Inflammation (acute and chronic); gross and microscopic appearance. Phagocytosis, cells engaged in inflammation, chemical mediators of inflammation

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)

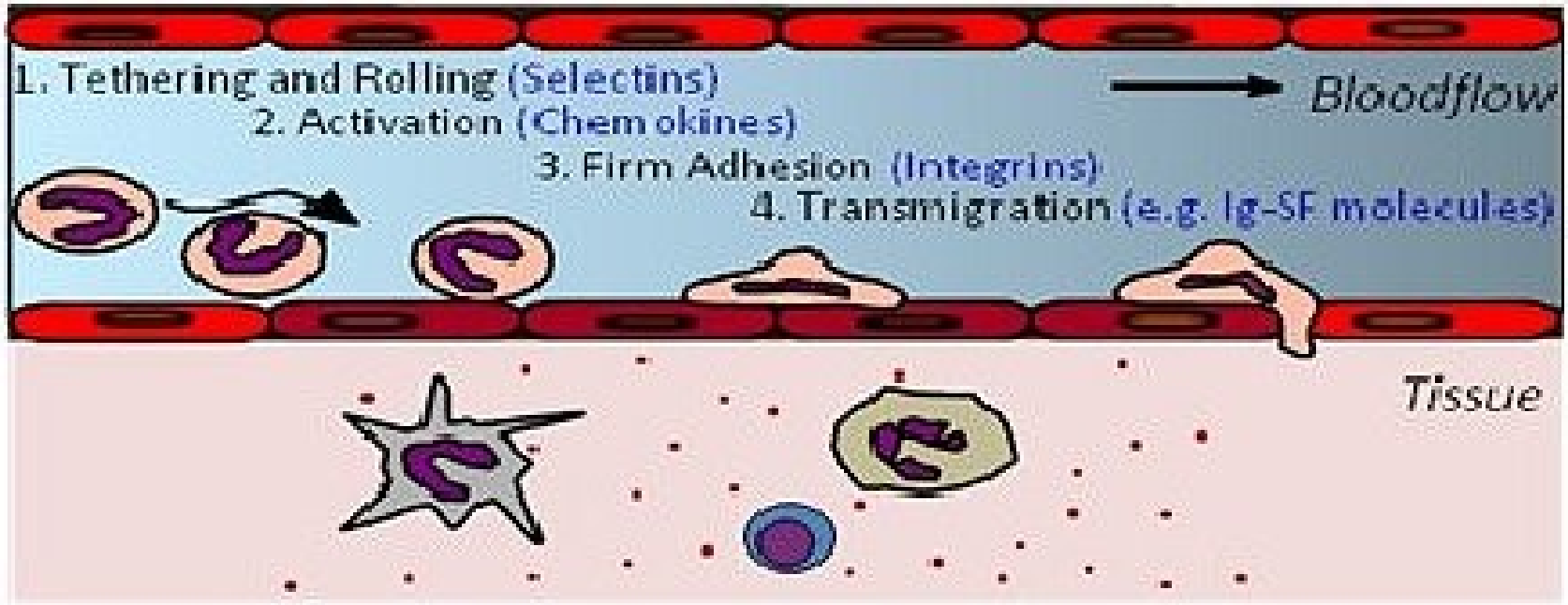
Early stages of acute inflammation

- **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**
  - emigration of the neutrophils polymorphs into the extravascular space)

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



Lymphocyte

Granulocyte

Inflammatory macrophage

Proinflammory Cytokines

Quiescent endothelium

Activated endothelium

Leukocyte recruitment to sites of inflammation

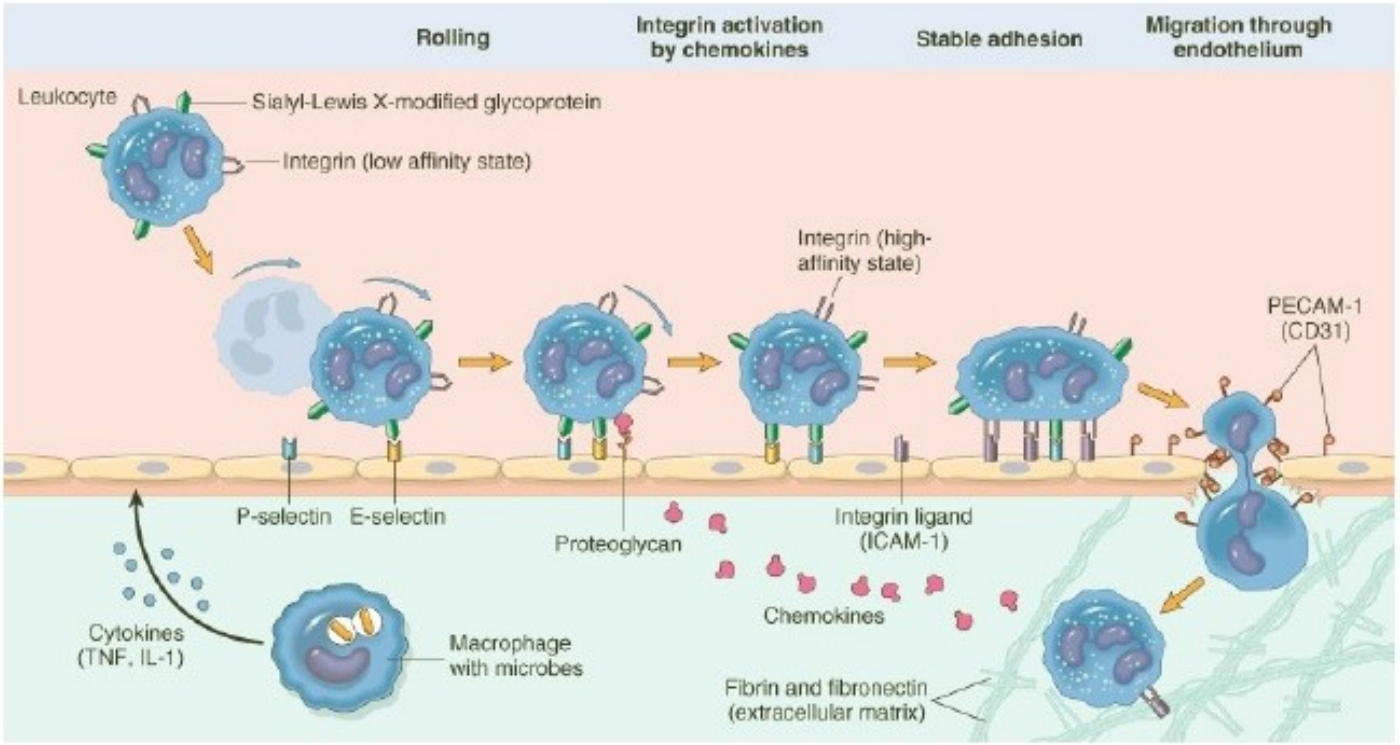
- Leukocytes recruited from the blood into extravascular tissues – migrate to the site of infection or tissue injury – are activated to perform their functions

- Leukocyte recruitment – multistep process:
  - Margination, loose attachment to and rolling on endothelium (selectins)
  - Firm attachment to endothelium (integrins)
  - Migration through inter-endothelial spaces – diapedesis (chemokines)
  - Migration in interstitial tissues toward chemotactic stimulus – chemotaxis

- Cytokines produced by macrophages and other cells (TNF, IL-1) promote expression of selectins and integrins ligands on endothelium; promote directional migration of leukocytes

- Neutrophils predominate in the early inflammatory infiltrate and are later replaced by macrophages

Leukocyte recruitment to sites of inflammation



Chemotactic stimuli

- Bacterial products
- Cytokines (chemokine family)
- Components of complement system (C5a)
- Products of lipooxygenase pathway (LTB_4)

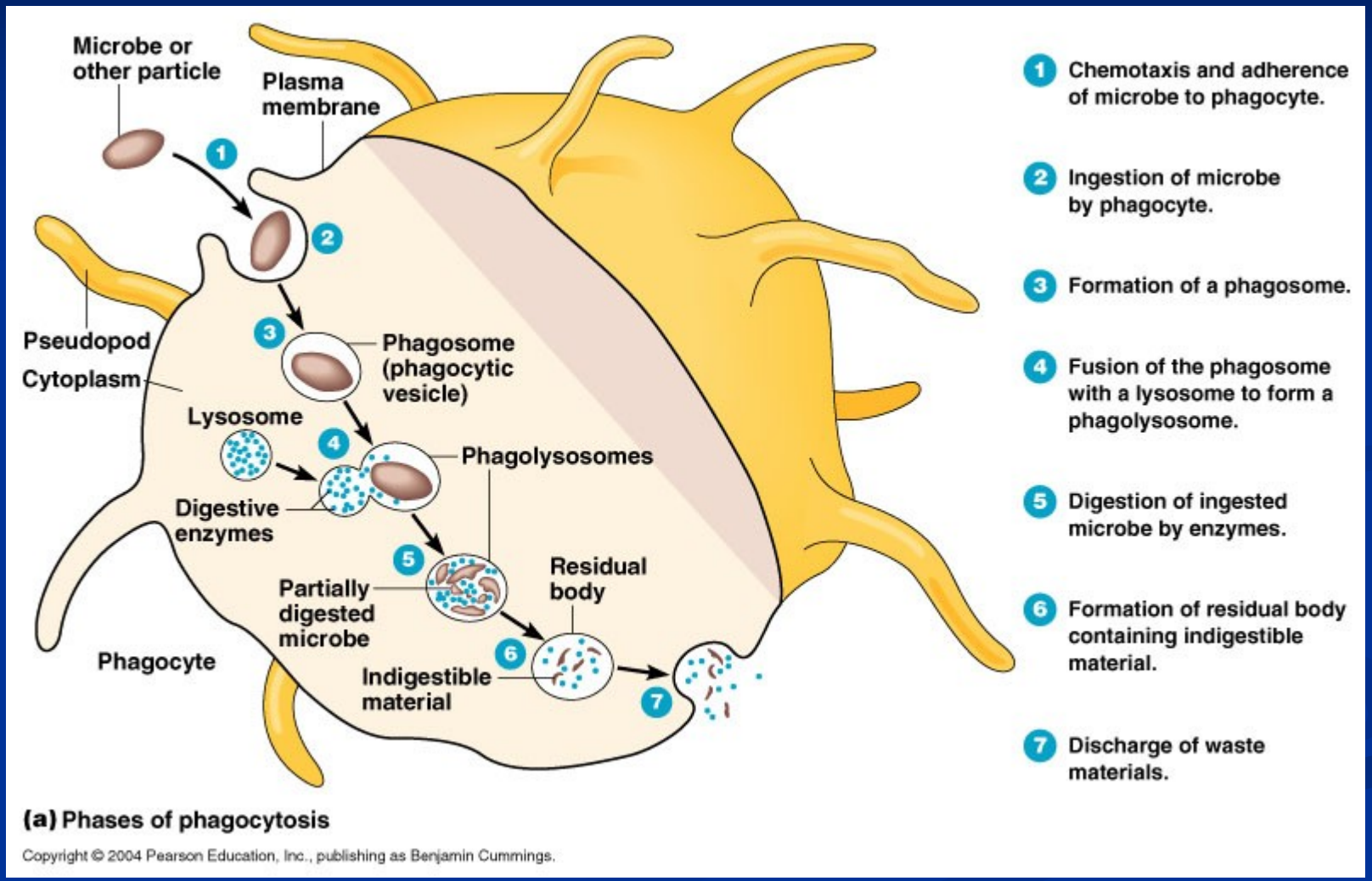
Leukocyte effector function

- 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

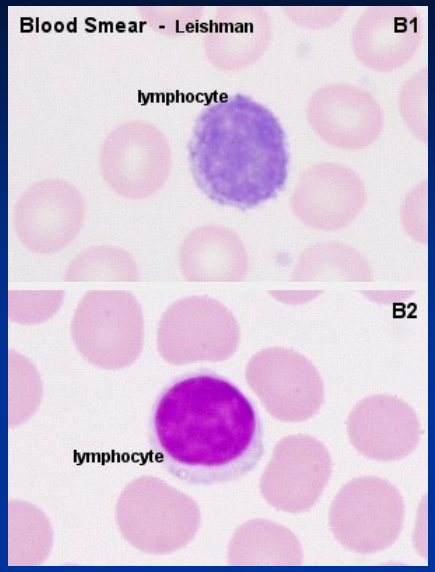
Phagocytosis

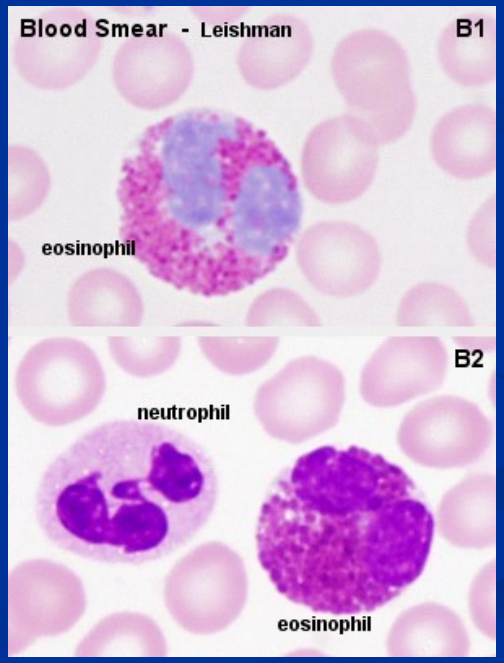


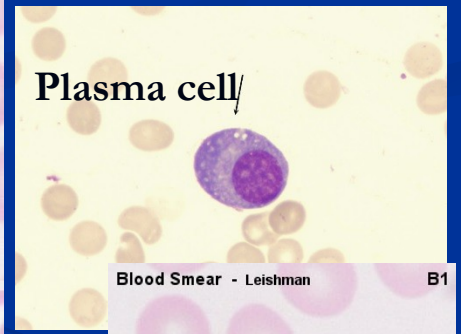
(a) Phases of phagocytosis

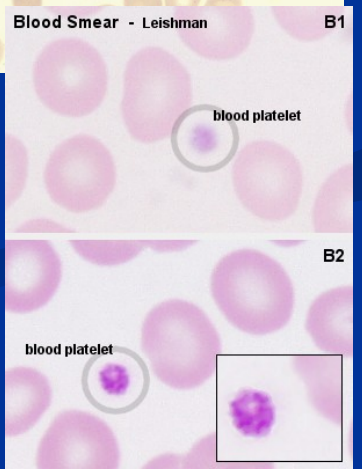
Cells involved in inflammation – components of cellular exudate

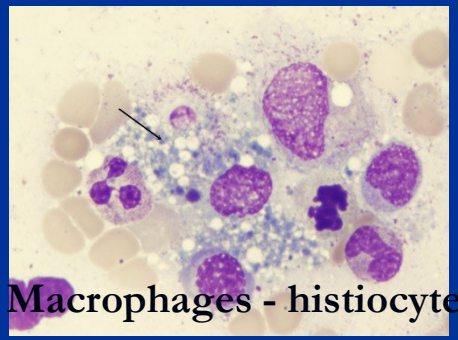
- Leukocytes – neutrophils
- Eosinophils, basophils
- Lymphocytes
- Plasma cells
- Macrophages
- Heparinocytes, mast cells
- Platelets
- Fibroblasts
- Erythrocytes

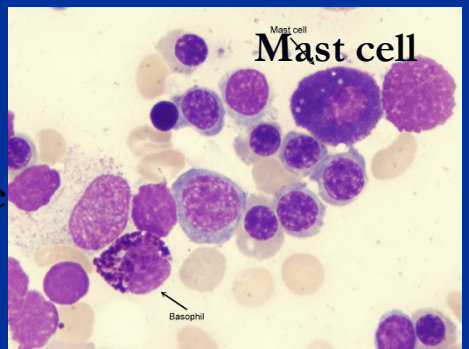




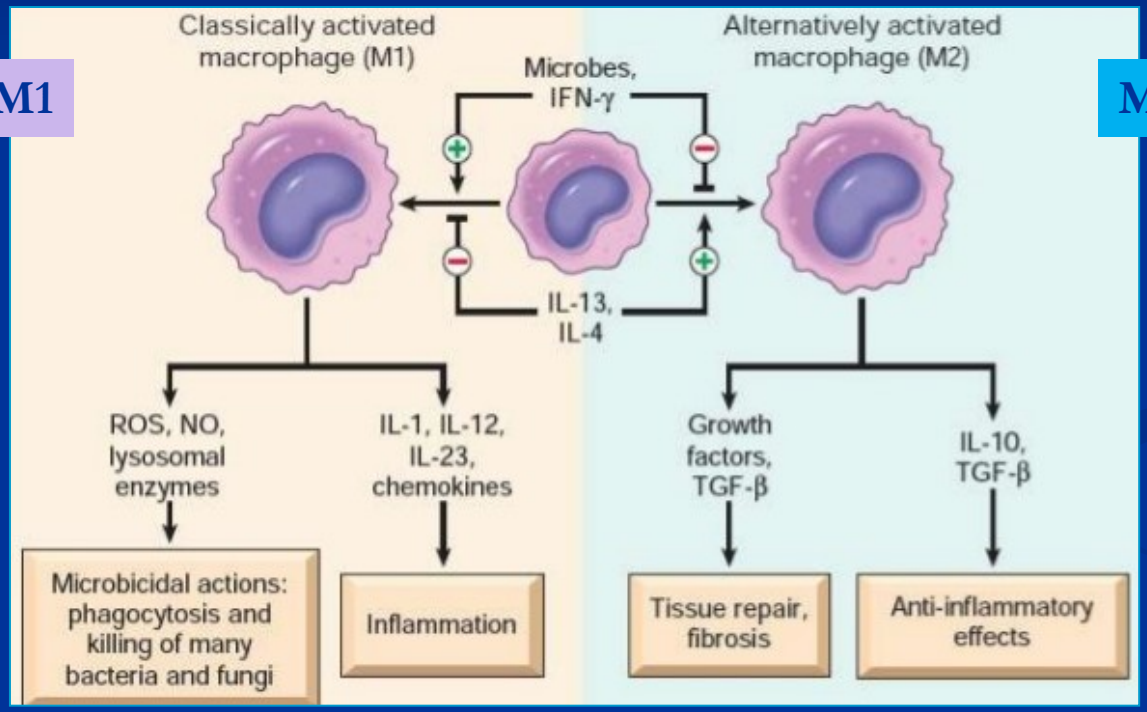






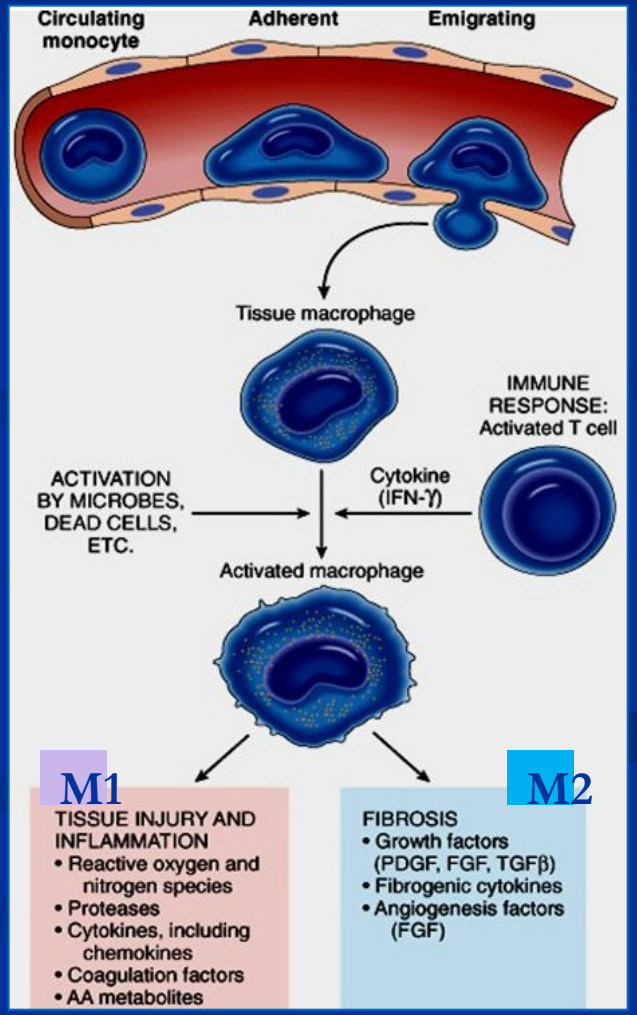


Activation of macrophages

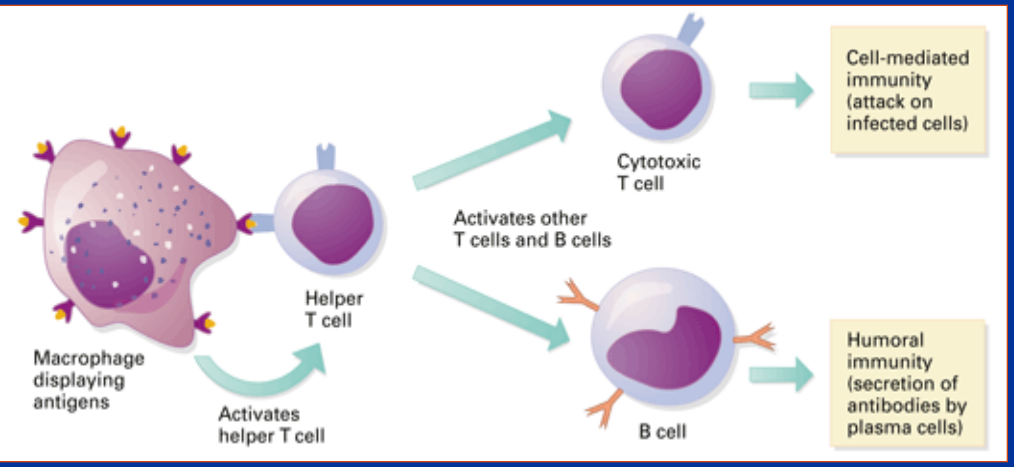


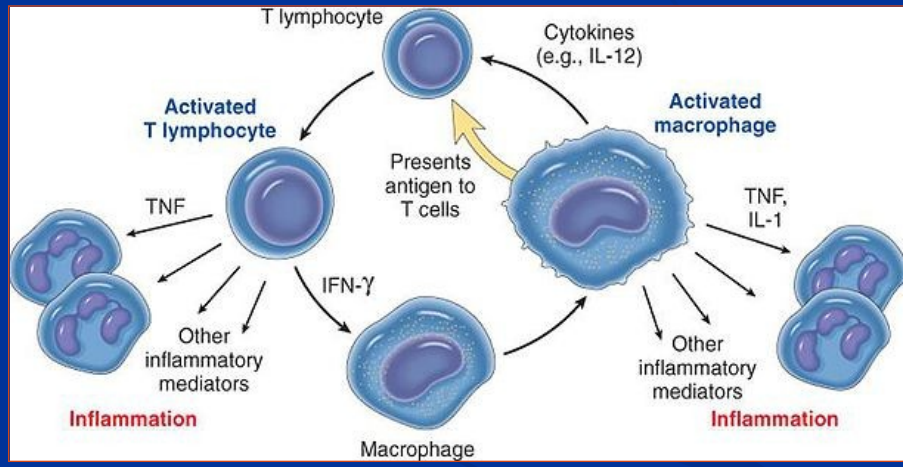
M1

M2



T and B lymphocytes



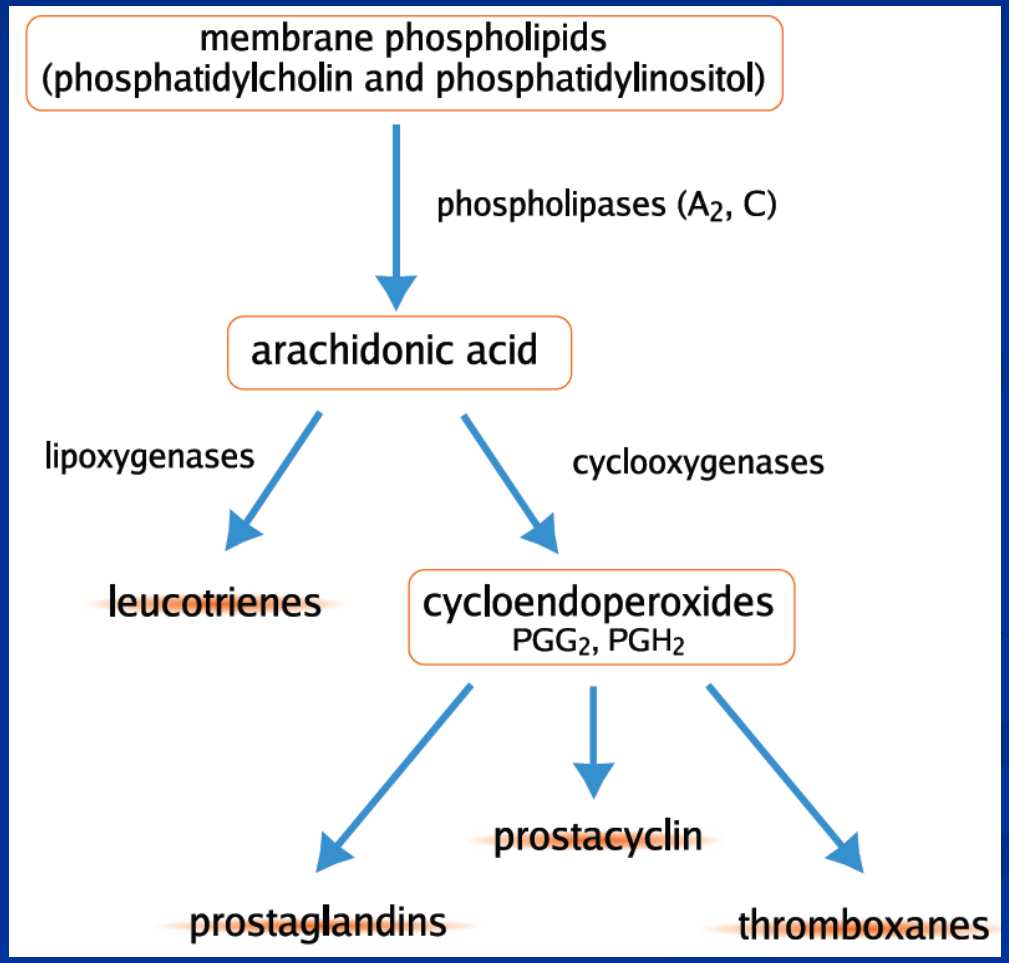


Mediator	Source	Principal action
Cell-derived		
Histamine	Mast cells, basophils, platelets	VD, ↑permeability, ↑endotel. activation
Serotonine	Platelets	VD, ↑permeability
Prostaglandins	Mast cells, leukocytes	VD, pain, fever
Leukotriens	Mast cells, leukocytes	↑permeability,CHT,leu adhesion+activ.
Platelet-activating 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

Arachidonic acid metabolites (Eicosanoids)

Action	Eicosanoid
Vasodilatation	PGI_2, PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotrienes B_4

The lipooxygenase and cyclooxygenase pathway. Membrane phospolipids are converted to arachidonic acid through the action of phospolipases, which is further metabolised through cyclooxygenase and lipooxygenase pathways. The cyclooxygenases convert the arachidonic acid to unstable cylcloendoperoxides, which are converted to prostaglandins, prostacyclin and thromboxanes. The lipoxygenases metabolise arachidonic acid through hydroperoxyeicosatetraenoic acids (HPETEs) to leukotrienes.



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:**

  produced by proteolytic cleavage of precursors: mediate vascular reaction, pain

Defects in leukocyte function

- **Bone marrow suppression** – decreased leukocyte numbers
- **Metabolic diseases** (DM – abnormal leukocyte function)
- **Malignancy, sepsis, immunodeficiencies, leukemia, anemia, malnutrition, hemodialysis**
- **Genetic disorders:**

- Defects in leukocyte adhesion and migration through endothelium, defective phagocytosis and generation of an oxidative burst (LAD-1, LAD-2: absence of sialyl-Lewis X (oligosaccharide on leukocytes that binds to selectins on activated endothelium))
- Defects in microbicidal activity (chronic granulomatous disease, AR, X-linked – genetic defect responsible for lack of ROS; MPO deficiency)
- Defects in phagolysosome formation (Chediak-Higashi syndrome – AR, disordered intracellular trafficing to organelles)

Classification of inflammation:

- acute
- chronic

- Granulomatous (specific)
- non-granulomatous (non-specific)

Non-specific inflammation

(leucocytes, lymphocytes, macrophages; non-specific granulation tissue):

- **Alterative**
- **Exsudative**
- **Proliferative**

Inflammation – microscopic appearance

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

Inflammation – microscopic appearance

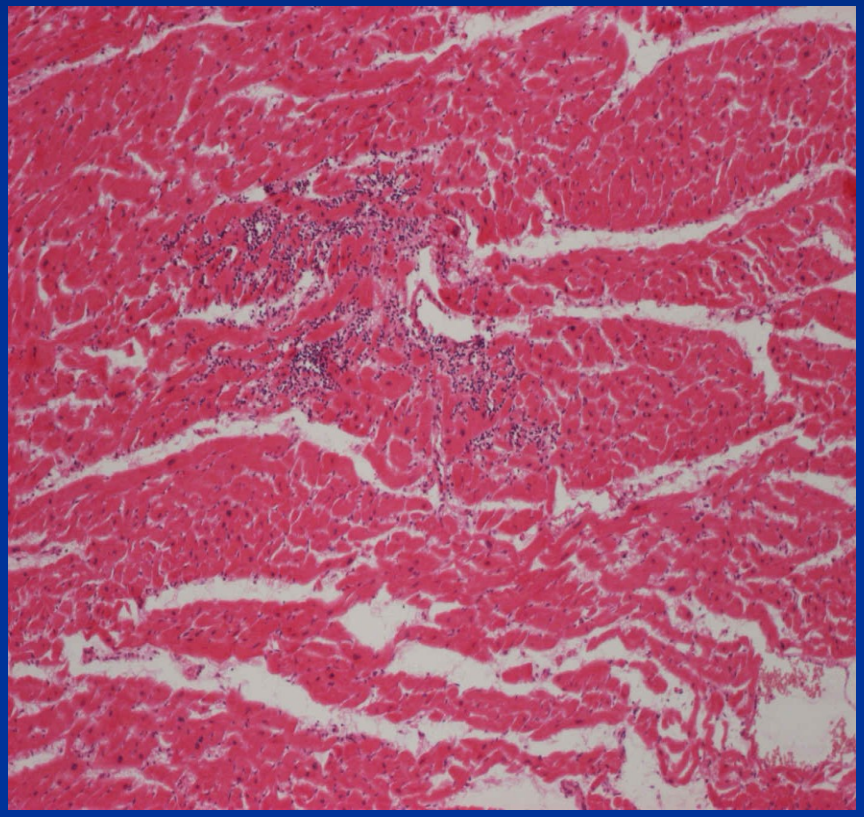
- PROLIFERATION:
  - proliferation of fibroblasts and capillaries
  - formation of granulation and fibrous tissue

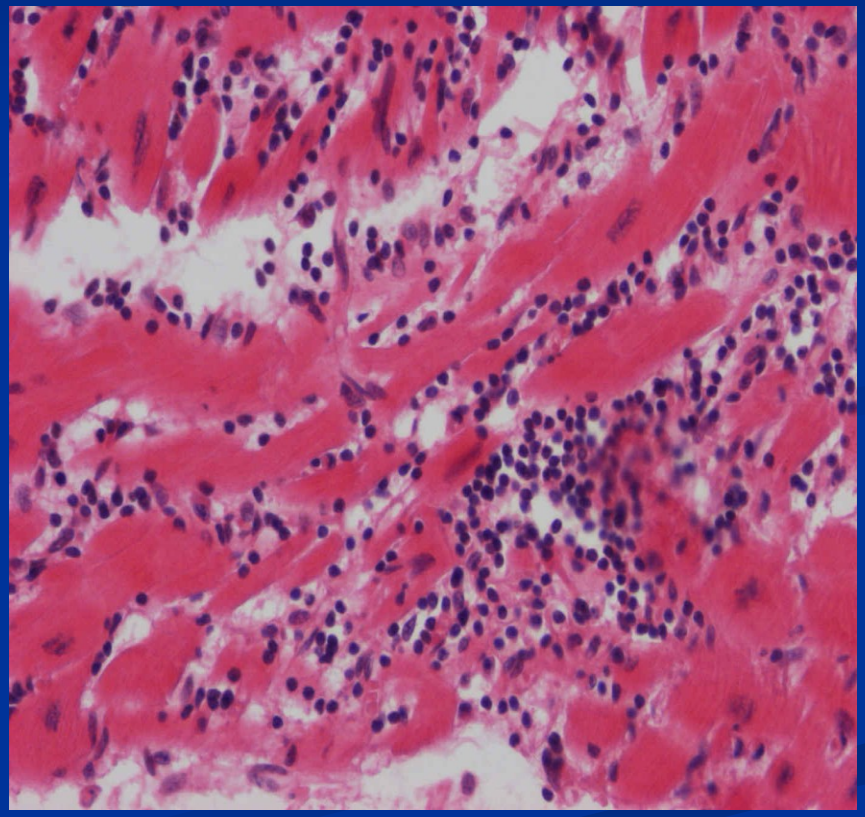
- IMMUNE RESPONSE:
  - antigen presentation
  - T and B-lymphocytes reaction
  - production of antibodies by plasma cells
  - memory cells

Morphologic patterns of acute inflammation

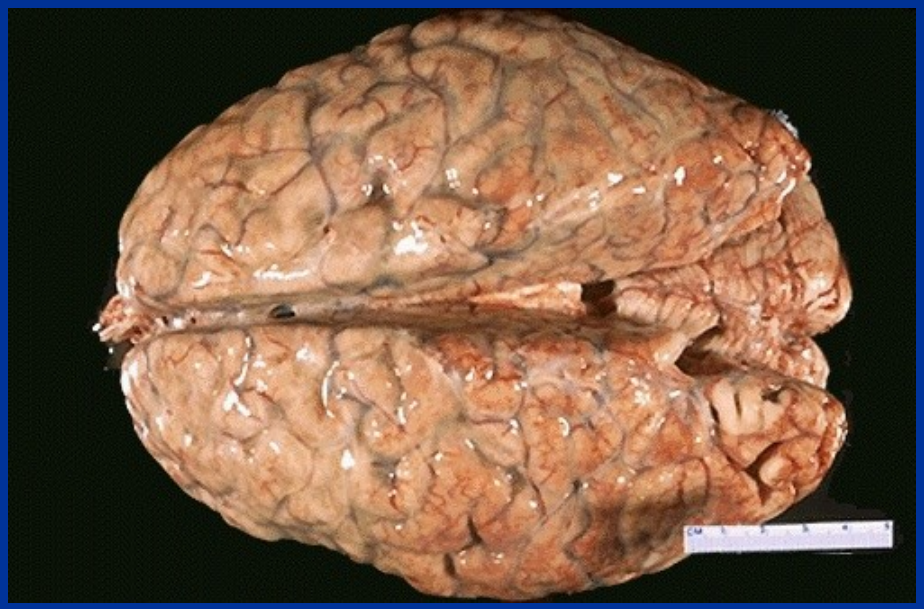
- Serous inflammation
- Catarrhal inflammation
- Fibrinous inflammation; pseudomembranes, ulcers
- Haemorrhagic inflammation
- Non-suppurative (lymphoplasmocytic) inflammation
- Suppurative (purulent) inflammation, abscess
- Necrotizing (gangrenous) inflammation

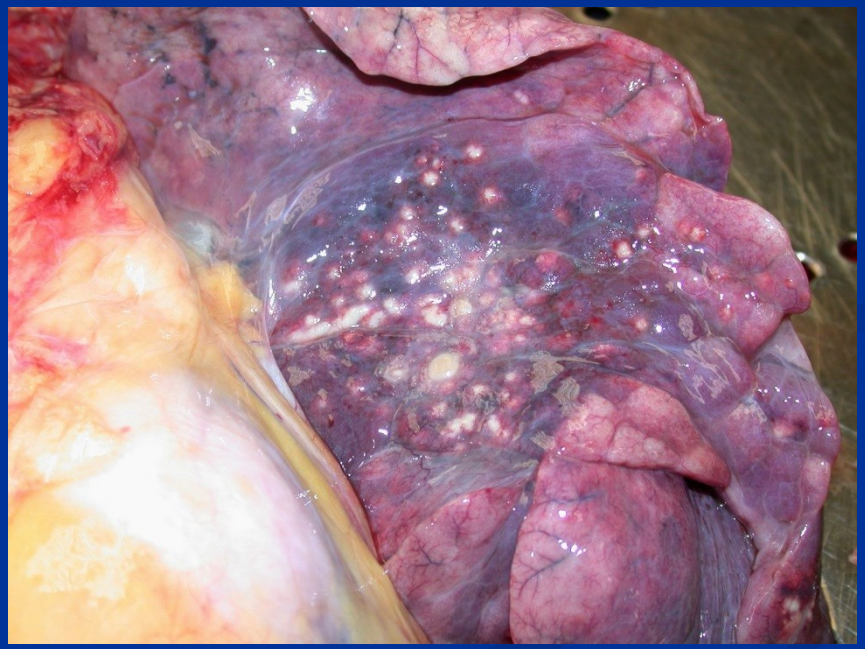
Non-suppurative inflammation – lymphoplasmocytic – interstitial myocarditis



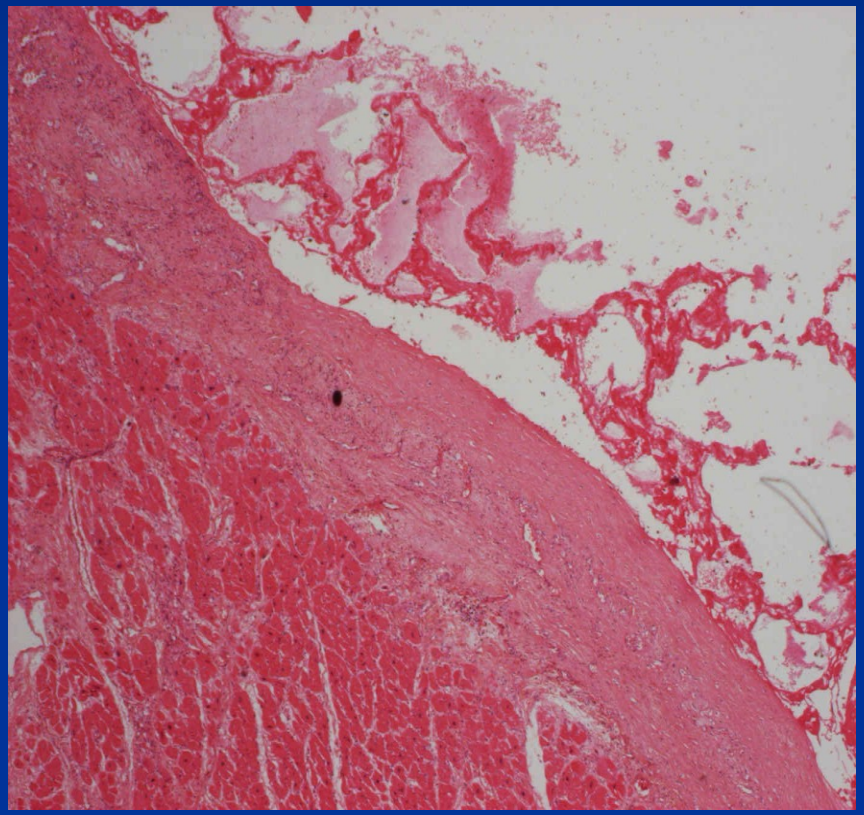


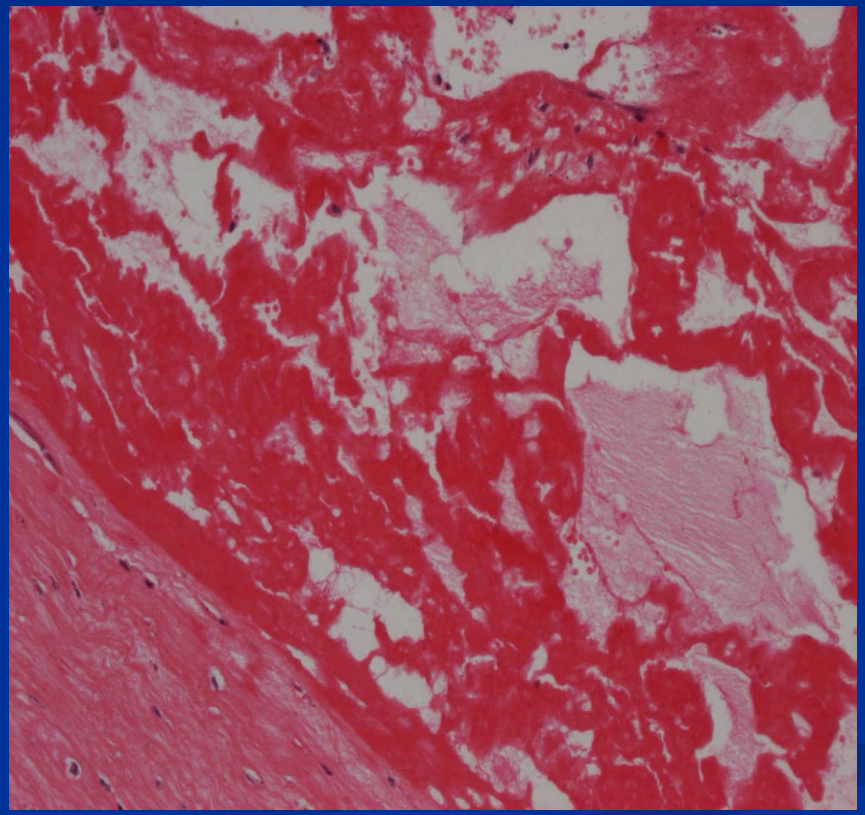
Suppurative (purulent) inflammation: purulent meningitis and absceding bronchopneumonia





Fibrinous pericarditis.





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)

Growth factors involved in regeneration and repair associated with inflammation

- Epidermal growth factor (EGF)

(regeneration of epithelial cells)

- Transforming growth factor alpha and beta (TGF)

(regeneration of epithelial cells)

- Platelet-derived growth factor(PDGF)

(stimulation of fibroblasts proliferation, collagen synthesis)

- Fibroblast growth factor(FGF)

(stimulation of fibroblasts proliferation, angiogenesis, regeneration of epithelial cells)

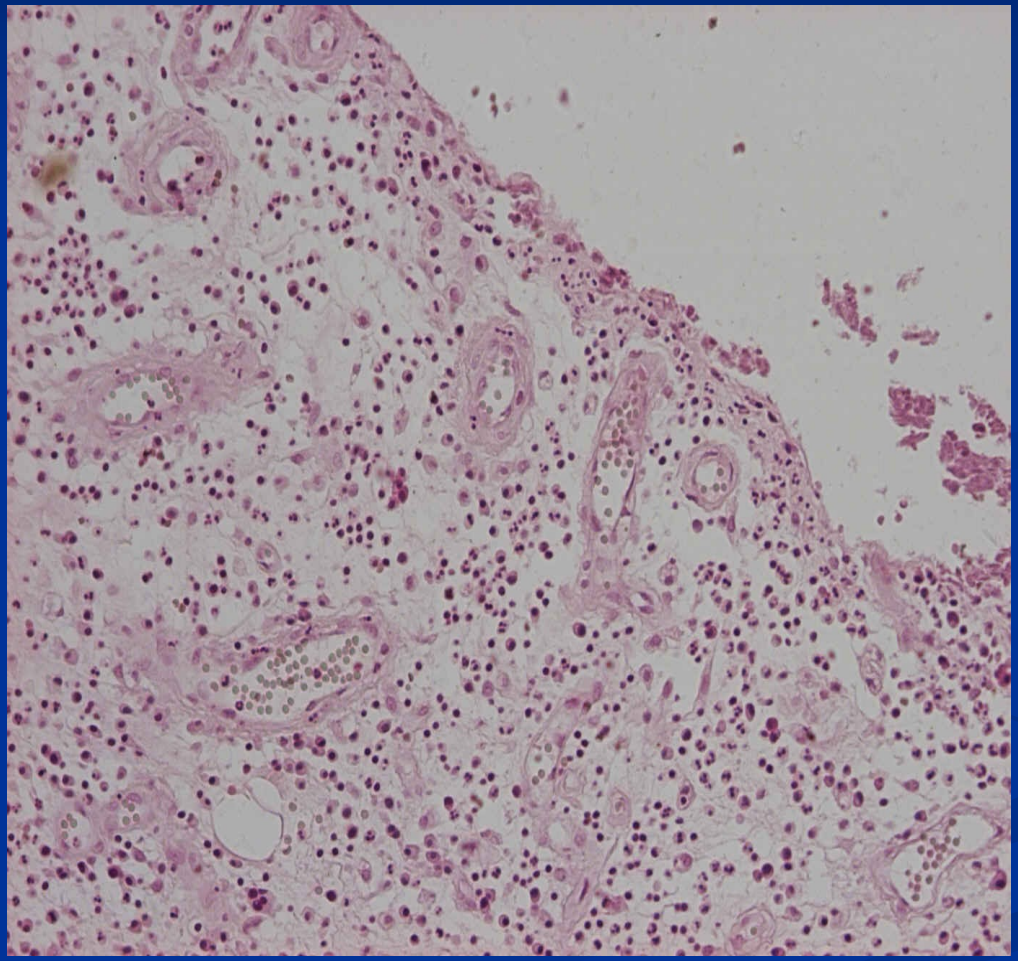
- Insulin-like growth factor (IGF-1)

(synergistic effect with othe growth factors)

- Tumor necrosis factor (TNF)

(stimulation of angiogenesis)

Granulation tissue:
(new vessels proliferation and fibrosis)



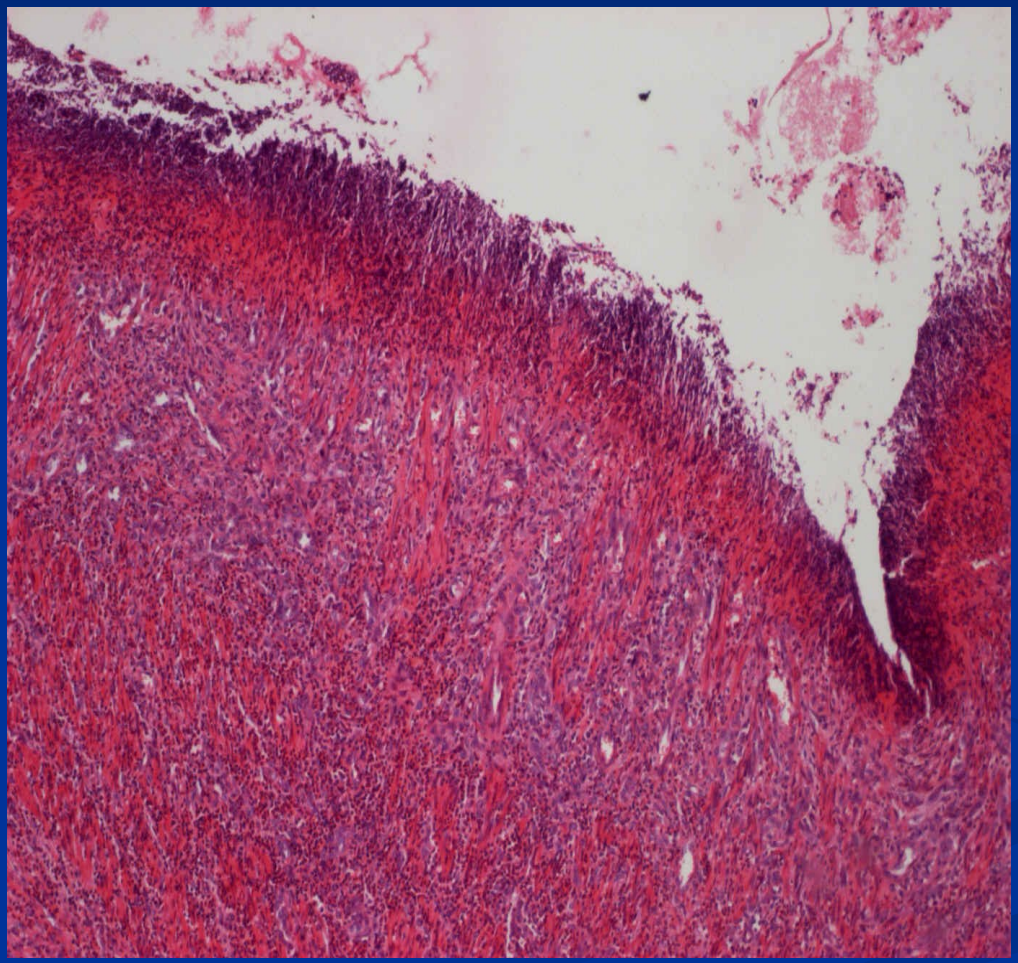
Granulation tissue

- 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

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

Chronic inflammatory cells and mediators (I)

- **Macrophages**
  - derived from circulatin blood monocytes
  - mononuclear phagocyte system: liver: Kupffer cells; lymph nodes, spleen: sinus histiocytes; CNS: microglia; lungs: alveolar macrophages
  - Activated by bacterial endotoxins, by cytokines from immune activated T cells (IFN-γ),…
  - Activated macrophages secrete a variety of biologically active products (acid and neutral proteases, ROS, NO, AA metabolites, IL-1, TNF, GFs influencing proliferation of smooth muscles and fibroblasts)

Chronic inflammatory cells and mediators (II)

- **Lymphocytes (B and T)**
  - Interaction with macrophages
  - TCR on macrophages, produce cytokines (IL-2) stimulating T-cells, which produce cytokines (IFN-γ) activating macrophages
  - Plasma cells derived from activated B-cells: production of antibodies against persistent antigens

- **Eosinophils** (immune reactions mediated by IgE)
  - in parasitic infections
  - in allergies

- **Mast cells**
  - In both chronic and acute inflammation
  - IgE coated mast cells release histamins, AA metabolites
  - Central players in allergic reactions, incl. anaphylactic shock

Relationship of chronic inflamation and carcinogenesis

- **Increased production of ROS, cytokines, pro-inflammatory transcription factors**

- **Mediators if inflammation:**

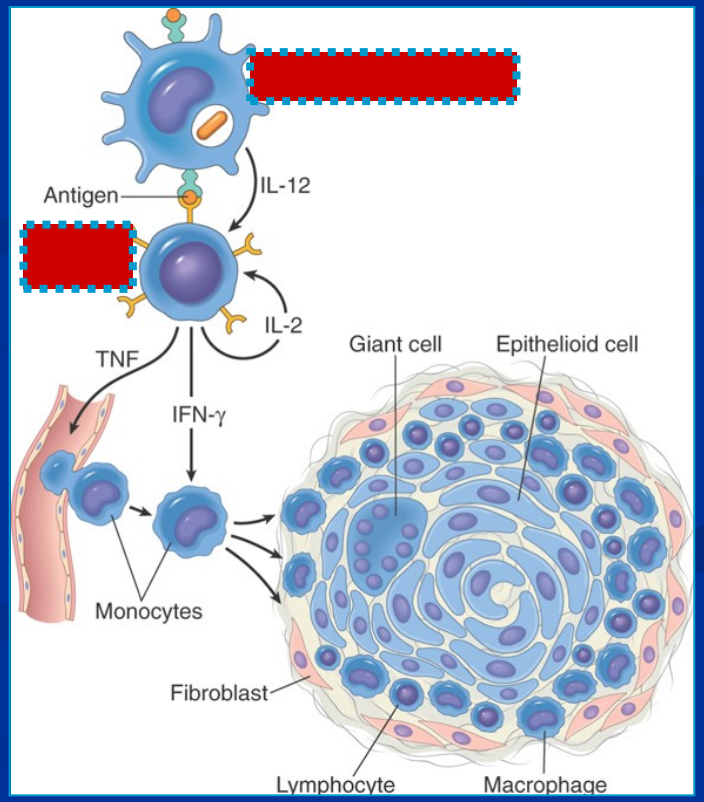
- Induction of genetic damage
- Induction of cell proliferation
- Inhibition of apoptosis
- Regulation of tumor angiogenesis

Relationship of chronic inflamation and carcinogenesis

- Barrett´s oesophagus – adenocarcinoma of qoesophagus
- Ulcerative colitis – colorectal cancer
- Chronic pancreatitis – pancreatic cancer
- Viral hepatitis B, C – hepatocellular carcinoma
- Atrofic gastritis – adenocarcinoma of stomach
- Chronic gastritis (Helicobacter pylori) – MALT lymphoma and adenocarcinoma of stomach
- Chronic lymphocytic thyreoiditis – carcinomas and lymhomas of thyroid

Granulomatous inflammation

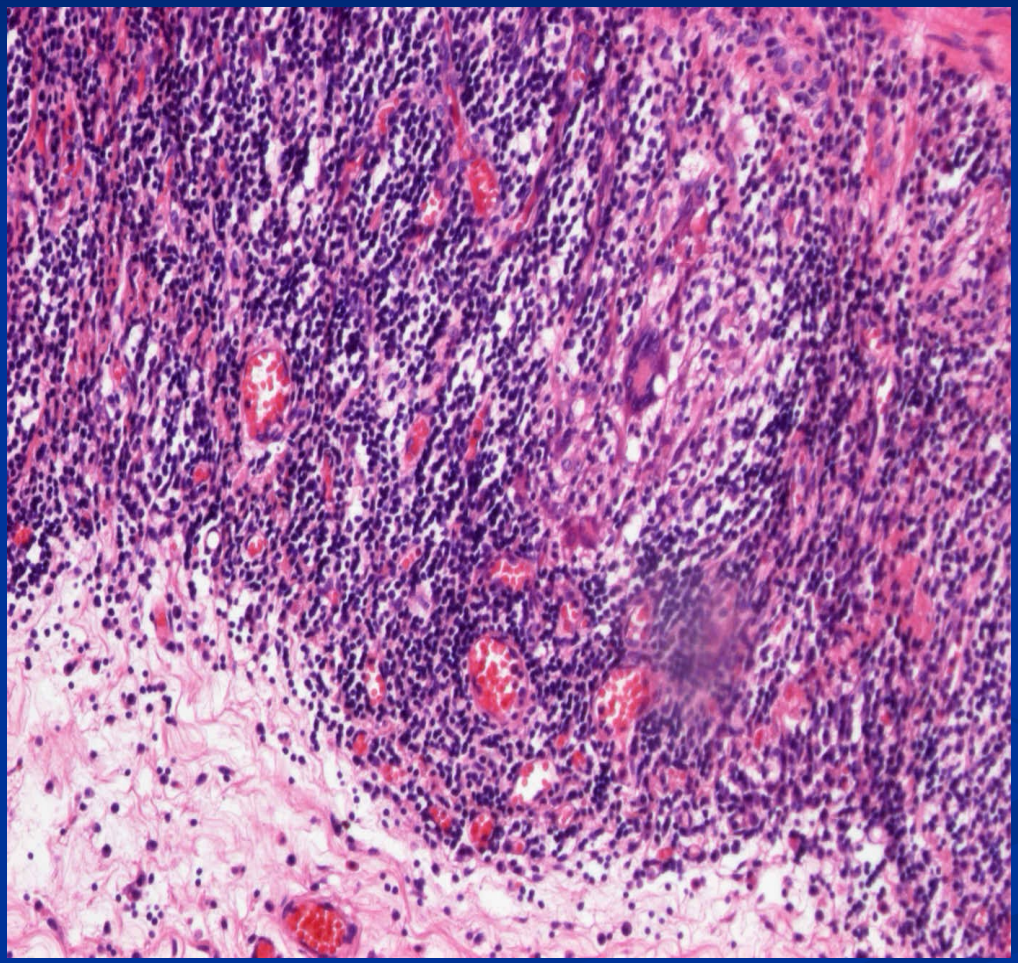
- Aggregates of activated macrophages (epitheloid)
- Non-immune granulomas (response to foreign bodies, chemicals)
- Immune granulomas
  - Necrotizing (tbc)
  - Non-necrotizing (sarcoidosis)
- Persistent T-cell response
- Tuberculosis –
  a prototype of granulomatous disease



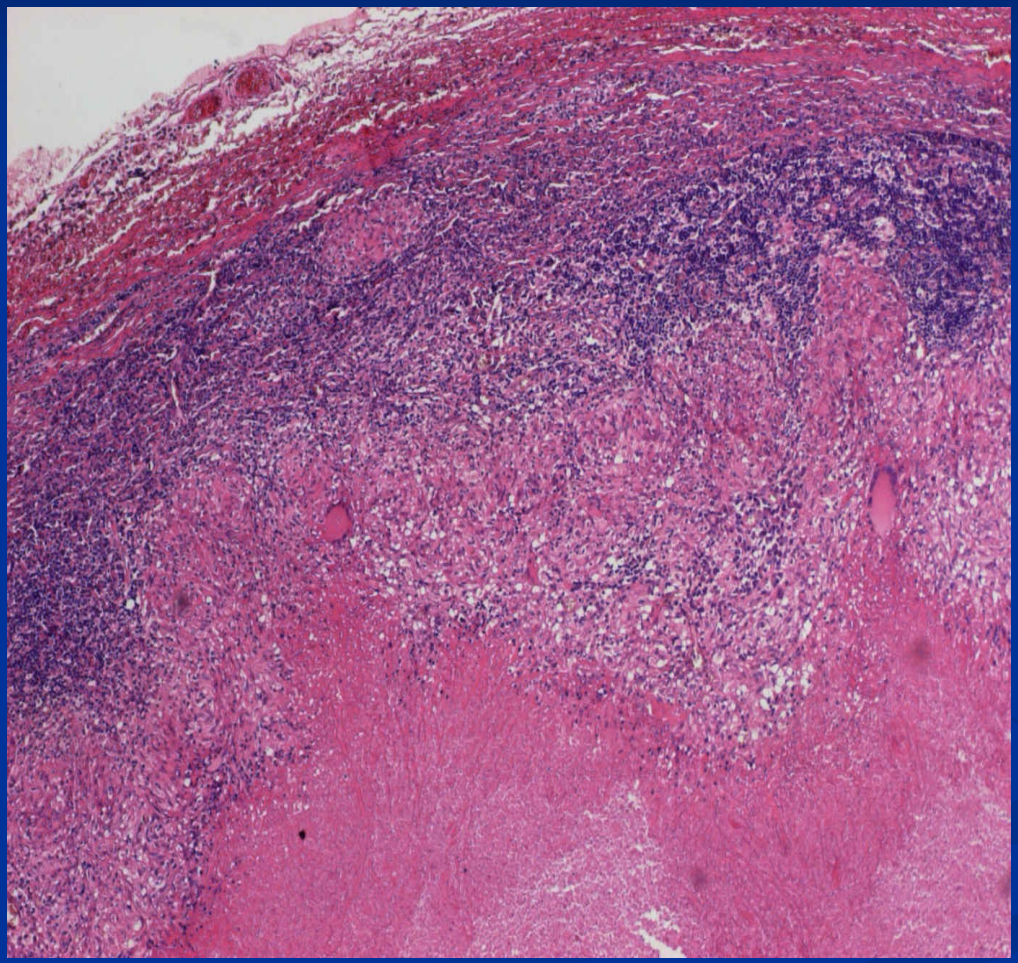
Examples of diseases with granulomatous inflammation

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, chemicals (berrylium)	Giant cell granulomas (foreign body granulomas)
Crohn disease (IBD)	Immune reaction against intestinal bacterial, self antigens	Occasional noncaseating granuloma in wall of intestine+chronic inflammatory infiltrate

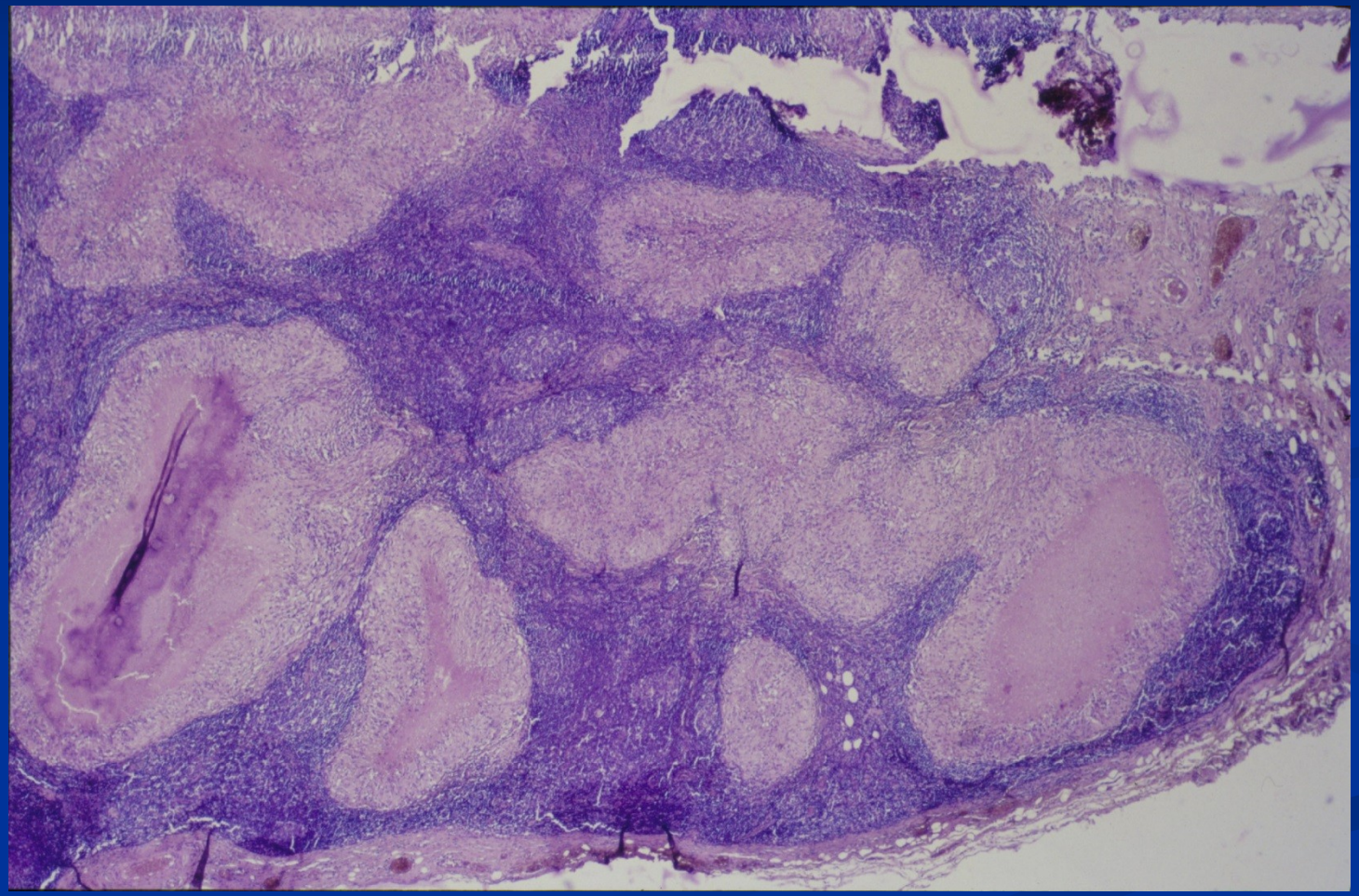
Morbus Crohn – noncaseous granuloma in subserous tissue.



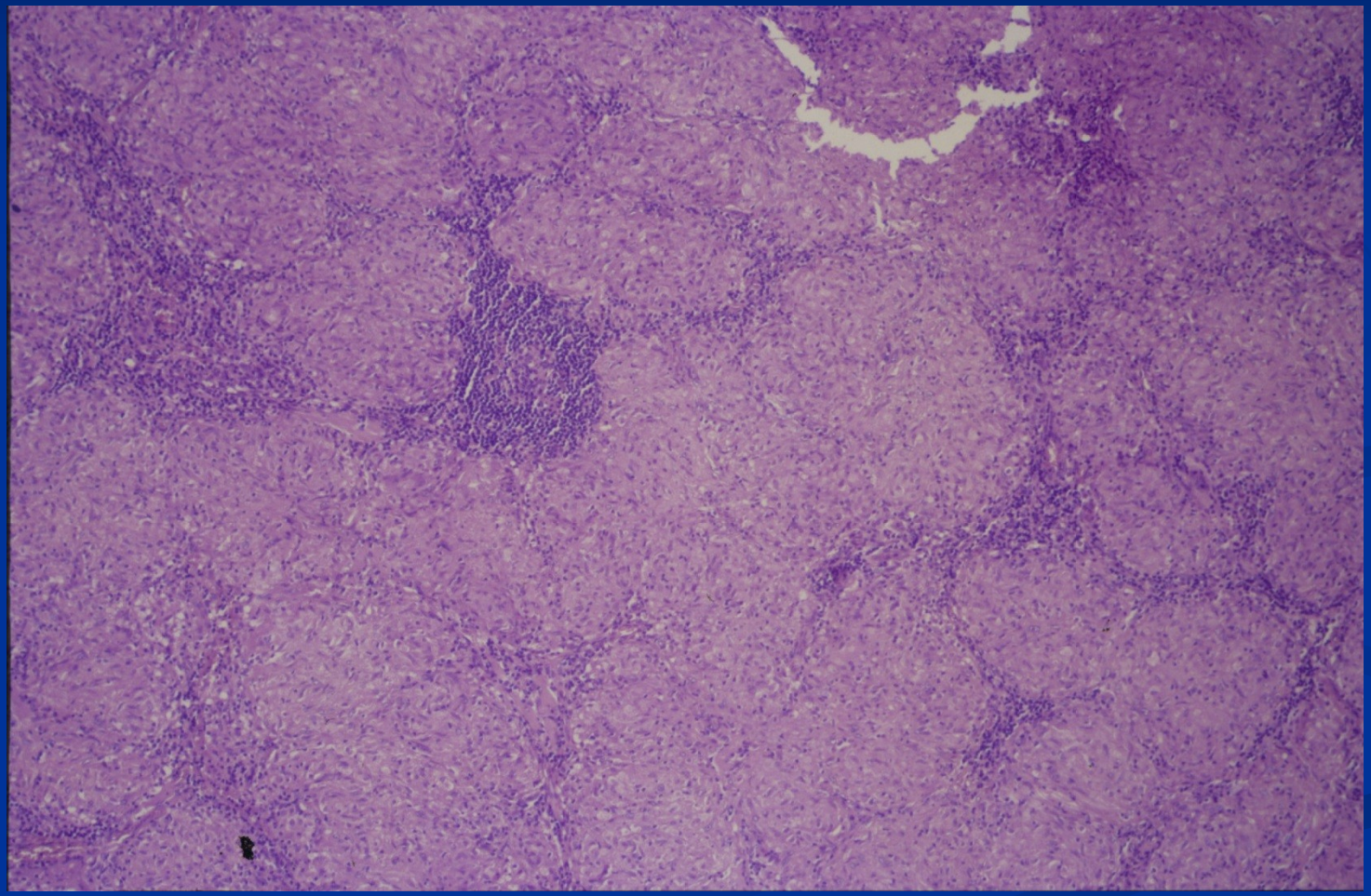
Tuberculous lymphadenitis.



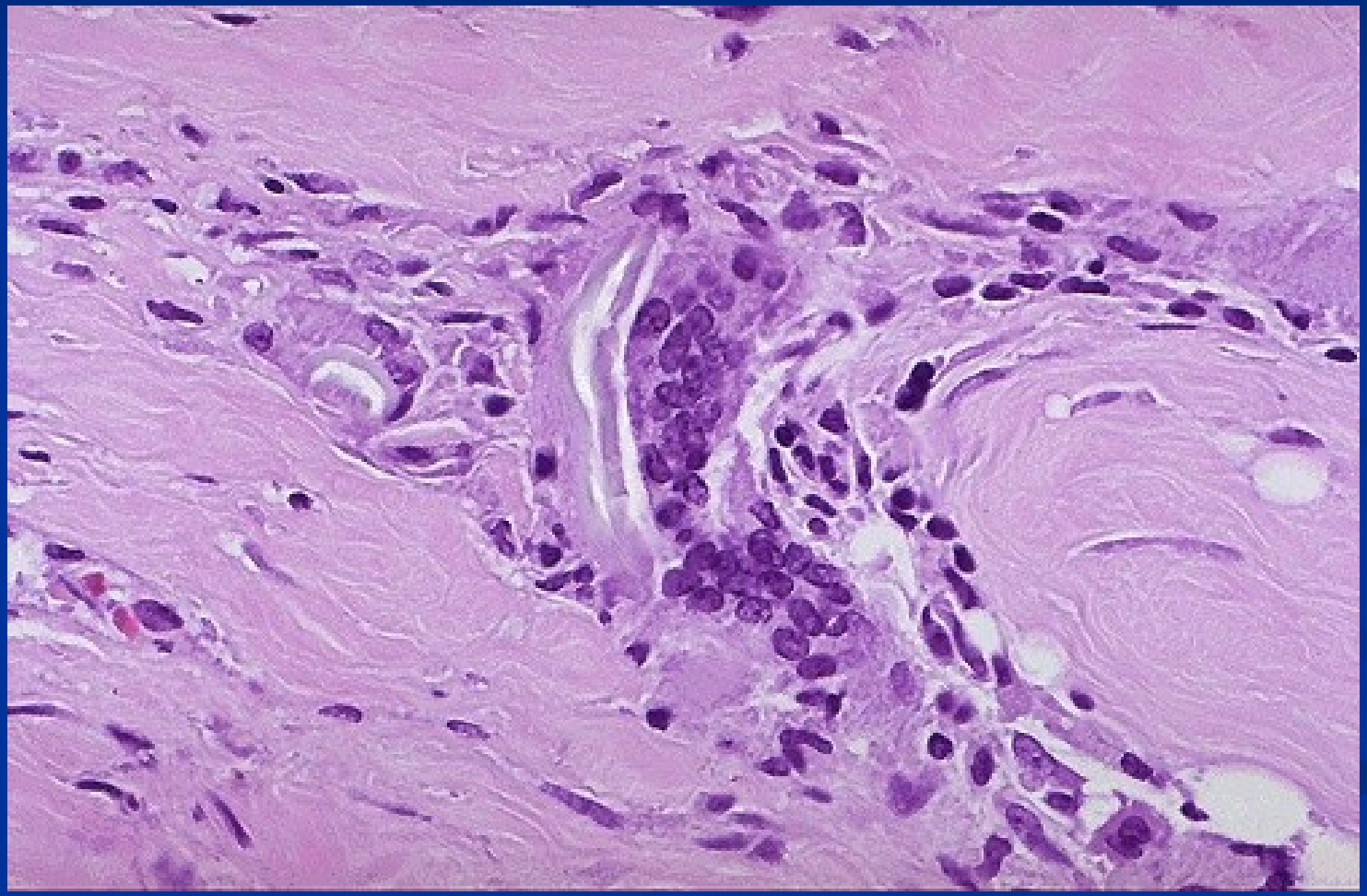
Granulomatous-purulent lymphadenitis – cat scratch disease.



Sarcoidosis of a lymph node



Granulomatous giant cell reaction around foreign bodies.



Systemic effects of inflammation

- **Fever**

  (cytokines (TNF, IL-1) stimulate production of PGs in hypothalamus)
- **Constitutional symptoms**

  (malaise, anorexia, nausea, weight loss in chronic inflammation)
- **Production of acute phase proteins**

  (CRP, fibrinogen, SAA – synthesis stimulated by cytokines (IL-6))
- **Haematological changes:** leukocytosis, increased erythrocyte sedimentation rate, anaemia
- **In some severe infections, septic shock** (↓BP, DIC, metabolic abnormalities)
- **Secondary amyloidosis** (in chronic inflammation)

Thank you for your attention …