ACUTE INFLAMMATION

Roman A. Benacka, MD, PhD, prof.

Department of Pathophysiology,

Medical Faculty, Safarik University, Kosice, Slovakia

The Immune System

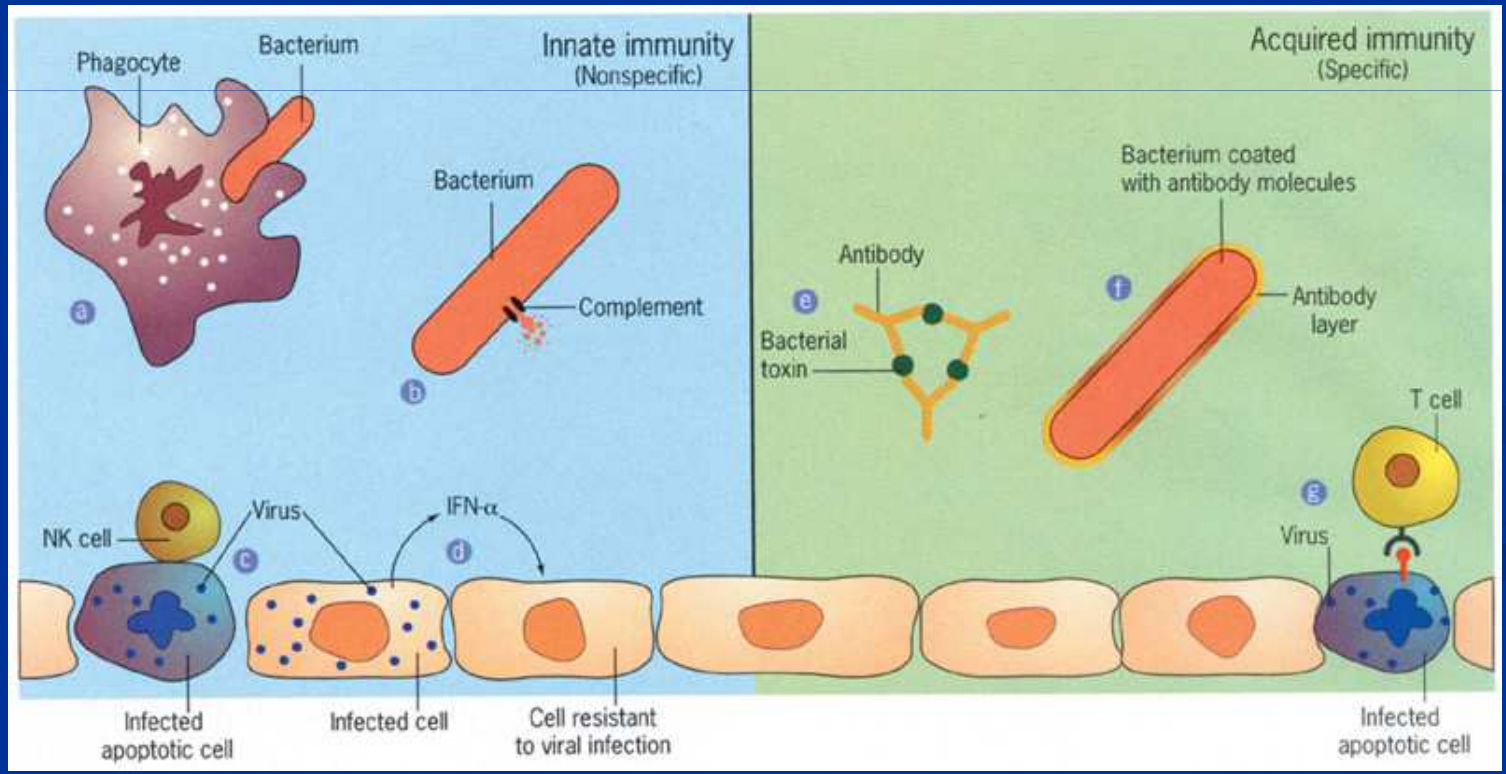
- Defense against pathogens
- Prevention of a neoplastic clone

Innate (natural) immunity

- first line of defence
- rapid; independent of previous exposure to a pathogen
- common to all members of a species

Acquired immunity

- induced by previous exposure to antigens that are
- perceived as non-self
- specific for each antigenic substance
- memory



Inflammation - Definition

Localized reaction of vascularised tissue to the local injury, that exceeded homeostatic measures

Purpose:

- To mobilize the inflammatory cells and plasma factors and bring them to the site of injury
- To destroy, dilute or wall off the injurious agents
- To start the healing process, scar formation
- To learn specific immune system

Causes:

- Physical, trauma, chemical, thermal injury (burns, frostbites), radiation (UV, X)
- Infections: Virus, bacteria, parazite, protozoa, fungi
- Hypersensitivity, Autoagression,
- Foreign bodies, implants

1. Clinical

Acute - minutes, hours (< 2 weeks)
Subacute – 2- 6 weeks
Chronic - > 6 weeks to years

2. Histological

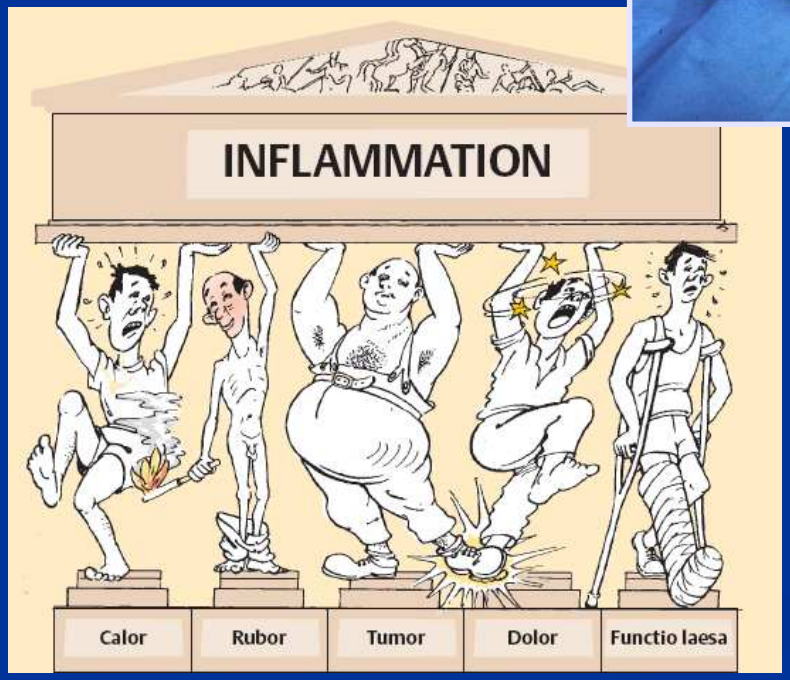
Acute - granulocytes (Neu, Eo, Ba), mastocytes, histiocytes, Mono/Macrofages
Chronic - lymphocytes, Mo/Mf, fibroblasts, atypical cell derivatives (e.g. giant cells, foam cells, etc.)

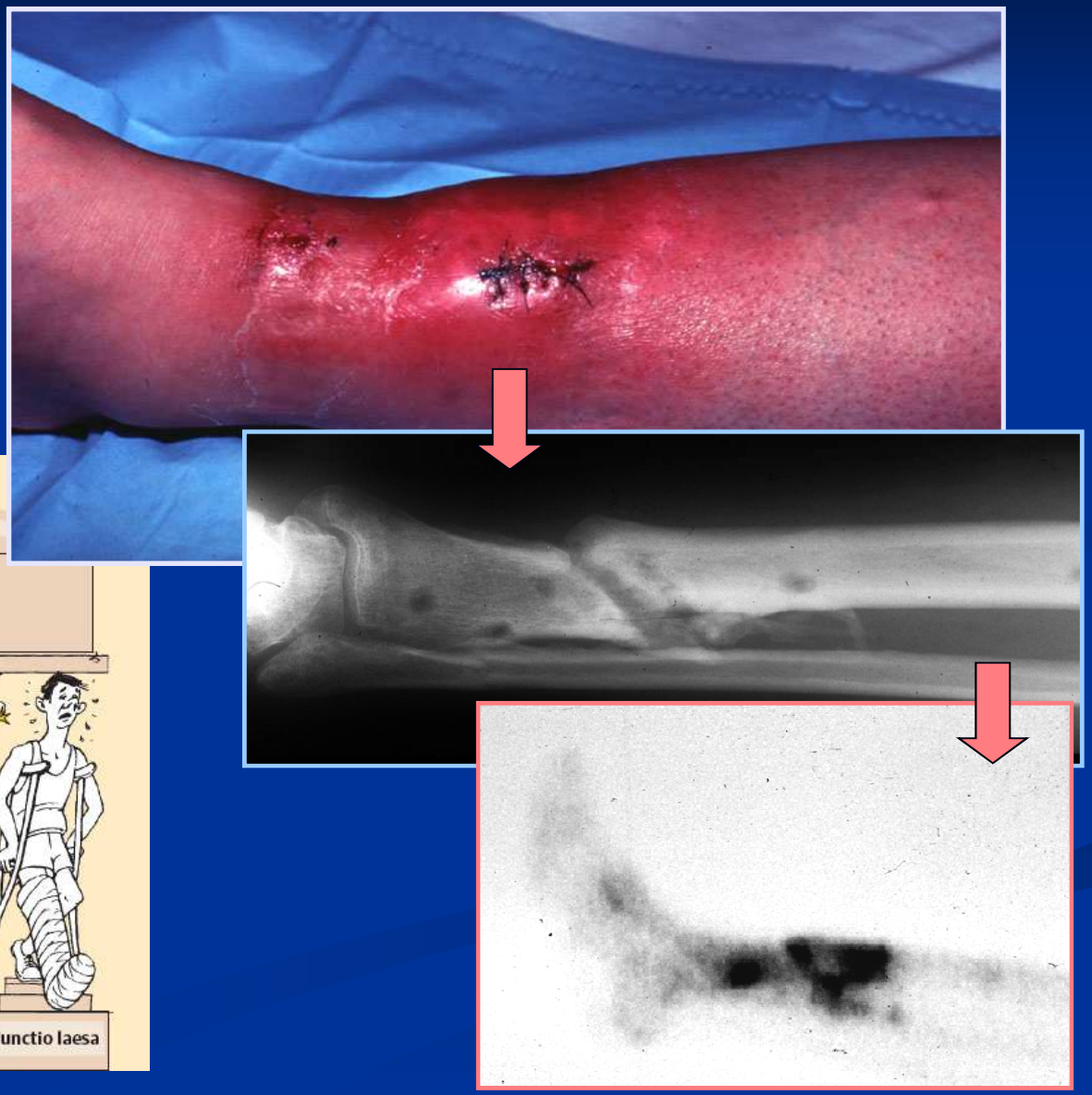
3. Depth

Superficial – skin, mucous membranes
Deep – muscles, fascias, mesenchyme

Acute inflammation - manifestations

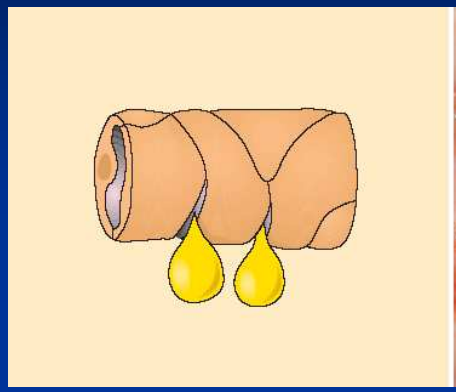
Classical hallmarks:
Redness
Heat
Swelling
Pain
Loss of function



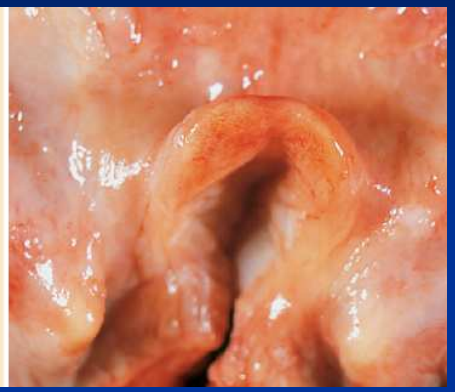


Inflammation - Histological classification

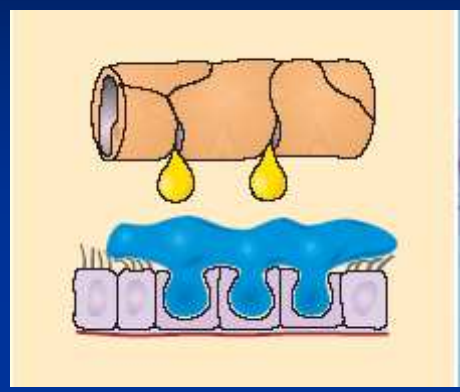
Serous



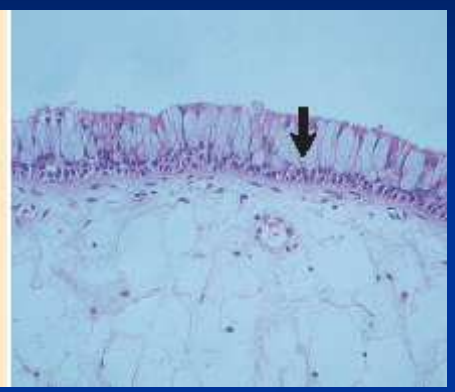
Laryngitis



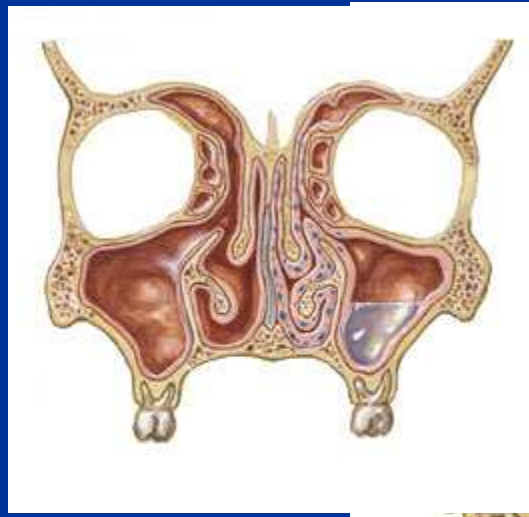
Seromucinous

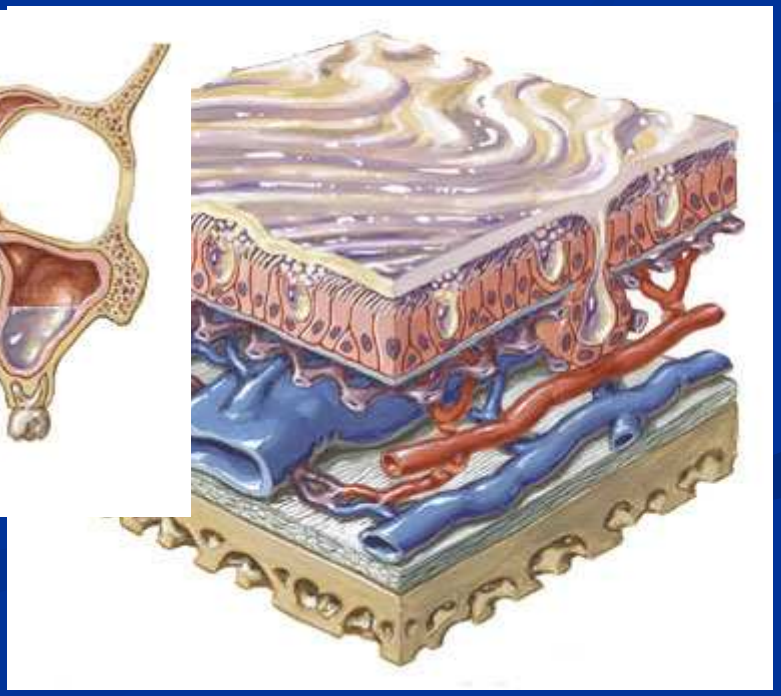


Rhinitis



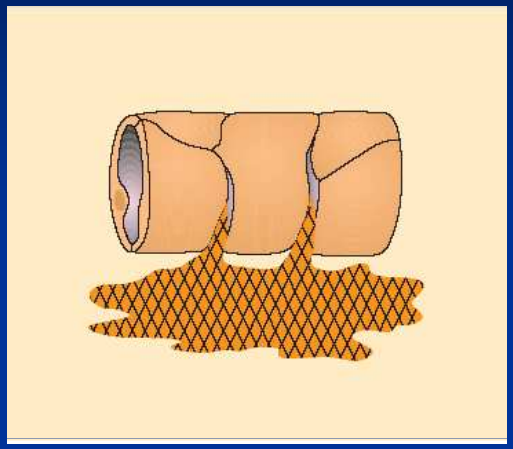
- Minimal to large amount of clear to cloudy colored fluid
- Produced by mesothelial cells
- May be caused by blood plasma
- Blisters are an example

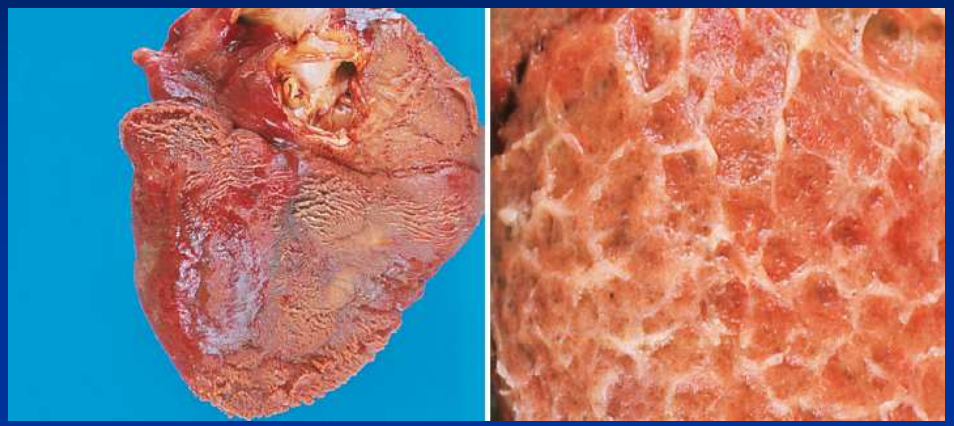




Inflammation - Histological classification

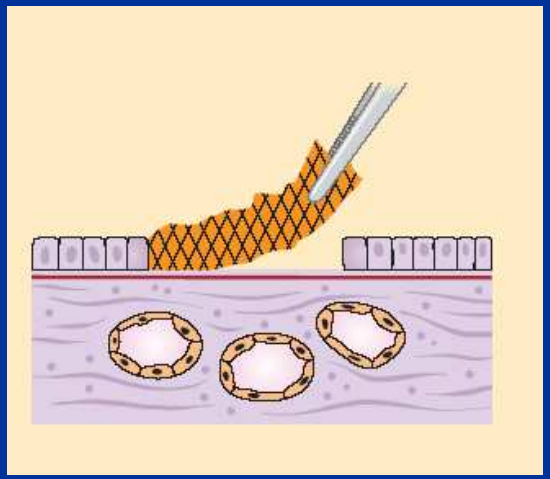
Fibrinose - Large amount of fibrin deposits, cavity formation

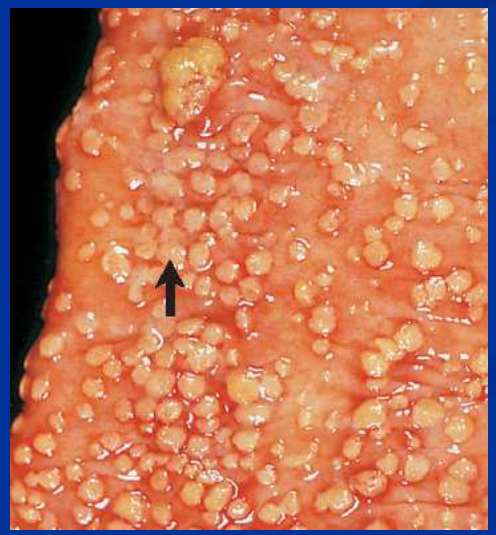




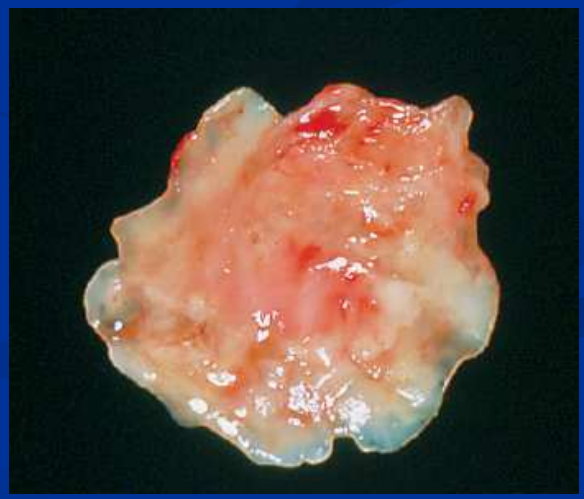
Pericarditis

Pseudomembranose



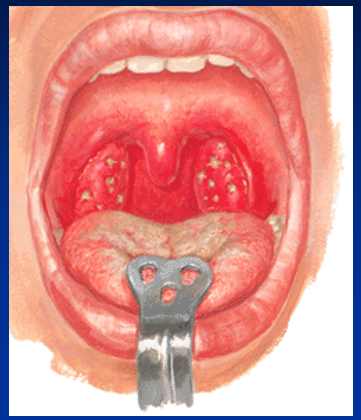


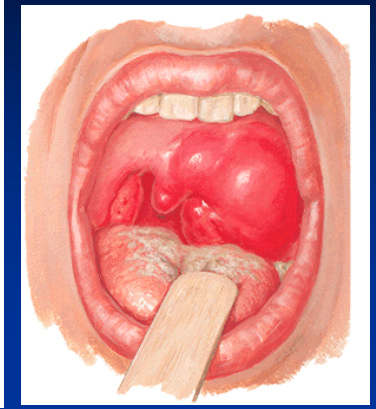
Laryngotracheitis

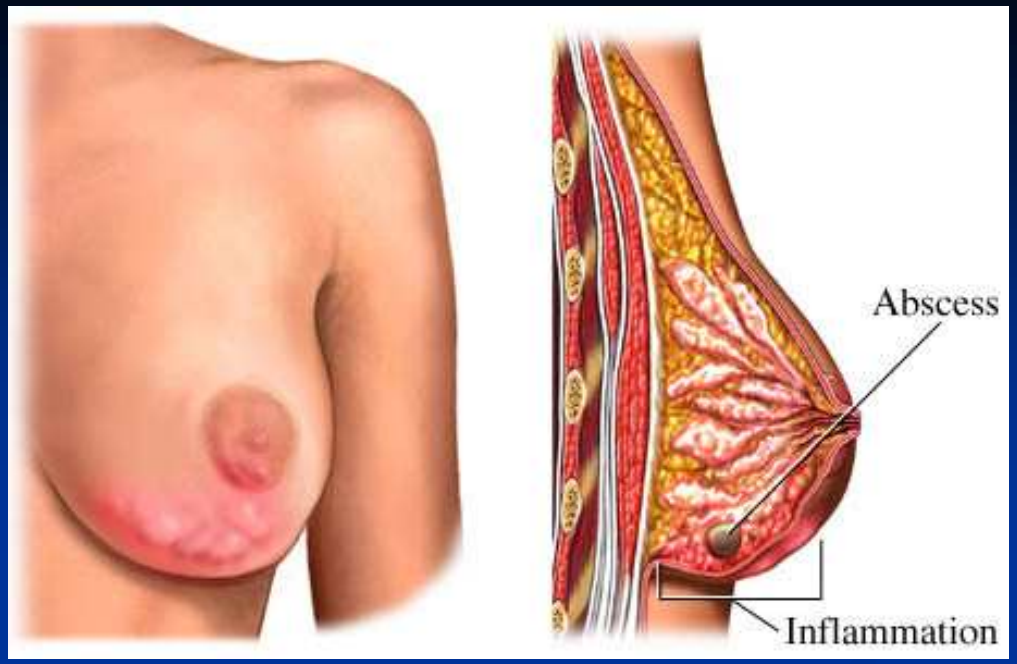


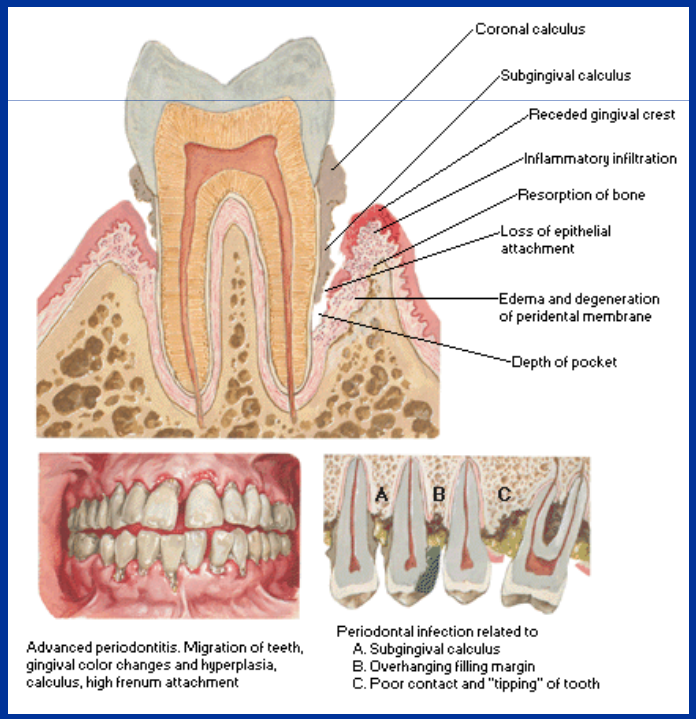
Suppurative

Tonsilitis

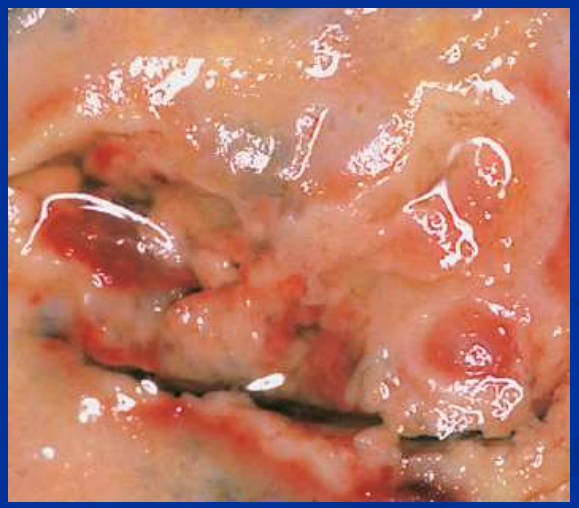




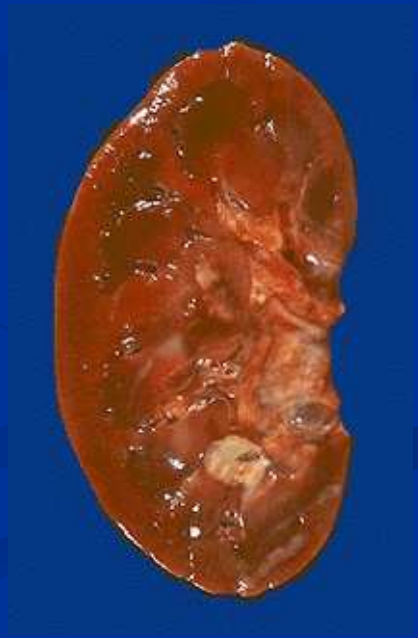




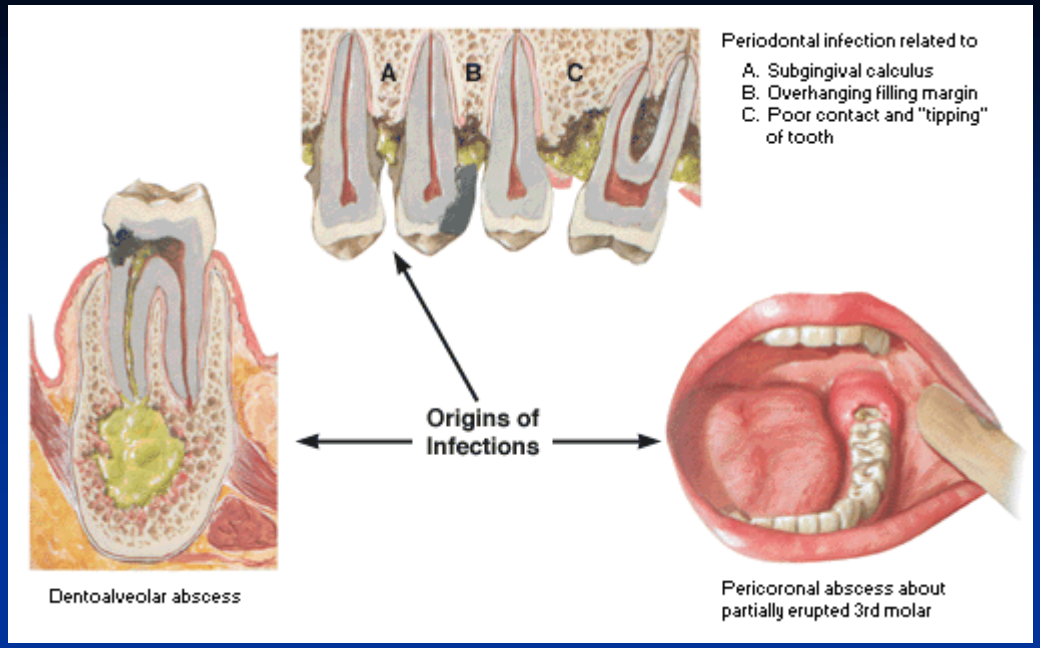
Periodontal disease



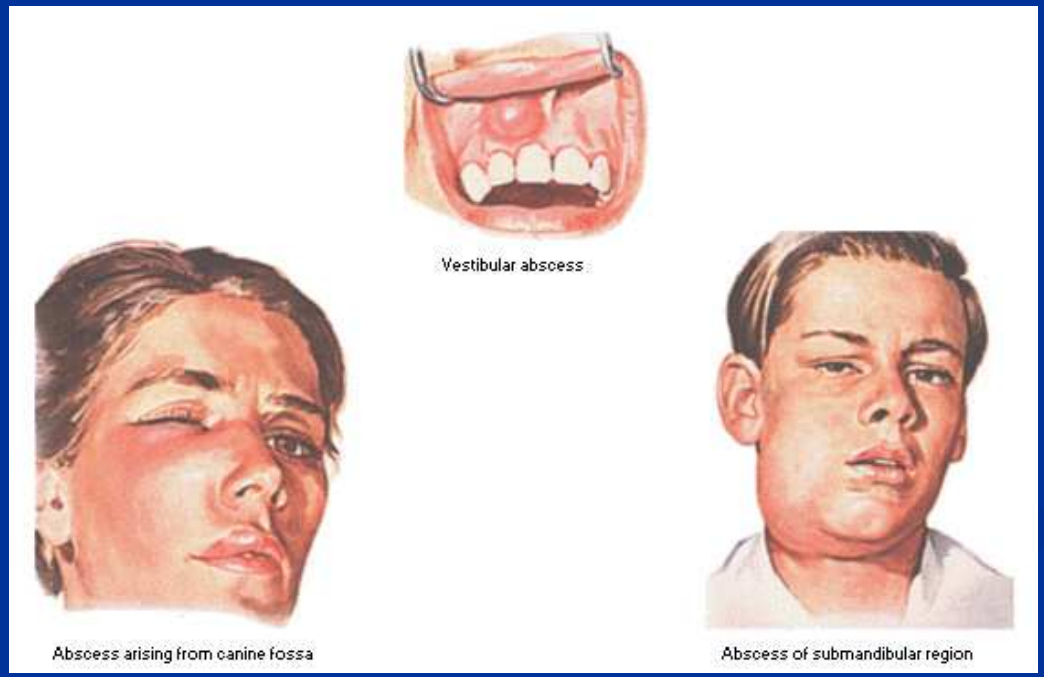
Bronchopneumonia



Renal abscess



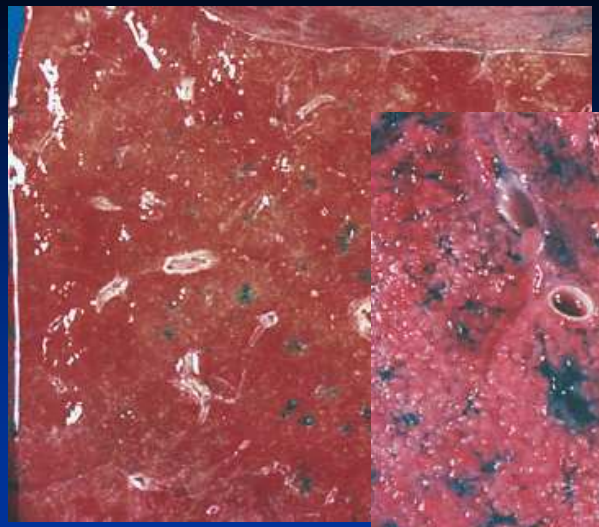
Odontogenic abscess



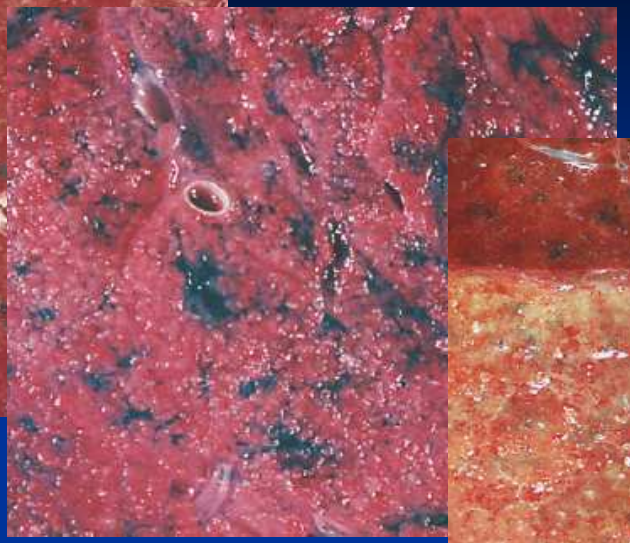
Renal abscess

Fibrinous - Suppurative

Lobar pneumonia

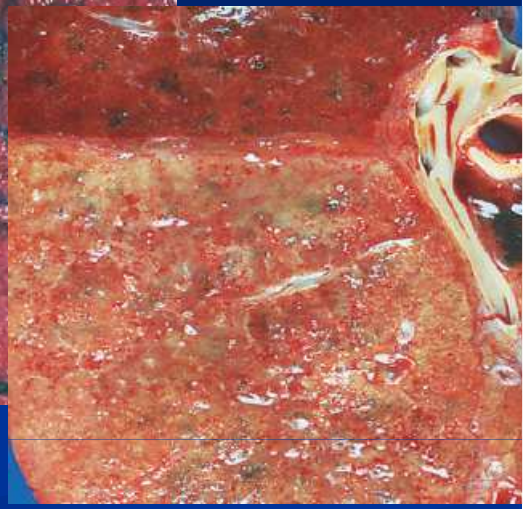


Red stage

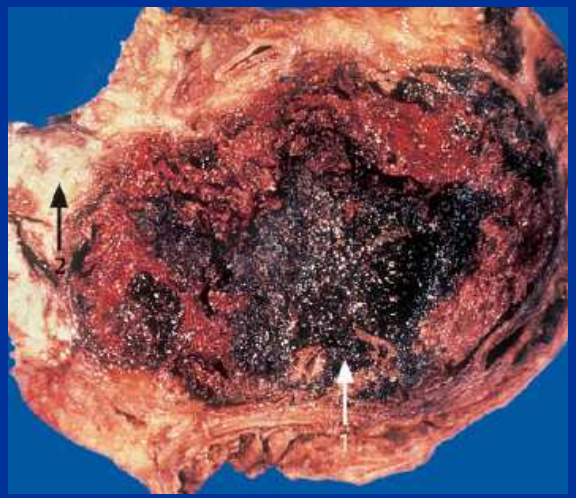


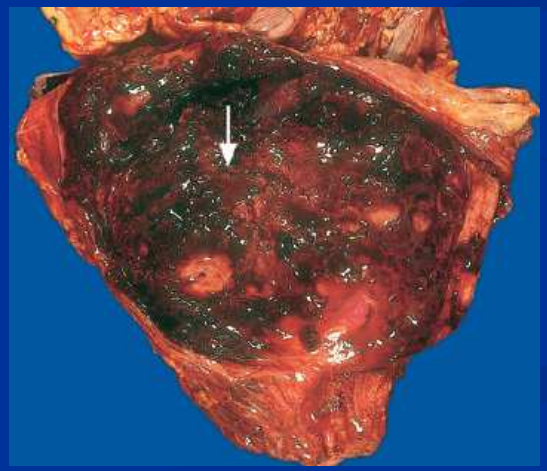
Gray stage

Yellow stage

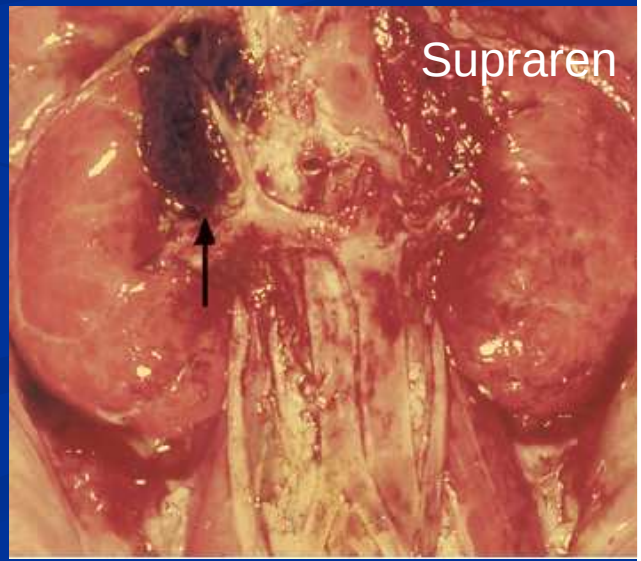


Hemorrhagic





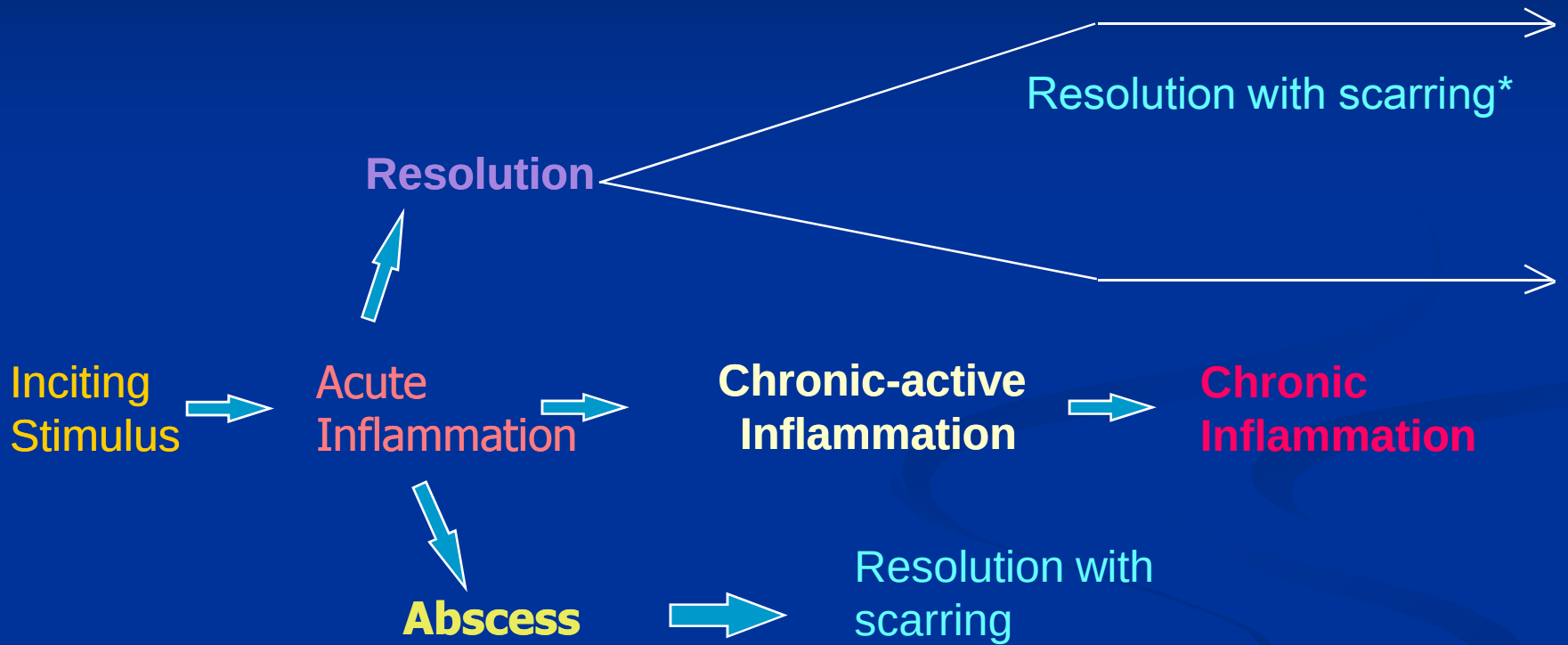
Cystistis



Supraren

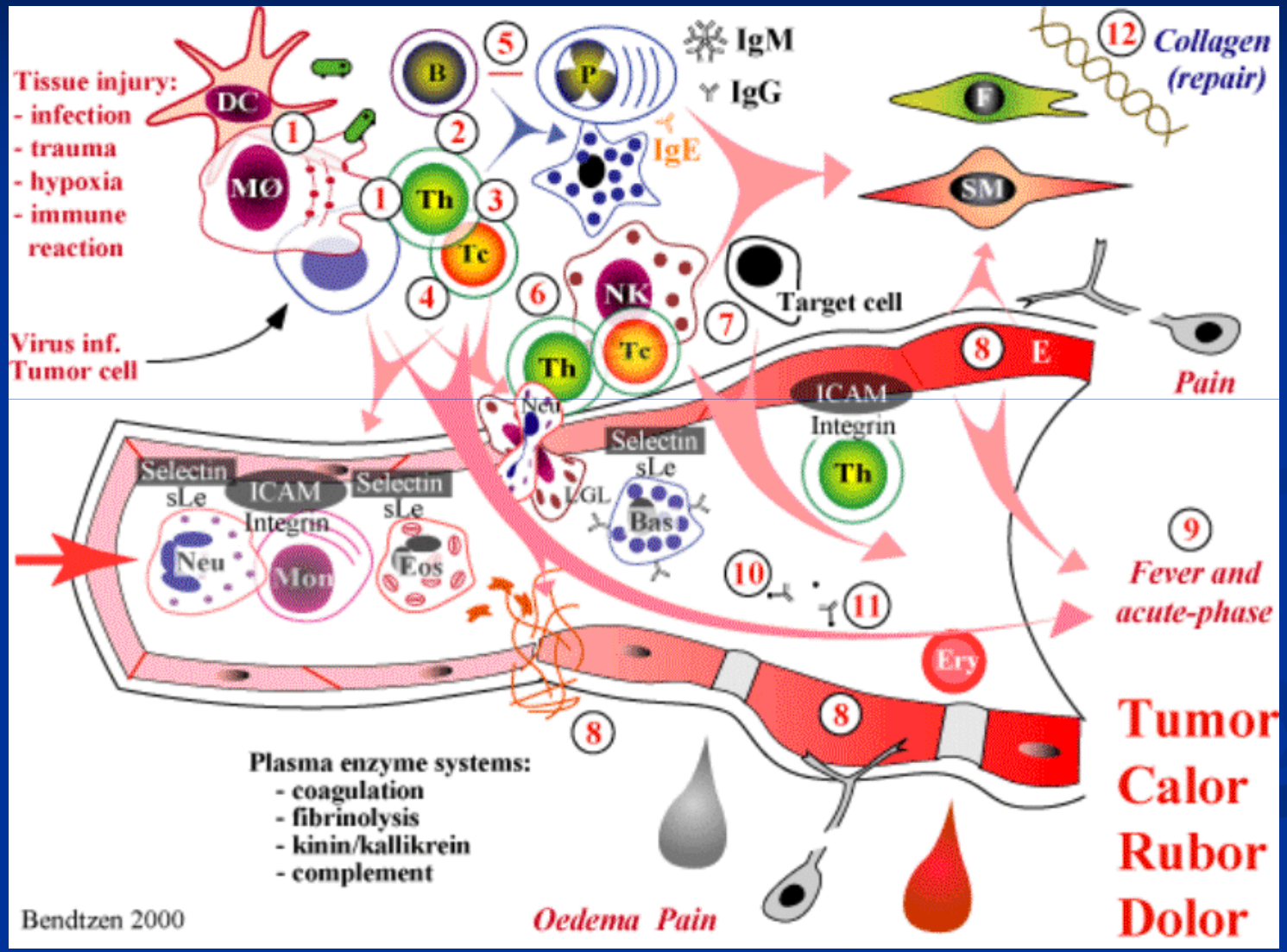
Inflammation

A dynamic continuum of change



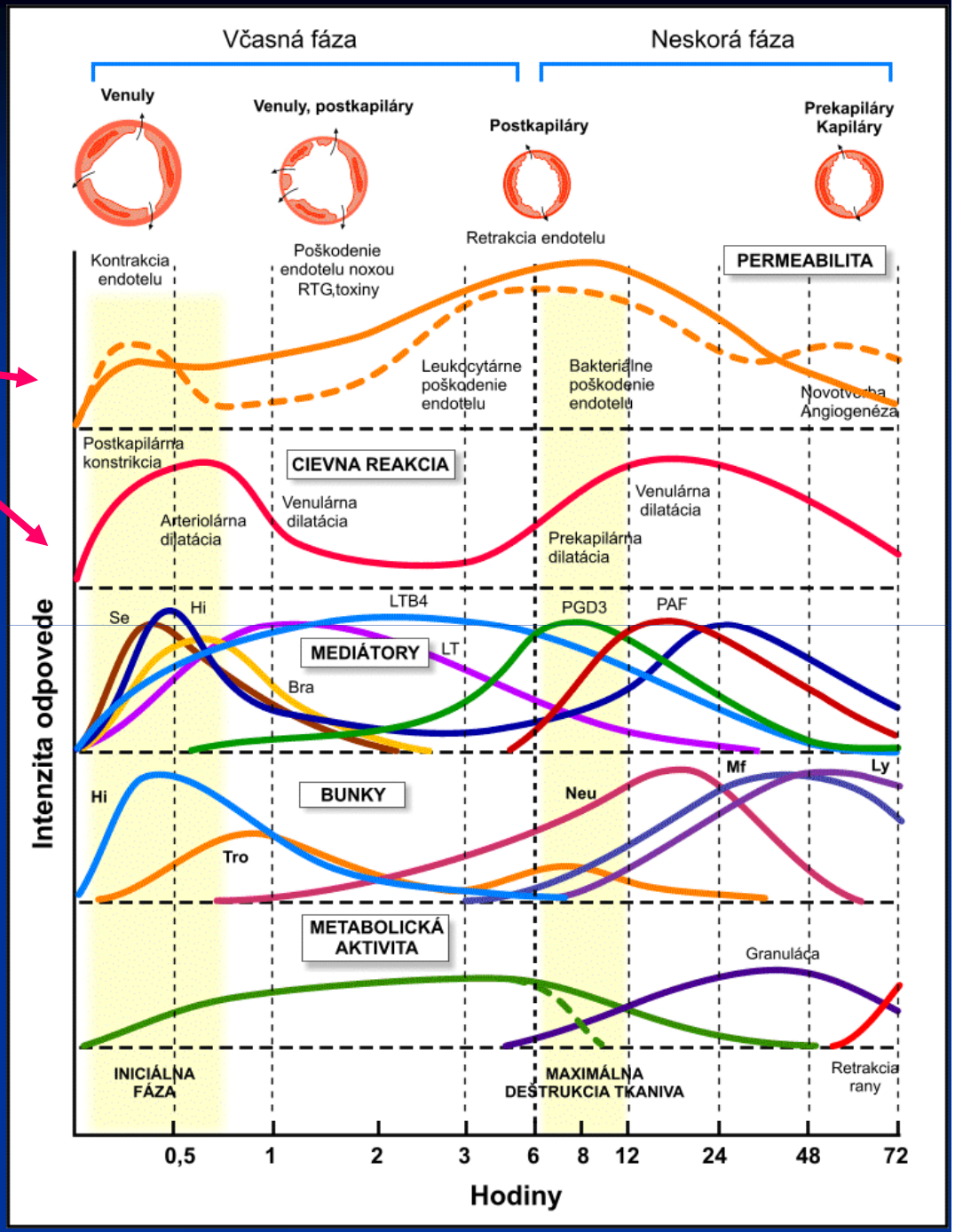
Mechanisms of acute inflammation

Inflammation – Overview



Acute Inflammation - Components

1. **Haemodynamic changes**
   Vasoconstriction
   /Vasodilatation
2. Cellular response
3. Humoral responses (Mediators)



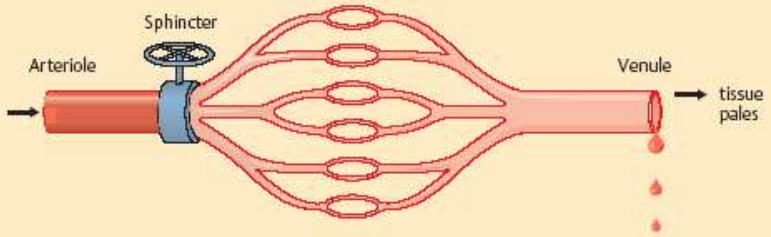
(1) Haemodynamic changes - summary

(1) **Vasoconstriction (transient, sec)**
(2) **Vasodilation (min-hours)**
(a) Early increase of intravascular pressure
- protein poor filtrate
(b) Late increase of vascular leakness/permeability
– protein rich filtrate, tissue osmolarity - oedema

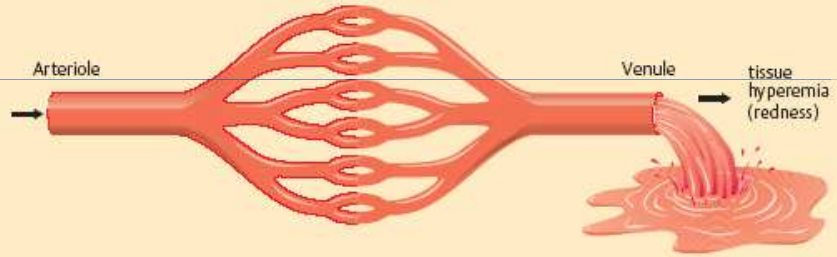
Mechanisms:

1. Endothelial contraction/retraction – histamin, bradykinin
2. Endothelial injury – direct, toxin injury, burns
3. Endothelial injury – indirect, leukocyte mediated
4. Endothelial transcytosis

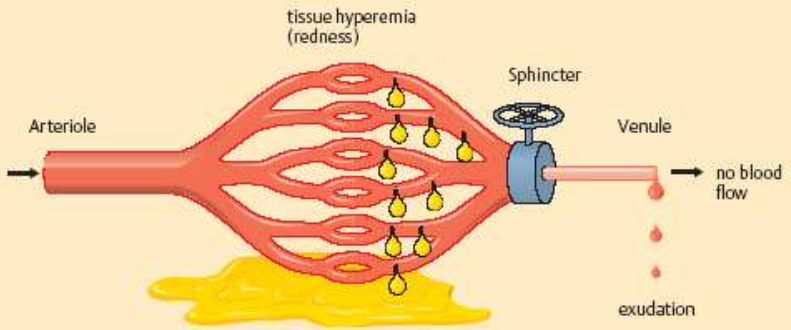
A **Changes in microcirculation:** first phase



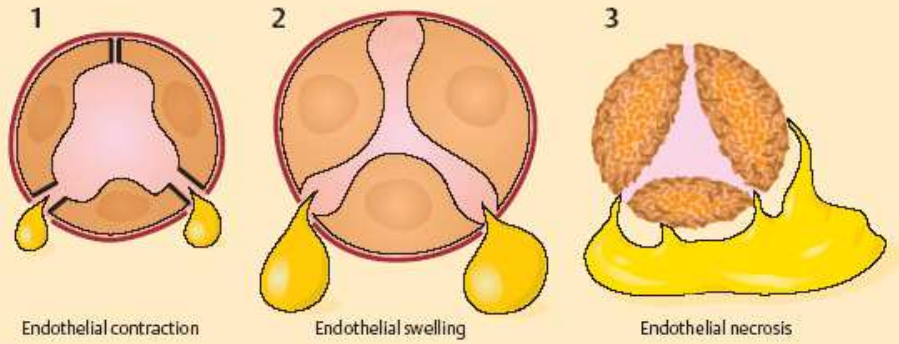
B **Changes in microcirculation:** second phase



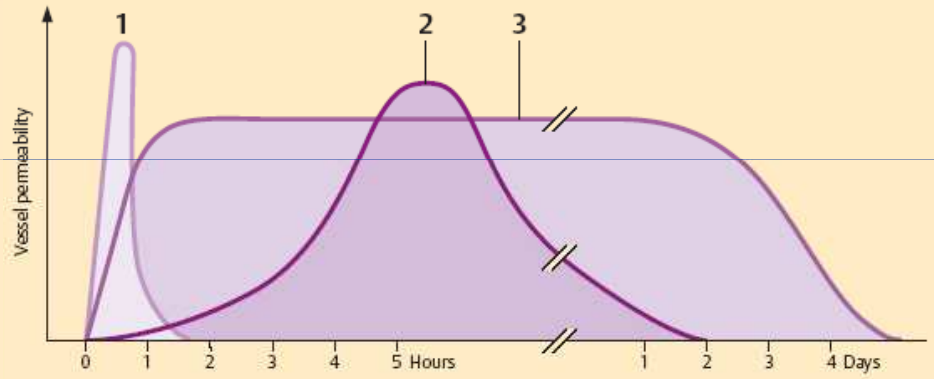
C **Changes in microcirculation:** third phase



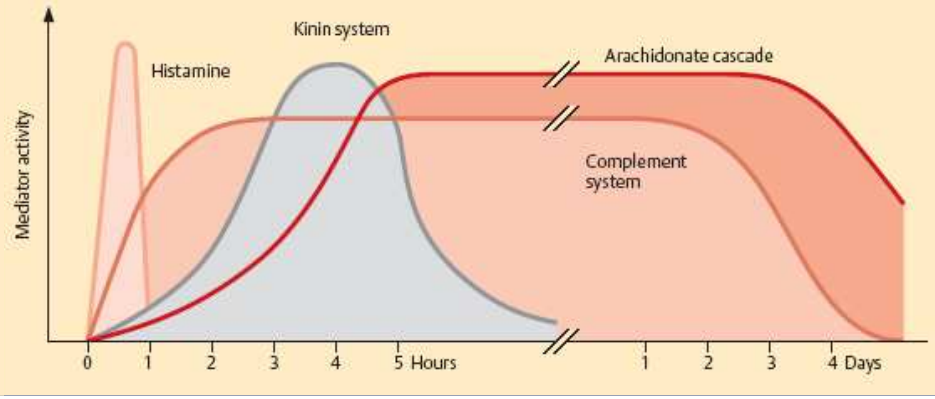
A **Endothelial damage leading to vascular permeability**



B **Types of changes in permeability**



C **Mediators of permeability changes**

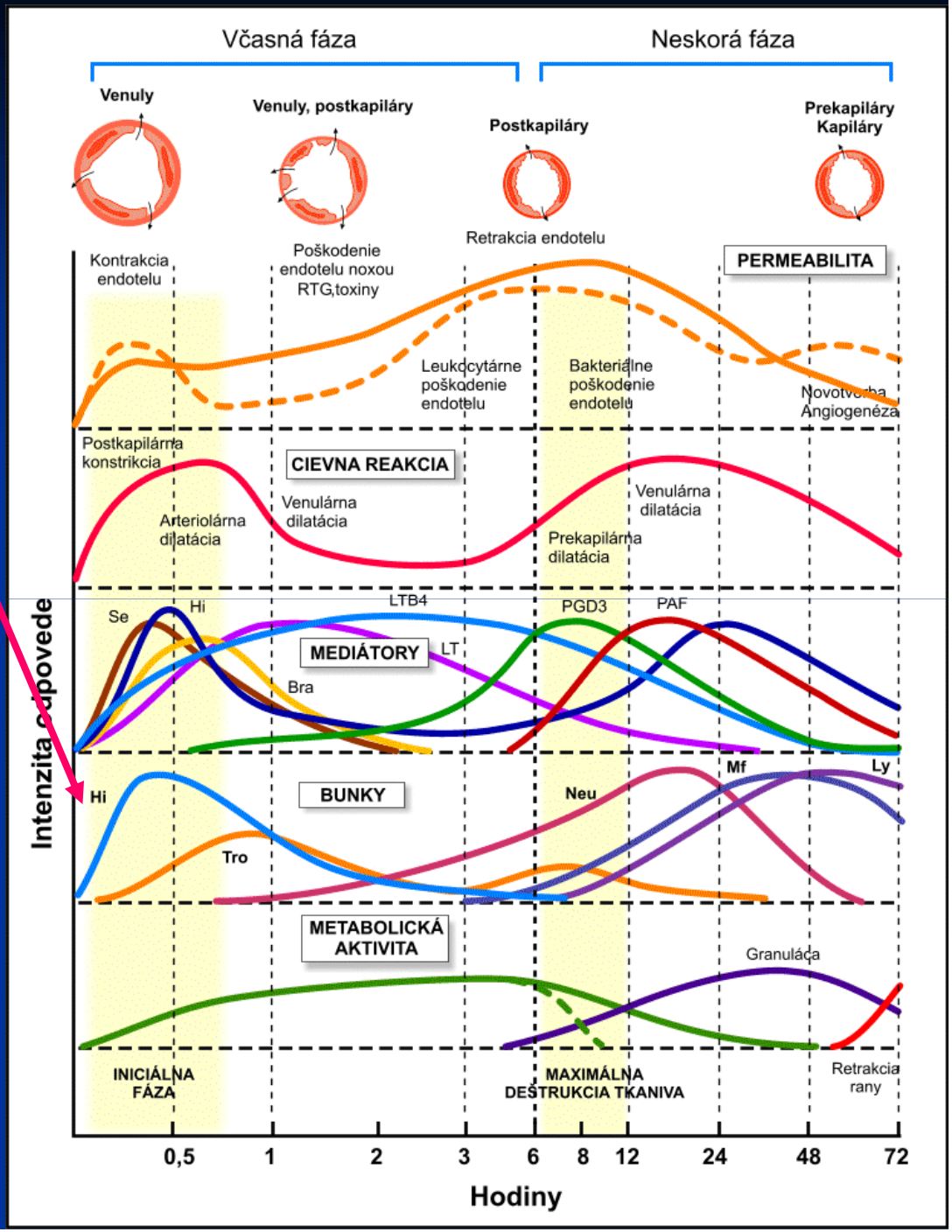


Acute inflammation - Components

(1) Haemodynamic changes

(2) Cellular responses

(3) Humoral response (Mediators)



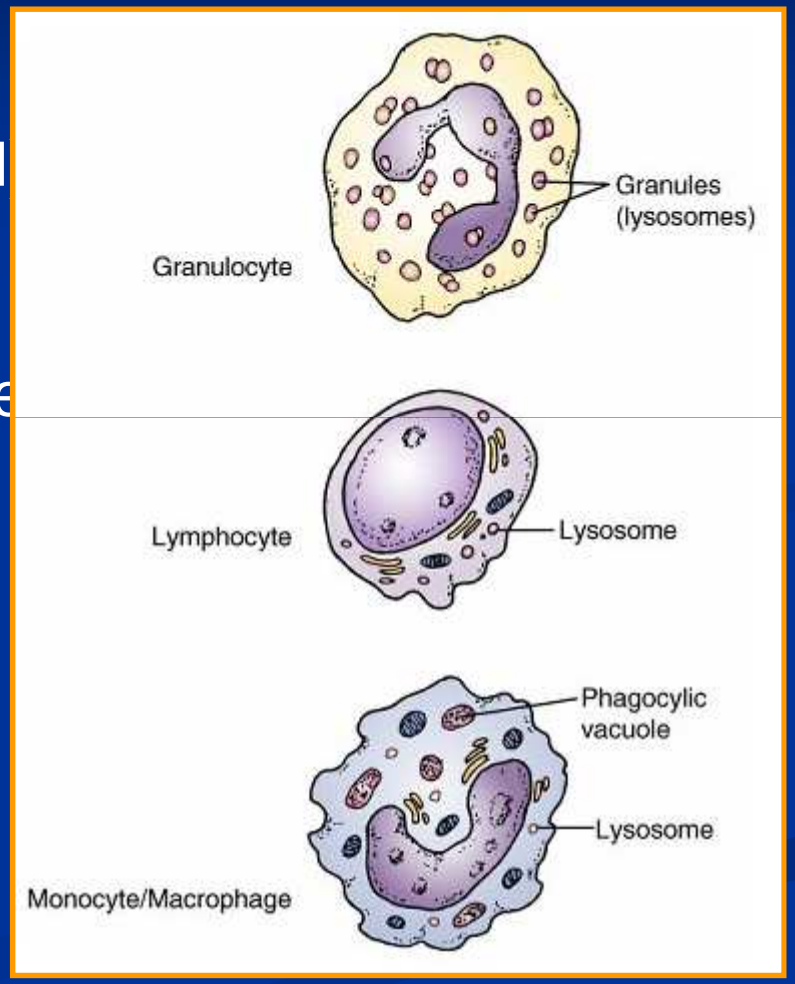
(2) Celullar response

Neutrophiles (granulocyte, PMN
- acute inflammation

Eosinophiles - allergies, parasite

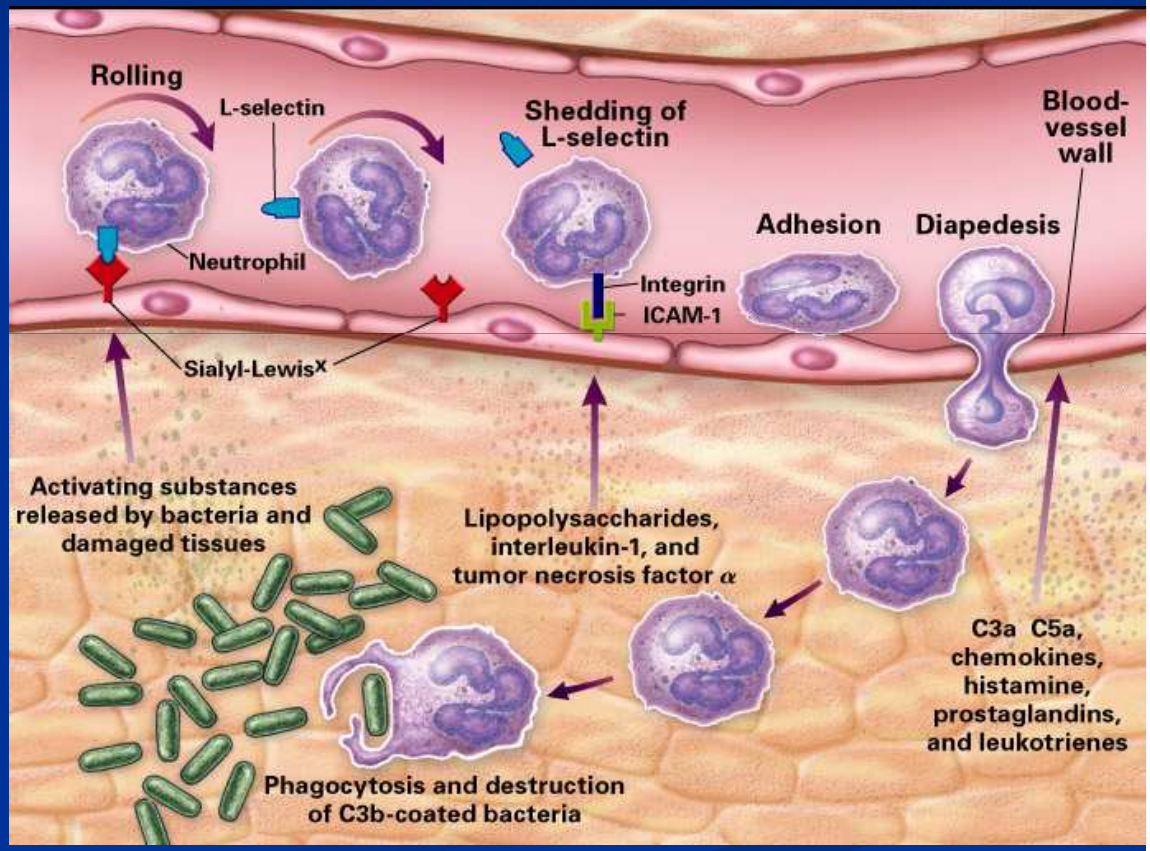
Monocyte/macrophages
- late, chronic

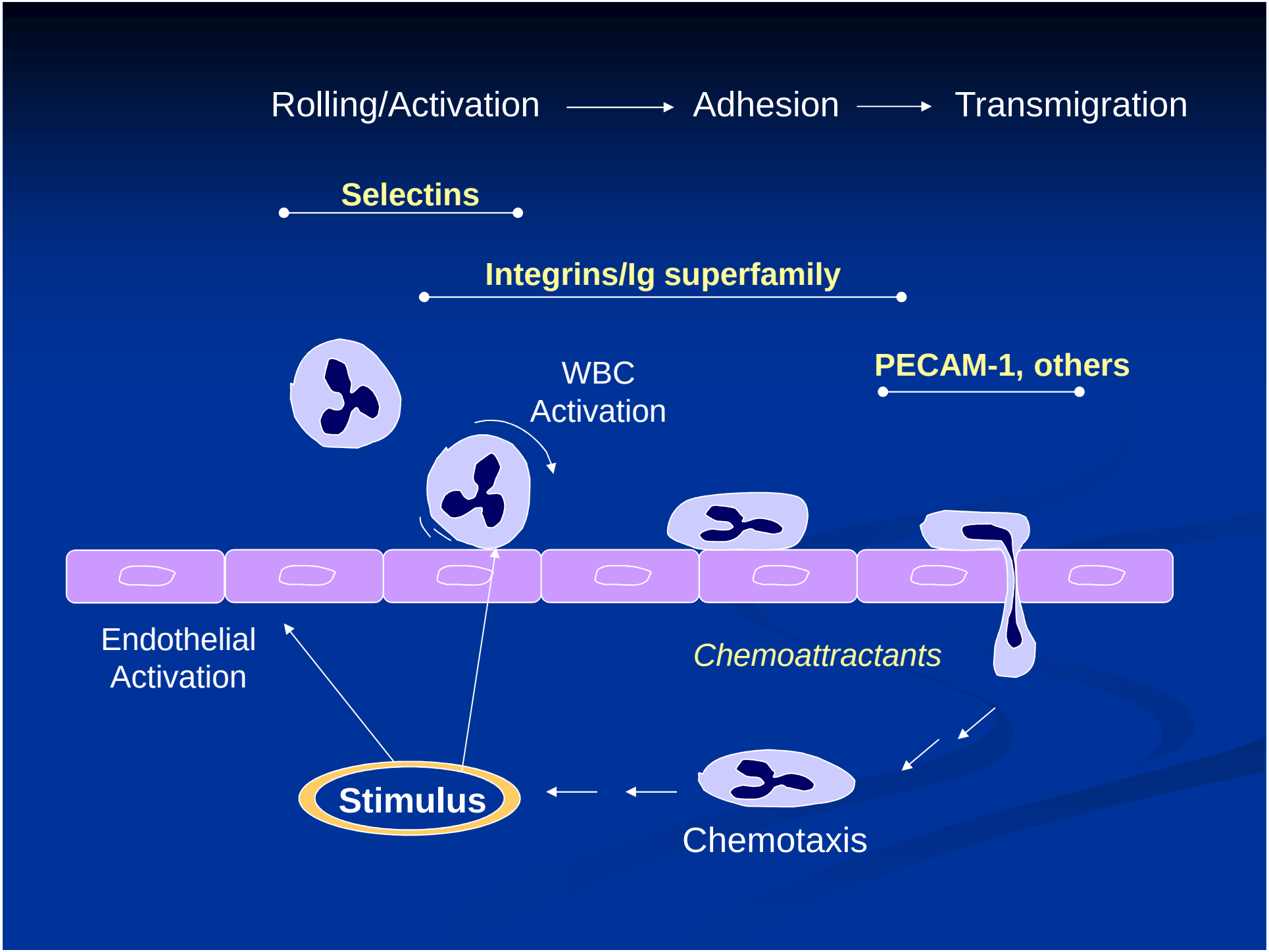
Lymphocytes - late, chronic

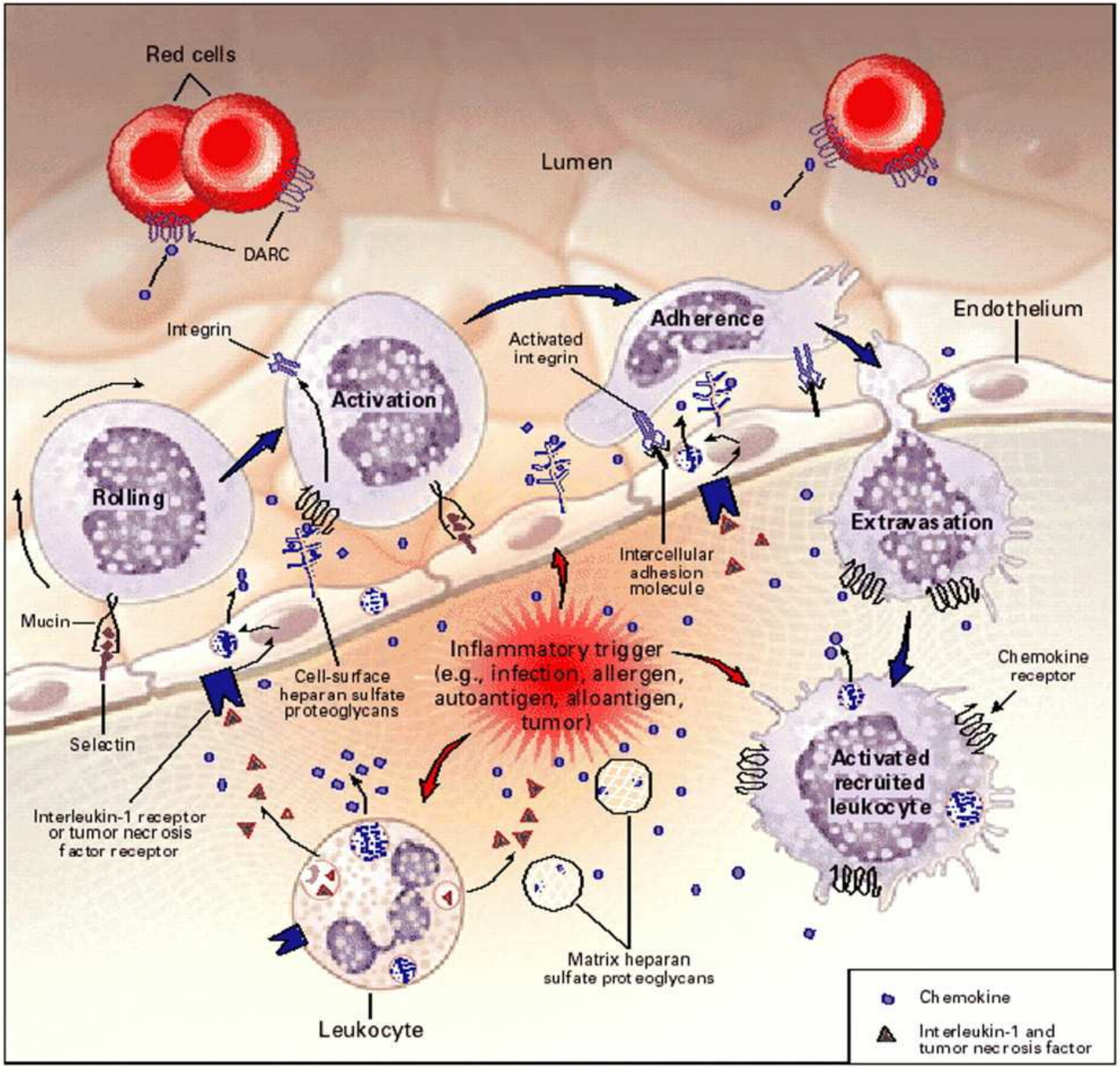


(2) Celullar response

1. **Chemotaxis**
2. **Margination/Rolling** - Selectins
3. **Firm Adhesion** - Integrins/Ig Superfamily
4. **Transmigration** - Junctional proteins
5. **Phagocytosis**
6. **Cytotoxic responses**




Rolling/Activation
Adhesion
Transmigration
Selectins
Integrins/Ig superfamily
PECAM-1, others
WBC
Activation
Endothelial
Activation
Chemoattractants
Stimulus
Chemotaxis


Red cells
DARC
Lumen
Endothelium
Integrin
Activation
Rolling
Activated integrin
Adherence
Extravasation
Intercellular adhesion molecule
Mucin
Selectin
Cell-surface heparan sulfate proteoglycans
Inflammatory trigger (e.g., infection, allergen, autoantigen, alloantigen, tumor)
Chemokine receptor
Activated recruited leukocyte
Interleukin-1 receptor or tumor necrosis factor receptor
Matrix heparan sulfate proteoglycans
Leukocyte
Chemokine
Interleukin-1 and tumor necrosis factor

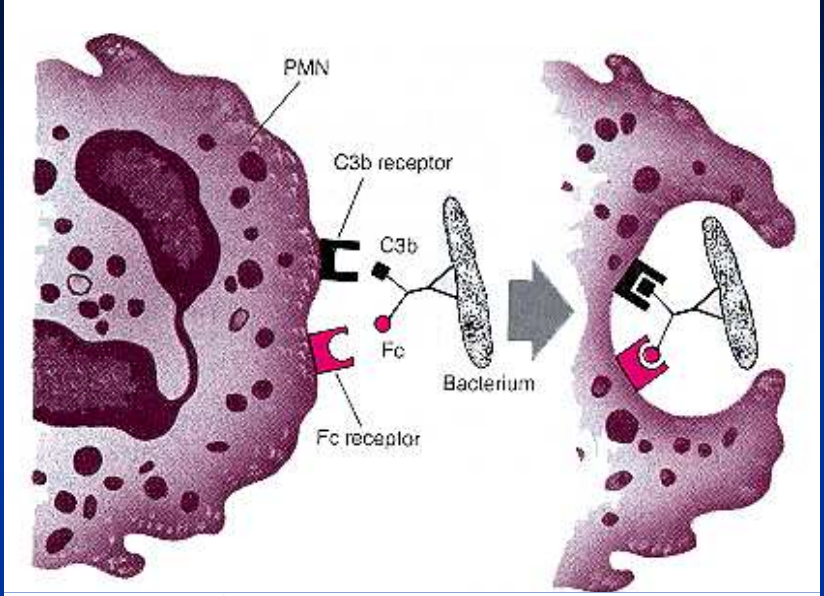
(2) Celullar response

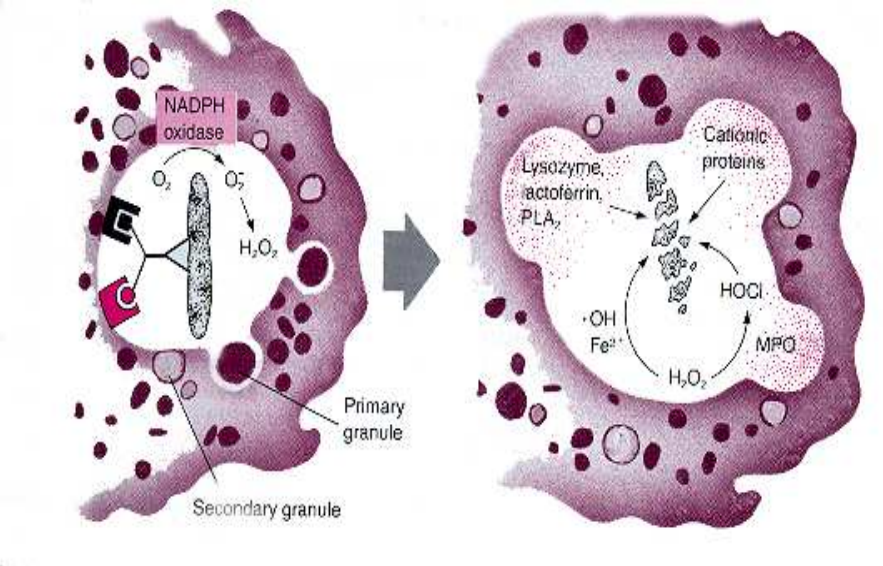
Phagocytosis

1. Recognition and Attachment
Opsonins - *C3b*, *Ab*, *collectins*

2. Engulfment
- cytoskeletal mechanisms
- degranulation

3. Killing or Degradation
- O_2-dependent - H_2O_2 ⌫ *HOCl*, *NO*
- O_2-independent - *lysozyme*, *cationic proteins*, *defensins*, *lactoferrin*





Inflammation - WBC defense content

1. Lysosomal enzymes

- Bactericidal permeability increasing protein (BPI)
- Lysozyme, Lactoferrin
- Defensins (punch holes in membranes)

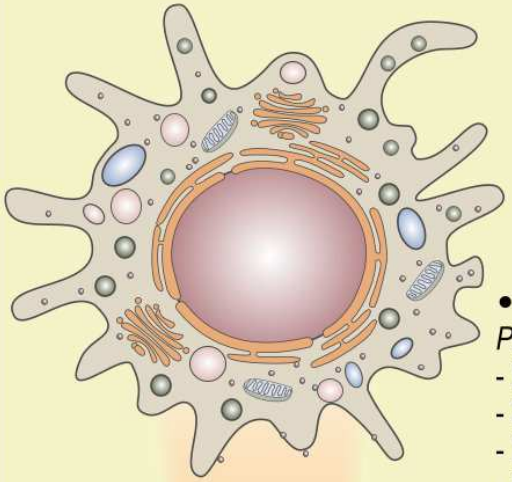
2. O_2-derived metabolites

- Hydrogen peroxide alone insufficient
- MPO (azurophilic granules) converts hydrogen peroxide to HOCl- (in presence of Cl-), an oxidant/antimicrobial agent
- PMNs can kill by halogenation, or lipid/protein peroxidation
- Reactive end-products only active within phagolysosome
- Hydrogen peroxide broken down to water and oxygen by catalase
- Dead microorganisms degraded by lysosomal acid hydrolases

3. Eicosanoids

Monocyty/ Makrofágy

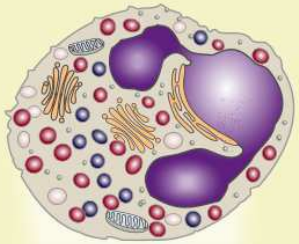
- Chronický zápal (princip. bunky)
- Akútny zápal (neskoré b., fagocytóza)
- Hojenie, koagulácia, fibribnolýza



- Lyzozomálne enzýmy
- Kyslé hydrolázy,
- Neutrálne serínové proteázy,
- Metaloproteázy (kolagenáza, elastáza, atď.),
- Prostaglandíny/Leukotriény,
- Plazminogénový aktivátor
- Cytokíny (TNFα, IL-1, IL-6, (chemokíny, IL-8, MCP-1)
- Reaktívne formy kyslíka

Neutrofily

- Akútny zápal (princip. bunky)
- Tkanivová deštrukcia



- Lyzozomálne enzýmy

Primárne (azurofilné) granuly
- Myeloperoxidáza, Manozidáza,
- Kyslé hydrolázy, Neutrof. elastáza,
- Defenzíny, Lyzozým, Katepsín G,
- BIP, Fosfolipáza A2

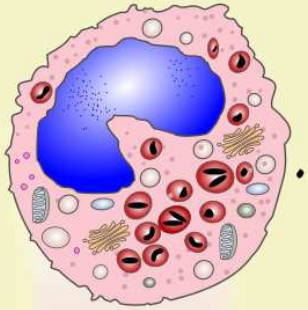
Sekundárne granuly - Laktoferín,
- Kolagenáza, Alkalická fosfatáza,
- Katelicidín. Fosfolipáza A2
- Lyzozým, Aktivátor komplementu,

Terciálne granuly Gelatináza,
- Katepsíny, Glukuronidáza, PAK.

- Reaktívne formy kyslíka, NADPH-oxidáza, superoxid dismutáza
- Cytokíny (TNFα, IL-1, IL-6, chemokíny

Eozinofily

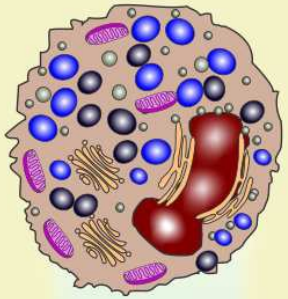
- Akútny zápal (parazit. inf.)
- Chronický zápal
- Hypersenzitivita



- Lyzozomálne enzýmy
- Katepsíny
- Hlavný bázický proteín (MBP)
- Eozinofilný kationický prot.
- Eozinofilná peroxidáza
- Kyslá fosfatáza, Histamináza
- β-glukoronidáza, Arylsufatáza B
- Fosfolipáza D,
- Prostaglandíny E1, E4
- Cytokíny
- Reaktívne formy kyslíka

Bazofily

- Akútny zápal (parazit. inf.)
- Hypersenzitivita (alergie)



- Histamín
- Proteoglykány (heparin, chondroitínsulfát),
- Enzýmy
- elastáza, lyzofosfolipáza,
- peroxidáza
- Cytokíny (TNFα, IL-4, ...)
- Leukotriény (LTC, LTD, LTE)
- PAF (trombocyty aktivujúci faktor)
- Eozinofilné chemotaktické faktory

Defects of leukocyte function

- **Defects of adhesion:**
  - LAD-1 (Leucocyte adhesion defect type 1) LFA-1 and Mac-1 subunit defects lead to impaired adhesion
  - LAD-2 (leucocyte adhesion defect type 2) absence of sialyl-Lewis X, and defect in E- and P-selectin sugar epitopes

- **Defects of chemotaxis/phagocytosis:**
  - Chediak-Higashi Syndrome - microtubule assembly defect leads to impaired locomotion and lysosomal degranulation

- **Defects of microbicidal activity:**
  - Chronic granulomatous disease - deficiency of NADPH oxidase that generates superoxide, therefore no oxygen-dependent killing mechanism

Acute inflammation - Components

(1)Haemodynamic changes

(2) Cellular response

(3) Humoral mediators

Plasma-derived:

-Complement, kinins,

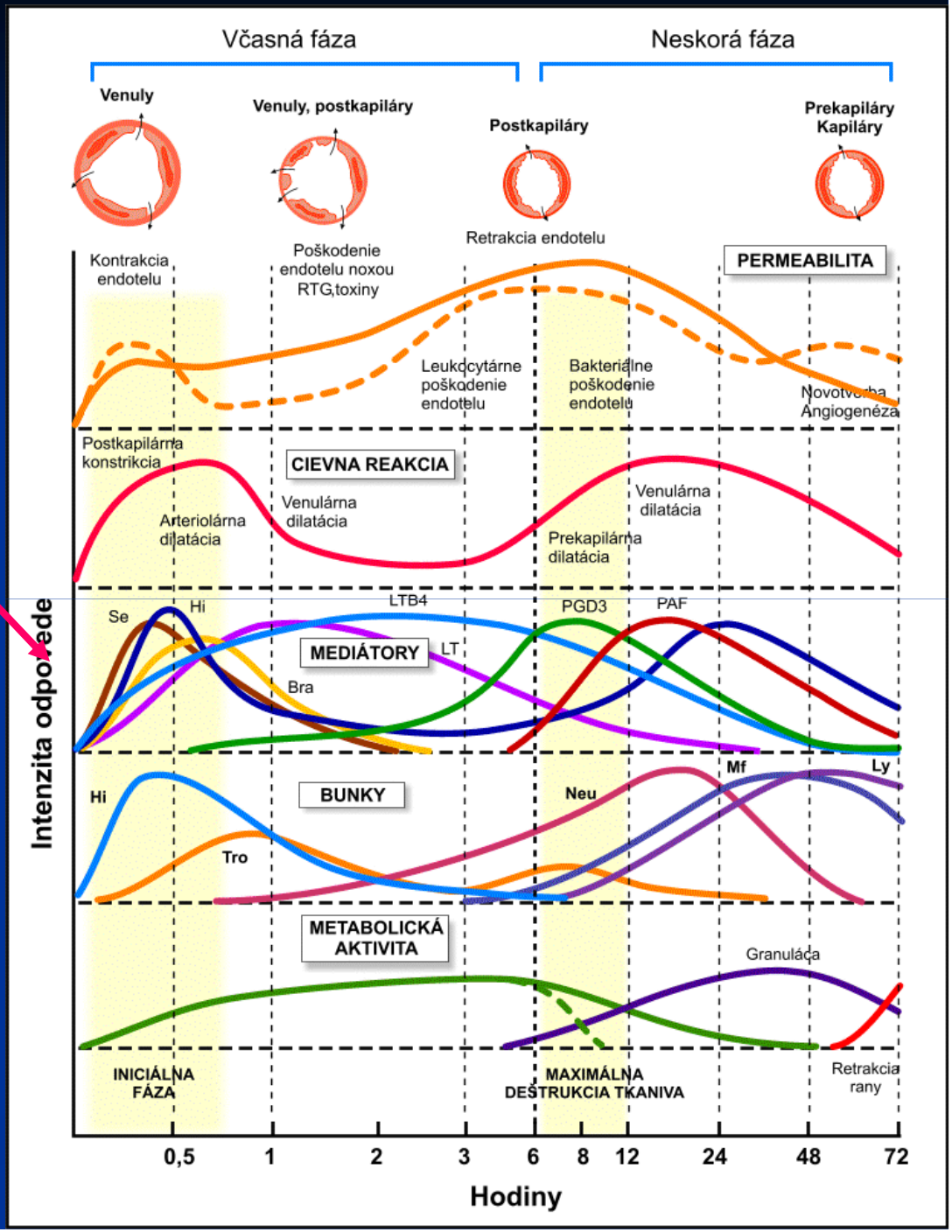
- Coagulation factors

- “pro-form” requiring activation (enzymatic cleavage)

Cell-derived:

- Preformed, sequestered and released (e.g.histamine)

- Synthesized as needed (e.g.prostaglandin)



(3) Mediators

1) Vasoactive amines - histamine

2) Plasma proteases - coagulation factors
- kinins
- complement system

3) Lipid Mediators - eicosanoids (prostaglandins, leukotrienes)
- platelet activating factor (PAF)

4) Cytokines & Chemokines - IL-1, IL-6, TNF
- IL-8

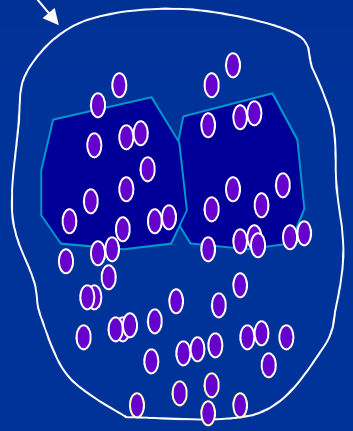
5) Nitric oxide (NO)

(1) Vasoactive amines

Histamine

- **Mast cells**, Basophils, Platelets -

Physical
Immune
Complement
Cytokines
WBC products

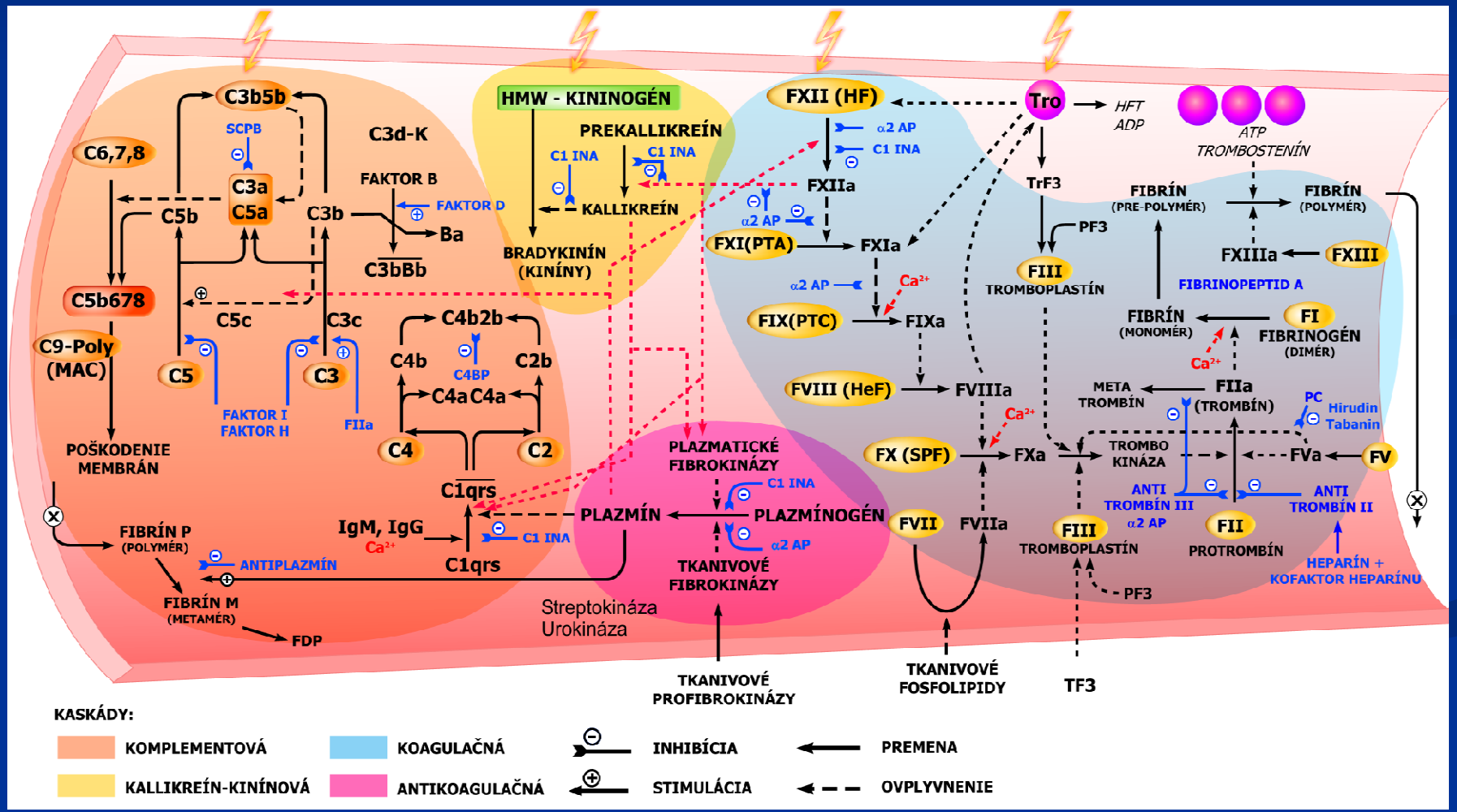


Degranulation

- Transient vasodilation (10-15 min)
- Increased vascular permeability

(2) Plasma Proteases

A) Coagulation factors + anticoagulations
B) Kinins
C) Complement



(2) Plasma Proteases

A) Coagulation - Clotting

Thrombin

- directly activates endothelium { endothelial contraction; WBC adhesion
- generation of fibrin ⌫ fibrinopeptides { chemotactic

↓

- Vascular permeability
- WBC migration
- Clot formation

(2) Plasma Proteases

A) Coagulation - Fibrinolysis

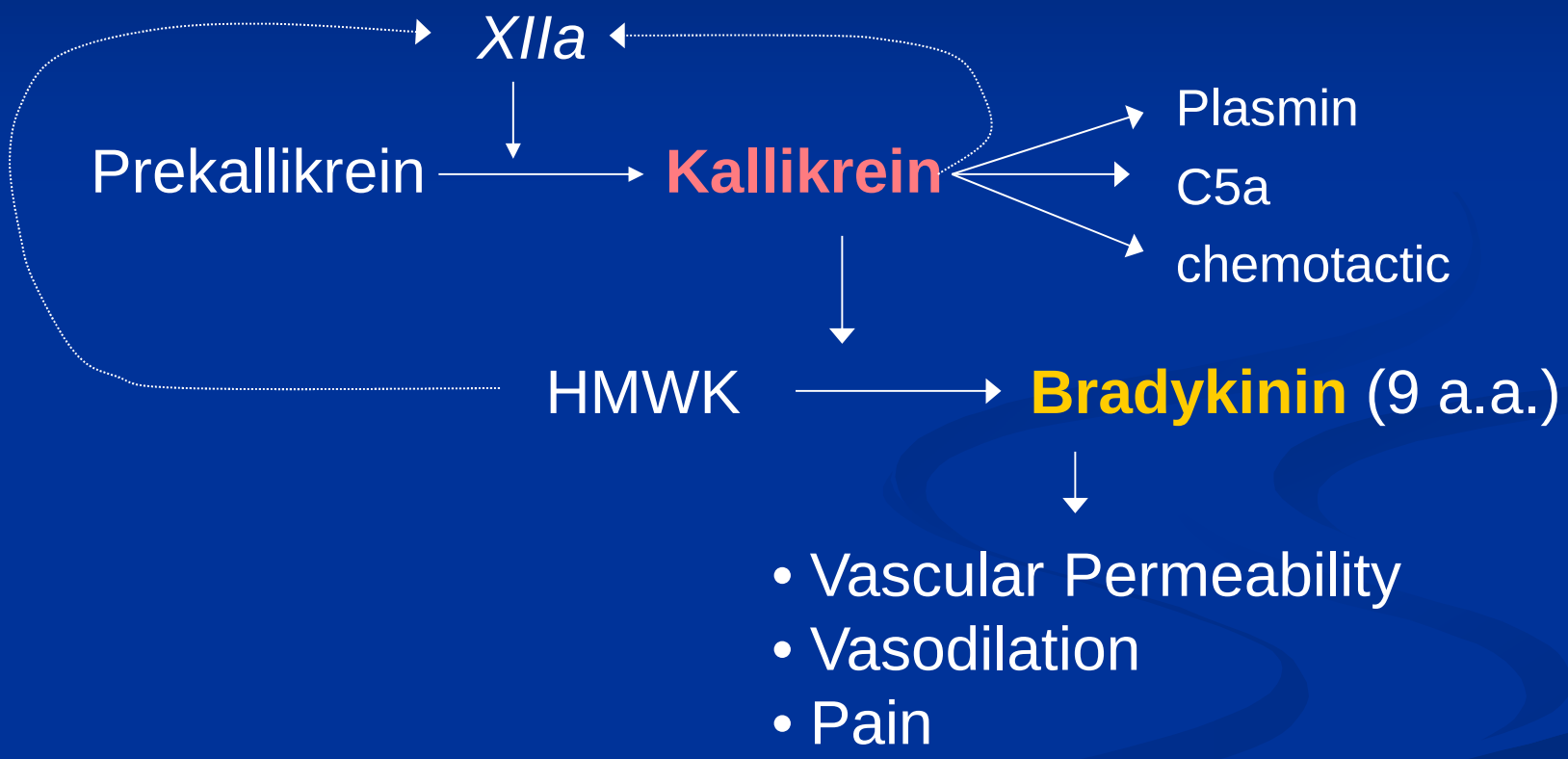
Plasmin

- degrades fibrin → fibrin degradation products
- cleaves complement C3 ⌫ C3a, C3b
- activates factor XII

↓

Vascular Permeability
- WBC migration
- Clot lysis

B) Kinin System



C) Complement System

Cell lysis:

- **C5-C9** (Membrane attack complex)

Vascular changes: vascular permeability, vasodilation

- **C3a**, **C5a**, (C4a) (*anaphylatoxins*)
- C5a - arachidonate metabolism

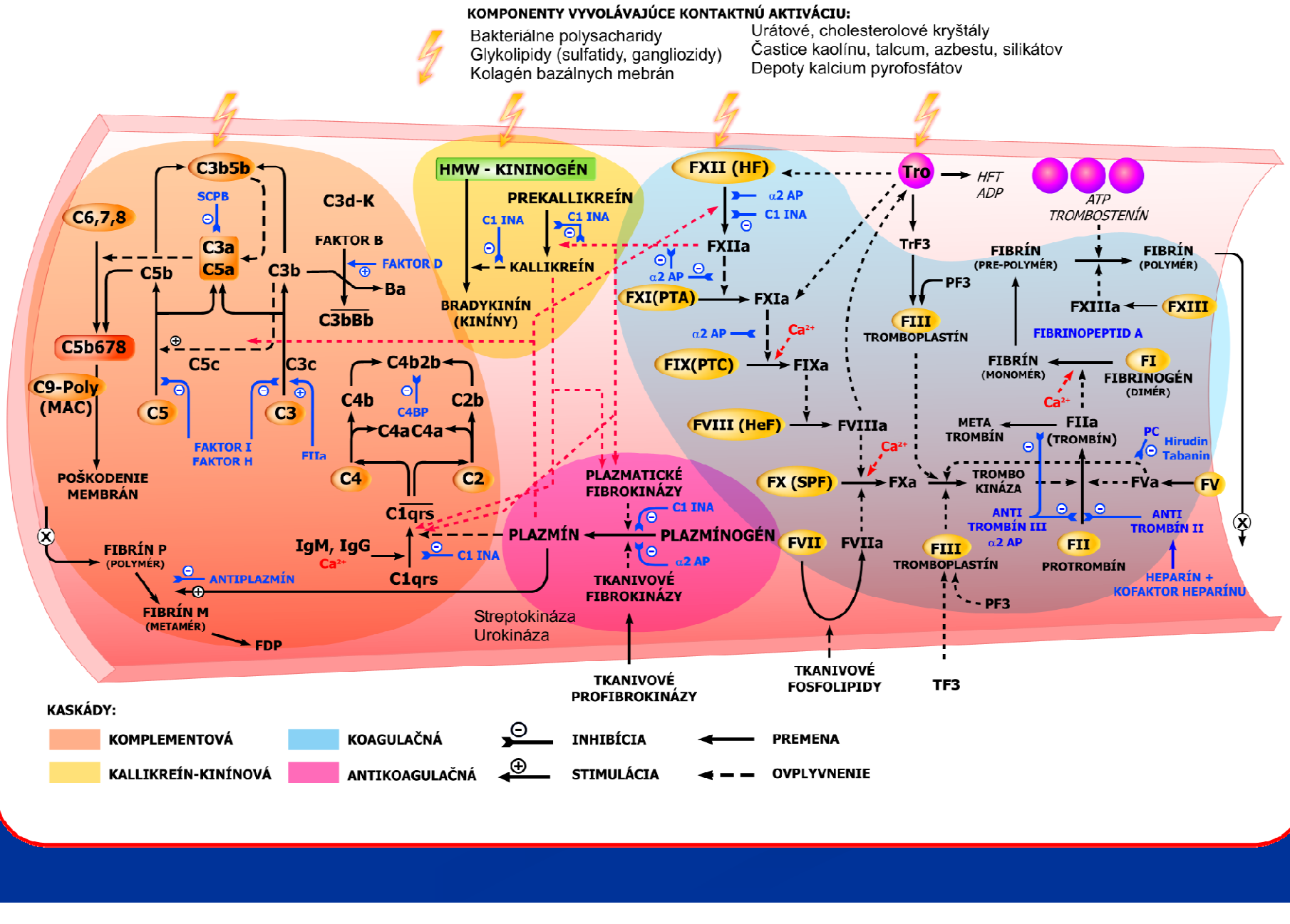
WBC adhesion, *chemotaxis* and *activation*

- **C5a**

Phagocytosis

- **C3b** - opsonization of particles, bacteria

KOOPERATÍVNE VZŤAHY PLAZMATICKÝCH HUMORÁLNYCH SYSTÉMOV PRI ZÁPALE

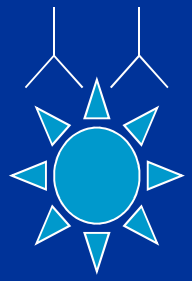


Complement System - Activation

CLASSICAL

Antigen-Antibody complex

C1q



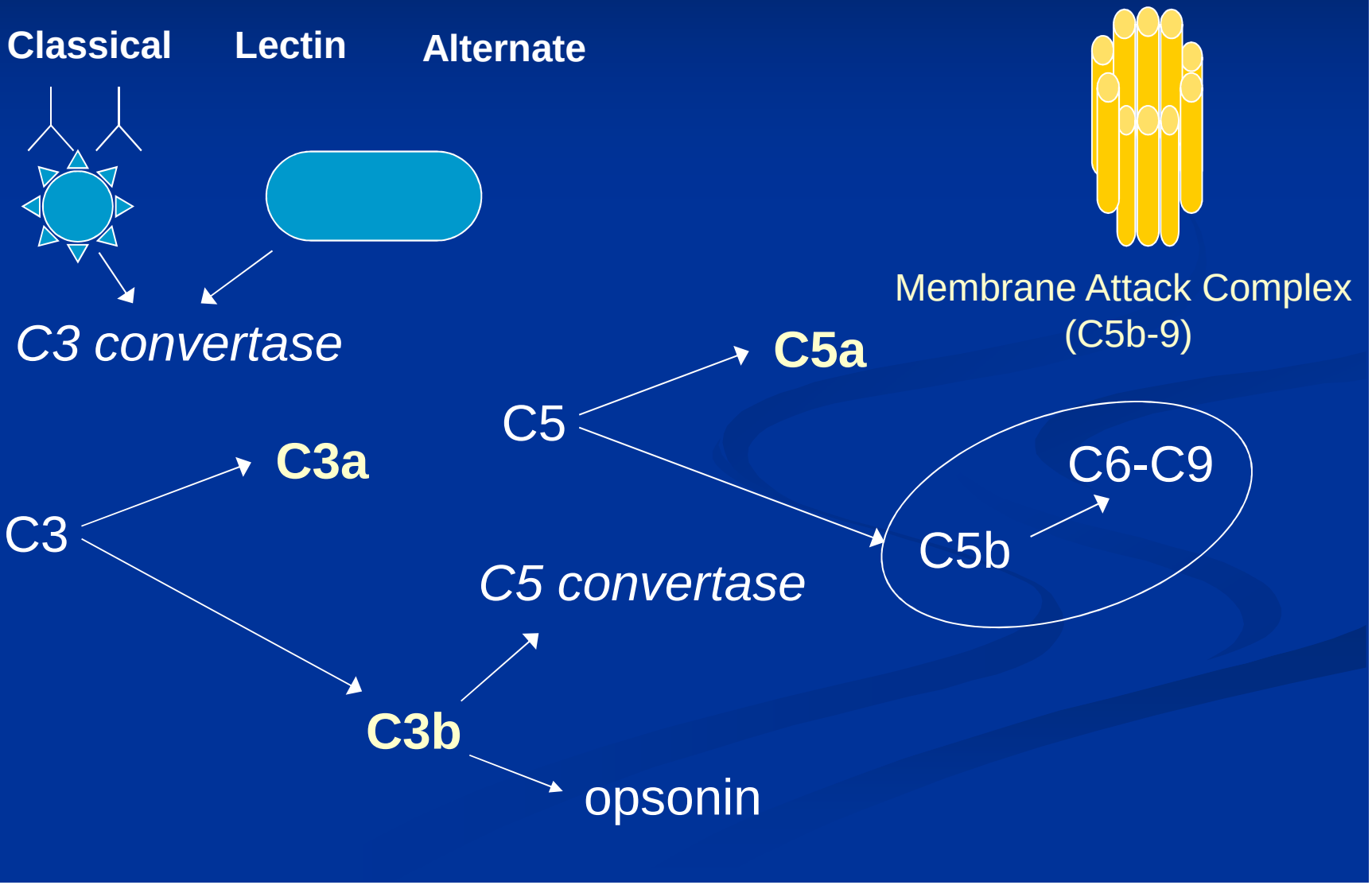
LECTIN

Mannose binding protein
Plasma proteases

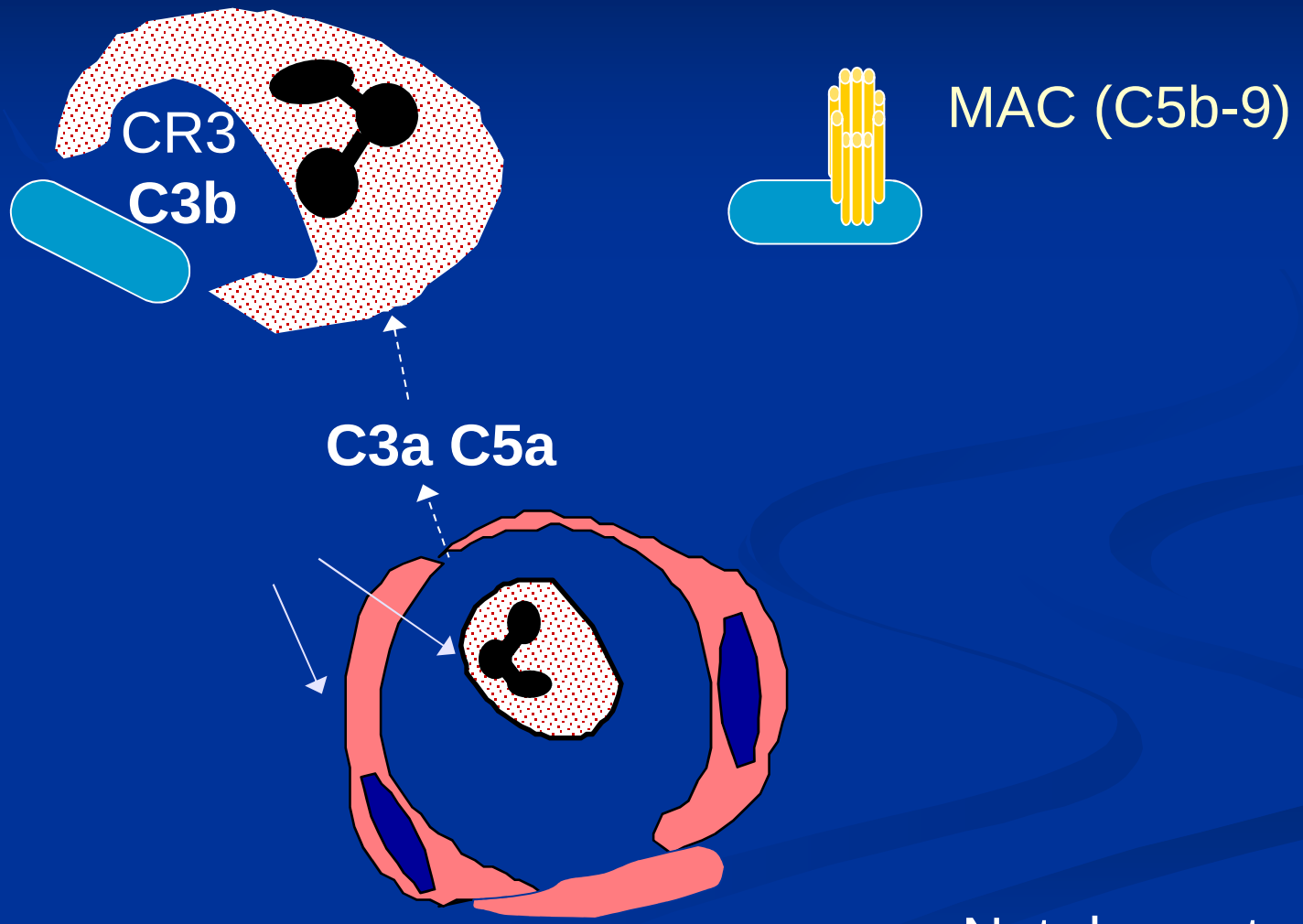
ALTERNATE

Pathogen surfaces
Properdins

Complement System - Activation



Complement System - Activation



Inhibitors of Plasma Proteases

Coagulation

- Antithrombin
- Plasminogen activator inhibitors

Kinin

- Kininase

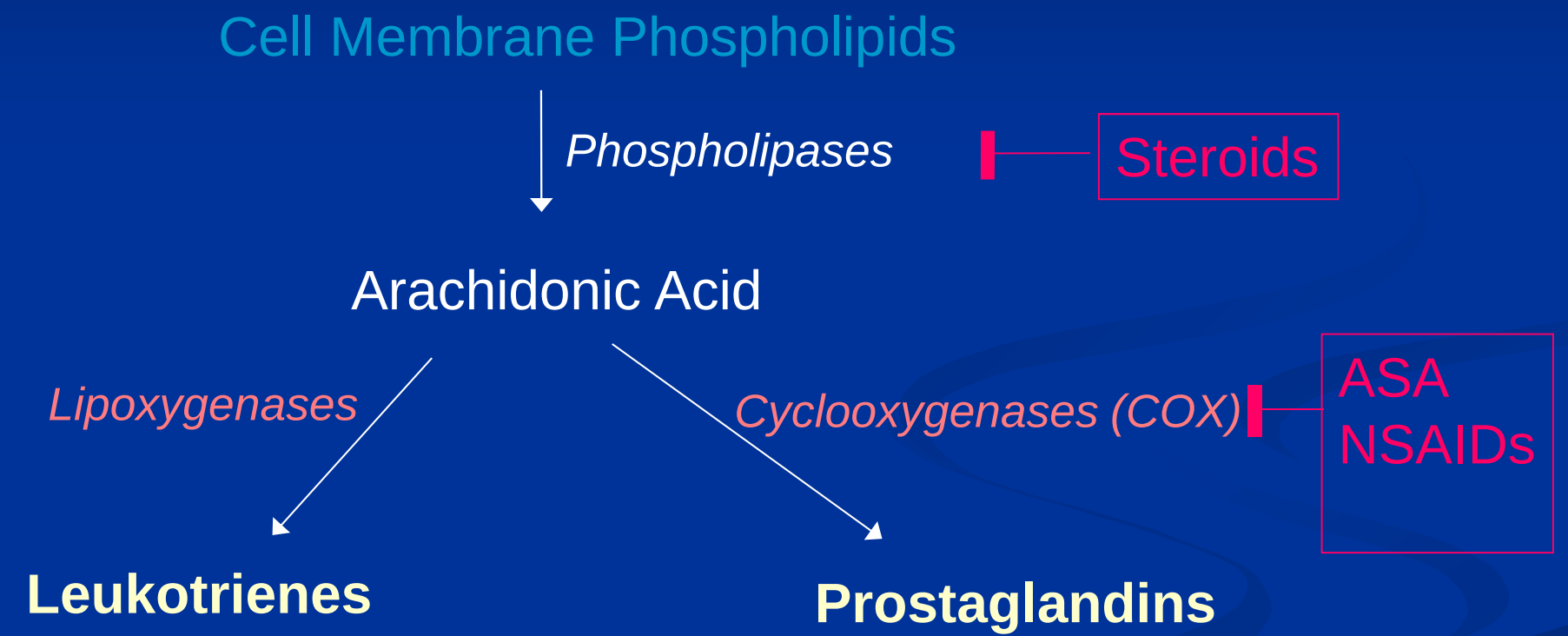
Complement - *Distinguish Host from Microbes*

- *Regulation of C3 and C5 convertases*
  - Decay accelerating factor (DAF)
  - Factor I - cleavage of C3b
- *Binding of active complement components*
  - C1 inhibitor
  - CD59 - inhibits MAC

3) Lipid Mediators

- **Eicosanoids** - Prostaglandins, Leukotrienes
- **Platelet activating factor (PAF)**

Lipid Mediators - Eicosanoids



Lipid Mediators - Eicosanoids

Prostaglandins

Prostacyclin (PGI_2)

- vasodilation, inhibits platelet aggregation

Thromboxane (TXA_2)

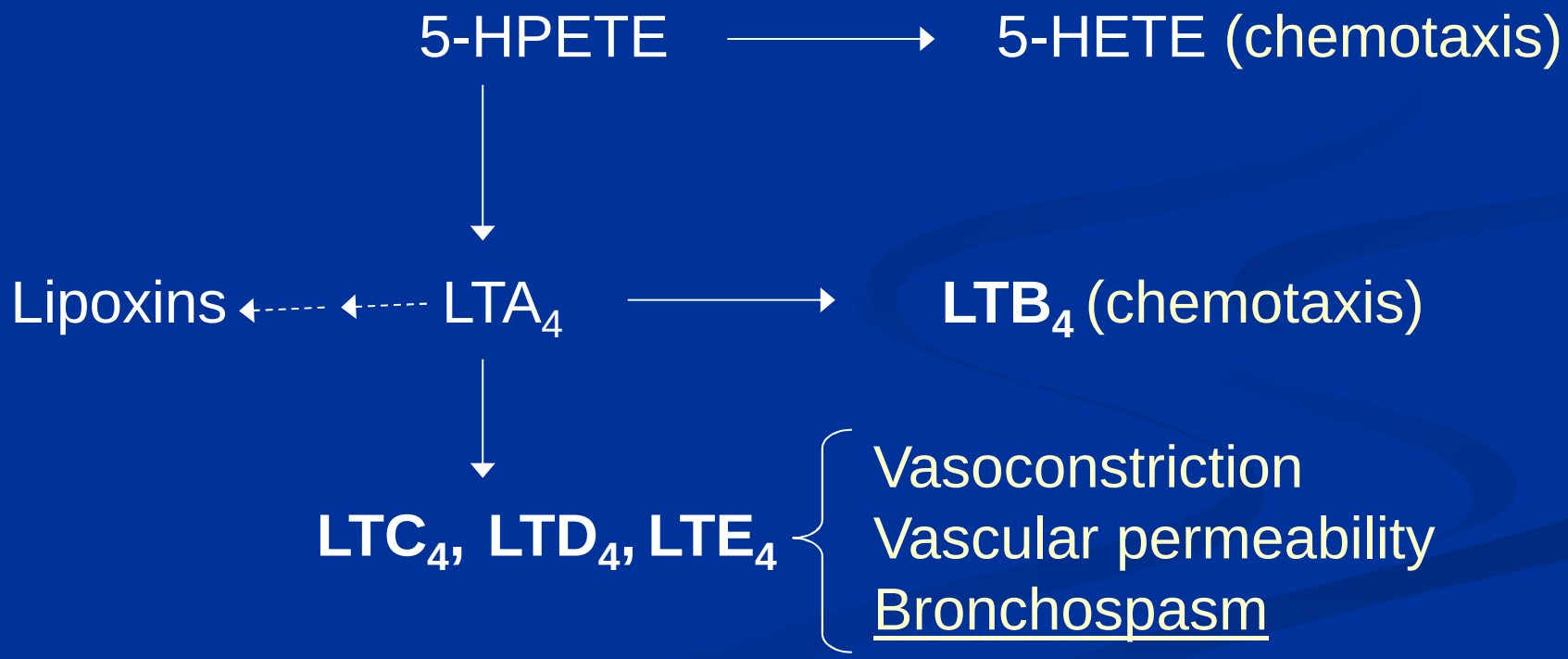
- vasoconstriction, promotes platelet aggregation

PGD_2, PGE_2, $PGF_{2\alpha}$

- vasodilation, edema

Lipid Mediators - Eicosanoids

Leukotrienes



Lipid Mediators - PAF

Platelet activating factor (PAF)

- Modified phospholipid
- Secreted by WBC, platelets, endothelial cells
- Can elicit most of the features of inflammation

Lipid Mediators - PAF

Platelet activating factor (PAF)

- Platelet activation
- Vascular permeability
- WBC aggregation, adhesion, chemotaxis
- Stimulation of mediator release e.g. LT

4) Cytokines and Chemokines

Proteins that are produced by many cell types

1) **TNF , Interleukin-1 (IL-1), Interleukin-6 (IL-6)**

- activate inflammatory cells and endothelium locally
- induction of the systemic *acute phase response*

2) **IL-8** - chemokine

- chemotactic activity for WBC

4) Cytokines and Chemokines

1) **TNF , Interleukin-1 (IL-1), Interleukin-6 (IL-6)**

Local (*paracrine*) effects:

- Activate endothelium

  - adhesion molecules
  - synthesis of other cytokines and chemokines

- Aggregation and priming of neutrophils

4) Cytokines and Chemokines

TNF -alpha, Interleukin-1 (IL-1), Interleukin-6 (IL-6)

Systemic effects: *Acute phase response*

Fever, anorexia, somnolence, leukocytosis, hypotension

Production of acute phase proteins by the liver:

- complement
- coagulation factors
- mannose binding protein (mannan binding lectin)

- Link to the adaptive immune response
- Promote antigen presentation
- Induction of costimulatory molecules

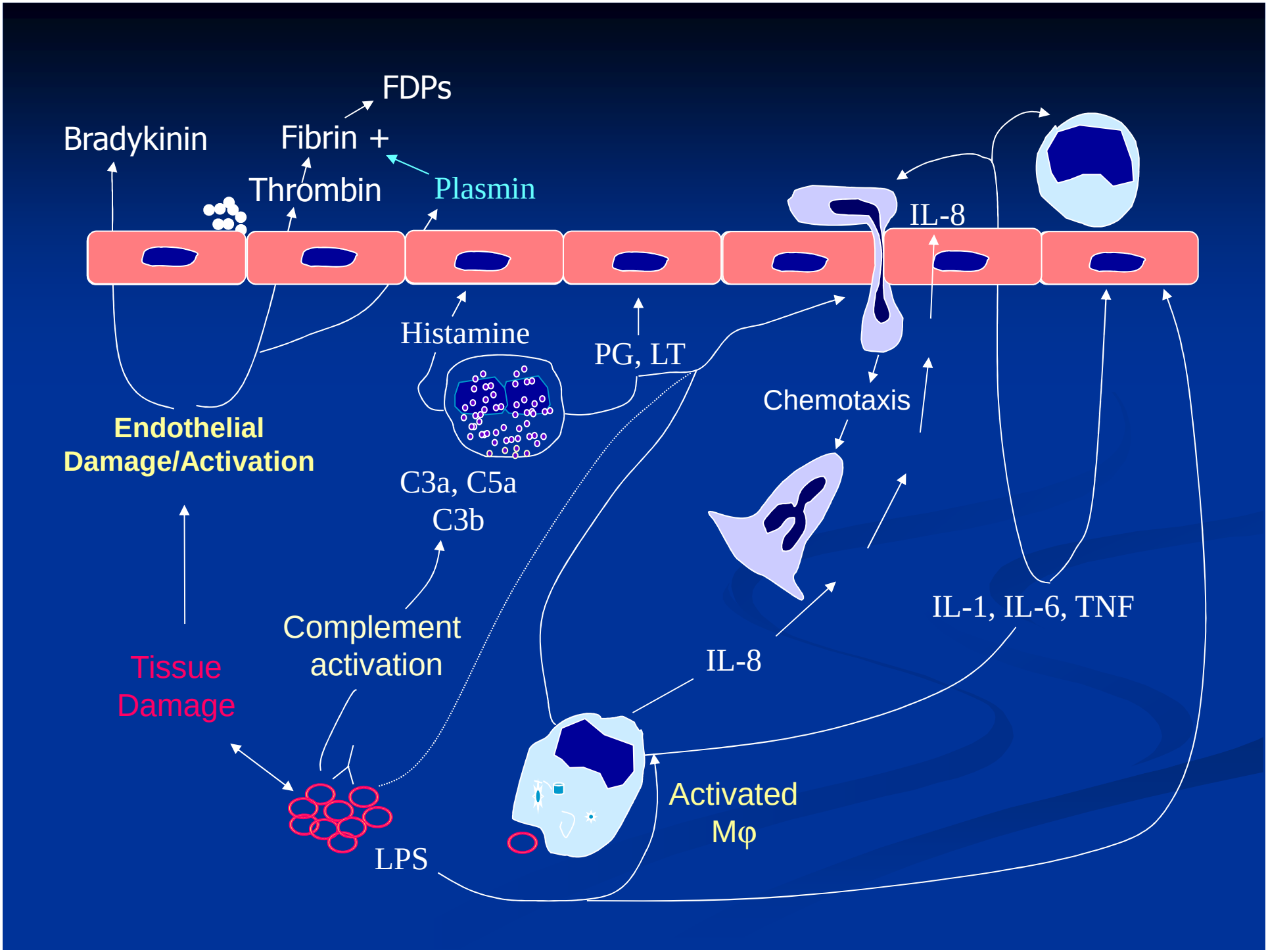
5) Nitric Oxide (NO)

- Soluble gas
- Produced by endothelial cells, macrophages, neurons

  - smooth muscle relaxation ⟶ vasodilation
  - microbial (and cell) killing activity
    ⟶ reactive oxygen species

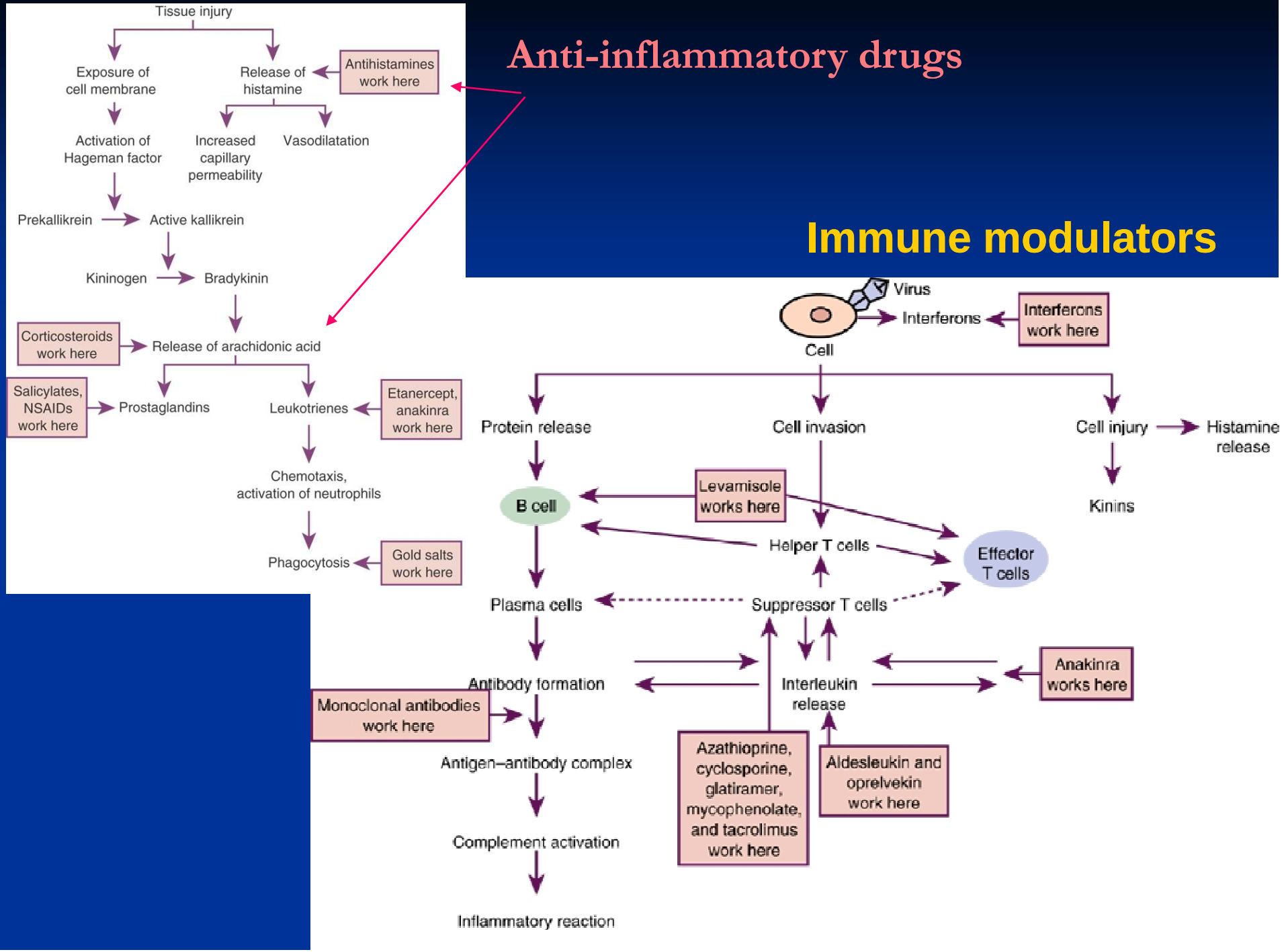
- NO is also anti-inflammatory

  - ↓ platelet aggregation and adhesion
  - ↓ WBC recruitment

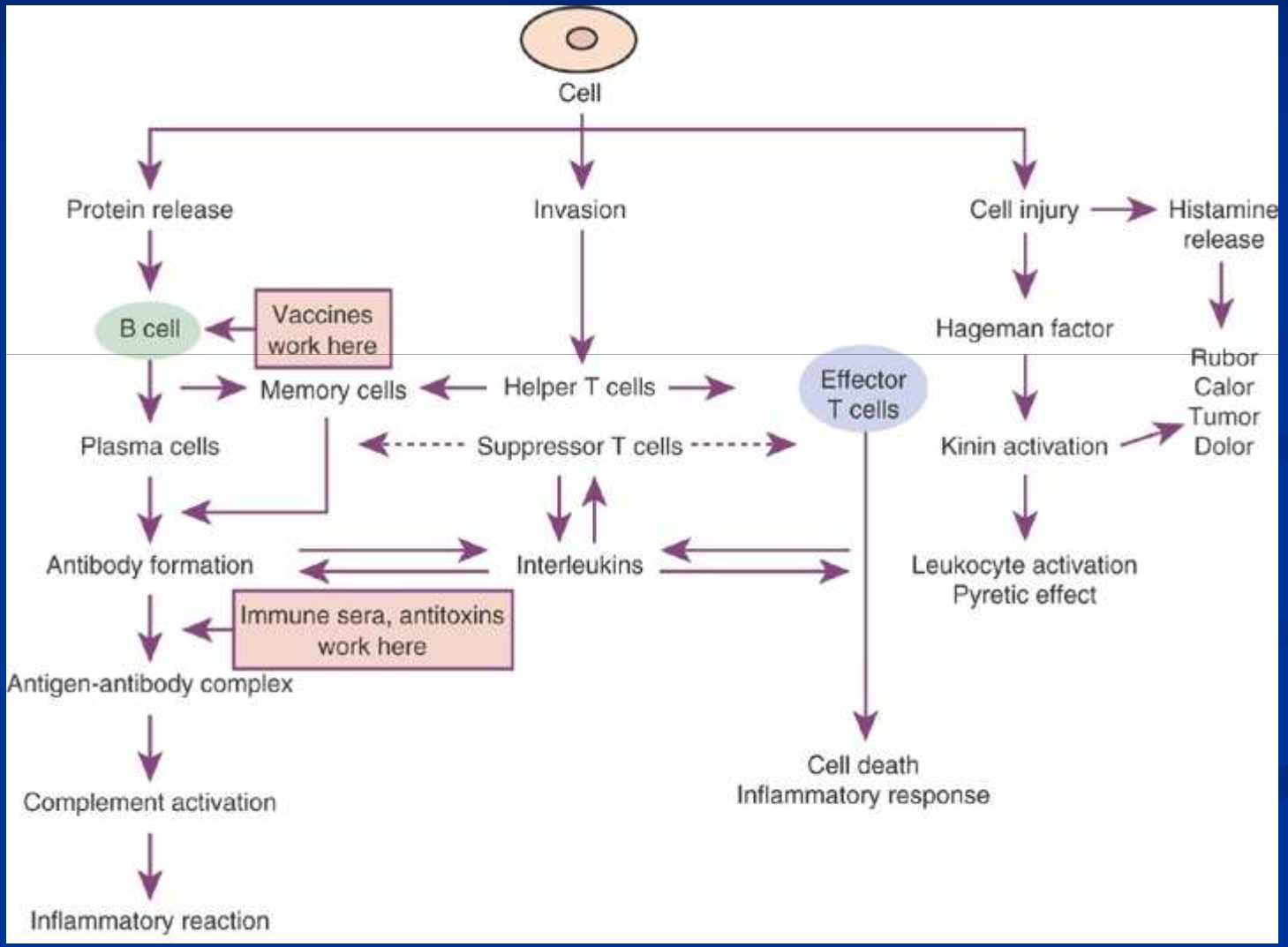

FDPs
Bradykinin
Fibrin +
Thrombin
Plasmin
IL-8
Histamine
PG, LT
Chemotaxis
Endothelial
Damage/Activation
C3a, C5a
C3b
IL-1, IL-6, TNF
Complement
activation
IL-8
Tissue
Damage
Activated
Mφ
LPS

Anti-inflammatory drugs

Immune modulators



Vaccines, immune sera antitoxins

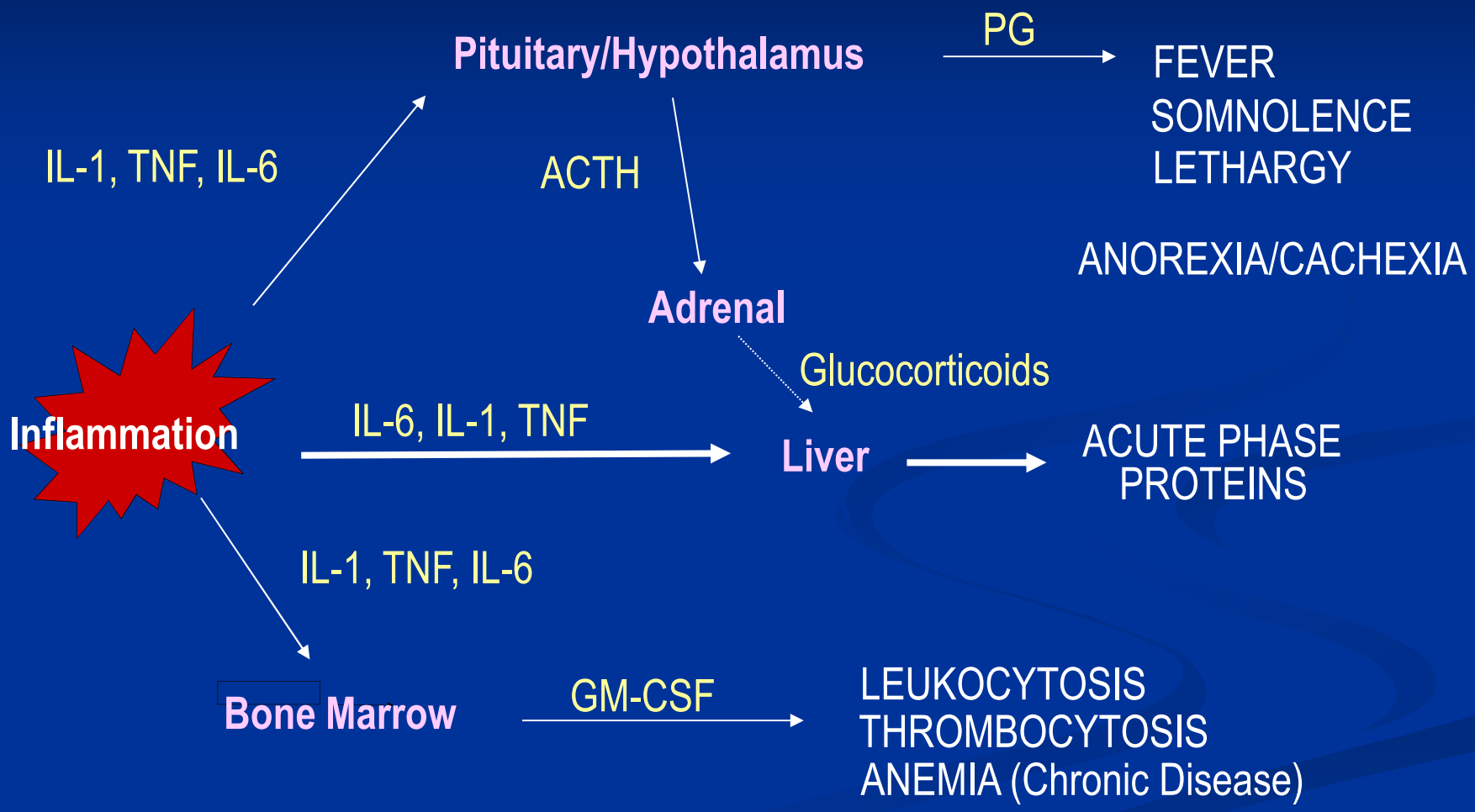


Systemic manifestations

Inflammation – Systemic response

- **Acute phase response** - the sum of the systemic (hematogenic, neural, behavioural) and metabolic changes occurred concurently with release of **acute phase proteins** (CRP, a1- AT, coagulation factors C3)
- **Leukocytosis** > 10.10^9/liter or **leucopenia** < 4.10^9/liter
- **Fever (febris, pyrexia)** (event. subfebrility)
- **Erytrocyte sedimentation rate (ESR, FW)**
- **Metabolic changes** - catabolic response
- **Stress response -** malaise, pain,

Acute Phase Response



ERS (Eytrocyte sedimentation; FW test)

- 1897 polish pathologist Edmund Biernacki; 1918 swedish pathologist Robert S. Fåhræus; Alf V. A. Westergren,
- non-specific test; typically a result of rise of globulins (find more in serum protein electrophoresis) or rise of fibrinogen (APP)
- Diagnostics; response to a therapy monitoring: rising/ decrease of ESRs

- Moderate rise = pregnancy, anemia
- Elevated ESR = inflammation (infections, cancers, autoimmune responses (systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease) chronic kidney diseases; tuberculosis, infective endocarditis.
- Very elevated ESR = severe infection, multiple myeloma, temporal arteritis, Takayasu's arteritis, systemic vasculitis, polymyalgia rheumatica; w/o inflammation= multiple myeloma Waldenstrom's macroglobulinemia
- ESR does not change as rapidly as CRP, and is affected by many factors

Age	20y	55y	90y
Male	12	14	19 mm/h
Female	18	21	23 mm/h

Acute phase proteins (APP)

Positive APP: increase mildly (50% cerrulopasmin) or heavily (1000x CRP, SAA) in inflammation;

Role ? different physiological immune functions

- **destroy or inhibit microbial growth:** C-reactive protein (CRP), mannose-binding protein (MBP), complement (C3a, C5A, C2), ferritin, ceruloplasmin (Cp), serum amyloid A and P (SAA) SAP, haptoglobin (Hp).
- **negative feedback on the inflammatory response**, e.g. serpins (a1AT, a1AChT),
- **coagulation** (trapping pathogens in clots): alpha 2-macroglobulin, coagulation factors

Negative APP: decrease in inflammation;

Role?: to save amino acids to rise "positive"APP

- albumin, transferrin, transthyretin, retinol-binding protein, antithrombin, transcortin.

APP differ in various animals in types of proteins and quantity

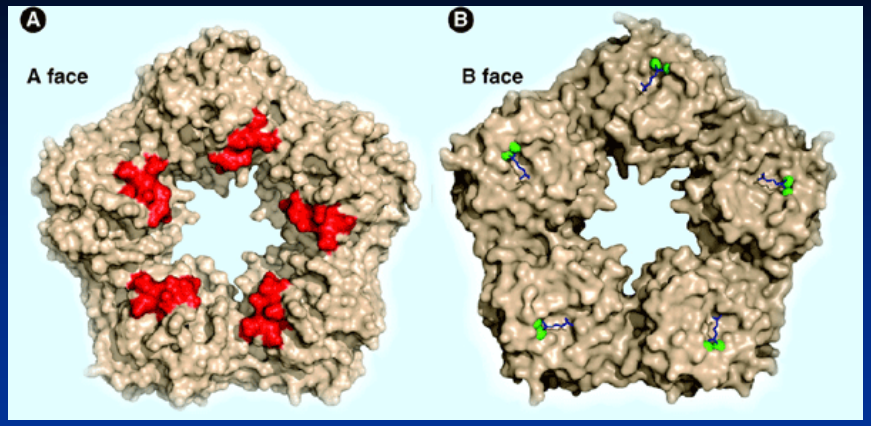
Mammals	Birds
Positive reactants	
TNF-α, IL-1, IL-6, cortisol	TNF-α, IL-1, IL-6, cortisol
SAA, CRP, Hp, AGP, etc.	SAA, CRP, hemopexin, AGP, etc.
Fibrinogen, Ceruloplasmin	Fibrinogen,Transferrin, Ceruloplasmin
Cu	Cu, Ca
Negative reactants	
TTR, RBP	Hp
Albumin, Transferrin	Albumin
Fe, Zn, Ca	Unbound serum iron, zink

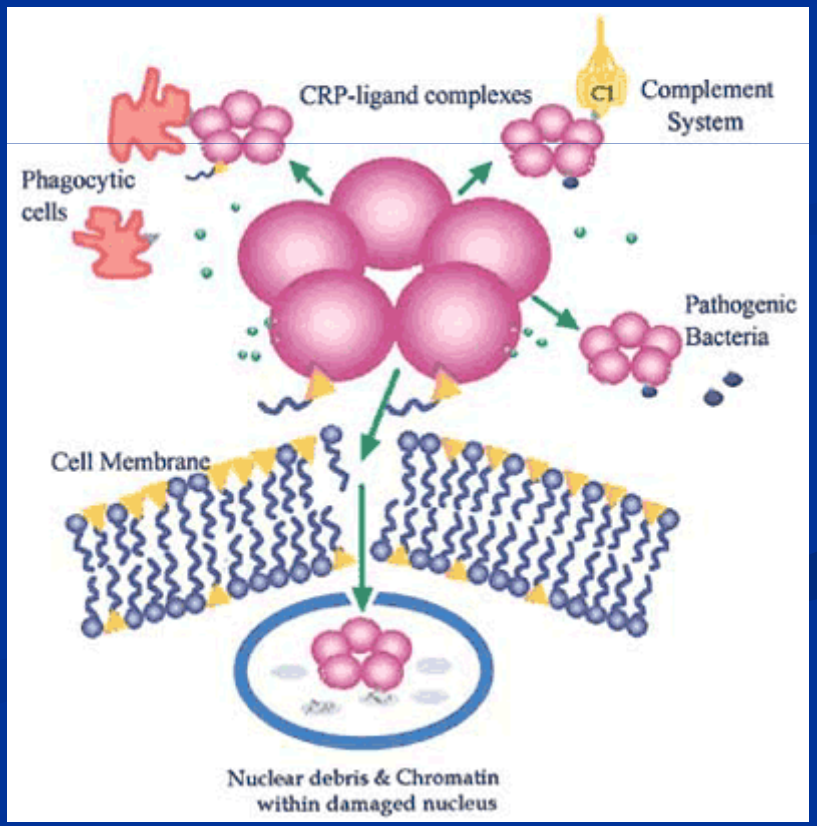
Acute phase proteins (APP)

C-reactive protein	Opsonin on microbes
Serum amyloid P	Opsonin
Serum amyloid A	Recruitment of immune cells to inflammatory sites Induction of enzymes that degrade extracellular matrix
Complement factors	Opsonization, lysis and clumping of target cells. Chemotaxis
Mannan-binding lectin	Mannan-binding lectin pathway of complement activation
Fibrinogen, prothrombin, VIII, von Willebrand factor	Coagulation factors, trapping invading microbes in blood clots.
Plasminogen	Degradation of blood clots
Alpha 2-macroglobulin	Inhibitor of coagulation by inhibiting thrombin.[4] Inhibitor of fibrinolysis by inhibiting plasmin
Ferritin	Binding iron, inhibiting microbe iron uptake [5]
Hepcidin	Stimulates the internalization of ferroportin, preventing release of iron bound by ferritin within intestinal enterocytes and macrophages
Ceruloplasmin	Oxidizes iron, facilitating for ferritin, inhibiting microbe iron uptake
Haptoglobin	Binds hemoglobin, inhibiting microbe iron uptake
Orosomucoid (Alpha-1-acid glycoprotein, AGP)	Steroid carrier
Alpha 1-antitrypsin	Serpin, downregulates inflammation
Alpha 1-antichymotrypsin	Serpin, downregulates inflammation

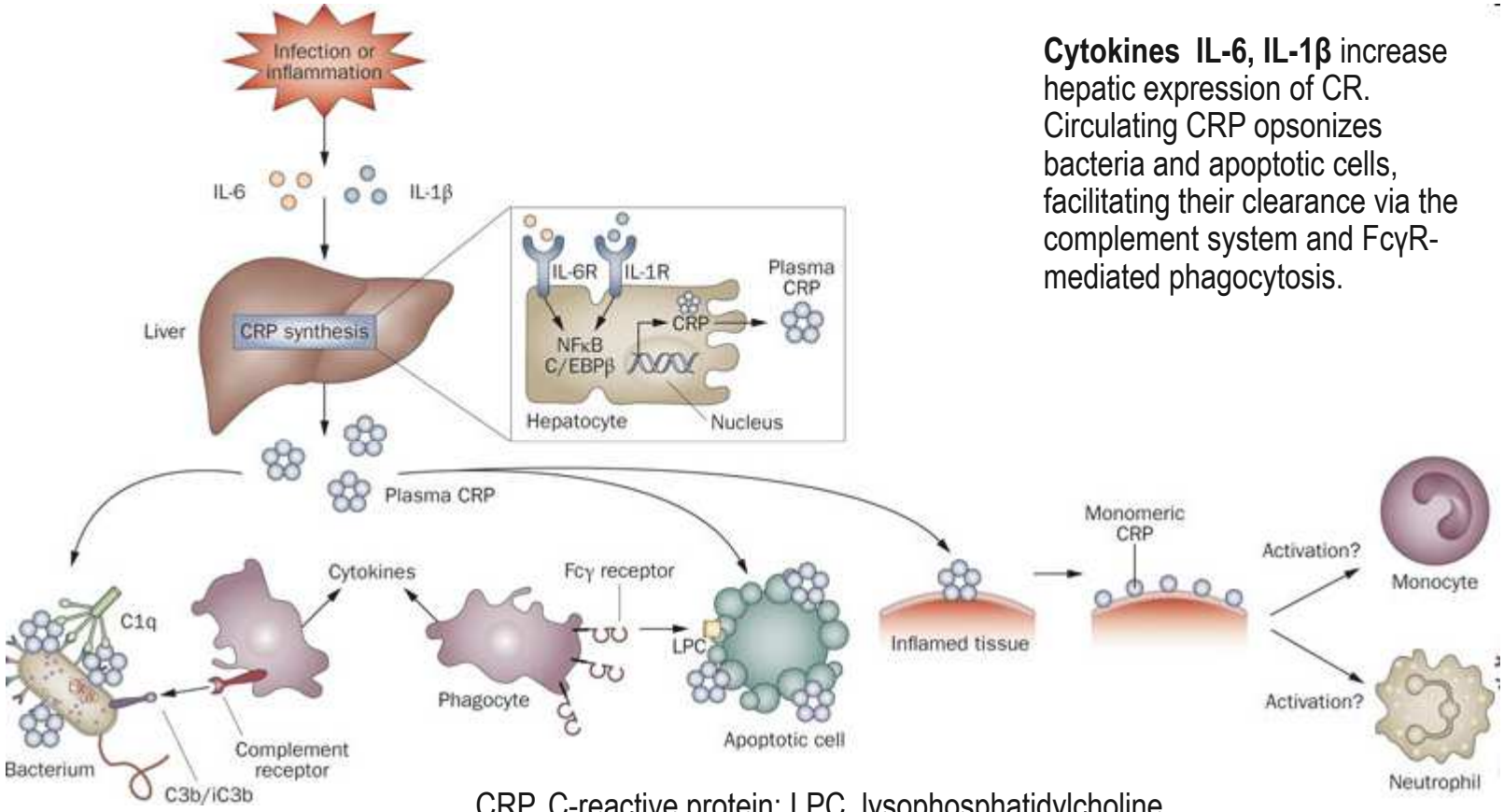
CRP + pentraxins

- Tillett and Francis (1930): first APP ; named after C-polysaccharide of Pneumococcus in pacs with acute phase of pneumonia
- half-life of 6-8 hours; fast working (rises & declines rapidly); CRP gene (1q21-q23); CRP has 224 amino acids
- Structure: **Pentraxins** = five identical non-covalently associated subunits (25106 D), which are arranged symmetrically around a central pore
  - short" pentraxins: CRP; serum amyloid P component (SAP);
  - long pentraxins (pattern recognition molecules): PTX3 (a cytokine modulated molecule) and several neuronal pentraxins.
- Function: bind to phosphocholine exp. on the surface of dead or dying cells and bacteria; to activate the complement system (C1Q complex)
- Synthesized by liver in response to macrophages and adipocytes.





Roles of C- reactive protein



Cytokines IL-6, IL-1β increase hepatic expression of CR. Circulating CRP opsonizes bacteria and apoptotic cells, facilitating their clearance via the complement system and FcγR-mediated phagocytosis.

CRP, C-reactive protein; LPC, lysophosphatidylcholine

- CRP ligation contribute to the release of cytokines such as **IL-10** by phagocytic cells.
- CRP deposited onto inflamed tissue breaks into biologically active monomeric subunits

Rhodes, B. *et al.* (2011) C-reactive protein in rheumatology: biology and genetics. *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2011.37

Serious systemic inflammatopry responses Cytokine storm

Systemic inflammatory response syndrome (SIRS)

- **Definition:** Systemic inflammatory response syndrome (SIRS)ICD-10 R65 is inflammatory state affecting the whole body, subset of cytokine storm, in which there is abnormal regulation of various cytokines

- **Etiology: infectious** (when bacteremia occurs - sepsis) or **noninfectious** (trauma, burns, pancreatitis, ischemia, and hemorrhage), complications of surgery, Adrenal insufficiency, Pulmonary embolism, Complicated aortic aneurysm, Cardiac tamponade, Anaphylaxis, Drug overdose

- **History:** 1983 introduced by William R. Nelson: multiple etiologies associated with organ dysfunction and failure following a hypotensive shock episode.
  - pathways include fibrin deposition, platelet aggregation, coagulopathies and leukocyte liposomal release.
  - may lead to renal failure, respiratory distress syndrome, central nervous system dysfunction and possible gastrointestinal bleeding.

Systemic inflammatory response syndrome (SIRS)

- **Criteria for SIRS** - 1992 *American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference;* manifestations of SIRS include, but are not limited to:
  - Body temperature < 36°C(96.8°F) or > 38°C(100.4°F)
  - Heart rate > 90 beats per minute
  - Tachypnea (high respiratory rate) > 20 breaths per minute; or an PaCO2 < 4.3 kPa (32 mmHg)
  - White blood cell count < 4 x 109 cells/L) or > 12 x 109 cells/L); or the presence of greater than 10% immature neutrophils (band forms).
  - Band forms greater than 3% is called bandemia or a "left-shift."
- SIRS can be diagnosed when two or more of these criteria are present

- T: solve the cause (i.e. adequate fluid replacement for hypovolemia, IVF/NPO for pancreatitis, epinephrine/steroids/diphenhydramine for anaphylaxis). Selenium, glutamine, eicosapentaenoic acid, antioxidants such as vitamin E have shown effectiveness

Sepsis

- **Definition:** whole-body inflammatory response to an infection (0bacteria, fungi, viruses, or parasites). By definition it is SIRS with positive cultivation for infection.
- Common signs and symptoms: fever, increased heart rate, increased breathing rate, and confusion.
- Symptoms related to a specific infection: cough with pneumonia, pain, dysuria etc.
- In the very young, old, and people with a weakened immune system, there may be no symptoms of a specific infection.
- Locations for the primary infection:: lungs, brain, urinary tract, skin, and abdominal organs.
- Risk factors: young or old age, a weakened immune system from conditions such as cancer or diabetes, and major trauma or burns
- Diagnosis is based on meeting at least two systemic inflammatory response syndrome (SIRS) criteria due to a presumed infection. Blood cultures are recommended preferably before antibiotics are started; however, infection of the blood is not required for the diagnosis
- Body temperature may be low or normal rather than high.
- **Severe sepsis** is sepsis causing poor organ function or insufficient blood flow.(hypotension), high blood lactate, or low urine output.
- **Septic shock** is low blood pressure due to sepsis that does not improve after reasonable amounts of intravenous fluids are given.

Multiple organ dysfunction syndrome (MODS)

- **Definition:** MODS (alt./old term: multiple organ failure (MOF), multisystem organ failure (MSOF) ICD-9-CM 995.92 altered organ function (2 or > 2 organ systems) in an acutely ill patient requiring medical intervention. Local and systemic responses are initiated by tissue damage.
  - **Respiratory failure** is commonest in the first 72 hours after the original insult.
  - **Liver failure** (5–7 days), **Gastrointestinal bleeding** (10–15 days)
  - **Kidney failure** (11–17 days)
- **Etiopathogenesis:** 1/3 of the patients no primary focus; 2/3 results from infection, injury (accident, surgery), hypoperfusion and hypermetabolism. Sepsis (septic shock) is the most common cause in operative and non-operative patients. In the absence of infection (SIRS). Final stage of a continuum: SIRS + infection --> sepsis --> severe sepsis -----> Multiple organ dysfunction syndrome.
- **1. Gut hypothesis:** splanchnic hypoperfusion, mucosal ischaemia and alterations; increased gut permeability, changed immune function of the gut --> increased translocation of bacteria. Liver dysfunction toxins escaping into circulation and activating an immune response. This results in tissue injury and organ dysfunction.

Multiple organ dysfunction syndrome (MODS)

- **Endotoxin macrophage hypothesis.** Gram- infections in MODS are common. Endotoxins propel pro-inflammatory mediators: TNF-α, IL-1,IL-6. TXA2, prostacyclin, platelet activating factor, and nitric oxide
- **Tissue hypoxia-microvascular hypothesis.I**nsufficient supply of oxygen causes cell death and organ dysfunction
- **Mitochondrial DNA hypothesis.** Mt-DNA, that is very similar-looking like bacterial DNA, massively leaks into the blood stream after cell destruction in major trauma. Confronted with bacteria, white blood cells, or Neutrophil granulocyte, behave like predatory spiders.They spit out a web, or net, to trap the invaders, then hit them with a deadly oxidative blast. **Neutrophil extracellular traps (NETs).** This result in catastrophic immune response leading to multiple organ dysfunction syndrome.
- **Integrated hypothesis**

- inactivation of the pro-inflammatory transcription factors **NF-κB** and **AP-1** would be appropriate targets in preventing sepsis and SIRS; problem is that required for normal healthy immune response,
- **increased IL-10** expression significantly reduced sepsis-induced MODS in mouse model sepsis/ peritonitis: cecal ligation and puncture (CLP) (male Balb/c mice);

Multiple organ dysfunction syndrome (MODS)

- European Society of Intensive Care (1994) **"Sepsis-Related Organ Failure Assessment (SOFA)"** score to describe and quantitate the degree of organ dysfunction in 6 organ systems.
- **Multiple Organ Dysfunction Score**
  - Stage 1: patient has increased volume requirements and mild respiratory alkalosis which is accompanied by oliguria, hyperglycemia and increased insulin requirements.
  - Stage 2: patient is tachypneic, hypocapnic and hypoxemic; develops moderate liver dysfunction and possible hematologic abnormalities.
  - Stage 3: patient develops shock with azotemia and acid-base disturbances; has significant coagulation abnormalities.
  - Stage 4: patient is vasopressor dependent and oliguric or anuric; subsequently develops ischemic colitis and lactic acidosis.

- **Prognosis:** Mortality varies from 30% to 100%;. Since the 1980s the mortality rate has not changed.