Injury, inflammation, healing and repair.

Markéta Hermanová

General features of inflammation

- A benefitial host response to foreign invadors and necrotic tissue; but itself capable of causing tissue damage

- Main component of inflammation: **vascular reaction** (vascular and exudative phase) and a **cellular response** (activated by mediators of inflammation derived from plasma protein and various cells)

- **Inflammatory response (5 Rs):**
  - Recognition of the injurious agent
  - Recruitment of leukocytes
  - Removal of the agent
  - Regulation of the response
  - Resolution (repair)

- **Outcome of acute inflammation:**
  - Elimination of the noxious stimulus, decline of the reaction, resolution-repair
  - Persistent injury resulting in chronic inflammation
  - Extensive destruction of the tissue resulting in scarring

Acute inflammation: rapid response to injury or microbes and other foreign substances

Stimuli for acute inflamation:

- Infections (bacterial, viral, fungal, parasitic)
- Trauma and physical and chemical agents
- Tissue necrosis (e.g. ischamic infarctions)
- Foreign bodies
- Immune reactions (=hypersensitivity reactions) against environmental substances or against self tissues → immune-mediated inflammatory disease

Macroscopis appearance of acute inflammation (Celsus signs)

- Redness (rubor)
- Heat (calor)
- Swelling (tumor)
- Pain (dolor)
- Loss of function (function laesa)

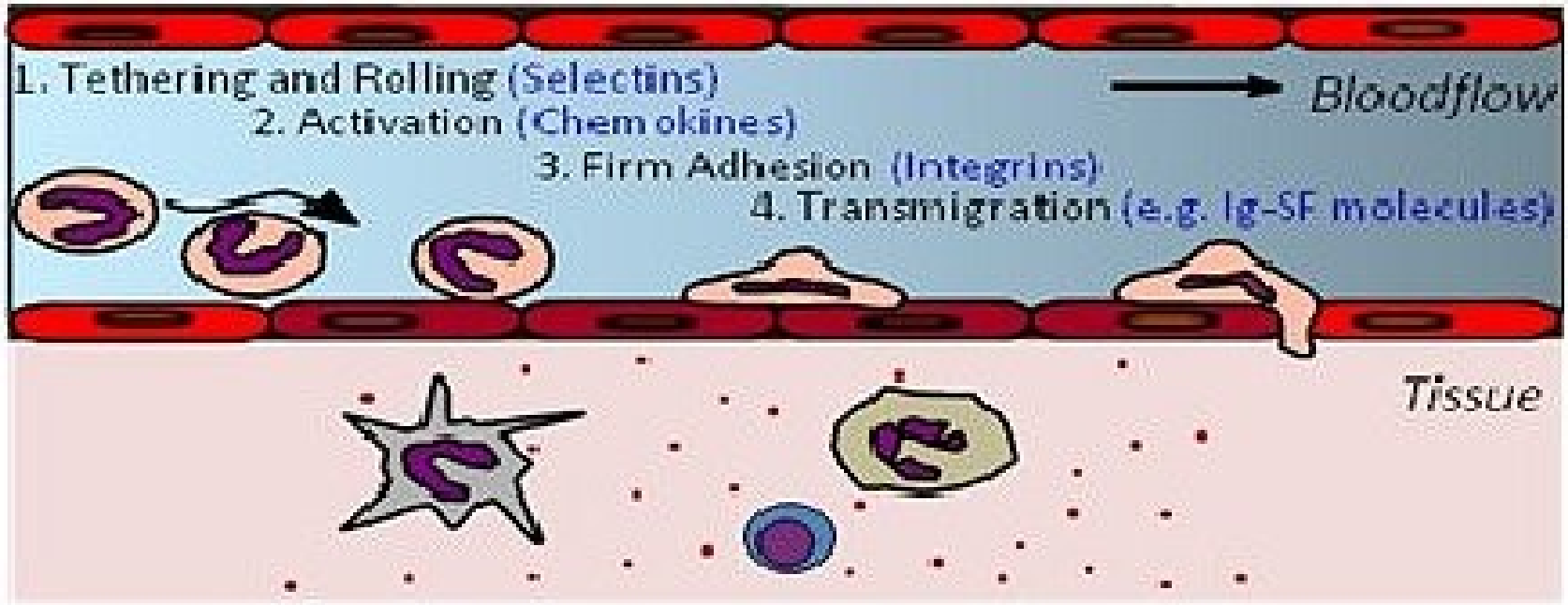
Early stages of acute inflammation

- **Changes in vascular caliber and flow**
  - *vasodilatation* – induced by chemical mediators (e.g. histamin) – causes *erythema* and *stasis*

- **Increased vascular permeability and formation of the protein rich fluid exudate**
  - induced by histamine, kinins, … → gaps between endothelial cells (by direct or leukocyte induced injury, by increased passage through the epithelium)

- **Formation of the cellular exudate**
  - Leukocytes recruited from the blood into extravascular tissues – migrate to the site of infection or tissue injury – are activated to perform their functions
  - Neutrophils predominate in the early inflammatory infiltrate and are later replaced by macrophages

- **Responses of lymphatic vessels**
  - increased lymph flow; secondary (reactive) lymphangitis, lymphadenitits



Lymphocyte

Granulocyte

Inflammatory macrophage

Proinflammory Cytokines

Quiescent endothelium

Activated endothelium

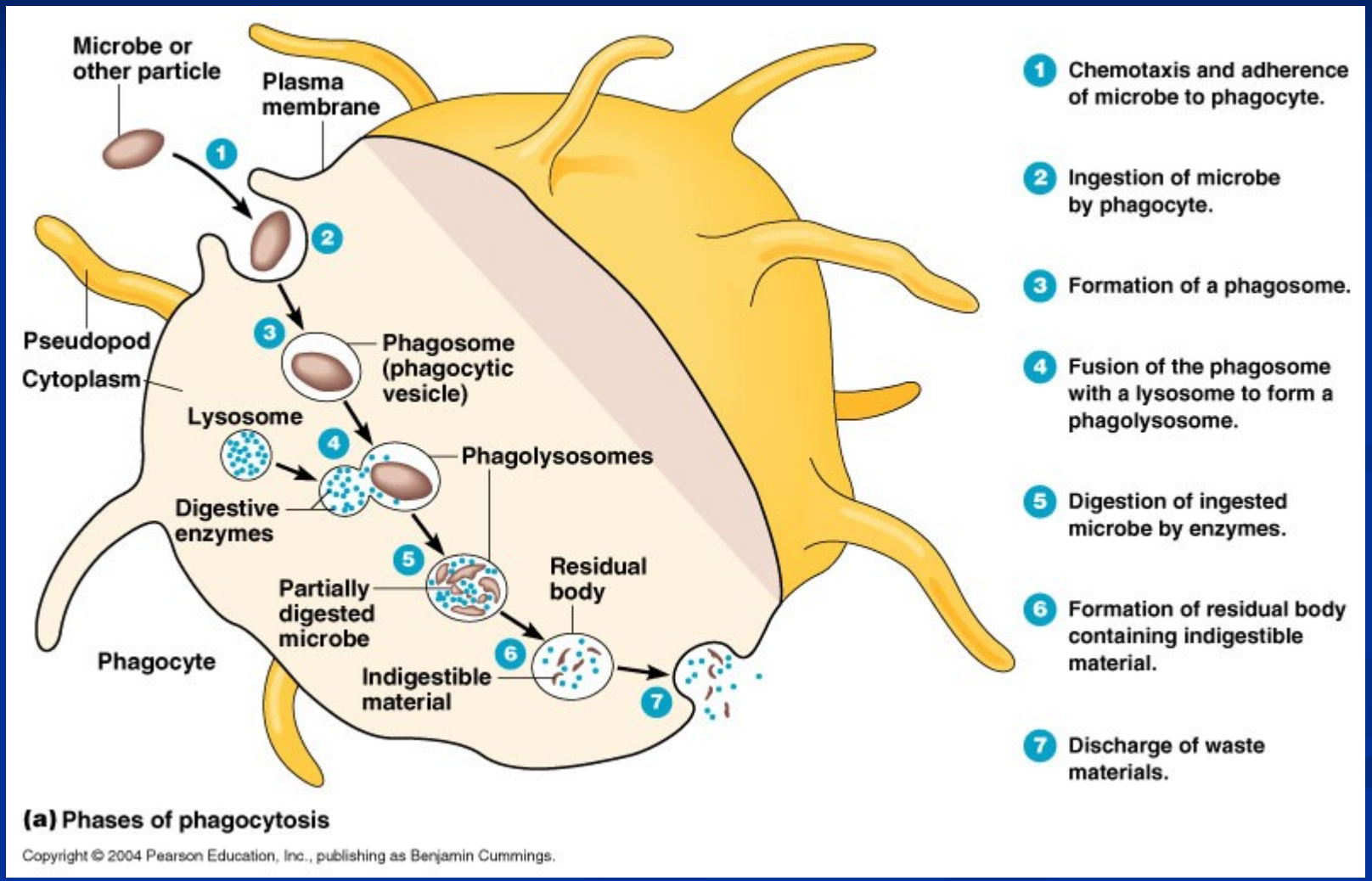
Leukocyte effector function

- Leukocytes eliminate microbes and dead cells by phagocytosis (with destruction on phagolysosomes)
- Destruction caused by free radicals (ROS, NO) generated in activated leukocytes and lysosomal enzymes
- Enzymes and ROS may be released into the extracellular environment
- Inflammation is also capable of damaging normal tissues (the pathologic consequences of inflammation)

Phagocytosis

- Recognition and attachment of the particle to the ingesting leukocyte
- Engulfment , with subsequent formation of phagocytic vacuole
- Killing and degradation of the ingested material

Phagocytosis



(a) Phases of phagocytosis

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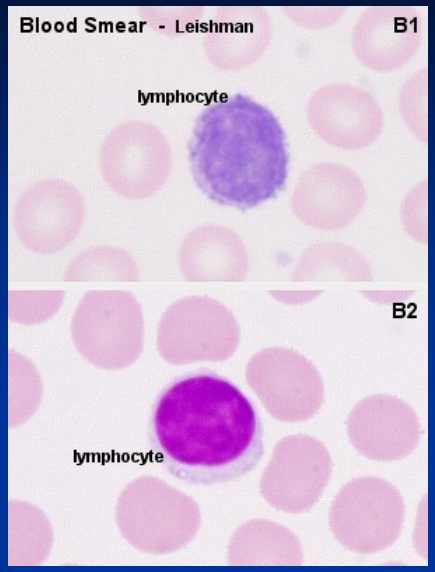
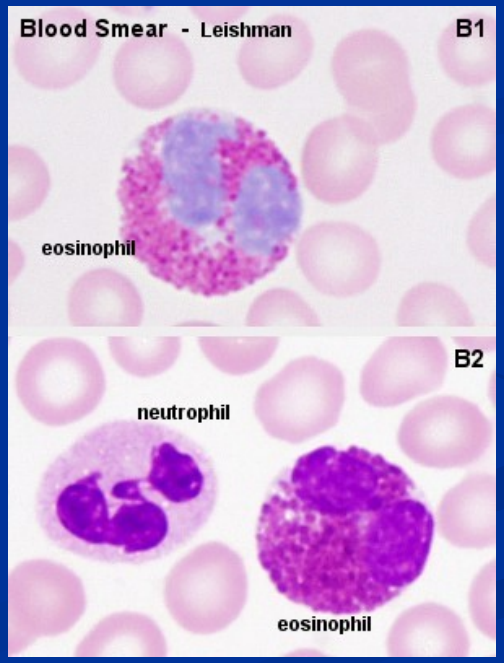
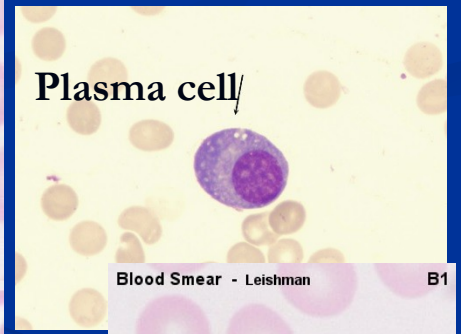
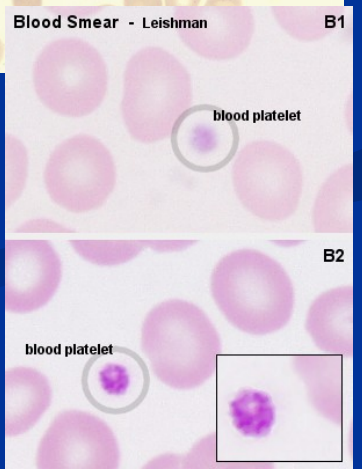
Cells involved in inflammation – components of cellular exudate

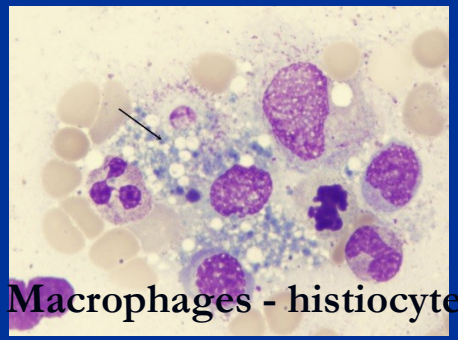
- Leukocytes – neutrophils
- Eosinophils, basophils
- Lymphocytes
- Plasma cells
- Macrophages
- Heparinocytes, mast cells
- Platelets
- Fibroblasts
- Erythrocytes

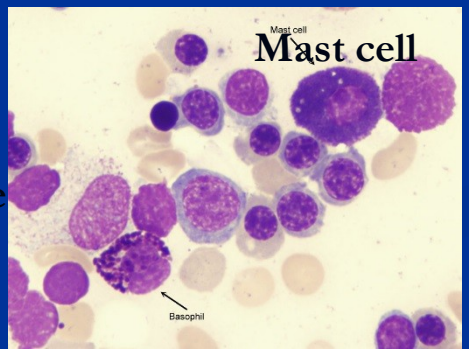












Mediator	Source	Principal action
Cell-derived		
Histamine	Mast cells, basophils, platelets	VD, ↑permeability, ↑endotel. activation
Serotonine	Platelets	VD, ↑permeability
Prostaglandins	Mast cells, leukocytes	VD, pain, fever
Leukotriens	Mast cells, leukocytes	↑permeability,CHT,leu adhesion+activ.
Platelet-activating factor	Leukocytes, endothelial cells	VD, ↑P, leu adhesion+activ., CHT,degranulation,...
Nitric oxide	Endothelium, macrophages	vascular SM relax., microbes killing
Cytokines (TNF, IL-1)	Leukocytes	↑endotel. activation, systemic acute phase damage
Reactive oxygen species	Macrophages, lymphocytes,..	Microbes killing,tissue damage
Chemokines	Leukocytes, macrophages	CHT, leu activation
Plasma protein-derived		
Complement	Plasma (produced in liver)	Chemotaxis,opsonization,VD
Kinins	Plasma	↑permeability, VD, pain,…
Proteases activated during coagulation	Plasma	Endothelial activation, leukocyte recruitment

Major cell-derived mediators of inflammation – summary:

- **Vasoactive amines: histamine, serotonine**; VD, ↑permeability
- **Arachidonic acid metabolites: prostaglandines and leukotriens;** vascular reaction, chemotaxis,…
- **Cytokines: IL-1, TNF, chemokines,…;** multiple effects in leukocytes recruitment and migration
- **Reactive oxygen species:** tissue damage, microbial killing
- **Nitric oxide:** VD, microbial killing
- **Lysosomal enzymes:** microbial killing, tissue damage

Plasma protein-derived mediators of inflammation

- **Complement proteins:**

  activation of complement→generation of multiple breakdown products→chemotaxis, opsonization, phagocytosis, cell killing

- **Coagulation proteins:**

  activated factor XII triggers: clotting, kinin and complement cascades, fibrinolytic system

- **Kinins:**

  produces proteolytic cleavage of precursors; mediate vascular reaction, pain

Inflammation – microscopic appearance

- ALTERATION:
  - tissue damage - regressive changes, necrosis
- EXUDATION:
  - vascular leakage of protein-rich fluid and blood cells

Inflammation – microscopic appearance

- PROLIFERATION:
  - proliferation of fibroblasts and capillaries
  - formation of granulation and fibrous tissue

- IMMUNE RESPONSE:
  - antigen presentation
  - T and B-lymphocytes reaction
  - production of antibodies by plasma cells
  - memory cells

Classification of inflammation:

- acute
- chronic

- non-specific (non-granulomatous)
- granulomatous

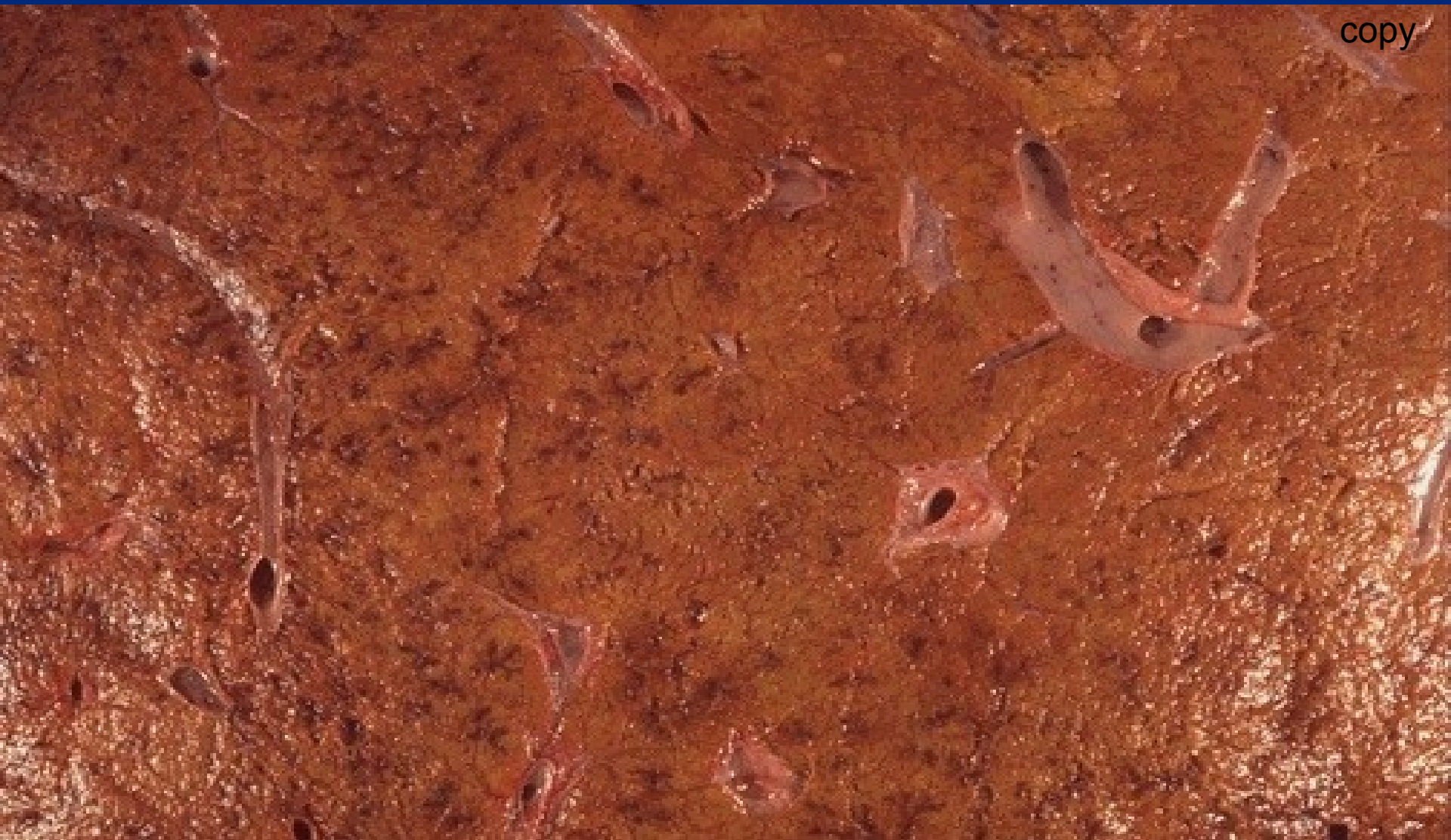
NONSPECIFIC inflammation

Classification:

- alterative:
  - alteration of tissue dominates
  - ***viral hepatitis, prion diseases [Creutzfeld-Jacob, BSE], diphteric myocarditis***
- exudative:
  - most common, exudation prevails
  - superficial and deep, interstitial
  - ***serous and catarrhal, fibrinous, nonpurulent, purulent, gangrenous***
- proliferative:
  - formation of fibrous tissue

Alterative inflammation

(liver necrosis)



Exudative inflammation

- **topography of inflammatory changes:**
  - ⇨superficial (mucous membrane, serous membranes, skin)
  - ⇨deep (interstitium)

- **exudate components:**
  - ⇨serous
  - ⇨fibrinous
  - ⇨nonpurulent
  - ⇨purulent
  - ⇨gangrenous

Exudative inflammation

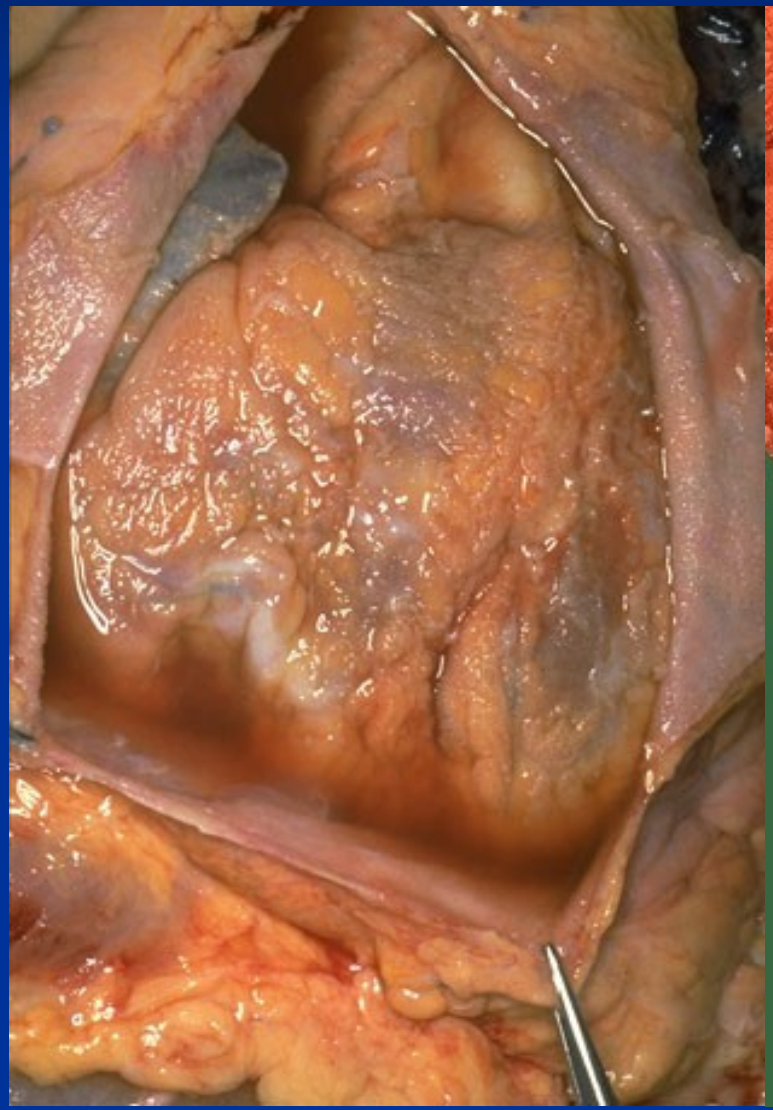
- **serous:**
  - watery exudate
    - few proteins (fibrinogen)
    - in mucous membranes – catarrhal (mucus)
  - heals by inhibition of exudation
  - examples:
    - superficial: catarrhal appendicitis
    - deep (interstitial): urticaria (hives)

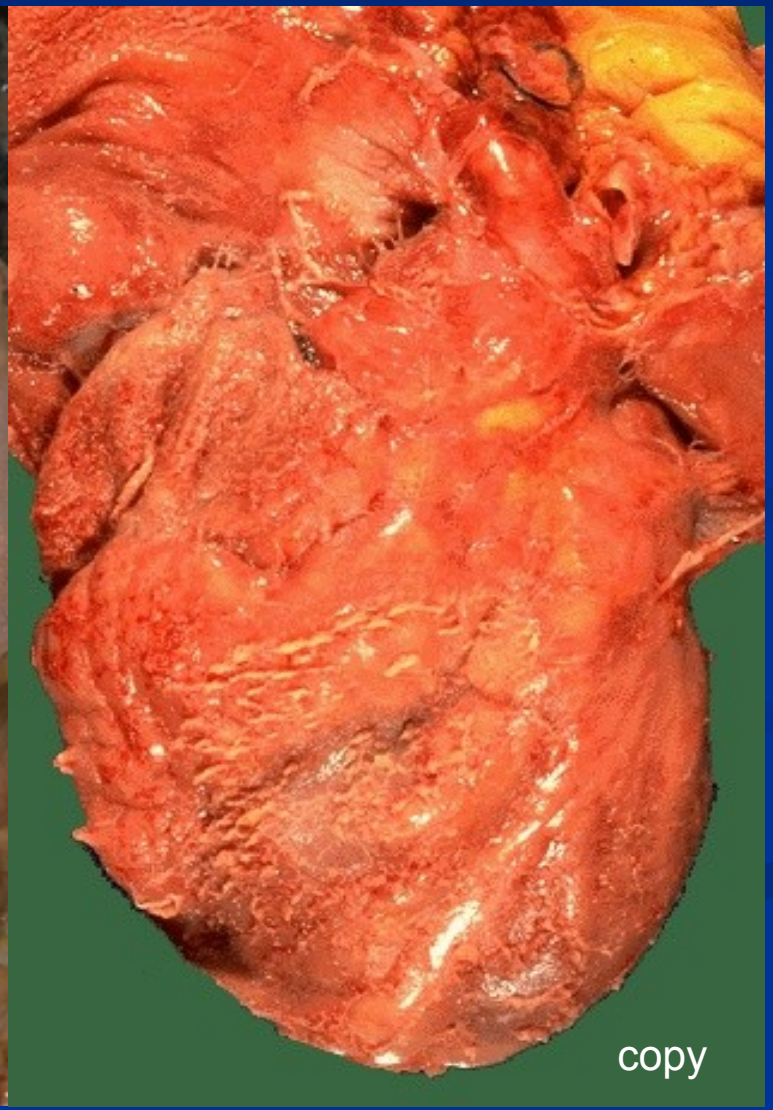
Exudative inflammation

- **fibrinous:**
  - ⇨high content of fibrinogen – fibrin in the exudate
  - ⇨healing is more complicated (fibroproductive inflammation)
  - ⇨examples:
    - superficial inflammation of serous membranes:
      - **fibrinous pericarditis** (upon uremia) = cor villosum, hirsutum
    - superficial infl. of mucous membranes ***(PSEUDOMEMBRANES)***:
      - **plaque-like inflammations**
    - deep:
      - **rheumatic fever**

Fibrinous pericarditis – cor villosum

(Superficial fibrinous inflammation of serous membranes)





Exudative fibrinous mucosal inflammation

Classification due to mucosal damage:

- croupous
  - ⇨little alteration, plaque is loose on the surface
    (croupous pneumonia)
- diphteric
  - ⇨deeper mucosal necrosis, after the pseudomembrane is peeled off »
    ulcus
    (pseudomembranous colitis)
- escharotic
  - ⇨extensive deep necrosis
    (necrotising tracheitis in flu)

Exudative inflammation

- **non-purulent:**
  - exudate made by chronic inflammatory cells

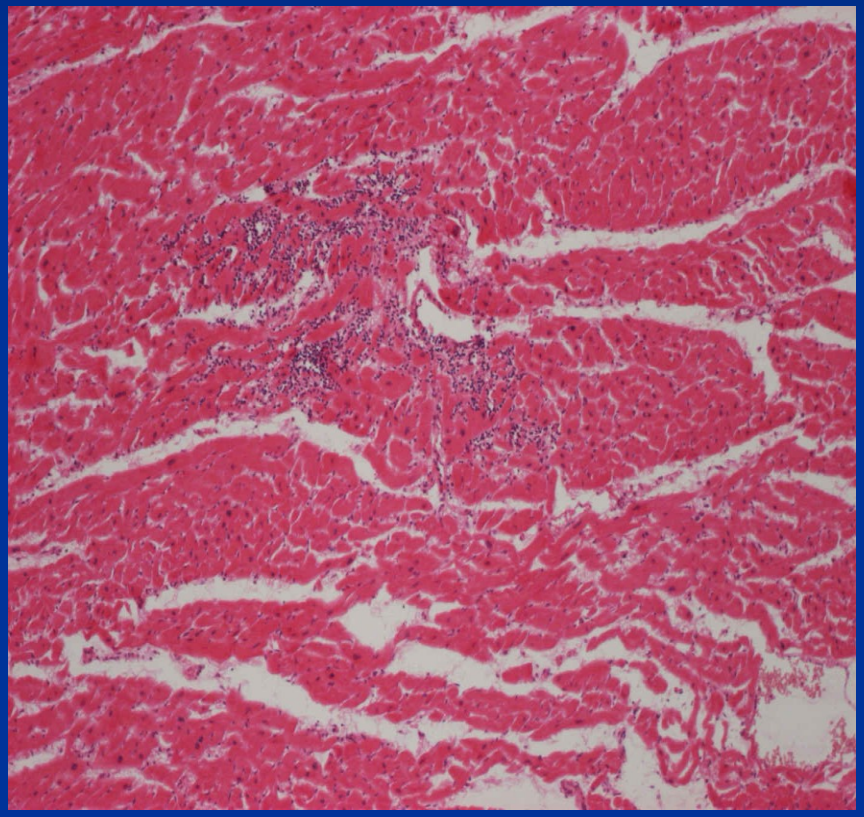
    (lymphocytes, plasma cells = mononuclear/lymphoplasmocytic inflammatory infiltration)

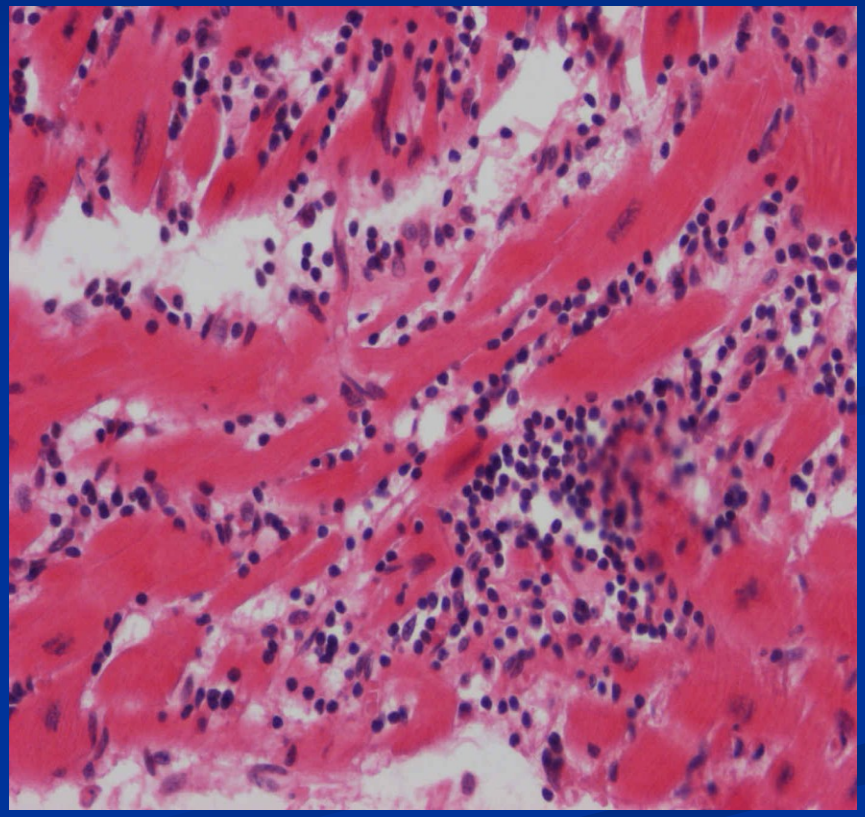
    Examples:
  - Interstitial pneumonia

    - infectious (viral, caused by small bacteria (Mycoplasma pneumoniae) or by fungi (Pneumocystis carinii))

    - idiopathic (v.s. autoimmune)
  - Interstitial myocarditis
  - Hashimoto`s lymphocytic thyreoiditis (autoimmune)

Non-suppurative/non-purulent inflammation – lymphoplasmocytic – interstitial myocarditis





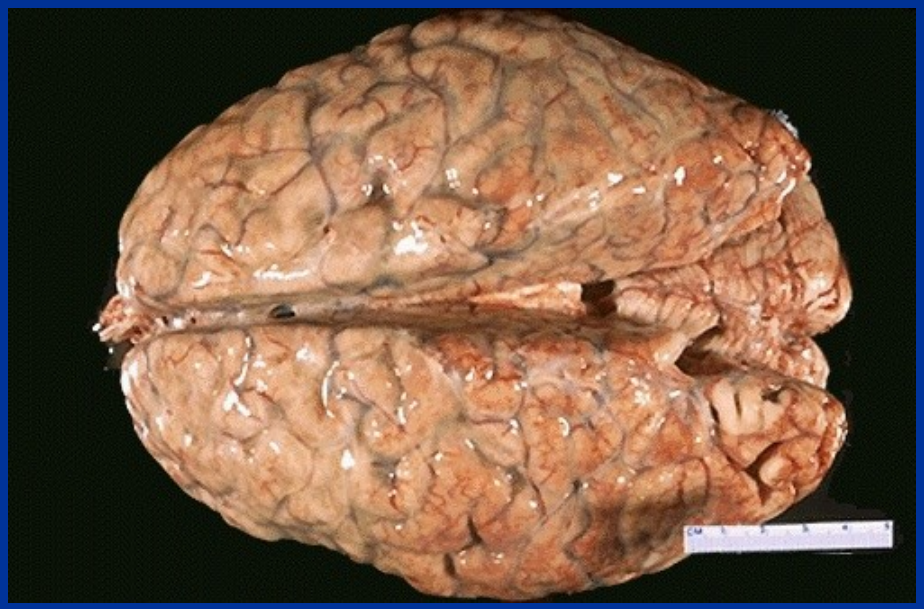
Exudative inflammation

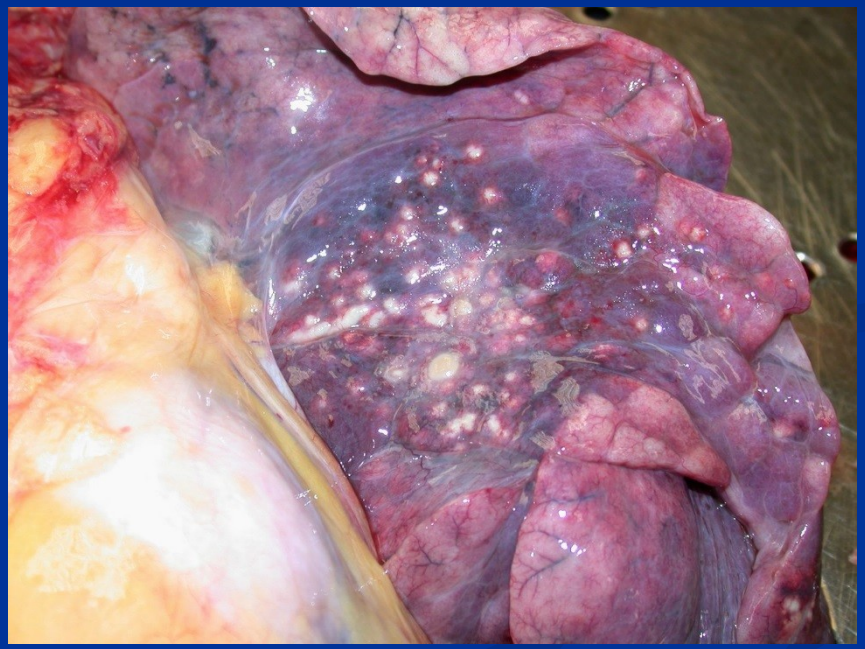
- **purulent:**
  - PRODUCTION OF PUS:

    neutrophil-rich exudate
  - GROSS:

    superficial pus, pus accumulation (abscess)
  - heals by inhibition of exudation and/or by proliferative inflammation
  - examples:
    - **superficial inflammation of meninges:**
      - purulent meningitis
    - **superficial mucosal inflammation:**
      - catarrhal-purulent bronchopneumonia
    - **deep (interstitial):**
      - phlegmona (e.g. phlegmonous appendicitis)
      - abscess

Suppurative (purulent) inflammation: purulent meningitis and absceding bronchopneumonia





Exudative inflammation

- **gangrenous:**
  - necrosis modified with putrid bacteria
  - examples: gangrenous cholecystitis

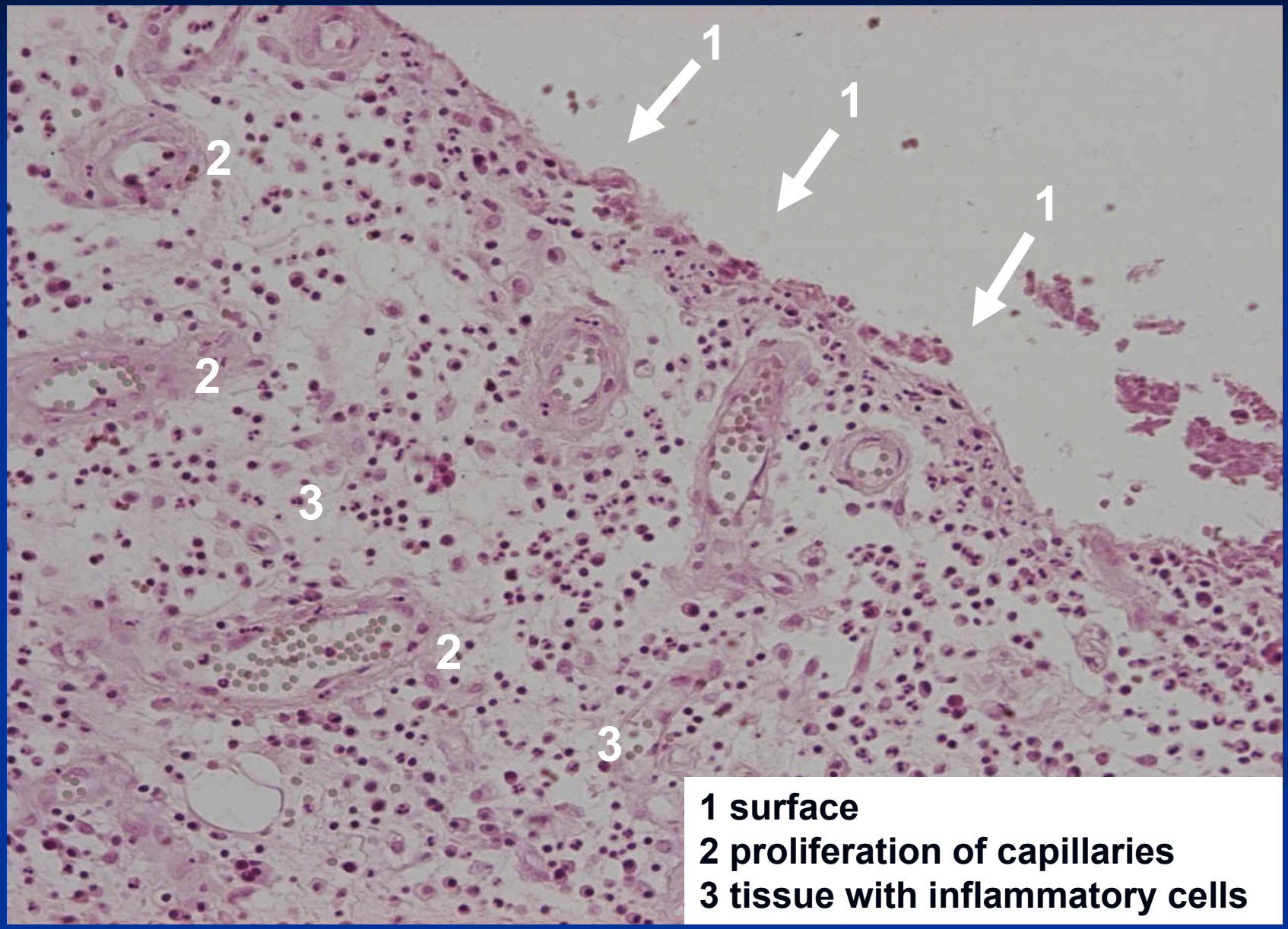
Proliferative inflammation

- formation of granulation tissue and fibrotisation in healing (reparation) of defects (wound, regressive changes, postinflammatory etc.)
- tissue damage → granulation tissue → scar
- often pronounced in chronic inflammation
- primary proliferative inflammation uncommon (fibromatosis)
- reactive fibro/myofibroblastic lesions
  - proliferation of myofibroblasts, occasionally forming tumour-like masses
    - nodular fasciitis, myositisossificans – may be posttraumatic, often idiopathic

Granulation tissue

- Formation of granulation tissue = major repair instrument
- In:
  - healing of wounds, fractures, ulcers; organisation of necrosis, thrombus, and haematoma
- Gross:
  - soft red tissue, granular surface (capillary loops)
- Micro:
  - fibrin fibers
  - inflammatory reaction
  - **fibroblasts, myofibroblasts**
  - starting collagen fibers production
  - **proliferating capillaries – angiogenesis**
  - later intercellular matrix + tissue remodeling, retraction – scar formation

Granulation tissue: (new vessels proliferation and fibrosis)



Chronic inflammation

- **Chronic inflammation developing from acute inflammation** (e.g. chronic osteomyelitis,…)

- **Primary chronic inflammation**

- Resistance of infective agents to phagocytosis and intracellular killing (tbc, leprosy, brucellosis,…)
- Foreign body reactions
- Some autoimmune diseases
- Specific diseases of unknown etiology (IBD,…)
- Primary granulomatous diseases (sarcoidosis, reaction to beryllium,…)

Chronic inflammation

- **Prolonged duration** – prolonged host response to persistent stimulus

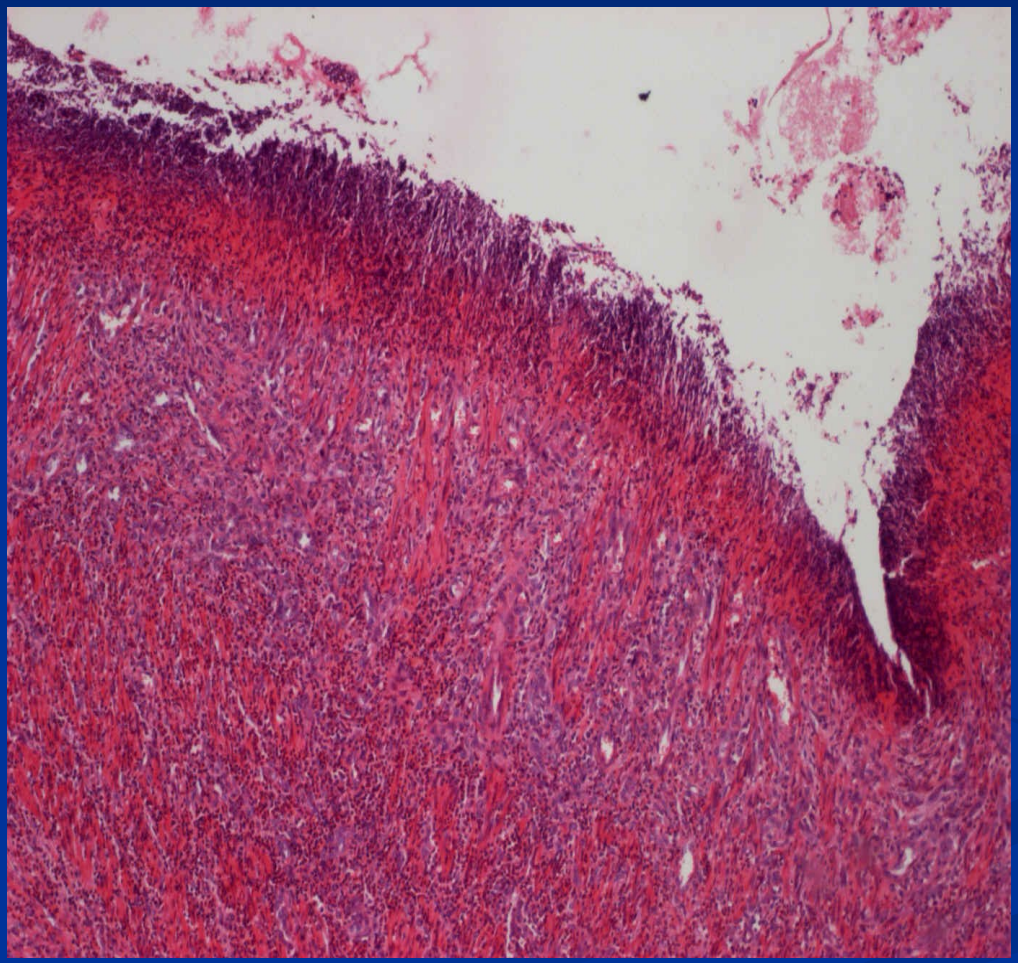
→ active inflammation+tissue injury+healing

- **Infiltration with mononuclear cells** (macrophages, plasma cells, lymphocytes)
- **Tissue destruction** (by products of the inflammatory cells)
- **Repair** (new vessel proliferation and fibrosis)

Macroscopic apperance of chronic inflammation

- Chronic ulcer
- Chronic abscess cavity
- Thickening of the wall of a hollow viscus
- Granulomatous inflammation
- Fibrosis

Chronic peptic ulcer in stomach.



Microscopic features of chronic inflammation

- Exudation not prominent
- Production of new fibrous tissue from granulation tissue
- Continuing destruction of the tissue+regeneration+repair
- Cellular reaction in chronic inflammation

- macrophages, plasma cells, lymphocytes, eosinophils, mast cells

Granulomatous/specific inflammation

- distinctive pattern of chronic inflammation
- historical classification of inflammation:
  - „non-specific“ /non granulomatous inflammation
    - common general microscopic picture, i.e. purulent infl.
  - „specific“/granulomatous
    - micro typical for a specific cause

- aggregated macrophages unable to destroy cause → transformation into epithelioid and multinuclear cells → granuloma
- delayed type hypersensitivity (T-cells, macrophages, sometimes eosinophils)
- foreign body granuloma x immune granuloma

Granulomatous inflammation

- Aggregates of activated macrophages (epitheloid)
- Non-immune granulomas (response to foreign bodies, chemicals)
- Immune granulomas
  - Necrotizing (tbc)
  - Non-necrotizing (sarcoidosis)
- Persistent T-cell response
- Tuberculosis – a prototype of granulomatous disease

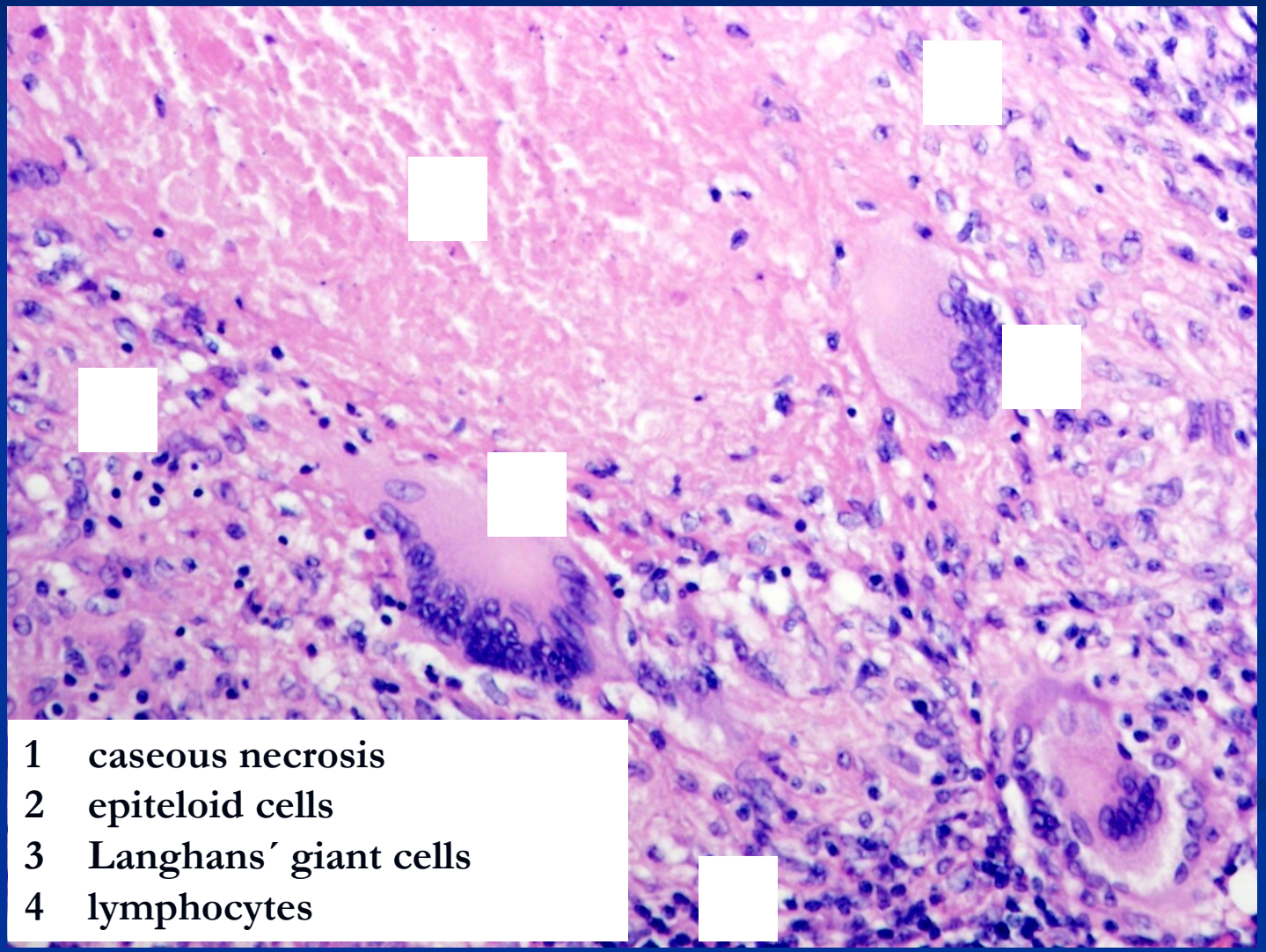
Examples of diseases with granulomatous inflammation

disease	cause	Tissue reaction
Tuberculosis	*Mycobacterium tbc*	Caseating tubercle –granuloma
Leprosy	*Mycobacterium leprae*	Noncaseating granuloma, acid-fast bacilli in macrophages
Syphilis	*Treponema pallidum*	Gumma: enclosing wall of histiocytes, plasma cells infiltrate, central cells necrotic
Cat-scratch disease	G- bacillus	Granuloma with central necrotic debris and neutrohils
Sarcoidosis	Unknown etiology	Noncaseating granuloma with abundant activated macrophages
Foreign body granulomas	Response to foreign bodies (endogeneous (keratin, necrotic bone, cholesterol crystals, urate) and exogeneous (suture material, silica, talc, asbestos), chemicals (berrylium)	Giant cell granulomas (foreign body granulomas)
Crohn disease (IBD)	Immune reaction against intestinal bacterial, self antigens	Noncaseating granuloma in bowel wall +chronic inflammatory infiltrate

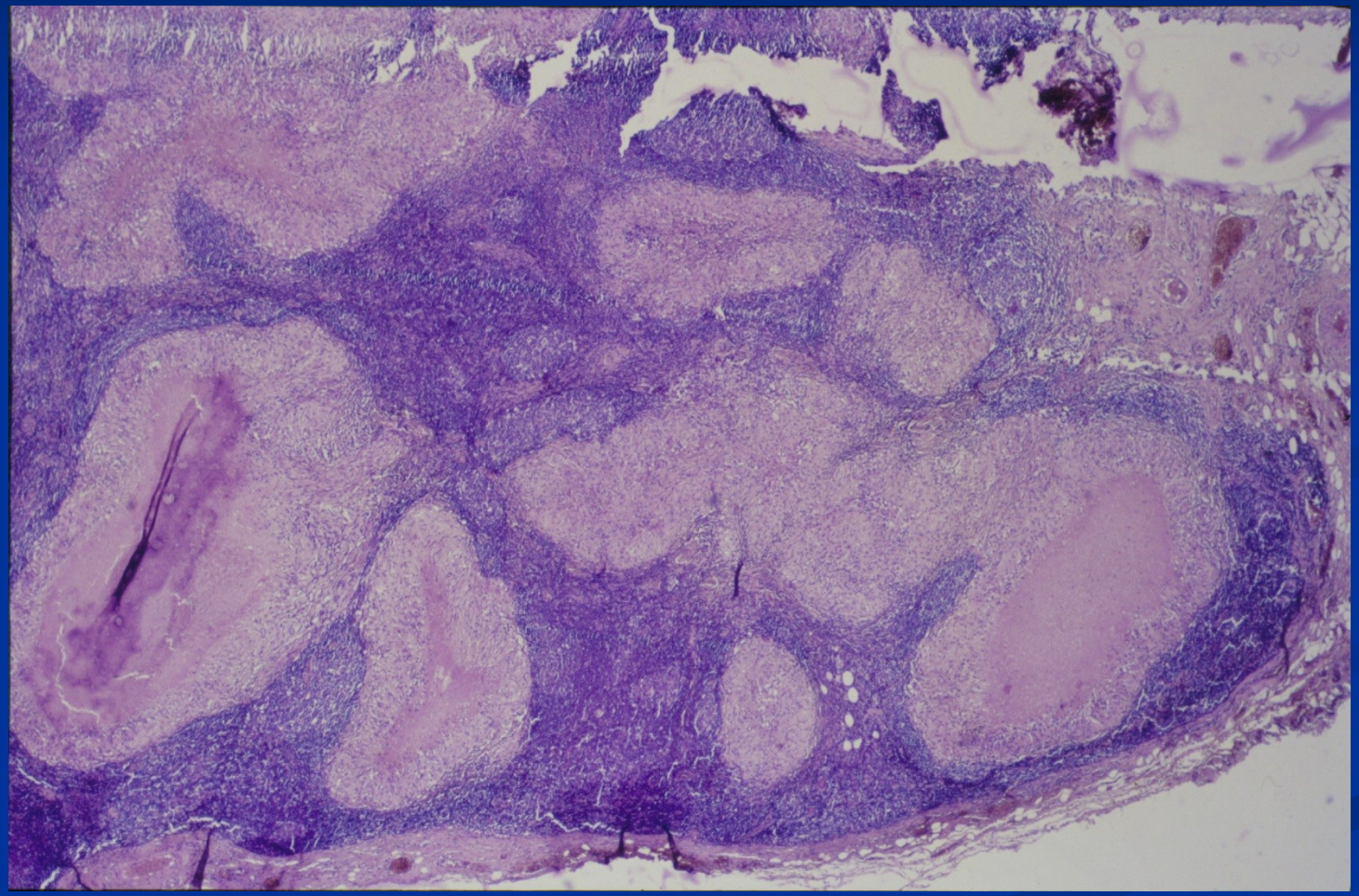
Tuberculosis

- **etiology**
  - Mycobacterium tuberculosis
    - Ziehl-Neelsen staining, acid-resistant bacteria , culture or PCR detection
- **tuberculous granuloma - basic morphology:**
  - central caseous necrosis (basophilic nuclear fragments)
  - epithelioid macrophages
  - multinucleated Langhans‘ giant cells (fusion of macrophages)
  - rim of T-cells

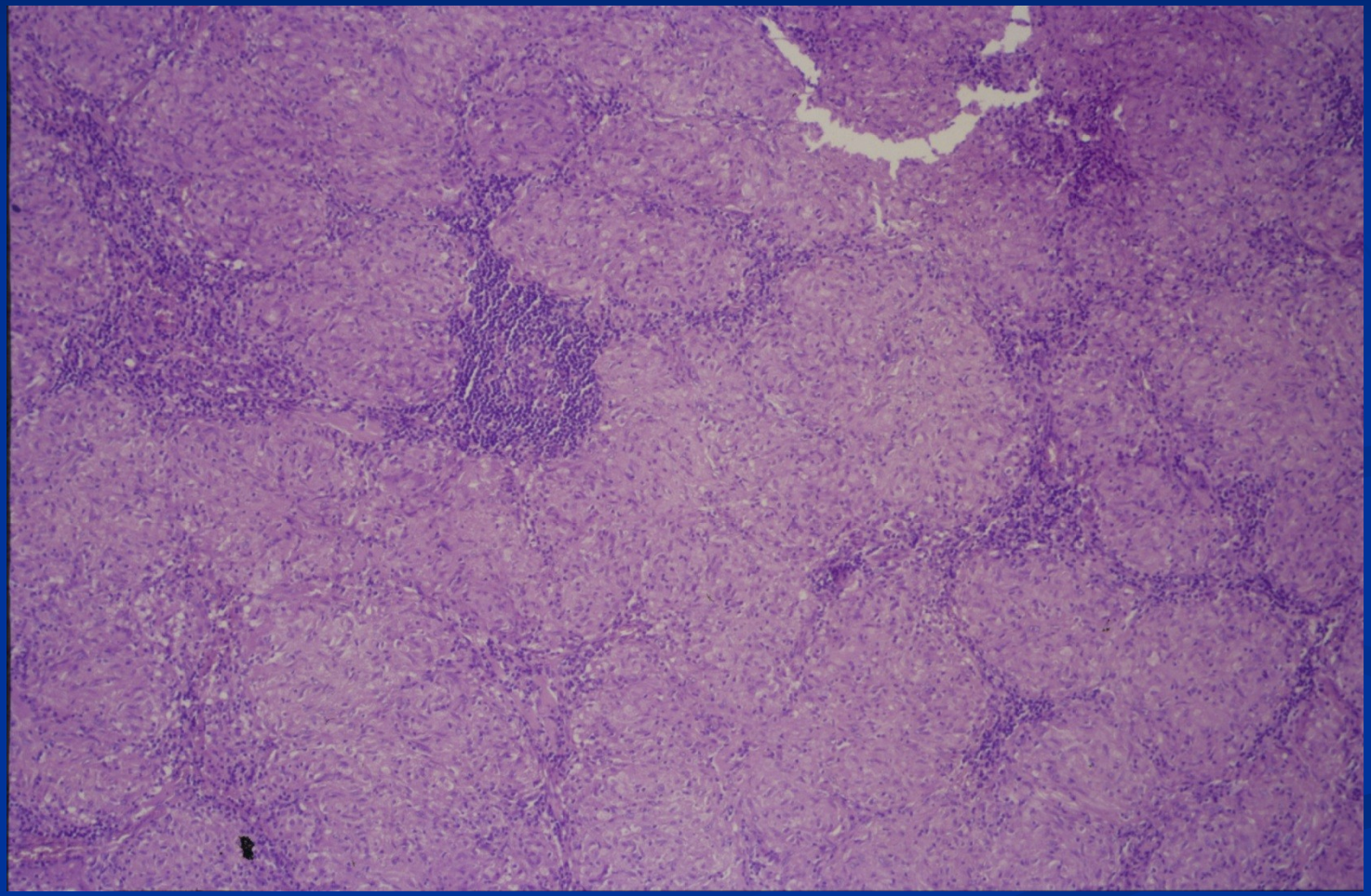
Tuberculous granuloma



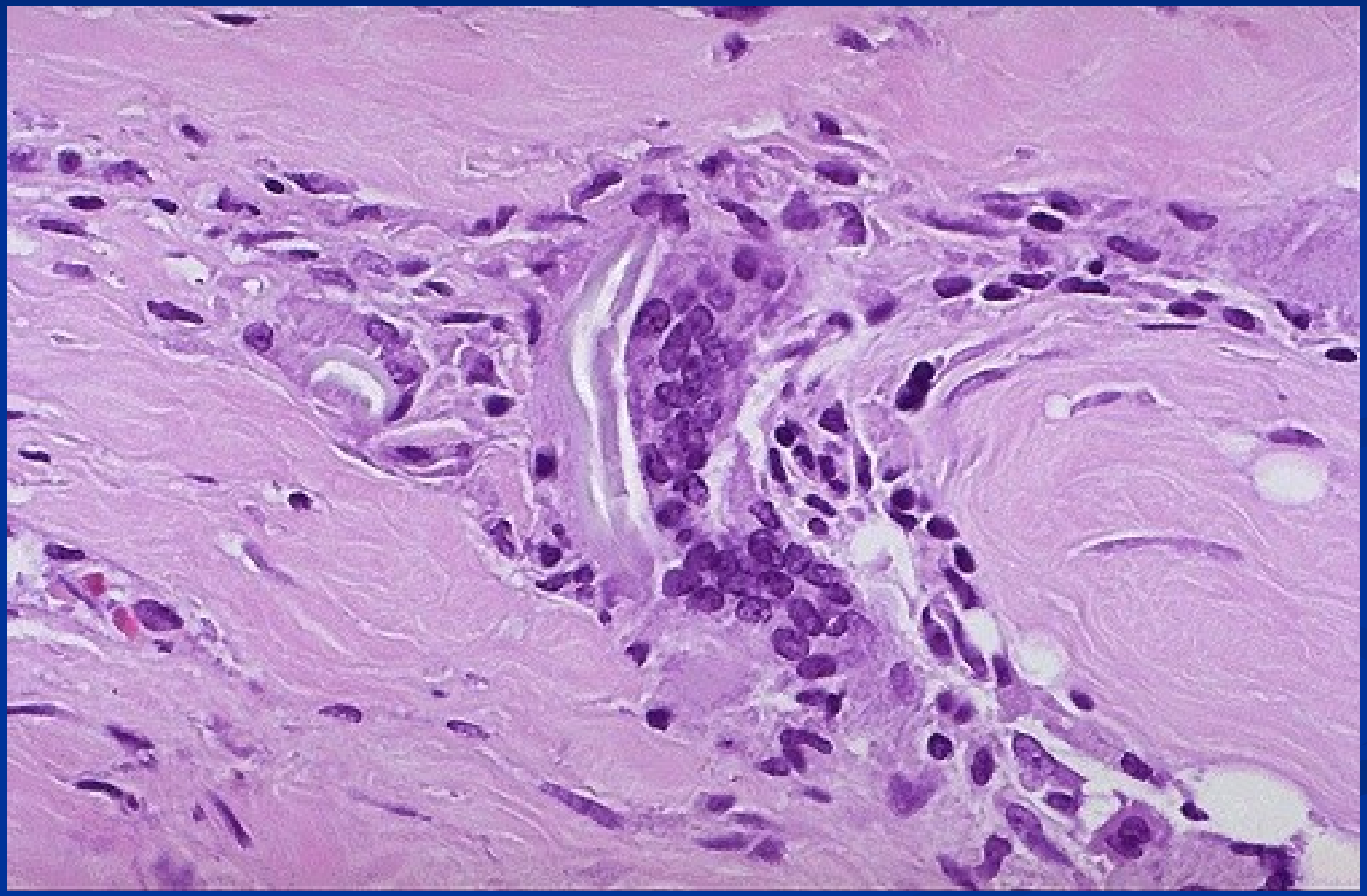
Granulomatous-purulent lymphadenitis – cat scratch disease.



Sarcoidosis of a lymph node



Granulomatous giant cell reaction around foreign bodies.



Progressive changes

- **healing of tissue defects**
  - Regeneration
  - Repair
    - regeneration and repair often in combination
- **tissue adaptation to the changed conditions**
  - Hypertrophy: increase in cell size without cell division
  - Hyperplasia: increase in cell number with mitosis
  - Combined hypertrophy and hyperplasia
  - Metaplasia: transformation of one mature differentiated cell type into another; affects epithelial and mesenchymal cells, oftes assoc. with increased risk of malignancy (e.g. squamous cell carcinoma assoc. With squamous metaplasia in bronchi)

REGENERATION

- **replacement by identical tissue – regrowth of original tissue (morphologically and functionally)**

- **according to regenerative ability:**
  - labile cells
    - epithelial cells of skin, gut,…, bone marrow,…,
    - permanent regeneration from stem cells (rapid „turn-over time“)
  - stable
    - liver, kidney (proximal tubule epithelial cells), smooth muscle
    - regeneration on demand in tissue loss
  - permanent (postmitotic)
    - neurons, cardiac muscle cells
    - mostly no complete functional regeneration

REPAIR

- replacement of lost tissue usually by granulation tissue → fibrotic scar (formation of connective tissue scar

- may affect the function of the organ
  - scar after myocardial infarction
  - lung fibrosis, cirhosis,…

Components of tissue healing

- **Fibronectin**

(in early stages; formation of scaffold, the provision of tensile strength, the ability to „glue“ other substances and cells together, attracts fibroblasts and macrophages, binds to collagenes and proteoglycans)

- **Proteoglycans and elastin**

(stabilizes tissue undergoing repair)

- **Collagen**

(structural support and tensile strength, different type of collagen give stability to healing tissue)

Factors influencing regeneration and repair

- Physiological variables (e.g., age, grawth factors, vascular sufficiency)
- General health of the individual; immunocompetency; psychological/emotional/spiritual well-being
- Presence of comorbidities (examples):
  - Diabtes mellitus
  - Decreased oxygen perfusion
  - Hematologic disorders
  - Cancer (local and systemic effect)
  - Incontinence
  - Alzheimer disease
  - Neurologic impairment
  - Immobility
- Tobacco, alcohol, coffeine, other substance use/abuse
- Local or systemic; presence of foreign bodies
- Type of tissue
- Medical treatment (e.g., prednisone, chemotherapy, radiation therapy)

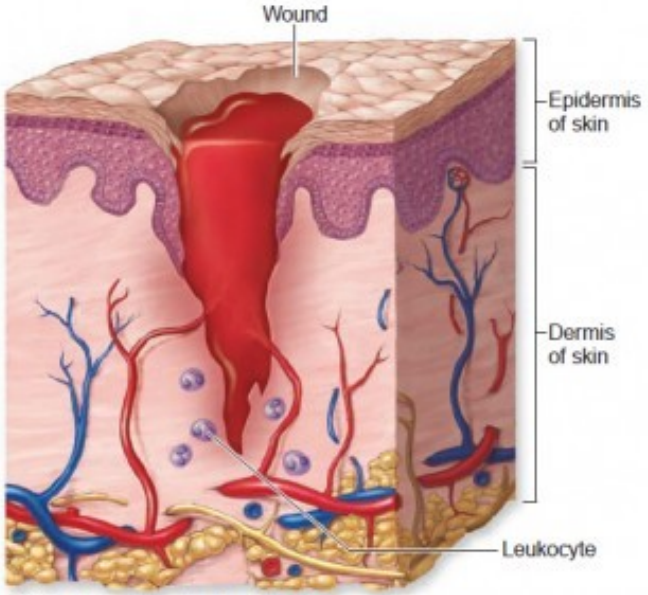
Phases of wound healing

- **Hemostasis and degeneration**
- **Inflammation**
- **Proliferation and migration phase**
- **Remodeling and maturation phase**
  - Tissue contraction and contracture
  - Tissue regeneration
  - Tissue repair (formation of scar tissue)

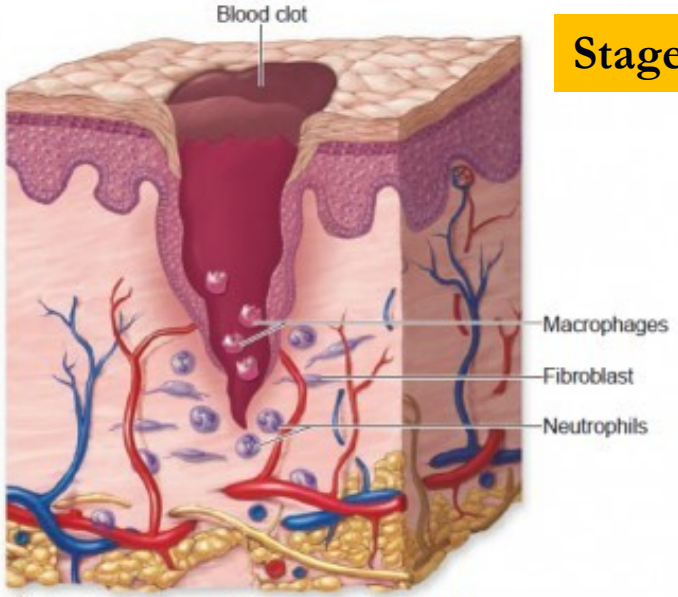
Phases of wound healing

- Bleeding, formation of a loose clot
- Mediators released by platelets (production of growth factors, recruitment of inflammatory cells)
- Proliferation and migration of fibroblasts, epithelial cells and vascular endothelial cells
- Production of fibronectin, proteoglycans, elastin, collagens by fibroblasts
- Reconstitution of extracellular matrix (=framework for the endothelial and parenchymal cells)
- Formation of granulation tissue
- Remodeling and maturation (decline of neovascularisation and fibroblasts proliferation; transformation of fibroblasts into myofibroblasts and contraction of the healing tissue)
- Formation of scar tissue

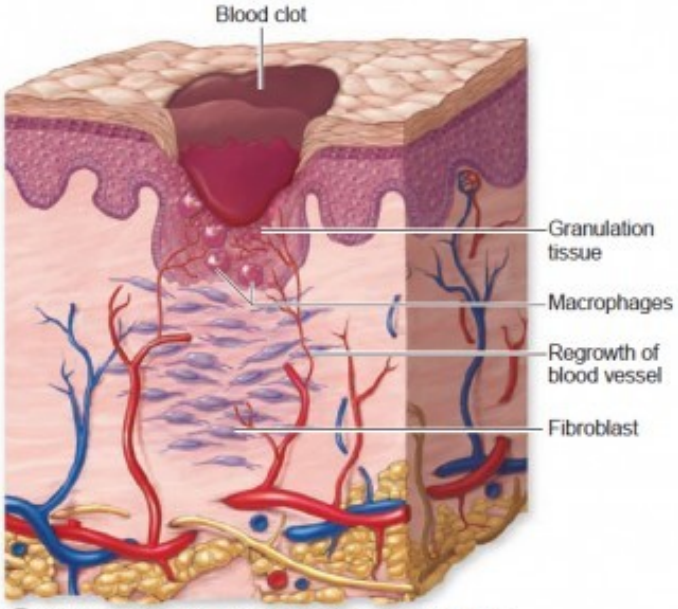
Stages of wound healing



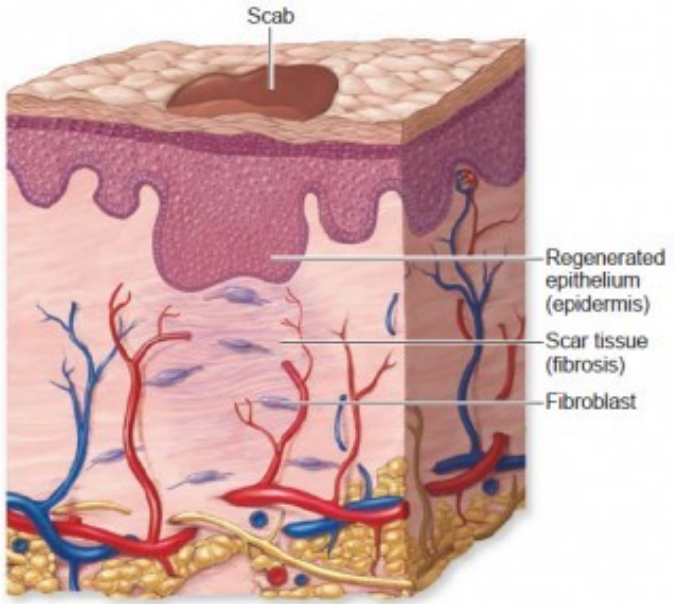
1 Cut blood vessels bleed into the wound.



2 Blood clot forms, and leukocytes clean wound.



3 Blood vessels regrow, and granulation tissue forms.

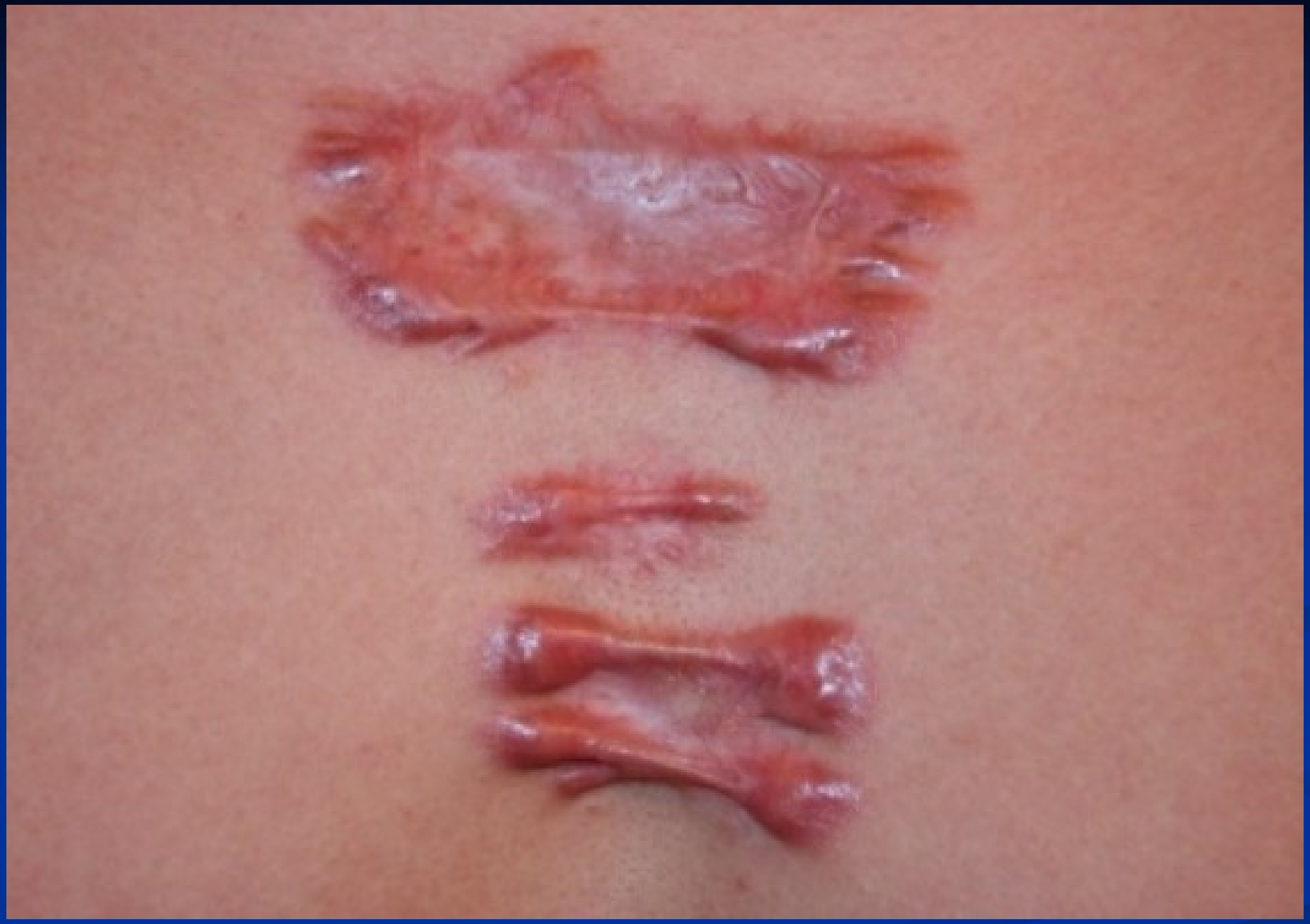


4 Epithelium regenerates, and connective tissue fibrosis occurs.

- **healing by first intention -** *per primam;* union of accurately coapted edges of a wound, with an irreducible minimum of granulation tissue, results in a thin scar.

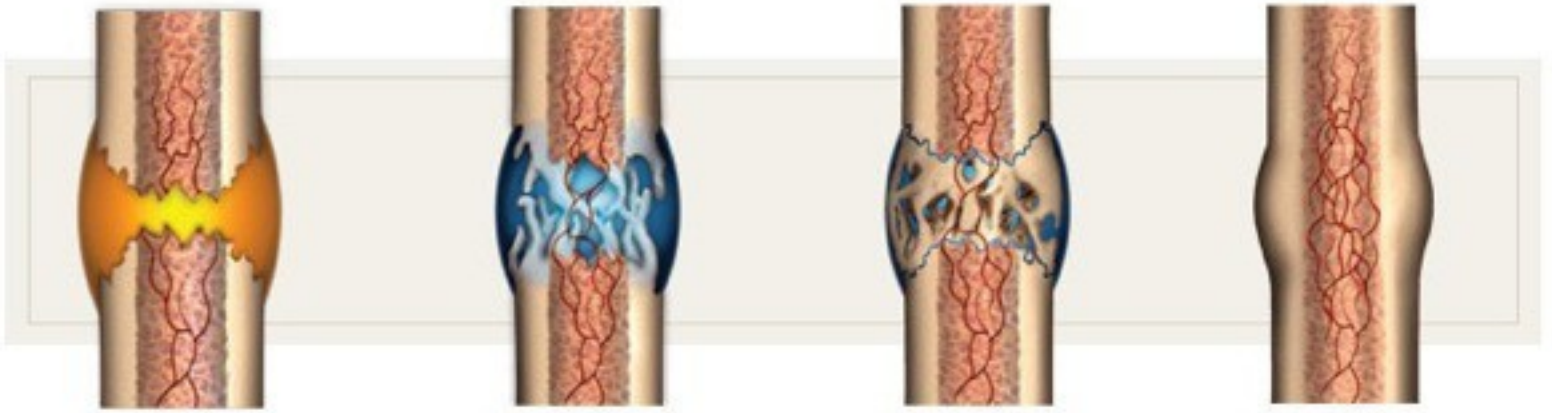
- **healing by second intention -** *per secundam;* union by adhesion of granulating surfaces.

- **healing by third intention -** *per tertiam;* union of a wound that is closed surgically several days after the injury.



Keloid – hypertrophic scar tissue due to excess collagen formation

Fracture healing and repair



Inflammation

Soon after a fracture occurs, a hematoma forms at the injury site. Macrophages and inflammatory leukocytes move into the damaged area to scavenge debris and begin producing the pro-inflammatory agents that initiate healing.

Soft callus

Inflammation triggers cell division and the growth of new blood vessels. Among the new cells, chondrocytes secrete collagen and proteoglycans, creating fibrocartilage that forms the soft callus.

Hard callus

Through endochondral ossification and direct bone formation, woven bone replaces the soft callus to create a hard callus around the broken fragments of bone.

Remodeling

Over time, mechanically strong, highly organized cortical bone replaces the weaker, disorganized woven bone. Because it is continually remodeled, bone is the only tissue to heal without a scar.

Skeletal muscle

- Transection of musles regenerate either by growth from undamaged stumps or by growth of new independent fibers (source of myoblasts for fiber regenerations - activated proliferating satellite cells)
- Granulation tissue formation and connective tissue scar replacing the damaged muscle fibers – repair

Peripheral nerve

- Myelin degeneration and axonal fragmentation
- Axonal sprouting and proliferation of Schwann cells in 24h
- Microsurgical approximation may result in reinervation

Tendon injury and healing

- as a result of proliferation of tenoblasts from the cut ends
- as a result of vascular ingrowth and proliferation of fibroblasts from the surrounding tissues

Ligament injury and healing

- Healing by the same basic phasis (hemorrhage, inflammation, repair, remodeling)
- Some with poor healing response

Cartilage injury and healing

- Requires source of cells, provision matrix, removal of stress concentration, intact subchondral bone plate
- Lack of articular cartilage vascularisation
- Healing by fibrous scar or fails to heal at all

Synovial membrane injury

- hemorrhage, hypertrophy, hyperplasia of synovial lining cells, and chronic inflammation

Disk degeneration

- Degerative changes with age
- Herniation of the disk

Thank you for your attention …