Characteristics of acute inflammation (cellular events, chemical mediators, systemic effects)

Morphologic patterns of acute inflammation according to the exudate

Chronic inflammation.

Granulomatous inflammation

Tissue repair and wound healing

INFLAMMATION

(4 objectives)

1. UNDERSTAND THE CHAIN, PROGRESSION OR SEQUENCE OF VASCULAR AND CELLULAR EVENTS IN THE HISTOLOGIC EVOLUTION OF ACUTE INFLAMMATION

2. LEARN (ROTE????) THE ROLES OF VARIOUS „CHEMICAL MEDIATORS" OF ACUTE INFLAMMATION

3. KNOW THE POSSIBLE OUTCOMES (THREE) OF ACUTE INFLAMMATION

4. VISUALIZE THE MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

Characteristics of acute inflammation - General terms

The inflammation is a universal and ancient form of host defence.

The inflammation is not a disease, is a protective immune response, it is non-specific.

Inflammation is not equal with infection

Inflammation may be of two types, ***acute*** and ***chronic***

Immunity:

Innate (~inflammation): delaying the need for adaptive immunity, (mechanisms are coded in genome)

Recognizes infectious non self

Execution

Serves to alert the clonal, adaptive immune system (dendritic cells!!)

Adaptive: it recognizes fine details of pathogenic organisms,

It is highly specific and remembers (but not heritable), gene rearrangement is necessary

It is responsible for allergy, autoimmunity,

Insufficient inflammation can lead to persistent infection of pathogens

Excessive inflammation can cause chronic or systemic inflammatory diseses.

STIMULI

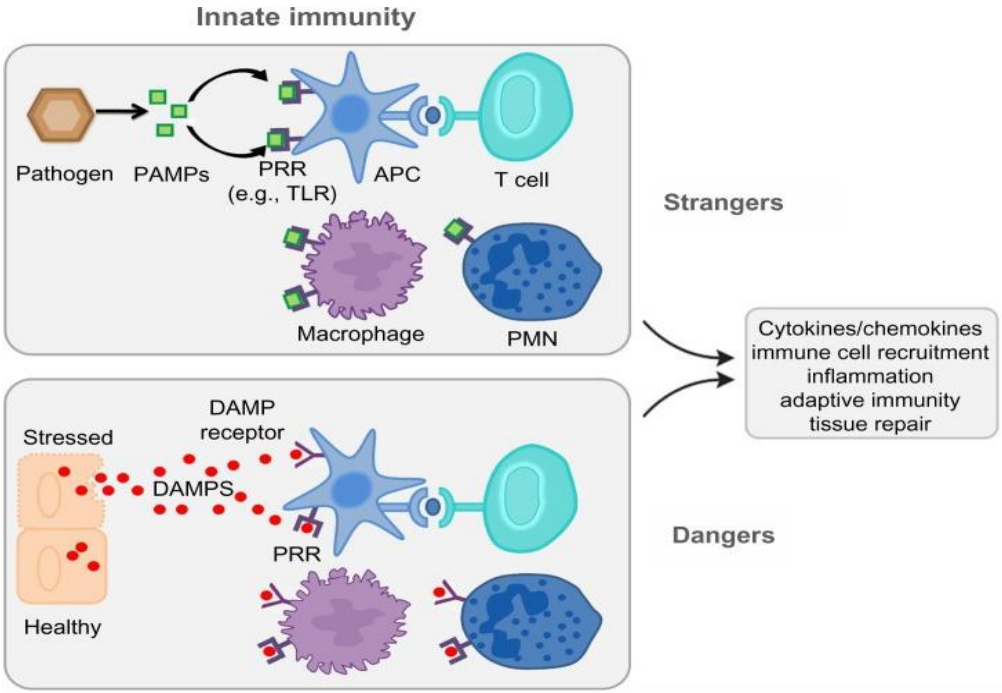
for acute inflammation

- **INFECTIOUS**
- **PHYSICAL**
- **CHEMICAL**
- Tissue Necrosis
- Foreign Bodies (FBs)
- Immune „responses” or „complexes”

Characteristics of acute inflammation-innate immunity

The first step in inflammatory responses is the recognition of microbes and necrotic cells by cellular receptors and circulating proteins.

- *Cellular receptors for microbes* . PRR (e.g. Toll-like receptors (TLRs) , which are named for the founding member, Toll , a gene that was discovered in Drosophila. TLRs recognize PAMPs/LPS,DNA,CpG
- *Sensors of cell damage*. Damage-associated molecular patterns (DAMPs). These molecules include **uric acid** (a product of DNA breakdown), **ATP** (released from damaged mitochondria), **reduced intracellular K + concentrations** (reflecting loss of ions because of plasma membrane injury), **DNA** (when it is released into the cytoplasm and not sequestered in nuclei, as it should be normally), and many others.
- *Circulating proteins*: complement system, mannose-binding lectin, collectins



Principal functions of induction of apoptosis

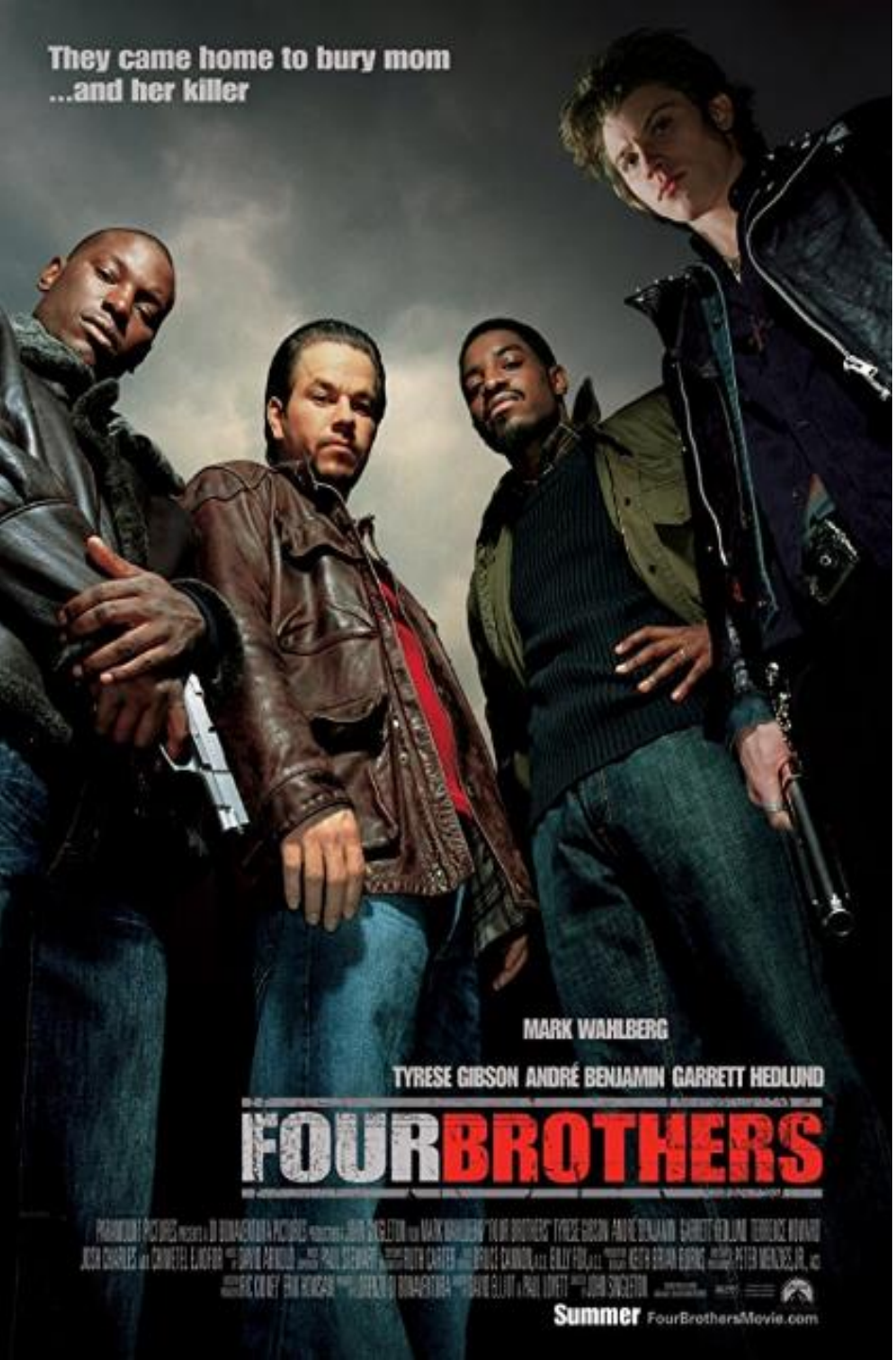
PRPs: activation of complement, coagulation, phagocytosis, pro inflammatory signaling cascades

Characteristics of acute inflammation

Terminology: +itis
Most common extraordinary names

/tissue

tongue	glossitis
oral mucose	stomatitis
cornea	keratitis
lung	pneumonia
stomach	gastritis
small intestine	enteritis
coecum	typhlitis
rectum	proctitis
testis	orchitis
vagine	colpitis
fallopian tube	salpingitis
belly bottom	omphalitis
breast	mastitis
adipose tissue	panniculitis
brain	encephalitis



Characteristics of acute inflammation

HISTORY
Egyptian papyrus (3000BC)

Celsus (1st century AD) 4 cardinal signs of inflammation „rubor, calor, tumor, dolor „

Virchow- 5th clinical sign „Functio laesa”

John Hunter (1973)- inflammation is not a DISEASE
but a non-specific response that has salutary effect on its host

Characteristics of acute inflammation

SEQUENCE OF EVENTS

- NORMAL HISTOLOGY ⟶
- *VASODILATATION* ⟶
- *INCREASED VASCULAR PERMEABILITY* ⟶
- *LEAKAGE OF EXUDATE* ⟶
- **MARGINATION, ROLLING, ADHESION** ⟶
- **TRANSMIGRATION (DIAPEDESIS)** ⟶
- **CHEMOTAXIS** ⟶
- **PMN ACTIVATION** ⟶
- **PHAGOCYTOSIS**: Recognition, Attachment, ⟶
  Engulfment, Killing (degradation or digestion) ⟶
- TERMINATION ⟶
- 100% **RESOLUTION**, **SCAR**, or **CHRONIC INFLAMATION** are the three possible outcomes

Troy, 2004

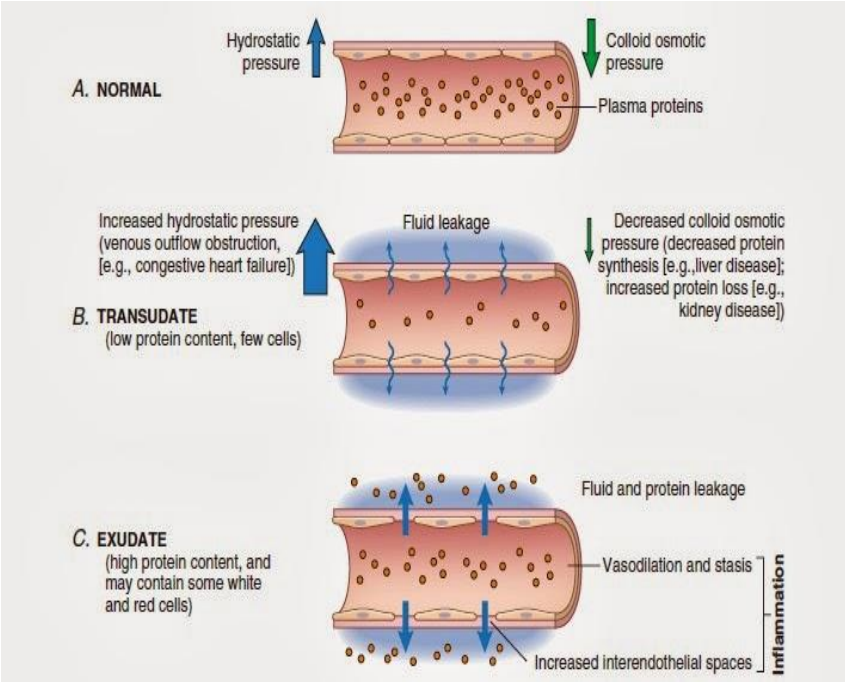
Vascular events of inflammation

The purpose of the inflammatory vascular reaction is to deliver the humoral and cellular factors to the site of defence reaction

Changes in vascular flow and caliber

Changes in vascular permeability

- *Dilatation*
- *Endothelial gaps*
- *Direct endothelial injury*
- *Leukocyte injury*
- *Transcytosis (endo/exo)*



LEAKAGE of a proteineaceous fluid EXUDATE and not TRANSUDATE!!!!!

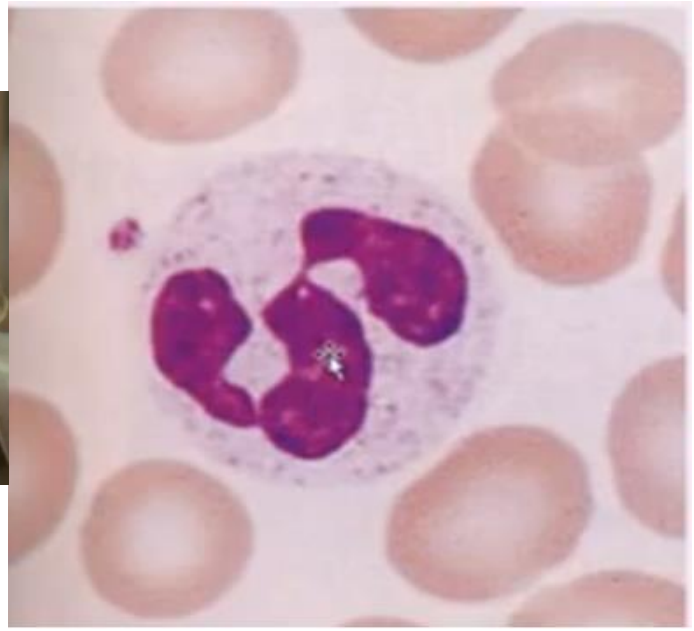
Characteristics of acute inflammation

Cellular elements of inflammmation

Neutrophil granulocyte (Polymorphonuclear Neutrophil or PMN or just POLY-s)

Eosinophil gr,Basophil, Mastcell, Macrophages, Endothel, Fibroblasts Thrombocyte, Lymphocyte

ACUTE INFLAMMATION



Neutrophil
Polymorphonuclear Leukocyte, PMN, PML
„ Leukocyte”
Granulocyte, Neutrophilic Granulocyte
„Poly-”
Polymorph

EXTRAVASATION of PMNs

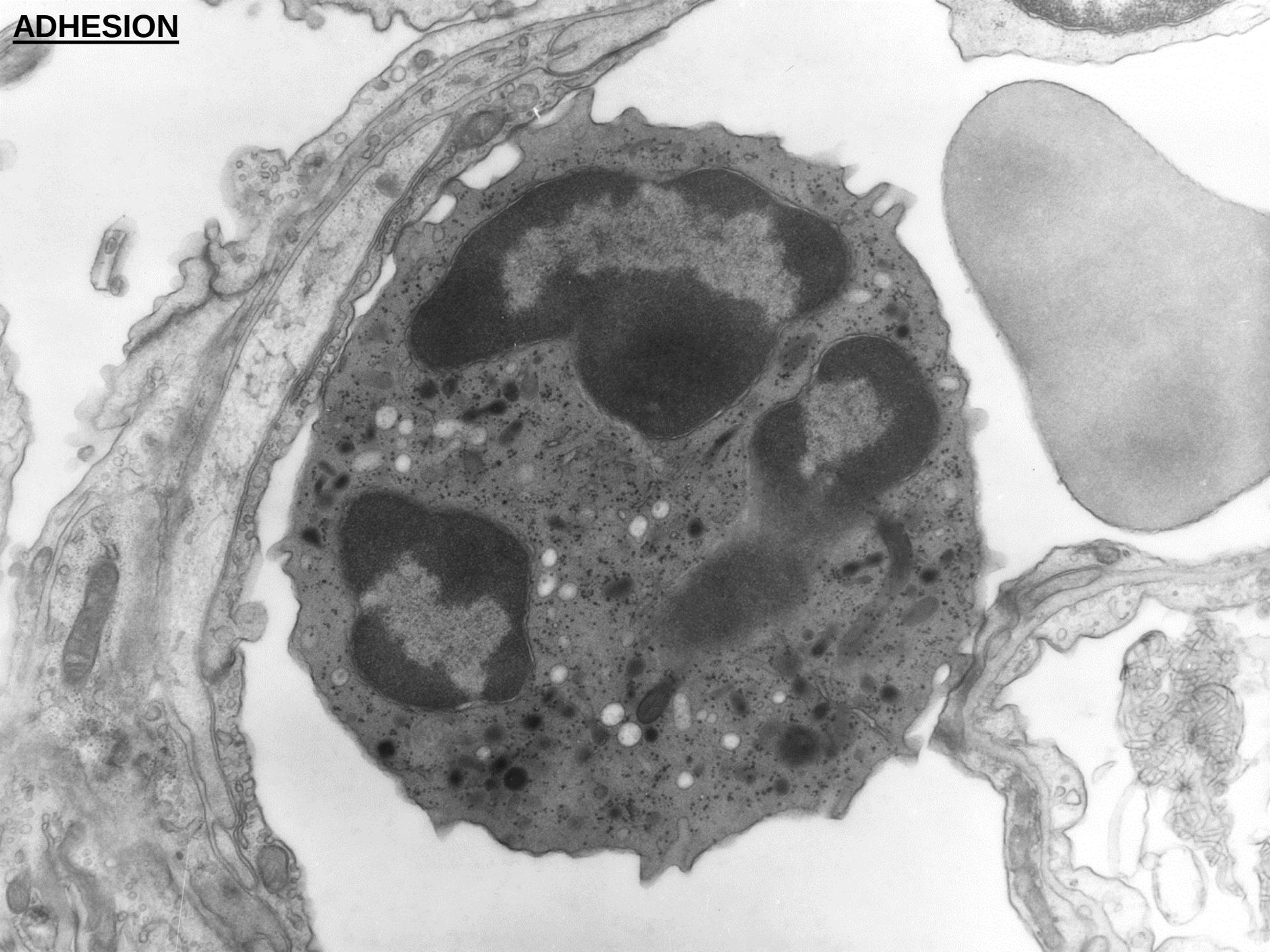
- **MARGINATION**
- (PMN's go toward wall)
- **ROLLING** (tumbling and HEAPING)
- **ADHESION**
- **TRANSMIGRATION** (DIAPEDESIS)

Adhesion molecules affecting adhesion and transmigration
1.Selectins (E,P and L) from endothelial cells (E and P) or leukocytes (L)
2.Integrins from many cells (ICAM, VCAM)

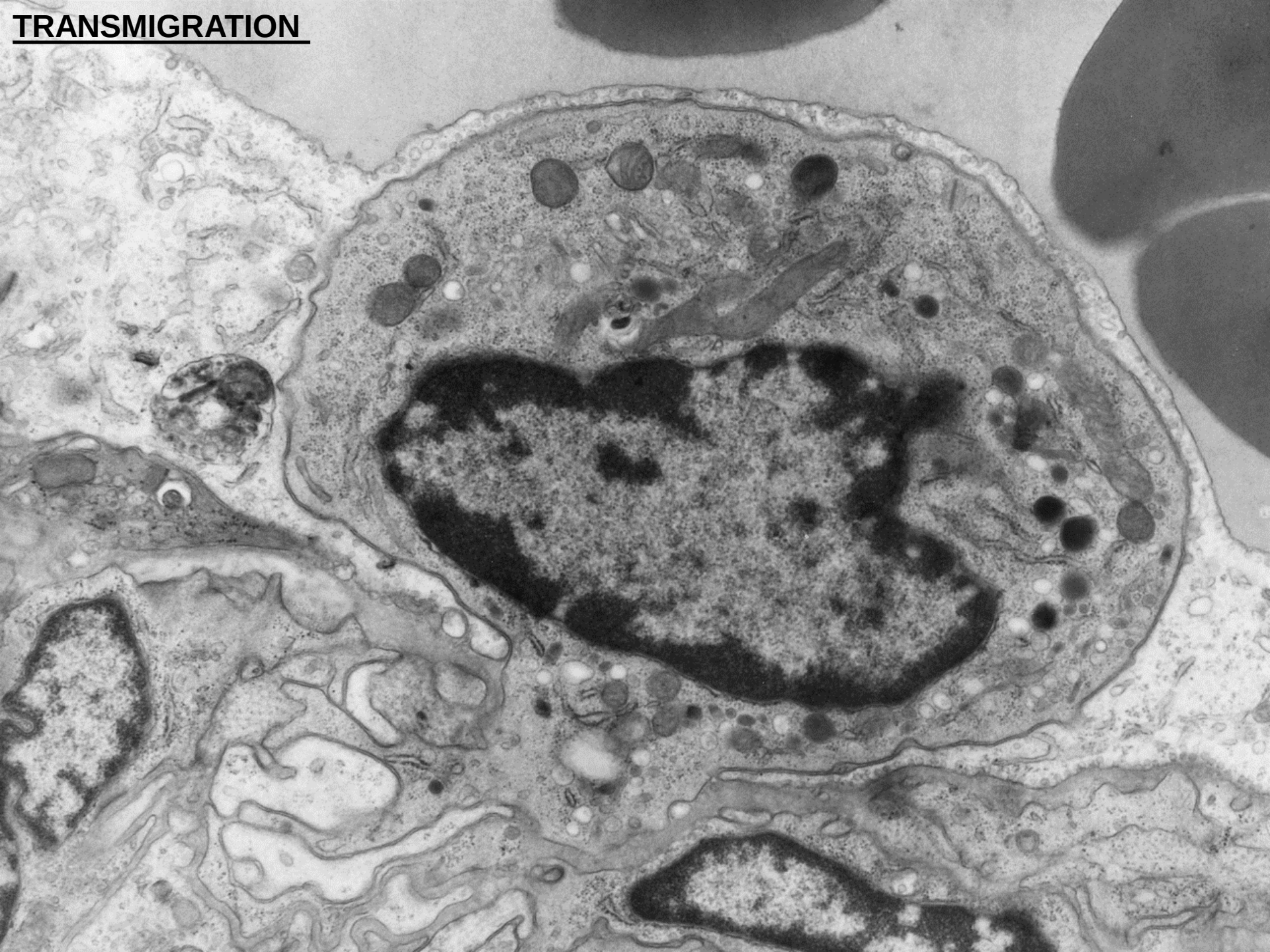
Transmigration: mediated by CD31

CHEMOTAXIS PMNs going to the site of the injury after transmigration (chemokines)

ADHESION



TRANSMIGRATION

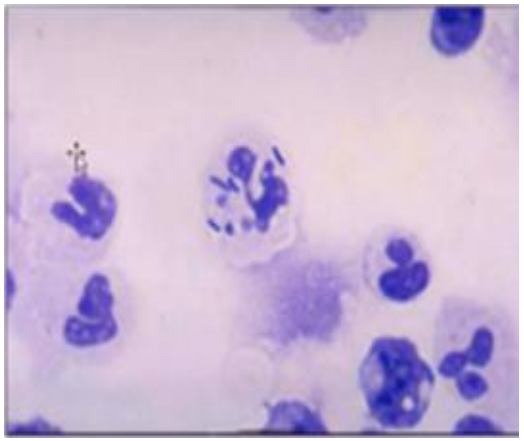


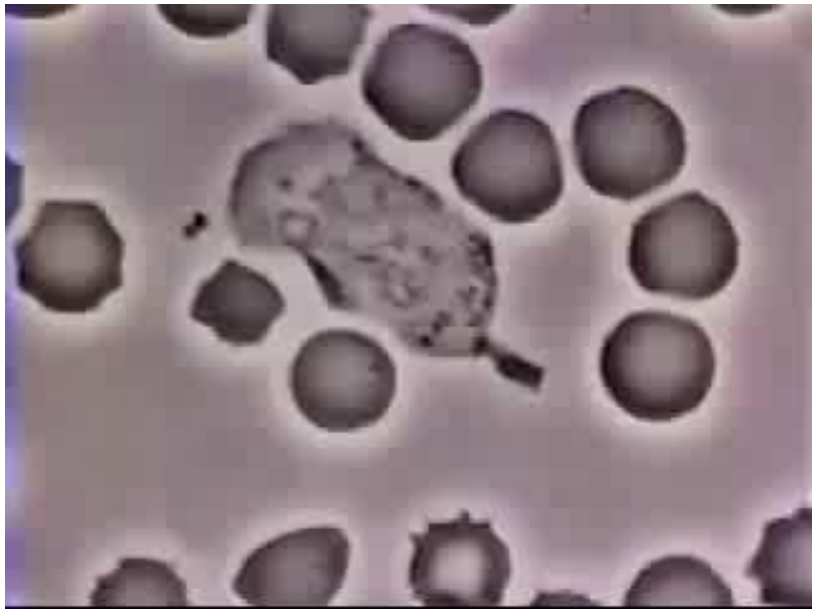
LEUKOCYTE „ACTIVATION”

- „triggered” by the offending stimuli for PMNs to:
  - 1) **Produce eicosanoids** (arachidonic acid derivatives)
    - Prostaglandin (and thromboxanes)
    - Leukotrienes
    - Lipoxins
  - 2) **Undergo DEGRANULATION**
  - 3) **Secrete CYTOKINES**

PHAGOCYTOSIS

- **RECOGNITION**
- **ENGULFMENT**
- **KILLING**





(DEGRADATION/ DIGESTION) (oxigen dependent and independent mechanisms)

An additional mechanism of killing microbes is the extracellular traps

Humoral elements „Mediators”

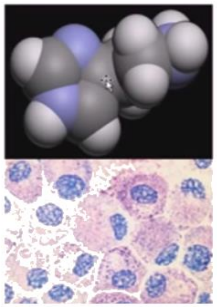
- Vasoactive amins: histamine, serotonine (vasodilatation, permeability, pain)
- Vasoactive peptids: bradykinin
- Complement system (MAC, vasodilatation, permeability, chemotaxis, opsonisation)
- Clotting, fibrinolitic cascade
- Immunglobulins
- Arahidonic acid derivatives
- Cyclooxigenase prostaglandins
- Lipoxigenase leukotriéns
- Cytokins TNF, IL-6, IL-1
- Exogenous mediators: fMLP, endotoxin, superantigens

CHEMICAL MEDIATORS „general”

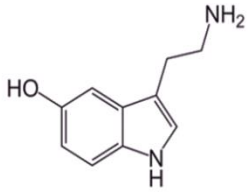
- From plasma or cells
- Have triggering stimuli
- Usually have specific targets
- Can cause a cascade
- Are short lived

HISTAMINE

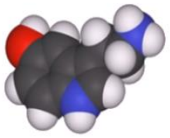
- Mast Cells, basophils
- POWERFUL Vasodilator
- Vasoactive „amine”
- IgE on mast cell



SEROTONIN

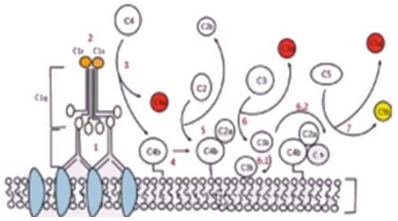


- (5HT, **5-H**ydroxy-**T**ryptamine)
- Platelets and EnteroChromaffin Cells
- Also vasodilatation, but more indirect
- Evokes N.O. synthetase (a ligase) from arginine



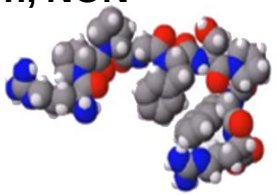
COMPLEMENT SYSTEM

- >20 components, in circulating plasma
- Multiple sites of action, but **LYSIS** is the underlying theme



KININ SYSTEM

- BRADYKININ is KEY component, 9 aa’s
- 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

CLASSIC MEDIATORS –Histamine, -Serotonine-Complement, -Kinins, -Clotting factors -Eicosanoids, -Nitric oxide , -etc

EICOSANOIDS (ARACHIDONIC ACID DERIVATIVES)

- Part of cell membranes
- **1)** Prostaglandins (incl. Thromboxanes)
- **2)** Leukotrienes
- **3)** Lipoxins (new)

MULTIPLE ACTIONS AT MANY LEVELS

PROSTAGLANDINS (THROMBOXANES INCLUDED)

- Pain
- Fever
- Clotting

LEUKOTRIENES

- Chemotaxis
- Vasoconstriction
- Increased Permeability

LIPOXINS

- INHIBIT chemotaxis
- Vasodilatation
- Counteract actions of leukotrienes

PLATELET-**A**CTIVATING **F**ACTOR **(PAF)**

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

CYTOKINES/CHEMOKINES

- **CYTOKINES** are PROTEINS produced by MANY cells, but usually LYMPHOCYTES and MACROPHAGES, numerous roles in acute and chronic inflammation

  -TNFα, IL-1 by macrophages

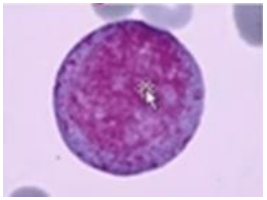
- **CHEMOKINES** are small proteins which are attractants for PMNs (>40)

NITRIC OXIDE

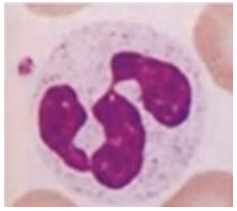
- Potent vasodilator
- Produced from the action of nitric oxide synthetase from arginine

LYSOMAL CONSTITUENTS

- PRIMARY
- Also called AZUROPHILIC, or NON-specific
- Myeloperoxidase
- Lysozyme (Bact.)
- Acid Hydrolases



- SECONDARY
- Also called SPECIFIC
- Lactoferrin
- Lysozyme
- Alkaline Phosphatase
- Collagenase



FREE RADICALS

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

Systemic effects of inflammation
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** C-reactive protein, fibrinogen, mediated by IL-6
- **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

OUTCOMES OF ACUTE INFLAMMATION

- 1) 100% complete RESOLUTION
- 2) SCAR
- 3) CHRONIC inflammation

Classification of acute inflammation based on the exudate

Serous Common cold, pleuritis exs., burns, catarrhal inflammation of mucous membranes

Fibrinous Serous membranes: Pleuritis/pericarditis sicca, Peritonitis fibrinosa
Mucous memebranes: Diphtery, typhoid fever, dysentery

Purulent folliculitis, furuncule, carbuncule

Abscess: circumscibed pus in parenchymal organs
Empyema: circumscribed pus in preformed body cavity
Phlegmone: inflammation spreading in tissue spaces

Haemorrhagic plague, smallpox, anthrax, flue

Gangraenous - failure of inflammation

Classification of acute inflammation based on the exudate

Serous („watery")

Serous inflammation: Is a type of acute inflammation which is characterised by the copious effusion of non-viscous serous fluid, commonly produced by mesothelial cells of serous membranes, but may be derived from blood plasma. The exudation of this inflammation is clear fluid with no WBCs or PMNs.

The serous fluid which is produced by these mesothelial membranes is pink in color and defined as plasma derived from blood or a thin clear watery fluid from secretions of mesothelial cells lining the peritoneal, pleural and pericardial cavities (called effusion).

Biologic purpose of serous exudation: Immediate dilution of the noxious agent at the site of inflammation.

Etiologic factors include:
1) Hypersensitive reactions.
2) Bacterial and viral tissue injury.
3) Physical and chemical tissue injury.

Morphology: According to tissue:

- **Serosa**: Erythema (Hyperemia) and inflammatory swelling from effusion with large numbers of displaced serosal covering cells and few macrophages in the exudate.
- **Skin**: Erythema and swelling that varies according to epidermal involvement.
- **Mucus membrane**: Erythema and swelling lead to mucosal edema with risk of stenosis.
- **Parenchyma**: Erythema and swelling are present with sparse leukocytic infiltrate. This expands the organ capsule, which is tender to palpation due to its sensory innervation. Here the exudate takes the form of an edema.

Examples of this type of Inflammation:

1) Skin blisters.

2) Inflammation of body cavities: Serous pericarditis, Pleuritis (Pleurisy), Peritonitis. Hydrothorax, hydropericardium

3) Rheumatoid arthritis (serous fluid in joints).

4) Seromucous Otitis.

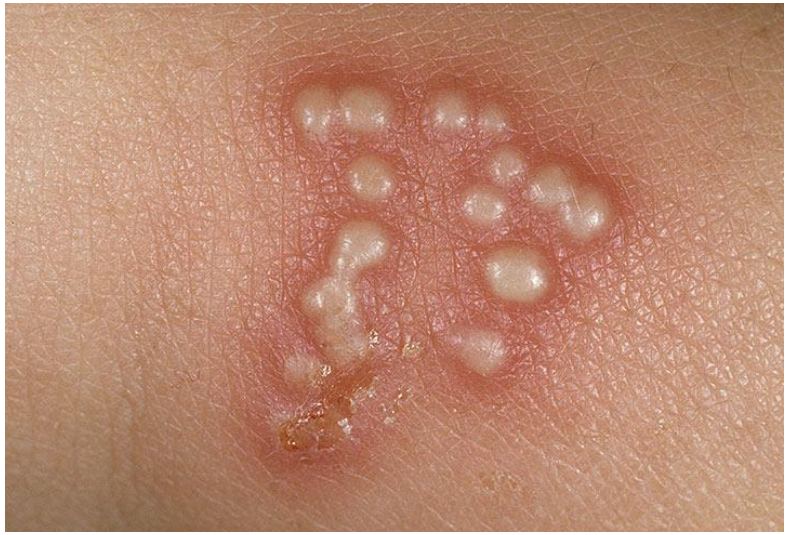
5) Acute Rhinitis.

6) Serous Pulmonary alveolitis.

7) Organ inflammation such as serous hepatitis, nephritis (acute interstitial nephritis), myocarditis and encephalitis.

8) Vesicular skin infections.

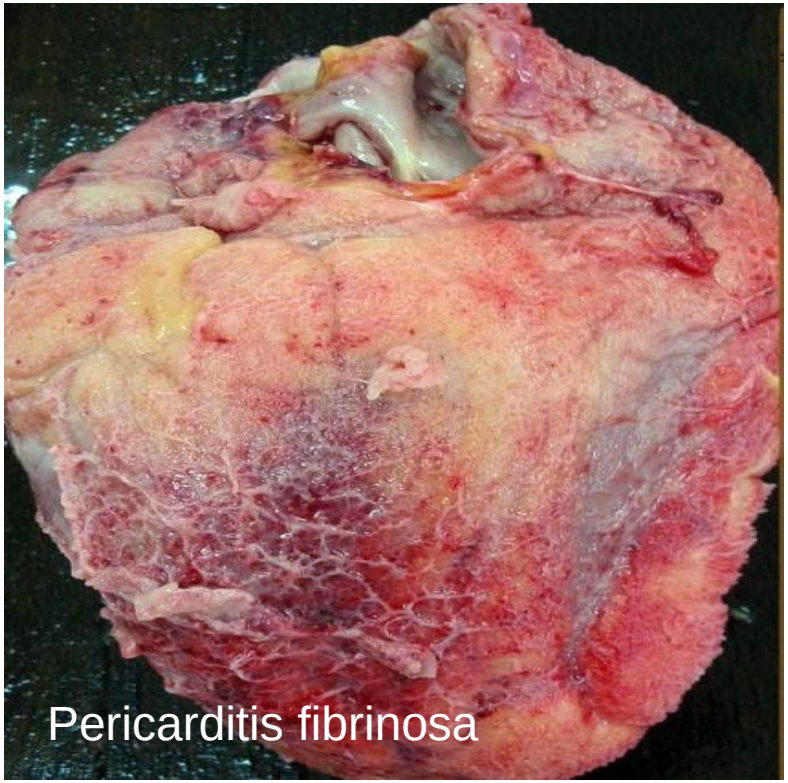
9) Sero-mucosal inflammations can lead to acute glottal and laryngeal edema with risk of asphyxia.



Classification of acute inflammation based on the exudate

Fibrinous

- fibrin is the endpoint of coagulation, and had a characteristic appearence both grossly and macroscopically
- Severe injury with excessive deposition of fibrin in serosus cavities
- The fibrinous exudate may be degraded by FIBRINOLYIS and removed by macrophages resulting in RESOLUTION
- Incomplete removal of fibrin resulting in organization and scarring with FIBROUS ADHESIONS of pleural or pericardial surfaces


Pericarditis fibrinosa

PSEUDOMEMBRANE results when the upper portion of a mucosal surface undergoes necrosis, freeing fibrinogen from vessels that then clots along the surface

- diphtheria (in the upper airway) or antibiotic-induced pseudomembranous colitis (in the lower gut).


Tonsillitis follicularis

Classification of acute inflammation based on the exudate

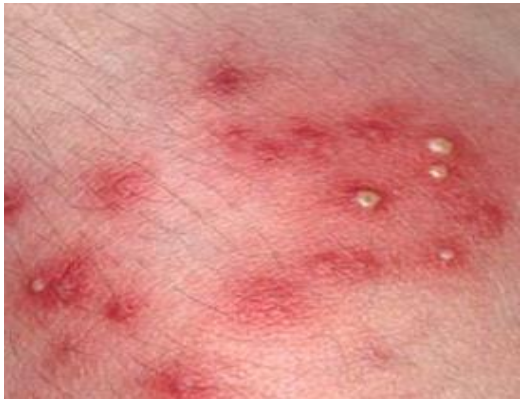
Purulent

Purulent inflammation: Inflammation resulting in large amount of pus, which consists of neutrophils, dead cells, and fluid. Infection by pyogenic bacteria such as staphylococci is characteristic of this kind of inflammation. Large, localised collections of pus enclosed by surrounding tissues are called abscesses.

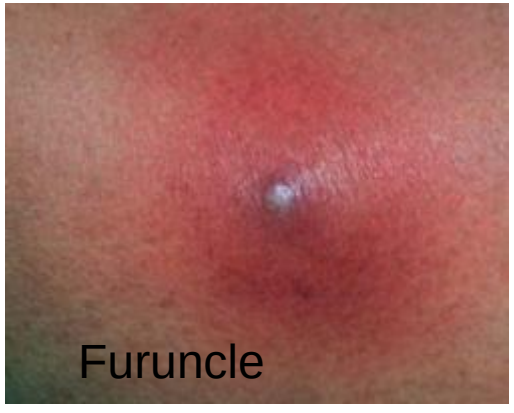
The **pus** which is the end product of this type of inflammation a whitish-yellow, yellow or yellow-brown exudate produced by vertebrates during inflammatory pyogenic bacterial infections. An accumulation of pus in an enclosed tissue space is known as an abscess, while a visible collection of pus within or beneath the epidermis is known as a pustule or pimple. Pus is produced from the dead and living cells which travel into the intercellular spaces around the affected cells.

Examples for this type of inflammation:

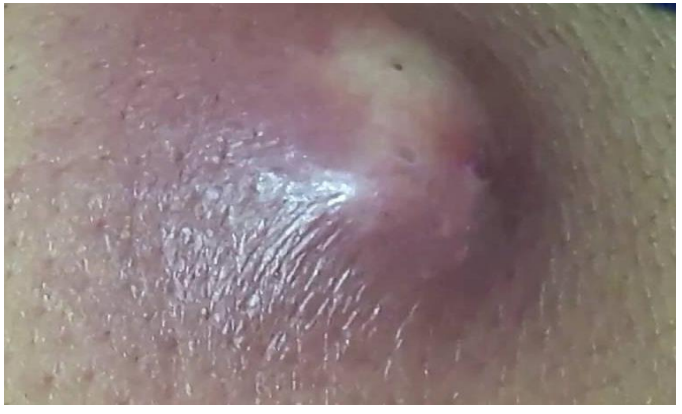
- Suppurative appendicitis
- Suppurative otitis
- Pyelonephritis
- Brain abscess
- Purulent meningitis
- Suppurative lymphadenitis



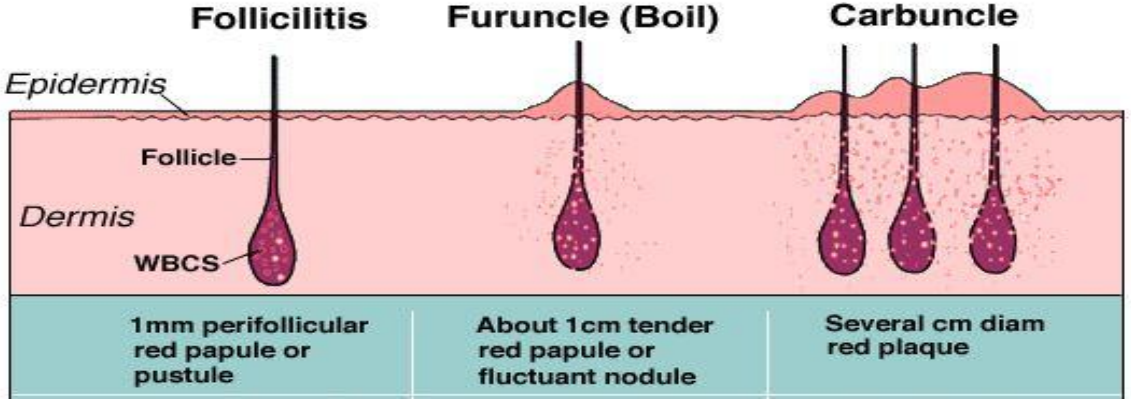
Folliculitis



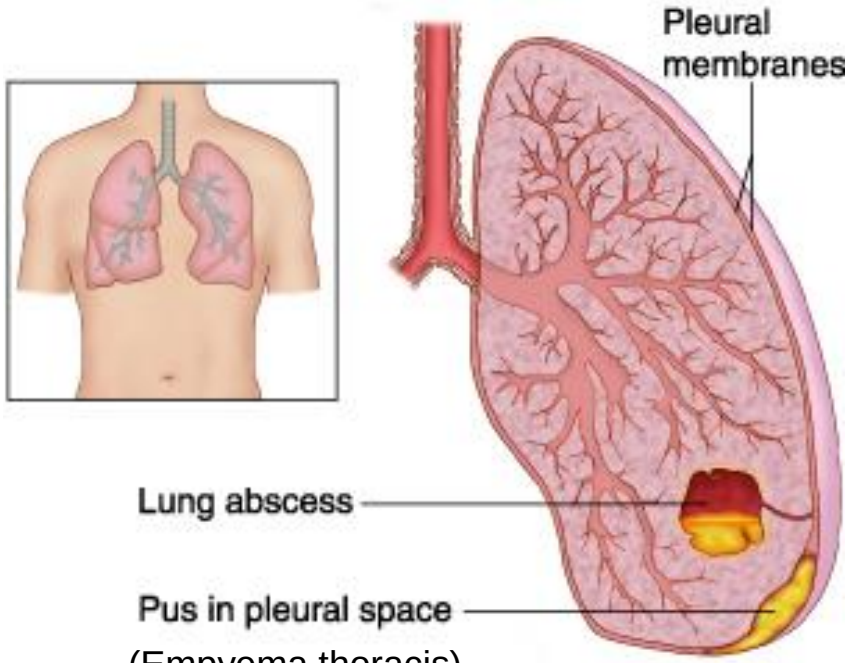
Furuncle



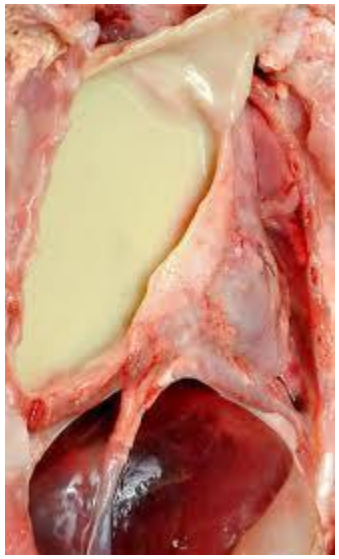
Carbuncle

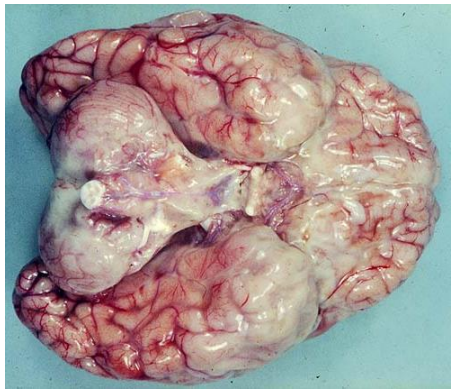


Classification of acute inflammation based on the exudate



(Empyema thoracis)


Empyema thoracis


Meningitis purulenta

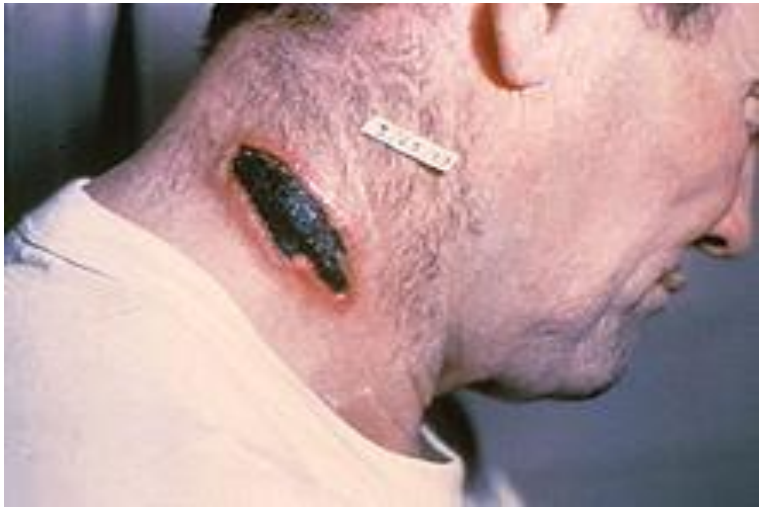

Empyema v.felleae

Abscess: circumscibed pus in parenchymal organs, in organs with non-preformed cavity
Empyema: circumscribed pus in preformed body cavity
Phlegmone: inflammation spreading in tissue spaces

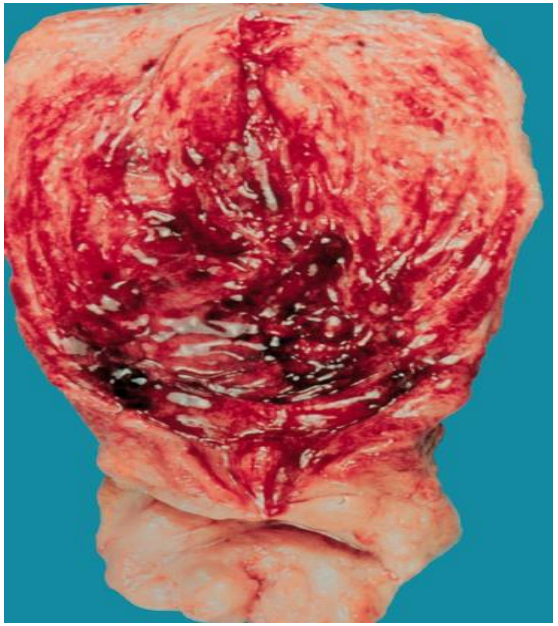
Classification of acute inflammation based on the exudate

Haemorrhagic inflammation

-marked haemorrhage is the predominant pathological change

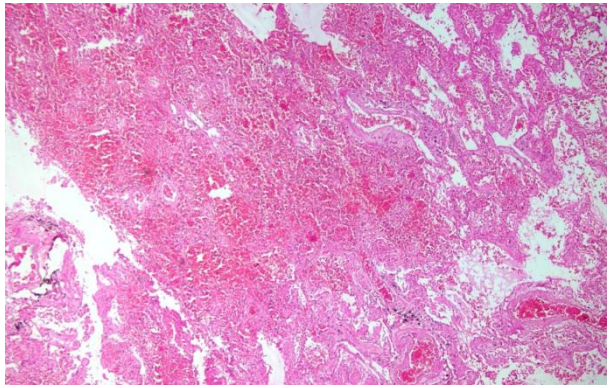


Skin anthrax



Urocystitis acuta

Variola vera

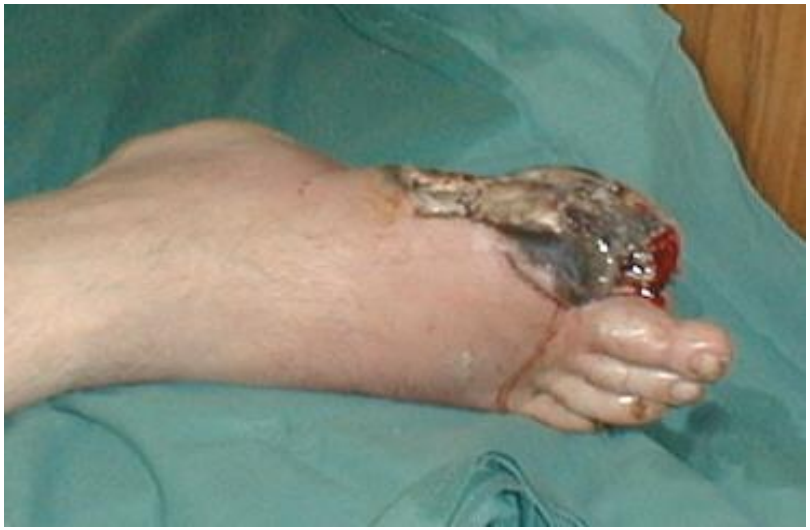


Influenza Virus Infections (lungs)

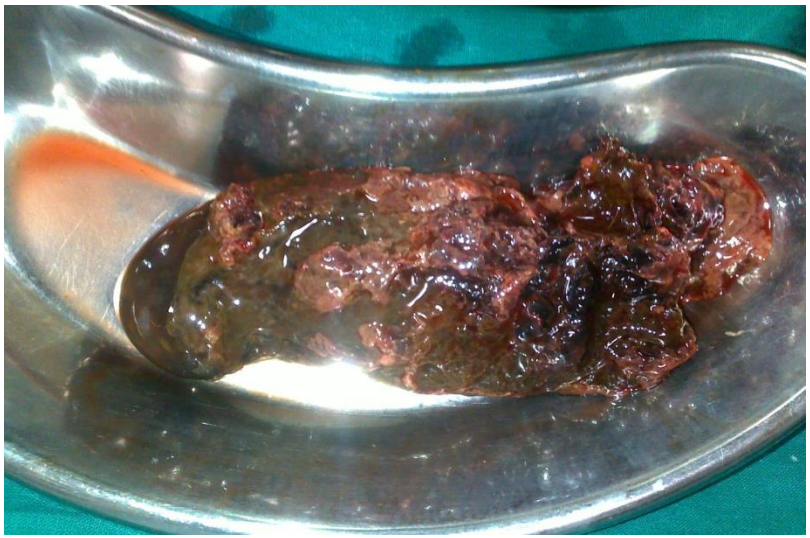
Classification of acute inflammation based on the exudate

Necrotizing inflammation

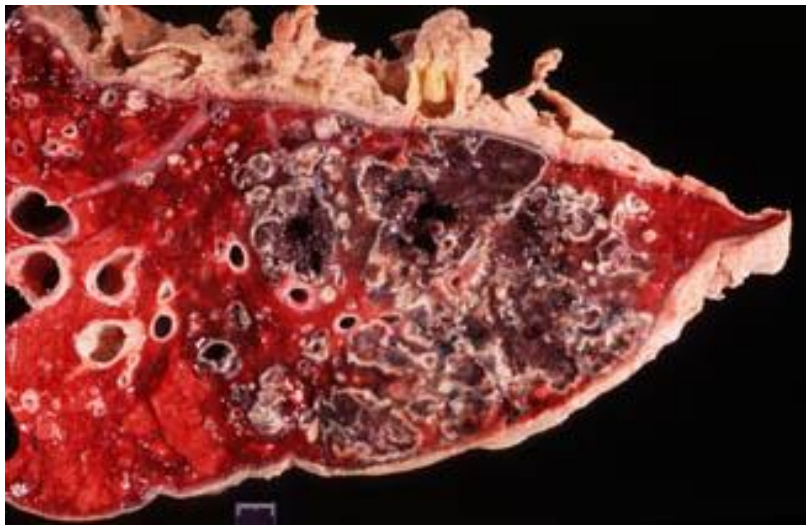
The combination of necrosis, inflammation and bacterial putrefaction is called gangrene.



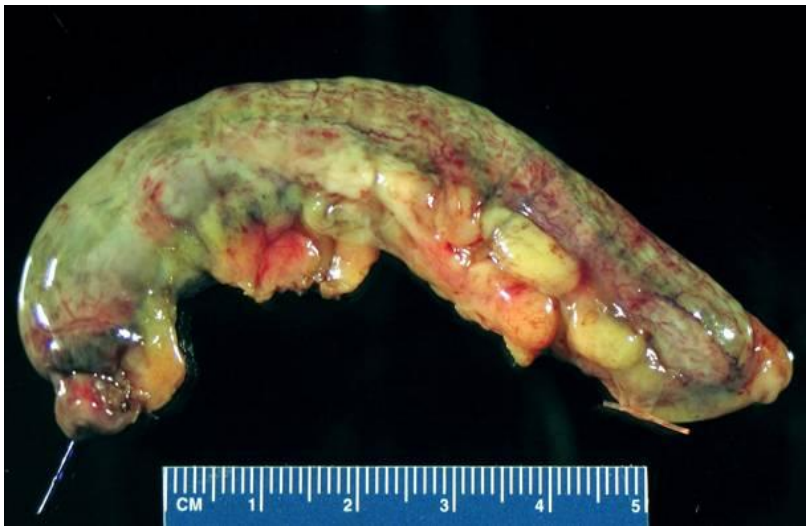
Gangrene



Cholecystitis acuta gangrenosa



Pneumonia gangrenosa

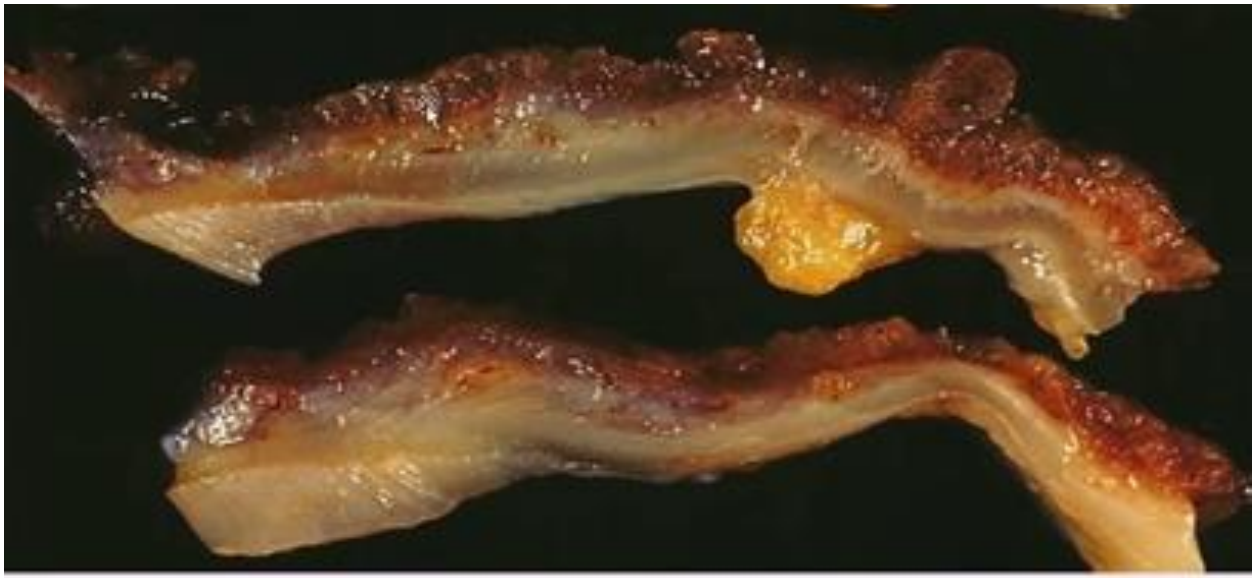


Appendicitis acuta gangrenosa

Classification of acute inflammation based on the exudate

Ulcerative

Ulcer: Ulcers are local defects on the surface of an organ produced by inflammation. Common sites for ulcerations are the stomach, duodenum, intestinal ulcers in typhoid fever, intestinal tuberculosis, bacillary and amoebic dysentery, ulcers of legs due to varicose veins etc. In the acute stage, there is infiltration by polymorphs with vasodilatation while long-standing ulcers develop infiltration by lymphocytes, plasma cells and macrophages with associated fibroblastic proliferation and scarring.



ULCERATIVE