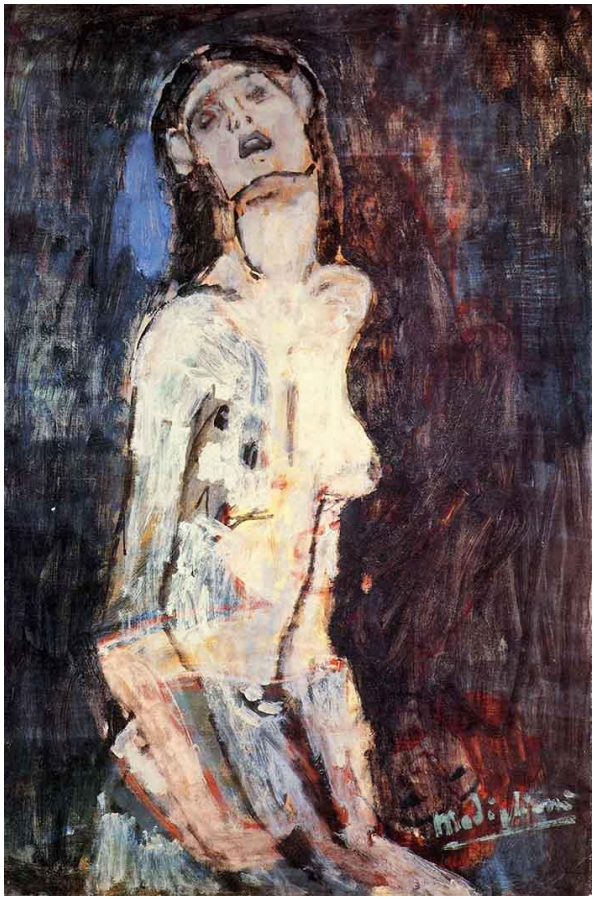
Acute inflammation



Modigliani: Nudo dolente

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Exam topics:

- **A/34.** Characteristics of acute inflammation (cellular events, chemical mediators, systemic effects)
- **A/35.** Morphologic patterns of acute inflammation according to the exudate

The pathology of inflammation

Basic features of inflammation:

- Inflammation is a basic biological **defense mechanism** aiming at the protection of the body against damaging effects
- Inflammation **IS NOT a disease** (except of autoinflammatory and autoimmune diseases)
- Inflammation **IS NOT the same as infection**
- Inflammation **can be acute and chronic**

The pathology of inflammation

Types of immunity:

- **Innate (inflammation):**
  - Rapid response (genetically encoded mediators, it „remembers” on a population level)
  - Not specific
  - Functions: Recognition of the infectious and other potentially harmful agents - neutralization / elimination
  - Activates the adaptive immunity (e.g.: dendritic cells)
- **Adaptive:**
  - Recognizes the specific molecular components of infectious (and other potentially harmful) agents
  - The response is highly specific and has a memory
  - It is not genetically encoded (gene rearrangements)
  - Defective function results in allergy and autoimmunity

The pathology of inflammation

Defects of inflammation can result in diseases in two main ways:

- **„Insufficient inflammation ”** – persistent infections
- **„Excessive inflammation”** – chronic or systemic inflammatory diseases (allergy, autoimmunity, etc.)

Factors provoking inflammation

- Infections (bacteria, viruses, fungi, parasites) – most frequent and medically most relevant factors
- Cell injury caused by **trauma** (blunt or penetrating), physical or chemical agents (e.g.: burns, irradiation, acid or lye, etc.)
- Tissue necrosis (of any etiology) – ischemia (e.g.: myocardial infarct), physical or chemical insults
- Foreign bodies (splinters, dusts, surgical thread, crystals)
- Immune reactions (hypersensitivity), caused by environmental or autoantigens

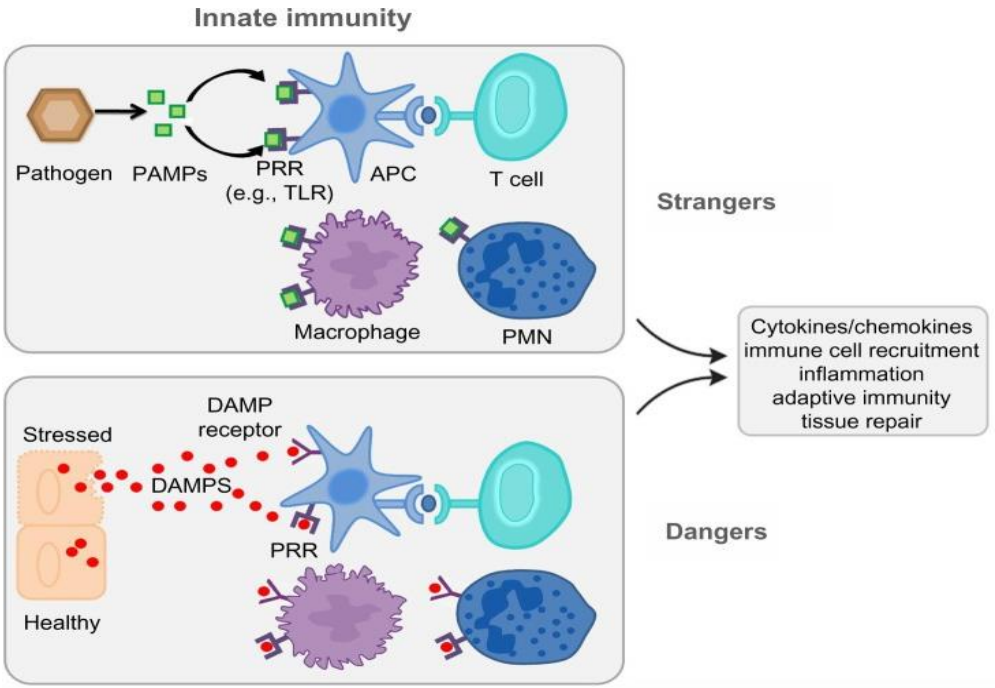
Recognition of pathogens, necrotic cells and foreign materials - Innate immunity

Pattern Recognition receptors (PRR):

1. **Toll-like receptors (TLR)**: Cellular receptors for the recognition of infectious agents.
   - The name of the receptor family comes from its firstly described member in *Drosophila* (Toll protein)
   - They recognize **Pathogen Associated Molecular Patterns (PAMP)** – e.g.: lipopolysaccharides (LPS), CpG DNA in bacteria
2. **Sensors of cellular injury**
   - They recognize **Damage-Associated Molecular Patterns (DAMP)**
3. **Circulating proteins**: **Complement cascade**, mannose-binding lectins, collectins, etc.

Main functions of PRRs:

- Activation of the complement system, coagulation and phagocytosis
- Initialization of inflammatory signal cascades
- Induction of apoptosis



Nomenclature of inflammatory diseases

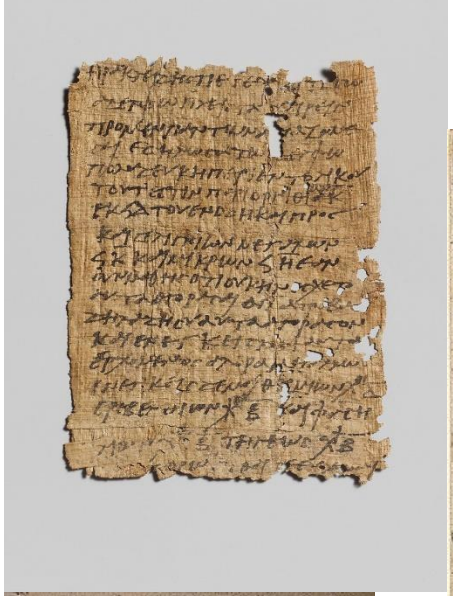
Basically: **Name of the tissue / organ + „itis”**

Examples of anomalous denominations:

Organ/tissue	Inflammatory disease
• **Tongue**	**Glossitis**
• **Oral mucosa**	**Stomatitis**
• **Cornea**	**Keratitis**
• **Lung (alveolar spaces)**	**Pneumonia**
• **Lung (interstitium)**	**Pneumonitis**
• **Stomach**	**Gastritis**
• **Small intestine**	**Enteritis**
• **Cecum**	**Typhlitis**
• **Rectum**	**Proctitis**
• **Testicle**	**Orchitis**
• **Vagina**	**Colpitis**
• **Fallopian tube**	**Salpingitis**
• **Navel**	**Omphalitis**
• **Spleen**	**Splenitis**
• **Breast**	**Mastitis**
• **Adipose tissue**	**Panniculitis**
• **Brain parenchyma**	**Encephalitis**

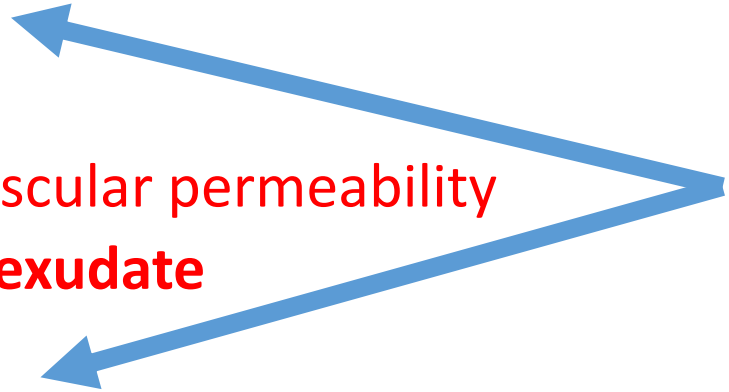
The history of inflammation

- Egyptian papyruses (B.C. 3000)
- ***Celsus*** (A.D. I. century):
  - 4 cardinal symptoms: **Rubor, tumor, dolor, calor**
- ***John Hunter*** (1728-1793):
  - Inflammation is not a disease, but a protective response
- ***Rudolf Virchow*** (1821-1902):
  - The 5th cardinal symptom: **Functio laesa**



Main steps of inflammation

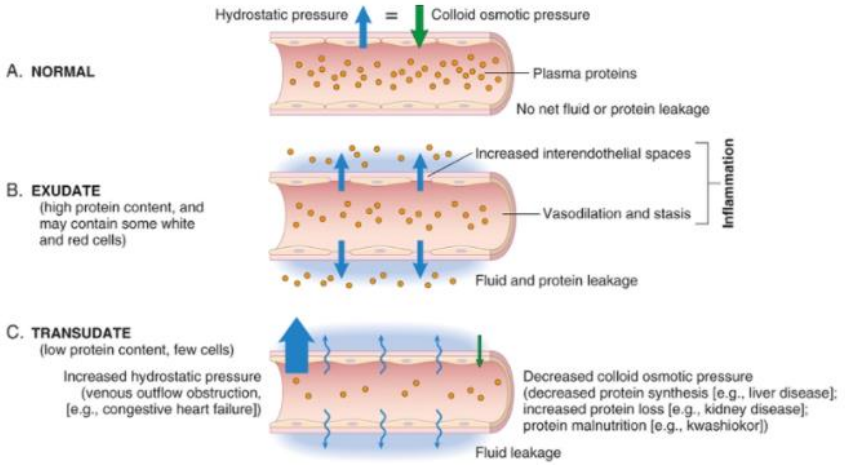
- **Vascular events:**
  - **Vasodilation**
  - Increase of vascular permeability
  - Formation of **exudate**
- **Cellular events:**
  - Margination, rolling, adhesion
  - Transmigration (diapedesis)
  - Chemotaxis
  - Activation of neutrophilic granulocytes
  - Phagocytosis: recognition, binding, engulfment, destruction
- **Resolution**
- The outcome can be: healing, formation of scar tissue, chronic inflammation



Chemical mediators

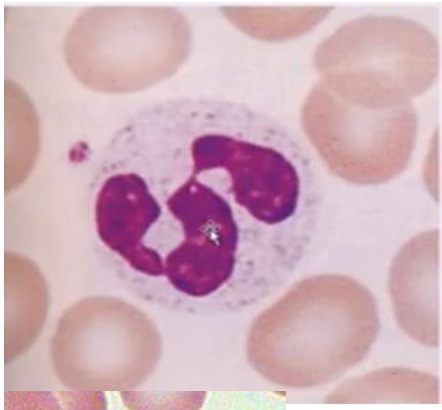
Vascular events

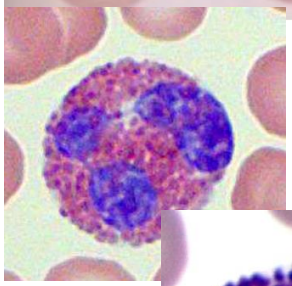
- The purpose of the inflammatory vascular reaction is the delivery of the humoral and cellular factors to the site of defense reaction
- **Changes of vascular diameter and flow** – arteriolar dilation (hyperemia) and stasis
- **Changes of permeability**
  - Endothelial cell retraction
    - Early phase (histamine, bradykinin) postcapillary venules
    - Late phase (TNF, IL-1, IFNγ) capillaries
  - Leakage from the new vessels
  - Direct endothelial and vascular wall damage
  - Damage caused by leukocytes
  - Transcytosis - VEGF
- Result: **EXUDATE** (not transudate)
  - High protein content!

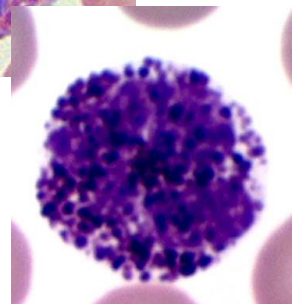


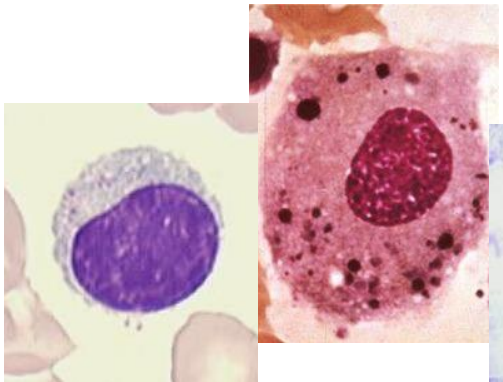
Cellular elements of inflammation

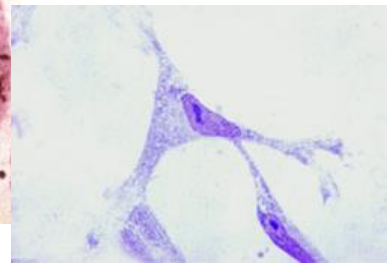
- ***Neutrophil granulocyte***
  - Major role in acute inflammation
  - Synonyms: Neutrophil, Polymorphonuclear, Leukocyte, PMN, PML, Granulocyte, „Poly", Polymorph
- ***Eosinophil granulocyte*** – parasites, worms
- ***Basophil granulocyte, mast cell*** – histamine, TNF storage
- ***Macrophages*** – phagocytosis, regulation of inflammation
- ***Endothelial cells*** – exudation, leukocyte migration
- ***Fibroblasts*** – regeneration
- ***Thrombocytes*** – PDGF, TGFβ, βFGF
- ***Lymphocytes***







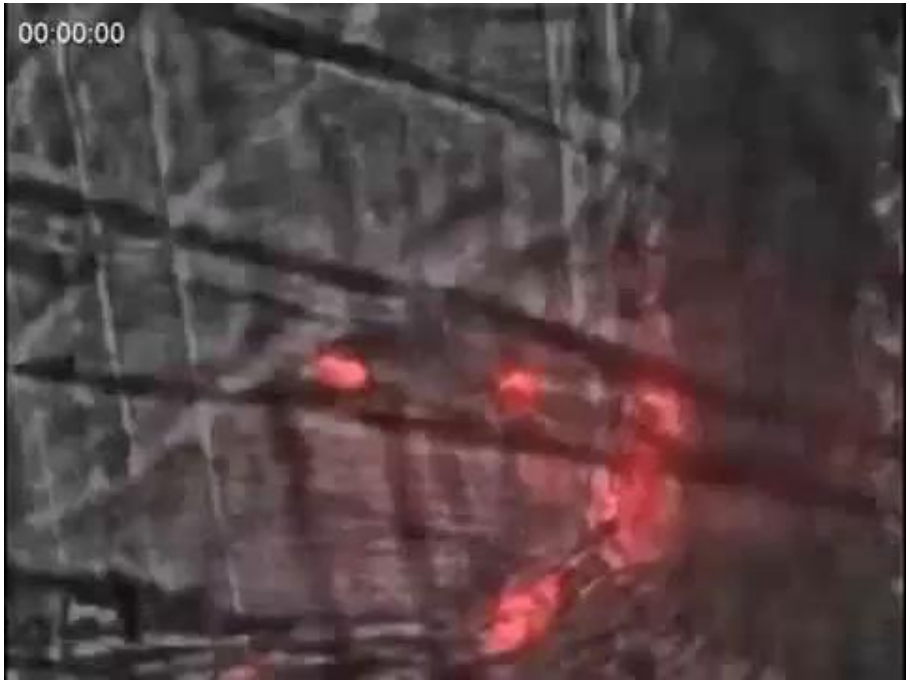




Leukocyte recruitment to sites of inflammation

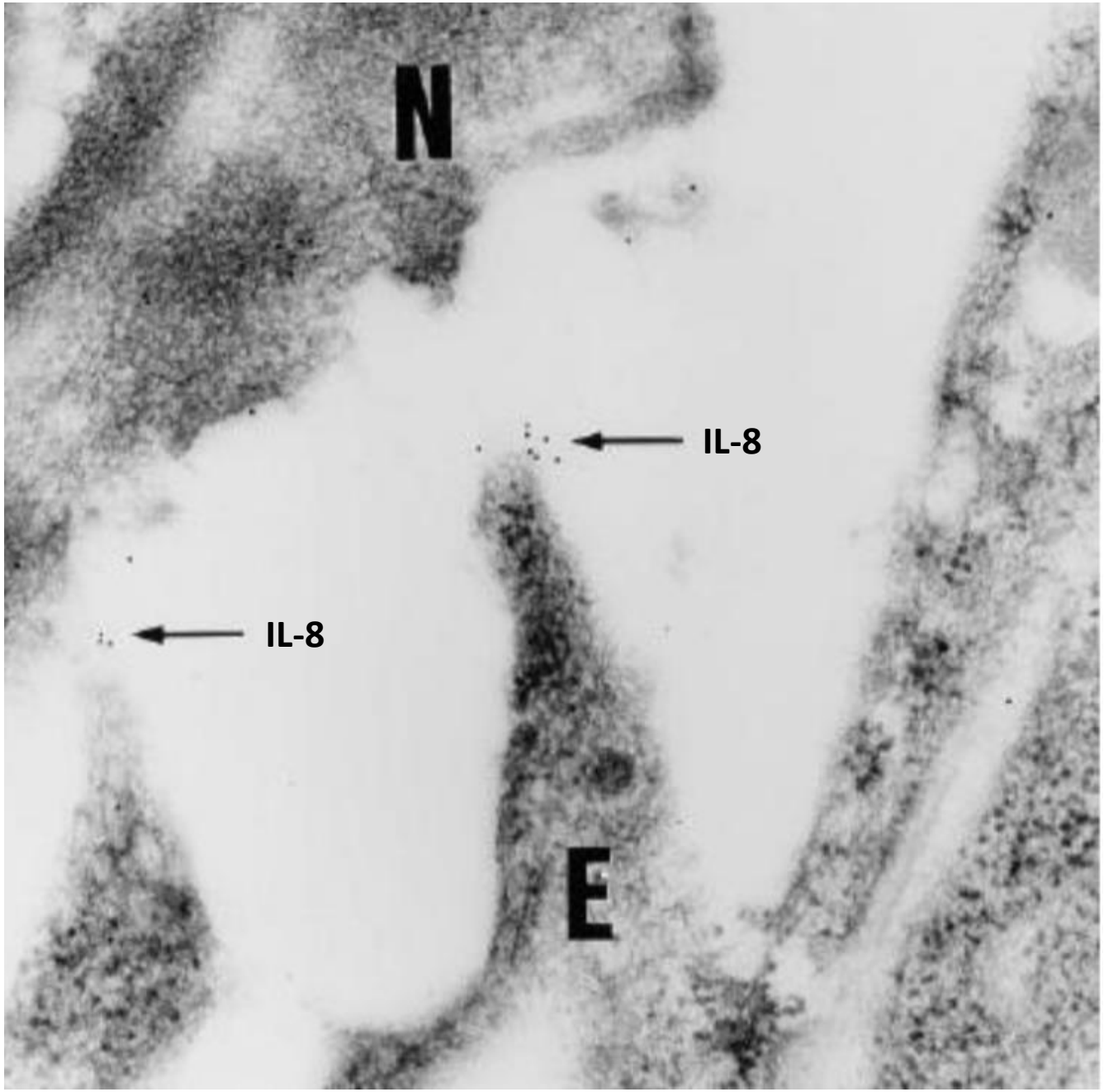
EXTRAVASATION of PMNs

- Main steps:
  - **Margination**: PMNs approach the endothelium
  - **Rolling**: tumbling and heaping on the endothelium
  - **Adhesion**
  - **Transmigration** (diapedesis)
  - **Chemotaxis**

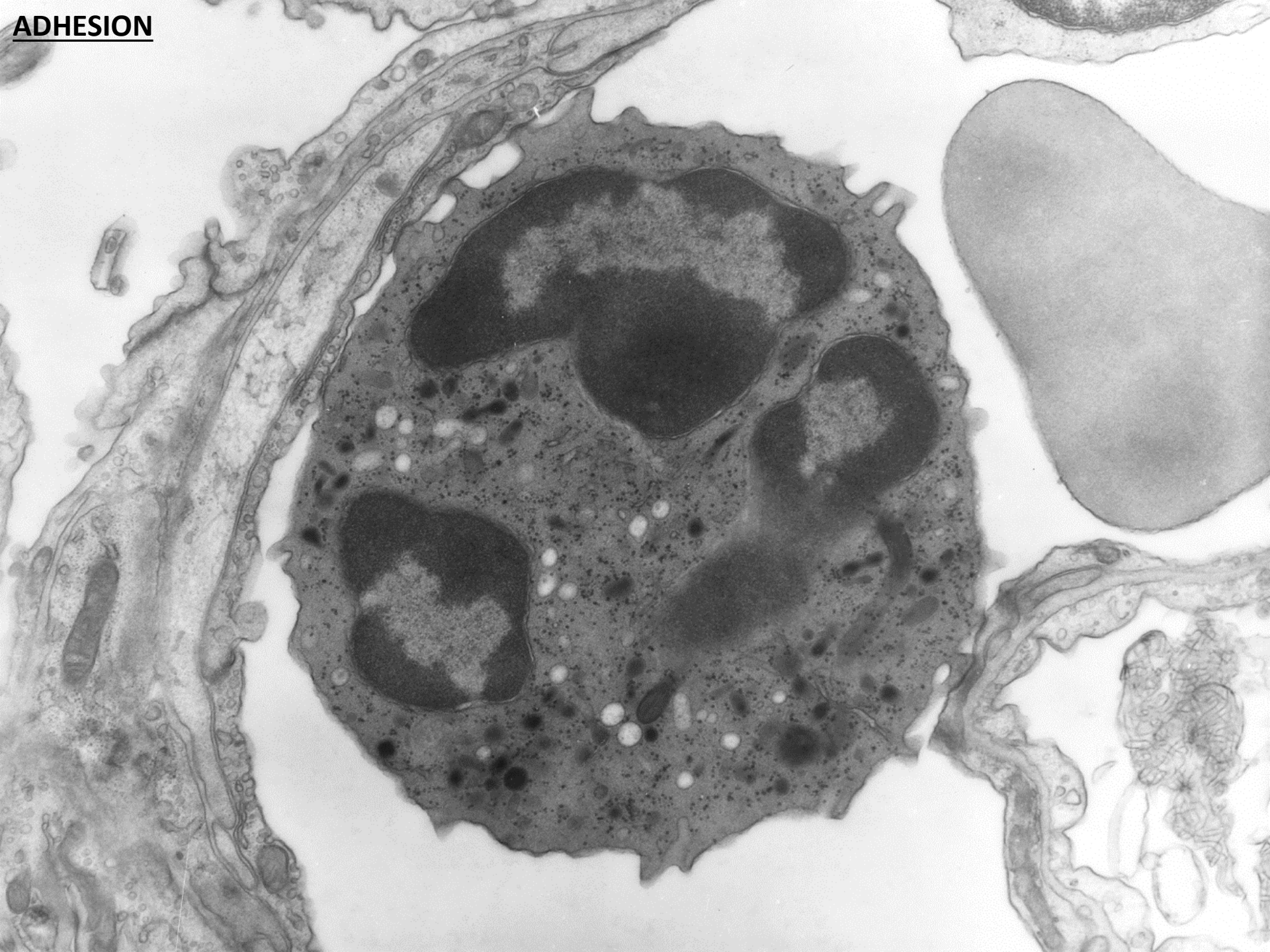


- Molecular mediators of various steps:
  - Rolling: E and P **selectins** on endothelial cells and L-selectins on leukocytes
  - Adhesion: **Integrins** (ICAM, VCAM)
  - Transmigration: **CD31** (in venules)
  - Chemotaxis: **chemokines** (specific cytokines) and other chemoattractants (N-formylmethionine, C5a, leukotrienes)

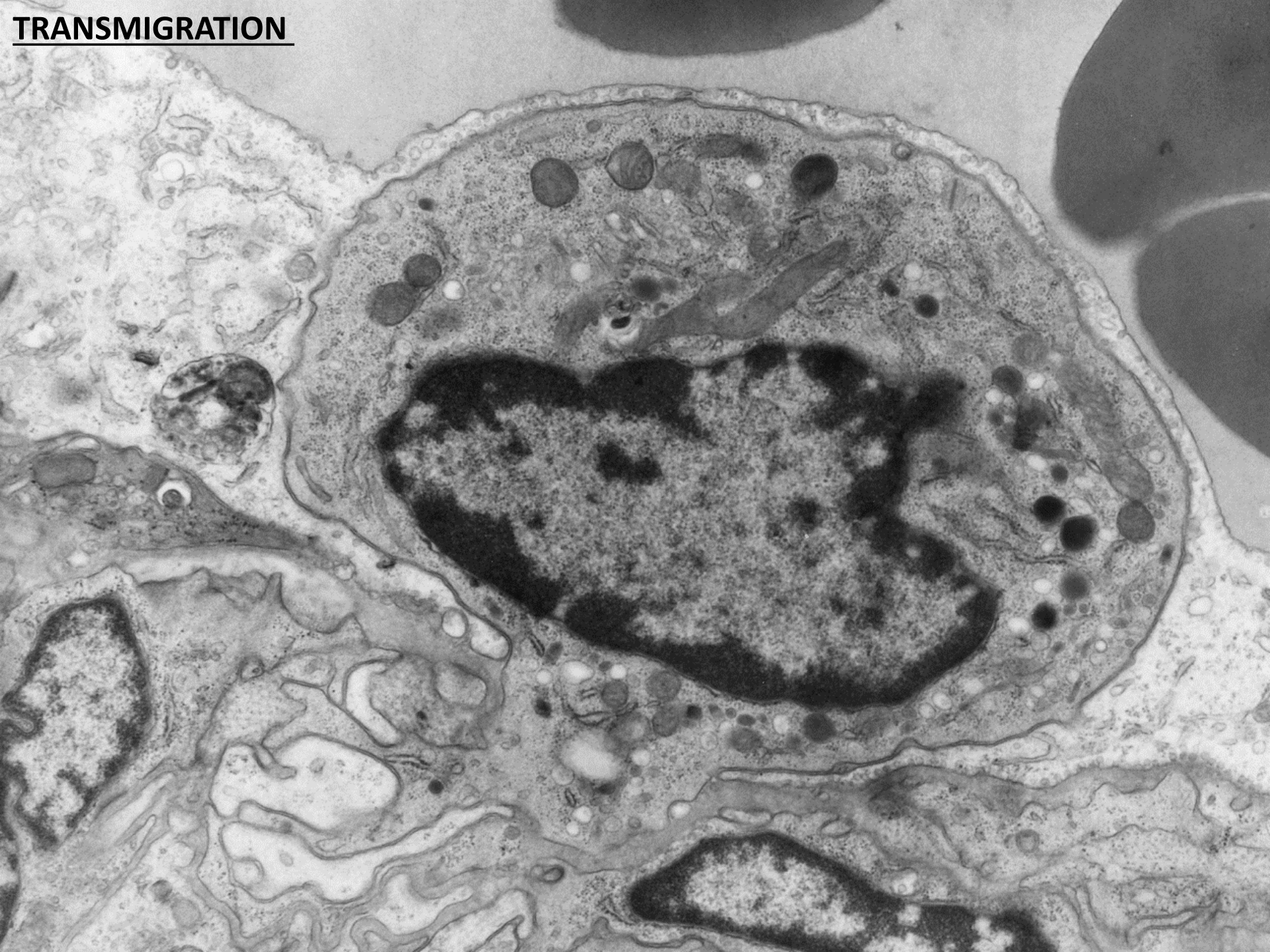
MARGINATION



ADHESION



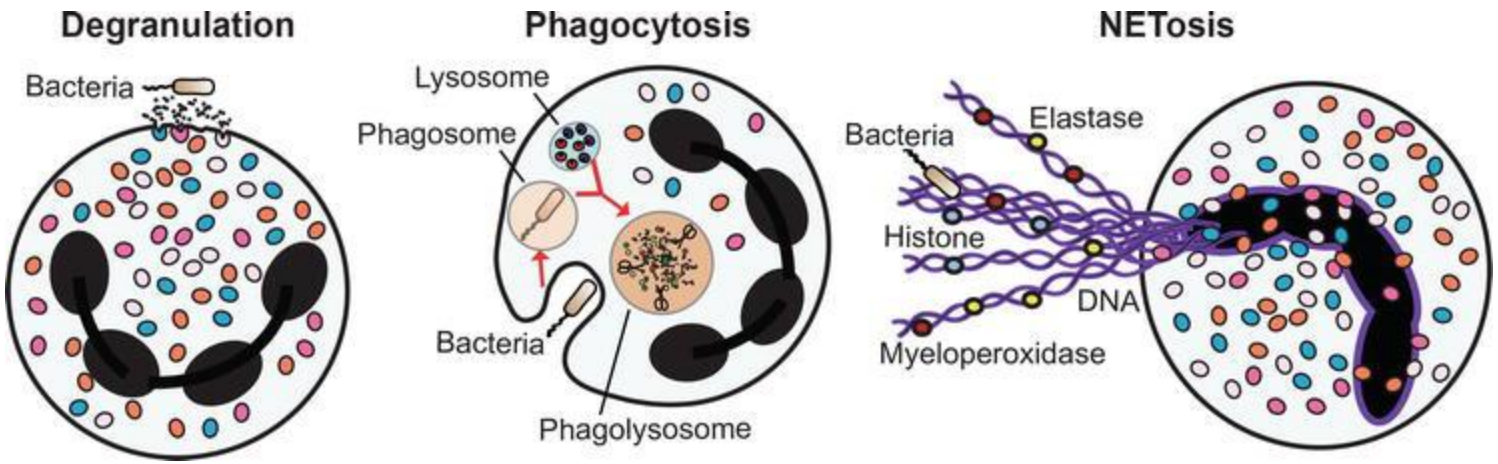
TRANSMIGRATION



Leukocyte activation

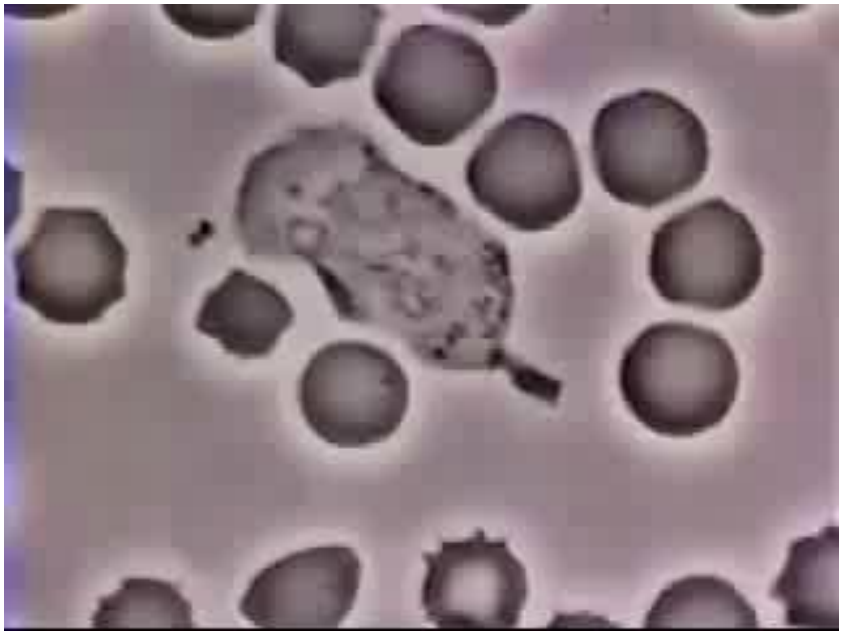
Triggered by the offending stimuli for PMNs to:

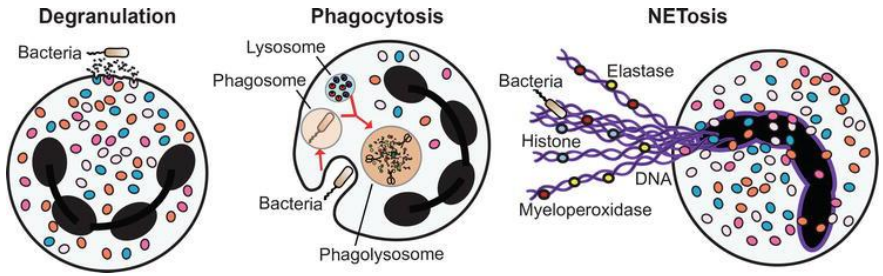
1. Produce eicosanoids (arachidonic acid derivatives)
   - Prostaglandins (and thromboxanes)
   - Leukotrienes
   - Lipoxins
2. Undergo **DEGRANULATION**
3. Secrete **CYTOKINES** (polypeptide mediators of inflammation)



Leukocyte activation - **PHAGOCYTOSIS**

- **Recognition**
  - Various receptors
  - Opsonization
- **Engulfment**
- **Degradation / digestion**
  - Oxygen dependent and independent mechanisms

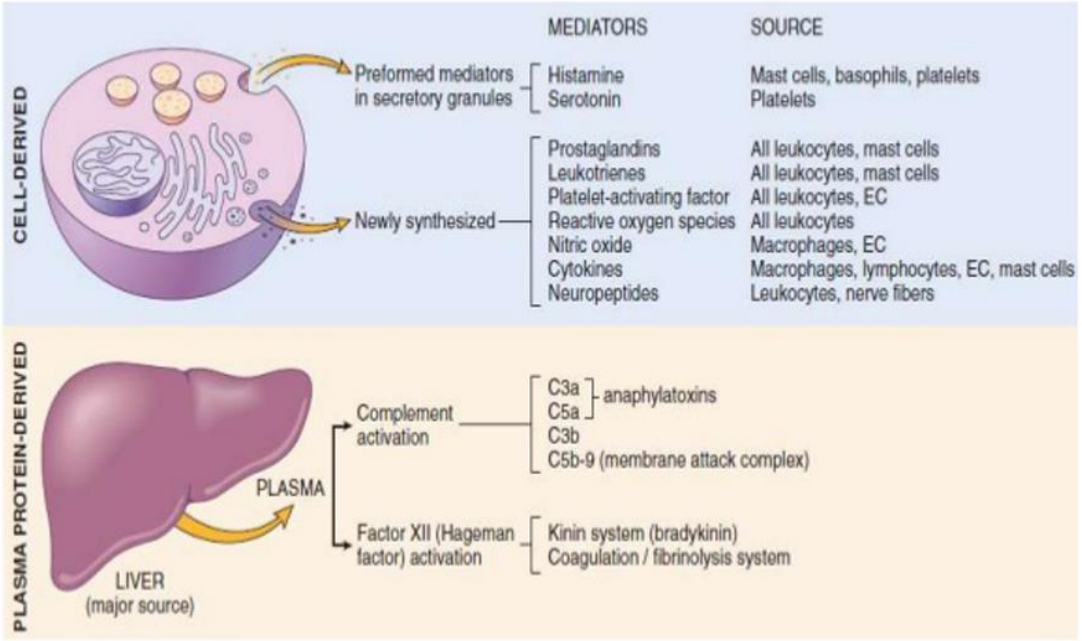




- An additional mechanism: **Neutrophil extracellular trap (NET)**
  - A web of nuclear chromatin from PMNs, in which microbicide molecules are concentrated

Humoral mediators of inflammation

- **Vasoactive amines**: histamine, serotonin (vasodilatation, permeability, pain)
- **Vasoactive peptides**: bradykinin
- **Complement system** - MAC, vasodilatation, permeability, chemotaxis, opsonization
- **Coagulation and fibrinolytic cascade**
- **Immunoglobulins**
- **Arachidonic acid derivatives**
  - Cyclooxygenase (COX) – prostaglandins
  - Lipoxygenase – leukotrienes
- **Cytokines** (polypeptide mediators of inflammation): TNF, IL-6, IL-1
- **Exogenous mediators**: fMLP, endotoxin, superantigens



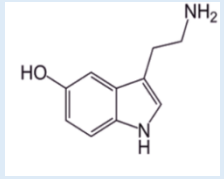
CHEMICAL MEDIATORS in general

- From plasma or cells
- Some need activation
- Usually have specific targets
- Can cause a cascade
- Usually short lifetime

HISTAMINE

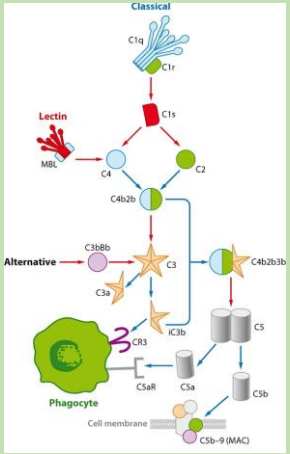
- Mast cells, basophils
- Vasoactive amine
- POWERFUL vasodilator
- IgE receptor on mast cell triggers the release

SEROTONIN



- =**5HT**, 5-**H**ydroxy-**T**ryptamine
- Platelets and enterochromaffin cells
- Also vasodilatation, but rather indirect
- Triggers NO synthesis from arginine

COMPLEMENT SYSTEM



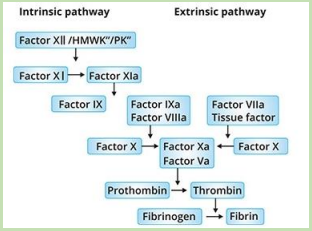
- >20 components, circulating in the plasma
- Multiple sites of action, but **LYSIS** is the main mechanism
- Opsonization

KININ SYSTEM

- BRADYKININ is the KEY component, 9 AA
- ALSO from circulating plasma
- Actions:
  - **Increased permeability**
  - **Smooth muscle contraction, NON vascular**
  - **PAIN**

CLOTTING FACTORS

- Also from circulating plasma
- Coagulation, i.e., production of fibrin
- Fibrinolysis



EICOSANOIDS

- **Arachidonic acid derivatives**, which is a component of cell membranes

1. **Prostaglandins (including thromboxanes)**
2. **Leukotrienes**
3. **Lipoxins**

MULTIPLE ACTIONS AT MANY LEVELS

PROSTAGLANDINS (THROMBOXANES INCLUDED)

- Fever - hypothalamus
- Pain
- Coagulation

LEUKOTRIENES

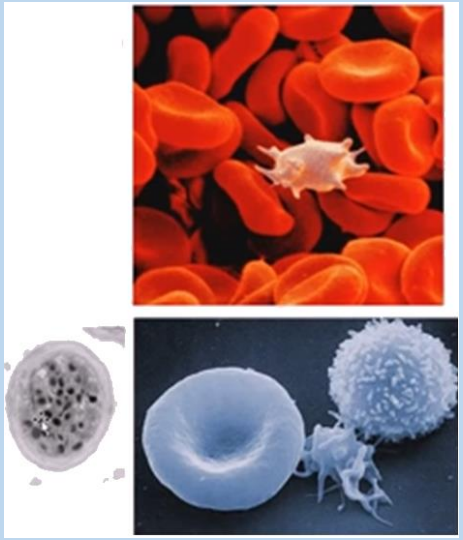
- Chemotaxis
- Vasoconstriction
- Increased Permeability

LIPOXINS

- INHIBIT chemotaxis
- Vasodilation
- Counteract actions of leukotrienes

PLATELET-ACTIVATING FACTOR (PAF)

- Phospholipid
- From MANY cells, like eicosanoids
- ACTIVATE PLATELETS, powerfully
- VASOCONSTRICTION



CYTOKINES/CHEMOKINES

- **CYTOKINES**
  - POLYPEPTIDES produced by MANY cells (usually LYMPHOCYTES and MACROPHAGES)
  - Multiple, basic role in acute and chronic inflammation
  - **TNFα**, **IL-1** from macrophages
- **CHEMOKINES** are small polypeptides, attractants for PMNs (>40)

FREE RADICALS

- O_2 (SUPEROXIDE)
- H_2O_2 (PEROXIDE)
- OH^- (HYDROXYL RADICAL)
- **VERY-VERY DESTRUCTIVE**

NITRIC **O**XIDE

- Potent vasodilator
- Produced from the action of nitric oxide synthetase from arginine

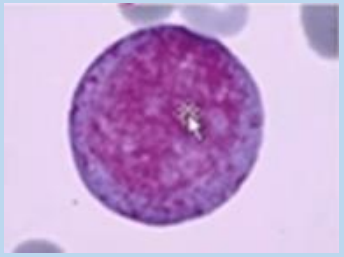
LYSOSOMAL COMPONENTS

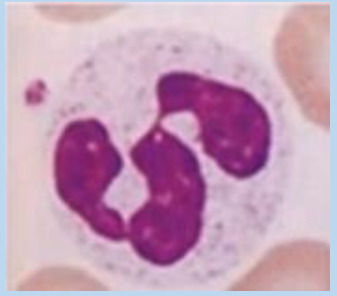
PRIMARY

- = AZUROPHILIC, or NON-specific granules
- Myeloperoxidase (MPO)
- Lysozyme (bactericide)
- Acid hydrolases

SECONDARY

- SPECIFIC granules
- Lactoferrin
- Lysozyme
- Alkaline phosphatase
- Collagenase





Systemic effects of inflammation – The acute phase response

Symptom, physical exam or lab finding	Comments	Mediators
Fever, malaise, somnolence, anorexia		TNF IL-1 Prostaglandins (fever)
↑ Production of acute phase proteins (e.g. **fibrinogen** and CRP)	Nonspecific markers of inflammation (ESR)	IL-6
Leukocytosis	-Initial early release -Increased production of WBC in bone marrow	-TNF & IL-1 -Colony stimulating factors
Shock	Hypotension, DIC, acidosis	High levels of: TNF & IL-1

- **Definition** Acute systemic reaction to TNF, IL-1 and IL-6
- **Fever** Systemic acute inflammation response, TNF, IL-1 and prostaglandin mediated
- **Leukocytosis** Systemic acute inflammation response, elevated WBC, TNF and IL-1 release WBC from bm as bands and CSF (colony stimulating factor) production increases
- **Acute phase proteins** mediated by IL-6 **C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA)**
- **Erythrocyte Sedimentation Rate** Distance RBC fall in an hour, if there is an acute phase protein (IL-6 mediated fibrinogen)-->RBC stack (rouleaux)-->fall larger distance than normal cells (lowest bar)
- **Septic Shock** Severe infection, causes hypotension, dic, and metabolic disturbances, TNF and IL-1

Potential outcomes of acute inflammation

1. Complete RESOLUTION, regeneration
2. SCAR formation
3. CHRONIC inflammation

Morphologic patterns of acute inflammation according to the exudate

Type	Example
Serous	Common cold, exudative pleuritis, burns, catarrhal inflammation of mucous membranes
Fibrinous	Serous membranes: pleuritis/pericarditis sicca, peritonitis fibrinosa Mucous membranes: diphtheria, typhoid fever, dysentery
Purulent	Folliculitis, furuncle, carbuncle ***Abscess***: circumscribed pus in parenchymal organs ***Empyema****:* circumscribed pus in preformed body cavity ***Phlegmon****:* inflammation spreading between soft tissue layers
Hemorrhagic	Plague, smallpox, anthrax, influenza pneumonia
Gangrenous	Gangrenous appendicitis / cholecystitis („inflammation bankrupts”)

I. Serous inflammation

Basic features:

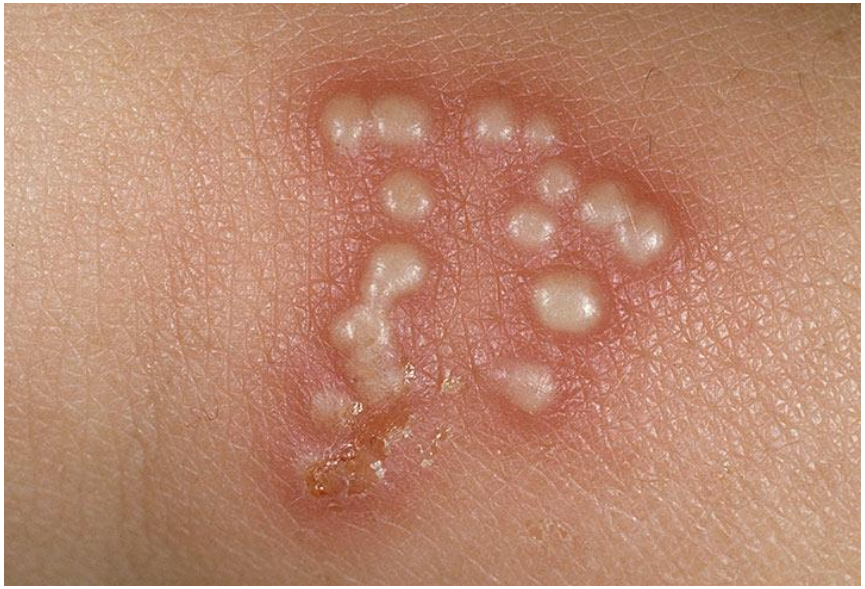
- Mild increase of vascular permeability
- Thin exudate which does NOT contain fibrin, RBCs and PMNs
- The exudate is derived from the plasma or secretion of mesothelial cells *(„effusion")*
- Purpose: fast dilution of damaging agents
- Etiology:
    - Hypersensitivity reactions
    - Bacterial / viral infections
    - Physical / chemical tissue injury

Examples:

- Common cold
- Allergic rhinitis / conjunctivitis
- Serous pleuritis / pericarditis / peritonitis
- Serous meningitis (usually viral)
- Skin blisters (e.g.: burns)
- ***Catarrhal (seromucous) inflammation*** of mucous membranes (e.g. sinusitis)

Morphology:

- **Serosa**: hyperemia, mesothelial cells and macrophages in the fluid
- **Skin and mucosal membranes**: erythema, swelling, blisters
- **Parenchymal organs**: hyperemia, swelling (edema), tenderness clinically, few inflammatory cells microscopically



II. Fibrinous inflammation

Basic features:

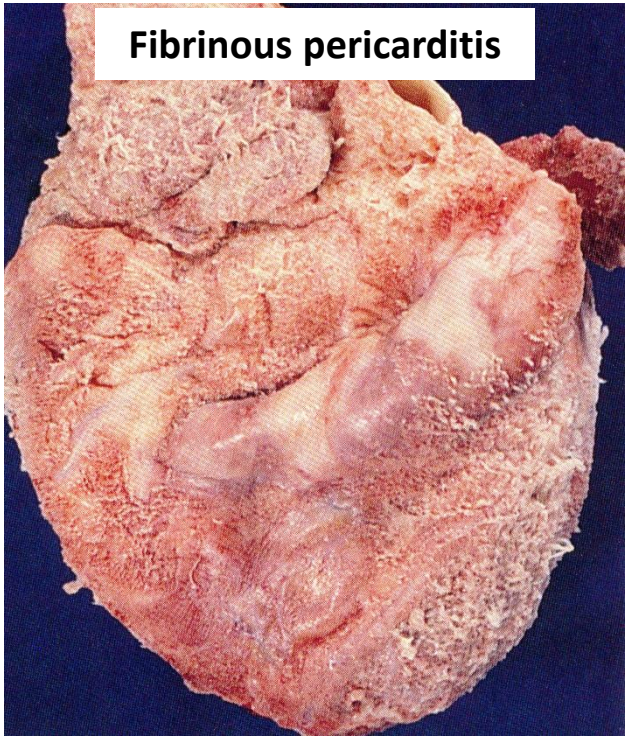
- Moderate increase of vascular permeability
- The exudate contains high amounts of fibrin, but no RBCs or PMNs
- Purpose: isolation of the inflammation

Morphology:

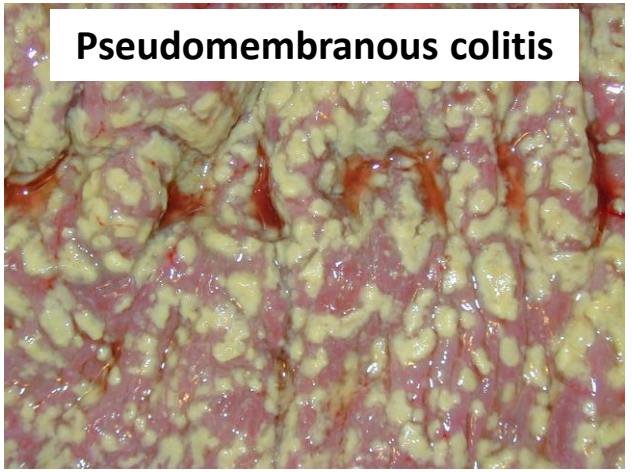
- Usually on serous membranes (***fibrinous pleuritis, pericardium, peritoneum***)
- Organs (e.g. ***lobar pneumonia – hepatisatio grisea***)
- Gross: filamentous deposit
- Microscopy: eosinophilic fibrin deposit
- Outcomes:
    - Resolution: degradation by fibrinolysis and macrophages
    - Organization: scar formation, fibrous adhesions

Pseudomembranous inflammation:

- Necrosis of mucous membranes + fibrinous exudate
- Examples:
    - ***Diphtheria*** (*Corynebacterium diphtheriae*)
    - ***Pseudomembranous colitis*** (*Clostridium difficile*)



Fibrinous pericarditis



Pseudomembranous colitis

III. Purulent (suppurative) inflammation

Basic features:

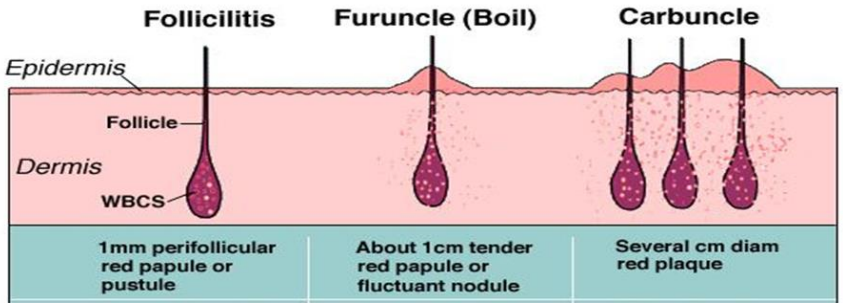
- Strong increase of vascular permeability
- The exudate contains PMNs and necrotic debris = **PUS**
- Pyogenic bacteria: species frequently causing pyogenic inflammation (e.g. *Staphylococci*, *Streptococci*)

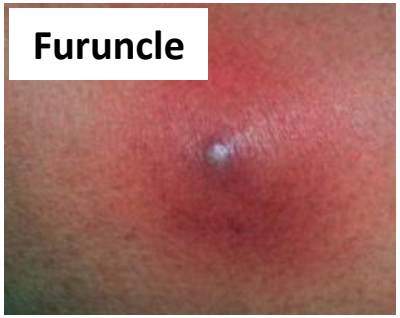
Morphology:

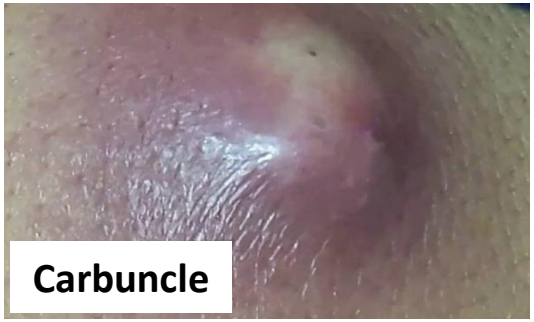
- Gross: thick, yellowish pus
- Microscopic: massive PMN infiltrate, necrotic debris
- **Abscess**: circumscribed pus in parenchymal organs
- **Empyema**: circumscribed pus in preformed body cavity
- **Phlegmon**: inflammation spreading between soft tissue layers

Examples:

- Hair follicles: folliculitis, furuncle, carbuncle



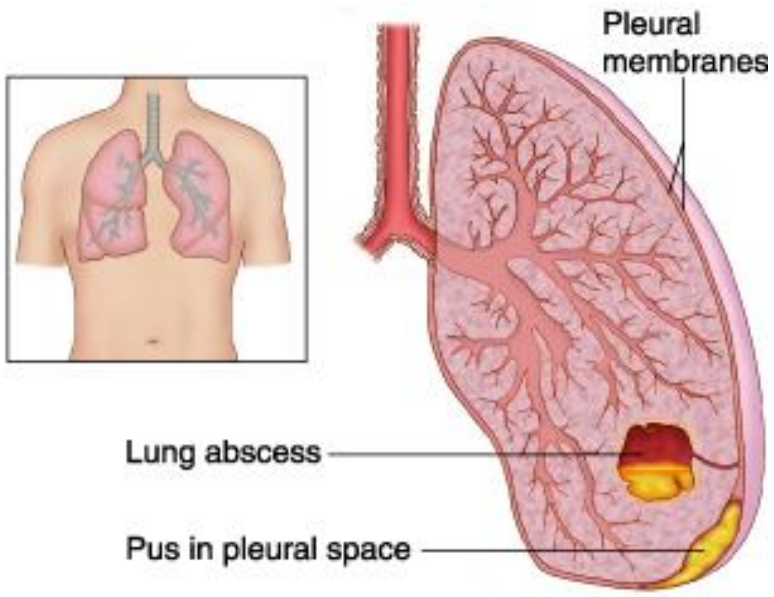


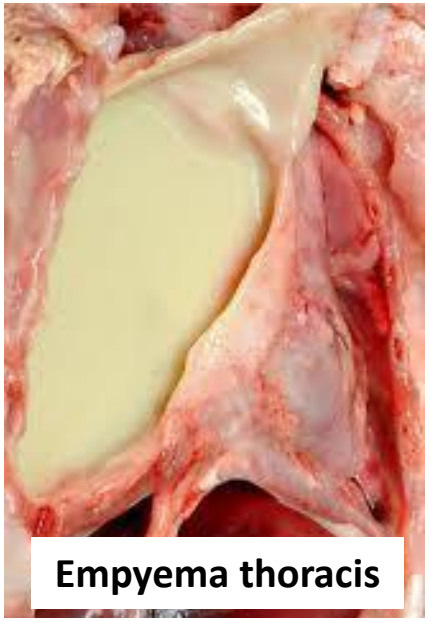


III. Purulent (suppurative) inflammation

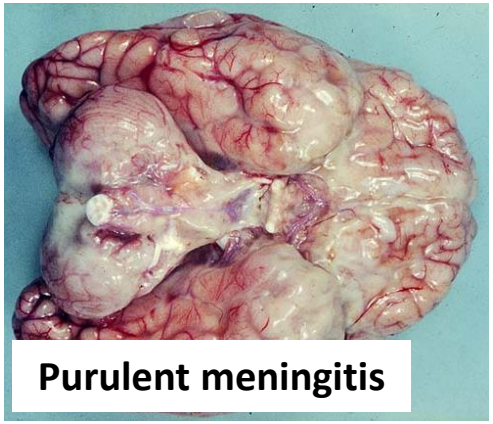
Examples:

- Brain, pulmonary, etc. abscess
- Empyema thoracis
- Bronchopneumonia
- Lobar pneumonia *(hepatisatio flava)*
- Purulent meningitis
- Pyelonephritis
- Suppurative appendicitis





Empyema thoracis



Purulent meningitis

Pulmonary abscess

Empyema vesicae felleae

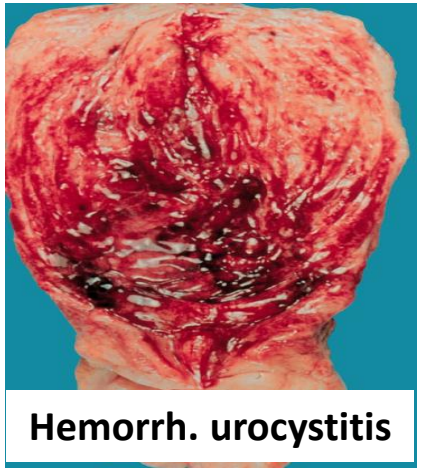
IV. Hemorrhagic inflammation

Basic features:

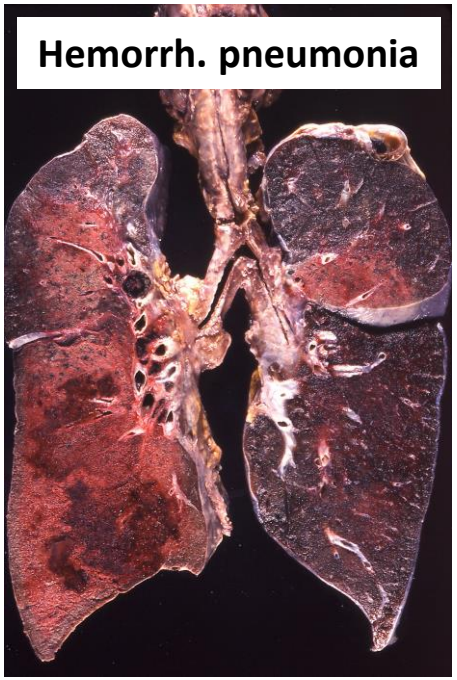
- The exudate contains blood (numerous RBCs)

Examples:

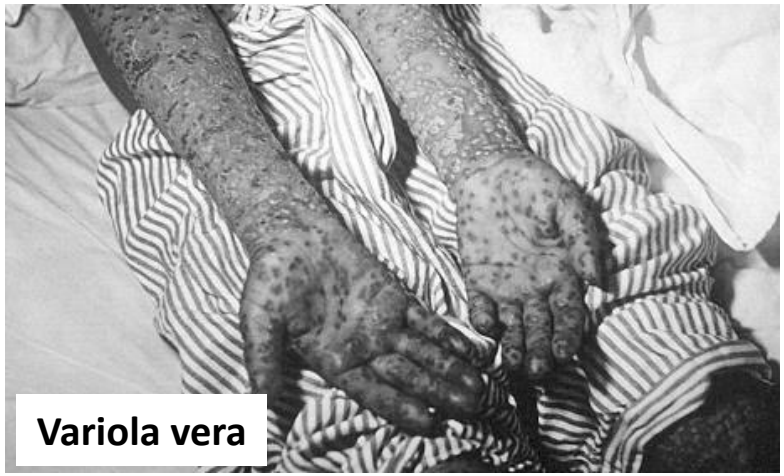
- Hemorrhagic pneumonia
  - Influenza
  - Lobar pneumonia *(hepatisatio rubra)*
- Anthrax *(Bacillus anthracis)*
- Smallpox *(Variola vera)*
- Hemorrhagic acute urocystitis



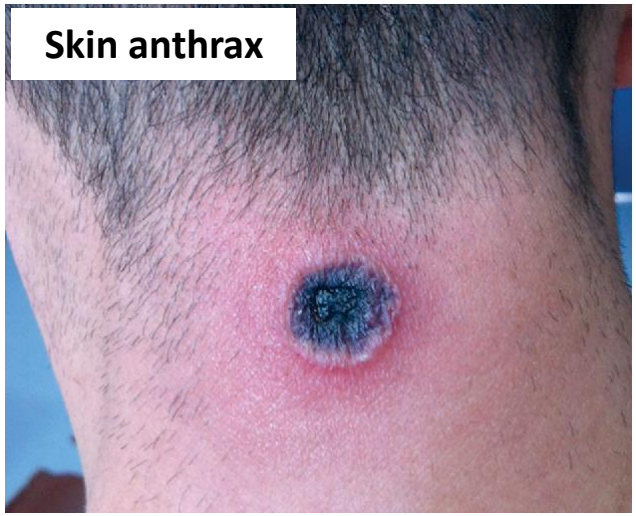
Hemorrh. urocystitis



Hemorrh. pneumonia



Variola vera



Skin anthrax

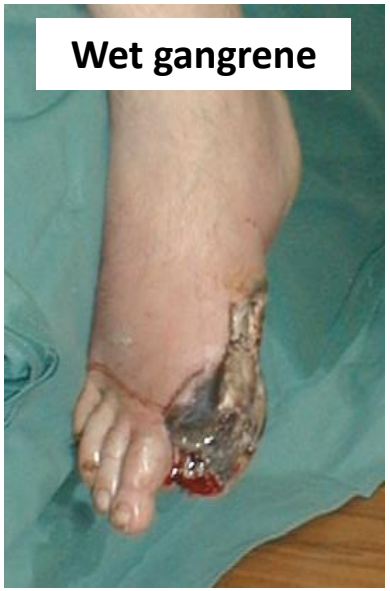
V. Gangrenous (necrotizing) inflammation

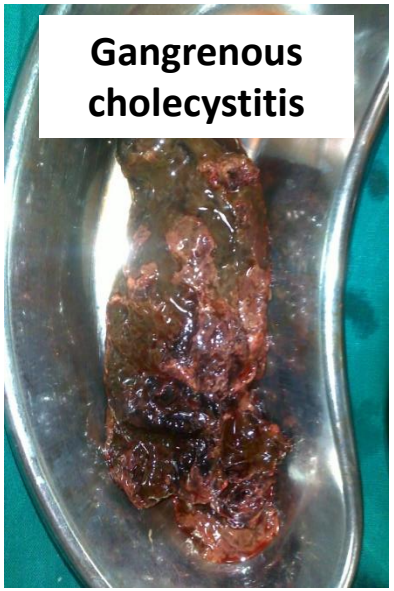
Basic features:

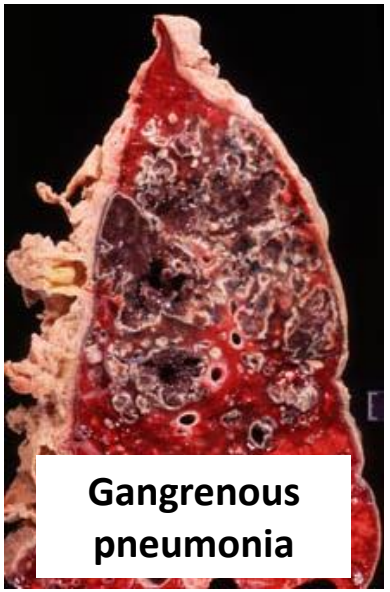
- The combination of necrosis, inflammation and bacterial growth
- „The inflammation bankrupts”

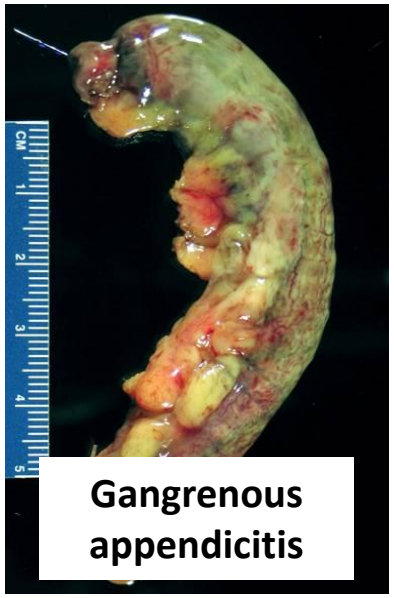
Examples:

- Wet gangrene
  - Atherosclerosis
  - Diabetes mellitus
- Pulmonary gangrene
- Mediastinal gangrene
- Gangraena gingivae *(„trench mouth”)*
- Gas gangrene *(Clostridium perfringens)*
- Gangrenous acute appendicitis / cholecystitis









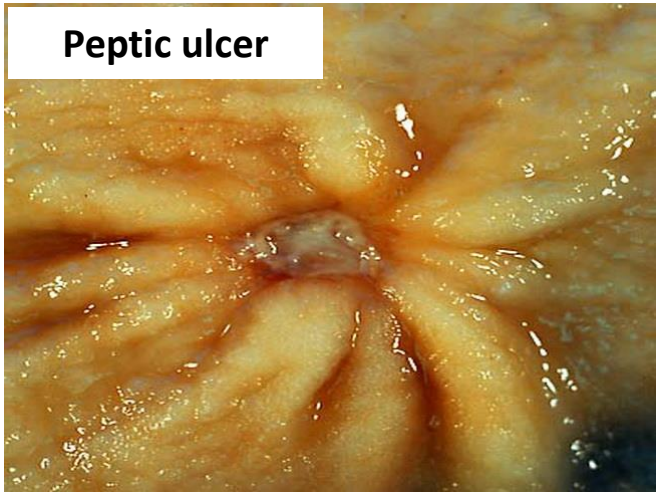
Ulcers, ulcerative inflammation

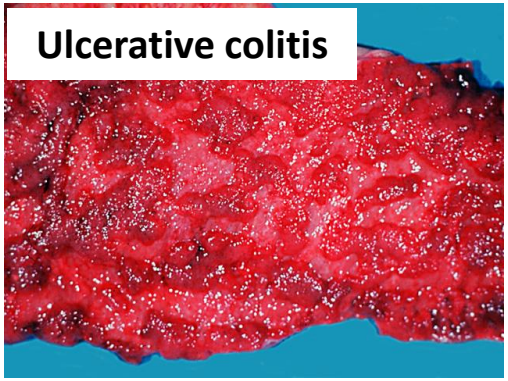
Basic features:

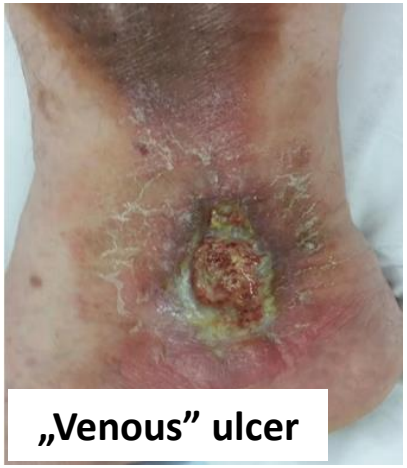
- NOT a type of inflammation, but frequently related to inflammation (can be both cause and consequence)
- Definition:
  - Defect of mucosa / skin AND underlying tissues caused by necrosis
  - Accompanied by inflammation, regeneration and scar formation

Examples:

- Peptic ulcer – stomach / duodenum
- Ulcerative colitis
- Venous congestion – skin of the lower extremities
- Ulcers of the oral cavity, genitourinary tract, etc.


Peptic ulcer


Ulcerative colitis


„Venous" ulcer

Csontváry: Old fisherman

Thank you for your attention!