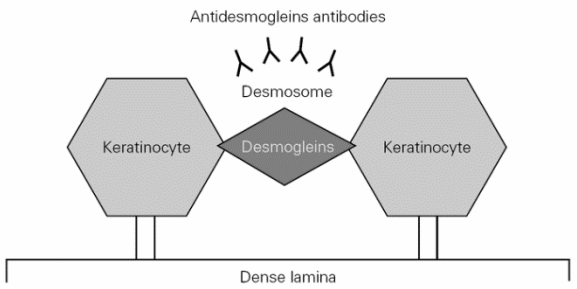
Herpes simplex type I

Varicellavirus

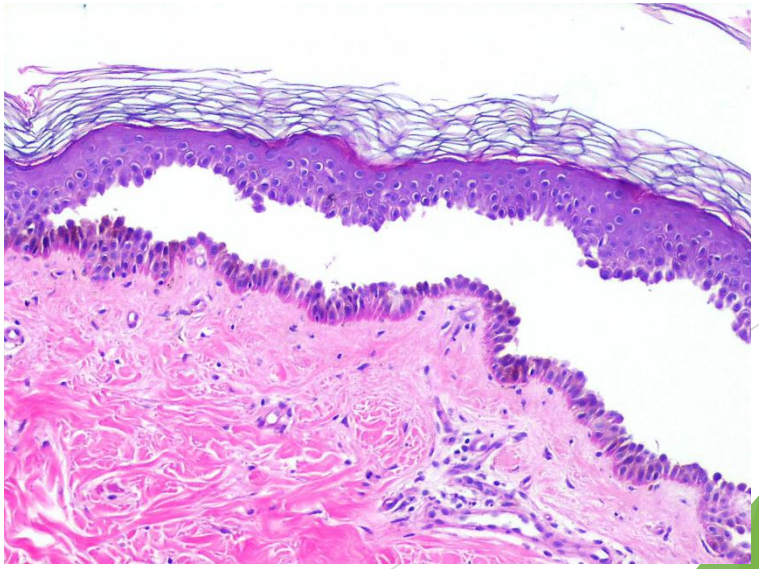


# Pemphigus vulgaris






- Autoimmune mechanism
- Type II. hypersensitivity
- Target: desmoglein
- Suprabasal achantolysis
- Skin bullae
- Tzanck-cells



# Outcome: usually favorable except

- serous meningitis
- severe burns,
- Cholera – dehydration
- Serous laryngitis (H. influenzae, drug allergies, inhalation of irritants)