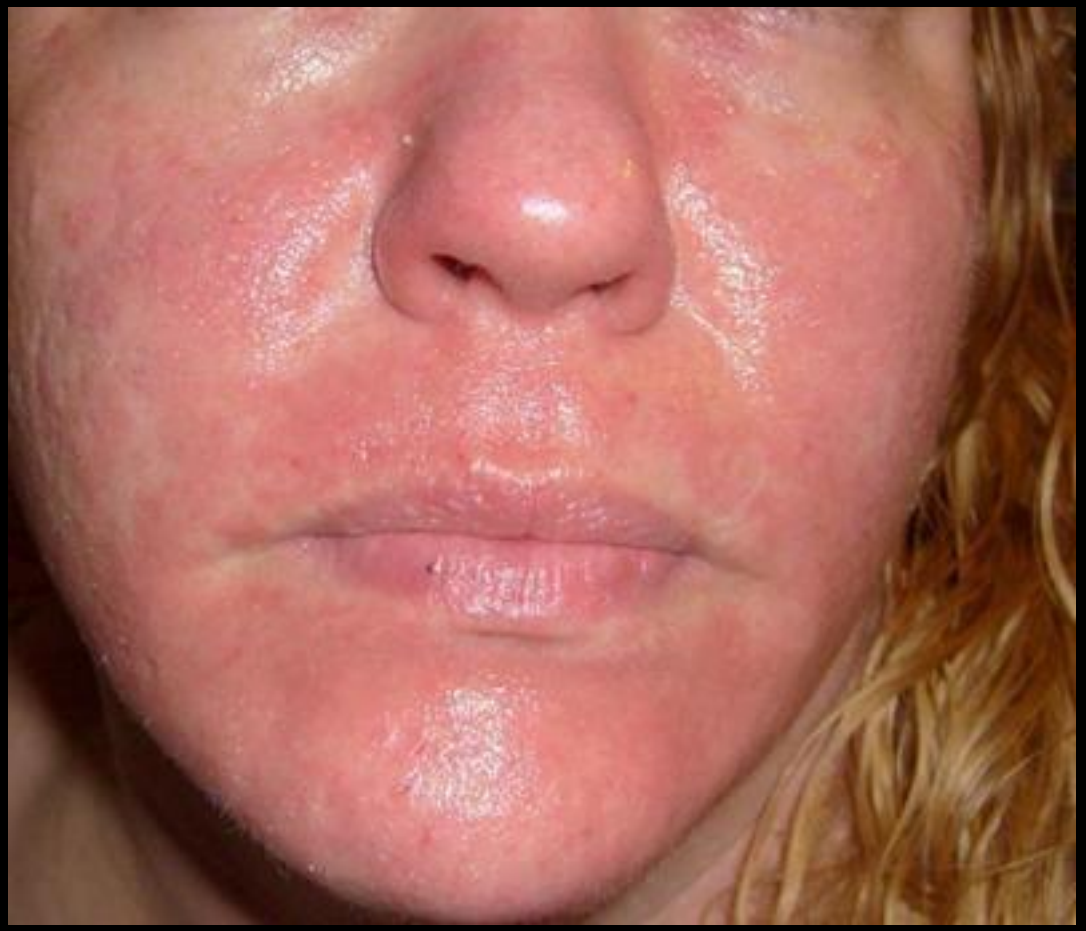
ACUTE INFLAMMATION

Árpád Szállási


10
9
10

Inflammare (Latin), to set on fire



Terminology: tissue+itis (Greek, „pertaining to”)

ασθένεια γαστήρ + „itis” (the disease of the stomach”)

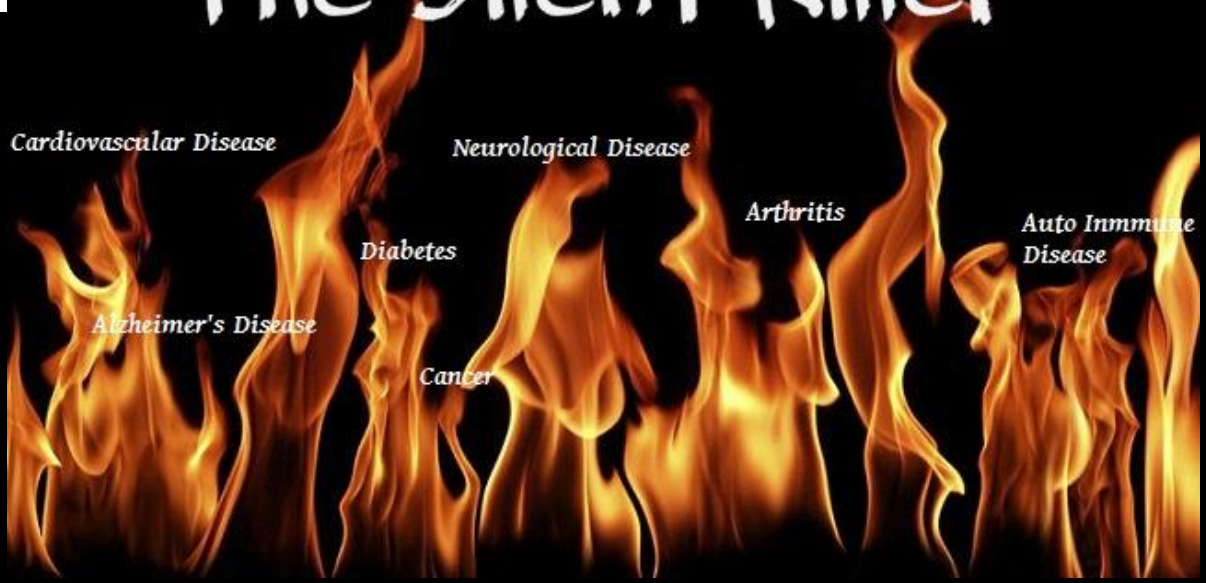
tongue	glossitis
oral mucose	stomatitis
cornea	keratitis
lung	if infectious: pneumonia (πνευμονία); if not, pneumonitis
stomach	gastritis
small intestine	enteritis
coecum	typhlitis
rectum	proctitis
testis	orchitis
vagine	colpitis
fallopian tube	salpingitis
belly bottom	omphalitis
breast	mastitis
adipose tissue	panniculitis
brain	encephalitis

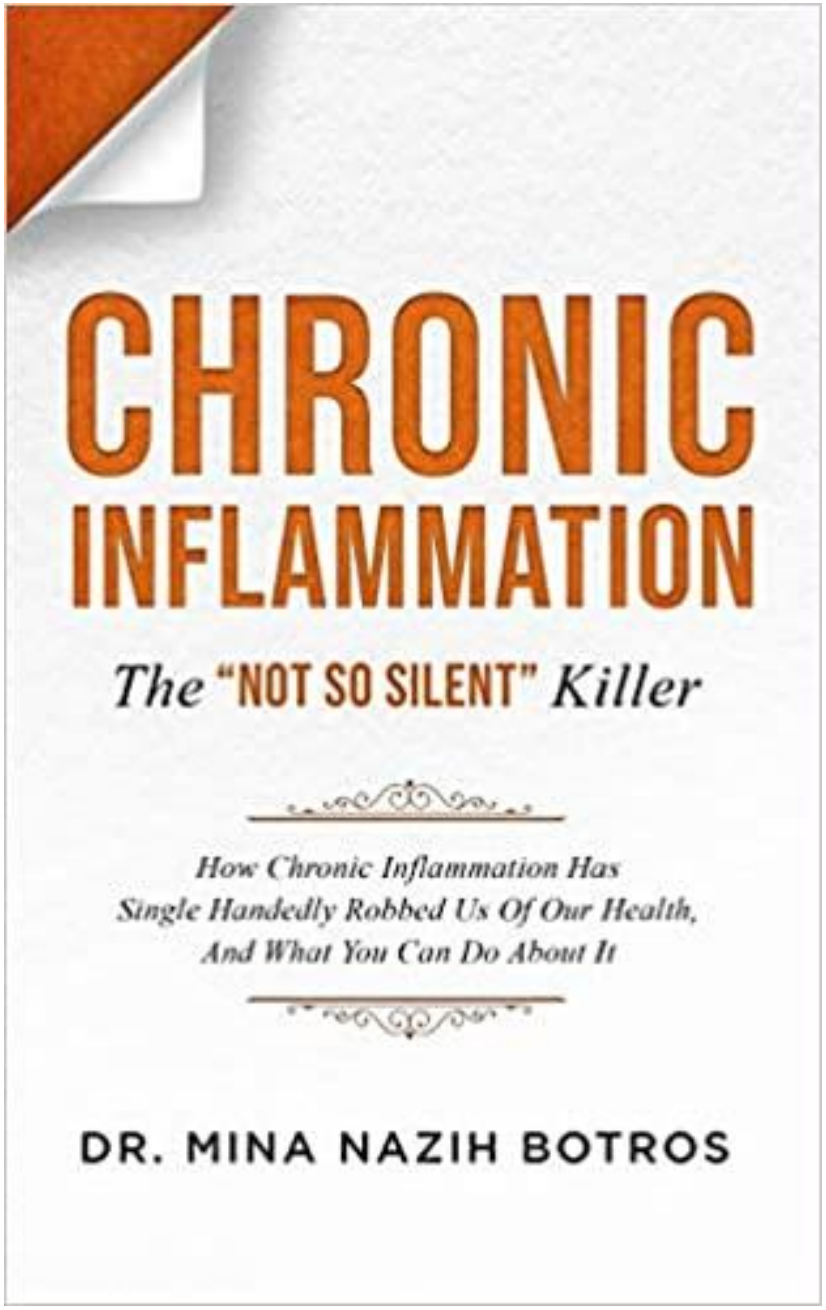
The objectives of the lecture

1. The inflammatory cascade: understand the chain of vascular and cellular events in the natural history of acute inflammation
2. Understand the roles of humoral factors (chemical mediators) during acute inflammation
3. Know the three possible outcomes of acute inflammation
4. Describe the morphologic patterns of acute inflammation


TIME
BUSH'S MILITARY RECORDS IS DISNEY MOUSETRAPPED?
THE SECRET KILLER
The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
What you can do to fight it

Chronic Inflammation
The Silent Killer

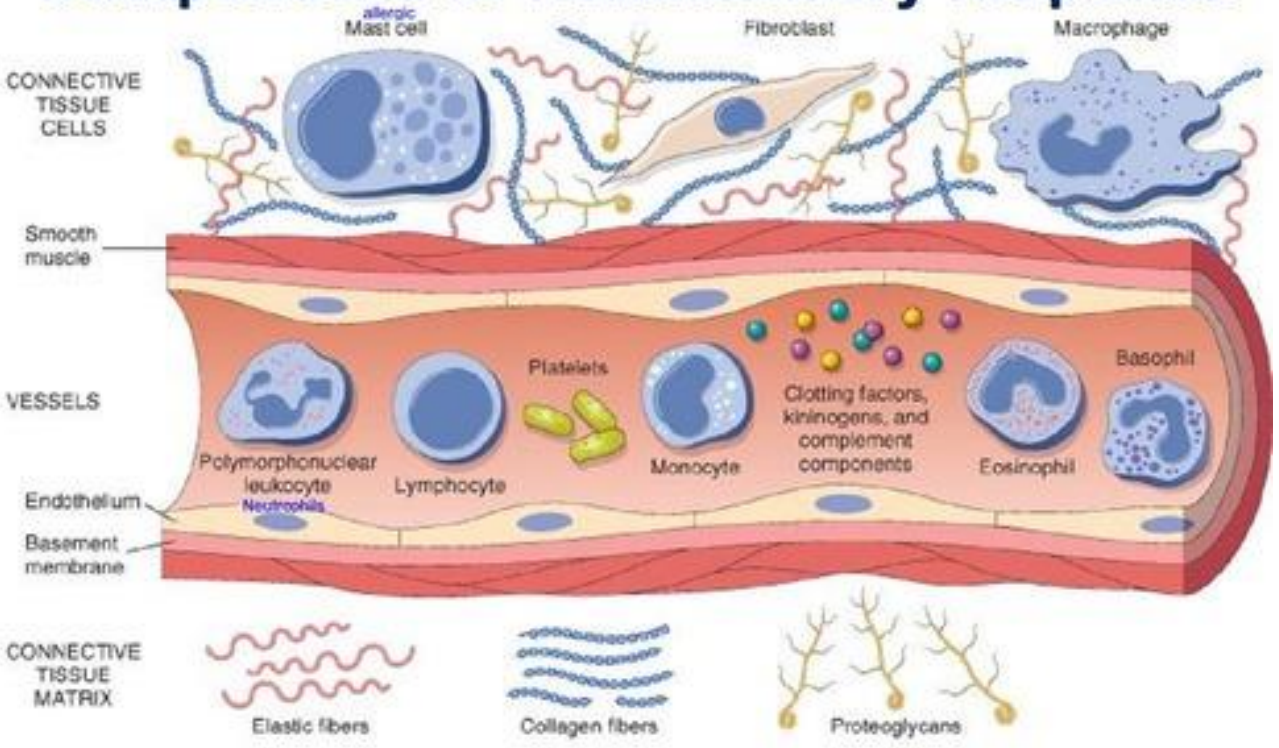



CHRONIC
INFLAMMATION
The "NOT SO SILENT" Killer
How Chronic Inflammation Has
Single Handedly Robbed Us Of Our Health,
And What You Can Do About It
DR. MINA NAZIH BOTROS

Inflammation can be protective (essential for survival), but can also be harmful

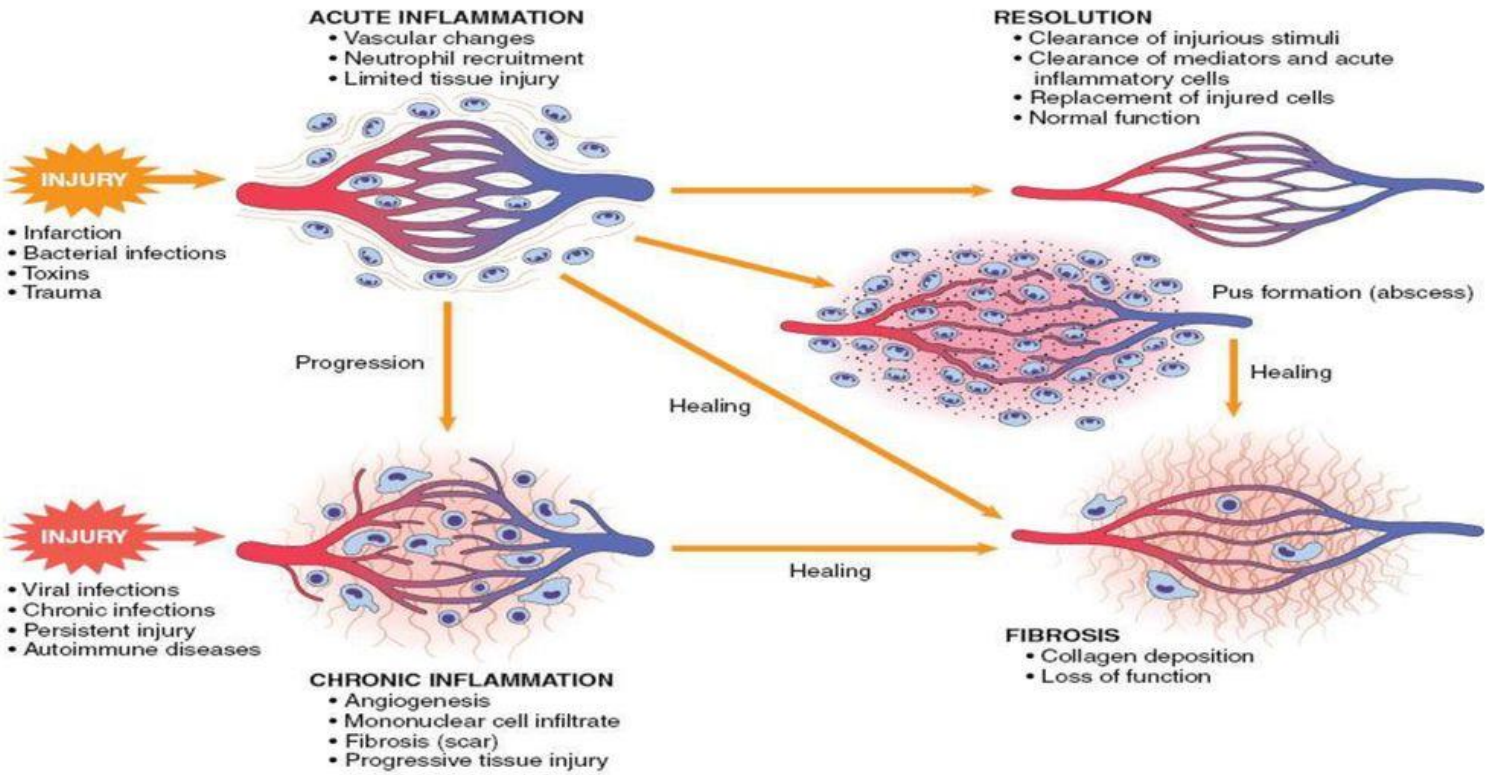
„A cascade of events by which our body fights things that can harm us, such as infections, injuries and toxins, in attempt to protect and heal itself.”

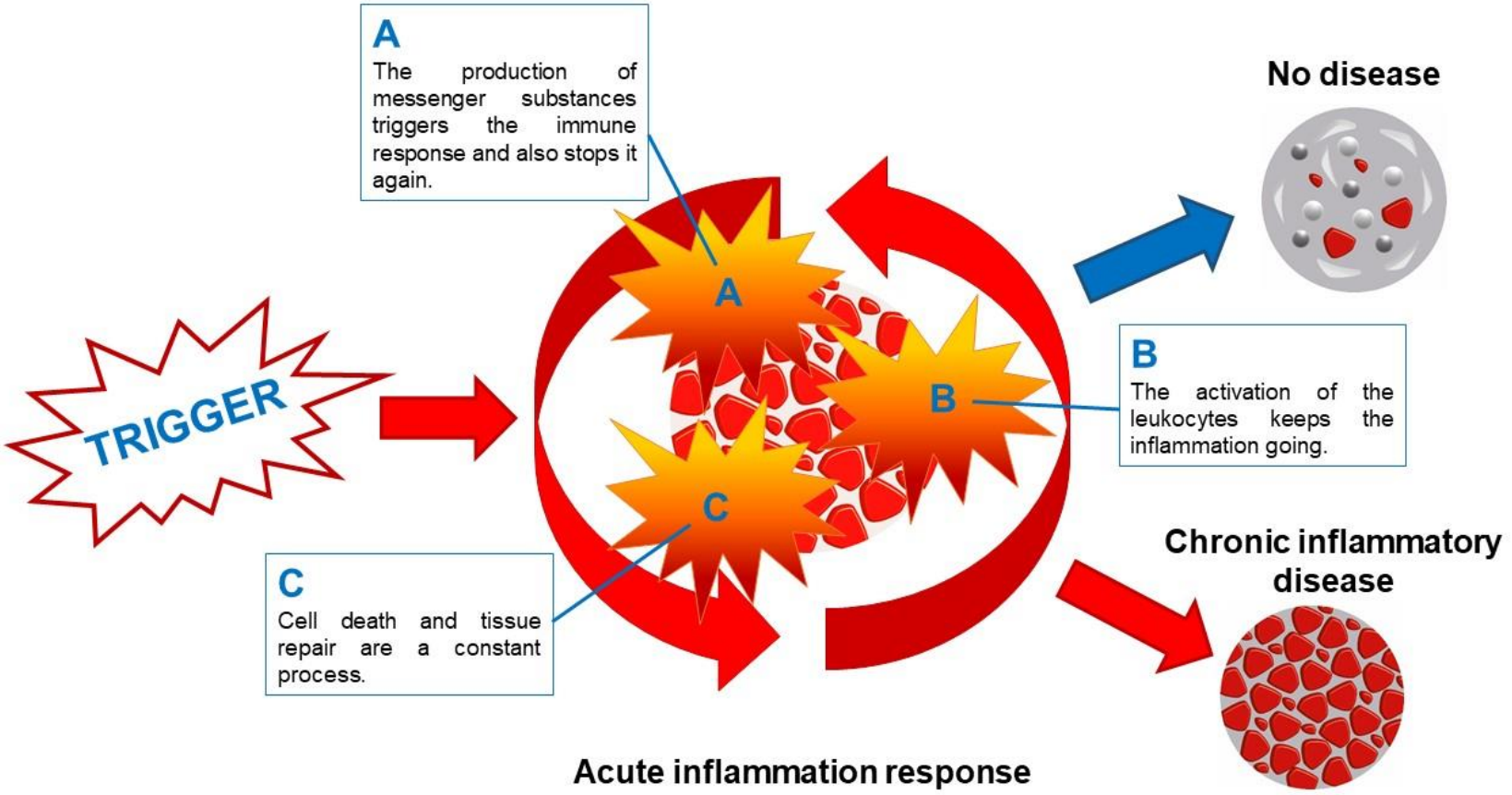
Components of inflammatory response



Prototypical inflammatory reaction

- The host recognizes the noxious agent, that
- Attracts leukocytes and humoral factors from the circulation
- The activated leukocytes act in concert with the humoral factors to kill/eliminate the noxious agent
- The response remains controlled and ends the same way
- The injured tissue heals itself

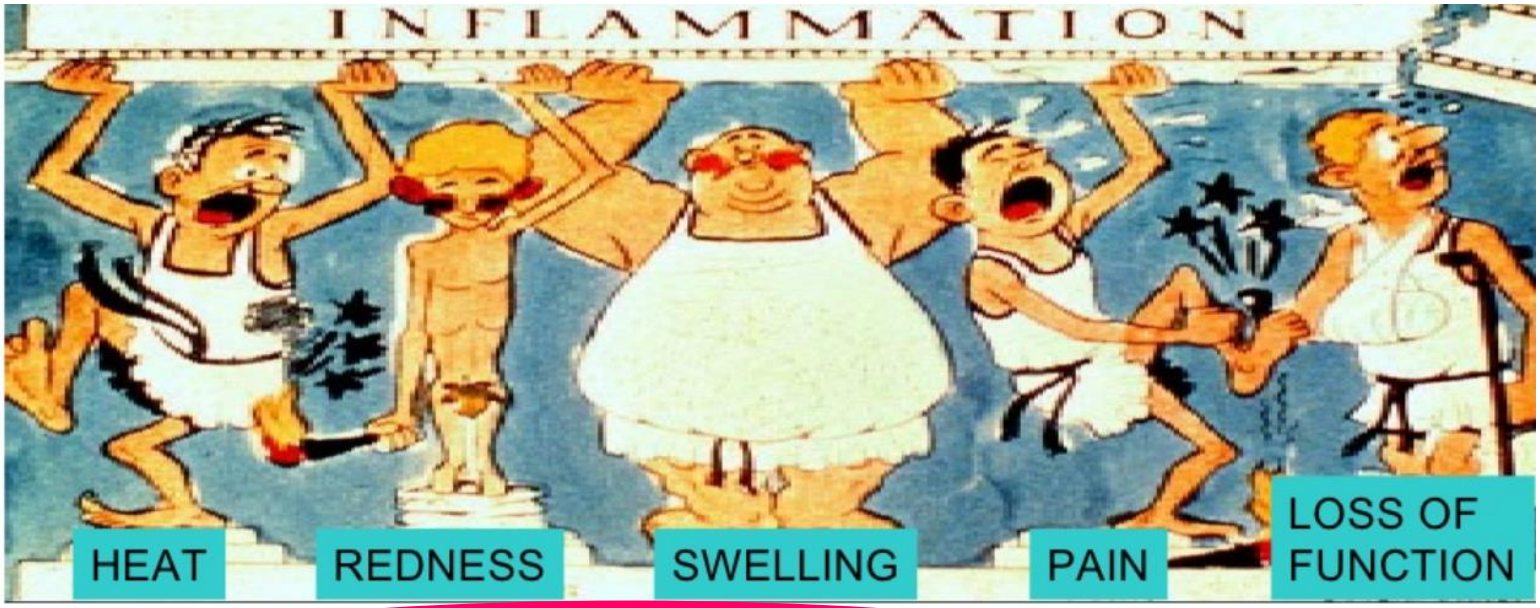



A
The production of messenger substances triggers the immune response and also stops it again.
No disease
TRIGGER
A
B
C
B
The activation of the leukocytes keeps the inflammation going.
C
Cell death and tissue repair are a constant process.
Chronic inflammatory disease
Acute inflammation response

Acute vs. Chronic Inflammation

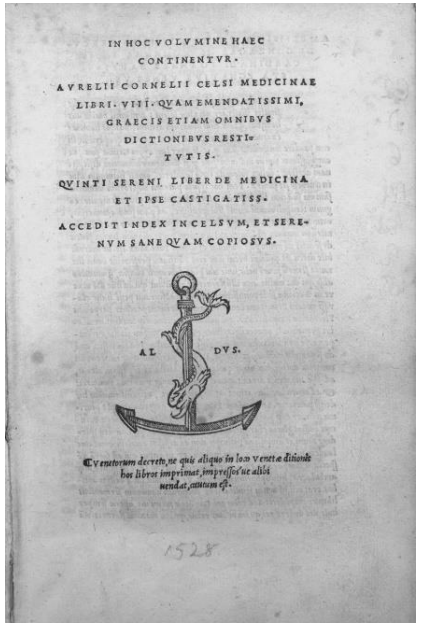
Feature	Acute	Chronic
Onset	Fast: minutes to hours Innate immune system	Slow: days Adaptive immune system
Duration	Hours to days	Weeks to months or years
Cellular infiltrate	Mainly neutrophils, followed by macrophages	Macrophages, plasma cells, and lymphocytes
Vascular changes	Prominent (vasodilation, increased permeability)	Not prominent; angiogenesis
Tissue injury	Self-limited	Progressive
Fibrosis	Usually mild	Often severe
Local and systemic signs	Prominent	Less

THE FIVE CARDINAL SIGNS OF ACUTE INFLAMMATION



Calor Rubor Tumor Dolor Functio laesa

Aulus Cornelius Celsus


IN HOC VOLVMINE HAEC
CONTINENTVR.

AVRELII CORNELII CELSI MEDICINAE
LIBRI. VIII. QVAM EMENDATISSIMI,
GRAECIS ETIAM OMNIBVS
DICTIONIBVS RESTI-
TVTIS.

QVINTI SERENI LIBER DE MEDICINA
ET IPSE CASTIGATISS.

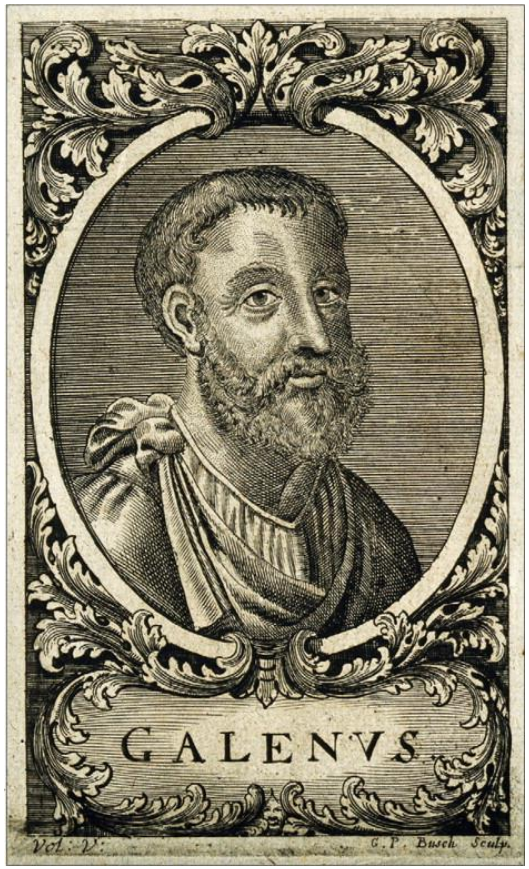
ACCEDIT INDEX IN CELSVM, ET SERE-
NVM SANE QVAM COPIOSVS.

AL DVS.

Venetorum decreto, ne quis aliquo in loco veneta editionis
hos libros imprimat, impressosve alibi
vendat, cautum est.

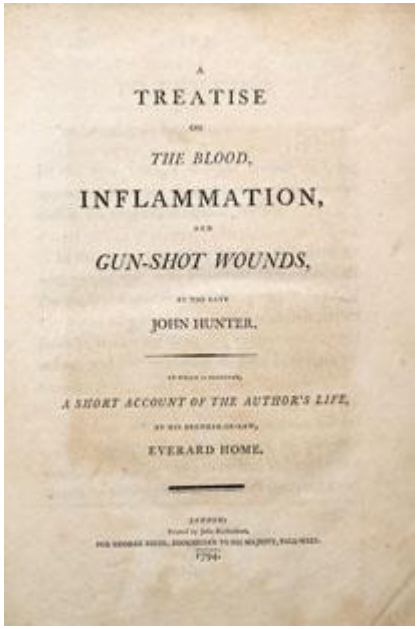
1528

De morborum: „Inflammation is a disease.”



Galenus added „functio laesa” (loss of function) as the 5th cardinal sign of inflammation

John Hunter (1728-1793)



A
TREATISE
ON
THE BLOOD,
INFLAMMATION,
AND
GUN-SHOT WOUNDS,
BY THE LATE
JOHN HUNTER.

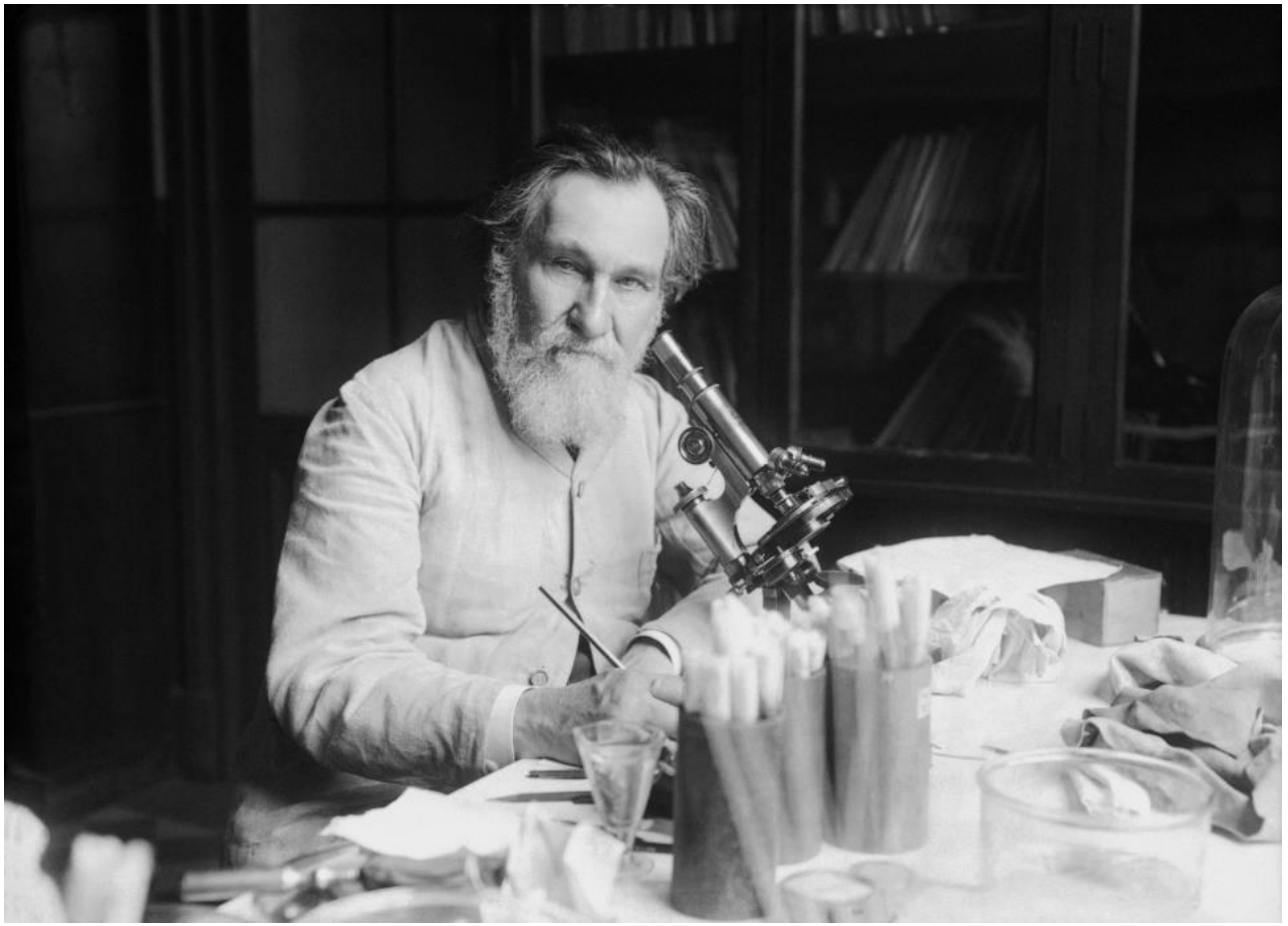
A SHORT ACCOUNT OF THE AUTHOR'S LIFE,
BY HIS BROTHER-IN-LAW,
EVERARD HOME.

LONDON:
1794.

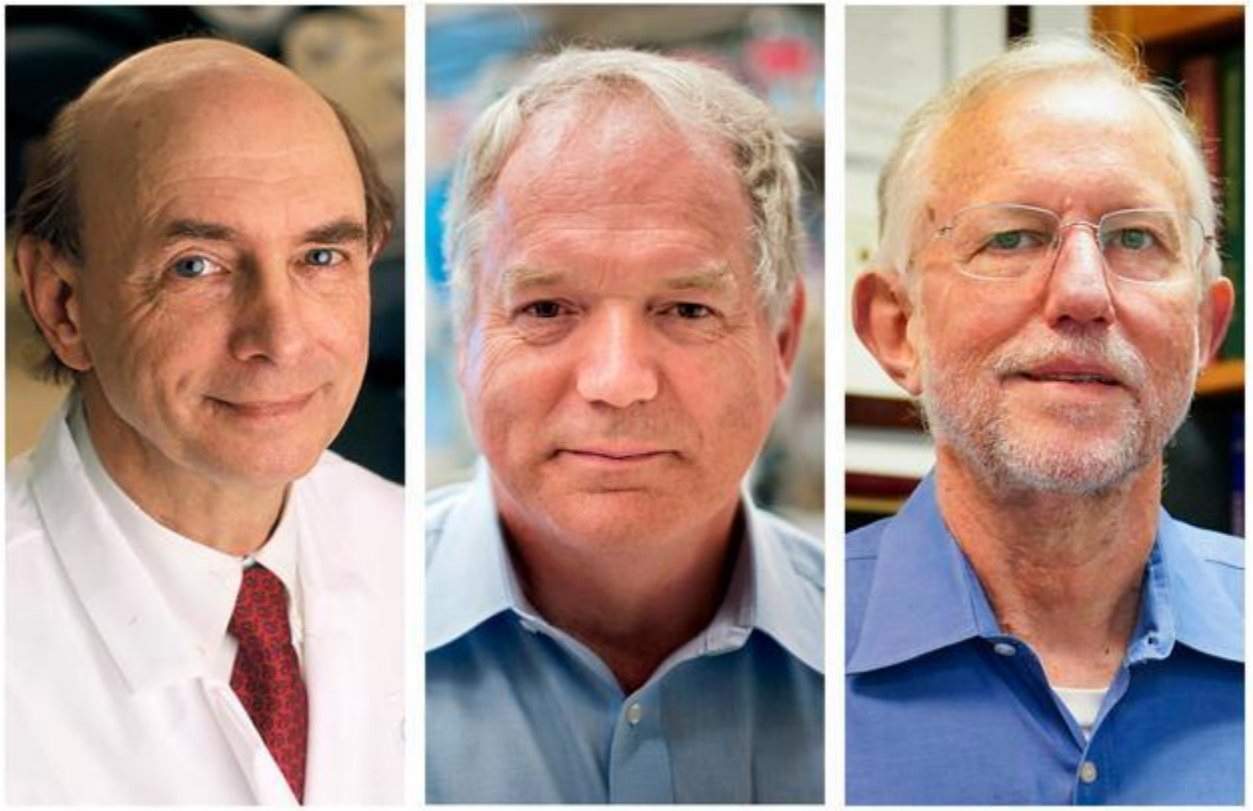
„Inflammation is not a disease but a non-specific response that has a salutary effect on its host.”

Julius Cohnheim (1839-1884), microscopic description of inflammation

Ilya Mechnikov (1845-1916) describes phagocytosis in 1882



Nobel prize, 2020, HCV



Harvey J. Alter (NIH), Michael Houghton (U. Alberta) and Charles M. Rice (Rockefeller U)

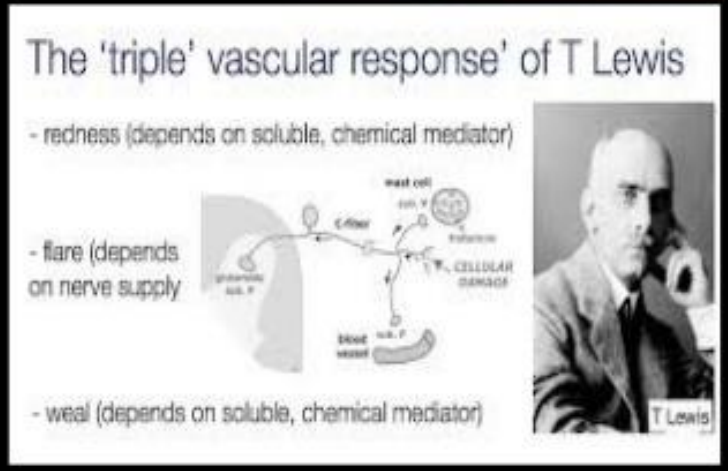
Sir Thomas Lewis (1881-1945), chemical substances mediate the vascular changes of inflammation

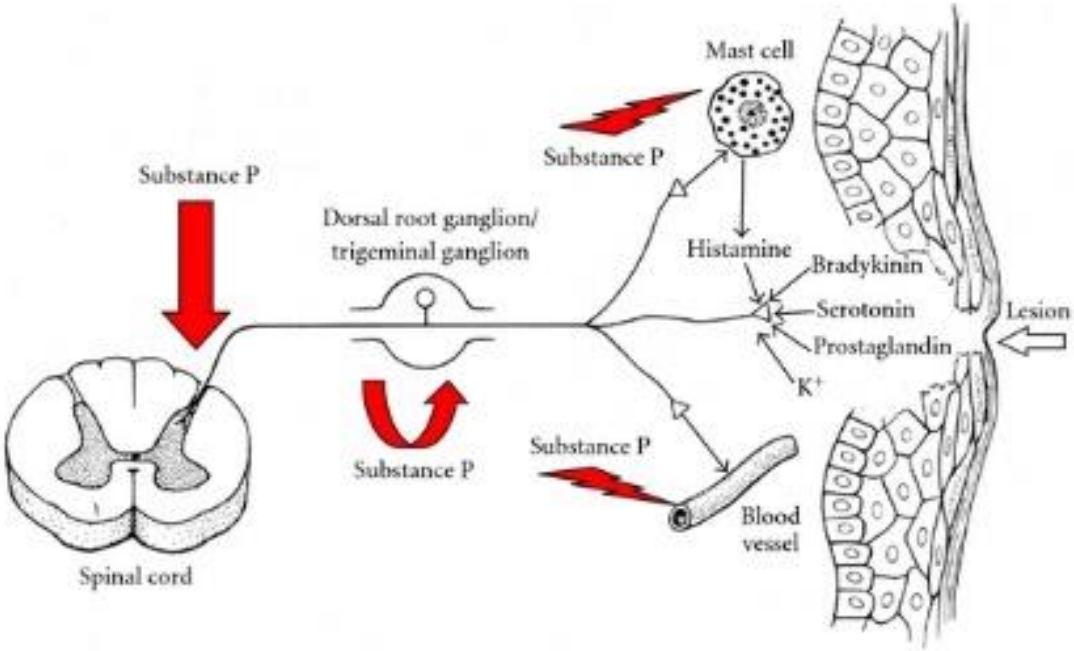
Lewis Triple Response

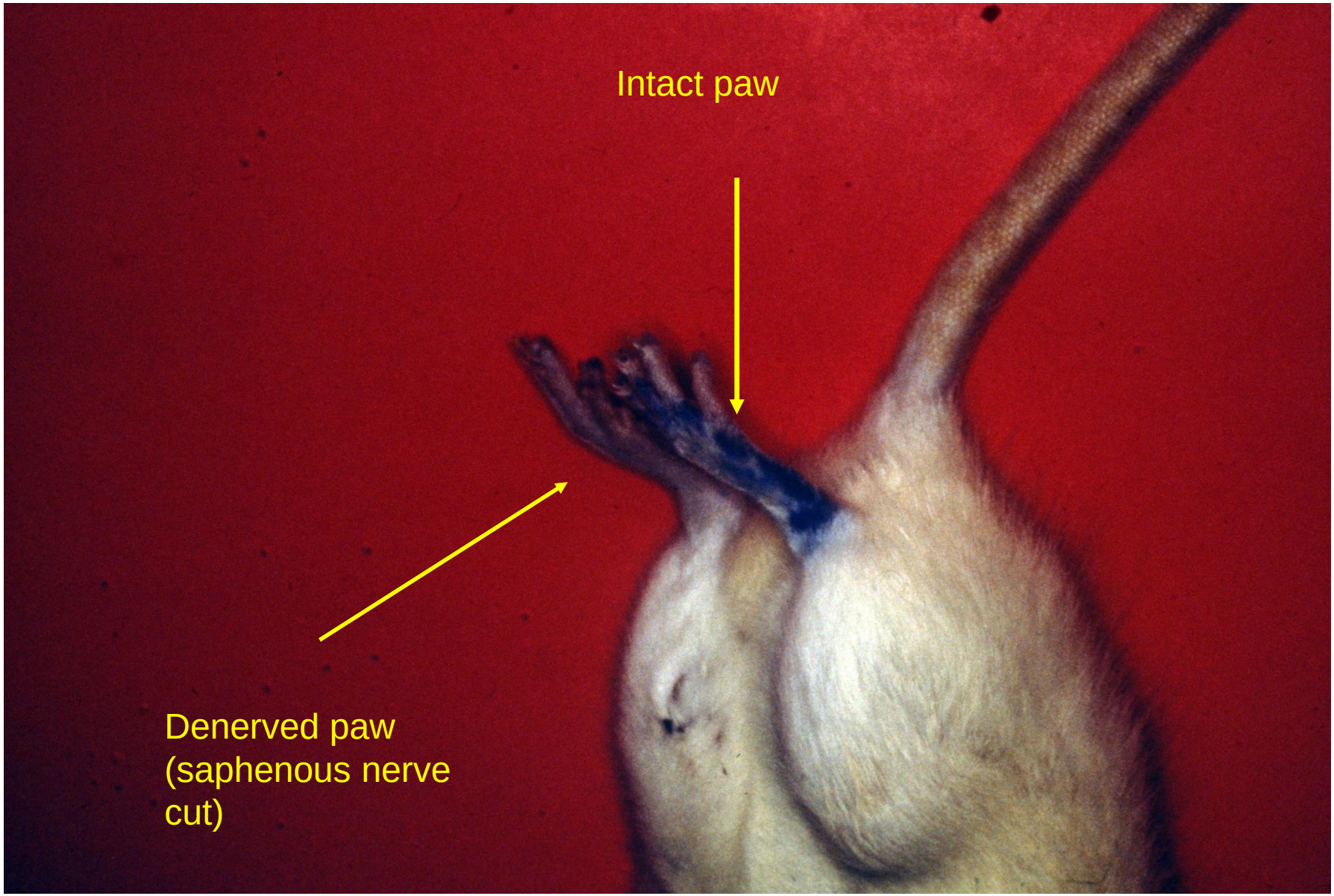
- Described by sir Thomas Lewis in 1924.
- Lewis triple response is the characteristic 3 part response that develops when a line is made by a pointed object (a key) on the skin. It is produced due to the release of histamine from the mast cells.

TRIPLE RESPONSE.

- When skin stroke more firmly with pointed objects
- 3 parts response occurs
- **Red reaction**
- **Flare**
- **Wheal**




Mast cell
Substance P
Substance P
Dorsal root ganglion/
trigeminal ganglion
Histamine
Bradykinin
Serotonin
Prostaglandin
K^+
Lesion
Substance P
Substance P
Blood
vessel
Spinal cord


Intact paw
Denerved paw
(saphenous nerve
cut)

Hőgyes Endre (1847-1906)

Ifj. Jancsó Miklós and Gábor Aranka

INFLAMMATION IS A UNIVERSAL AND ANCIENT FORM OF HOST DEFENCE

NOT A DISEASE *PER SE*!; RATHER IT IS A PROTECTIVE, NON-SPECIFIC RESPONSE TO VARIOUS NOXIOUS AGENTS

INFLAMMATION IS NOT EQUAL WITH INFECTION!

INFLAMMATION MAY BE OF TWO TYPES, ACUTE (THIS LECTURE) AND CHRONIC (THE TOPIC OF NEXT LECTURE)

The objectives of the lecture

1. **The inflammatory cascade: understand the chain of vascular and cellular events in the natural history of acute inflammation**
2. Understand the roles of humoral factors (chemical mediators) during acute inflammation
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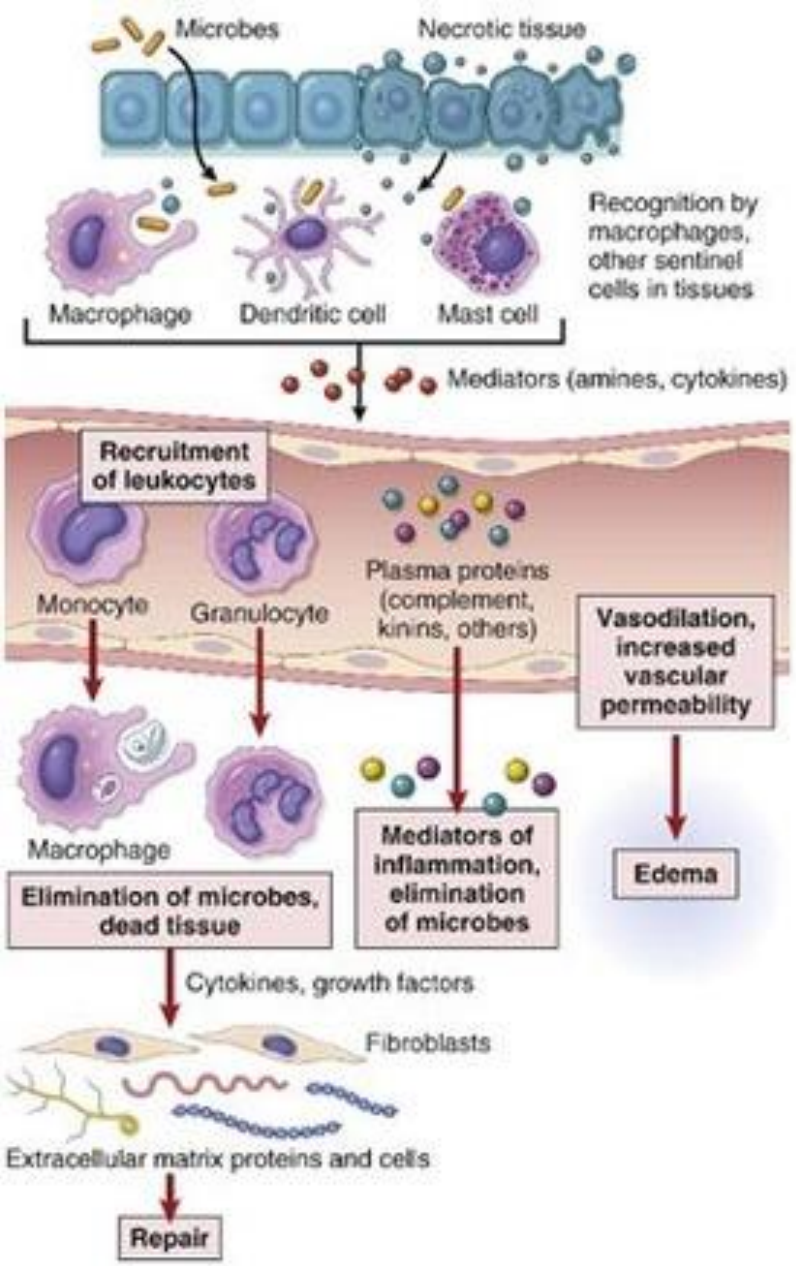


Reaction to: Injury, Infection, Insult, Itself

Recruitment of leukocytes

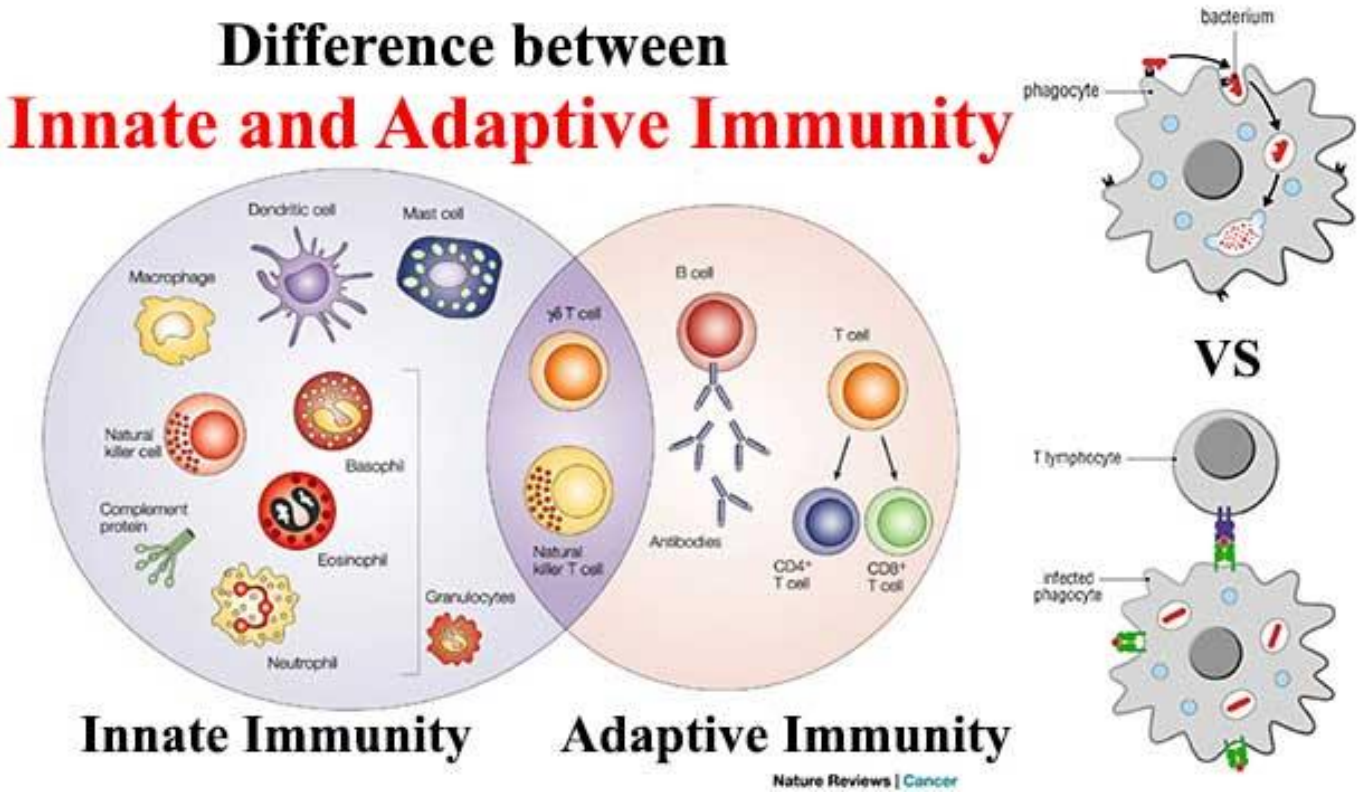
Removal of inciting agent

Regulation of response by mediators

Resolution and repair of damaged tissues

Stimuli that can evoke acute inflammation

- Infections
- Tissue necrosis (e.g. ischemia, trauma, thermal or chemical injury)
- Foreign body
- Hypersensitivity reaction



Innate immunity (~ acute inflammation): evolutionary ancient defense strategy that recognizes „non-self”

Adaptive immunity: highly adaptable system that creates immunological „memory” (it becomes a problem when „maladaptive”!)

Robert A. Good (1922-2003) discovers adaptive immunity

COMMENT

US NATL LIB. MEDICINE

Max Cooper in Robert Good's lab at the University of Minnesota in the mid-1960s.

Fifty years of B lymphocytes

Alexander D. Gitlin and **Michel C. Nussenzweig** reflect on the discovery of two lineages of adaptive immune cells, and how it influenced vaccination, cancer therapy and the development of a class of antibody-based drugs.

When Max Dale Cooper joined Robert Good's laboratory at the University of Minnesota in Minneapolis in 1963, there were two camps in immunology. Neither was particularly fond of the other.

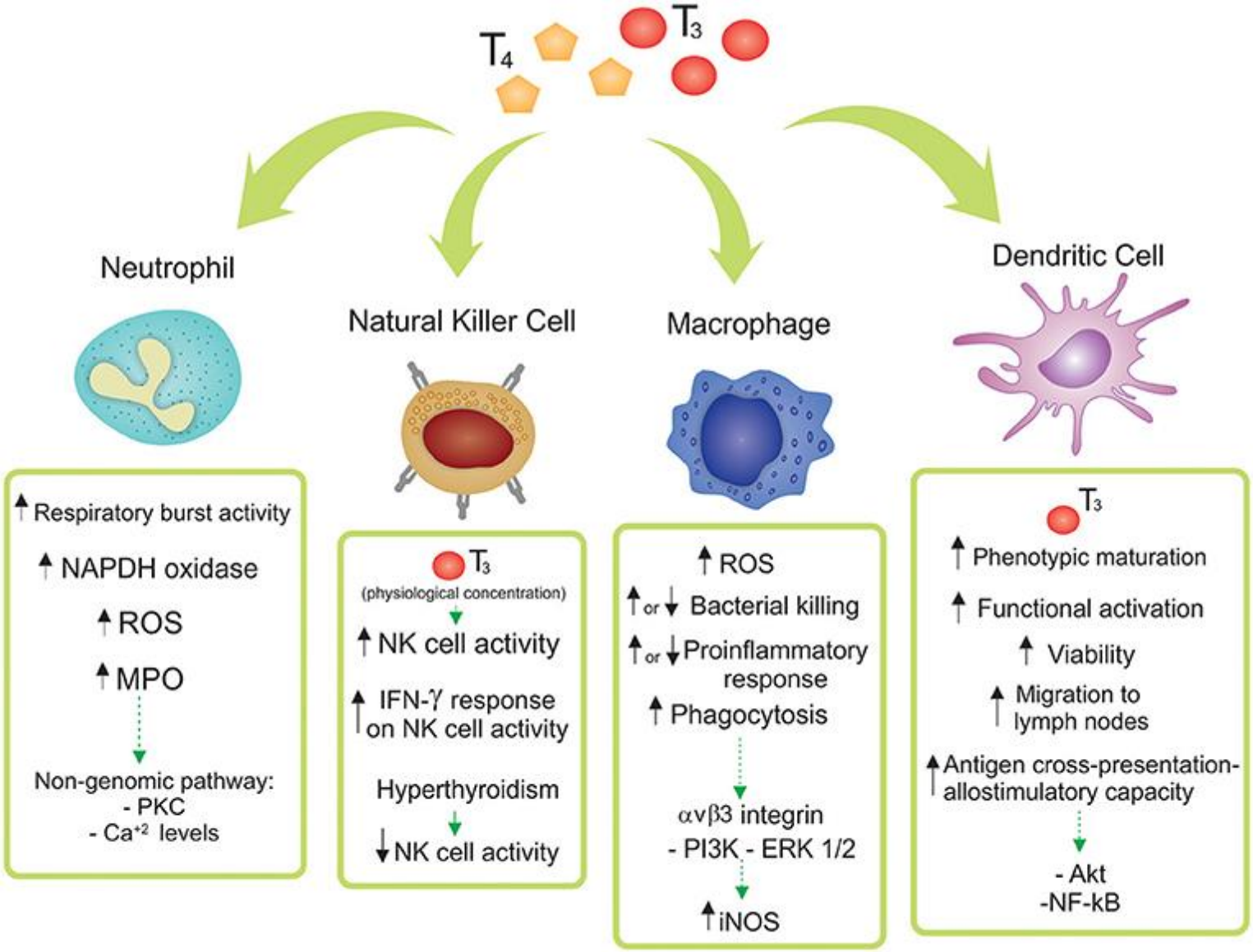
At the time, the central question in immunology was how vertebrates tailor their defences to bacteria and viruses, whose chemical structures show nearly unlimited diversity. Within two years of joining Good's laboratory, Cooper had made a discovery about the cells that accomplish this task — lymphocytes — that proved essential to cracking the mystery, and ultimately to unifying the camps of his field.

Fifty years ago this week, Good, Cooper and their colleague Raymond Peterson published a paper[1] in this journal revealing that there are two types of lymphocyte. The insight shaped the course of modern immunology and influenced the study and care of immunodeficiency conditions, cancers of the immune system and the development of monoclonal antibodies — powerful research tools and therapeutics.

CLONE WARFARE

In the 1960s, one camp of immunologists dealt mainly in chemical terms and had by then made considerable progress. This group had discovered that antibody molecules are proteins with two binding sites that recognize an extraordinary range of foreign molecules (antigens), even synthetic ones; and that antibodies are composed of two heavy and ▶

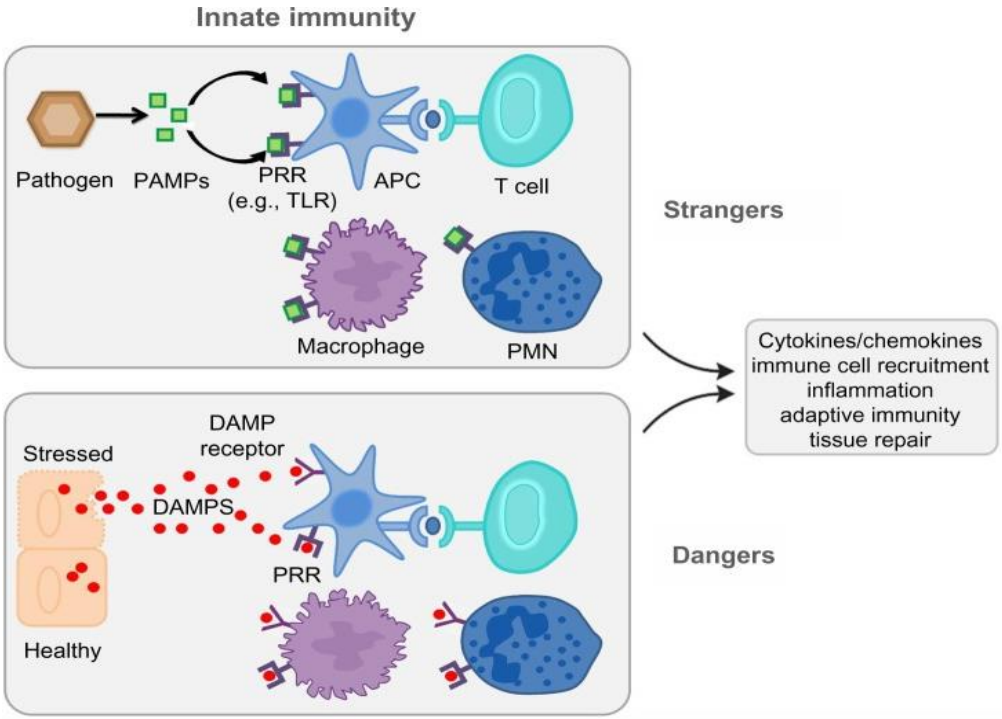
In 1965, Max Cooper and Robert Good published a landmark study in *Nature* that led to the birth of the B cell field. Working with chickens, they showed that cells that develop in the bursa of Fabricius ('B cells') are responsible for antibody production, whereas those cells that develop in the thymus ('T cells') are necessary for delayed-type hypersensitivity responses.

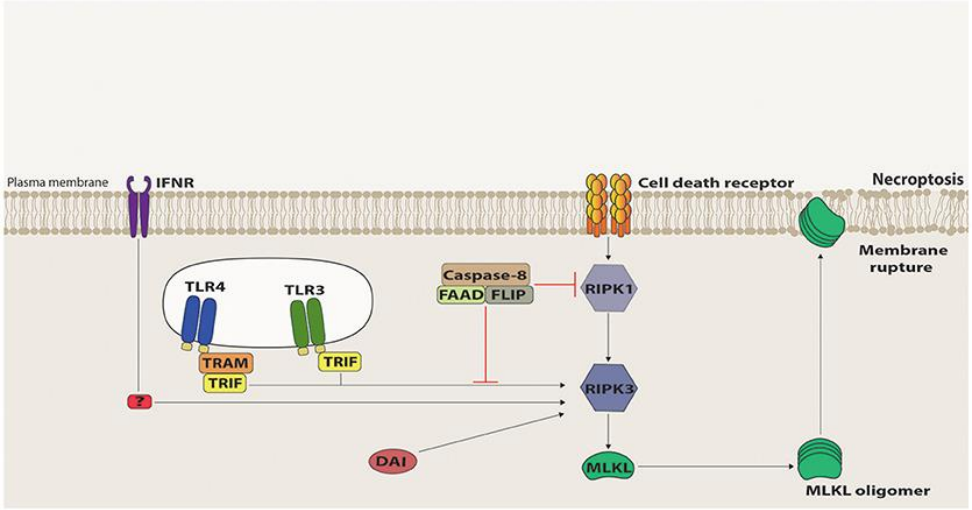

T4
T3
Neutrophil
Natural Killer Cell
Macrophage
Dendritic Cell
Respiratory burst activity
NAPDH oxidase
ROS
MPO
Non-genomic pathway:
- PKC
- Ca+2 levels
T3
(physiological concentration)
NK cell activity
IFN-γ response on NK cell activity
Hyperthyroidism
NK cell activity
ROS
or Bacterial killing
or Proinflammatory response
Phagocytosis
αvβ3 integrin
- PI3K - ERK 1/2
iNOS
T3
Phenotypic maturation
Functional activation
Viability
Migration to lymph nodes
Antigen cross-presentation-allostimulatory capacity
- Akt
-NF-kB

1st step: to recognize the danger: Pattern Recognition Receptors (PRRs)

Cellular receptors for microbes PRRs recognize PAMPs (pathogen-associated molecular pattens)

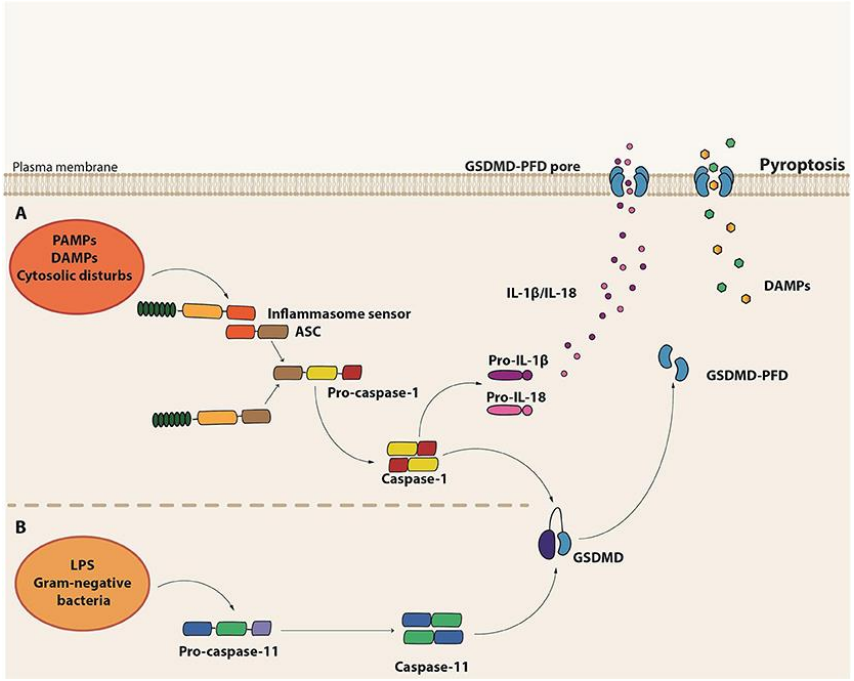
Sensors of cell damage PRRs recognize DAMPs (damage-associated molecular patterns), that is, molecules released from damaged cells; **uric acid** (a product of DNA breakdown), **ATP** (released from damaged mitochondria), **reduced intracellular K + concentrations** (reflecting loss of ions because of plasma membrane injury), **DNA** (when it is released into the cytoplasm and not sequestered in nuclei, as it should be normally), and many others.



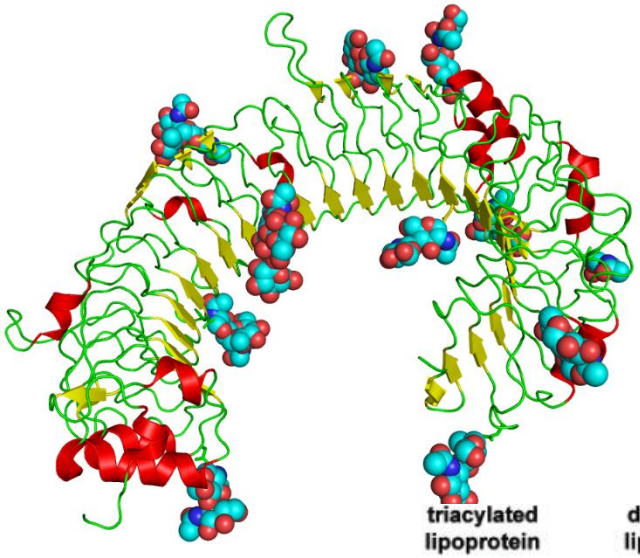


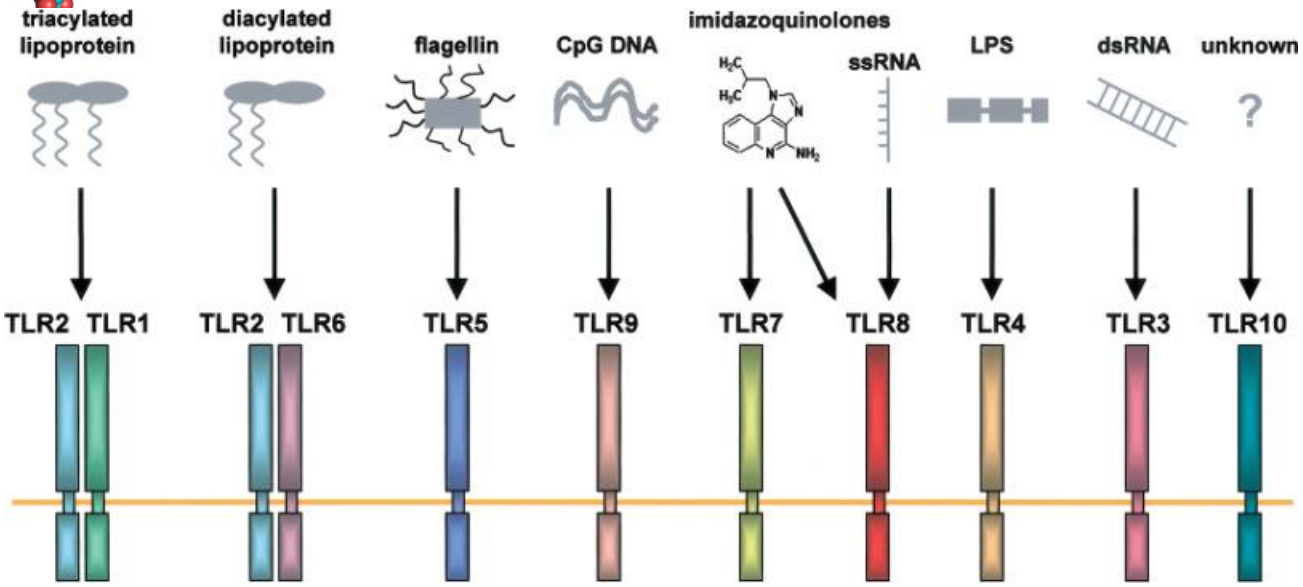
Necroptosis = a „fail-safe" mechanism to eliminate infected cells when virus blocks apoptosis

Pyroptosis = host cell death triggered by intracellular pathogens

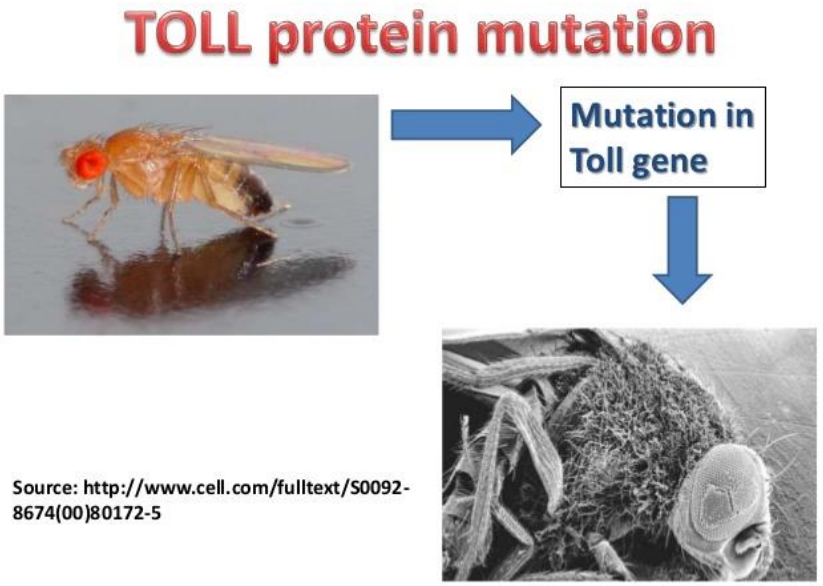


Toll-like receptors

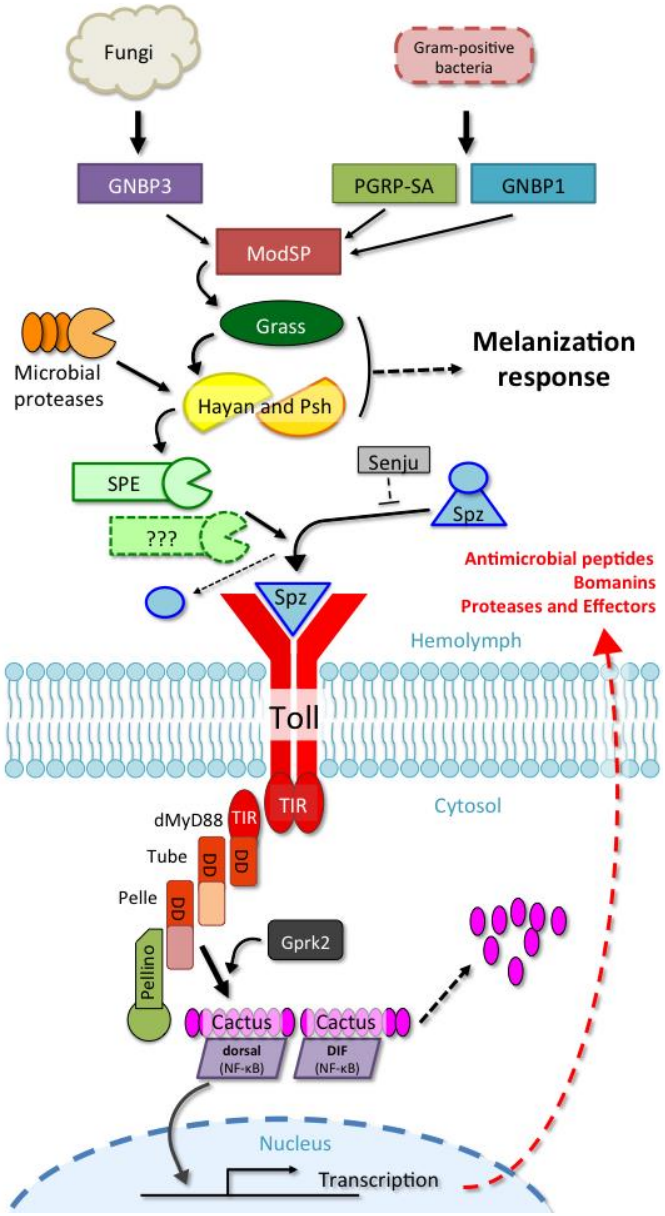




„das ist toll!” (this is great!)



Christiane Nüsslein-Volhard (1942), Nobel prize 1995


Fungi
Gram-positive bacteria
GNBP3
PGRP-SA
GNBP1
ModSP
Grass
Melanization response
Microbial proteases
Hayan and Psh
SPE
Senju
Spz
???
Antimicrobial peptides
Bomanins
Proteases and Effectors
Spz
Hemolymph
Toll
TIR
Cytosol
dMyD88
TIR
DD
Tube
DD
Pelle
DD
Gprk2
Pellino
Cactus
Cactus
dorsal (NF-κB)
DIF (NF-κB)
Nucleus
Transcription

The cascade of acute inflammation

- Vasodilation
- Increased vascular permeability/leakage of exudate
- Leukocytes:
    - margination, rolling, and adhesion
    - diapedesis (transmigration)
    - chemotaxis
    - PMN activation
    - phagocytosis (recognition, engulfment, killing)

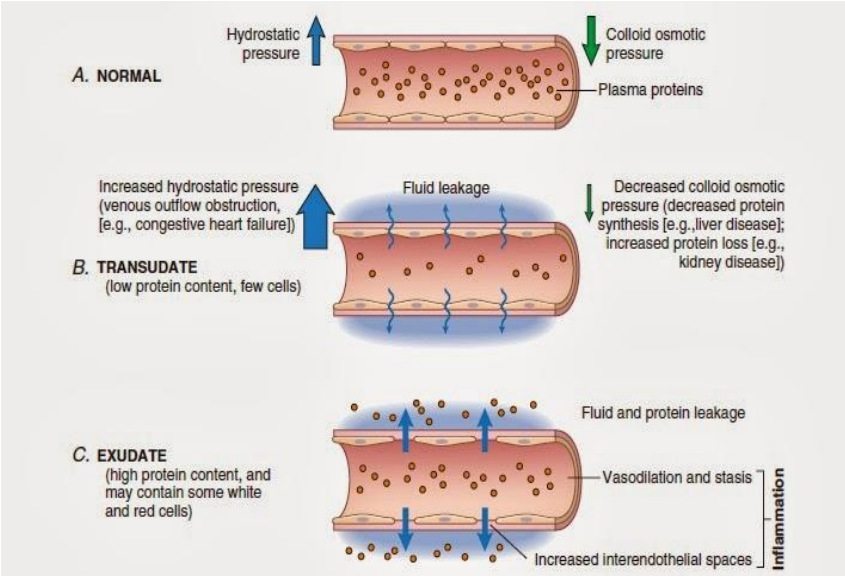
Vascular events of inflammation

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

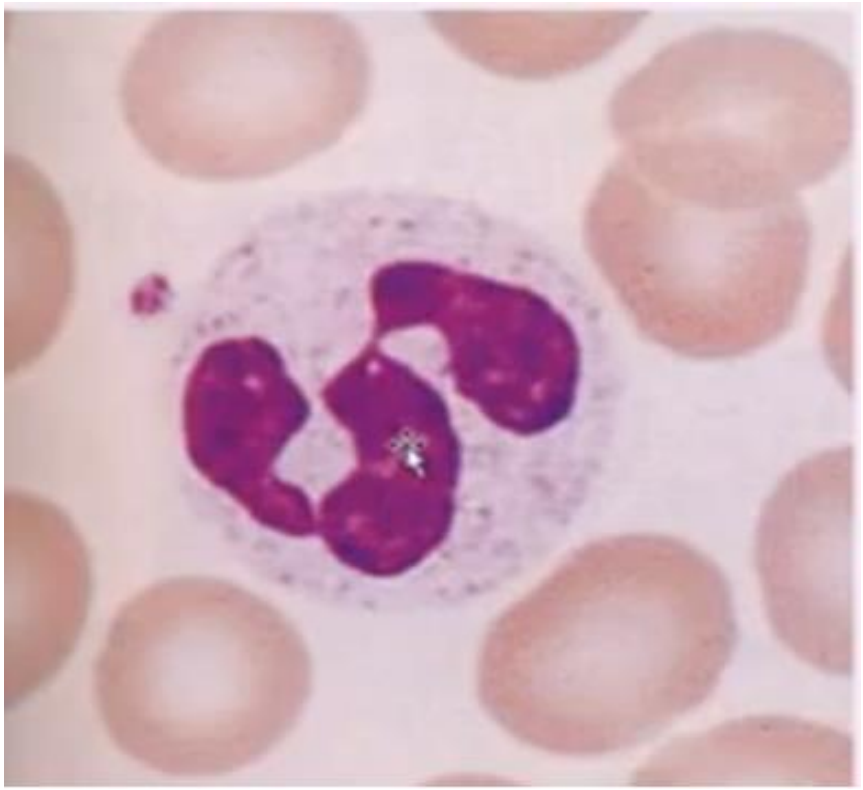
Changes in vascular flow and caliber- **Arteriolar dilation,**

Changes in vascular permeability

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



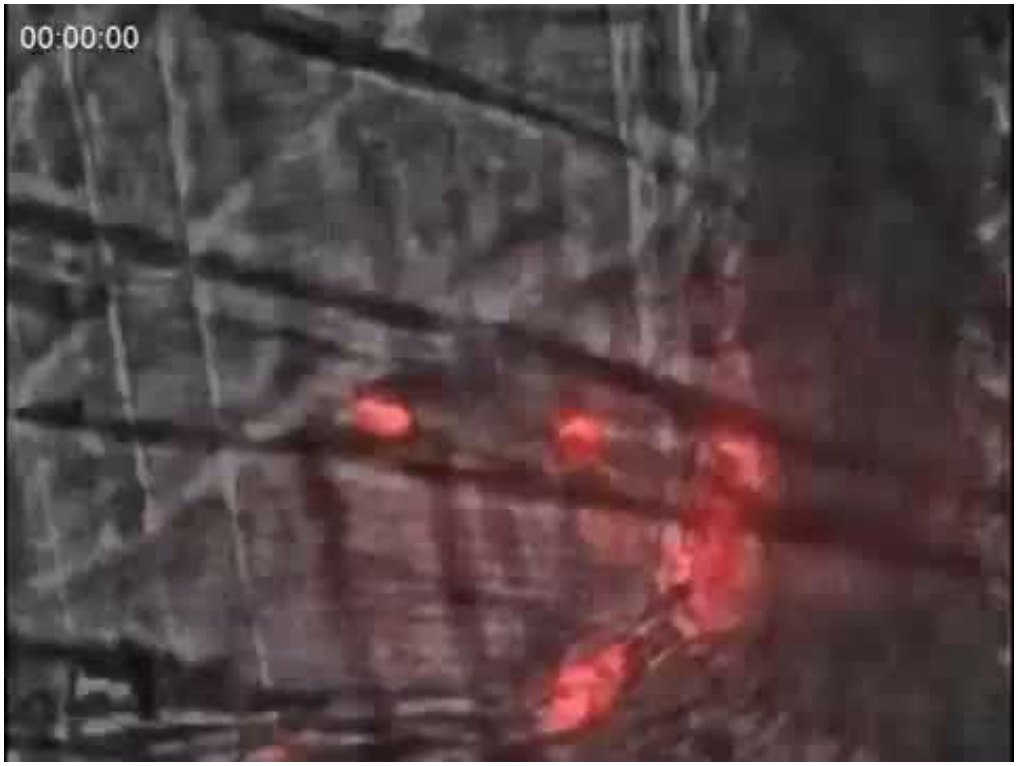
LEAKAGE of a proteineaceous fluid EXUDATE and not TRANSUDATE!!!!!



Neutrophils (PMN granulocyte)

EXTRAVASATION of PMNs

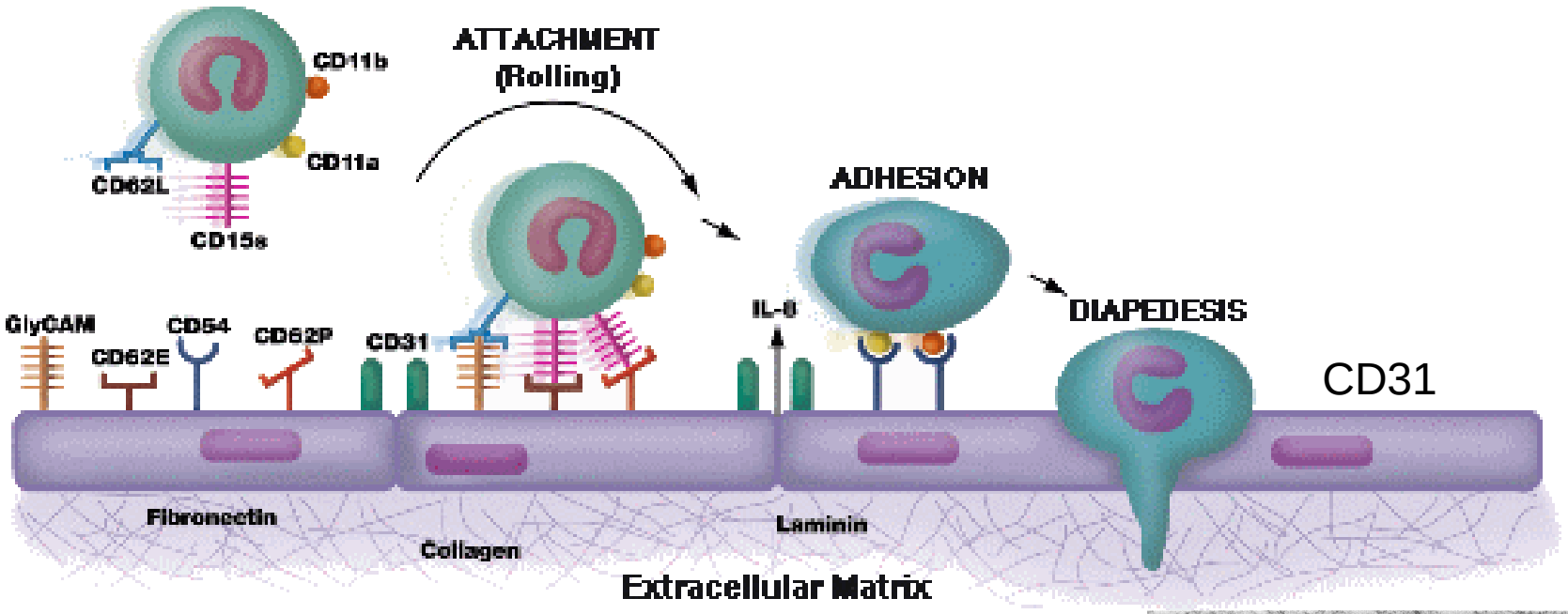
- **MARGINATION**
- (PMN's go toward wall)
- **ROLLING** (tumbling and HEAPING)
- **ADHESION**
- **TRANSMIGRATION** (DIAPEDESIS)

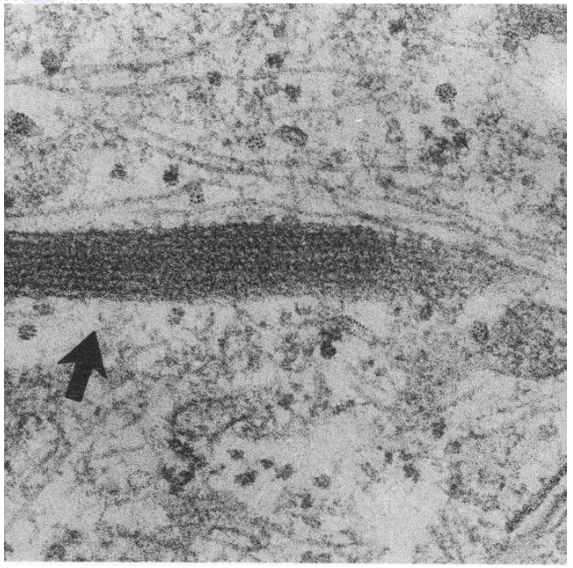


Adhesion molecules affecting rolling and adhesion
1.Selectins (E,P and L) from endothelial cells (E and P) or leukocytes (L)-rolling
2.Integrins from many cells (ICAM, VCAM)-adhesion

Transmigration: mediated by CD31

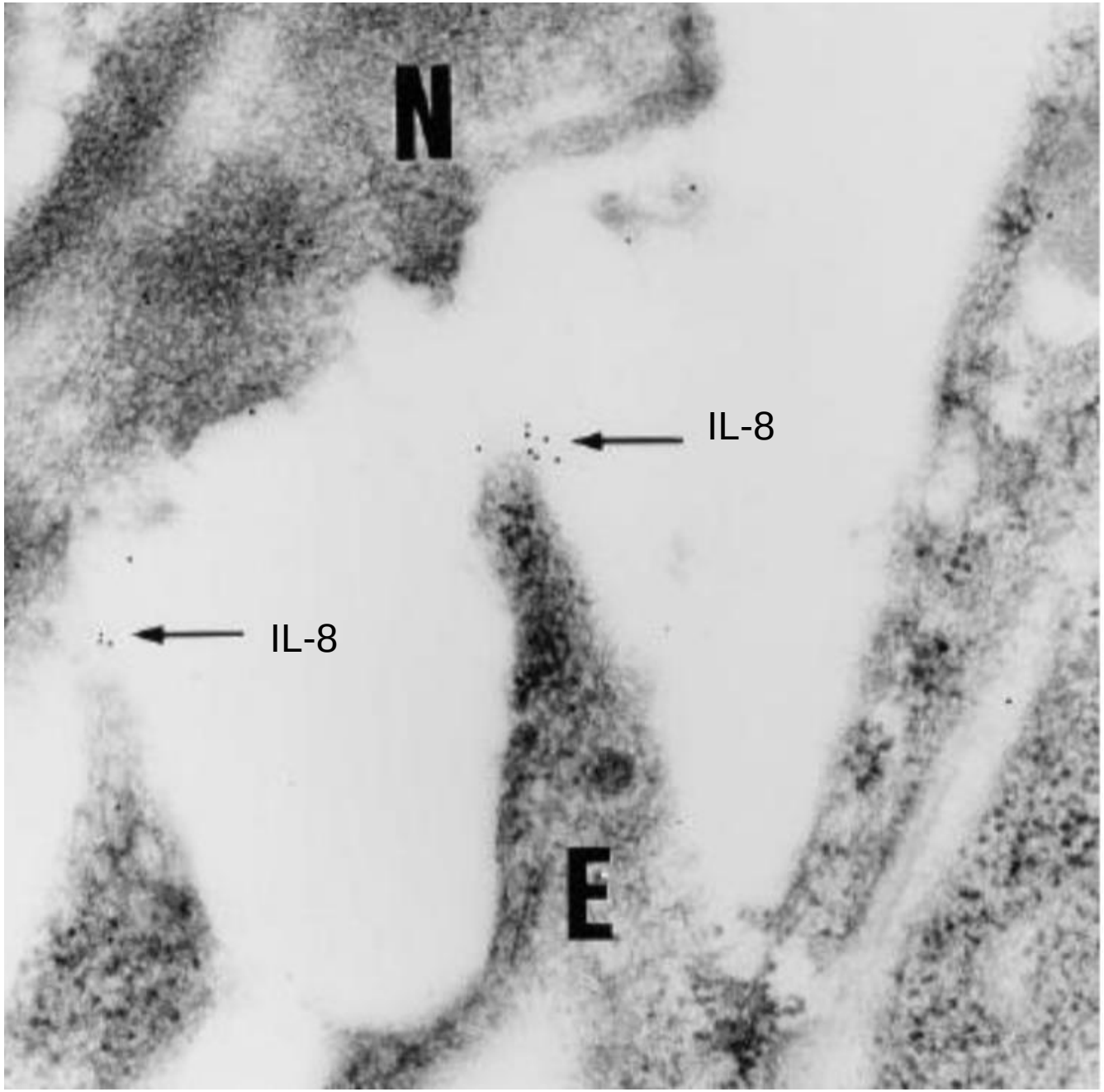
CHEMOTAXIS PMNs going to the site of the injury after transmigration (chemokines)
Chemoattractants: N-formylmethionine, C5a, leukotrienes



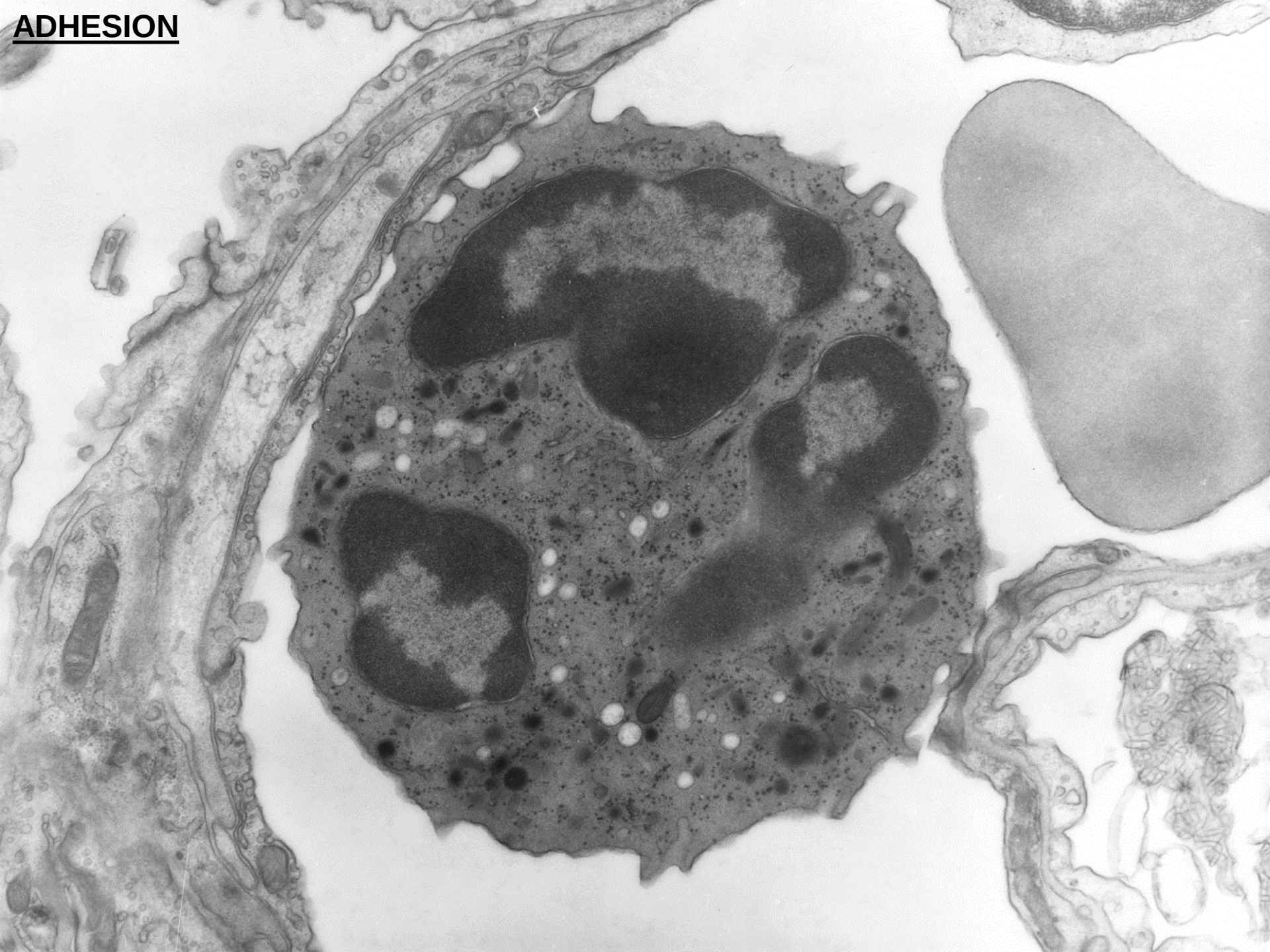


Weibel-Palade body stores CD62P in edothelium

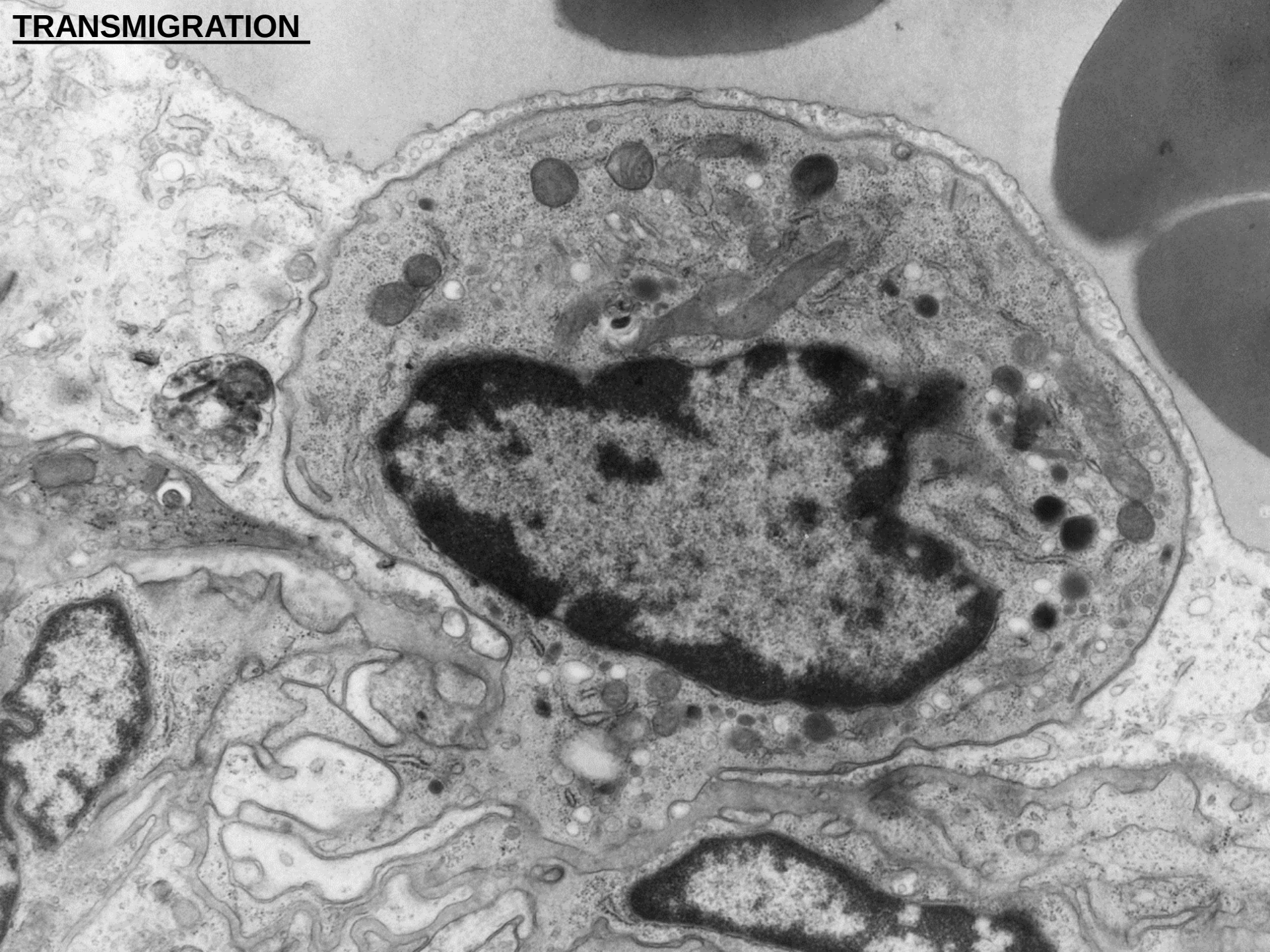
MARGINATION

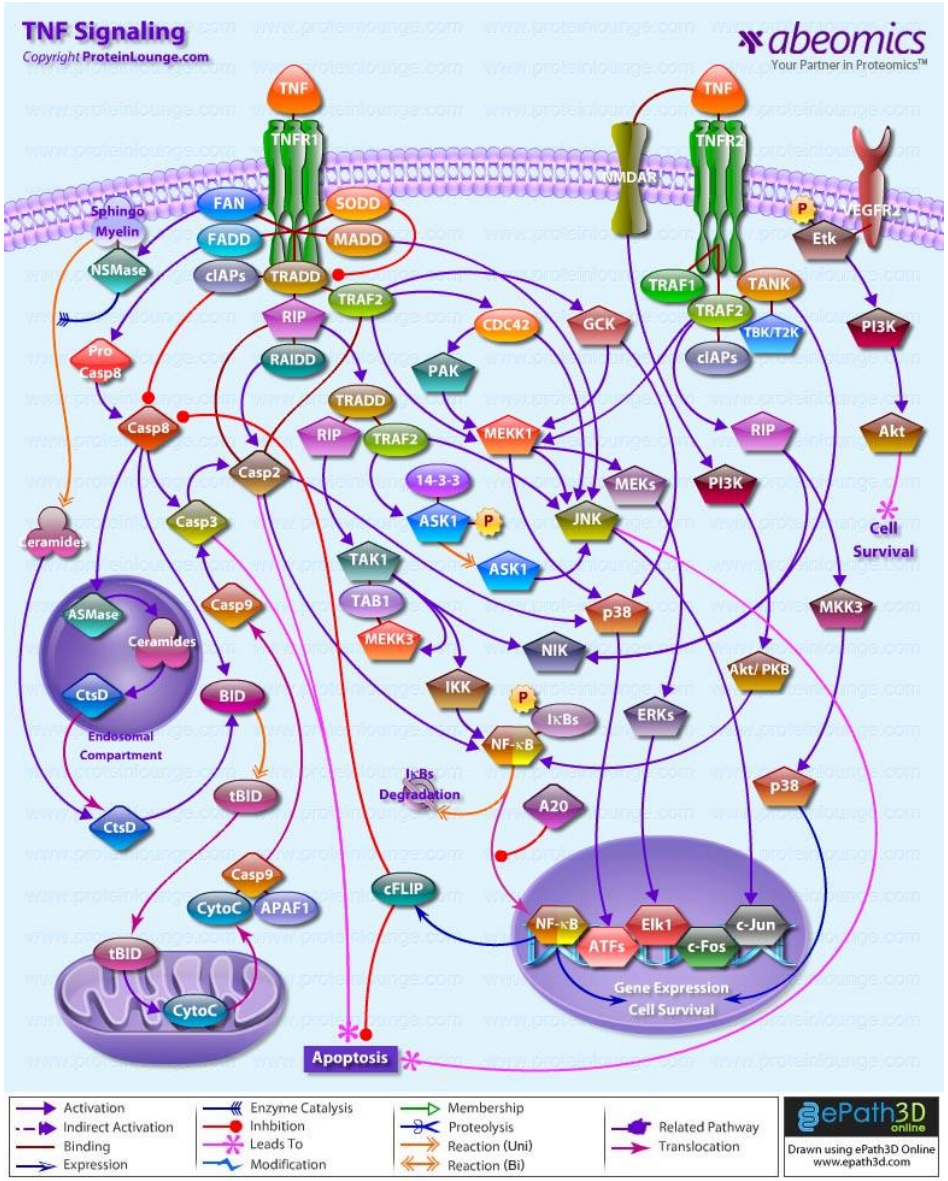


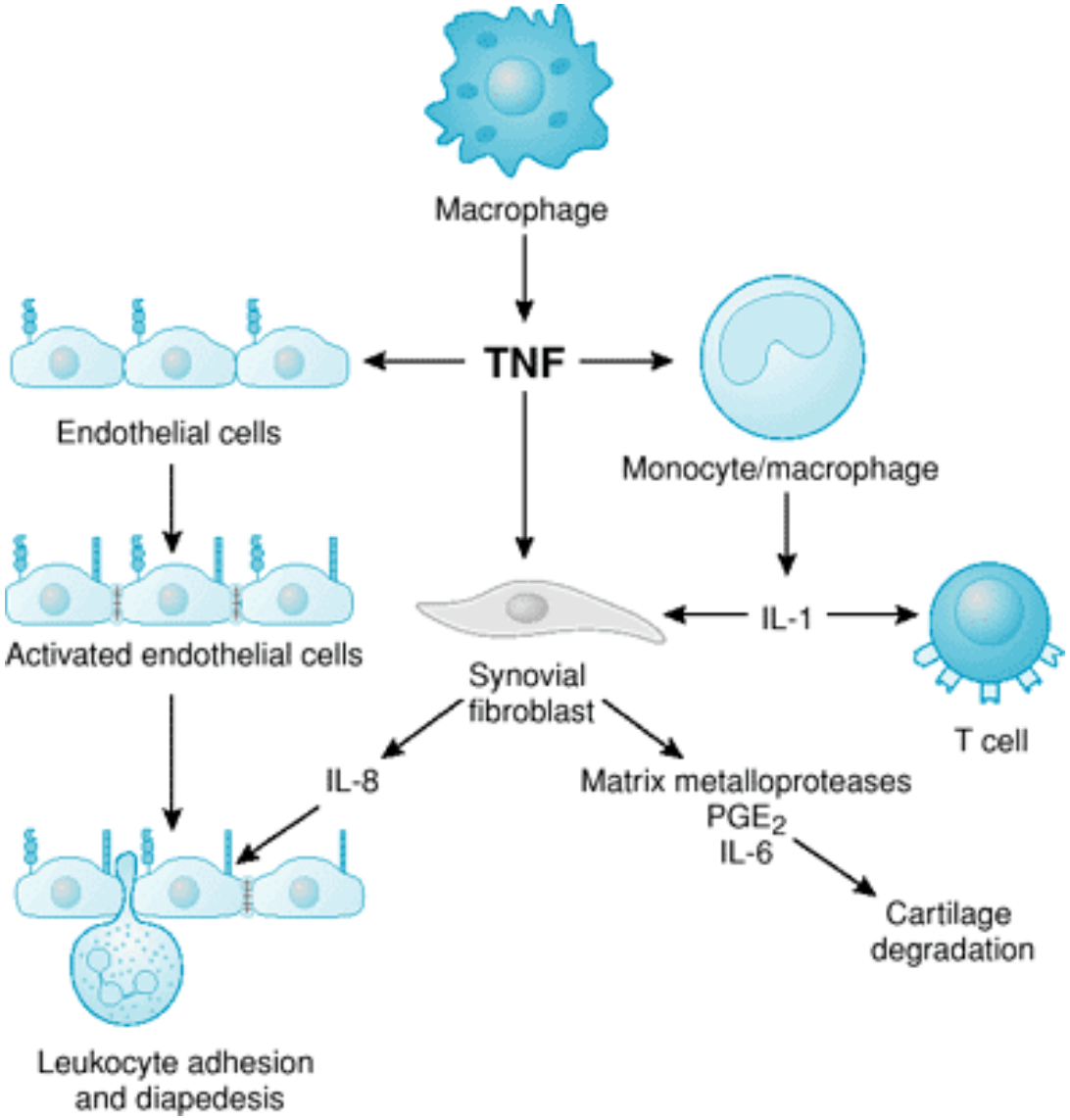
ADHESION



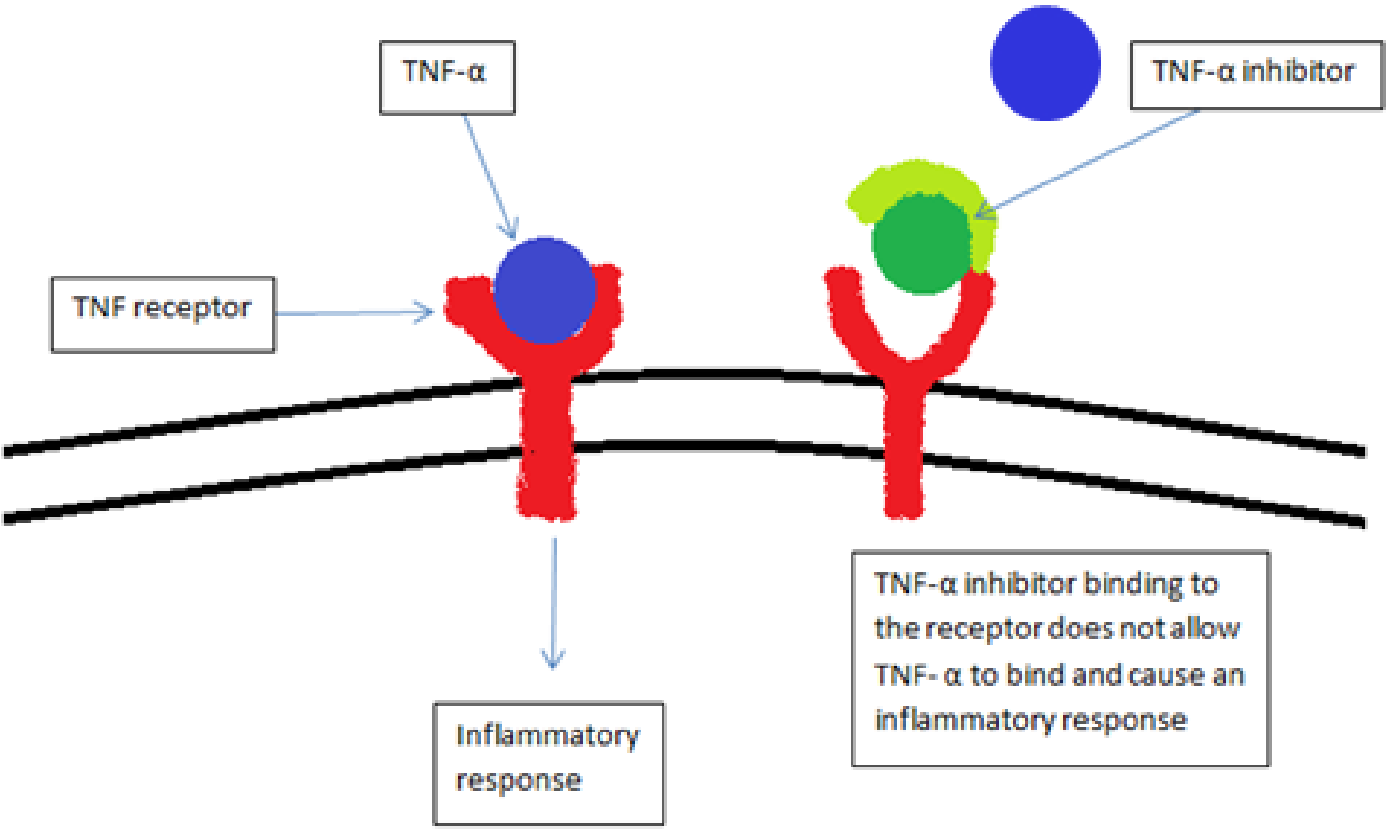
TRANSMIGRATION



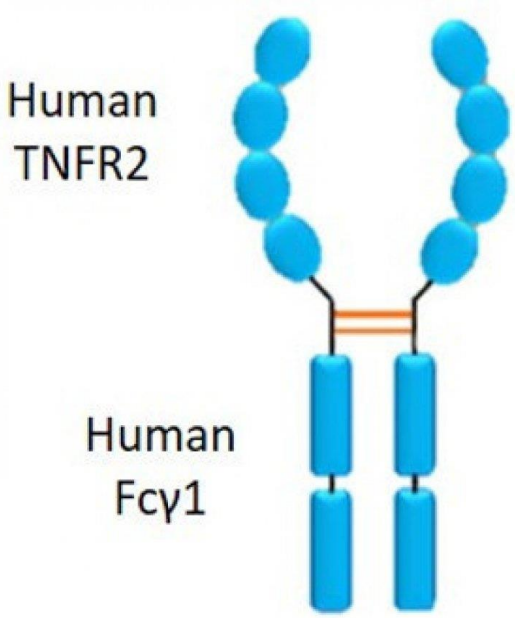

TNF Signaling
Copyright ProteinLounge.com
abeomics
Your Partner in Proteomics™
TNF
TNFR1
TNF
TNFR2
VMDAR
VEGFR2
P
Etk
FAN
SODD
FADD
MADD
Sphingo
Myelin
NSMase
cIAPs
TRADD
TRAF2
TRAF1
TANK
TRAF2
TBK/T2K
cIAPs
RIP
RAIDD
CDC42
GCK
PI3K
Pro
Casp8
PAK
TRADD
RIP
TRAF2
MEKK1
RIP
Akt
Casp8
Casp2
14-3-3
MEKs
PI3K
Casp3
ASK1
P
JNK
Cell
Survival
Ceramides
TAK1
ASK1
TAB1
p38
MKK3
Casp9
ASMase
Ceramides
MEKK3
NIK
CtsD
BID
IKK
P
IκBs
ERKs
Akt/ PKB
Endosomal
Compartment
NF-κB
IκBs
Degradation
p38
tBID
A20
CtsD
Casp9
cFLIP
CytoC
APAF1
NF-κB
Elk1
c-Jun
ATFs
c-Fos
tBID
Gene Expression
Cell Survival
CytoC
Apoptosis
Activation
Indirect Activation
Binding
Expression
Enzyme Catalysis
Inhbition
Leads To
Modification
Membership
Proteolysis
Reaction (Uni)
Reaction (Bi)
Related Pathway
Translocation
ePath3D online
Drawn using ePath3D Online
www.epath3d.com


Macrophage
TNF
Endothelial cells
Monocyte/macrophage
Activated endothelial cells
IL-1
Synovial fibroblast
T cell
IL-8
Matrix metalloproteases
PGE2
IL-6
Cartilage degradation
Leukocyte adhesion and diapedesis

TNF inhibitors as a new generation of antiinflammatory drugs



For rheumatoid arthritis, psoriasis, etc

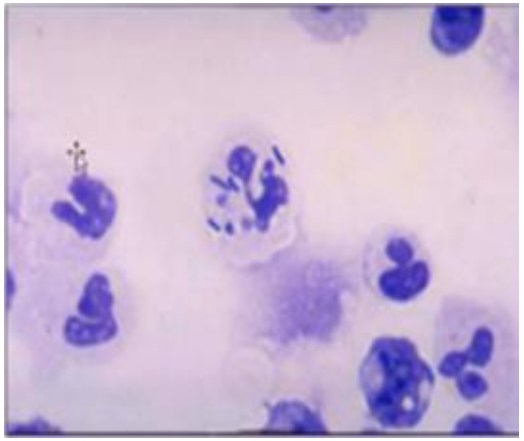


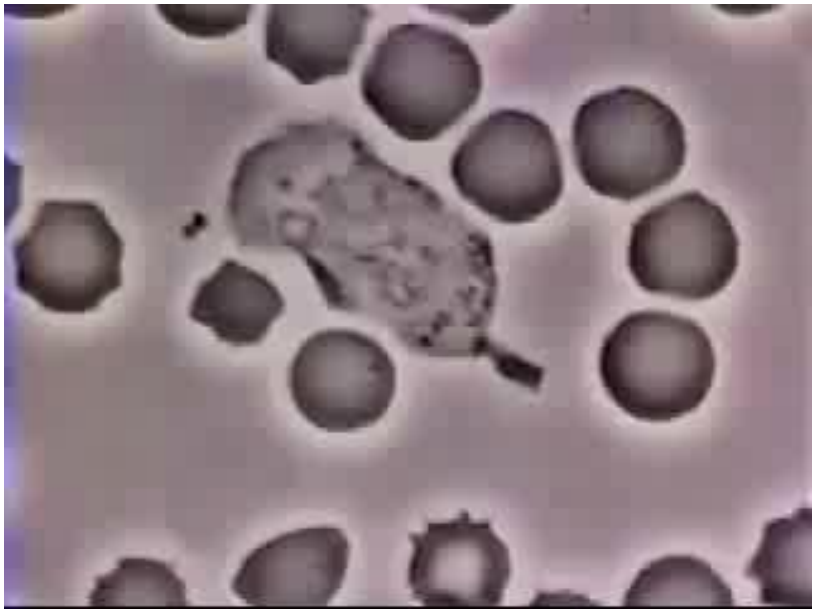
LEUKOCYTE „ACTIVATION”

- „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

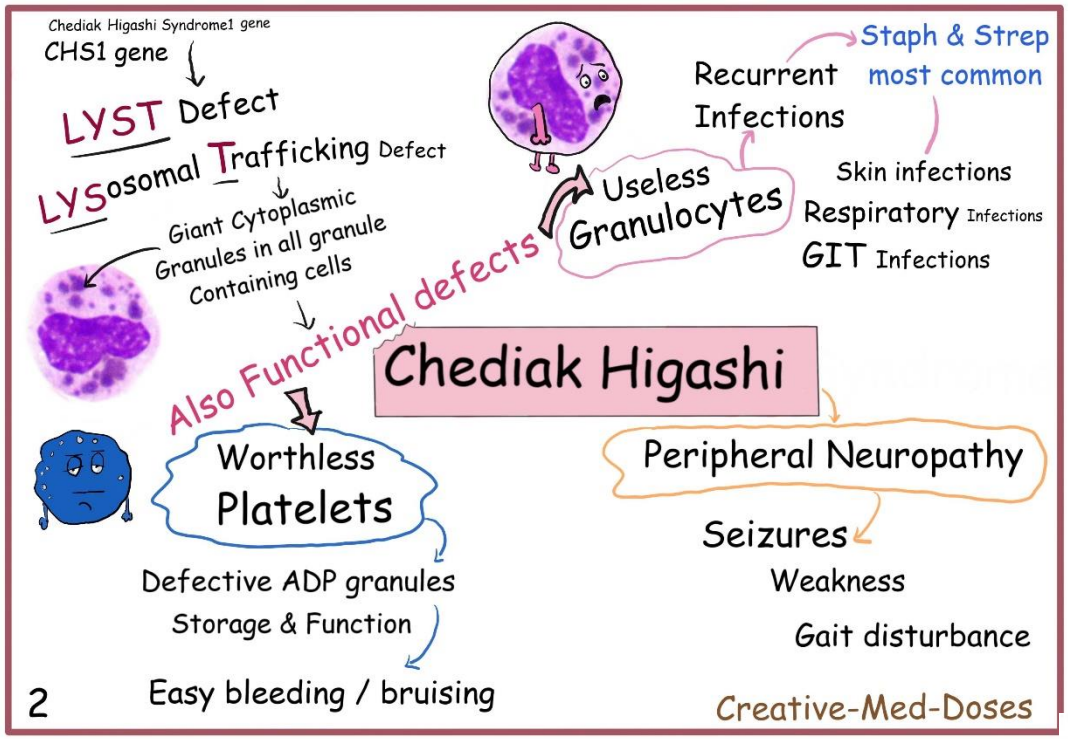
- **RECOGNITION**
- **ENGULFMENT**
- **KILLING**

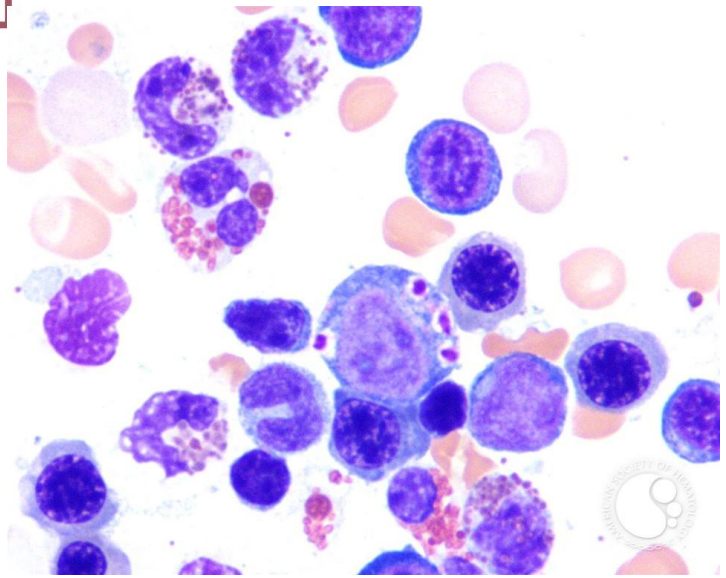




(DEGRADATION/ DIGESTION) (oxigen dependent and independent mechanisms)

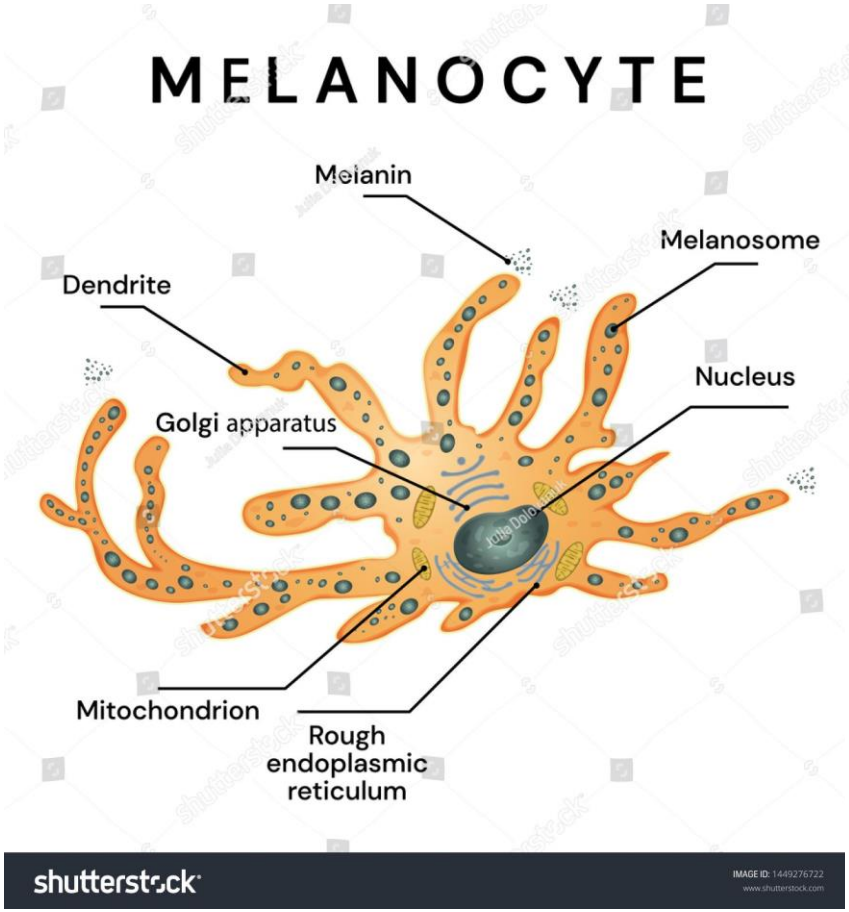
An additional mechanism of killing microbes is the extracellular traps-NETosis

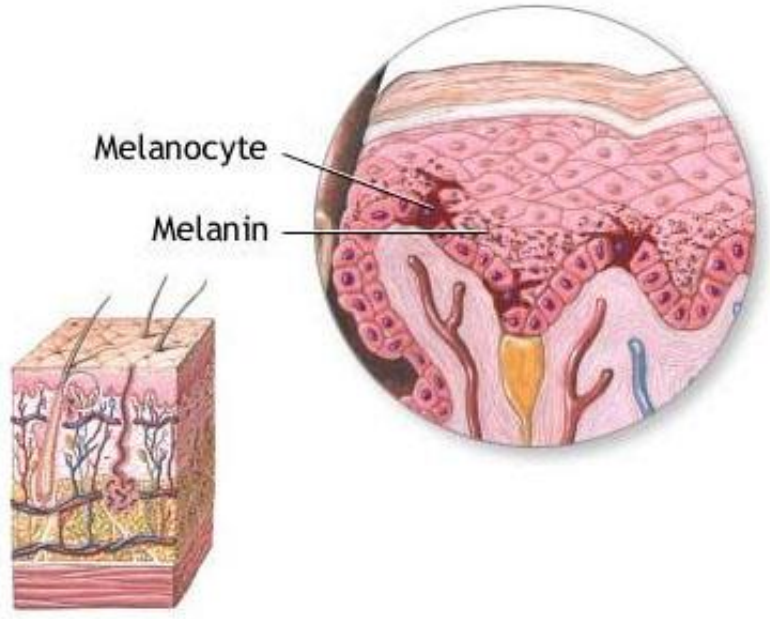

Chediak Higashi Syndrome1 gene
CHS1 gene
LYST Defect
LYSosomal Trafficking Defect
Giant Cytoplasmic Granules in all granule Containing cells
Also Functional defects
Useless Granulocytes
Recurrent Infections
Staph & Strep most common
Skin infections
Respiratory Infections
GIT Infections
Chediak Higashi
Peripheral Neuropathy
Seizures
Weakness
Gait disturbance
Worthless Platelets
Defective ADP granules Storage & Function
Easy bleeding / bruising
2
Creative-Med-Doses



Oculocutaneous albinism

White tiger (a big cat with Chediak-Higashi!)


MELANOCYTE
Melanin
Melanosome
Dendrite
Nucleus
Golgi apparatus
Mitochondrion
Rough endoplasmic reticulum
shutterstock
IMAGE ID: 1449276722
www.shutterstock.com


Melanocyte
Melanin

Oculocutaneous albinism: melanin is produced but not packed into melanosomes

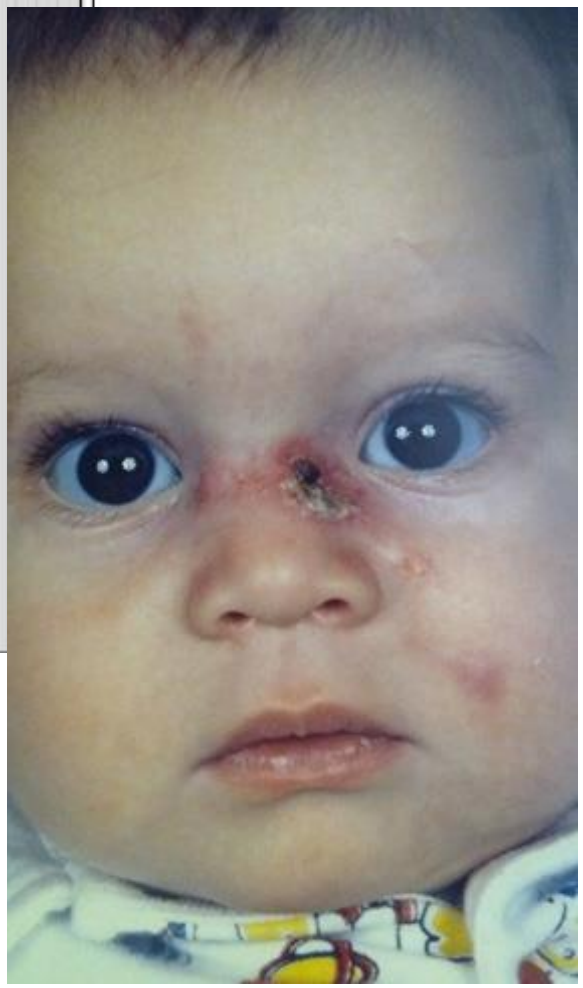
Albino: no melanin production due to Tyrosinase deficiency

CHRONIC GRANULOMATOUS DISEASE(CGD):

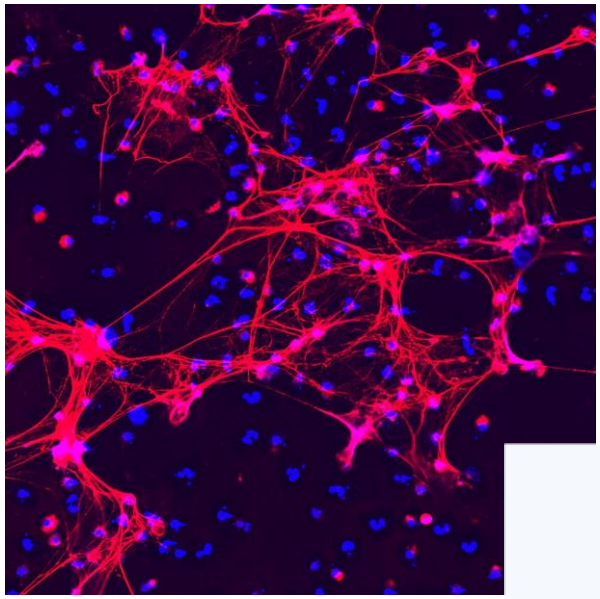
- CGD is an inherited disorder in which neutrophil's phagocytic function do not work properly.
- Also known as Bridges–Good syndrome,Chronic granulomatous disorder, and Quie syndrome.
- It was first recognized in 1954.
- TYPES OF CGD:
- CGD has atleast 2 distinct forms:

i. X-linked form (70% of patients)

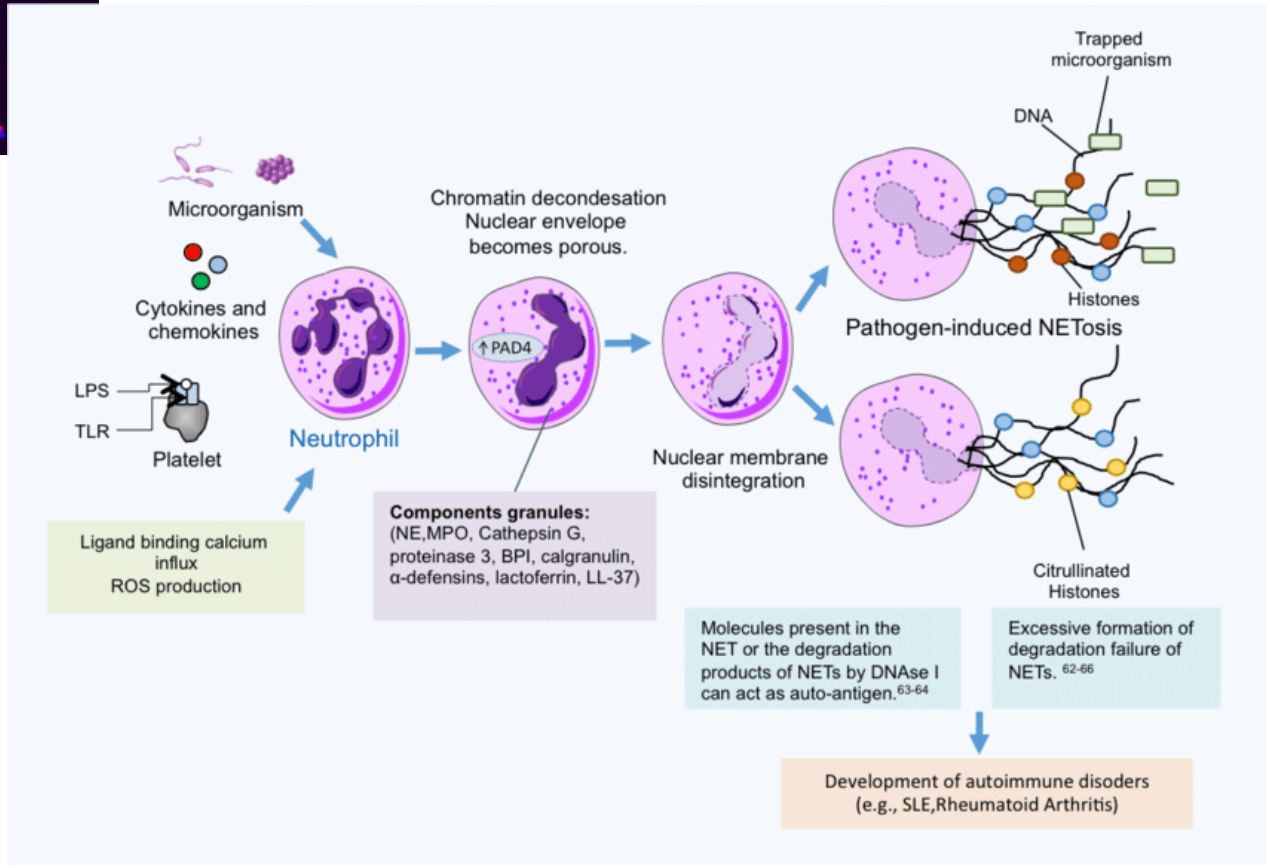
ii. Autosomal recessive form.



Defective NADPH oxidase



Neutrophil Extracellular Trap



The objectives of the lecture

1. The inflammatory cascade: understand the chain of vascular and cellular events in the natural history of acute inflammation
2. **Understand the roles of humoral factors (chemical mediators) during acute inflammation**
3. Know the three possible outcomes of acute inflammation
4. Describe the morphologic patterns of acute inflammation

Humoral elements „Mediators”

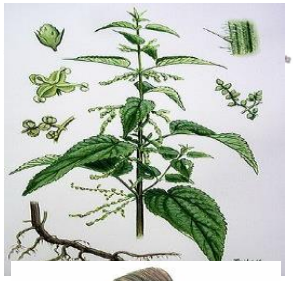
- Vasoactive amins: histamine, serotonine (vasodilatation, permeability, pain)
- Vasoactive peptids: bradykinin
- Complement system (MAC, vasodilatation, permeability, chemotaxis, opsonisation)
- Clotting, fibrinolitic cascade
- Immunglobulins
- Arahidonic acid derivatives
- Cyclooxigenase prostaglandins
- 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

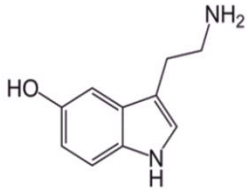
HISTAMINE

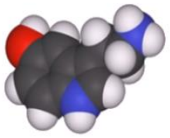
- Mast Cells, basophils
- POWERFUL Vasodilator
- Vasoactive „amine”
- IgE on mast cell



SEROTONIN

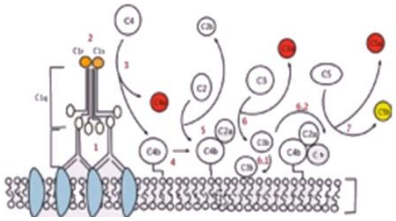
- (5HT, **5-H**ydroxy-**T**ryptamine)
- Platelets and EnteroChromaffin Cells
- Also vasodilatation, but more indirect
- Evokes N.O. synthetase (a ligase) from arginine





COMPLEMENT SYSTEM

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



KININ SYSTEM

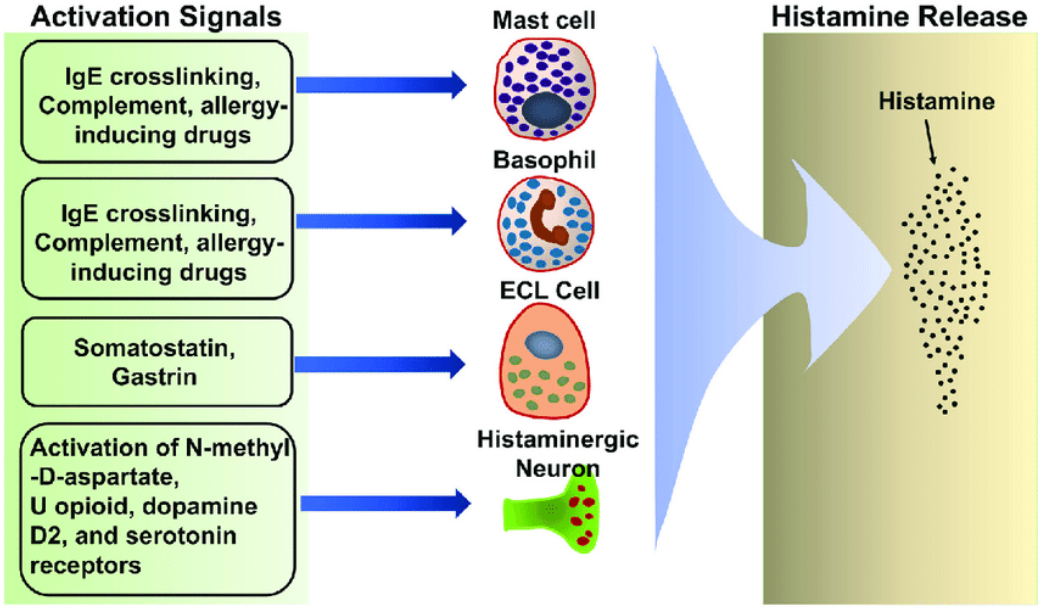
- BRADYKININ is KEY component, 9 aa’s
- ALSO from circulating plasma
- ACTIONS
  - **Increased permeability**
  - **Smooth muscle contraction, NON vascular**
  - **PAIN**

CLOTTING FACTORS

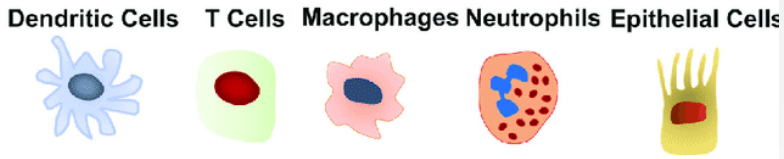
- Also from circulating plasma
- Coagulation, i.e., production of fibrin
- Fibrinolysis

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

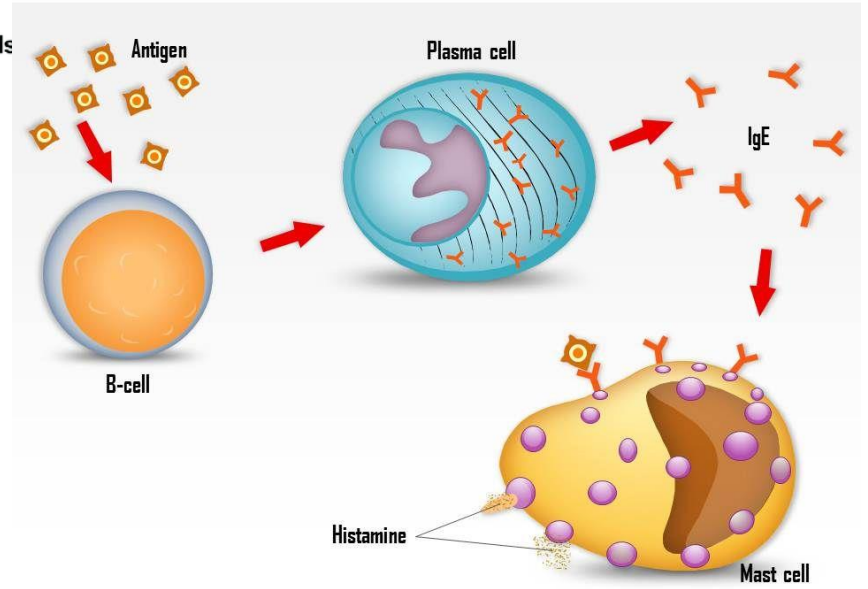
Major Histamine-producing Cells

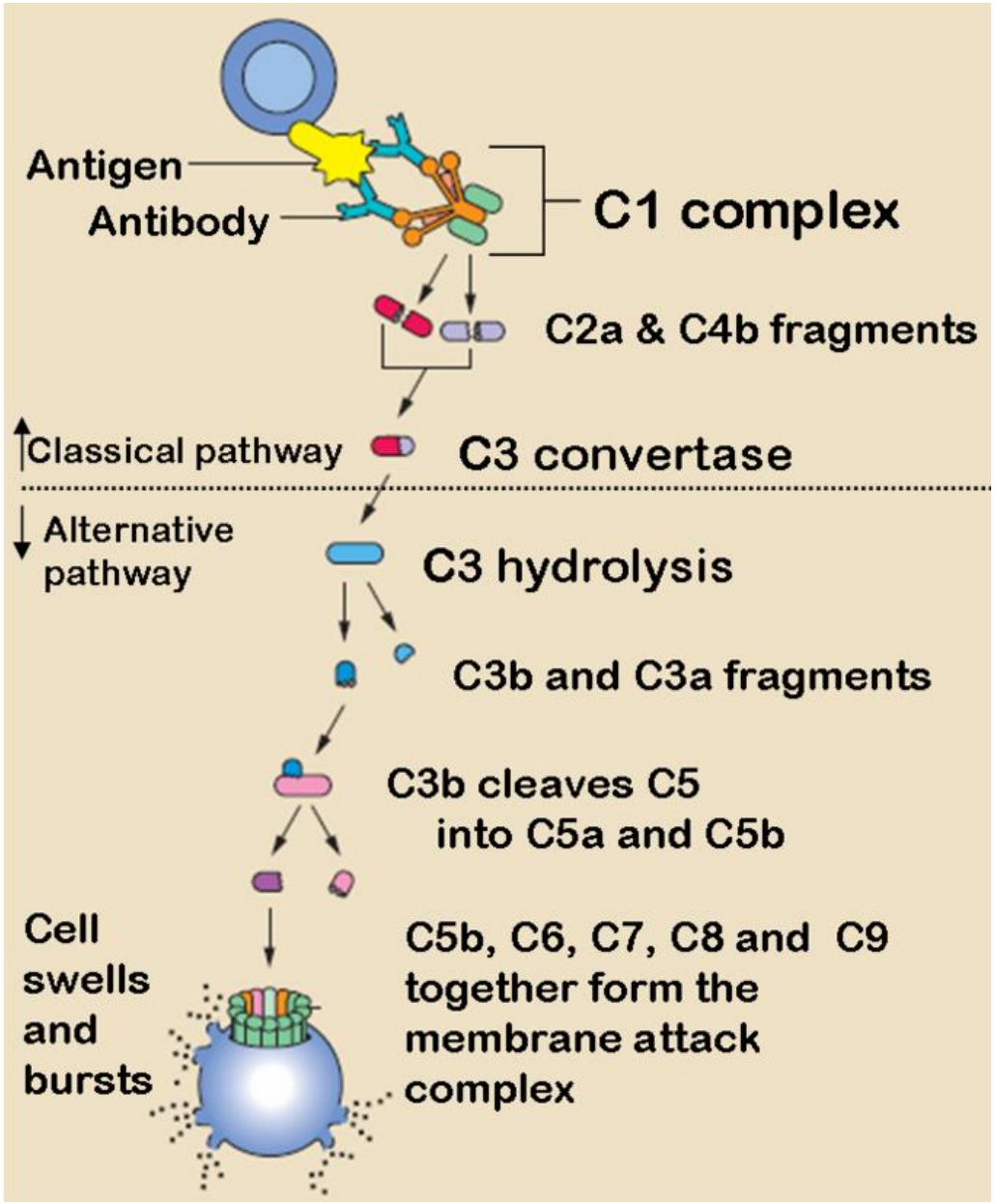


Minor Histamine-producing Cells

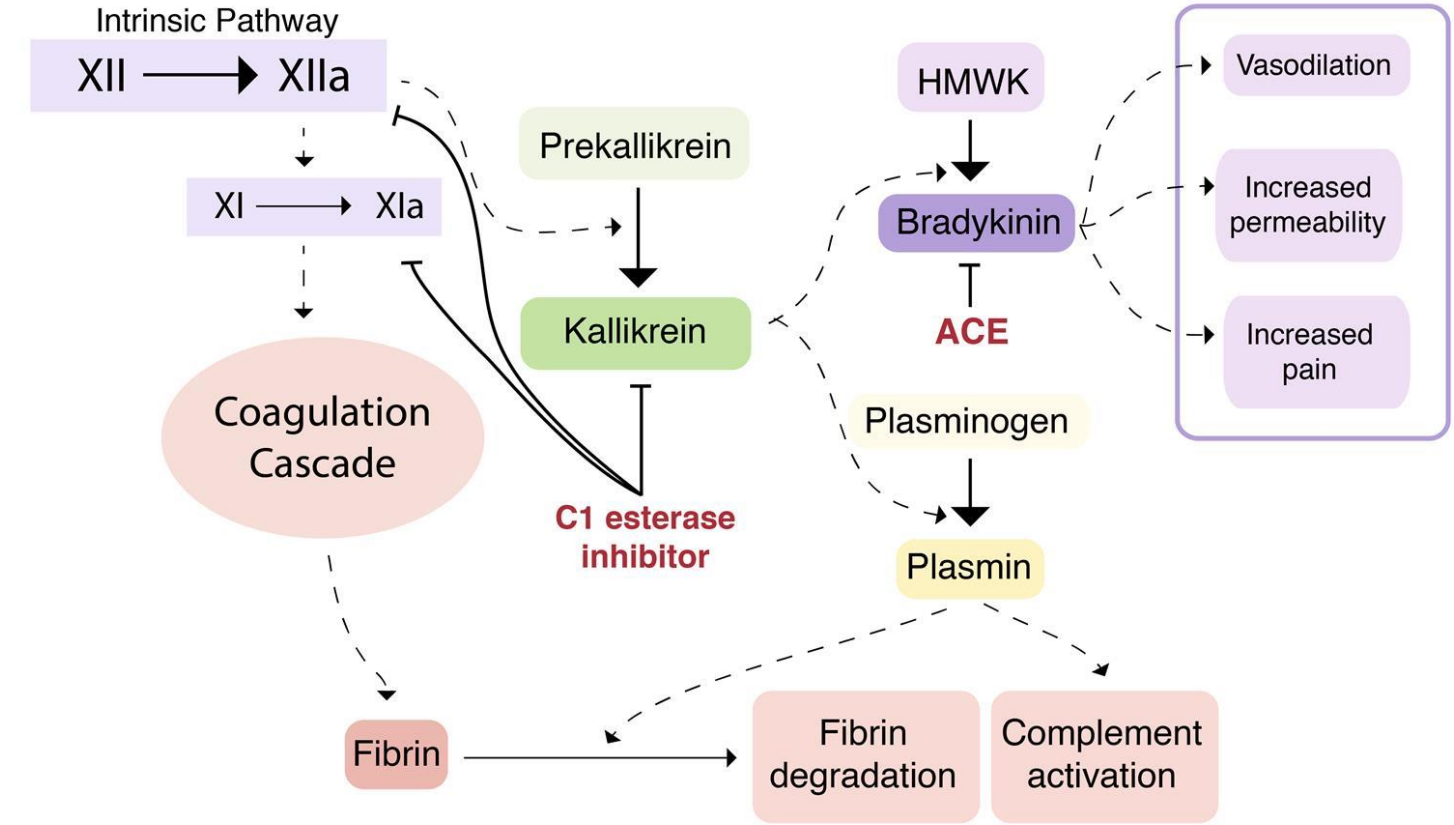


Anaphylactic Reaction




Antigen
Antibody
C1 complex
C2a & C4b fragments
Classical pathway
C3 convertase
Alternative pathway
C3 hydrolysis
C3b and C3a fragments
C3b cleaves C5 into C5a and C5b
Cell swells and bursts
C5b, C6, C7, C8 and C9 together form the membrane attack complex

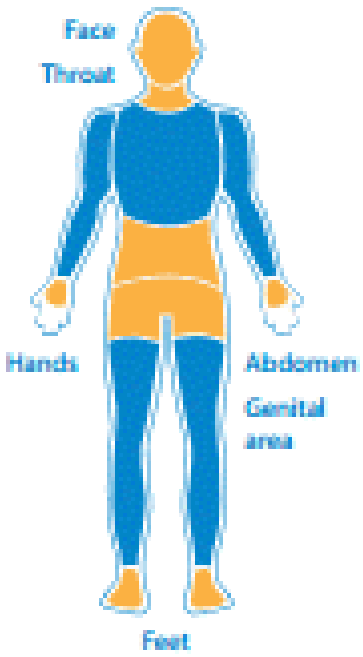
Kallikrein-Bradykinin Pathway



Lucy Liu

What is Hereditary Angioedema (HAE)?

HAE is a rare inherited condition characterized by painful, recurring attacks of swelling in parts of the body including:[1,2]



It is the result of a problem with a protein called C1 esterase inhibitor.

There are three types of hereditary angioedema:

Type I

- 85% of cases[3]
- C1-INH is decreased or not present[4]

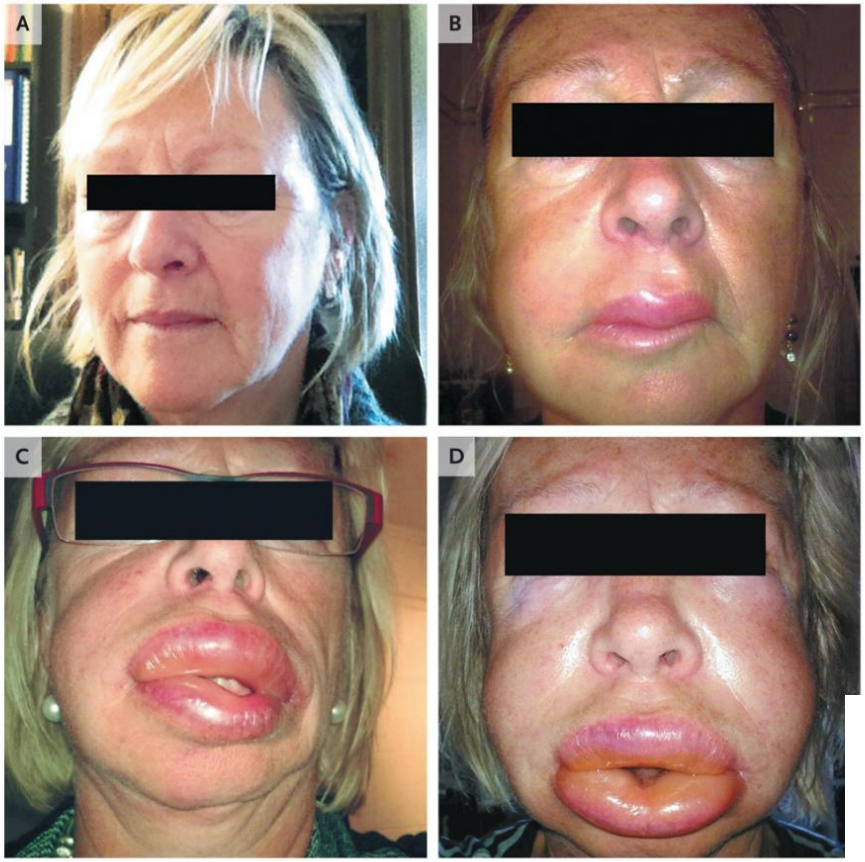
Type II

- 15% of cases[3]
- C1-INH is not working properly[4]

Type III

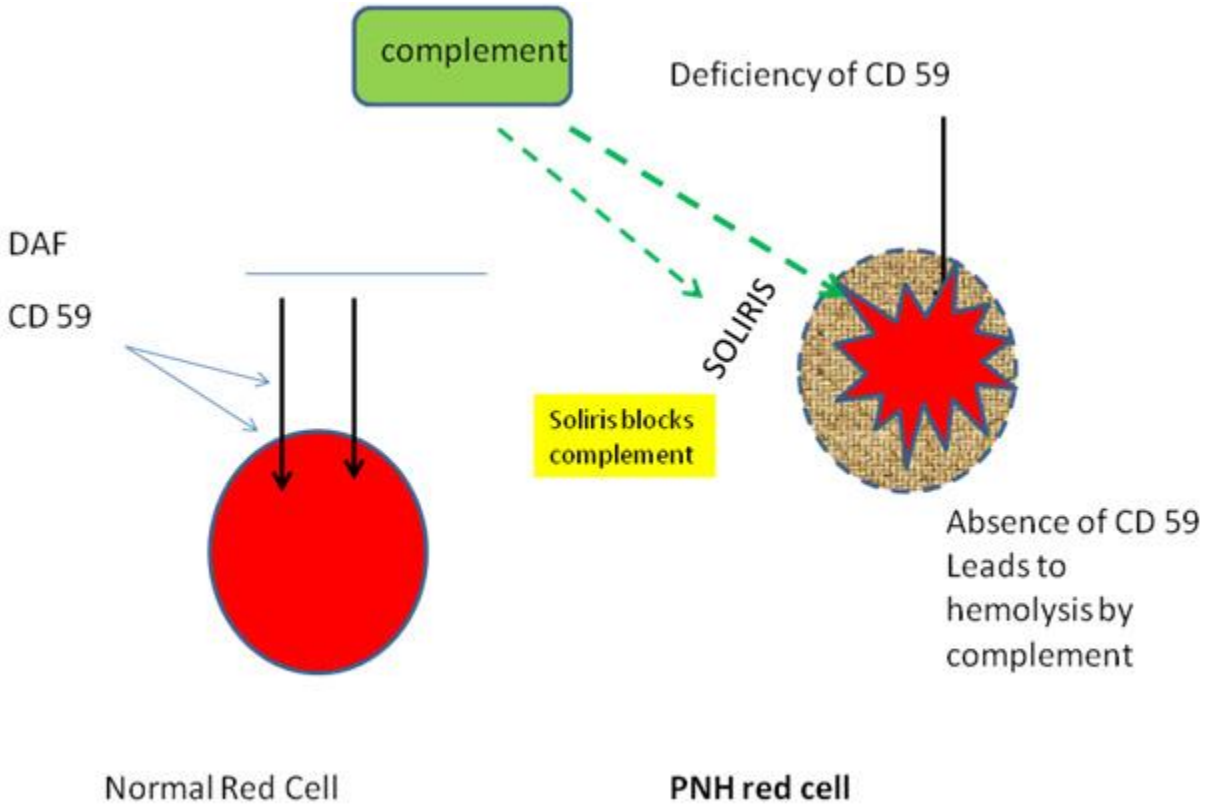
- Rare; prevalence is unknown[3]
- Diagnosed by genetic testing[4]

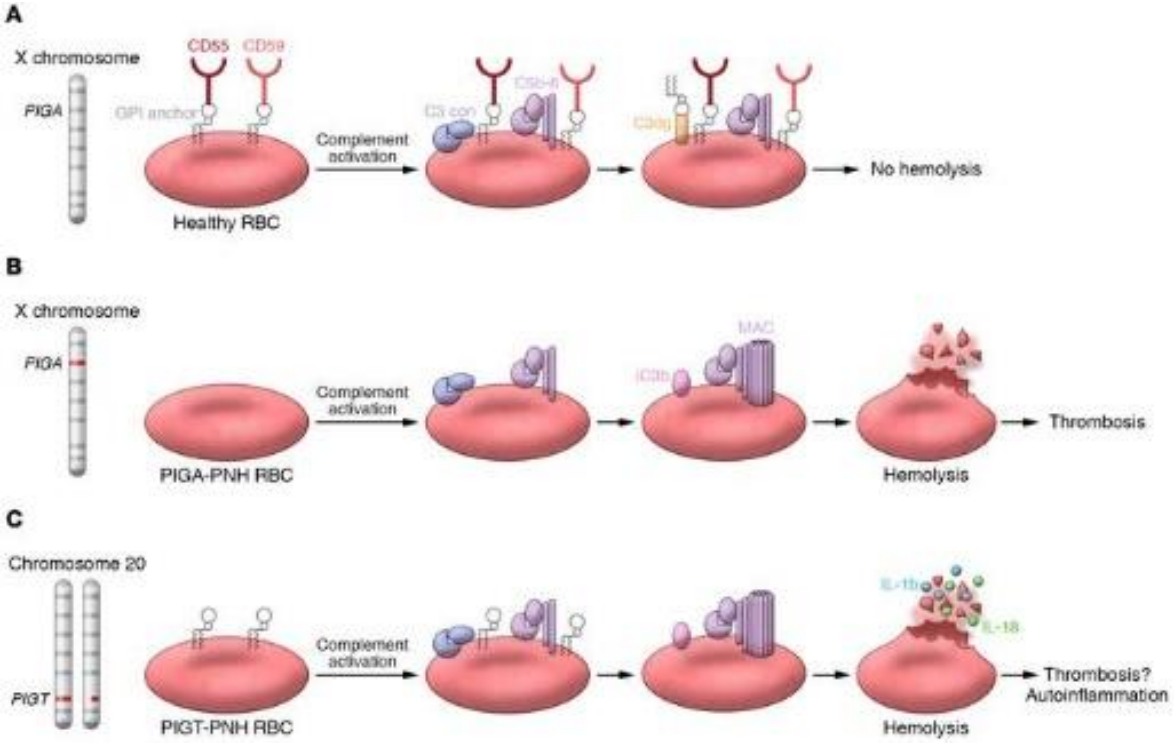
FIGURE 1. Progressive Swelling Resulting From Angioedema Attack[14]



Images used with permission. Ebo DG, Bridts CH. Images in clinical medicine. Disfiguring angioedema. *N Engl J Med*. 2012;367(16):1539. doi: 10.1056/NEJMicm1200960.

Paroxysmal Noctural Hemoglobinuria (PNH)




A
X chromosome
PIGA
CD55
CD59
GPI anchor
Healthy RBC
Complement activation
C3 con
C3b-H
C3(b)
No hemolysis
B
X chromosome
PIGA
PIGA-PNH RBC
Complement activation
MAC
(C3b)
Hemolysis
Thrombosis
C
Chromosome 20
PIGT
PIGT-PNH RBC
Complement activation
IL-1b
IL-18
Hemolysis
Thrombosis?
Autoinflammation

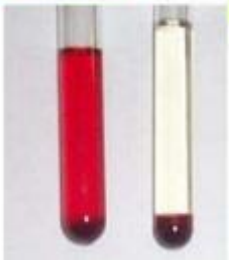
HAM'S TEST

【Principle】 The complement present in serum is responsible for lysis of PNH cells with sensitivity to acidifiction.

patient's red cells suspension

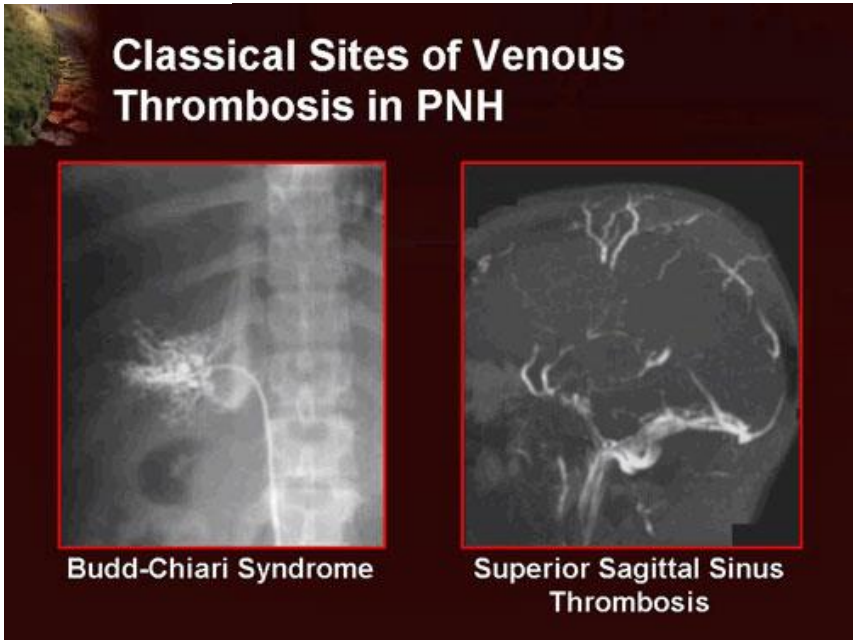
+

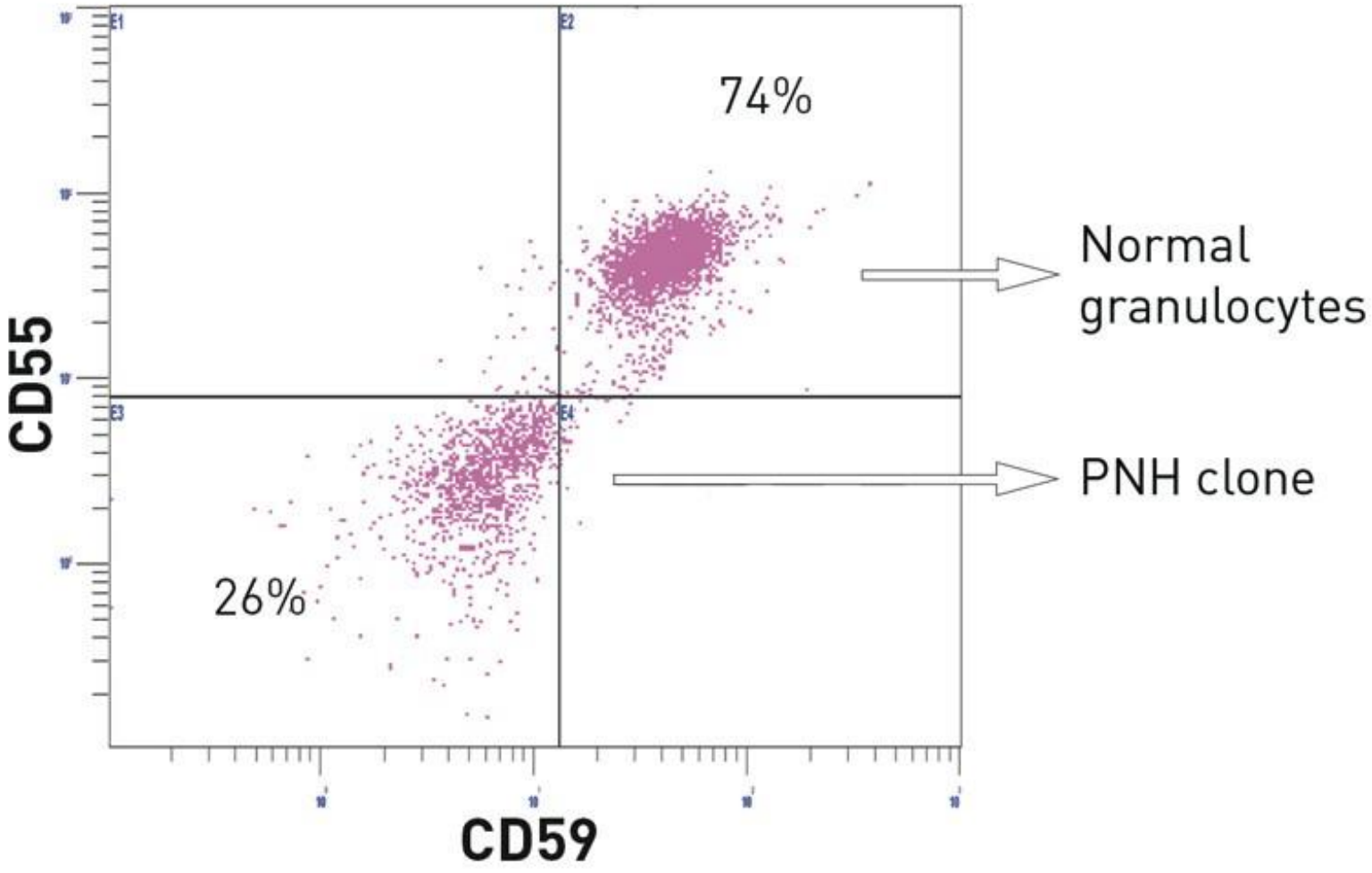
acidified pH6.5 , 37°C1h ⇨ mixed with fresh complement (same type control serum or patient's own serum)

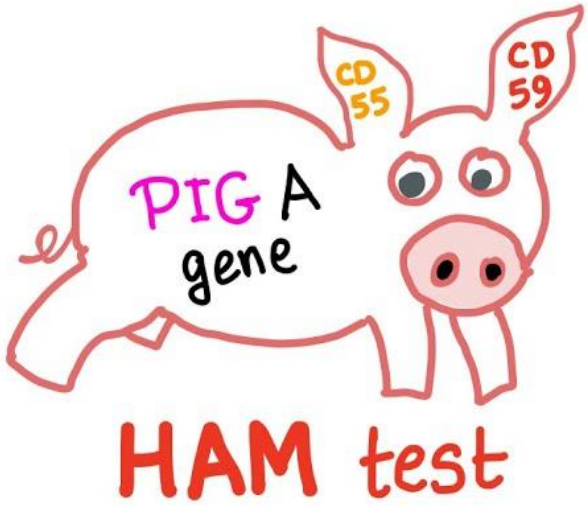


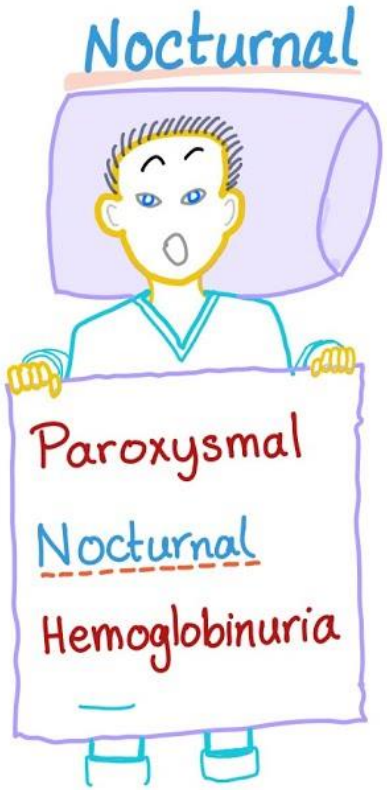
lysis: PNH

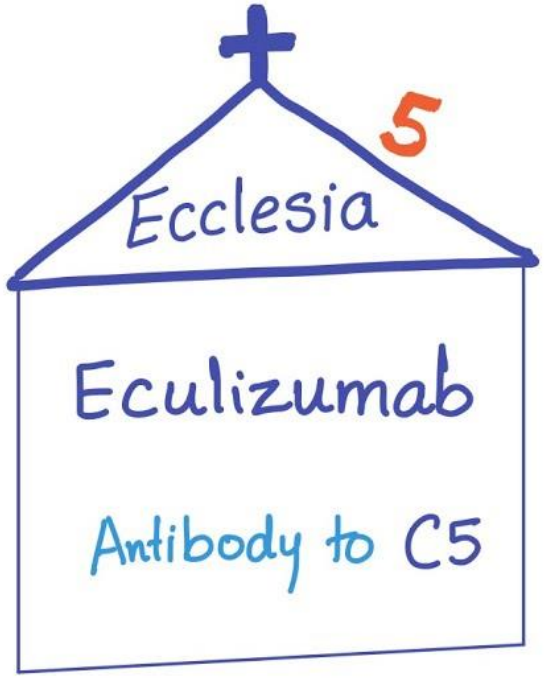
no lysis: normal or lack of PNH cells




74%
26%
CD55
CD59
Normal granulocytes
PNH clone


CD 55
CD 59
PIG A gene
HAM test


Nocturnal
Paroxysmal
Nocturnal
Hemoglobinuria


5
Ecclesia
Eculizumab
Antibody to C5

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

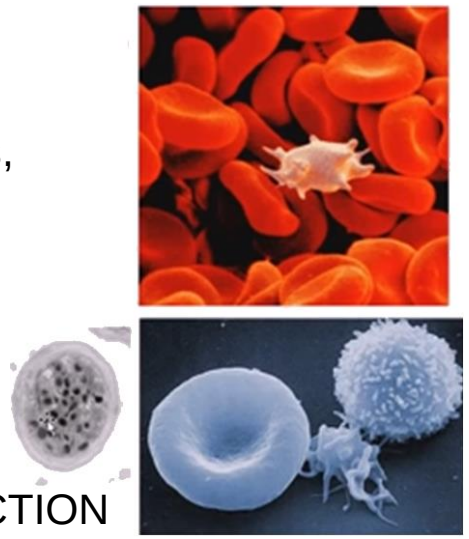
- Chemotaxis
- Vasoconstriction
- Increased Permeability

LIPOXINS

- INHIBIT chemotaxis
- Vasodilatation
- Counteract actions of leukotrienes

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

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



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

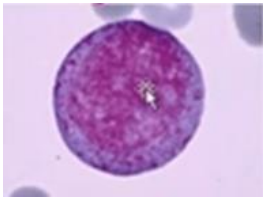
- **CHEMOKINES** are small proteins which are attractants for PMNs (>40)

NITRIC OXIDE

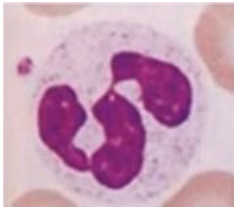
- Potent vasodilator
- Produced from the action of nitric oxide synthetase from arginine

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**

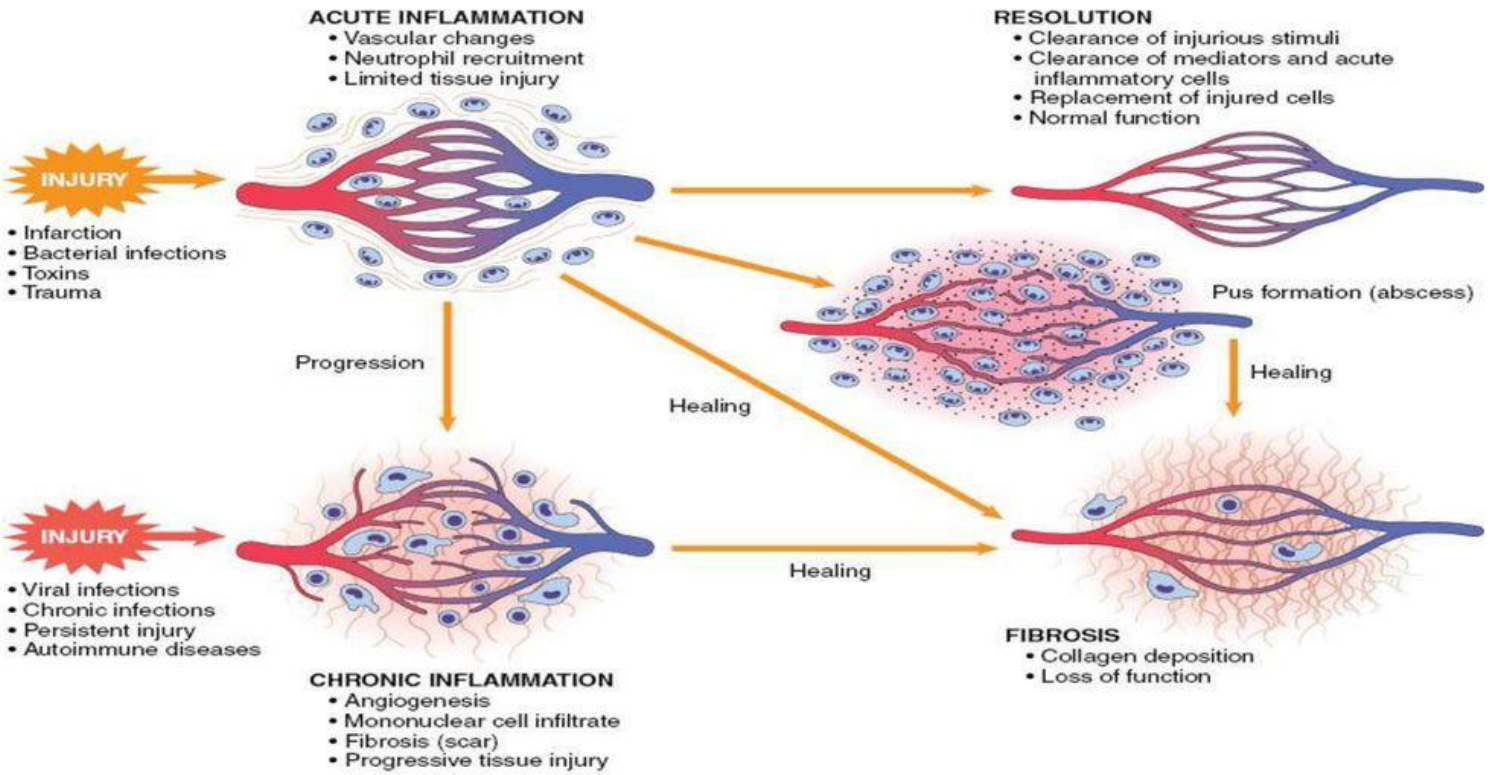
Systemic effects of inflammation
Acute phase response

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

The objectives of the lecture

1. The inflammatory cascade: understand the chain of vascular and cellular events in the natural history of acute inflammation
2. Understand the roles of humoral factors (chemical mediators) during acute inflammation
3. **Know the three possible outcomes of acute inflammation**
4. Describe the morphologic patterns of acute inflammation



OUTCOMES OF ACUTE INFLAMMATION

- 1) 100% (COMPLETE) RESOLUTION
- 2) SCAR
- 3) CHRONIC INFLAMMATION (next lecture!)

The objectives of the lecture

1. The inflammatory cascade: understand the chain of vascular and cellular events in the natural history of acute inflammation
2. Understand the roles of humoral factors (chemical mediators) during acute inflammation
3. Know the three possible outcomes of acute inflammation
4. **Describe the morphologic patterns of acute 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).

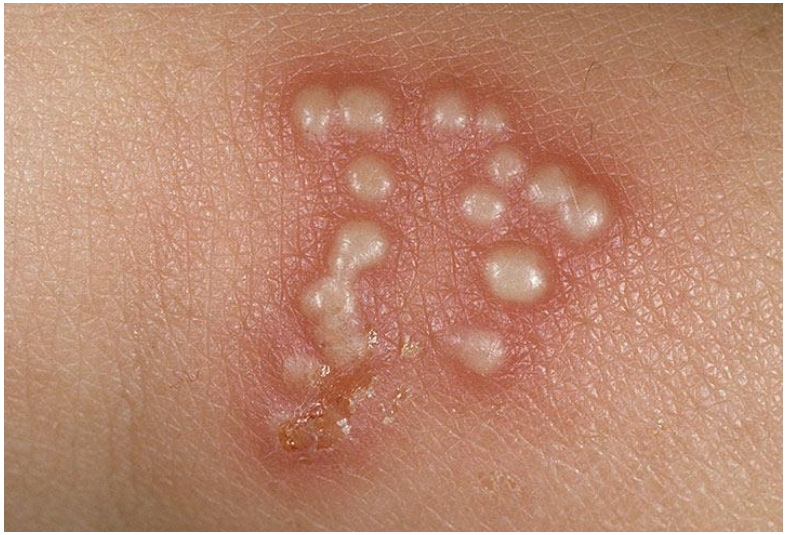
Biologic purpose of serous exudation: Immediate dilution of the noxious agent at the site of inflammation.

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.

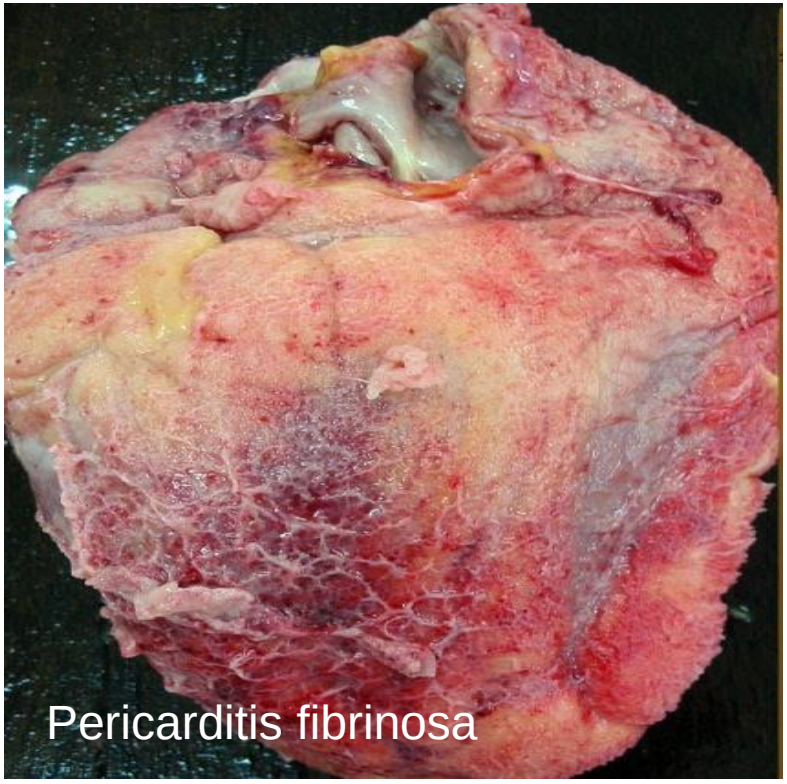
Examples for this type of inflammation!!!!!!!



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

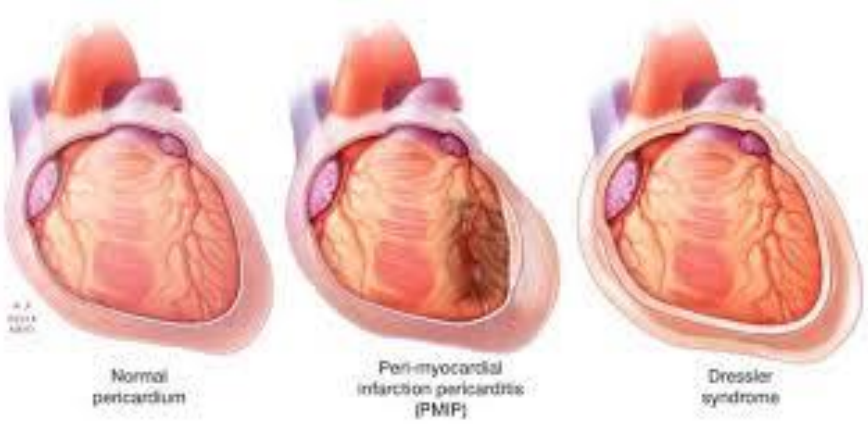
PSEUDOMEMBRANE results when the upper portion of a mucosal surface undergoes necrosis, freeing fibrinogen from vessels that then clots along the surface

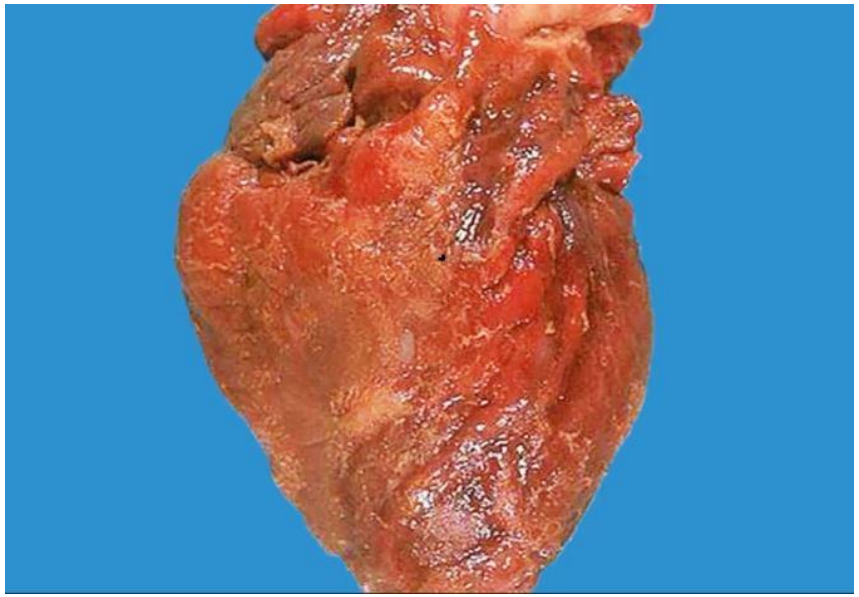
- diphtheria (in the upper airway) or antibiotic-induced pseudomembranous colitis (in the lower gut).

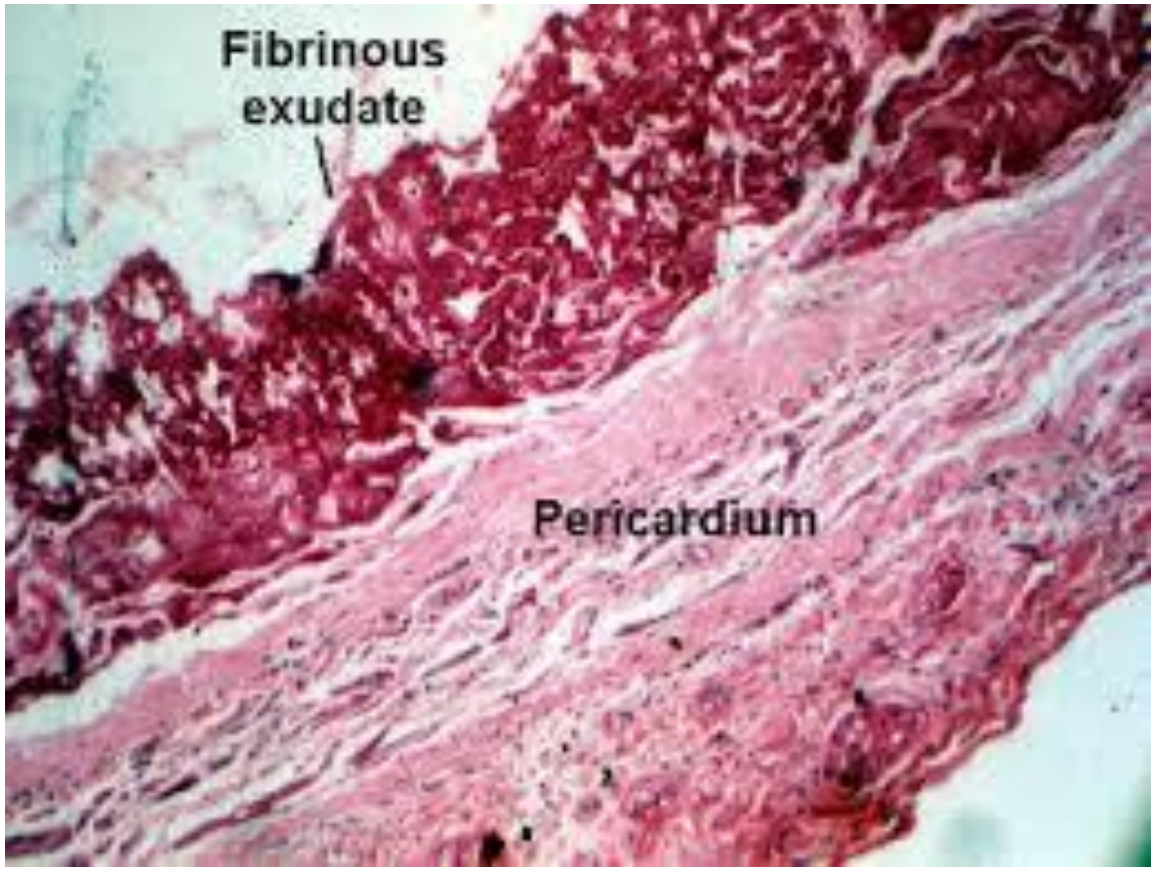

Tonsillitis follicularis

Dressler syndrome

(described by William Dressler in 1956)






Fibrinous
exudate
Pericardium

Classification of acute inflammation based on the exudate

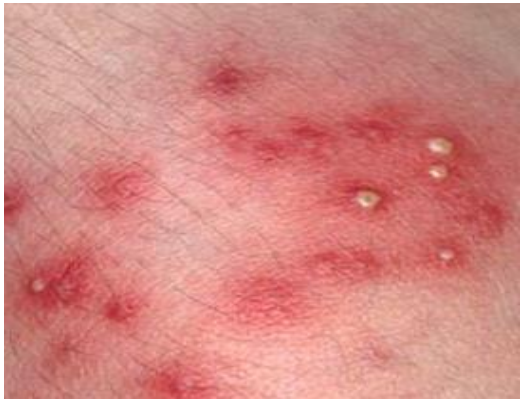
Purulent

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.

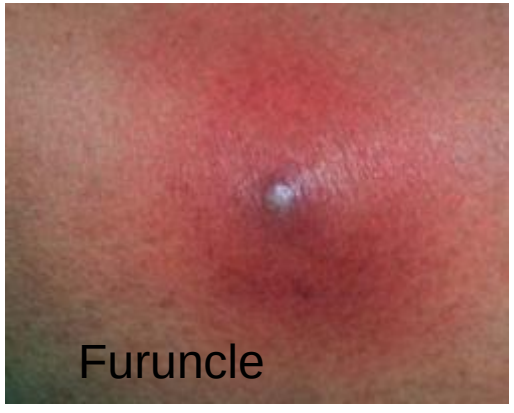
The **pus** which is the end product of this type of inflammation a whitish-yellow, yellow or yellow-brown exudate produced by vertebrates during inflammatory pyogenic bacterial infections. An accumulation of pus in an enclosed tissue space is known as an abscess, while a visible collection of pus within 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:

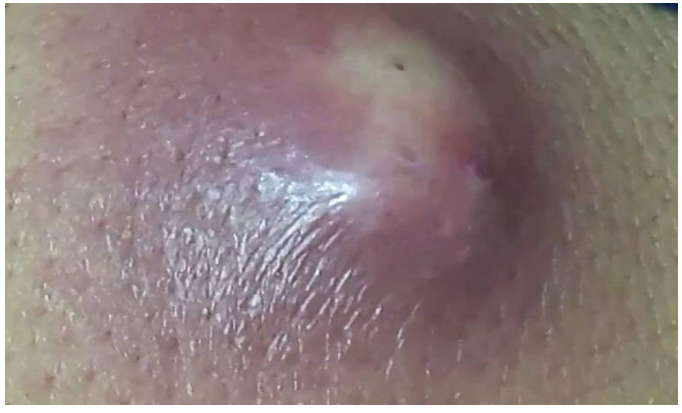
- Suppurative appendicitis
- Suppurative otitis
- Pyelonephritis
- Brain abscess
- Purulent meningitis
- Suppurative lymphadenitis



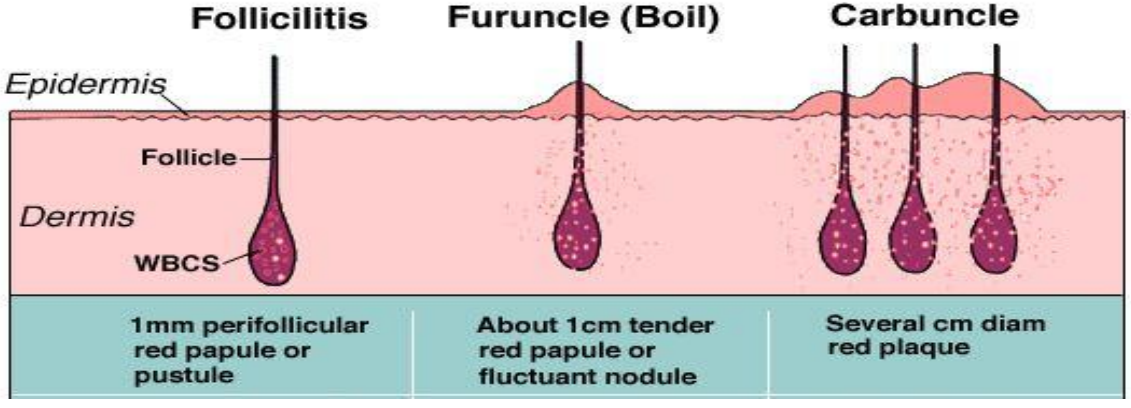
Folliculitis

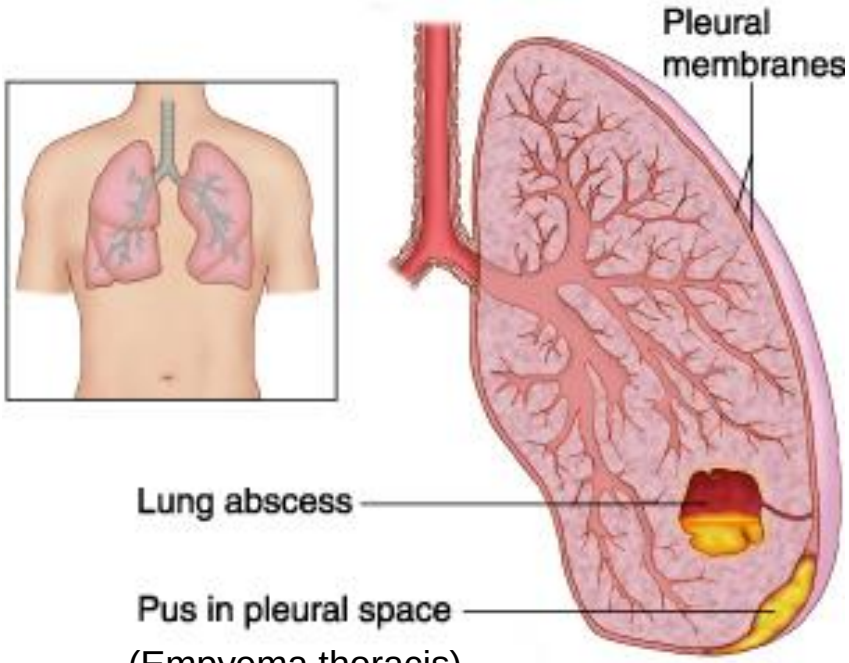


Furuncle

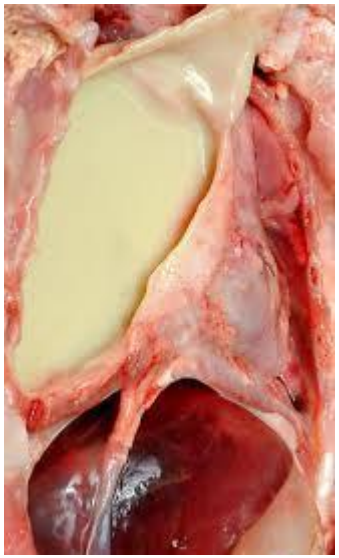


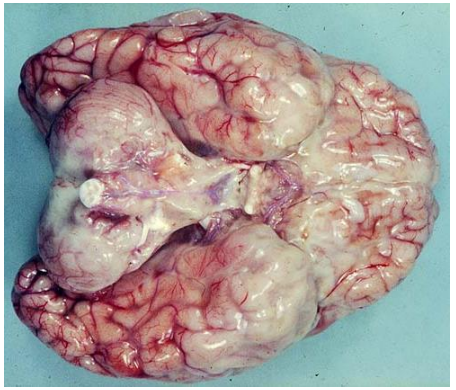
Carbuncle





(Empyema thoracis)

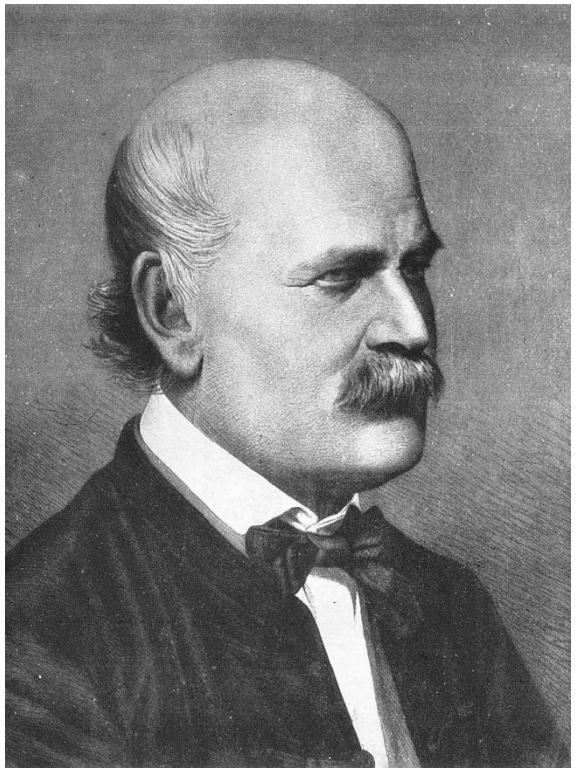

Empyema thoracis

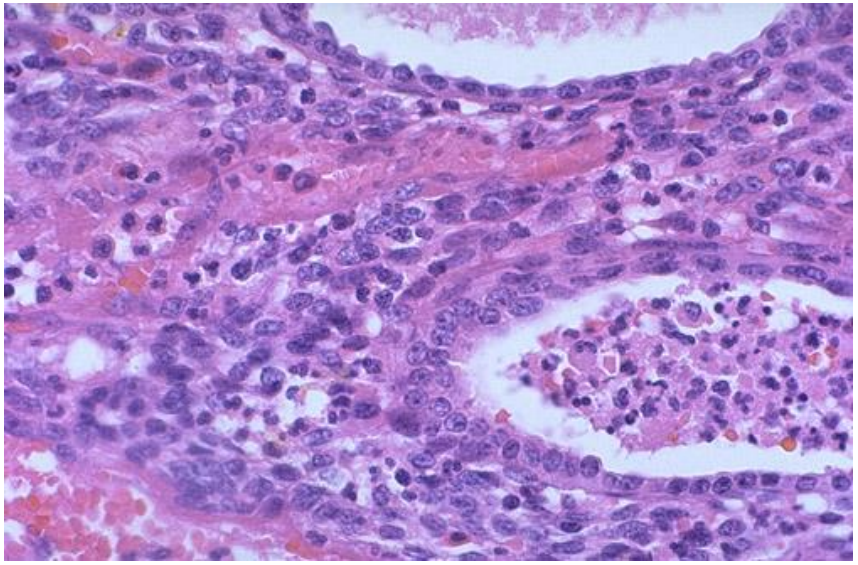

Meningitis purulenta


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

Sepsis puerperalis (childbed fever)

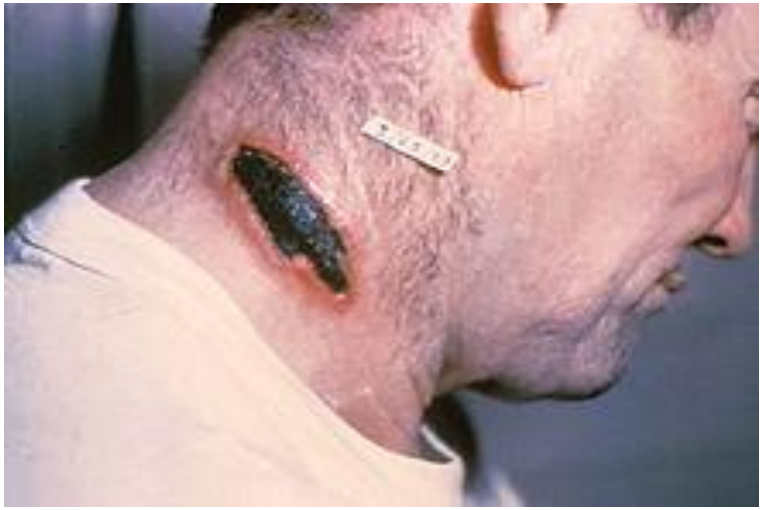




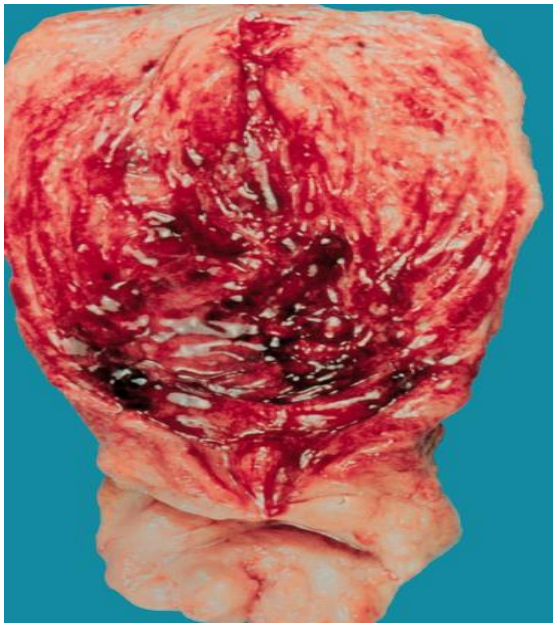
Ignác Semmelweis (1818-1865)

Semmelweis Museum of Medical History (his birthplace)

Haemorrhagic inflammation

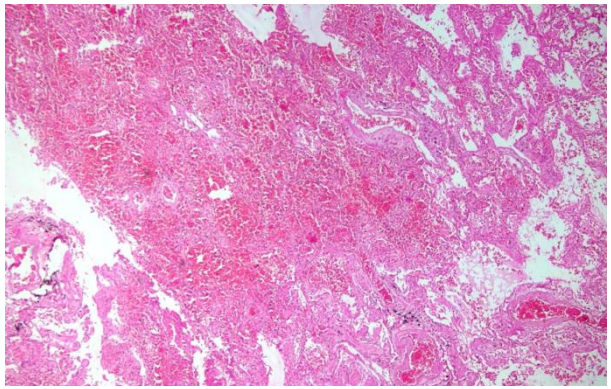


Skin anthrax



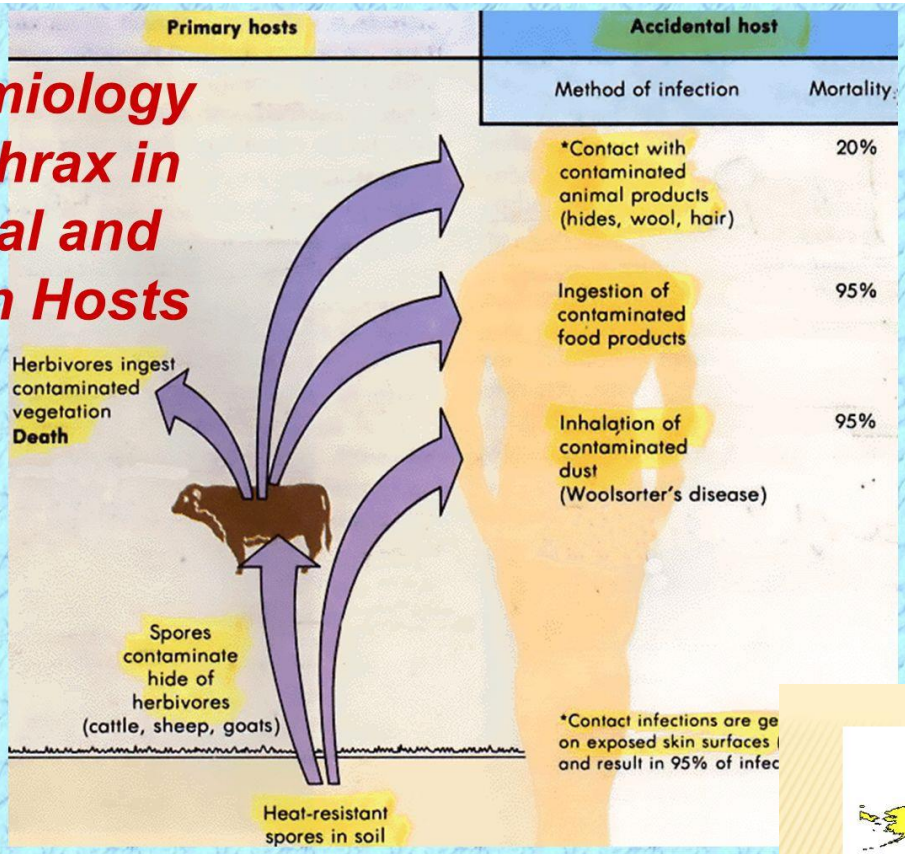
Urocystitis acuta

Variola vera

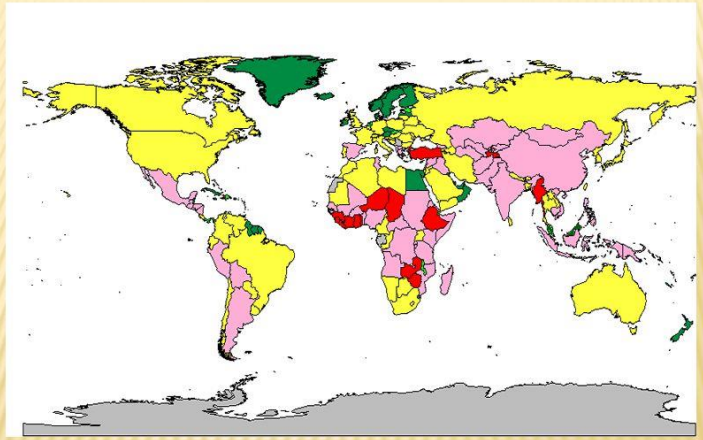


Influenza Virus Infections (lungs)

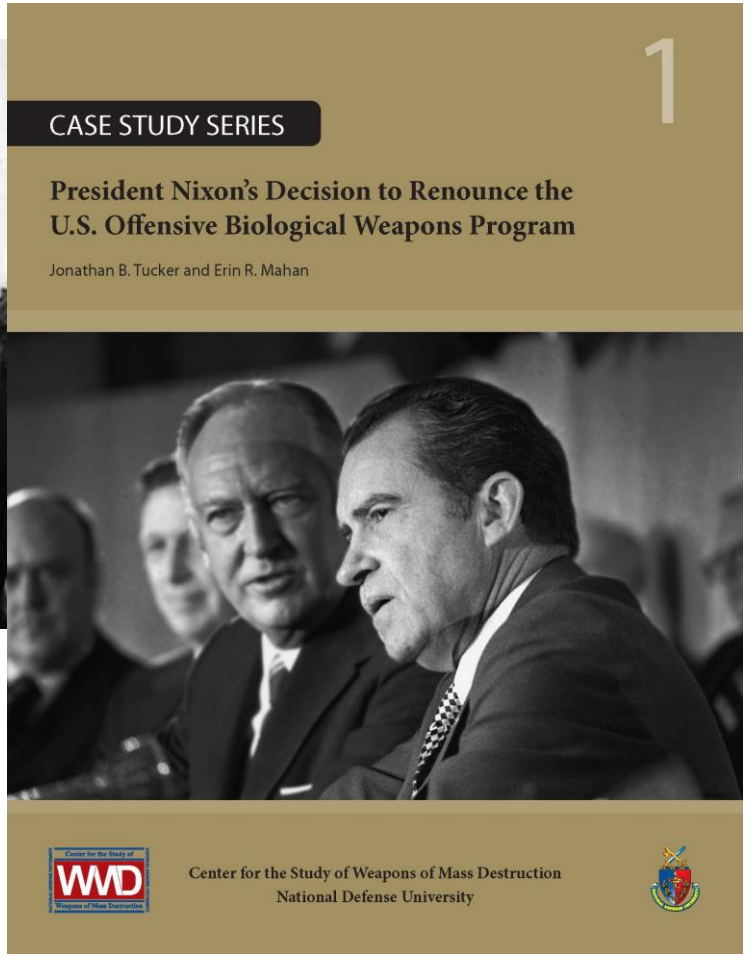
Epidemiology of Anthrax in Animal and Human Hosts



Distribution of anthrax in the world

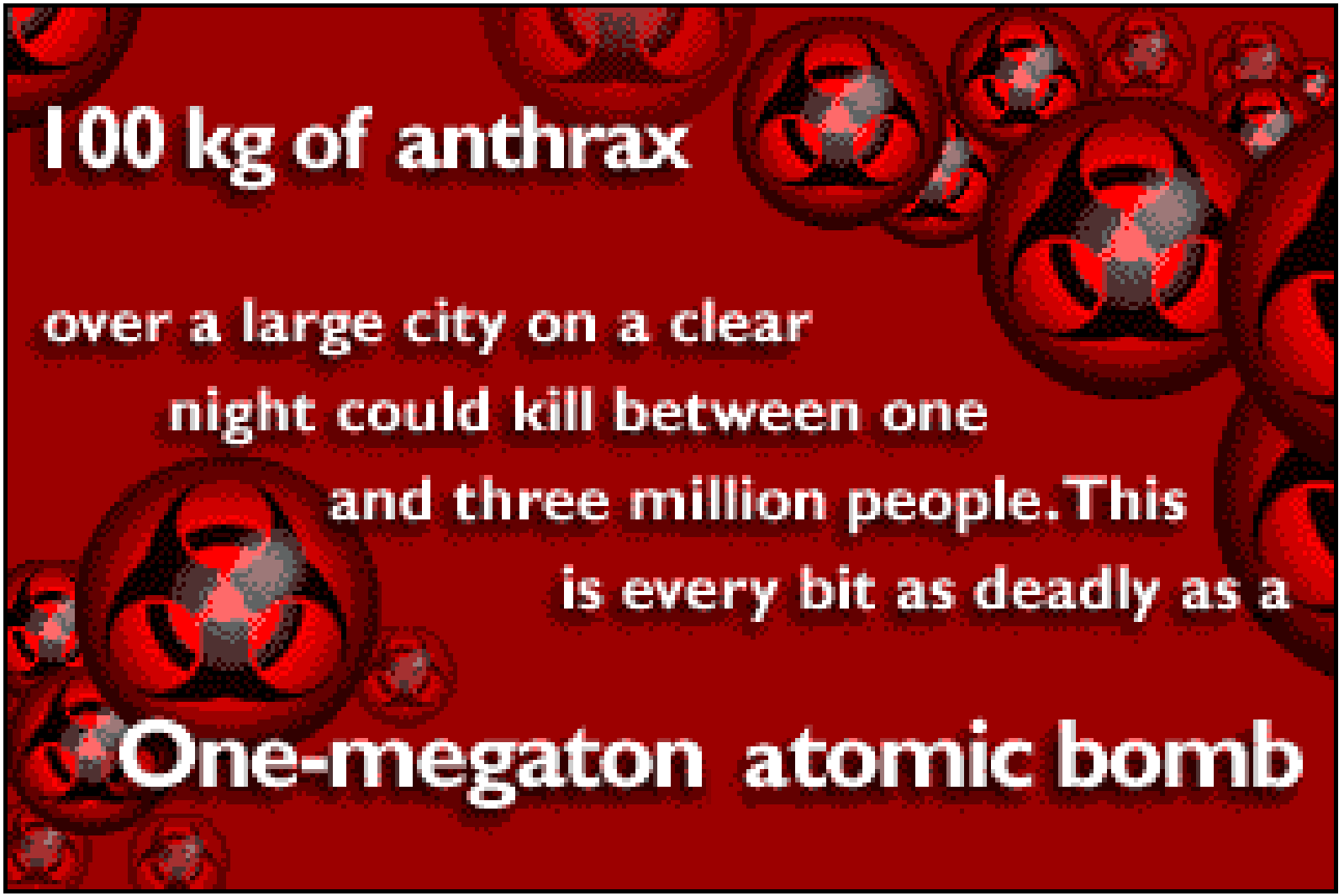


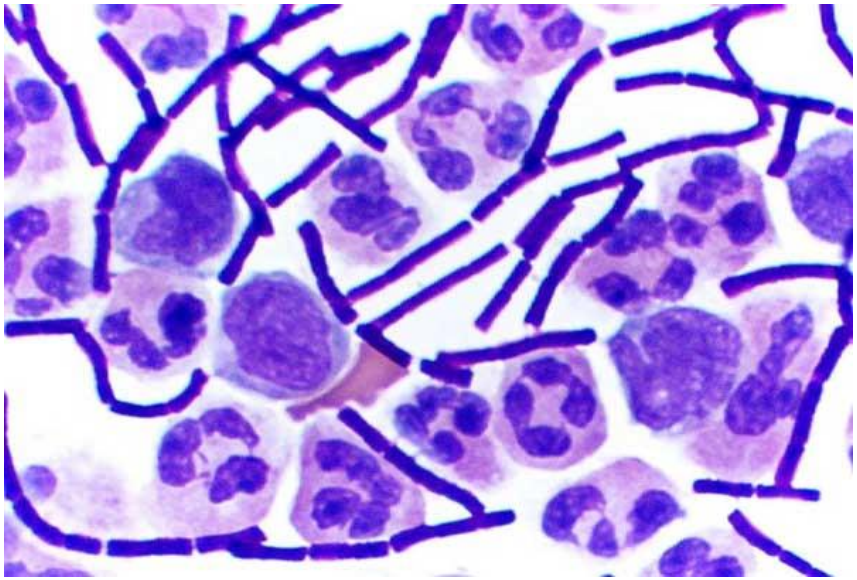
Anthrax as biological weapon

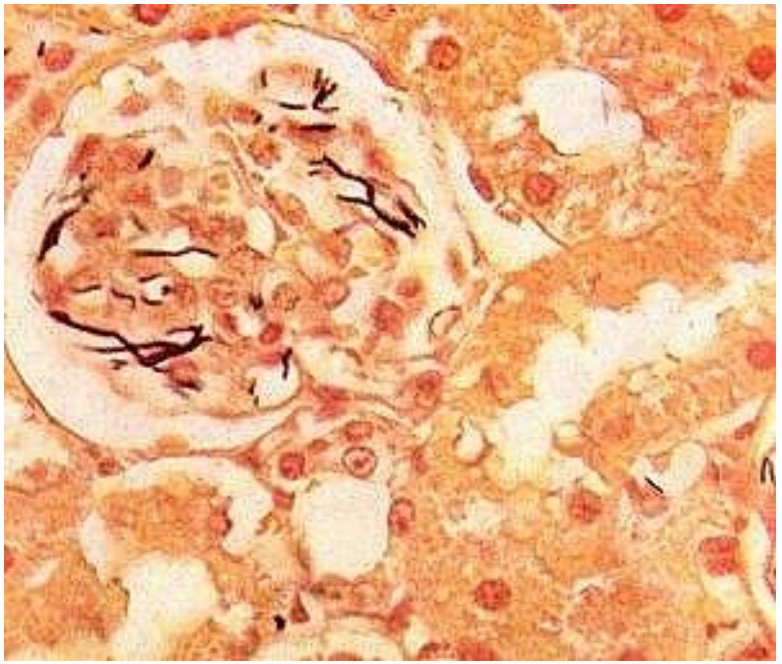


1979, Swerdlows (USSR), military research facility accidentally releases anthrax

Anthrax as tool for terrorists


100 kg of anthrax
over a large city on a clear
night could kill between one
and three million people.This
is every bit as deadly as a
One-megaton atomic bomb





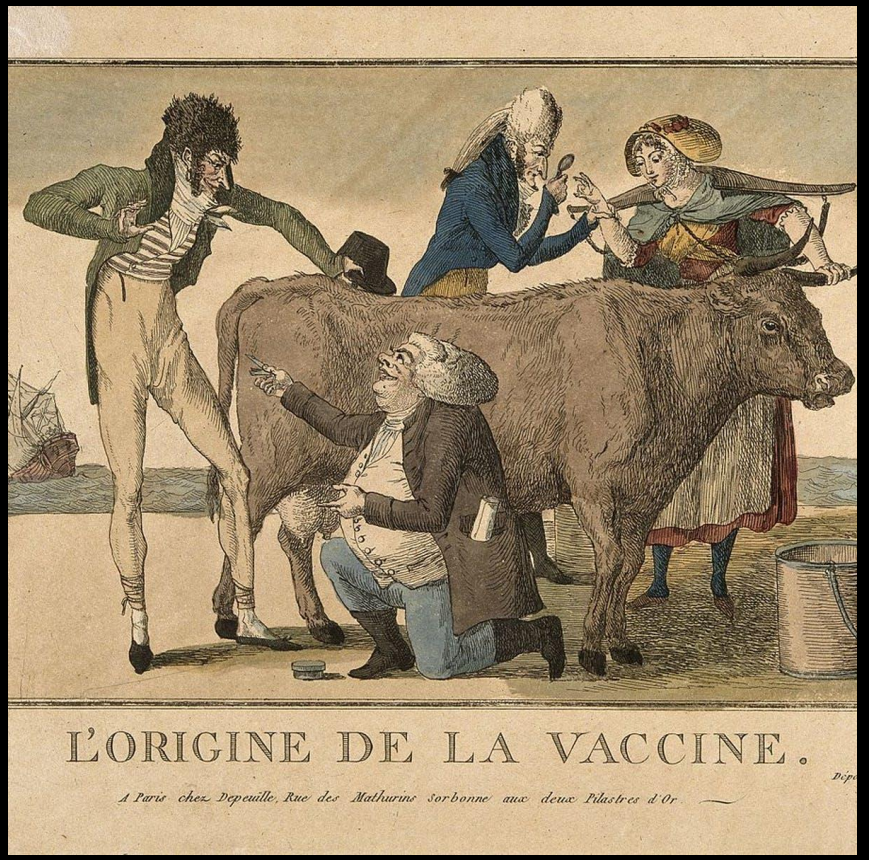
Smallpox: 12,000 years of terror!

Pharaoh Ramses V – 1196 B.C.

Believed to have died due to smallpox.

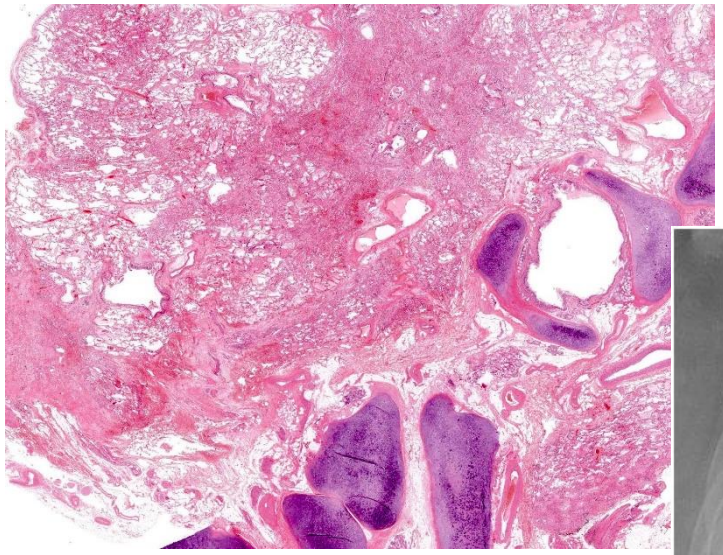
Pustular lesions were found on the face and body of the mummy.

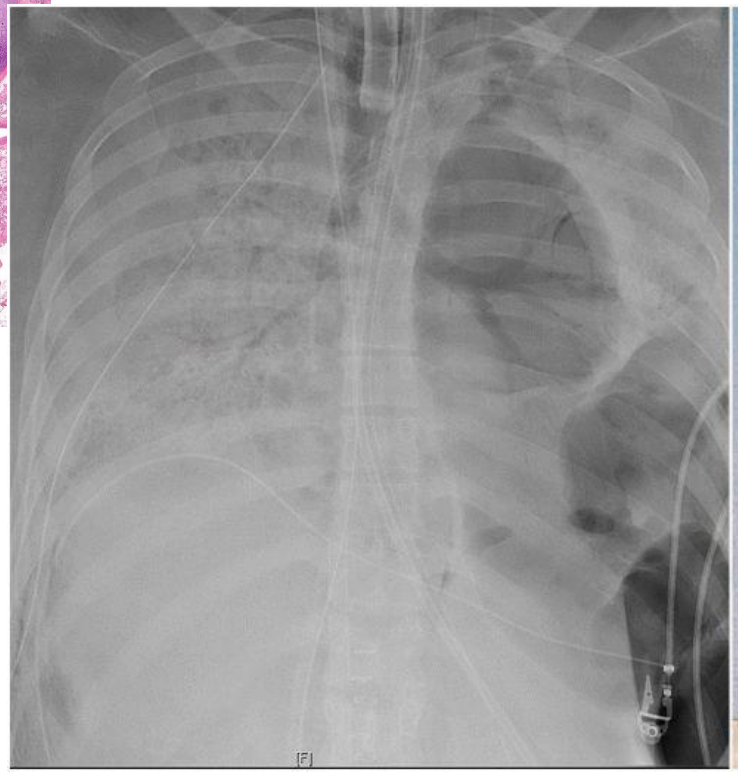

Edward Jenner M.D.

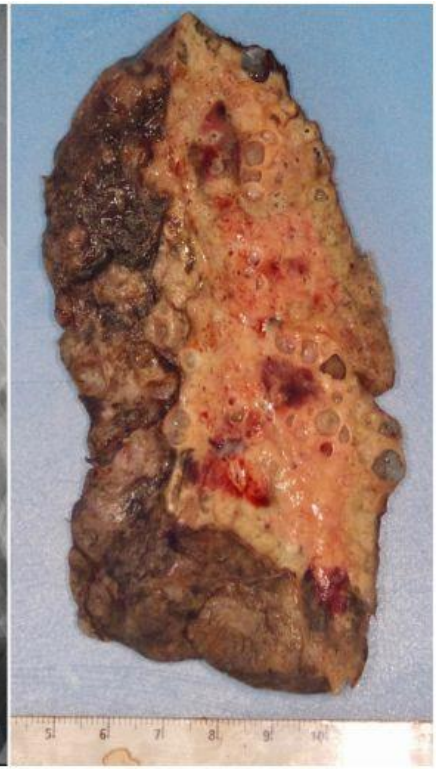

L'ORIGINE DE LA VACCINE.
A Paris chez Depeuille, Rue des Mathurins Sorbonne aux deux Pilastres d'Or

Variola vera (smallpox), eliminated in 1977
last outbreak was in Yugoslavia (1972)

COVID-19 (SARS-CoV-2)

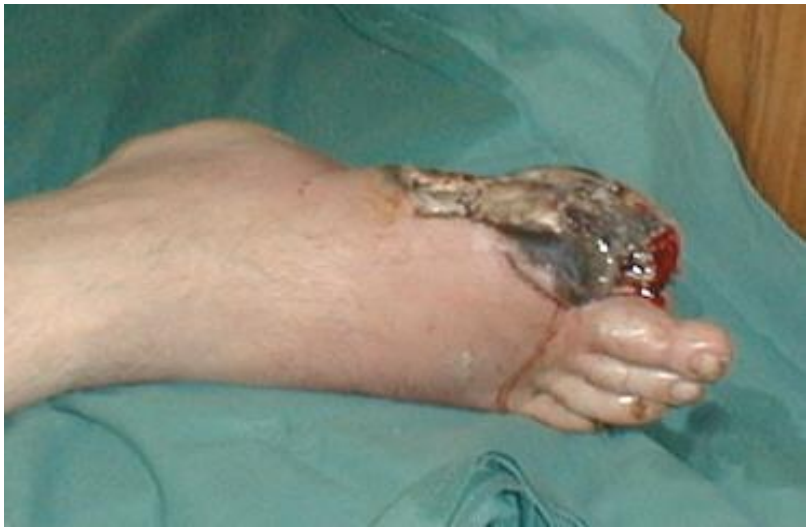




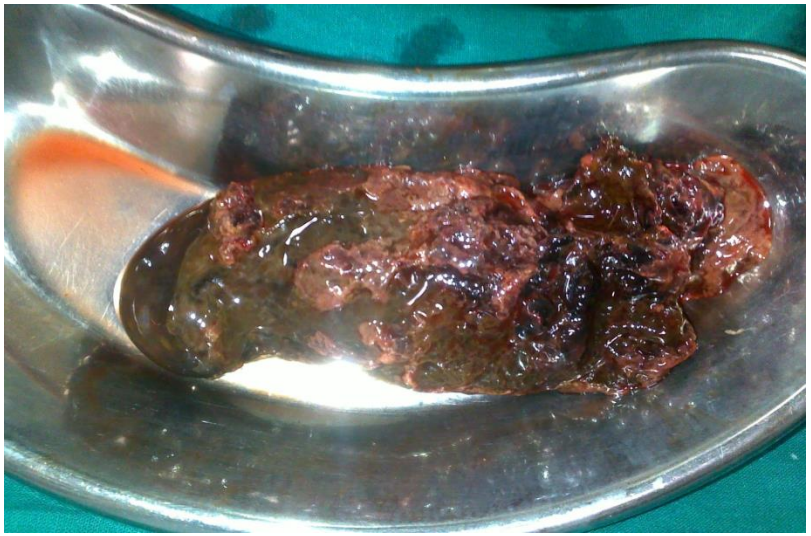


Necrotizing inflammation

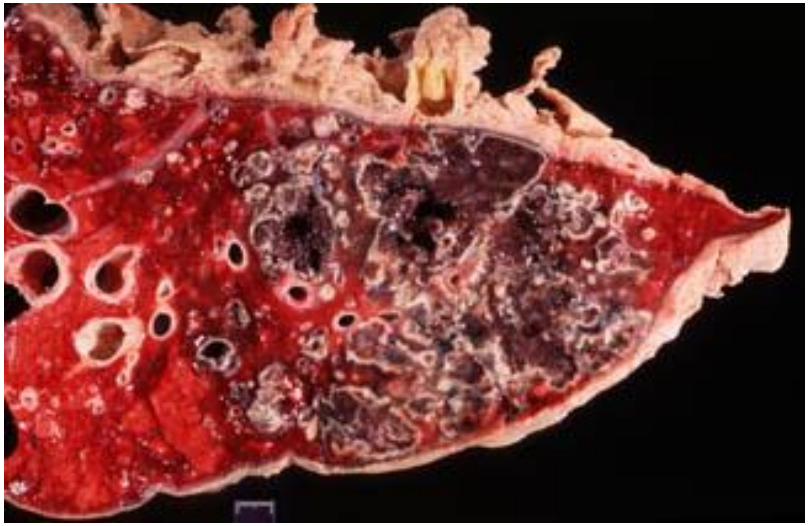
The combination of necrosis, inflammation and bacterial putrefaction is called gangrene.



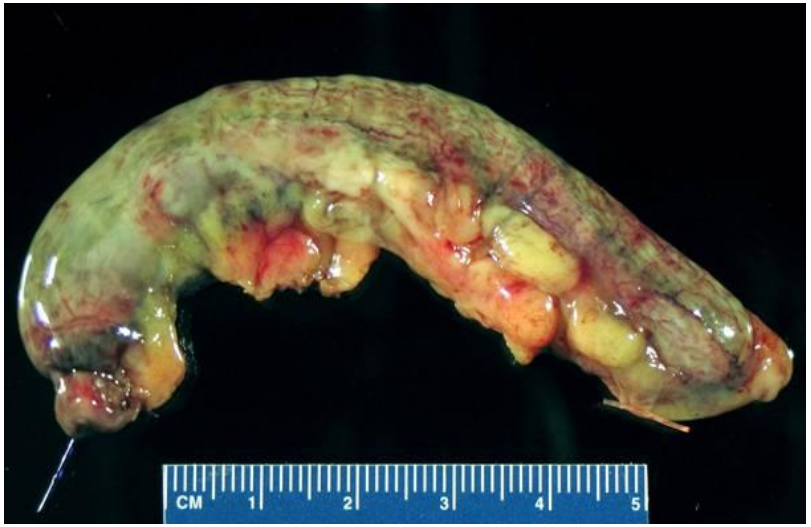
Gangrene



Cholecystitis acuta gangrenosa



Pneumonia gangrenosa

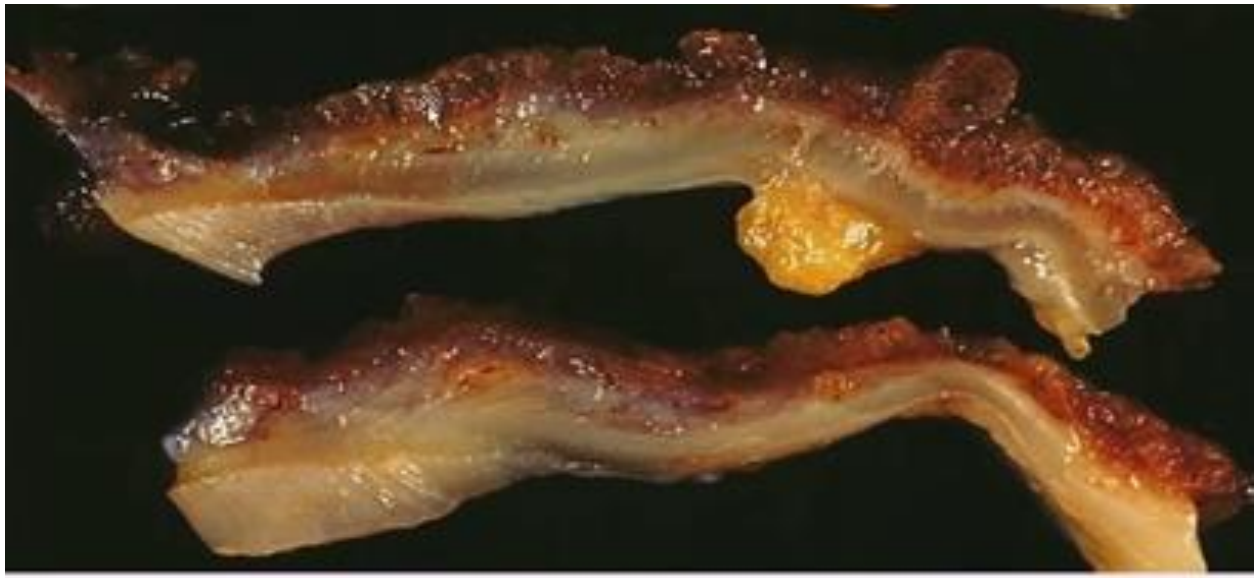


Appendicitis acuta gangrenosa

Classification of acute inflammation based on the exudate

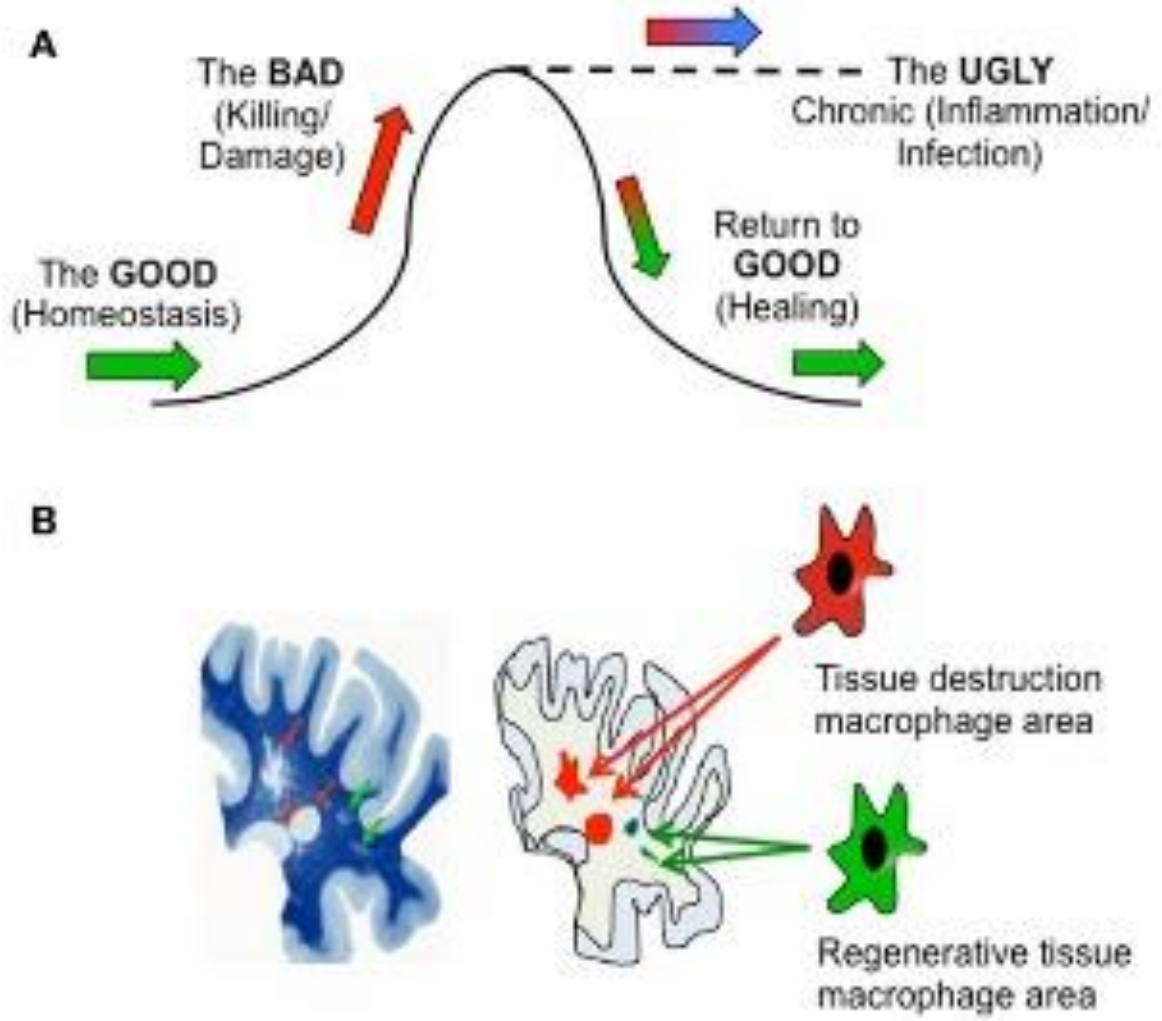
Ulcerative

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

INFLAMMATION


A
The BAD
(Killing/
Damage)
The UGLY
Chronic (Inflammation/
Infection)
The GOOD
(Homeostasis)
Return to
GOOD
(Healing)
B
Tissue destruction
macrophage area
Regenerative tissue
macrophage area