Volgograd state medical university

Department of pathological anatomy

Lecture

INFLAMMATION

Dentistry faculty

Inflammation is a **protective response** intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult

Etiology of Inflammation

Physical agents:

- extreme temperatures,
- electricity,
- irradiation,
- mechanical injures, etc.

Chemical agents:

- Products of metabolism,
- acids,
- alkalis,
- drugs,
- tissue necrosis

Biological agents:

- Microorganisms (bacteria, viruses, fungi),
- parasites (helmints, insects),
- immune cells and complexes

Inflammatory phases

1. **Alteration** – damage\injury (dystrophy and necrosis) and production of mediators.

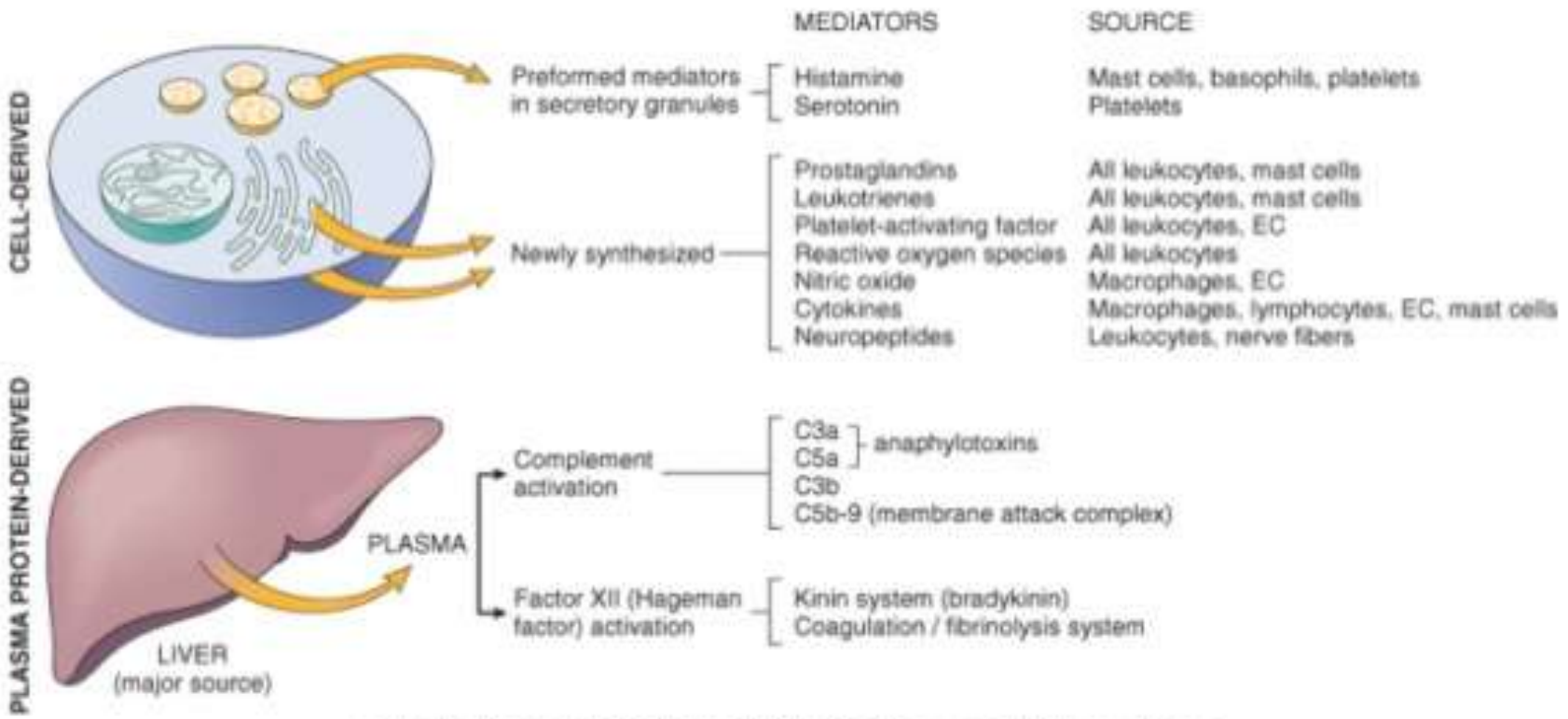
2. **Exudation** – the reaction of microcirculation, formation of liquid exudate, migration of leukocytes, phagocytosis .

3. **Proliferation** - proliferation of cell of hematogenous (macrophages, lymphocytes) and histiogenous (fibroblasts) cells.

Chemical mediators of inflammation

Chemical mediators

- Plasma-derived:
  - Complement, kinins, coagulation factors
  - Many in "pro-form" requiring activation (enzymatic cleavage)
- Cell-derived:
  - Preformed, sequestered and released (mast cell histamine)
  - Synthesized as needed (prostaglandin)



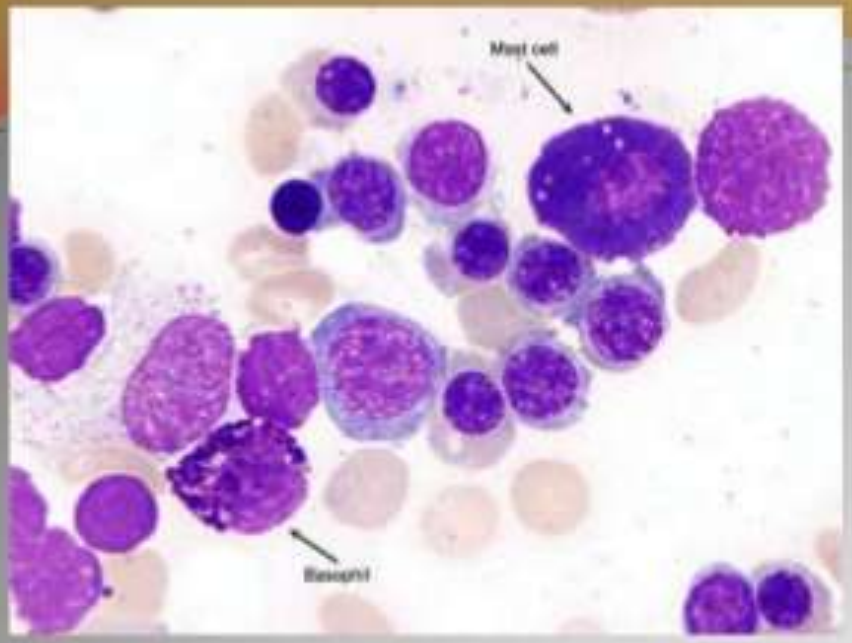
Diversity of Effects of Chemical Mediators

Prostaglandins :

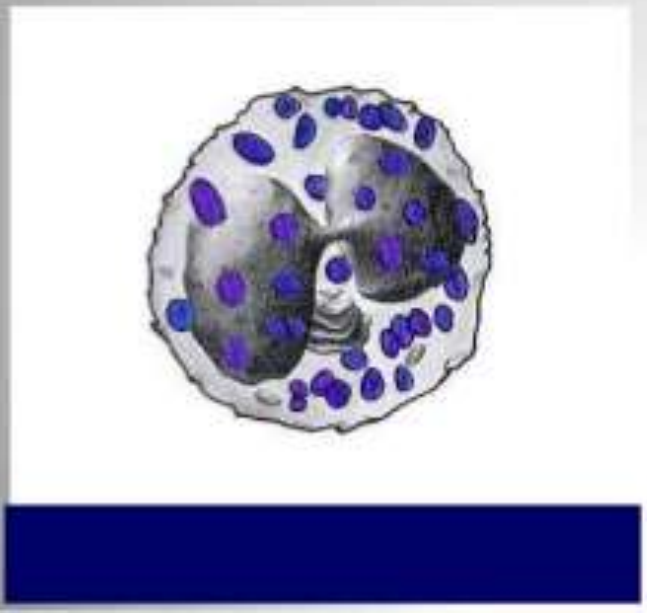
- Vasodilation
- Pain
- Fever
- Potentiating edema

IL-1 and TNF:

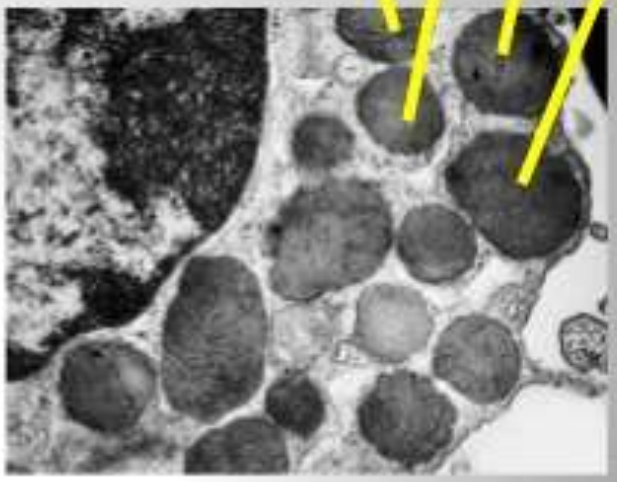
- Endothelial-leukocyte interactions
- Leukocyte recruitment
- Production of acute-phase reactants



Basophils & Mast Cells



Histamine



Role of Mediators in Different Reactions of Inflammation

Vasodilatation	Prostaglandins Nitric oxide Histamine
Increased vascular permeability	Vasoactive amines C3a and C5a (through liberating amines) Bradykinin Leukotrienes C4, D4, E4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	C5a Leukotriene B4 Chemokines IL-1, TNF Bacterial products
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites Nitric oxide

Summary of Mediators of Acute Inflammation

	ACTION			
Mediator	Source	*Vascular Leakage*	*Chemotaxis*	*Other*
Histamine and serotonin	Mast cells, platelets	+	-	
Bradykinin	Plasma substrate	+	-	Pain
C3a	Plasma protein via liver	+	-	Opsonic fragment (C3b)
C5a	Macrophages	+	+	Leukocyte adhesion, activation
Prostaglandins	Mast cells, from membrane phospholipids	Potentiate other mediators	-	Vasodilatation, pain, fever
Leukotriene B_4	Leukocytes	-	+	Leukocyte adhesion, activation
Leukotrienes C_4 D_4 E_4	Leukocytes, mast cells	+	-	Bronchoconstriction, vasoconstriction
Platelet Activating Factor (PAF)	Leukocytes, mast cells	+	+	Bronchoconstriction, leukocyte priming
IL-1 and TNF	Macrophages, other	-	+	Acute-phase reactions, endothelial activation
Chemokines	Leukocytes, others	-	+	Leukocyte activation
	Macrophages, endothelium	+	+	Vasodilatation, cytotoxicity

Acute inflammation has two major components

- Vascular changes
- Cellular events

Vascular

- Changes in Vascular Caliber and Flow
- Increased Vascular Permeability

Pathogenesis of exudation phase

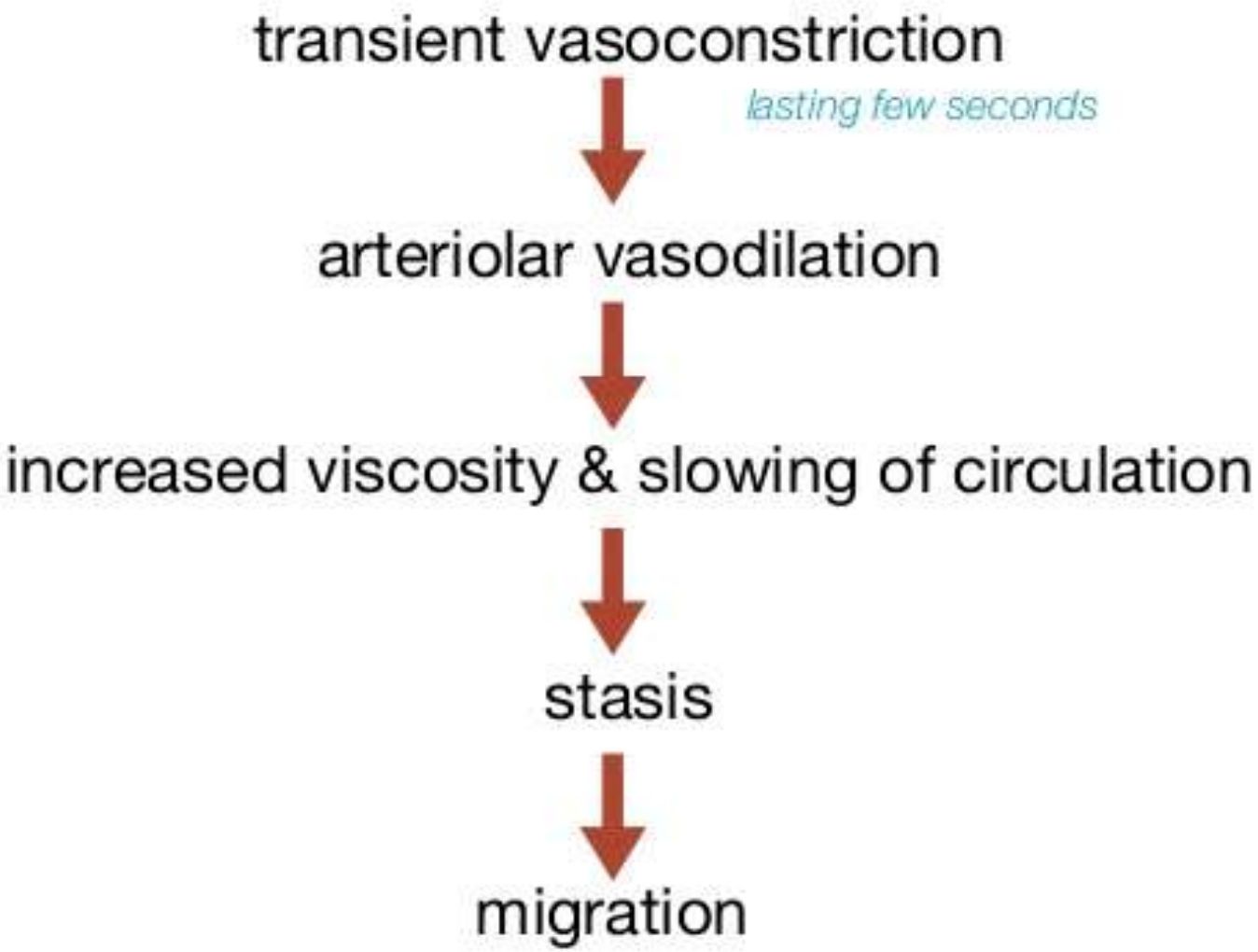
1. Initial short-term microvascular spasm, followed be a long persistent dilation

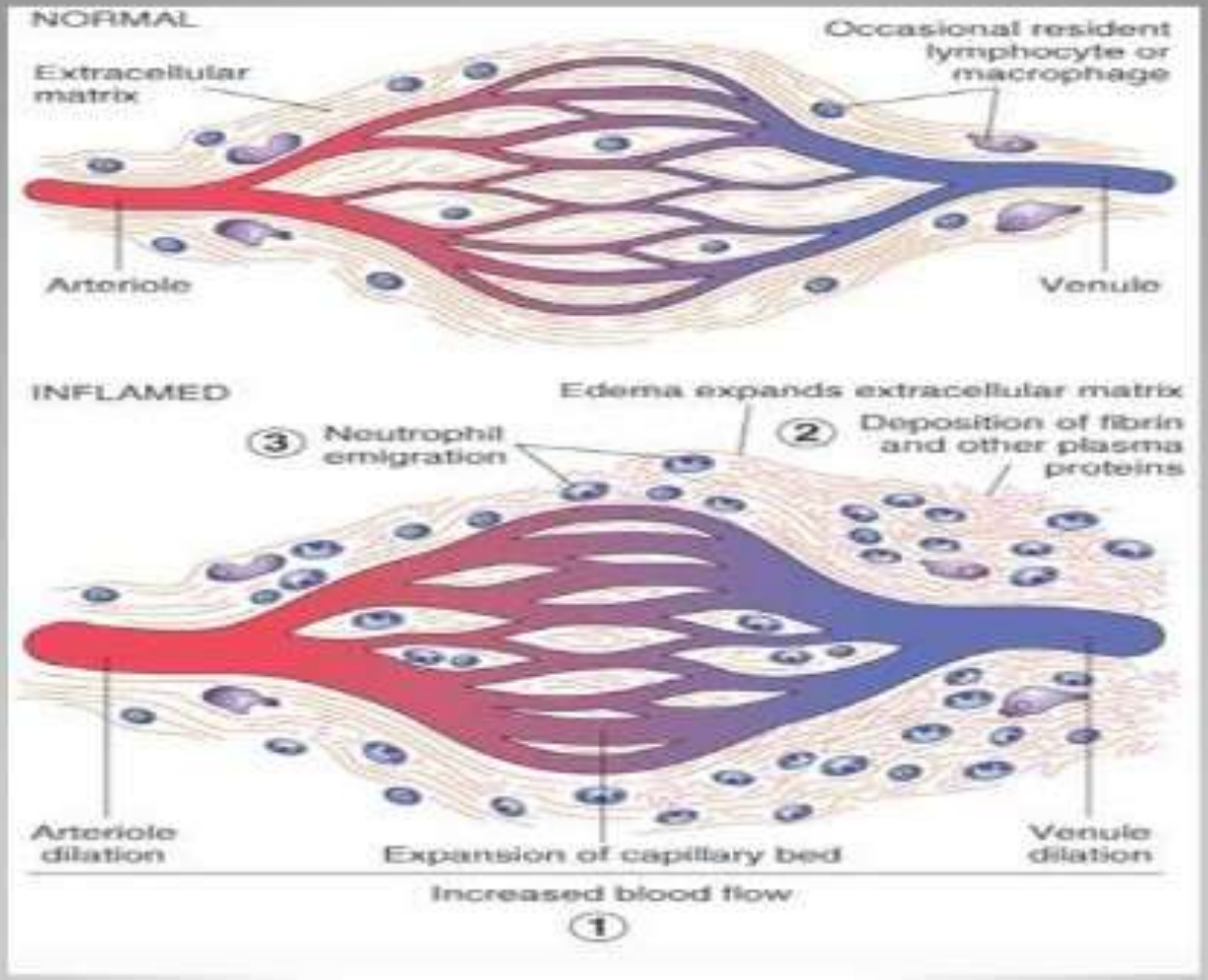
2. Release of plasma and its protein components (albumin, globulins, fibrinogen)

3. Stasis, diapedesis of leukocytes and red blood cells in the surrounding tissue

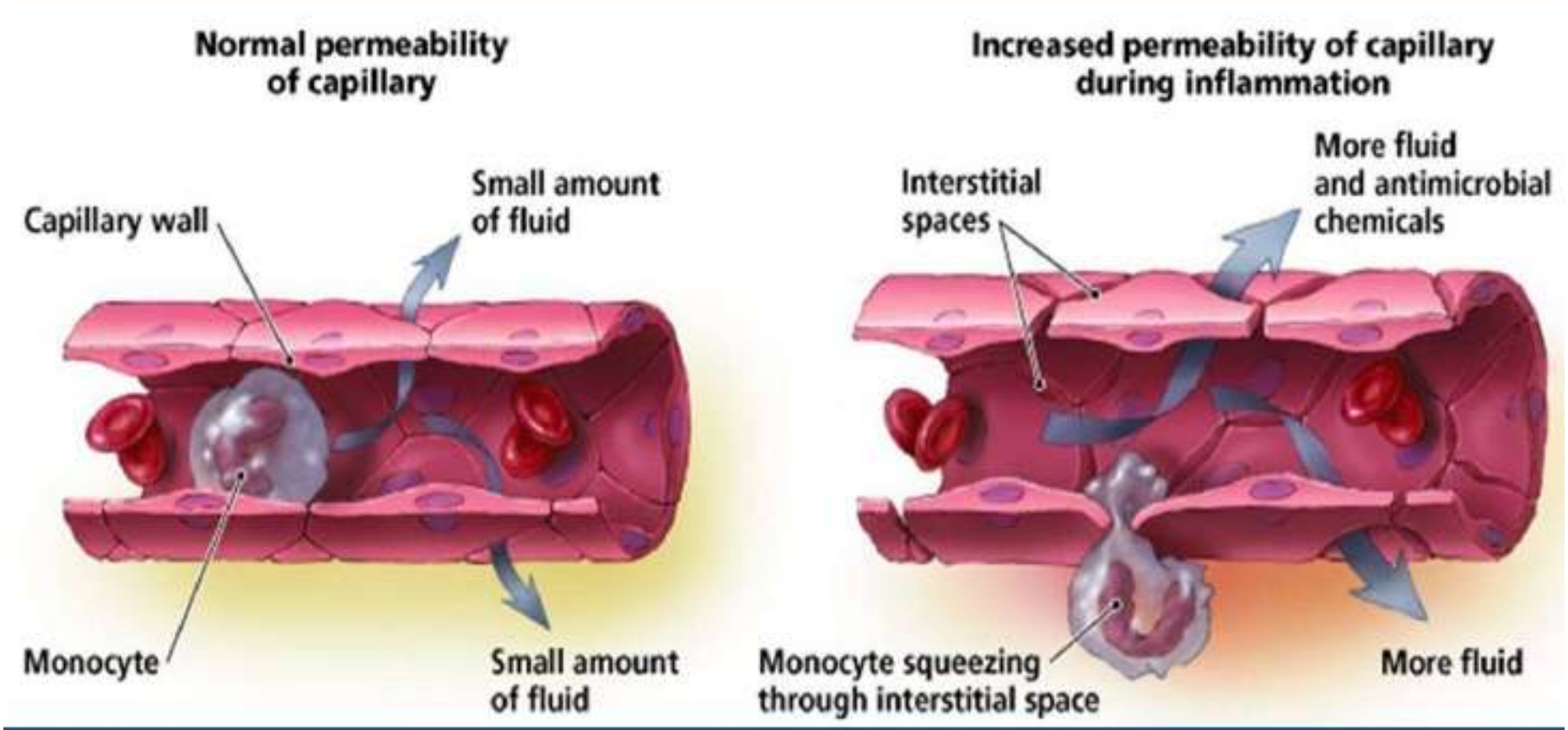
4. Formation of exudate

5. Phagocytosis


transient vasoconstriction
lasting few seconds
arteriolar vasodilation
increased viscosity & slowing of circulation
stasis
migration


NORMAL
Occasional resident lymphocyte or macrophage
Extracellular matrix
Arteriole
Venule
INFLAMED
Edema expands extracellular matrix
3 Neutrophil emigration
2 Deposition of fibrin and other plasma proteins
Arteriole dilation
Expansion of capillary bed
Venule dilation
Increased blood flow
1

Increased Vascular Permeability

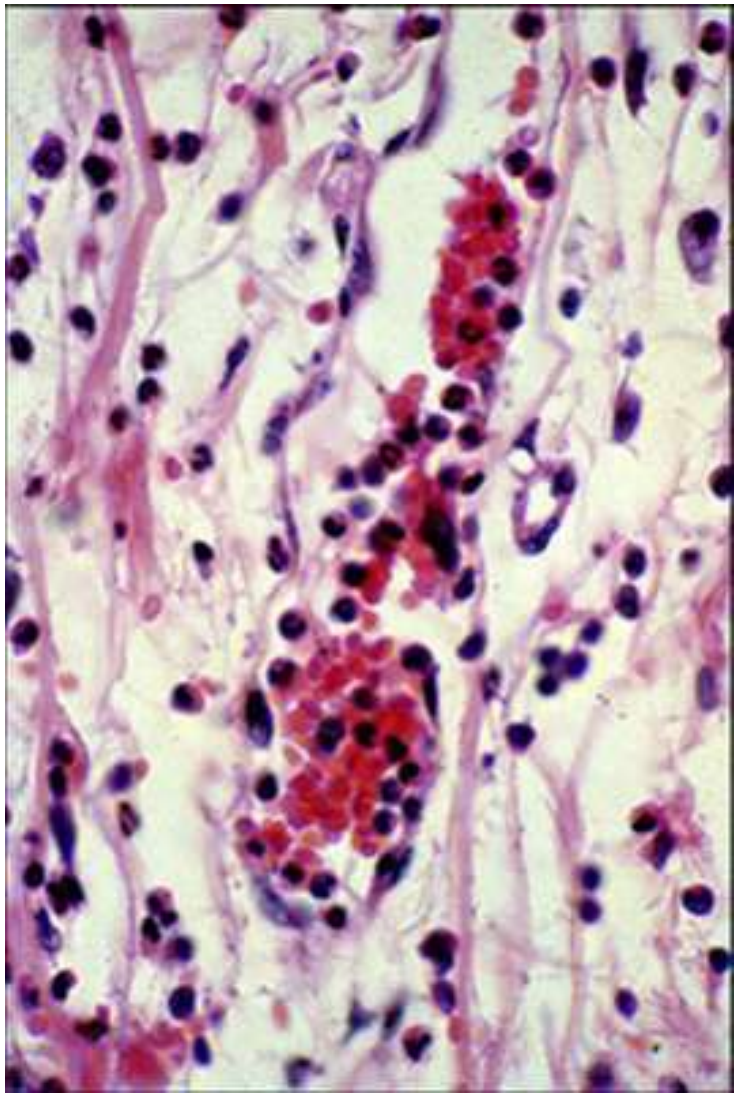


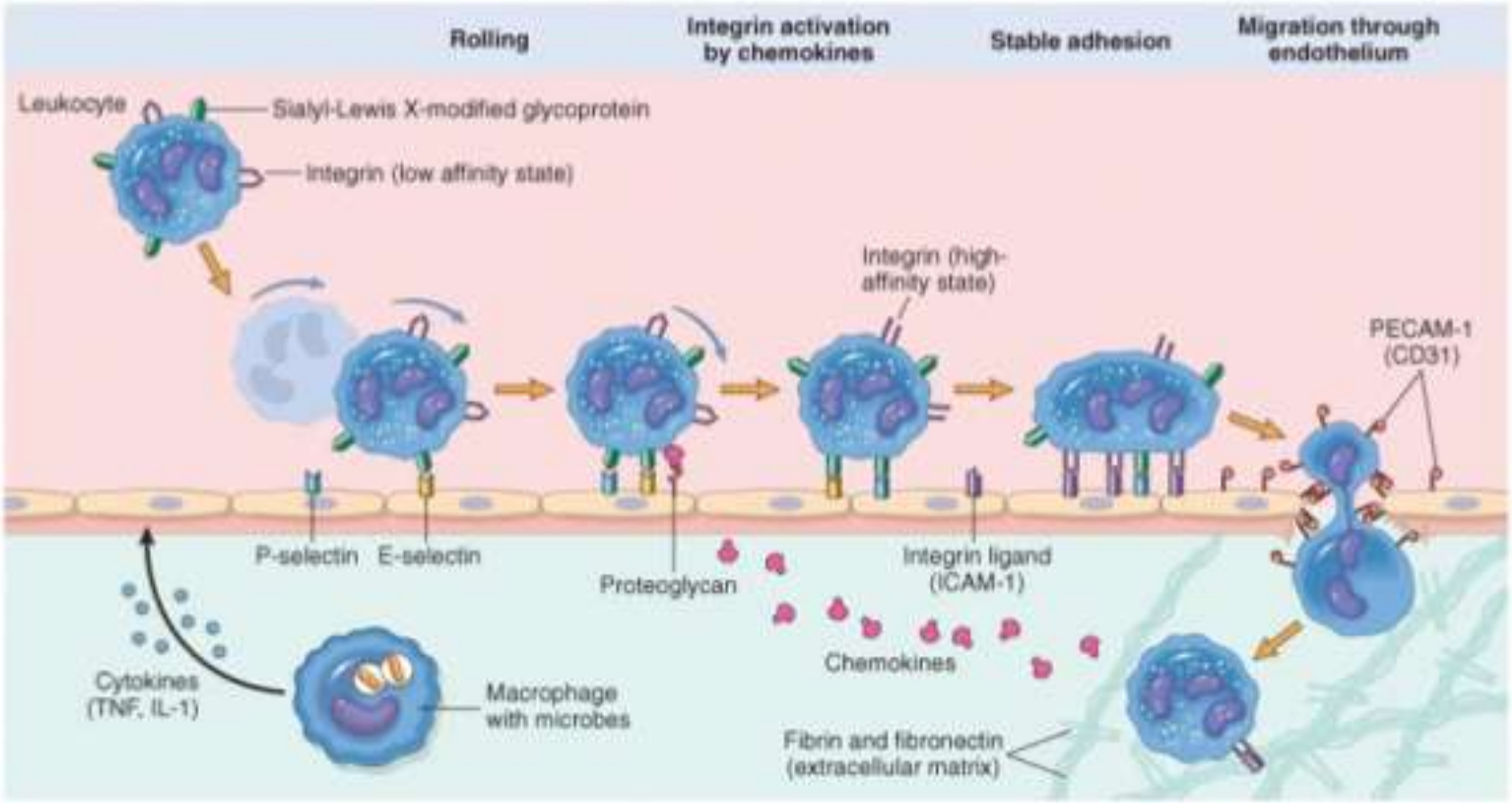
Cellular Events

- an important function of the inflammatory response is to deliver leukocytes to the site of injury and to activate them

EXTRAVASATION of PMNs

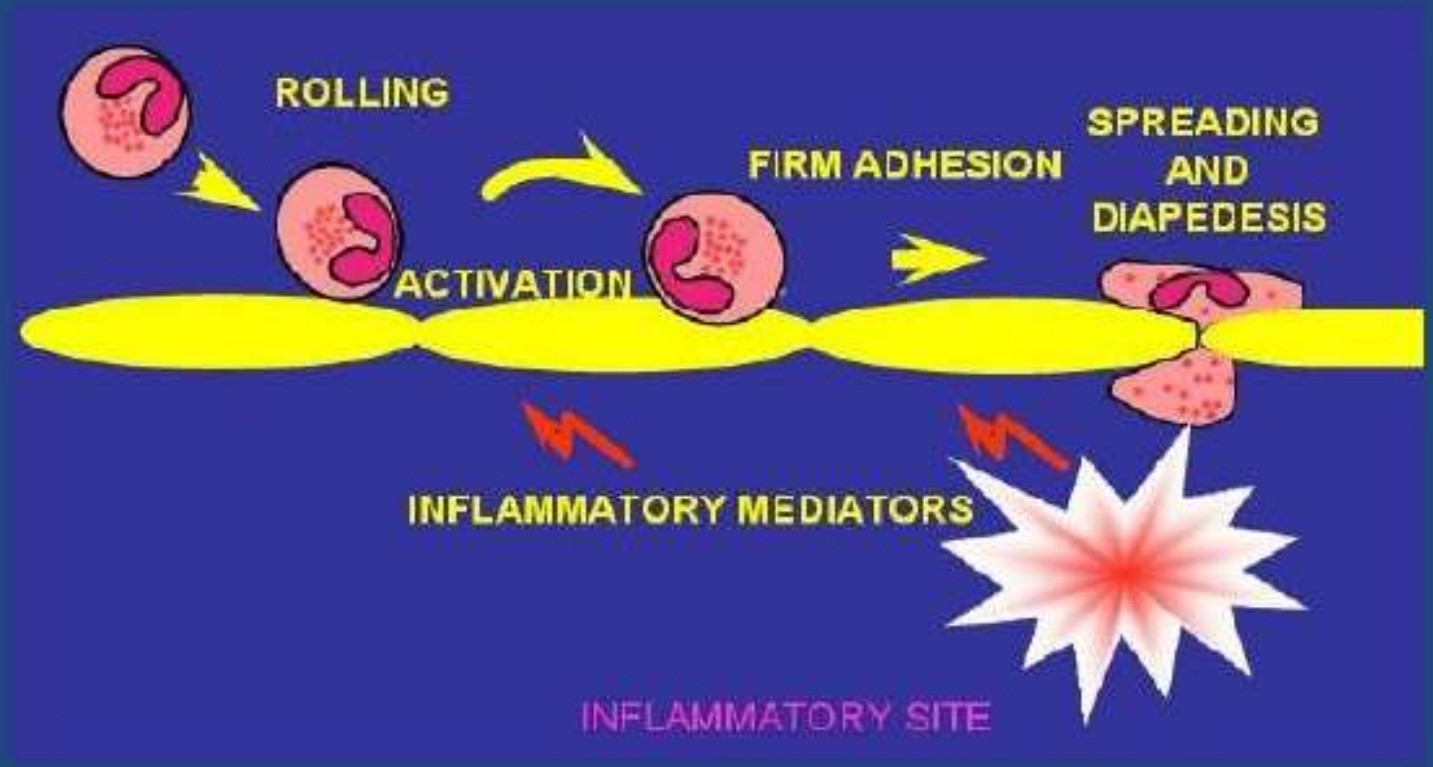
- **MARGINATION** (PMN's go toward wall)
- **ROLLING** (tumbling and HEAPING)
- **ADHESION**
- **TRANSMIGRATION** (DIAPEDESIS)



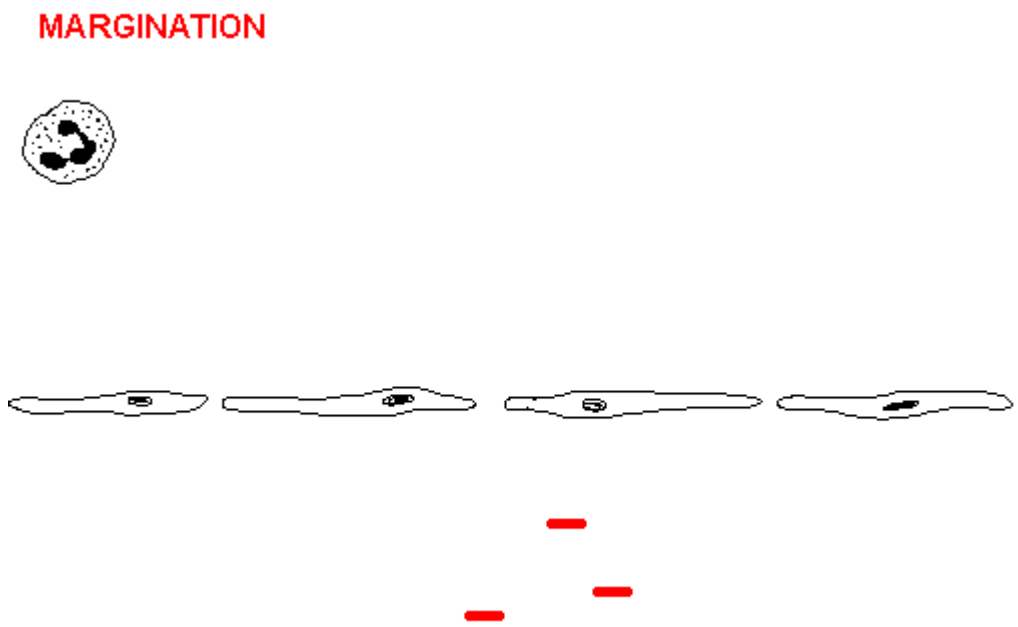


Leukocyte Recruitment

- Margination: Slow blood flow
  - White cells redistribute along periphery of lumen



Leukocyte recruitment



Chemotaxis

- Leukocytes follow chemical gradient to site of injury (chemotaxis)
  - Soluble bacterial products
  - Complement components (C5a)
  - Cytokines (chemokine family **e.g.**, IL-8)
  - LTB_4 (AA metabolite)(lymphotoxin beta -LTB,AA-Arachidonic acid)
- Chemotactic agents bind surface receptors inducing calcium mobilization and assembly of cytoskeletal contractile elements

Types of exudate

1. Serous exudate.
2. Fibrinous exudate.
3. Purulent (suppurative) exudate.
4. Hemorrhagic exudate.
5. Mixed exudate.

Phagocytosis

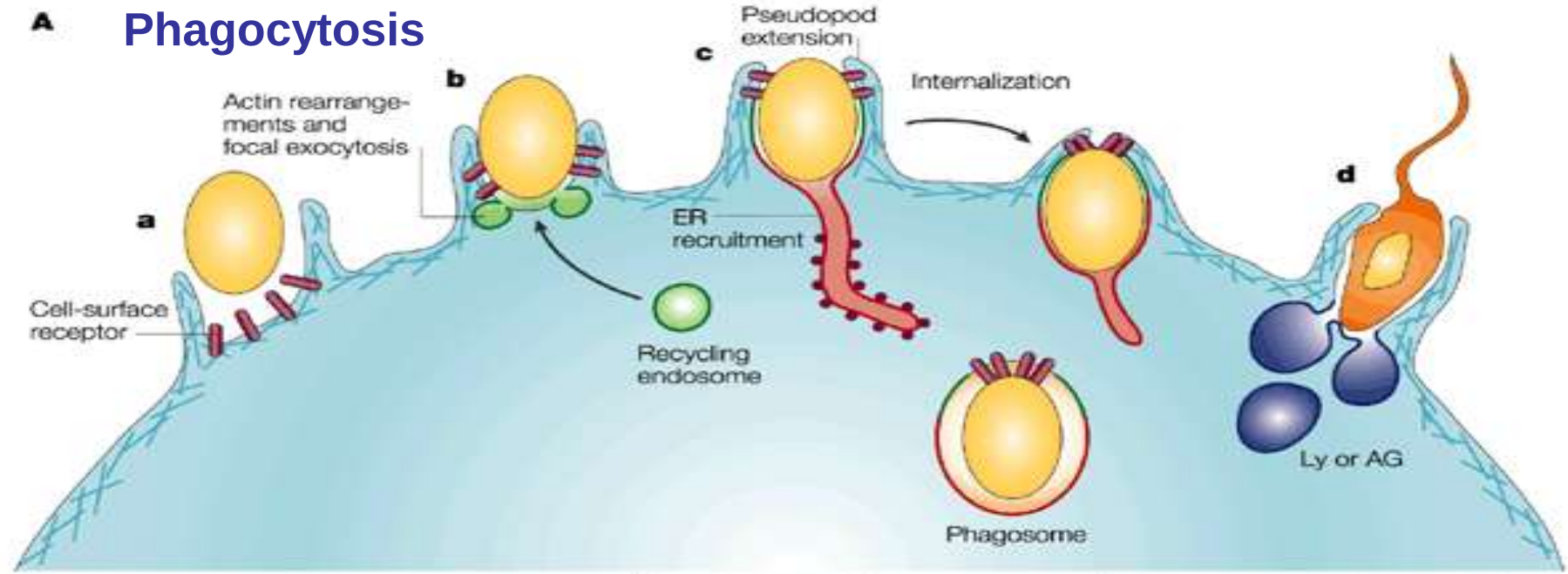
Consists of 3 distinct but interrelated steps

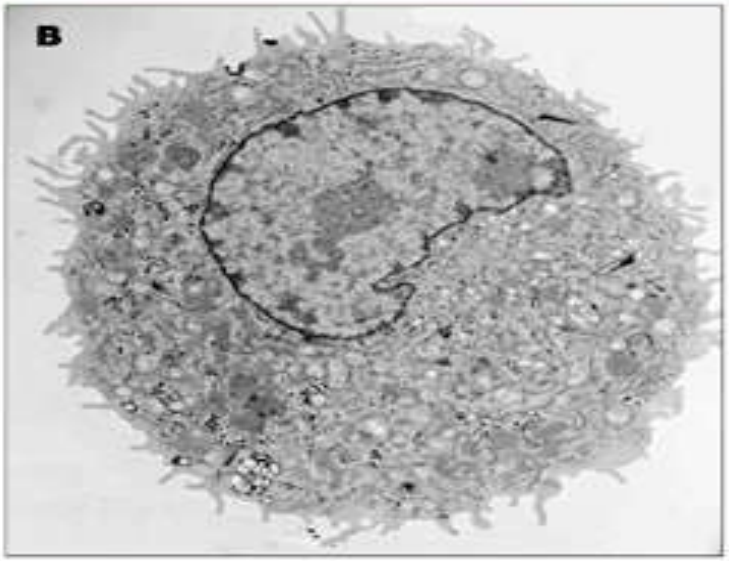
1. recognition and attachment of the particle to the ingesting leukocyte
2. engulfment, with subsequent formation of a phagocytic vacuole
3. killing and degradation of the ingested material.

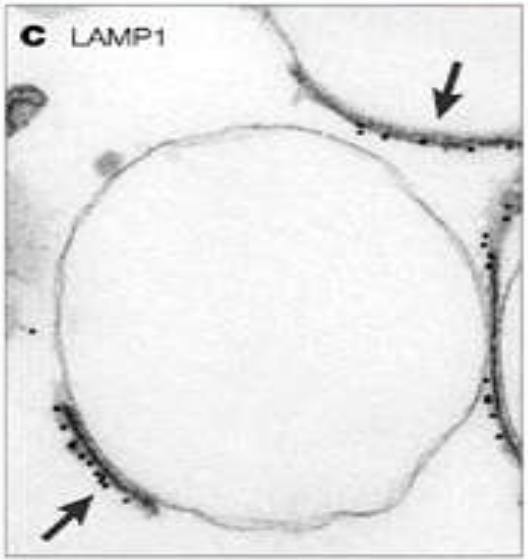
PHAGOCYTOSIS

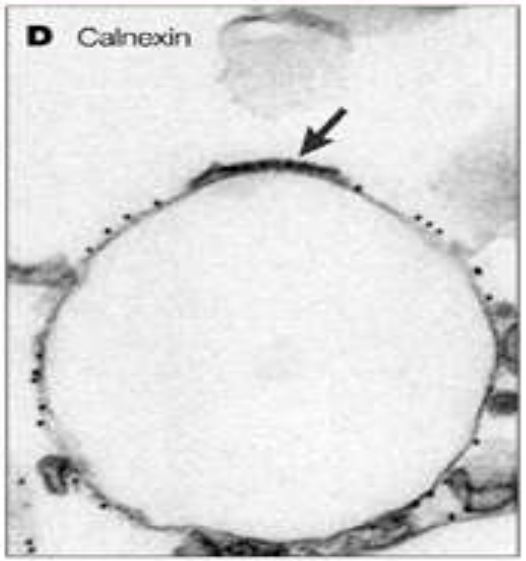
- The process of engulfment of solid particulate material by the cells.
- 2 main types of phagocytic cells
  - **Polymorphonuclear neutrophils (PMNs)** : early in acute inflammatory response, also known as *microphages*
  - ***Macrophages*** *:* Circulating monocytes and fixed tissue mononuclear phagocytes
- This phagocytic cells releases proteolytic enzymes - lysozyme, protease, collagenase, elastase, lipase, proteinase, gelatinase and acid hydrolases

Phagocytosis





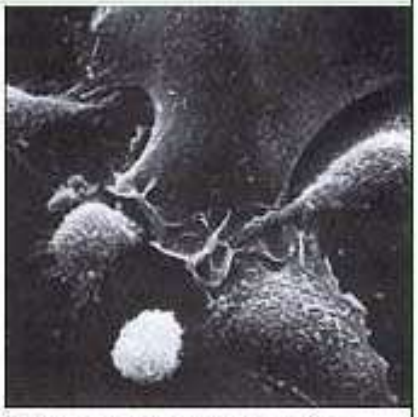




Macrophage Phagocytosis

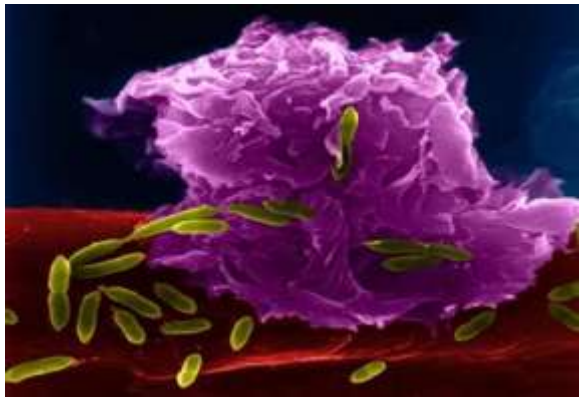
(a) Cancer cells

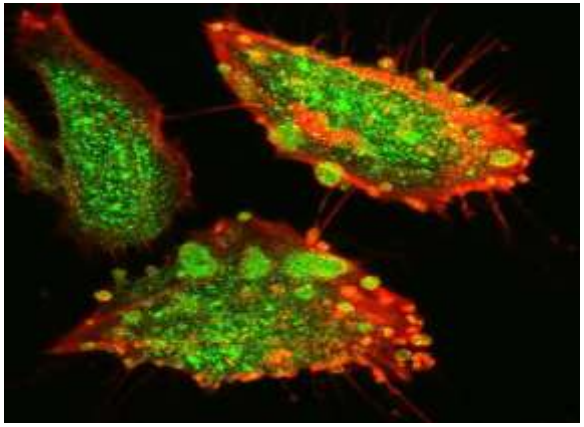
(b) Cancer cells is proliferating



(c) Macrophage (white ball)

(d-f) Macrophage phagocytosis





Purpose of proliferative phase

1. Completing of phagocytosis - final destruction and elimination of the etiologic agent

2. Delimitation of inflammatory focus from healthy tissue

3. Complete regeneration/Replacement lesion scar tissue

SIGNS OF INFLAMMATION

- **RUBOR**- REDNESS DUE TO INCREASED BLOOD BLOW AND VASODILATION
- **CALOR**- OR HEAT DUE TO INCREASE BLOOD FLOW TO THE PERIPHERY
- **TUMOR**- SWELLING FROM INFLAMMATORY EDEMA
- **DOLOR**-PAIN FROM SWELLING AND PRESENCE OF INFLAMMATORY MEDIATORS
- **FUNCTIO LAESA**-LOSS OF FUNCTION DUE TO MAIN AND STRUCTURAL NECROSIS

Systemic effects

- Fever
  - One of the easily recognized cytokine-mediated (esp. IL-1, IL-6, TNF) *acute-phase reactions* including
    - Anorexia
    - Skeletal muscle protein degradation
    - Hypotension
- Leukocytosis
  - Elevated white blood cell count

	TRANSUDATE	EXUDATE
COLOR	Clear, water-like, or pale yellow of plasma	Cloudy, white, yellow or red
CONSISTENCY	Thin and watery, no tissue fragments	Thick and creamy, contains tissue fragments
ODOR	None	May have an odor
pH	Alkaline	Acid
SPECIFIC GRAVITY	1.015 or lower	1.018 or higher
PROTEIN CONTENT	Low, less than 3%	High, more than 4%
CELL COUNT	Low; none or few WBC and RBC	High; many WBC and RBC
ENZYME CONTENT	Low	High
BACTERIA	None	May be present
INFLAMMATION	None present	Associated with Inflammation

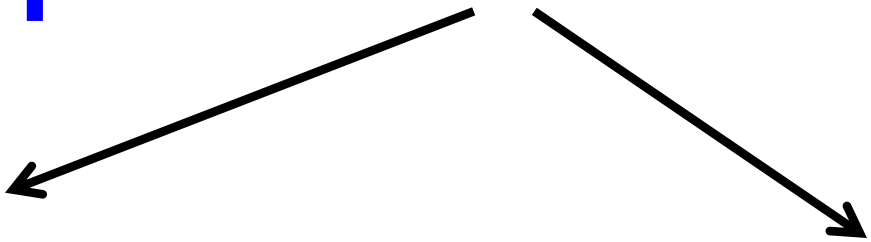
Types of inflammation

- **Acute inflammation** − lasts from several days up to several months − in the focus of inflammation - neutrophils, intravascular platelet activation − Exudative inflammation and rarely observed productive (viruses)

- **Subacute inflammation** − lasts from several weeks up to several months − in the focus of inflammation - neutrophils, lymphocytes, plasmocytes, macrophages (approximately in equal proportions) − exudative-productive inflammation

- **Chronic inflammation** − lasts from a few months up to tens of years − alternating exacerbations and remissions − in the focus of inflammation – mononuclear cells (lymphocytes, plasmocytes, macrophages), in case of exacerbations neutrophils are added − productive inflammation, during exacerbations an exudative reaction is added − presence of fibrosis is essencial

Types of inflammation



- **Exudative infl.**
- **Proliferative (productive) infl.**

Types of acute inflammation

1. Serous inflammation;
2. Fibrinous inflammation → croupous;
   → diphtheritic;
3. Purulent inflammation → abscess,
   → phlegmon,
   → empyema,
   → furuncle, carbunckle;
4. Hemorrhagic inflammation
5. Catarrhal inflammation
6. Mixed inflammation

MORPHOLOGICAL PATTERNS OF ACUTE INFLAMMATION

- SEROUS INFLAMMATION
- Outpouring of thin fluid
- Depends on secretion of mesothelial cells – peritoneal pleural , pericardial cavities- effusions
- Skin blister- viral ,burns- large accumulation of serous fluid
- Watery, protein-poor effusion (e.g., blister)

- FIBRINOUS INFLAMMATION
  - Fibrin accumulation
  - Either entirely removed or becomes fibrotic

- Inflammation in the lining of body cavities – meninges pericardium, pleura
- Scarring

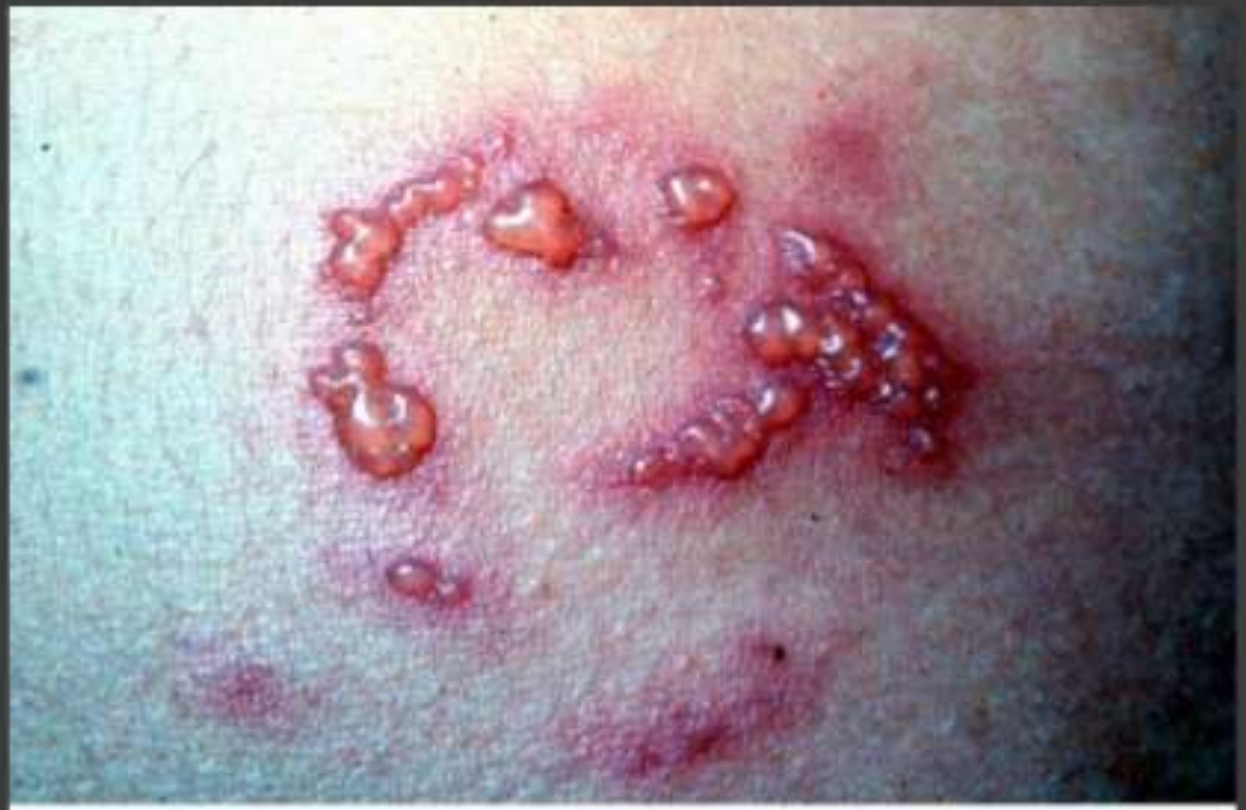
Morphologic Patterns

Serous Inflammation

- Inflammation of serous membrane characterized by clear fluid in serous cavity (pleural, peritoneal pericardial & synovial cavities)

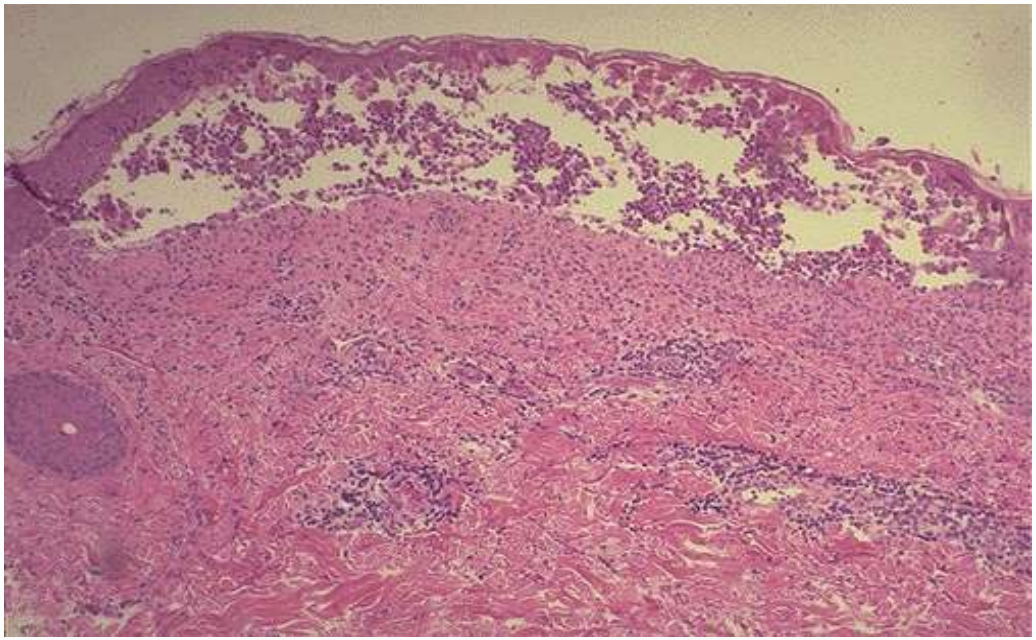
- E.g. skin Blisters caused by Burns OR viral infection

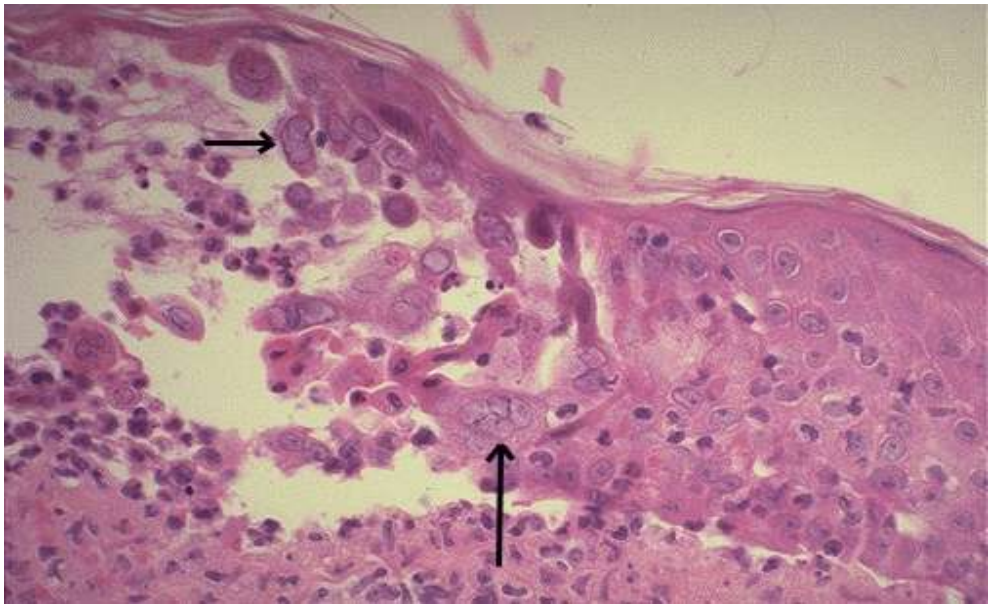
Morphologic Patterns



CONTACT DERMATITIS BLISTERS FROM THE POISON IVY PLANT'S TOXIC PRINCIPLE, URUSHIOL. THIS IS A CLASSIC EXAMPLE OF A SEROUS EXUDATE.

Serous inflammation



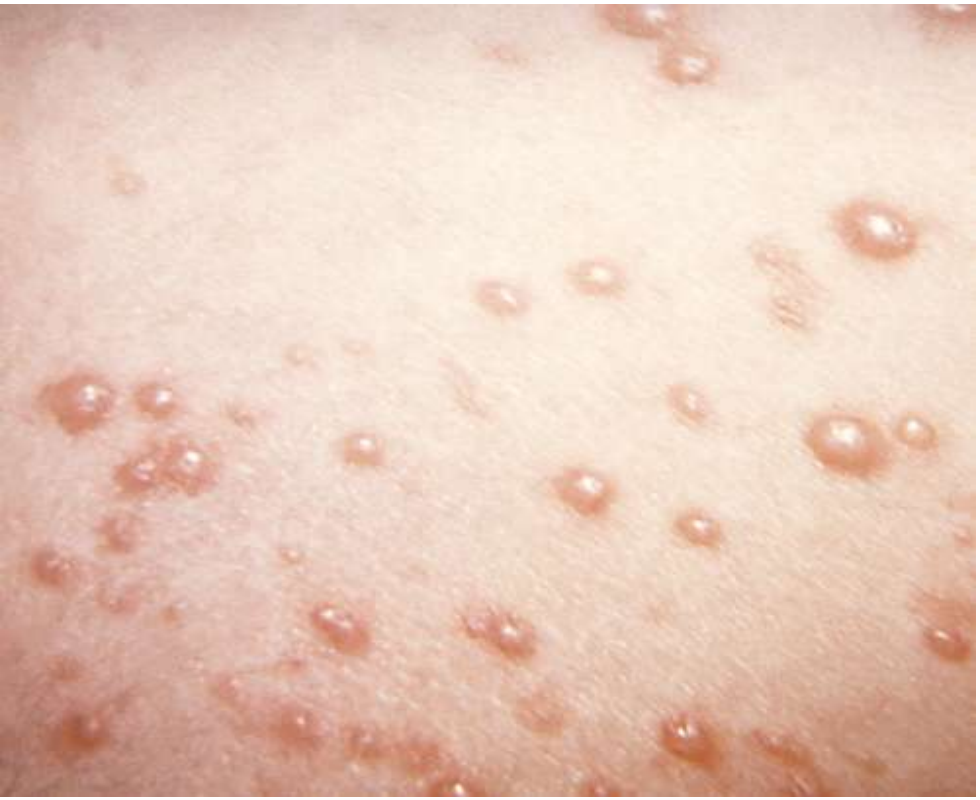


Herpes simplex:

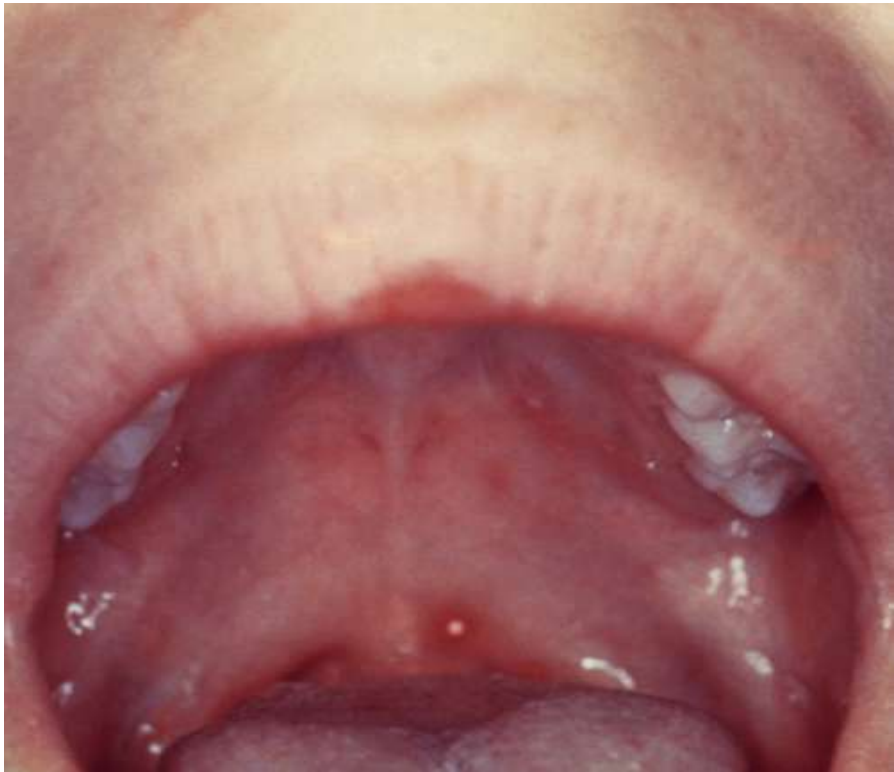
- Vesicles of the skin;

- Multi-nuclear cells and intranuclear inclusions.

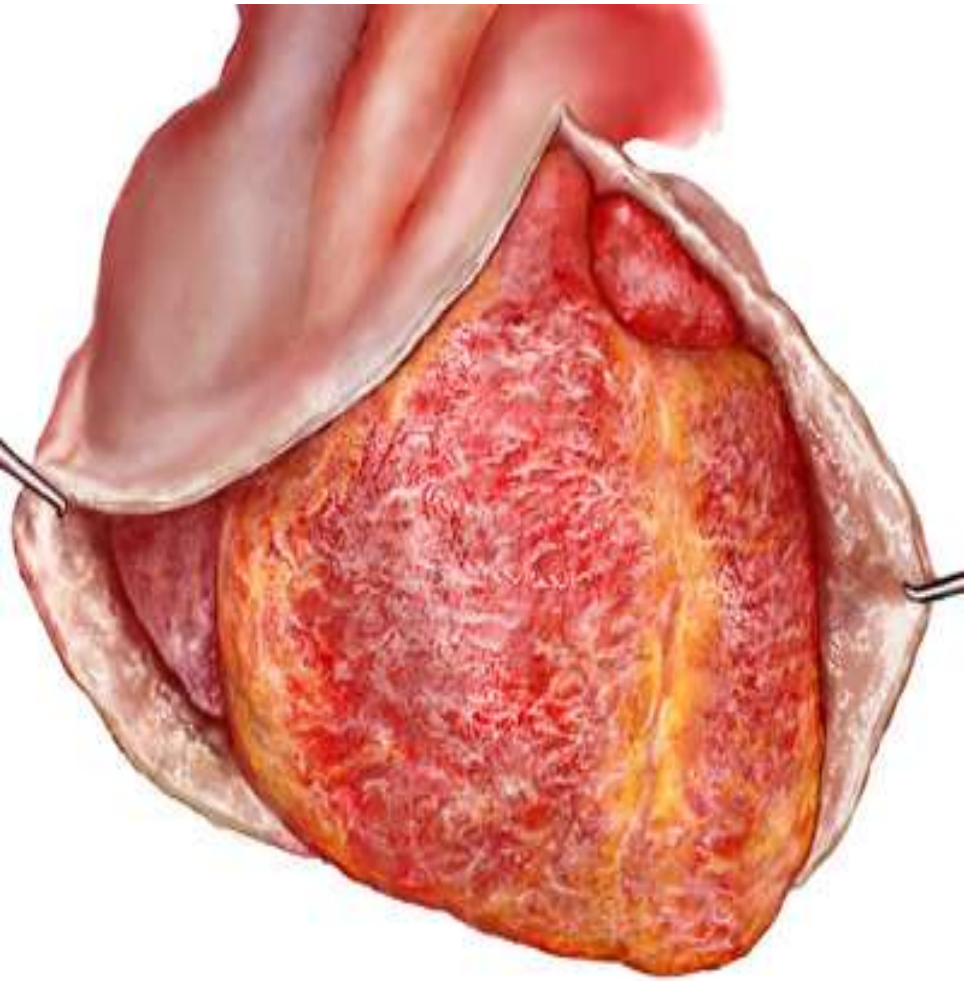
Serous inflammation

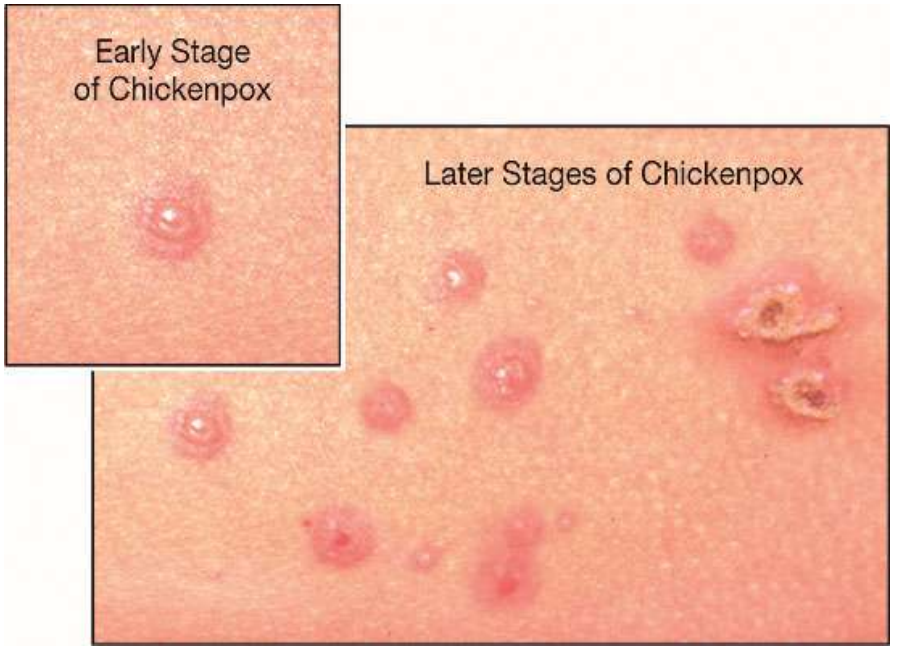


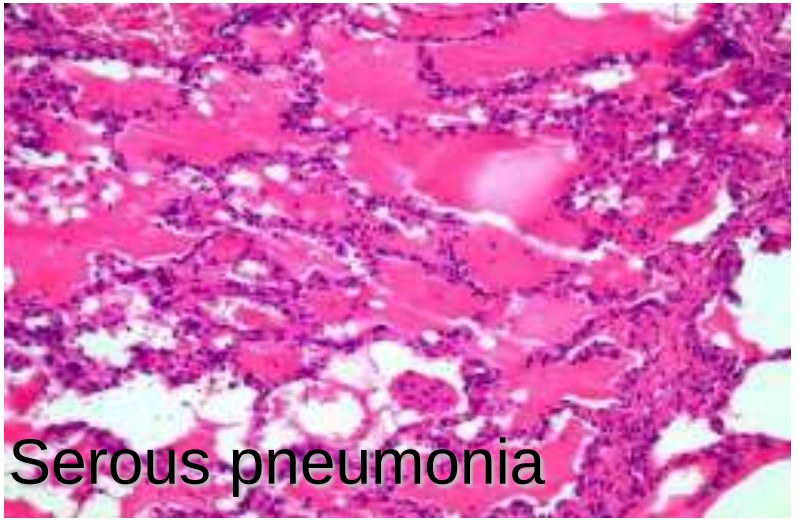
- Chickenpox



Serous inflammation







Serous pneumonia

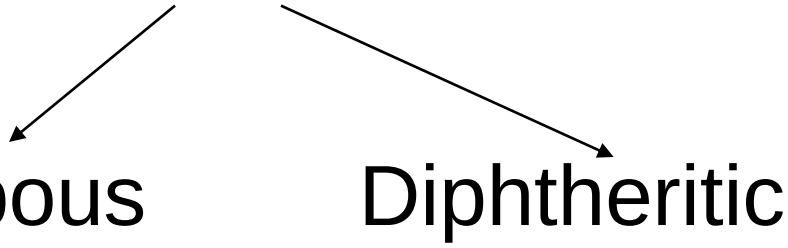
Morphologic Patterns

Fibrinous Inflammation

- Severe injury with excessive deposition of Fibrin in serous cavity
- Exudate and Fluid is removed by lymphatic
- Fibrinous exudate may be degraded by Fibrinolysis and removed by macrophage resulting in Resolution.
- Incomplete Removal of fibrin resulting in organization and scarring with
- Fibrous Adhesion of pleura OR pericardium.

Fibrinous Inflammation

1. Fibrinous Parenchymal Inflammation
2. Fibrinous Serosal Inflammation
3. Fibrinous Mucosal Inflammation



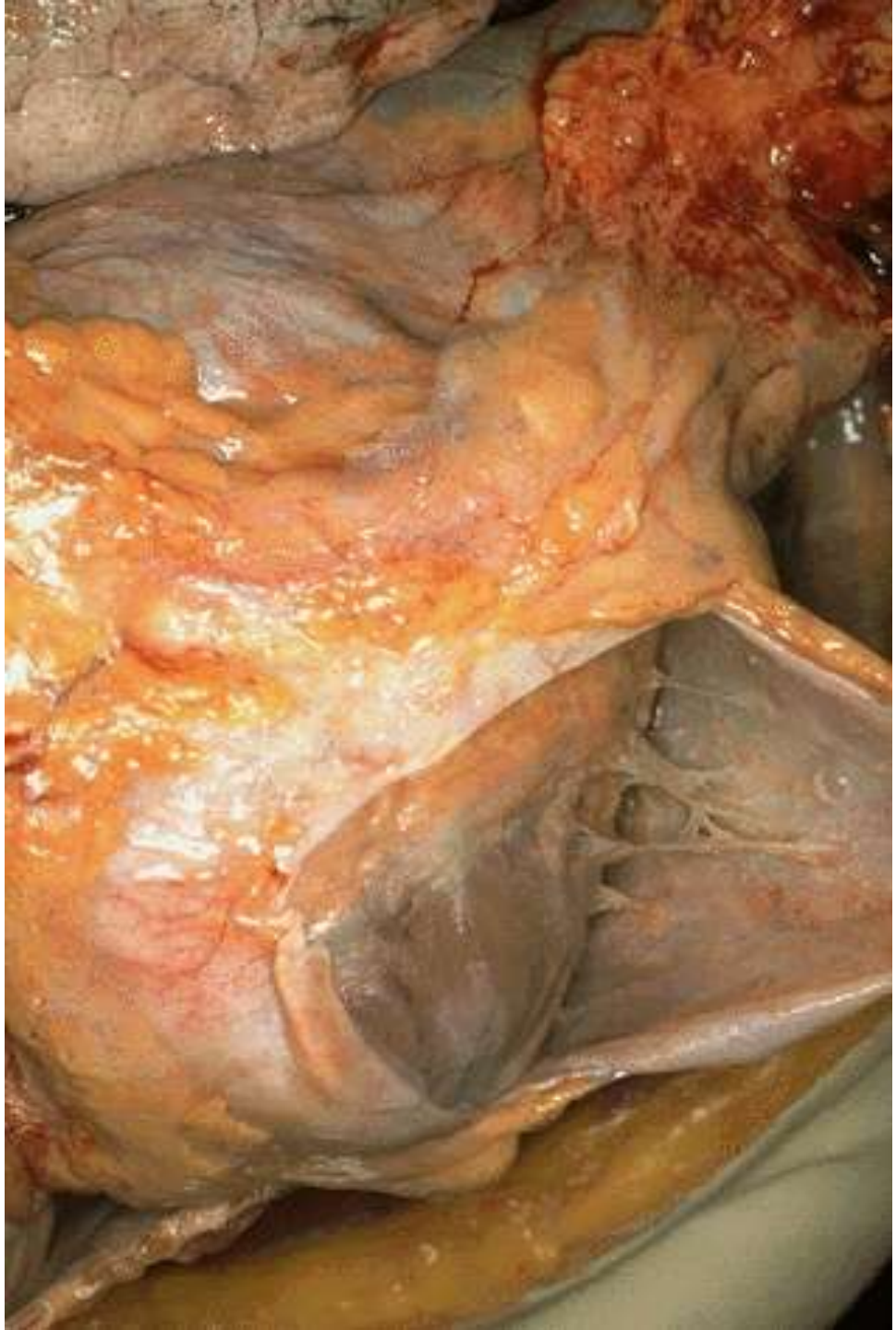
Fibrinous inflammation

Croupous Type

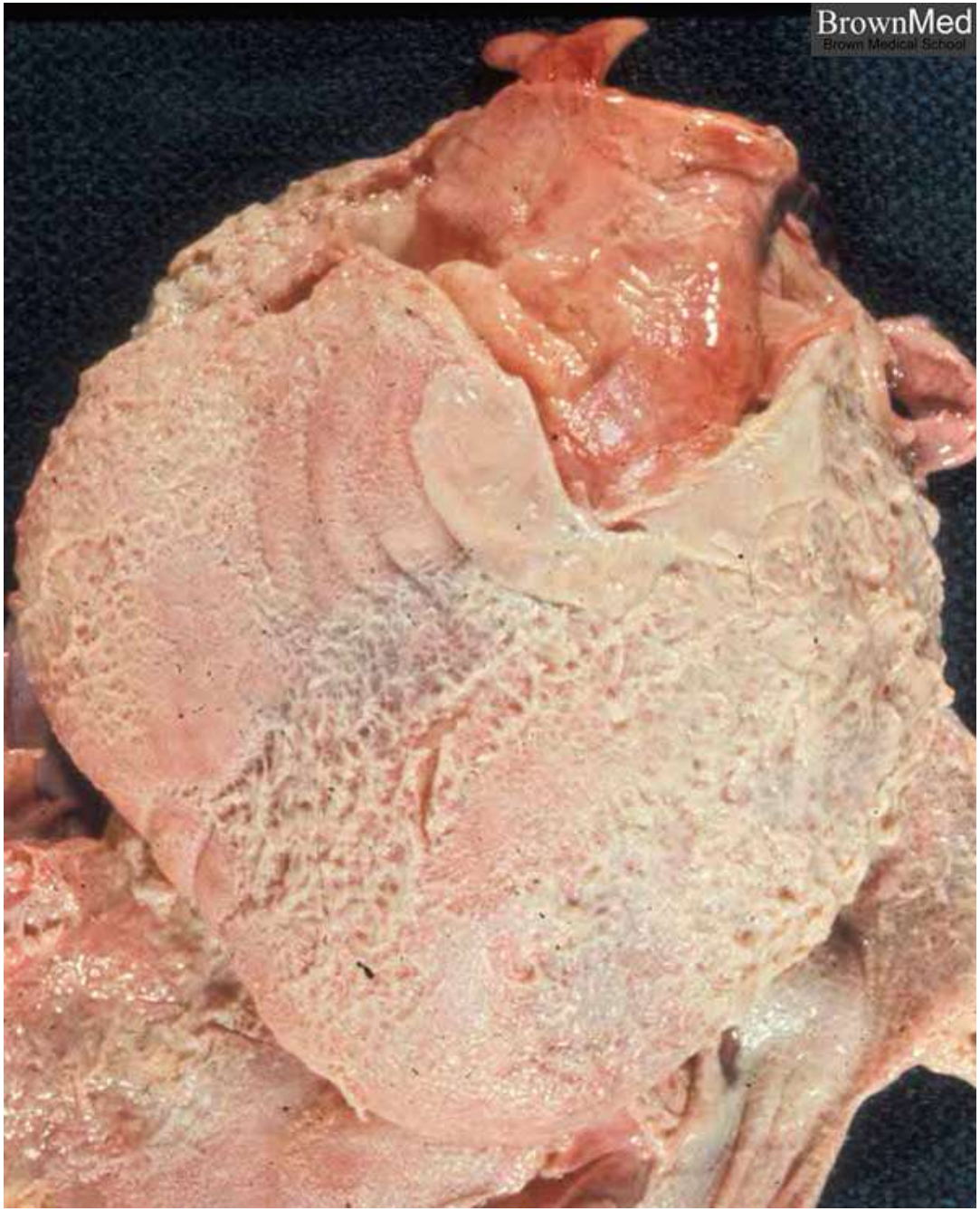
- an easily removable pseudomembrane covering the necrosis, which is limited to the mucosal epithelium
- Expl: Diphtheric laryngotracheitis

Diphtheritic Type

- necrosis extending into the submucosa,
- a wide area of fibrinous exudate is covered by an adhesive pseudomembrane that can only be forcibly removed.
- Expl: • Diphtheric tonsillitis and pharyngitis, • Dysentery, • Antibiotic associated colitis (pseudomembranous colitis)

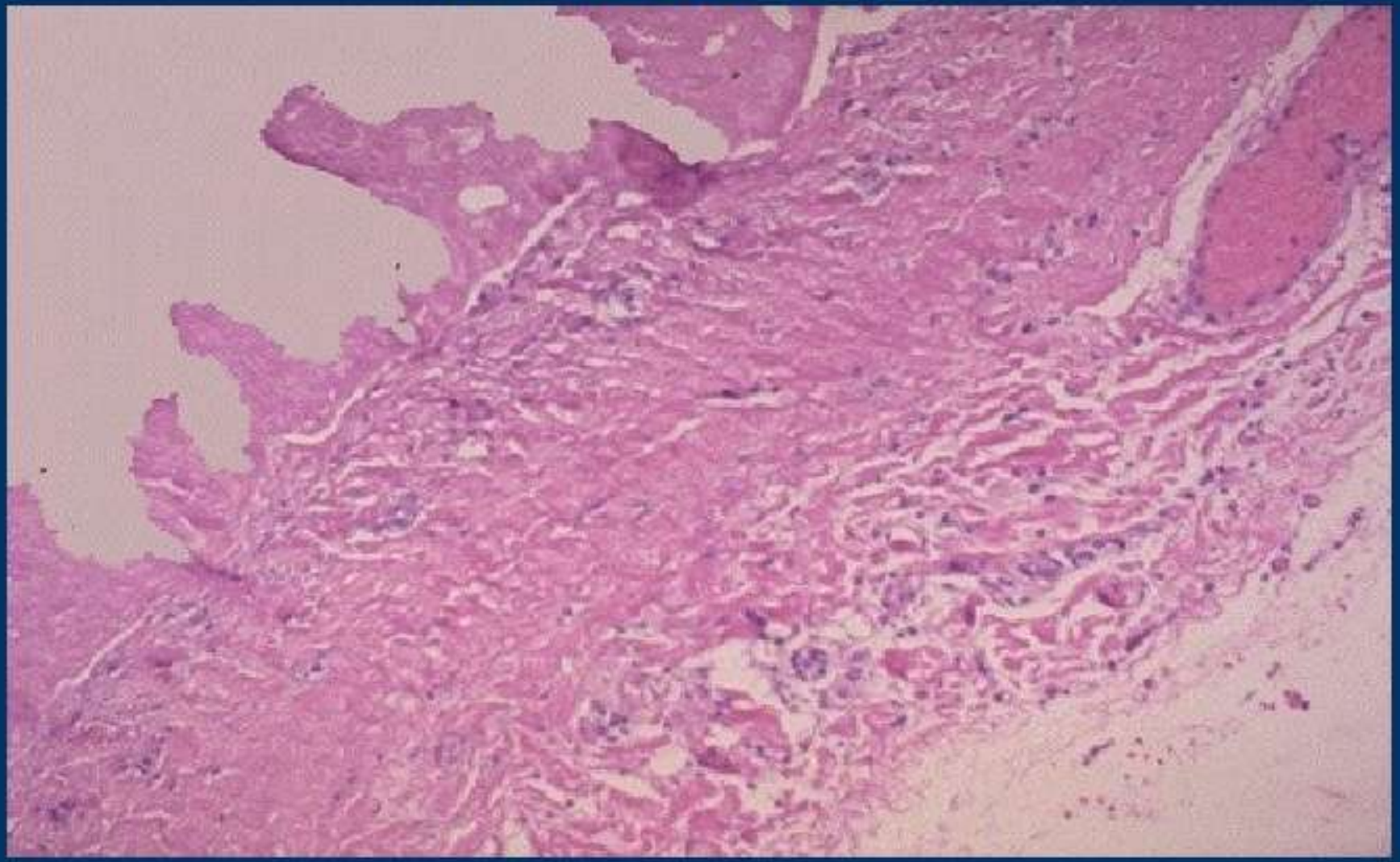


Fibrinous pericarditis



Fibrinous pericarditis

FIBRINOUS INFLAMMATION-PERICARDIUM



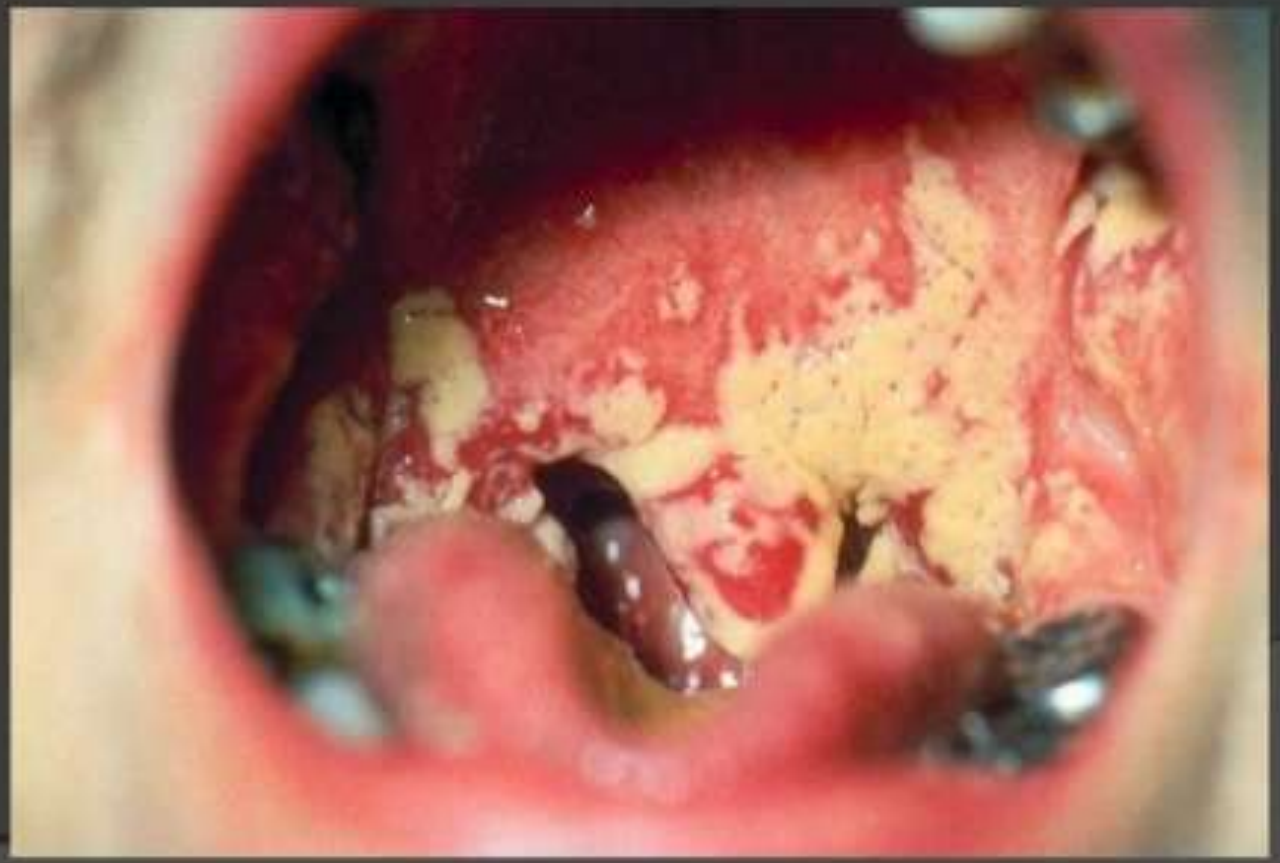
Morphologic Patterns

Pseudomembraneous Inflammation

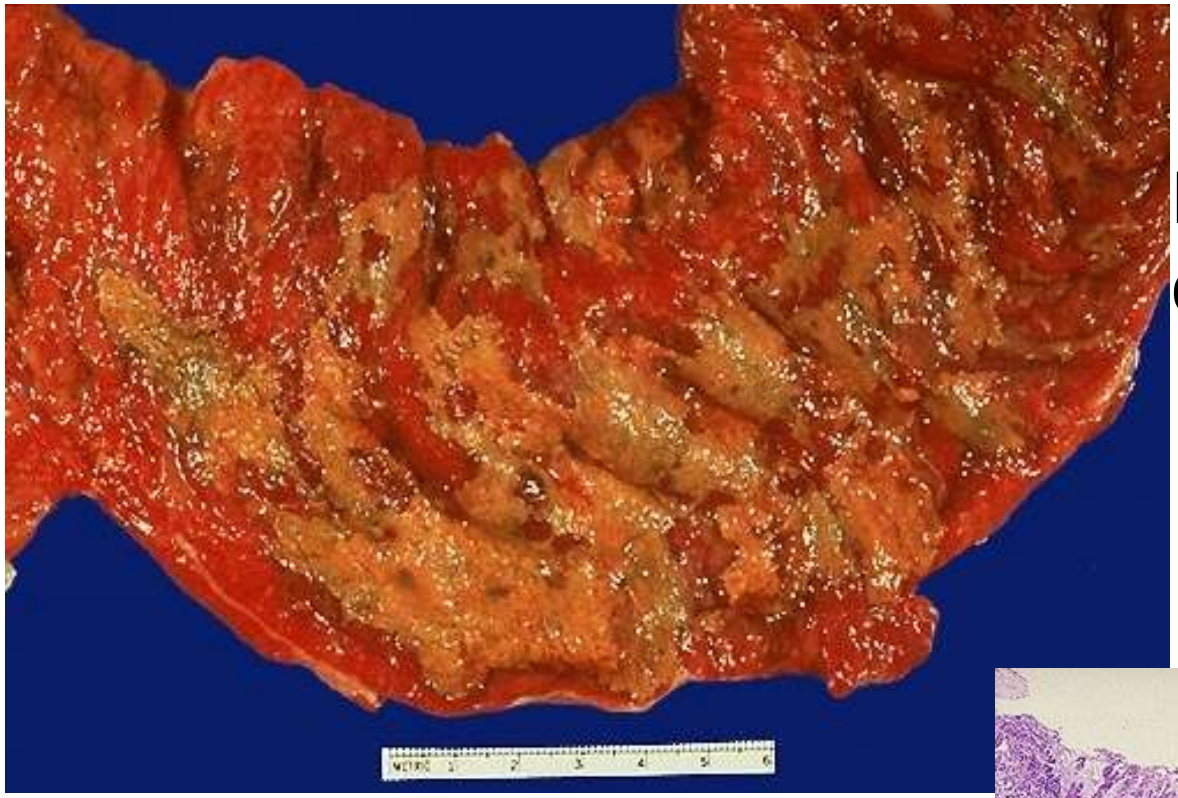
- Very severe ulcerative inflammation of mucous membranes
- Extensive Necrosis of surface epithelium
- Severe acute Inflammation of underlying tissue
- Pseudo membrane, consisting of exudate, fibrin, neutrophils RBC, Bacteria and tissue debris
- e.g. Diphtheria – Larynx . pseudomembraneous Colitis – clostridium difficile

Morphologic Patterns

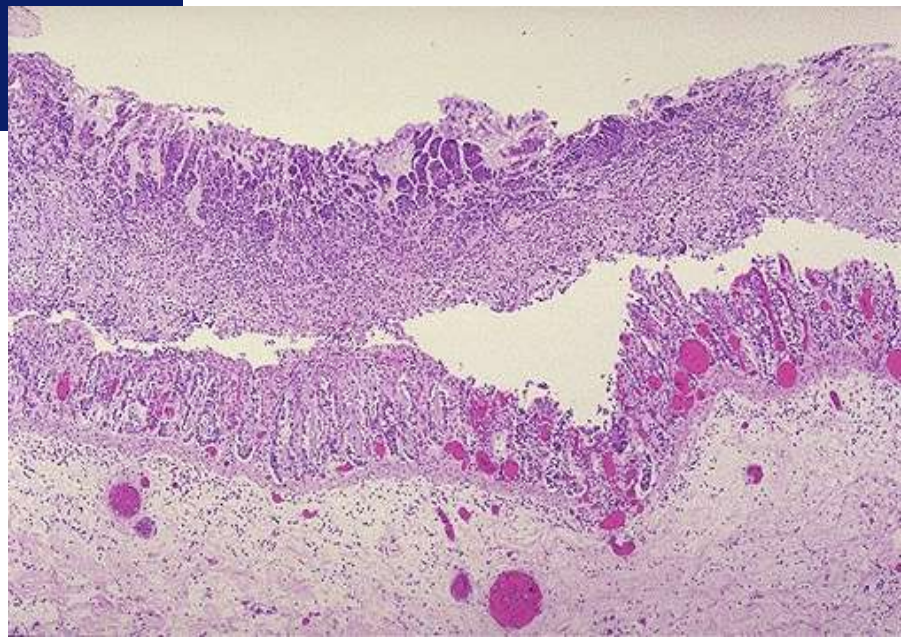
Pseudomembraneous Inflammation



Fibrinous inflammation

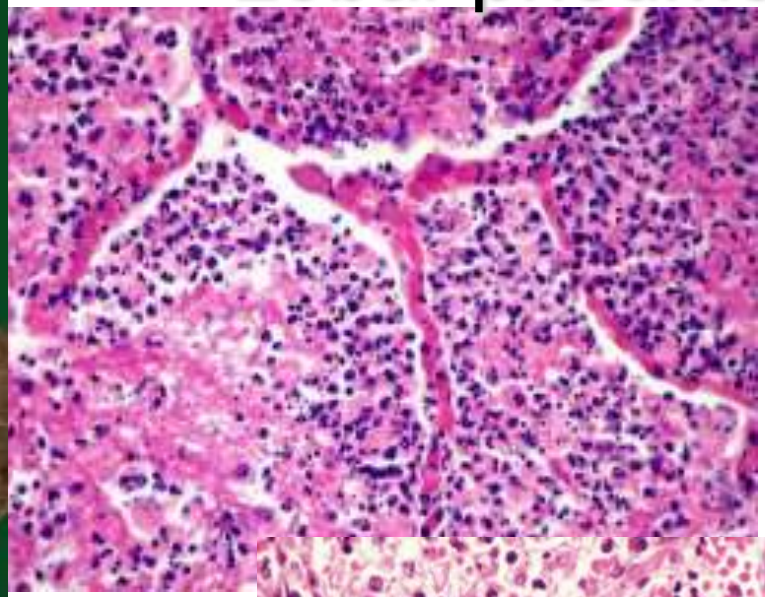


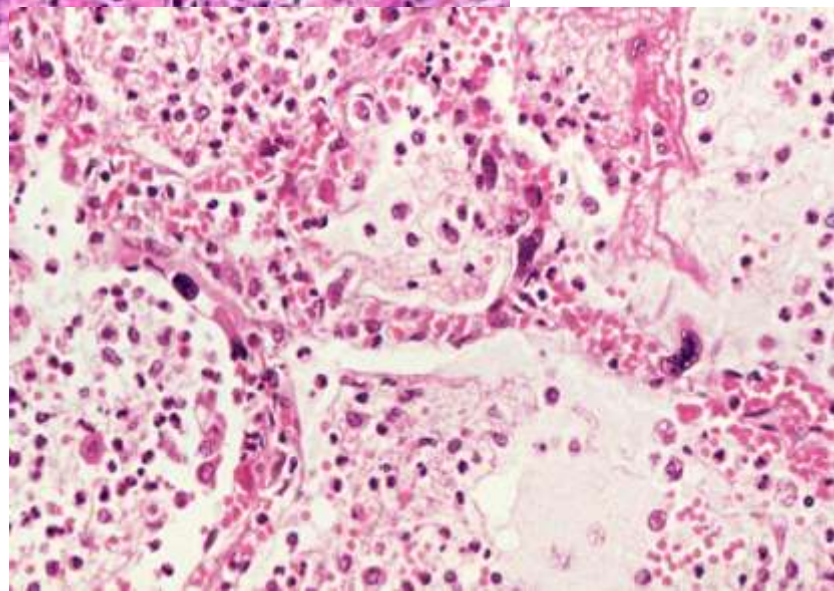
Pseudomembranous colitis



Fibrinous inflammation

- Lobar pneumonia





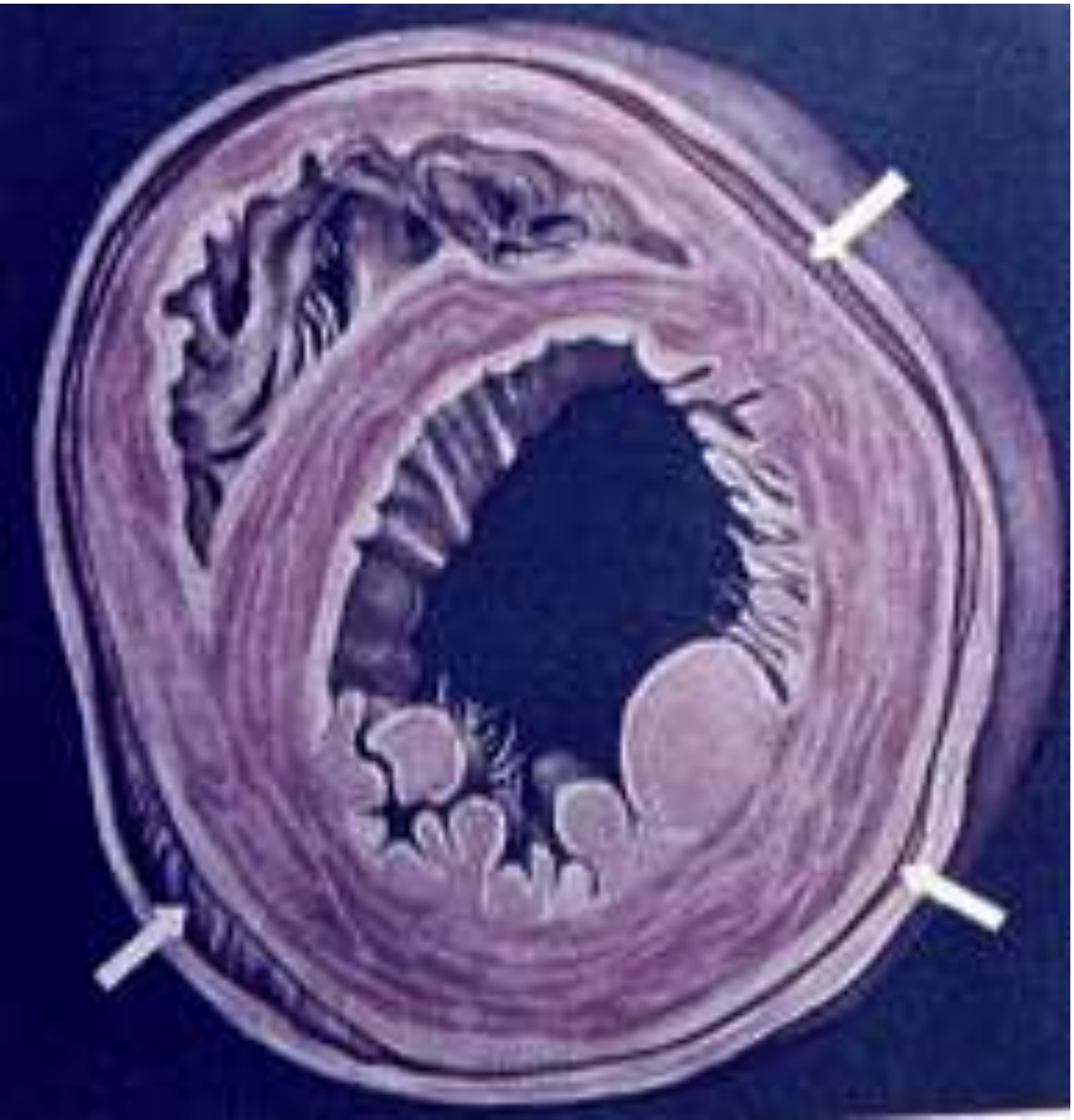
Outcomes of fibrinous inflammation

1. Resolution of exudate.
2. Formation of adhesions in body cavities up to obliteration of cavities.

The value of fibrinous inflammation:

- This is very large, since it constitutes the morphological basis of diphtheria, dysentery, is observed with intoxications (uremia).
- With the formation of films in the larynx, the trachea - the danger of asphyxia; when tearing films in the intestine - bleeding from the resulting ulcers.
- Adhesive pericarditis and pleurisy are accompanied by the development of pulmonary heart failure.

Outcomes of fibrinous inflammation



- Formation of adhesions in body cavities up to obliteration of cavities

Purulent Inflammation

- General definition: Inflammation with exudate consisting primarily of died neutrophils and cellular debris (detritus).

Types of purulent inflammation

1. Abscess (acute and chronic);
2. Phlegmon (hard and soft);
3. Empyema;
4. Furuncle;
5. Carbuncle.

Abscess

- local purulent inflammation with the formation of a cavity filled with pus;

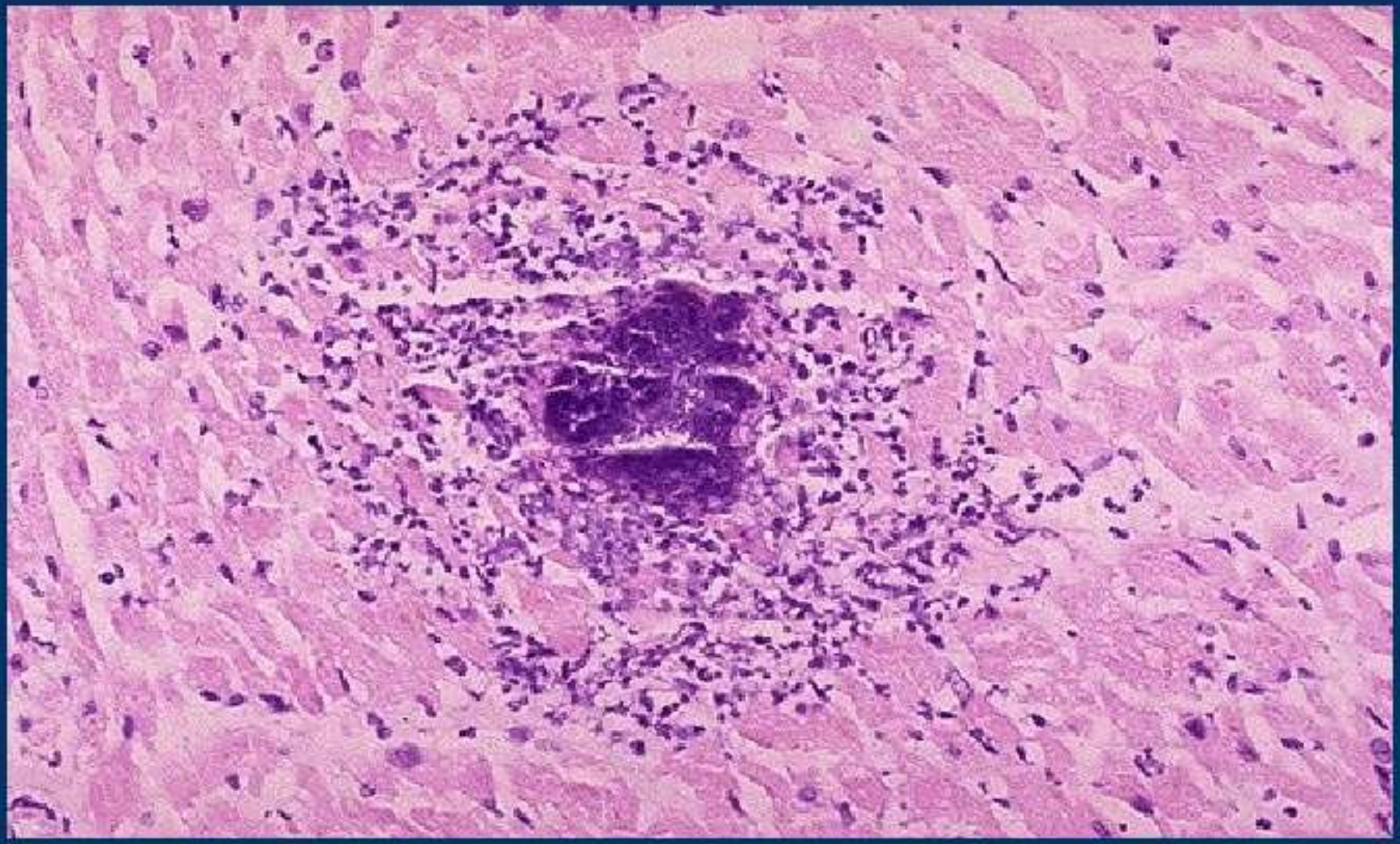
The wall of acute abscess consists of 2 layers:

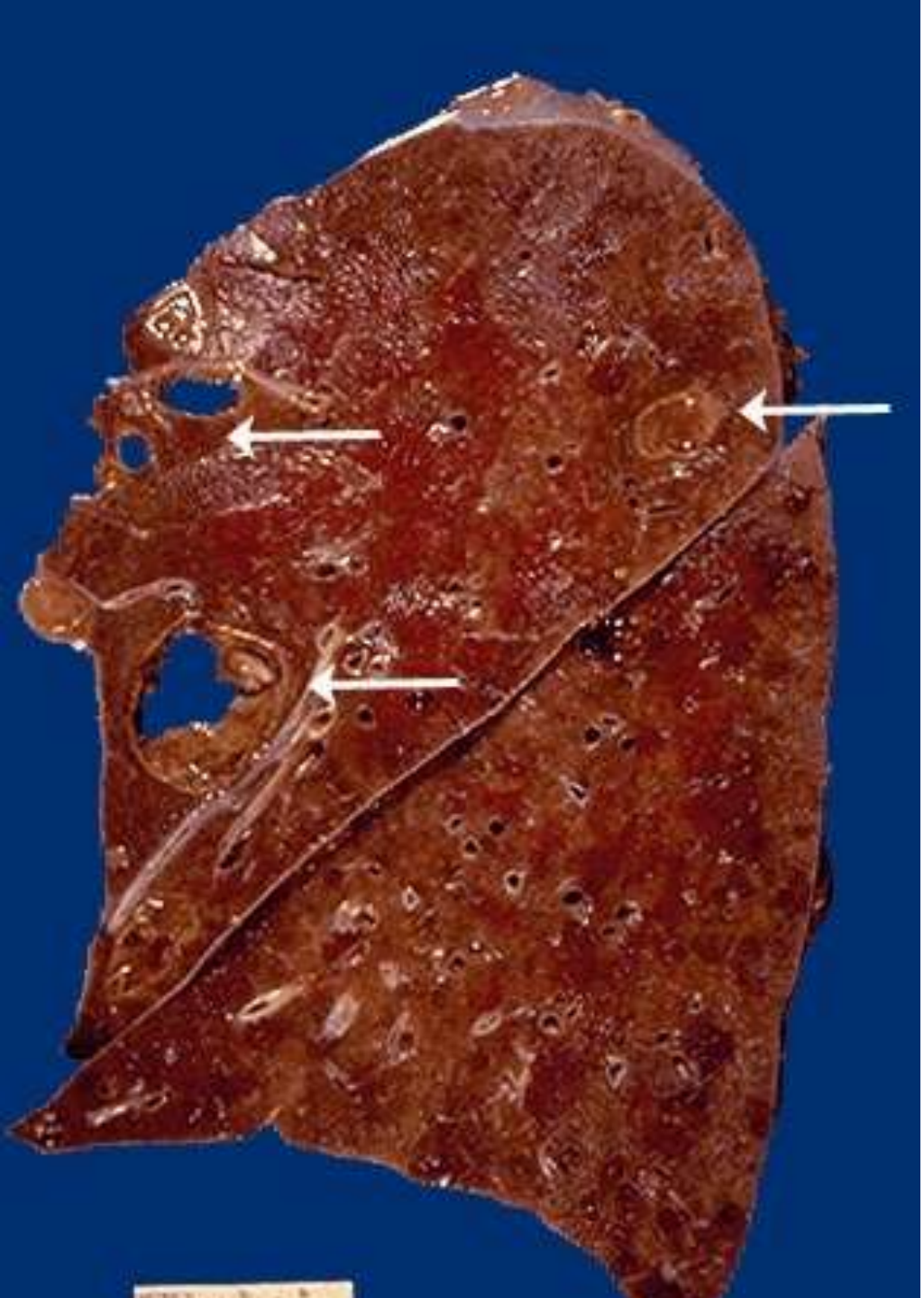
- 1) the inner layer (granulation tissue) is a pyogenic membrane;
- 2) the outer layer - compressed surrounding healthy tissue;

The wall of the chronic abscess consists of 3 layers:

- 1) inner layer - purulent-necrotic masses;
- 2) the middle layer is a granulation tissue;
- 3) outer layer - connective tissue capsule.

ABSCESS-HEART

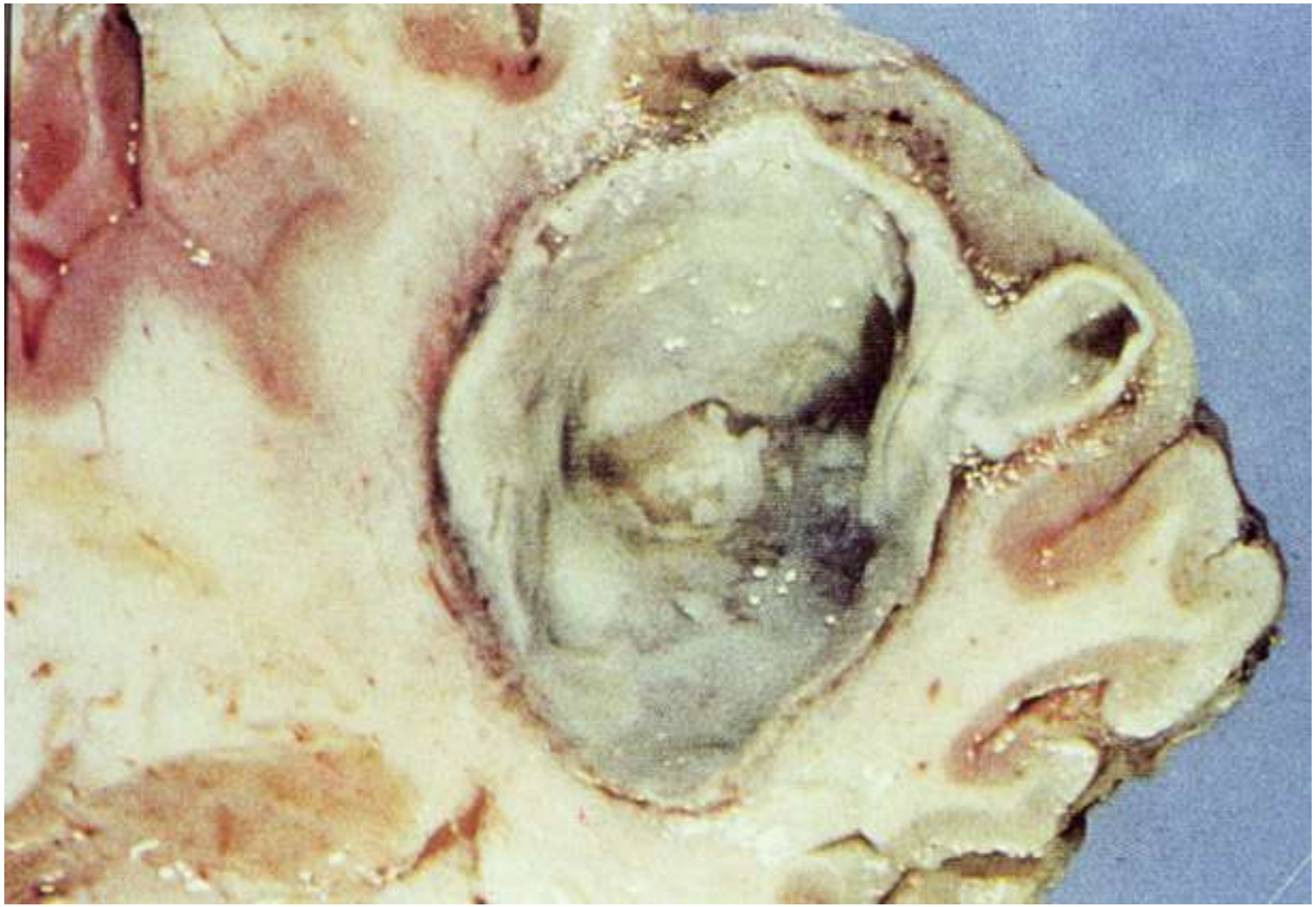


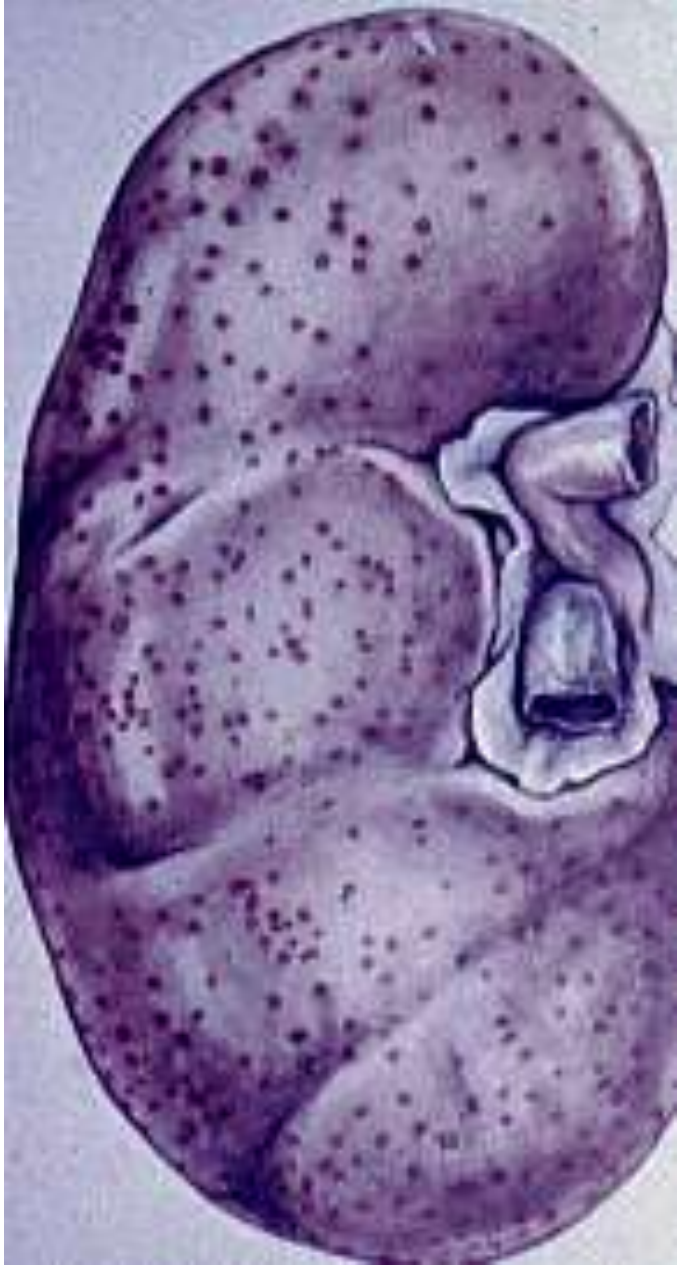


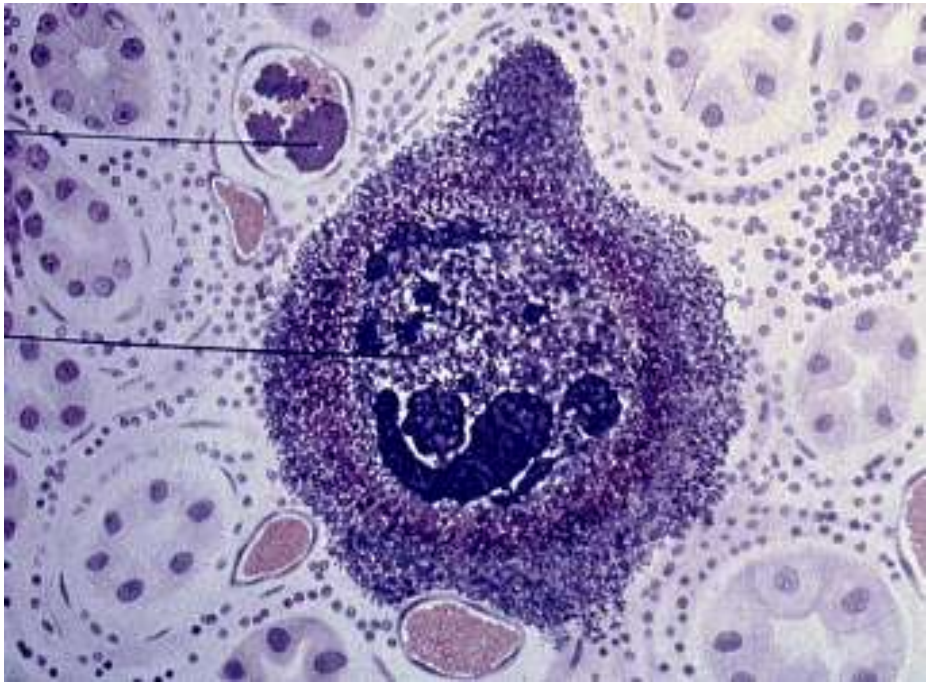
Purulent inflammation

- Abscesses of the lung;

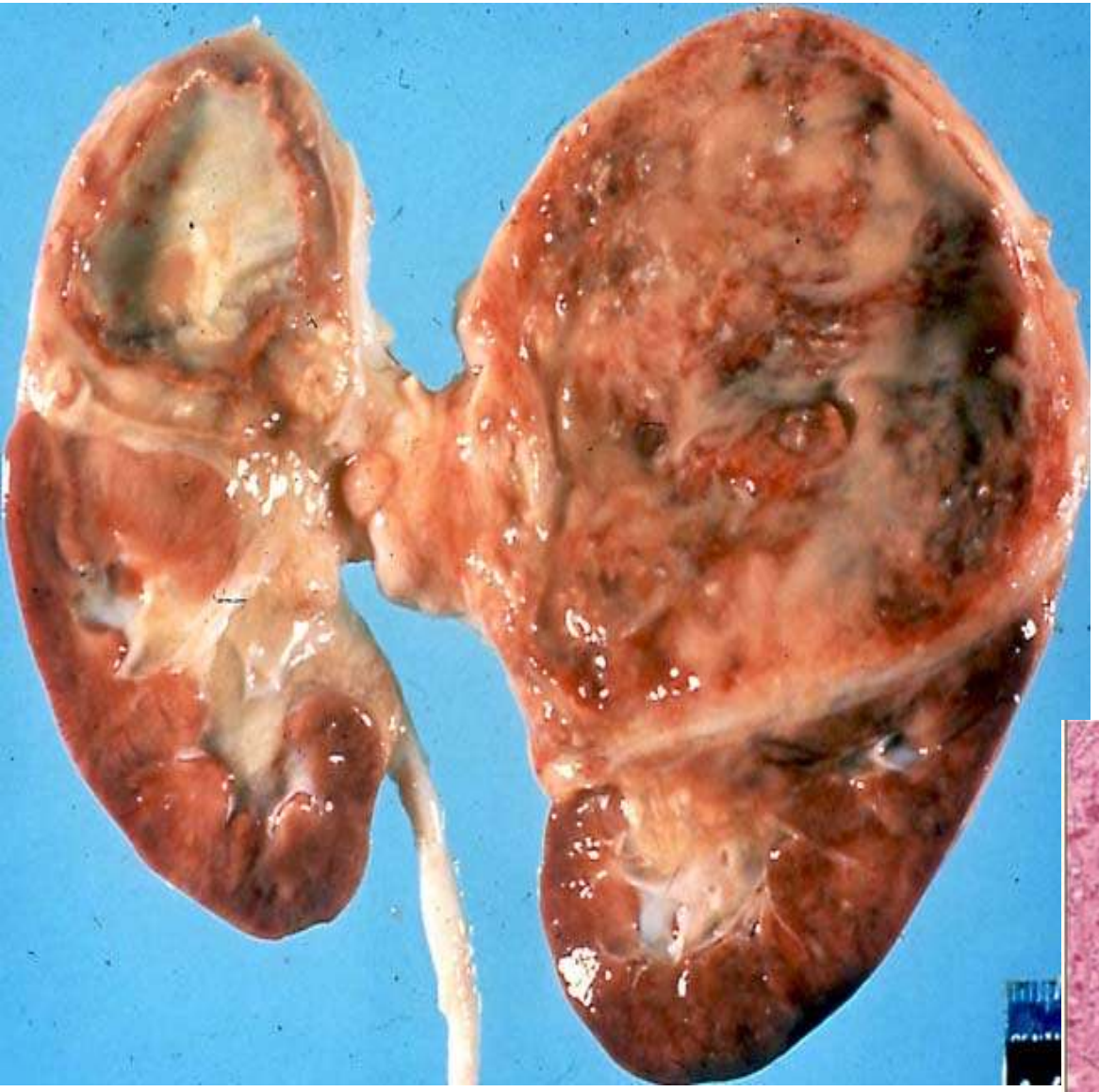
Abscess of the brain



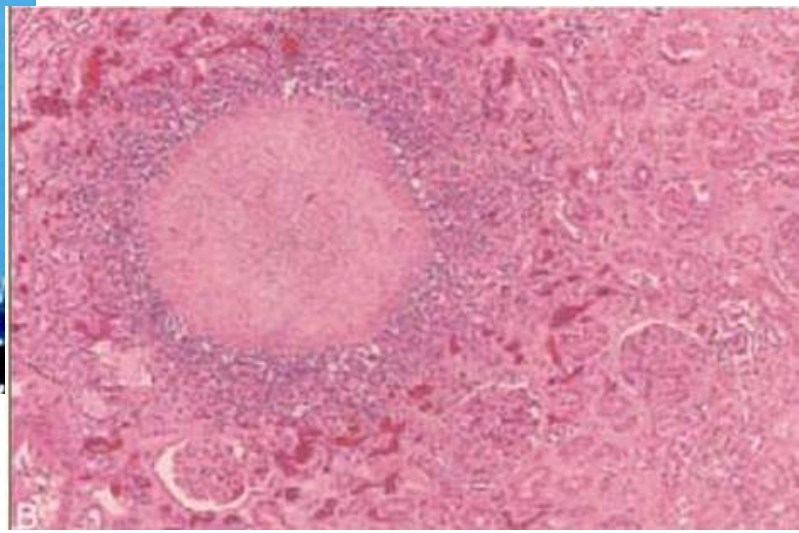




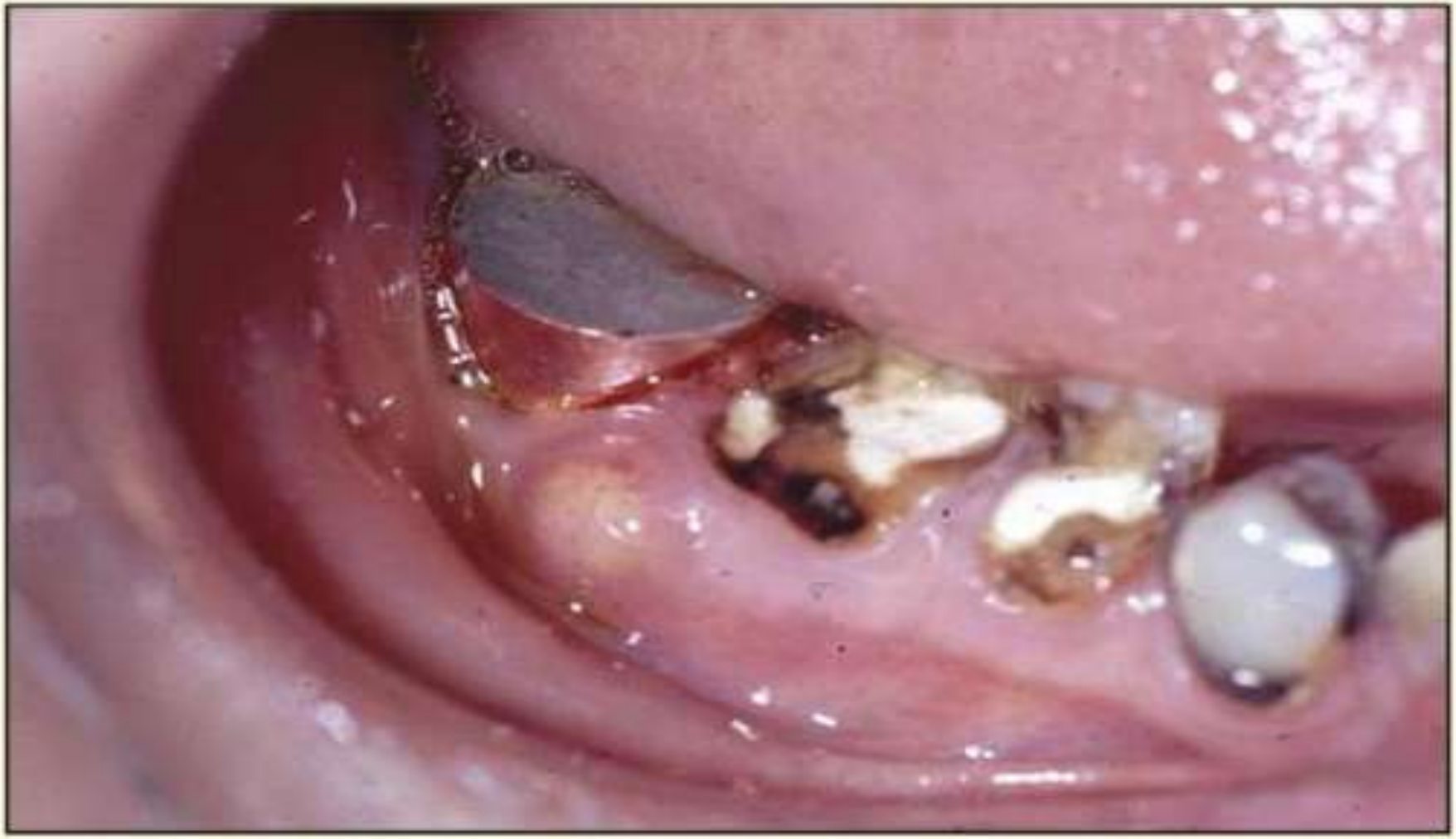
Metastatic kidney abscesses



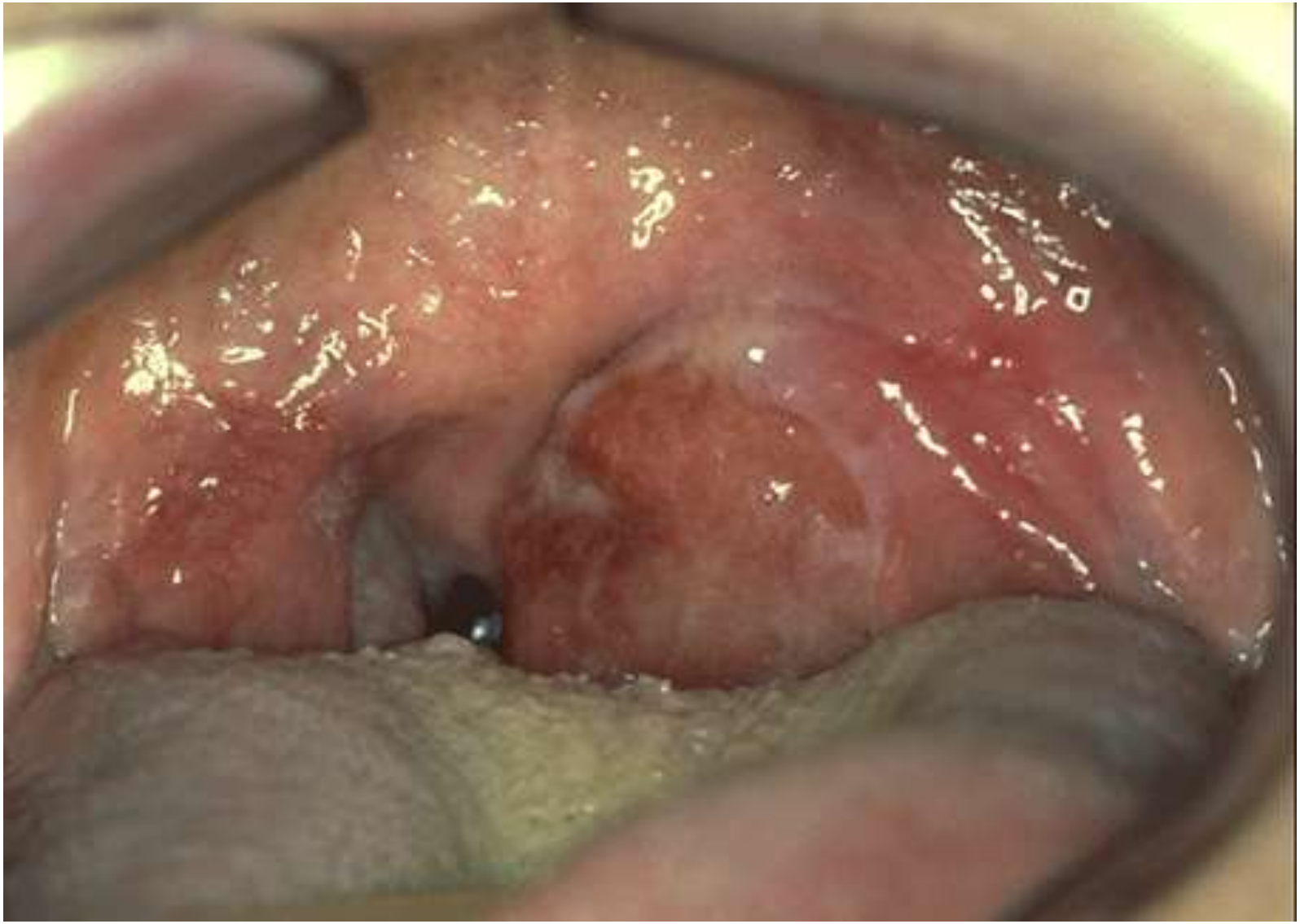
- kidney abscesses



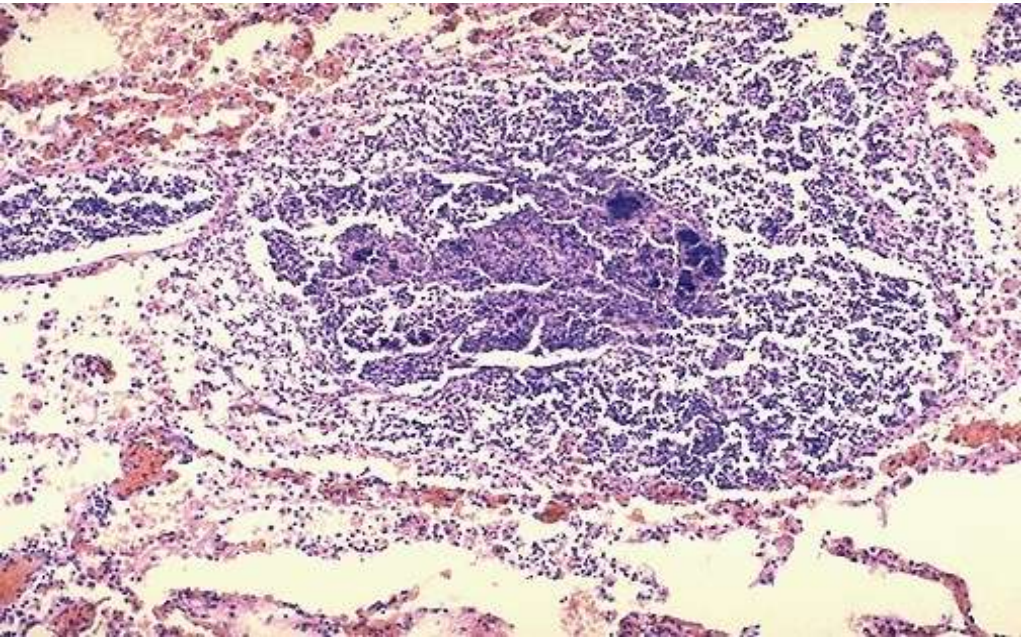
Periodontal Abscess



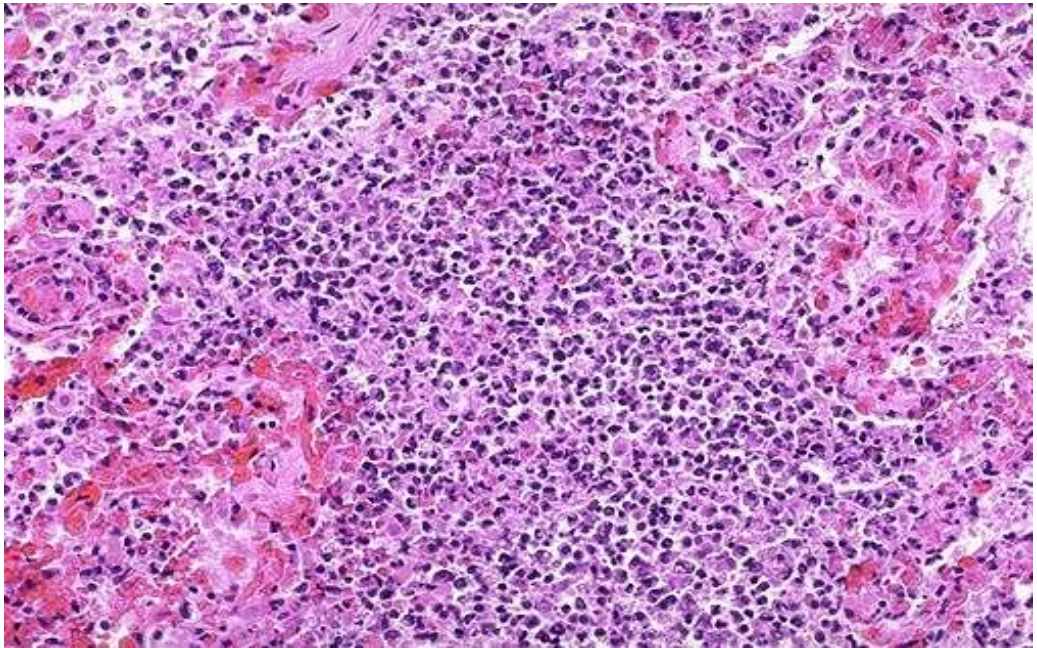
Paratonzillar abscess



Purulent inflammation



- Abscess of the lung;



- Abscessed pneumonia.

Empyema

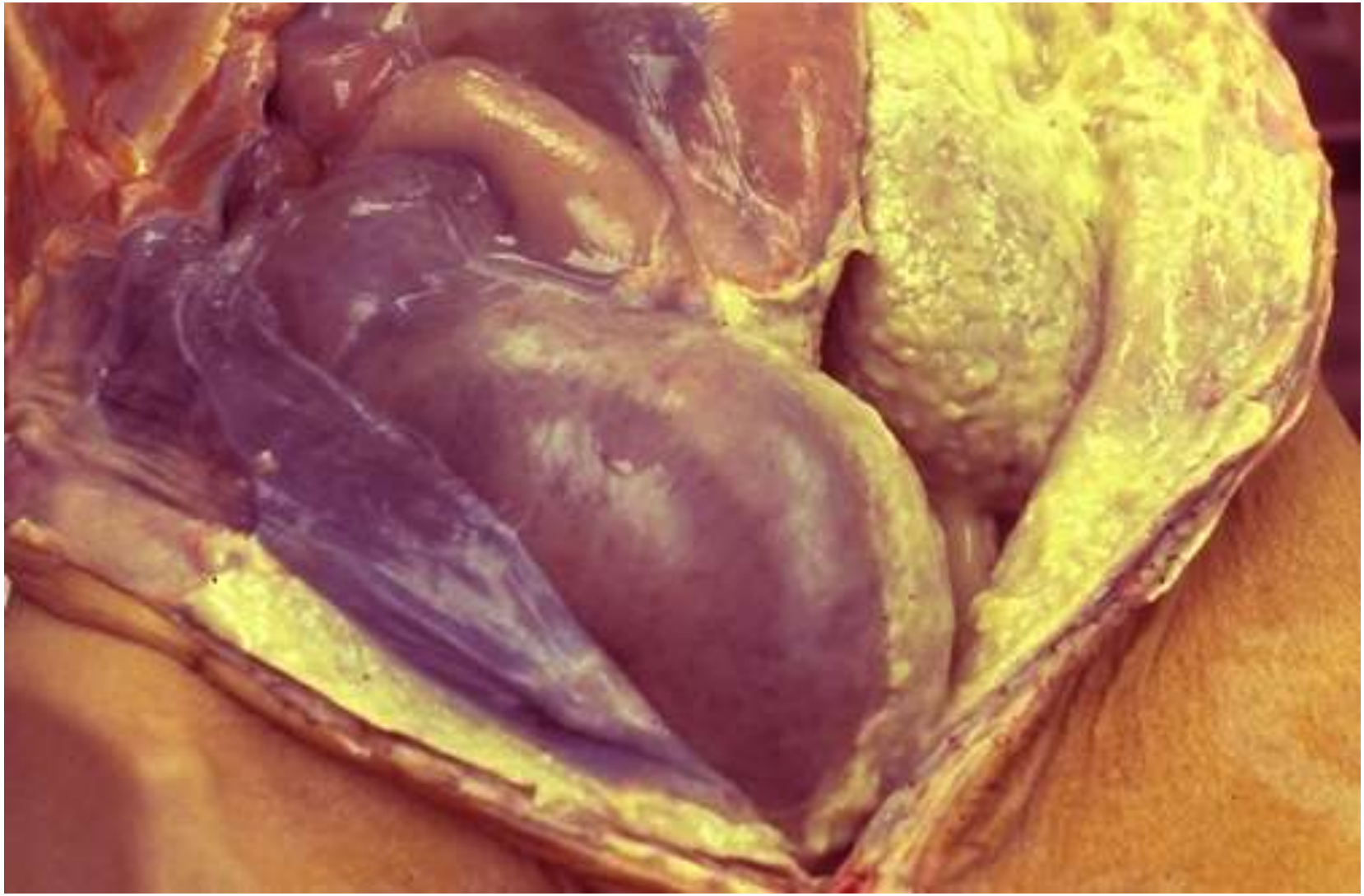
- **Definition**: Suppurative inflammation in a body cavity.

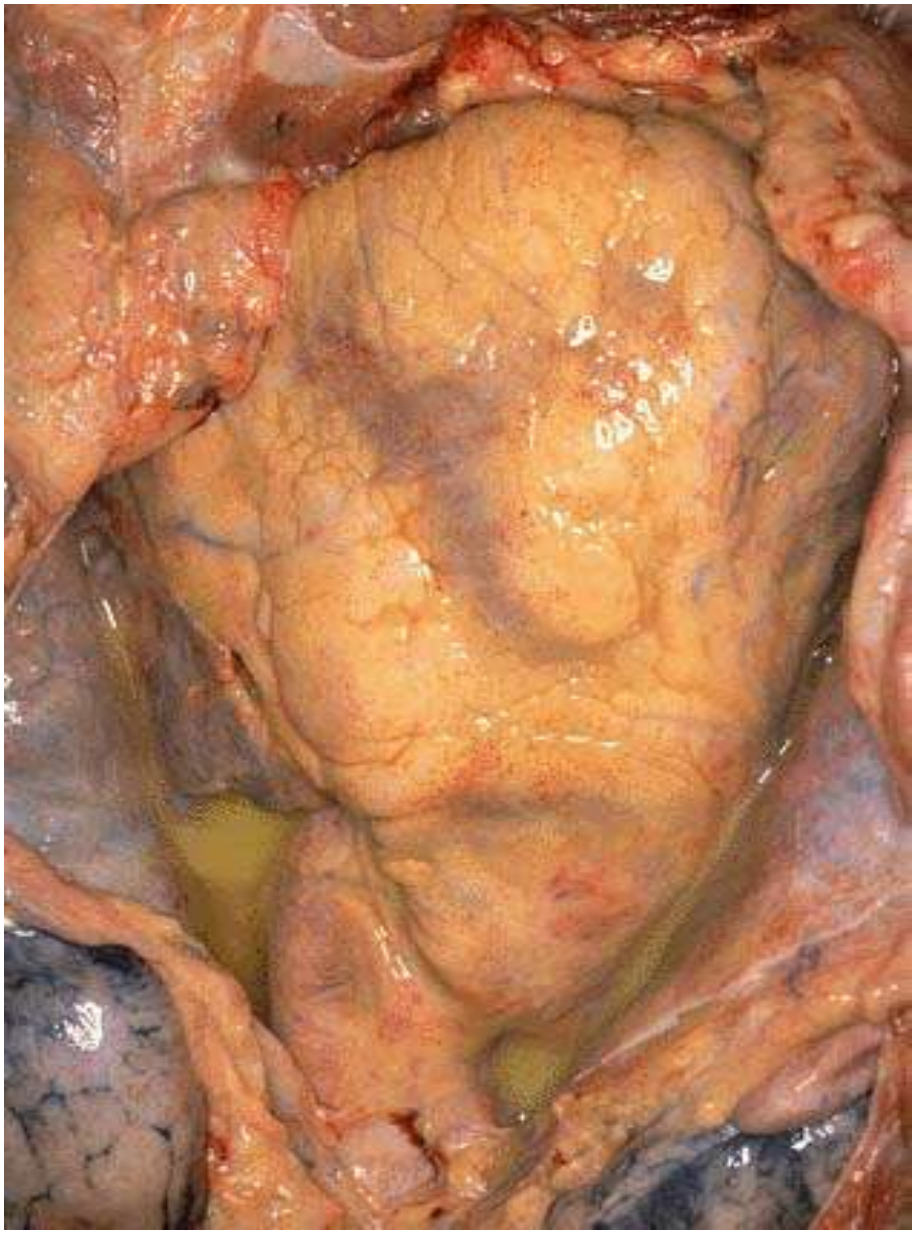
- **Pathogenesis:** An empyema usually occurs when a suppurative inflammation of an organ breaks through into an adjacent cavity.

- **Examples:**

• Pericardial, peritoneal, and pleural empyema
• Gallbladder and appendiceal empyema;
• Middle ear and nasal sinus empyema;
• Pyosalpinx (pus in the uterine tube);
• Pyocephalus (pus in the cranial cavity);
• Hypopyon (pus in the anterior chamber of the eye).

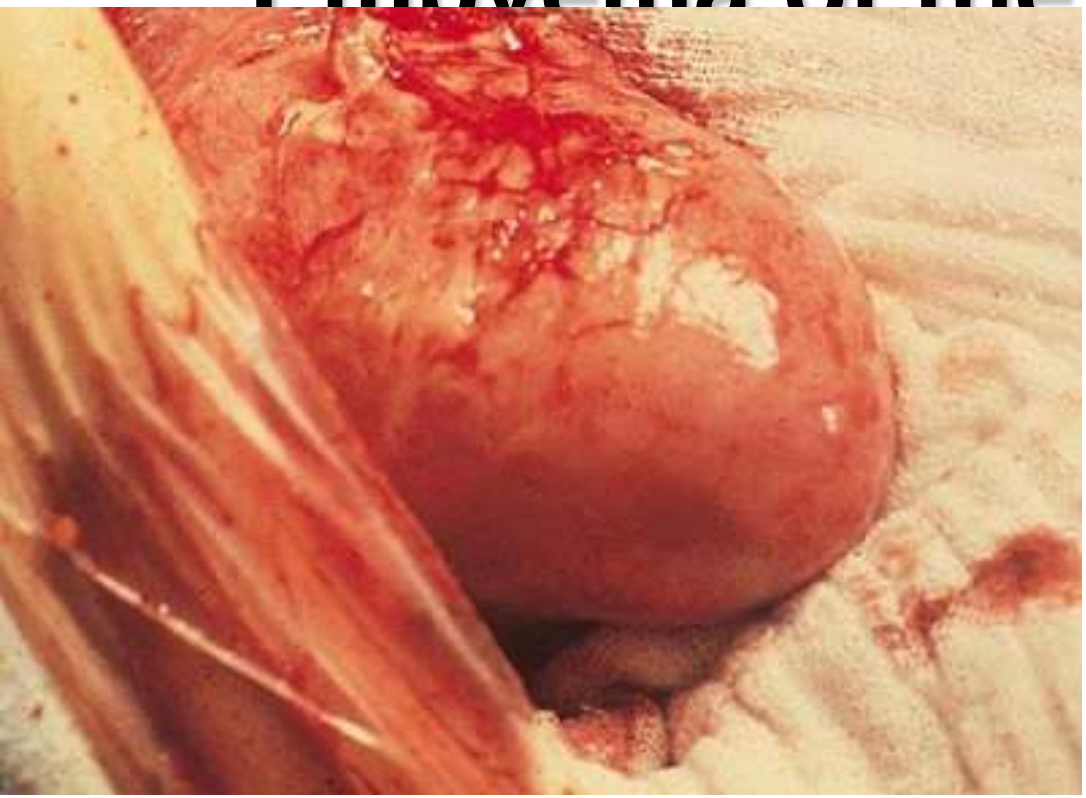
Purulent peritonitis





Purulent pericarditis

Empyema of the gallbladder



Phlegmon

- **Definition:** Diffuse suppurative inflammation that spreads primarily in loose fibrous connective tissue without sharp demarcation.

- **Examples:**

— Muscular phlegmon;

— Phlegmon of the floor of the mouth;

— Mediastinal phlegmon;

— Phlegmon of the walls of hollow organs (such as phlegmon in cholecystitis, appendicitis).

— Erysipelas, inflammation in the connective tissue of the skin usually caused by beta-hemolytic streptococci involving a map-like pattern of erythema and swelling;

Phlegmon

- Diffuse (diffuse) purulent inflammation;
- It develops in the subcutaneous fatty cellulose, cellulose surrounding the internal organs;
- **Solid phlegmon** – is characterized by the presence of foci of coagulation necrosis, which do not undergo melting, and are gradually rejected.
- **Soft phlegmon** – is characterized by a lack of visible foci of necrosis in the tissues;

Phlegmon

- **Paronychia** is an acute purulent inflammation of the peri-osseous tissue.

- **Panaritium** - acute purulent inflammation of the subcutaneous tissue of the finger.

- **Phlegmon neck** - acute purulent inflammation of the cellulose neck, develops as a complication of pyogenic infections of the tonsils, maxillofacial system.

- Danger of phlegmon neck - a purulent process can spread to the mediastinal fiber (purulent mediastinitis), pericardium (purulent pericarditis), pleura (purulent pleurisy).
- Phlegmon is always accompanied by severe intoxication and may be complicated by sepsis.

Phlegmon

- **Mediastinitis** is an acute purulent inflammation of the mediastinal fiber.
- Distinguish: anterior and posterior purulent mediastinitis.
- **Anterior mediastinitis** is a complication of suppurative inflammatory processes of the anterior mediastinum organs, pleura, phlegmon of the neck.
- **Posterior mediastinitis** is most often caused by the pathology of the esophagus: for example, traumatic injuries caused by foreign bodies (the bone bone is especially dangerous), decaying esophagus cancer, purulent necrotic esophagitis, etc.
- Purulent mediastinitis is a very severe form of purulent inflammation, accompanied by severe intoxication, which is the cause of the patient's death.

Phlegmon

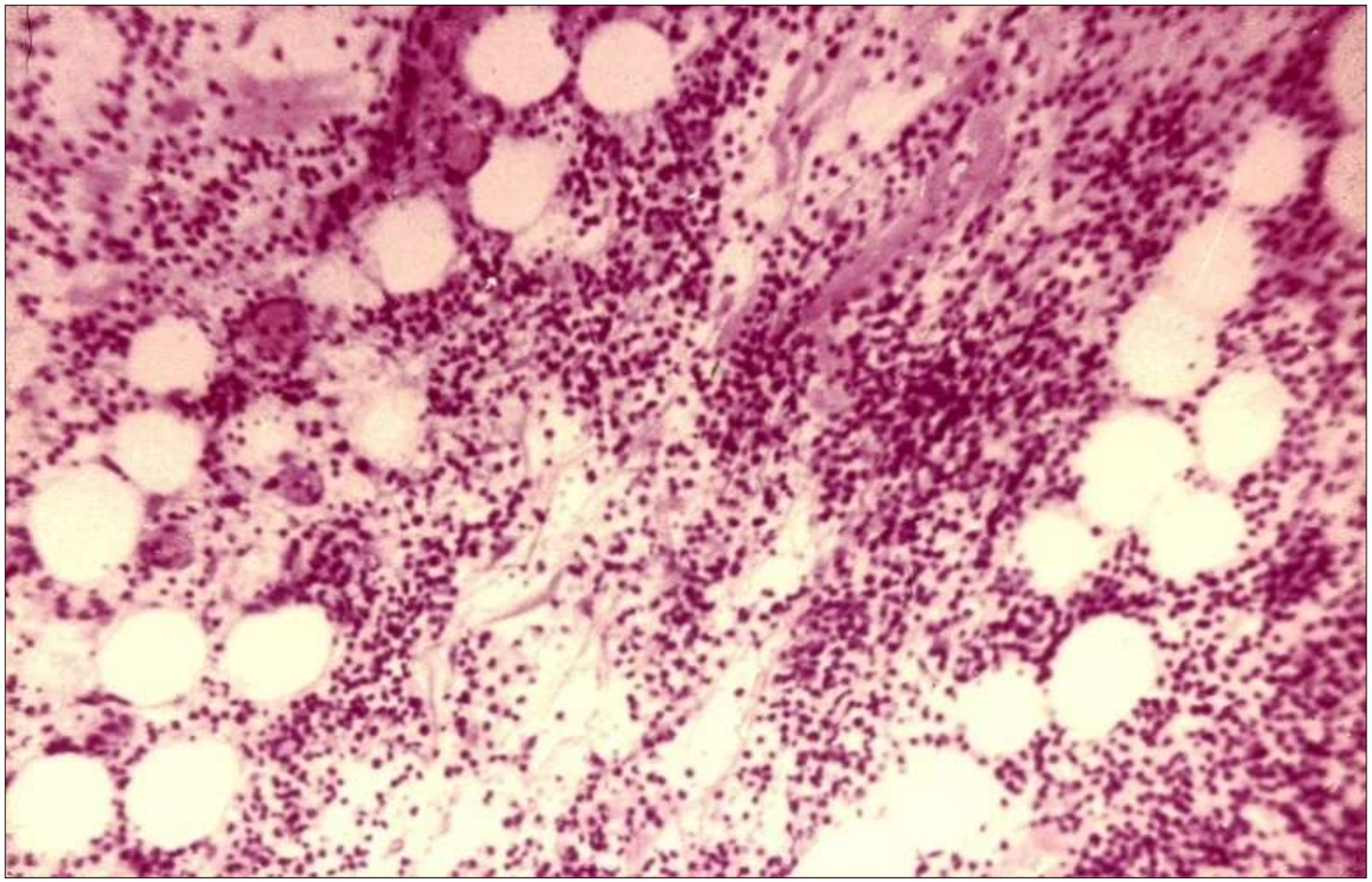
- **Paranephritis** is a purulent inflammation of the perineal tissue.
- is a complication of purulent nephritis, septic infarction of the kidneys, decaying kidney tumors.
- Meaning: intoxication, peritonitis, sepsis.

- **Parametritis** is a purulent inflammation of the periarticular tissue.
- It occurs in septic abortions, infected labor, decay of malignant tumors.
- First - purulent endometritis, then parametrite.
- Meaning: peritonitis, sepsis.

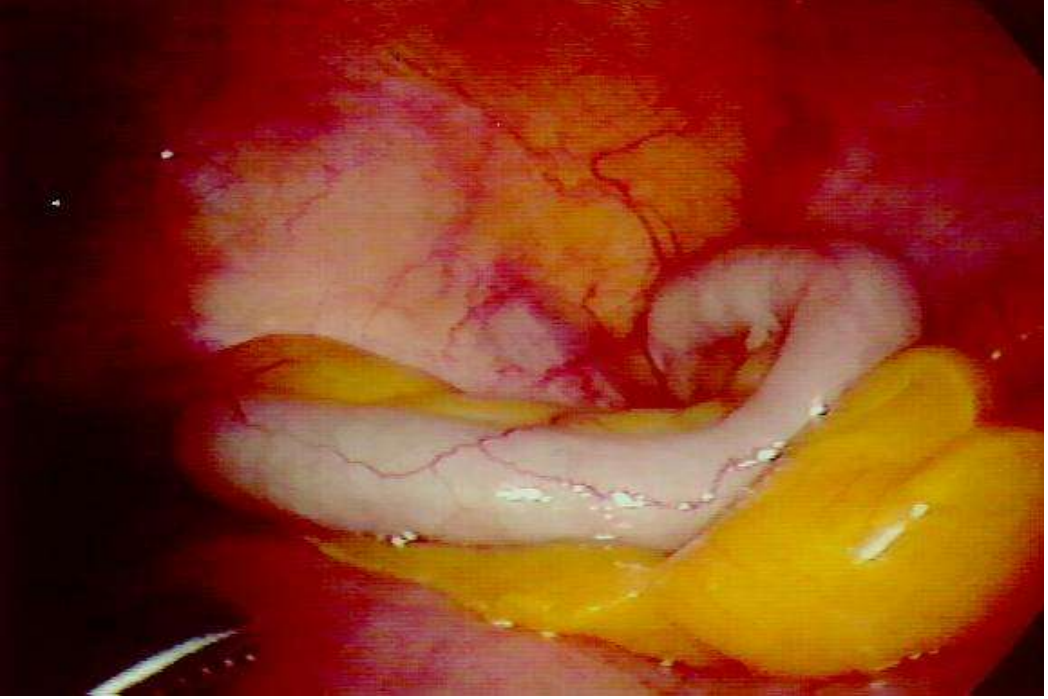
- **Paraproctitis** is the inflammation of the tissue surrounding the rectum.
- Causes: dysentery ulcers, ulcerative colitis, decaying tumors, anal fissures, hemorrhoids.
- Meaning: intoxication, the appearance of pararectal fistulas, the development of peritonitis.

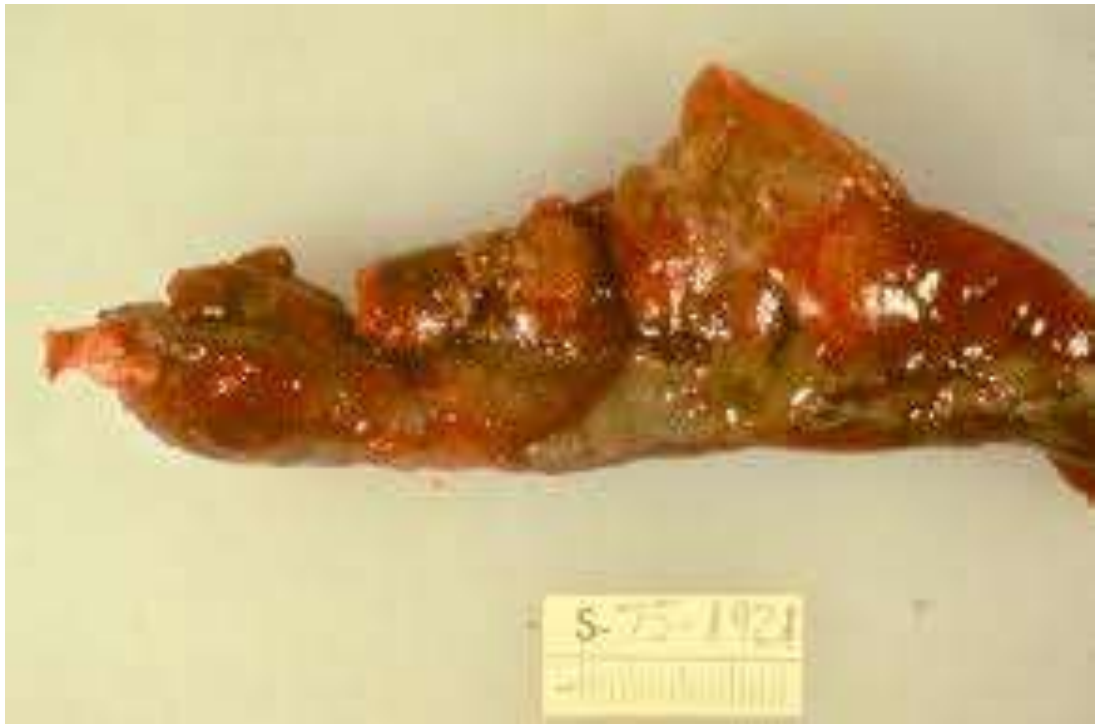
Phlegmon

Phlegmon

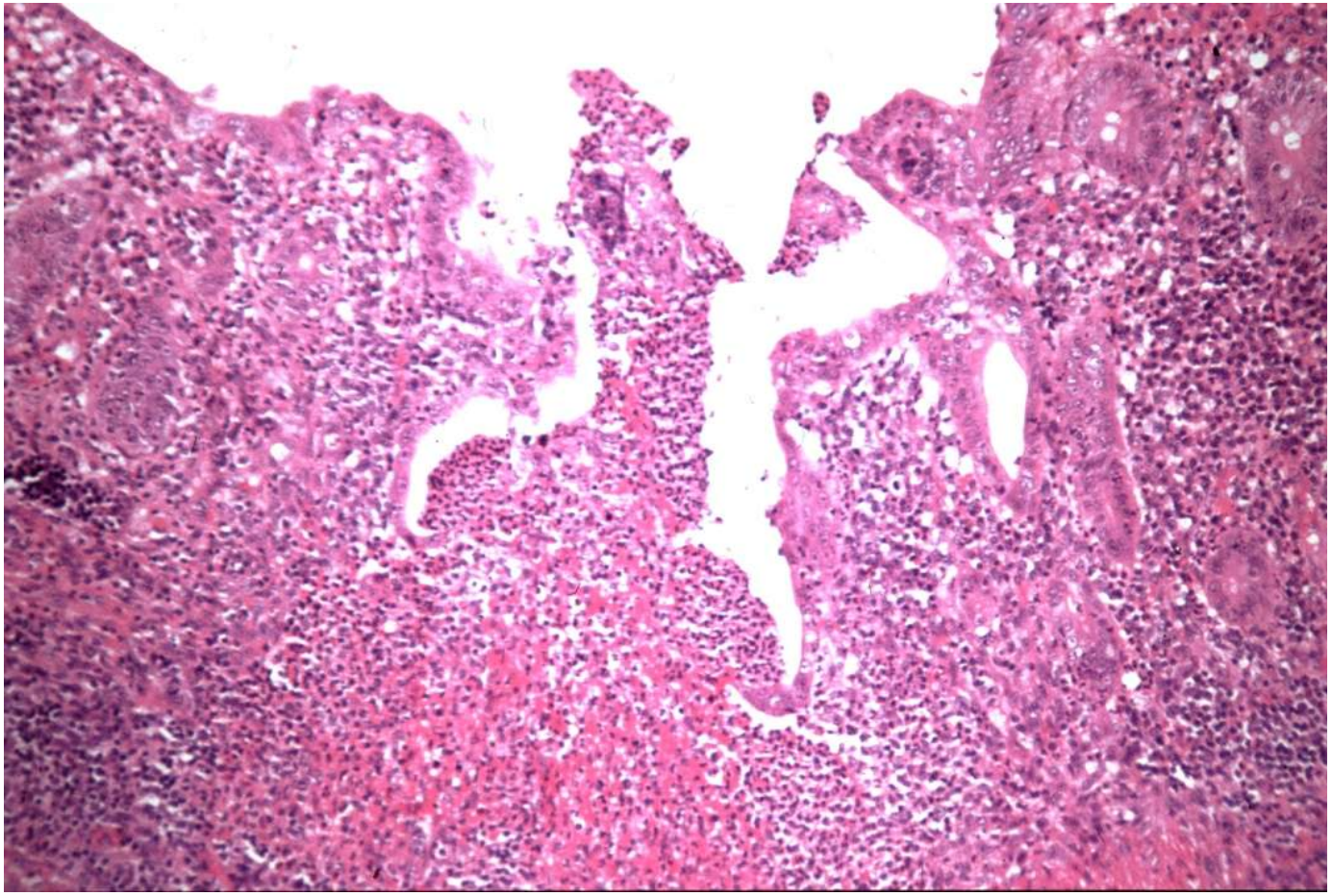


Phlegmonous appendicitis

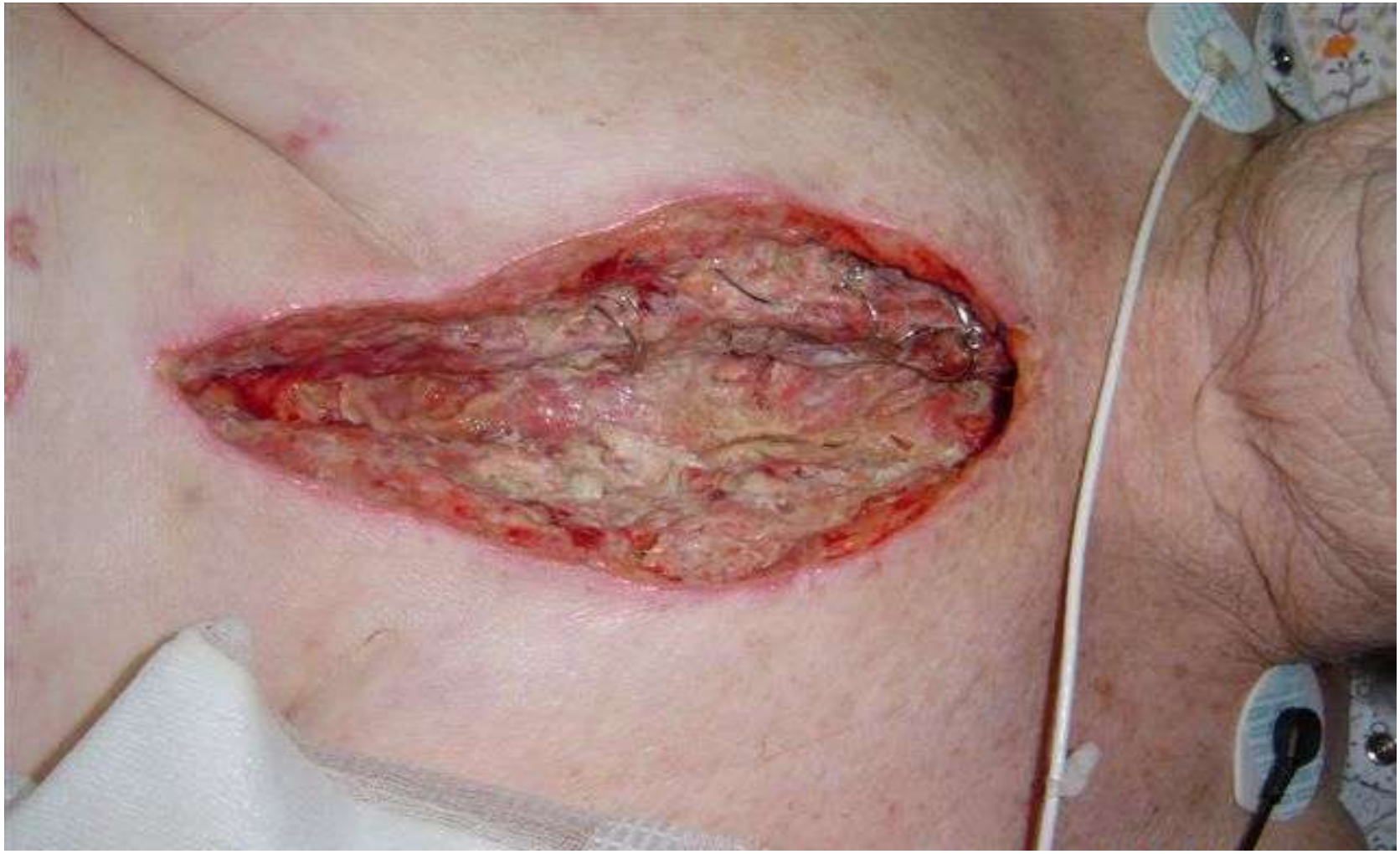




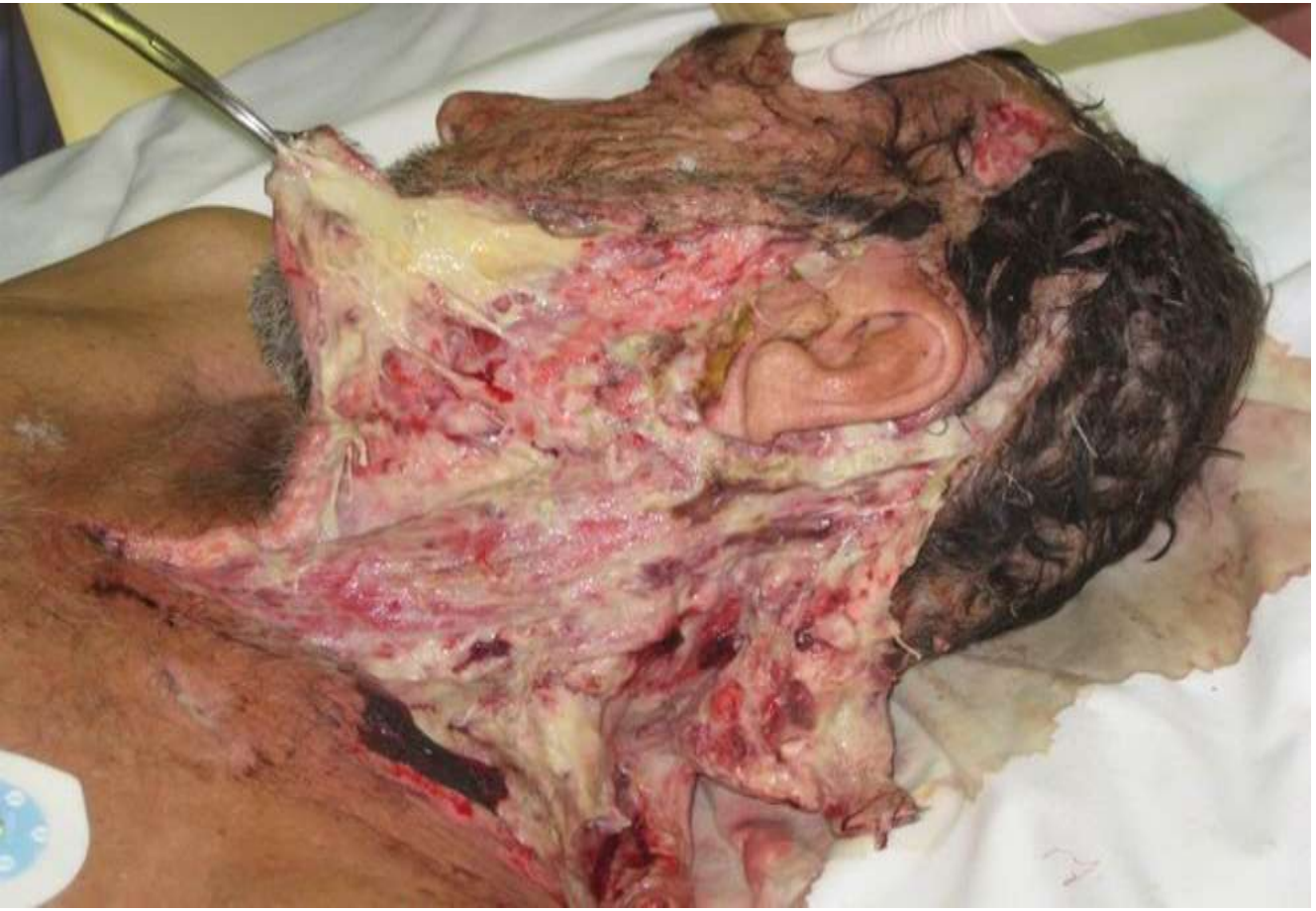
Phlegmonous appendicitis

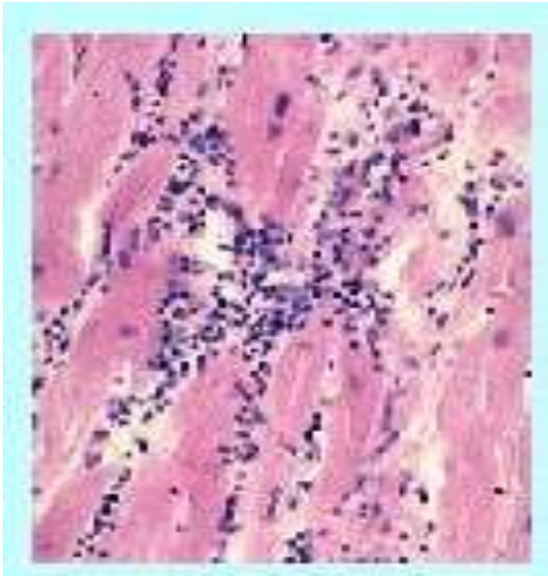


Purulent mediastinitis



Odontogenic phlegmon of face and neck





Furuncle

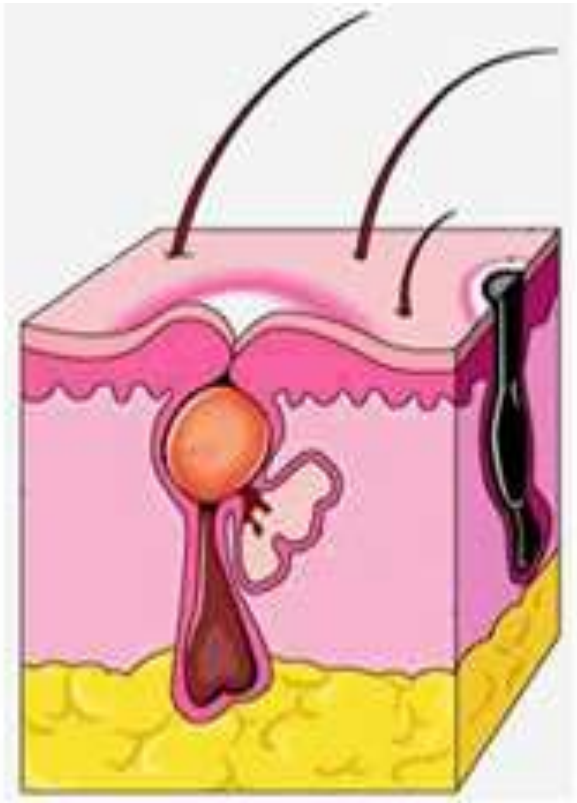
- this is an acute purulent-necrotic inflammation of the hair follicle (follicle) and associated with it the sebaceous gland with surrounding fiber.

- **Causes:** Staphylococcus aureus, streptococcus.

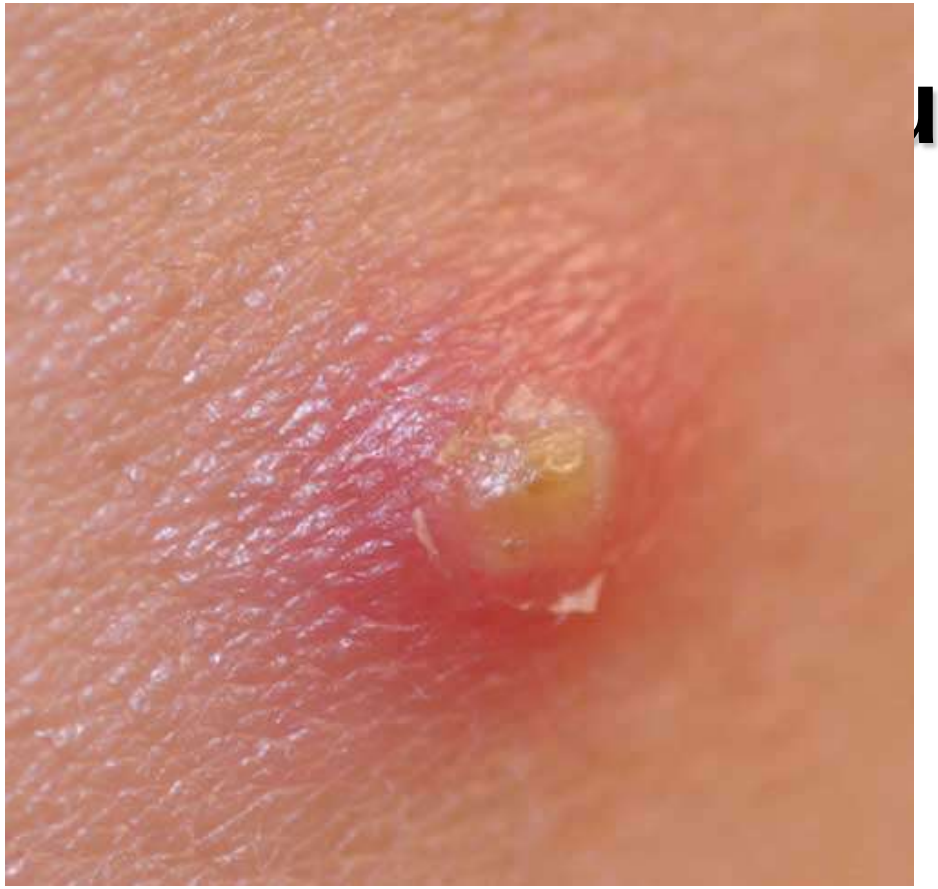
- **Conditions** conducive to the development of furuncle:

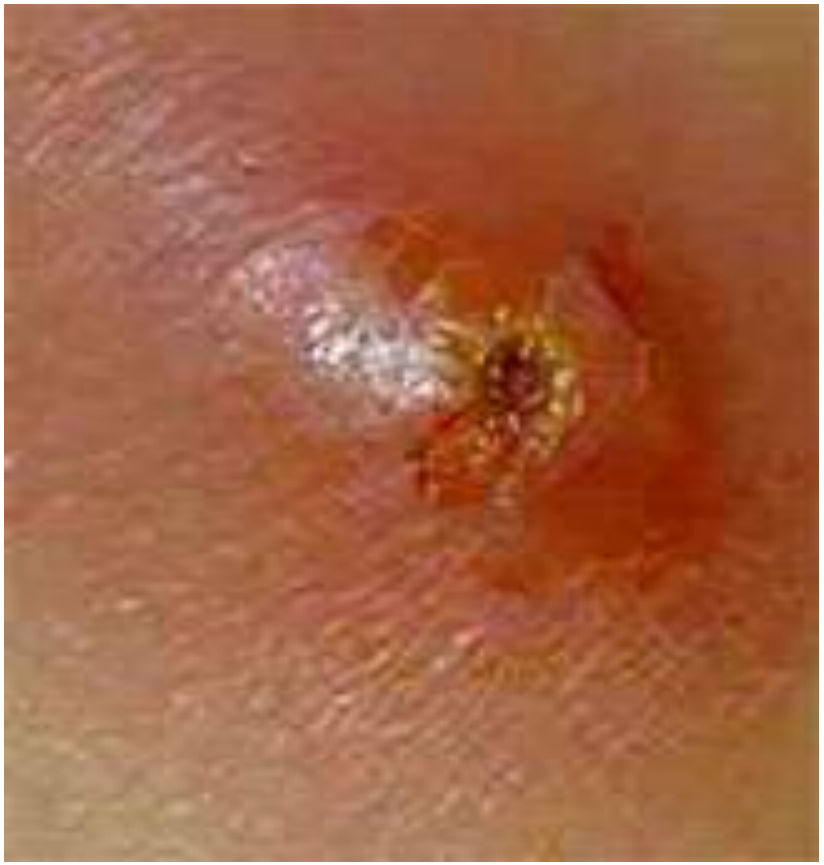
1. constant contamination of the skin and rubbing clothes,
2. irritation with chemicals, abrasions, combs and other micro-traumas,
3. intensified activity of sweat and sebaceous glands, beriberi,
4. metabolic disorders (eg, diabetes mellitus),
5. starvation,
6. weakening of the body's defenses.

Furuncle



uncle





Carbuncle

- this is an acute purulent inflammation of several nearby arranged hair follicles and sebaceous glands with necrosis of the skin and subcutaneous tissue of the affected area.

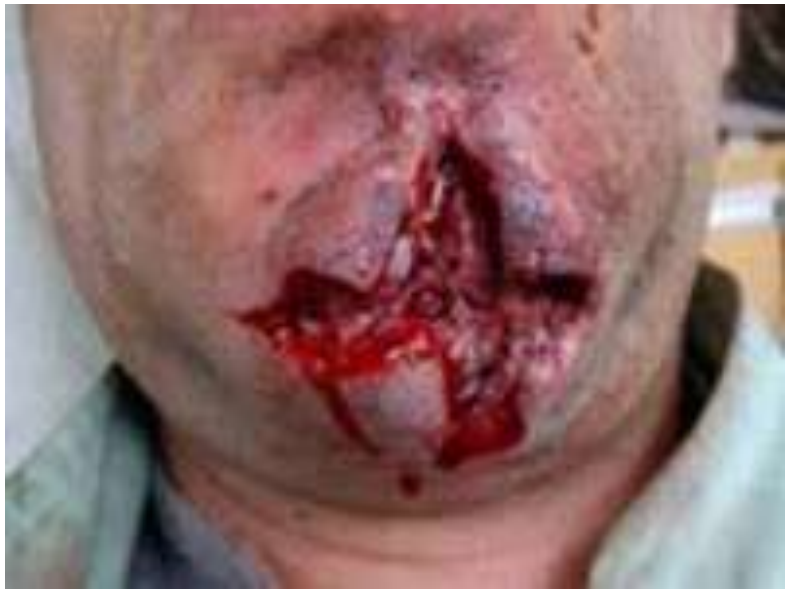
- Occurs: when pyogenic microbes enter the ducts of the sebaceous or sweat glands, as well as when they penetrate the skin through minor lesions, squeezing out the furuncle.

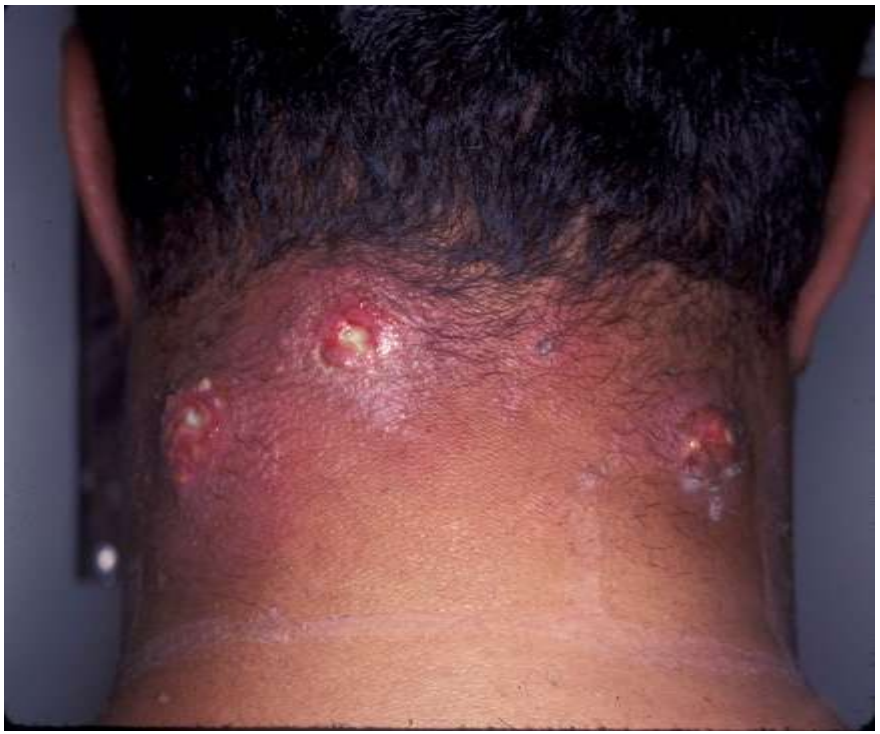
- The conditions of development and localization are the same as in the furuncle.
- **Macroscopically**: an extensive dense, red-crimson infiltration on the skin, in the center of which there are several purulent "heads".

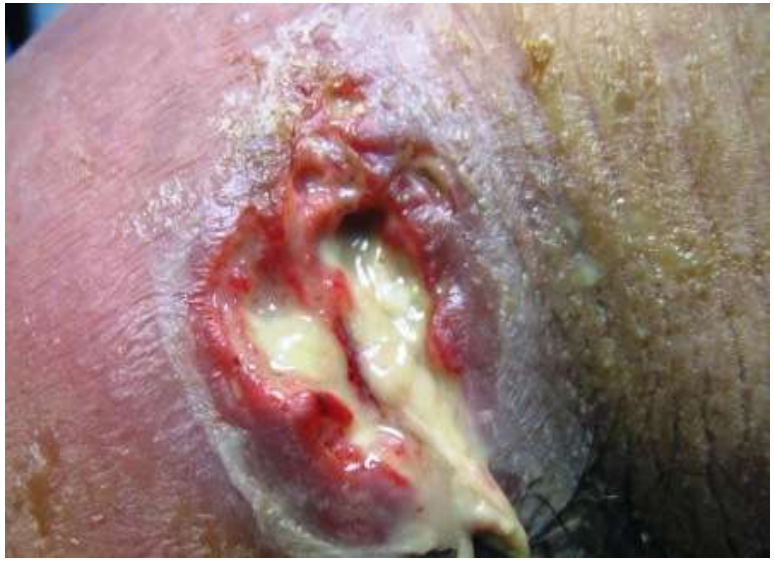
Carbuncle

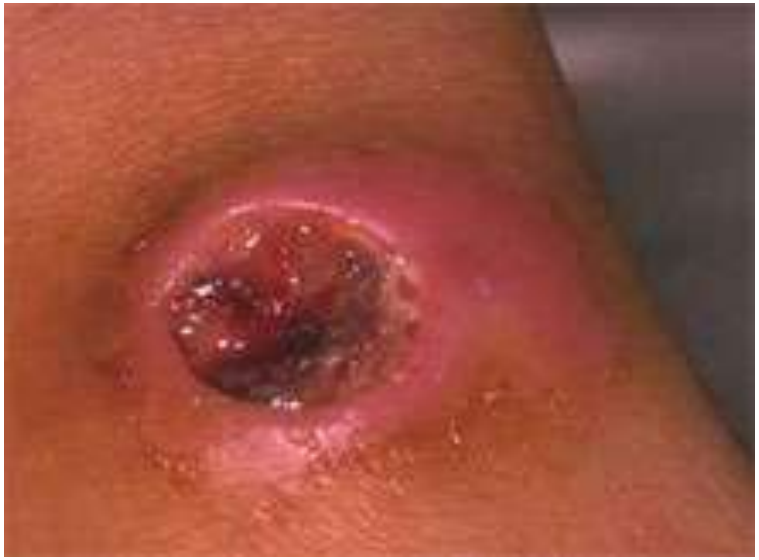
- The most dangerous carbuncle of the nose and especially the lips, in which a purulent process can spread to the membranes of the brain, resulting in purulent meningitis.
- Treatment - operative; at the first symptoms of the disease you need to consult a surgeon.
- Value. Carbuncle is more dangerous than a boil, is always accompanied by severe intoxication.
- Complications: purulent lymphadenitis, purulent thrombophlebitis, erysipelas, phlegmon, sepsis.

Carbuncle









Outcomes of purulent inflammation

1. Formation of external (in the external environment) and internal (in some kind of hollow organ) fistula;

2. "Purulent fouling" (blind pockets with pus, departing from the focus of purulent inflammation);

3. Formation of sequestration (sequestration);

4. Scar formation (organization) after evacuation of the purulent inflammation site;

5. Formation of the capsule (encapsulation).

Hemorrhagic Inflammation

- **Definition:** Exudative inflammation involving microvascular injury with massive microvascular bleeding, producing an exudate with a high erythrocyte content.

- Biologic purpose: Exudative inflammation due to severe vascular injury.

- **Morphology:** The inflamed area is usually necrotic and filled with blood.

- **Etiologic factors:**

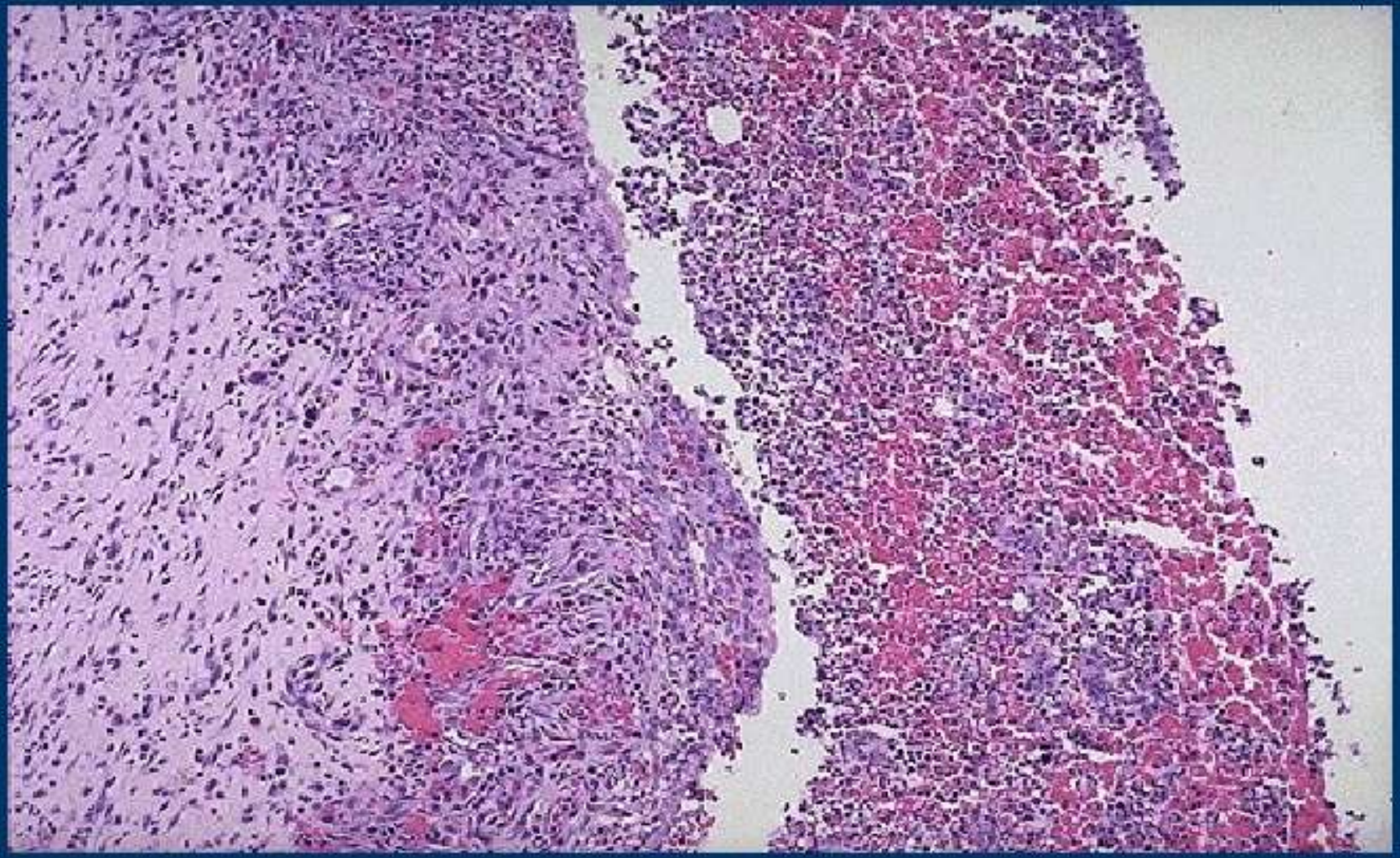
— bacterial exotoxins and endotoxins;
— viral cytopathic effect on endothelium;
— proteolytic tissue destruction;
— cytotoxic injury in hypersensitivity type III.

Hemorrhagic Inflammation

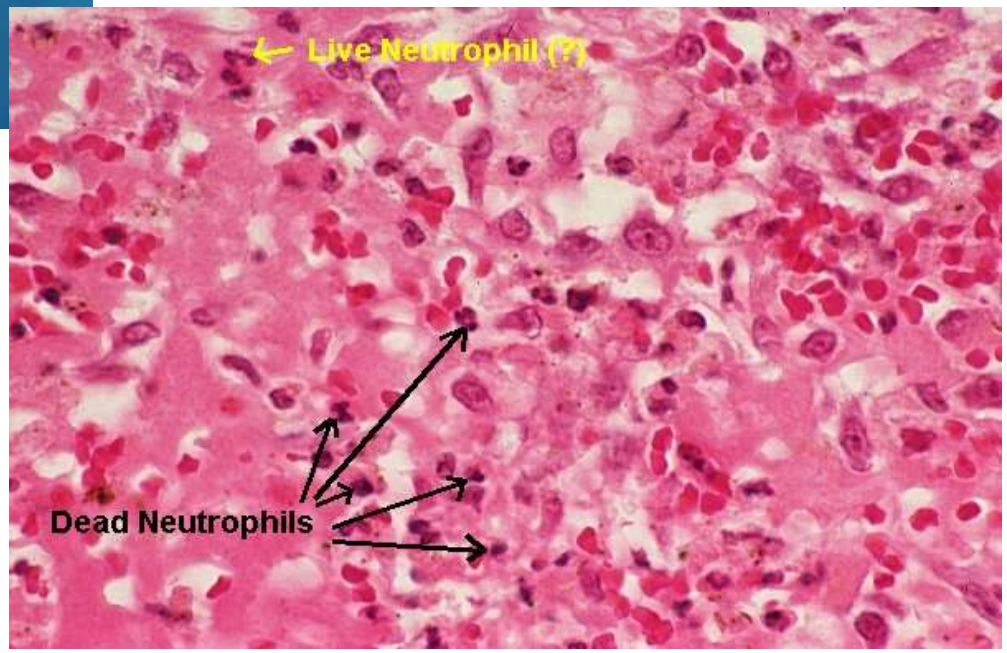
Examples:

- Plague
- Influenzal Pneumonia
- Disorders Associated with Enterohemorrhagic E. Coli
- Anthrax
- Viral Hemorrhagic Fever
- Acute Pancreatitis

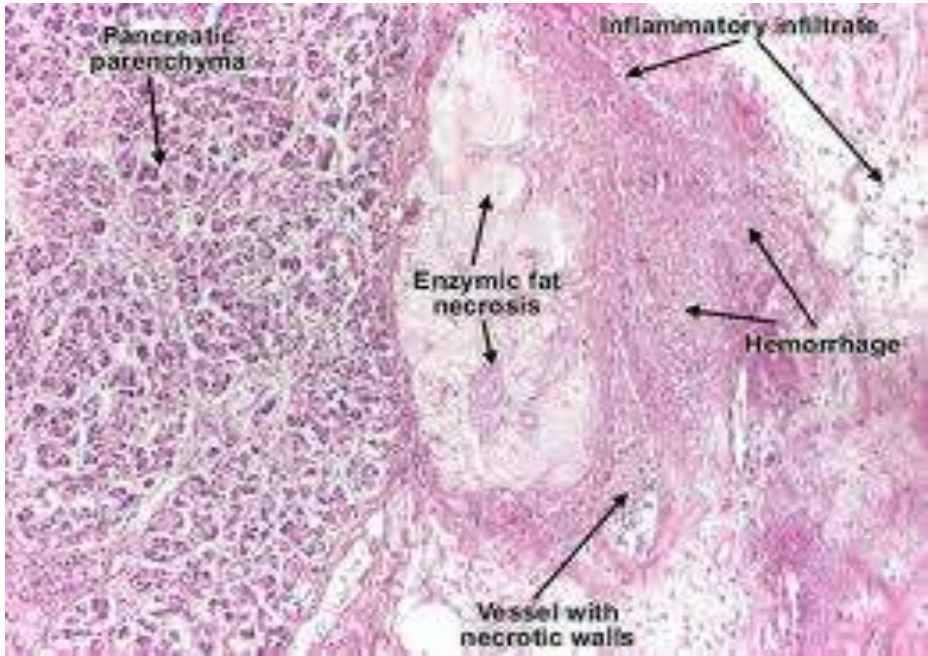
HEMMORRHAGIC INFLAMMATION-RIGHT



Hemorrhagic Inflammation



Hemorrhagic pancreatitis



- Hemorrhagic form of herpes

Catarrhal Inflammation

- **Definition:** Exudative inflammation occurring exclusively on the mucous membranes of the respiratory and gastrointestinal tracts and producing a watery exudate of serum and mucus.

- **Subtypes:** mucus (most frequent), serous, purulent, hemorrhagic

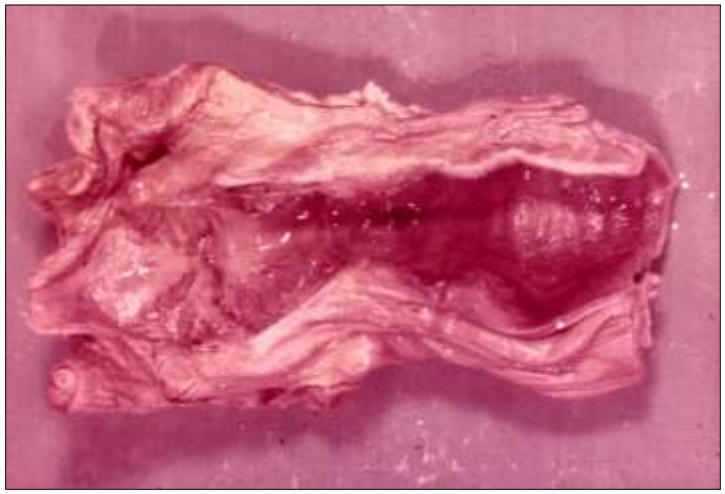
- **Etiologic factors:**

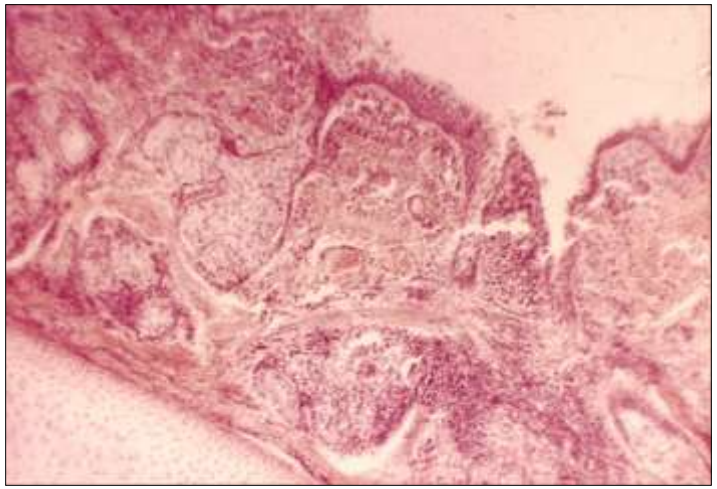
— hypersensitivity reactions;

— bacterial and viral tissue injury;

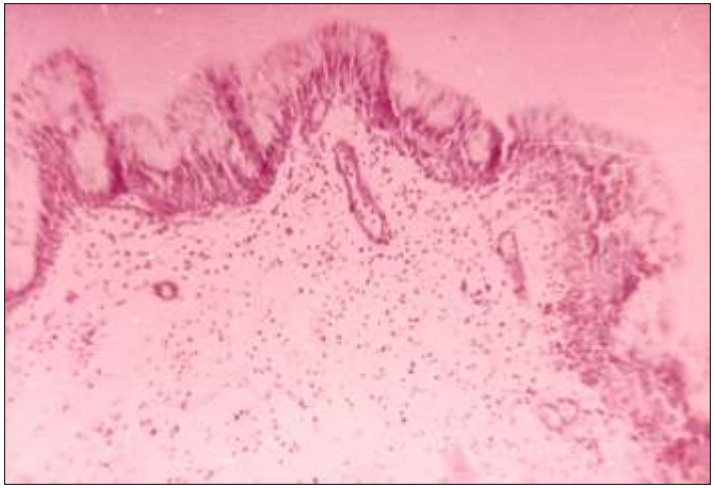
— physical and chemical tissue injury.

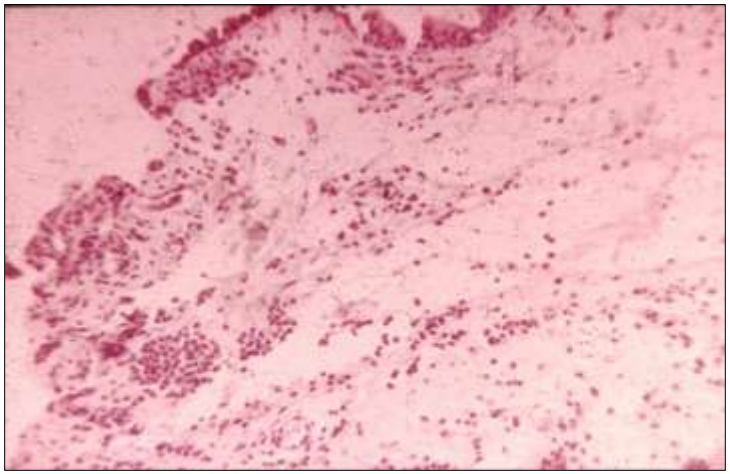
Catarrhal tracheitis

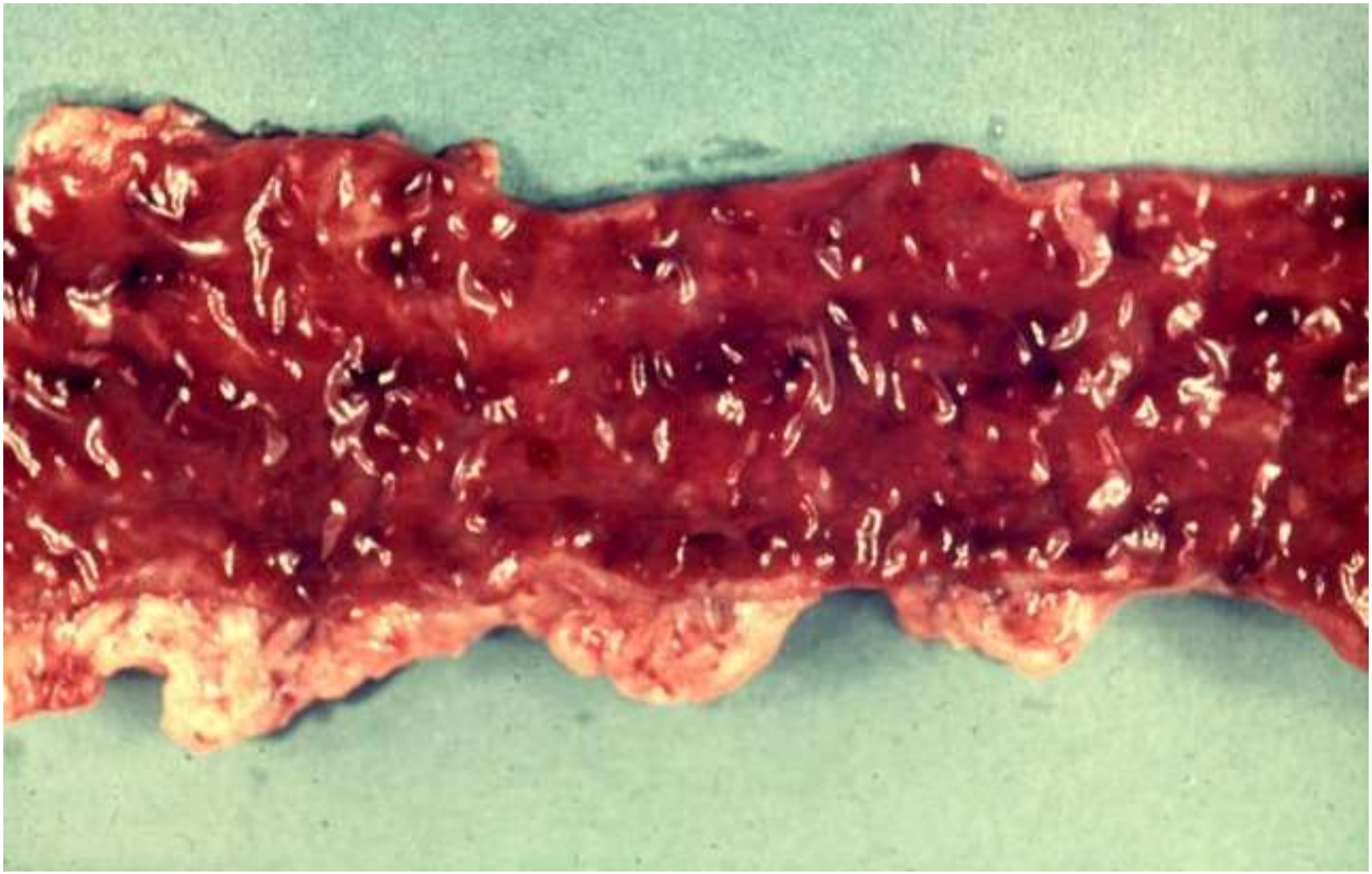




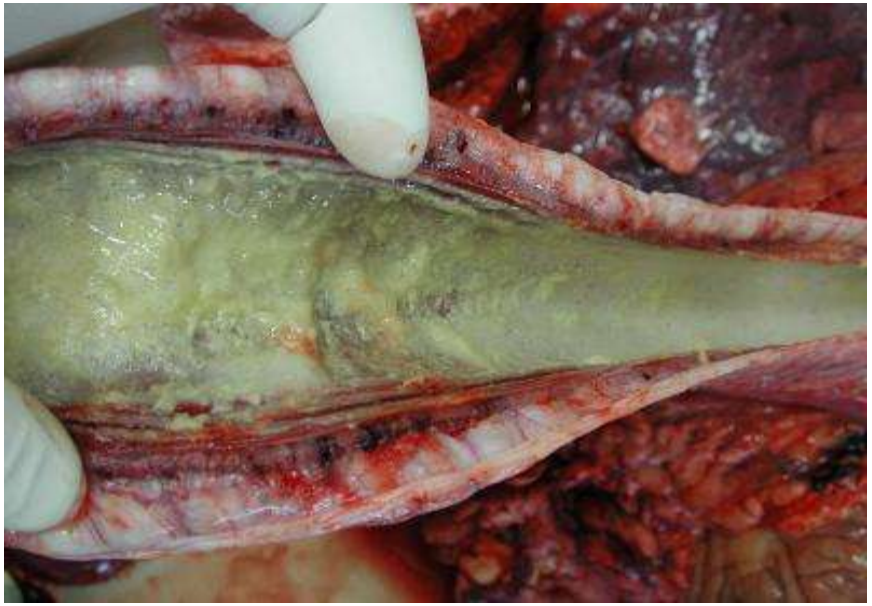
Catarrhal sinusitis



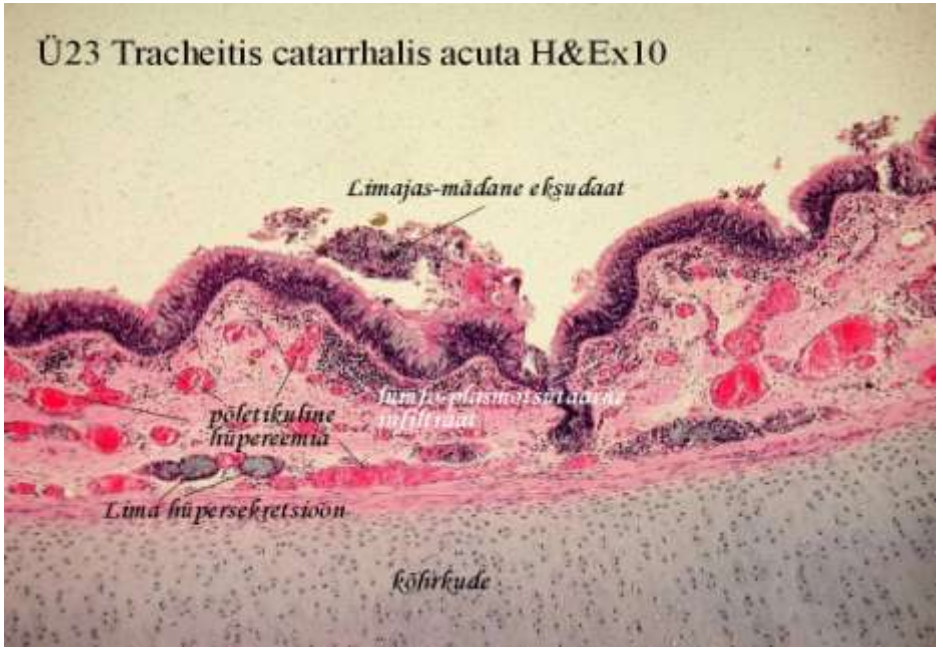


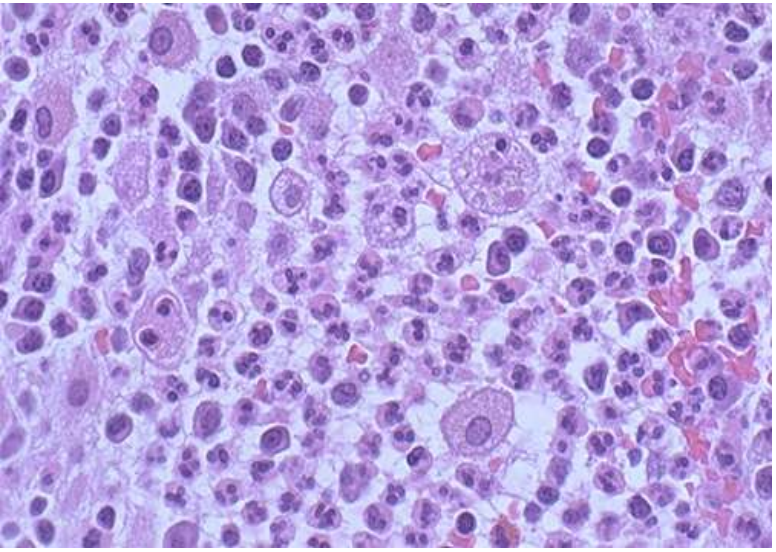


Catarrhal colitis



Catarrhal tracheitis





Mixed Inflammation

- In those cases when one exudate is joined by another, mixed inflammation is observed.

- serous-fibrinou inflammations,
- purulent-hemorrhagic inflammations,
- fibrinous-hemorrhagic inflammation.

- Most often, a change in the type of exudative inflammation is observed with the *addition of a new infecti*on, *a change in the reactivity of the organism*.

Outcomes of acute inflammation

Favorable:

- Absorption,
- tissue repair (the most favorable outcome)
- Organization – scar formation

Unfavorable:

- Acute organ insufficiency
- Abscess formation - pyonecrotic cavity
- Persistence of inflammation and chronicity

Possible outcomes of acute inflammation

- Complete resolution
  - Little tissue damage
  - Capable of regeneration &restoration of injury cell to normal
  - Resolution involves – neutralization, spontaneous decay of chemical mediators ,subsequent return of normal vascular permeability ,cessation of leukocyte infiltration ,death by apoptosis removes edema ,protein, foreign substance & necrotic debris .
- Scarring (fibrosis)
  - In tissues unable to regenerate
  - Excessive fibrin deposition organized into fibrous tissue
  - in many pyogenic infection – intense neutrophil infiltration &liquefaction of tissue – pus formation- fibrosis.

Outcomes (cont'd)

- Abscess formation occurs with some bacterial or fungal infections
- Pneumonia, chronic lung abscess, peptic ulcer of duodenum or stomach –persist months or yrs
- Progression to chronic inflammation (next)

Chronic Inflammation

- is inflammation of prolonged duration **(weeks to months to years)** in which active inflammation, tissue injury, and healing proceed simultaneously.

Chronic Inflammation

- Inflammation for a prolonged period (weeks-months)
- Onset
  - After Acute Inflammation
    - When injurious agent is not removed promptly
    - More and more inflammatory cells are recruited to site of injury
  - Insideous Onset
    - Low intensity injury for long period of time
    - Inflammatory response is not overwhelming
    - Injury and inflammation persist

Chronic inflammation arises in the following settings:

1. T lymphocyte-mediated immune response called delayed-type hypersensitivity
2. Immune-mediated inflammatory diseases
3. autoimmune diseases

Chronic Inflammation - Causes

- Persistent infection
  - MTB
  - Viruses
  - Fungi
  - Parasites
- Immune mediated
  - Autoimmune diseases (Rheumatoid arthritis)
  - Allergic diseases (Broncial asthma)
- Prolonged exposure
  - Silicosis (Pulmonary fibrosis)

Chronic Inflammation - Features

- Inflammatory infiltrate
  - Macrophages
  - Lymphocytes
  - Plasma Cells
- Tissue destruction
  - Persistent injury
  - Inflammatory cells and Mediators
- Repair
  - Angiogenesis
  - Fibrosis

Chronic Inflammation - Cells

- Macrophages
- Lymphocytes
- Plasma Cells
- Eosinophils
- Mast Cells
- Neutrophils!

Chronic inflammation

Chronic productive inflammation:

1. Interstitial inflammation;
2. Granulomatous inflammation;
3. Inflammation with the formation of polyps and genital warts.

Chronic exudative inflammation:

1. Chronic abscess;
2. Chronic catarrhal inflammation.

The main types of productive (proliferative) inflammation

1. Interstitial (interstitial) inflammation;

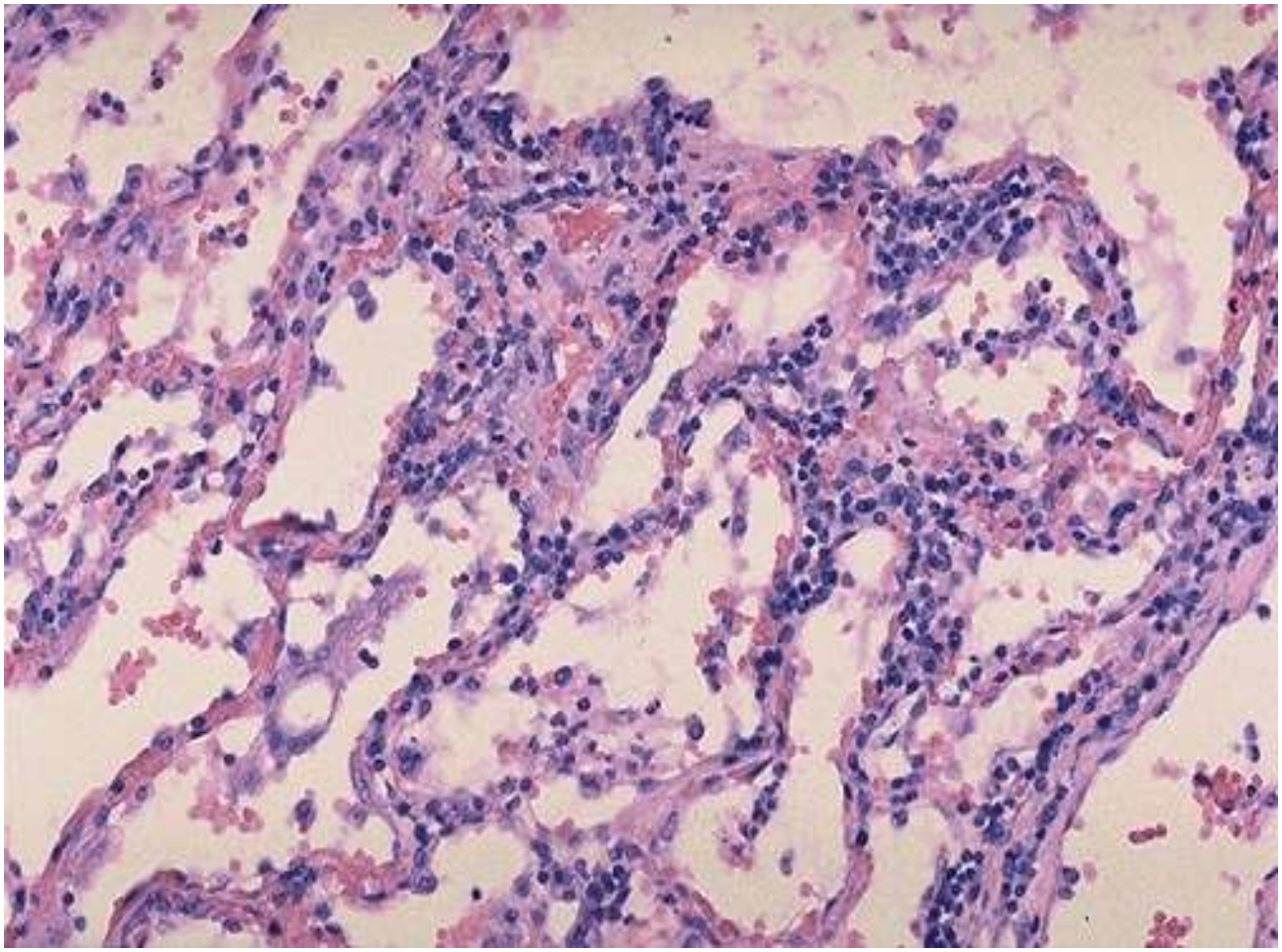
2. Granulomatous inflammation;

3. Inflammation with the formation of polyps and genital warts.

Interstitial Inflammation

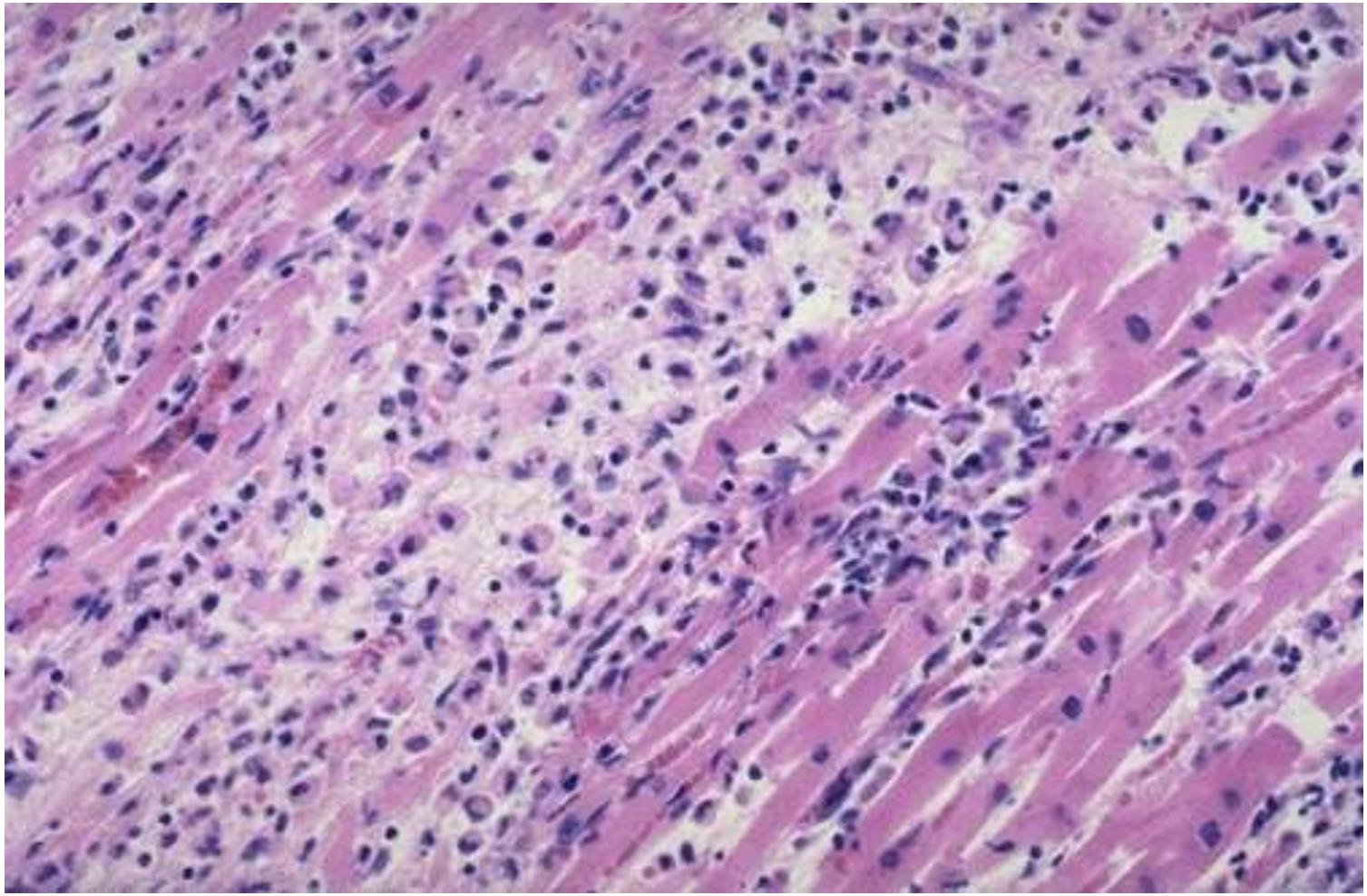
- **Characteristic:** the formation of focal or diffuse inflammatory cell infiltrate in the stroma of parenchymal organs - myocardium, liver, kidneys, lungs.
- **The main cells**: lymphocytes, histiocytes, plasma cells, single neutrophils, eosinophils and mast cells.
- **In the parenchymal elements** - dystrophic and necrobiotic changes.
- **Examples:** acute and chronic interstitial pneumonia, idiopathic myocarditis Abramov-Fiedler, chronic interstitial nephritis during chronic pyelonephritis.
- **Outcome** is sclerosis.

Interstitial inflammation



- Interstitial pneumonitis

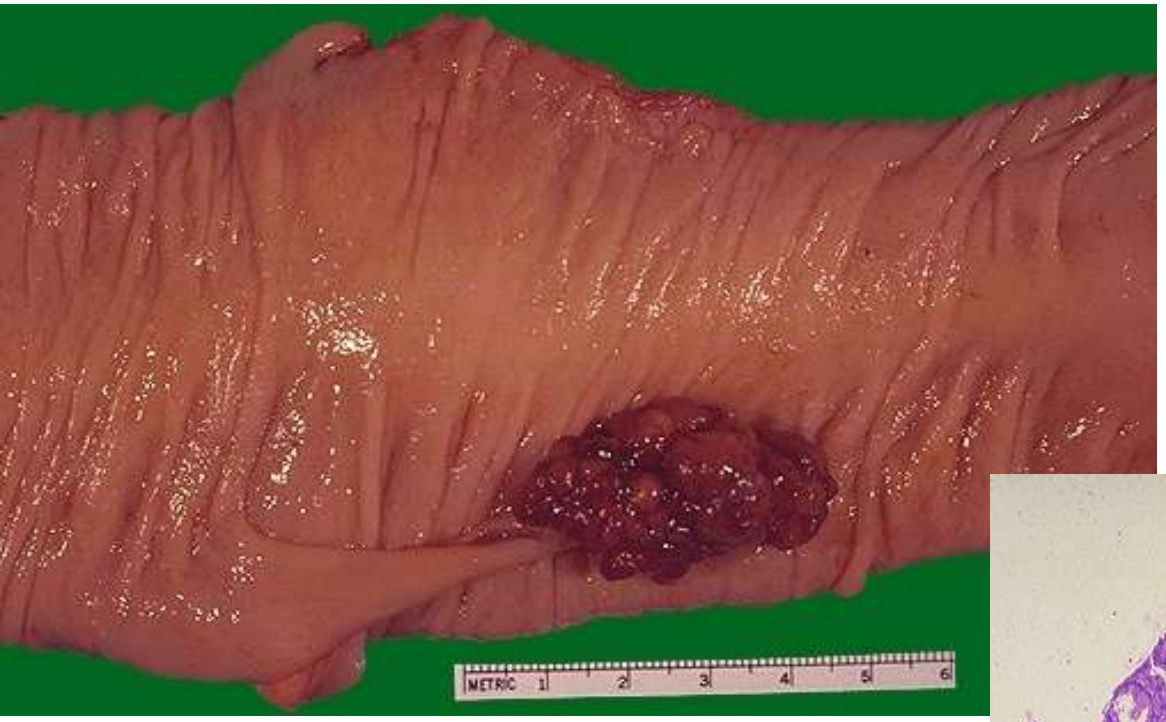
Interstitial myocarditis

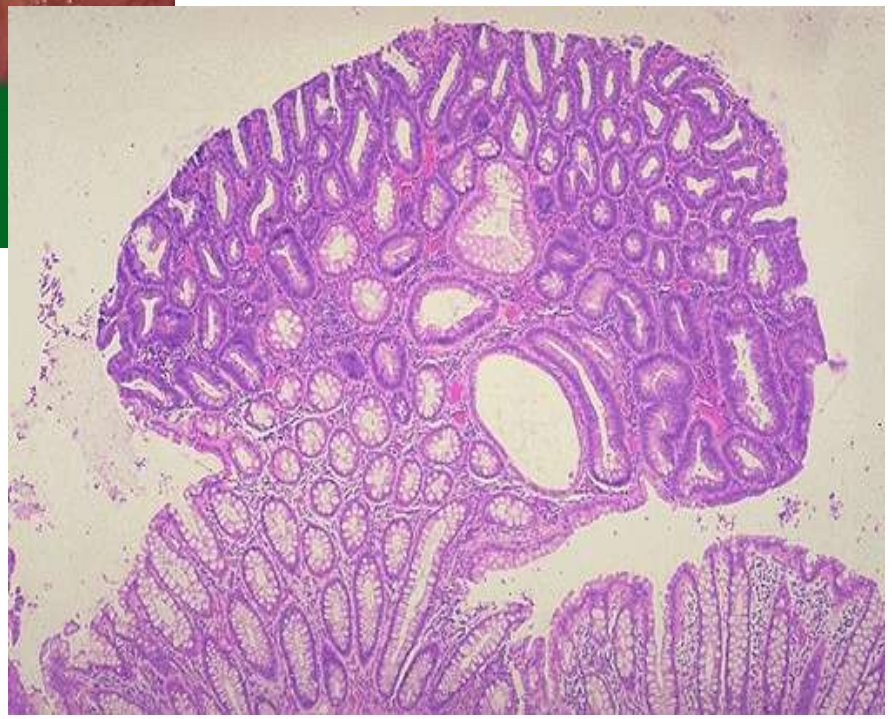


Inflammation with the formation of polyps and genital warts

- Productive inflammation, in which there is a simultaneous proliferation of parenchymal elements and stroma;
- The stroma is diffusely infiltrated by mononuclears.
- Characteristic of chronic course;
- Typical localization is the mucous membranes.
- Examples: polyps of the nasal cavity, maxillary sinuses, bronchi, gastric mucosa, intestine, uterus.

Polyp of intestine



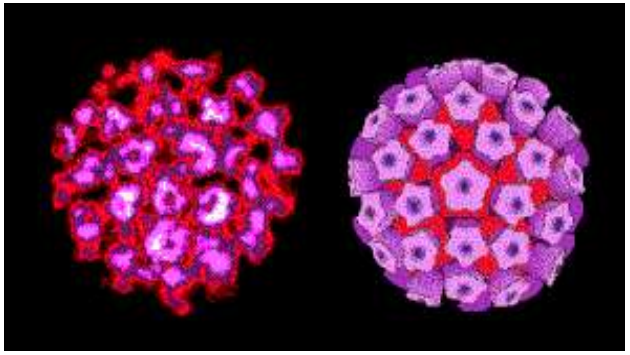


- **Pointed condylomas** - formed at the junction of the flat and prismatic epithelium (anus, genitalia);

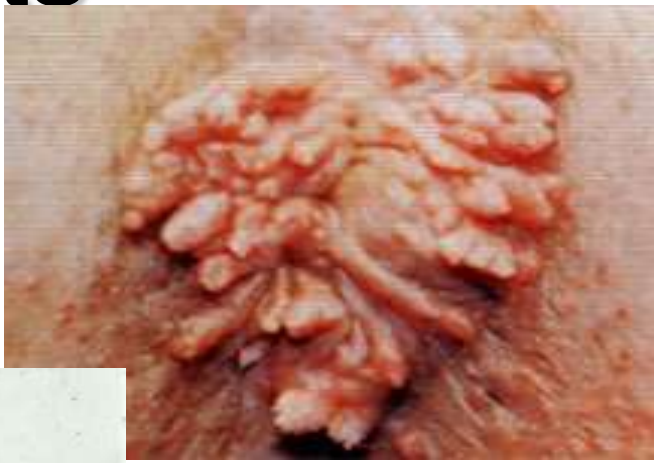
- are caused by papillomavirus (HPV);

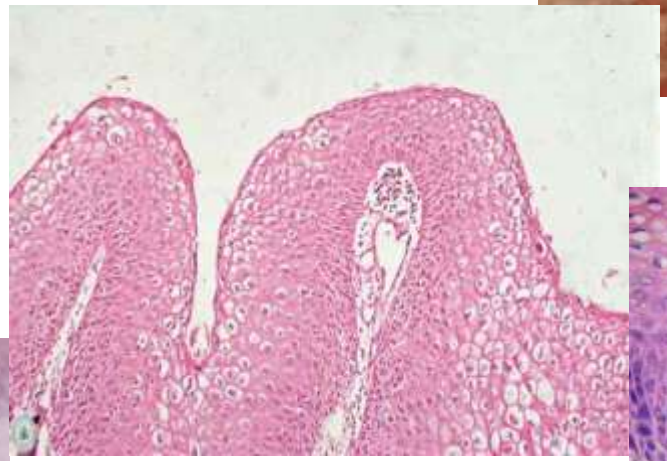
- may be accompanied by dysplasia; are a risk factor for squamous cell carcinoma.

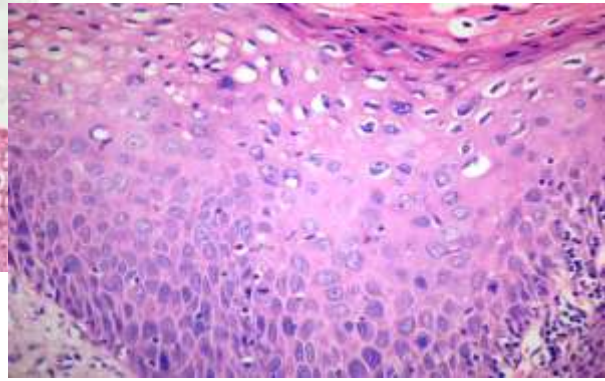
Genital Warts



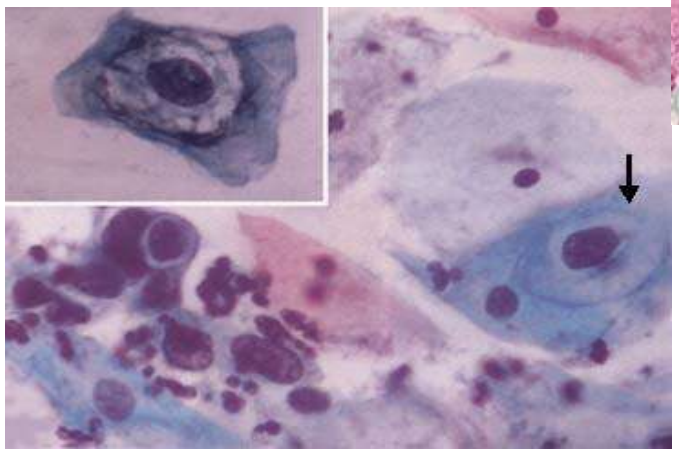
Papillomavirus







Acanthosis, hyperkeratosis, parakeratosis, cytoplasmic vacuolation, koylocytosis



Coilocyte reaction

Granulomatous Inflammation

- Distinctive type of chronic inflammation
- Attempt to contain an offending agent that is difficult to eradicate
- Strong activation of T cells and Macrophages

- Examples:
  - TB
  - Leprosy
  - Fungal Infection
  - Sarcoidosis
  - Syphilis
  - Crohn's

GRANULOMATOUS INFLAMMATION

- Granulomatous inflammation occurs after the acute-phase response and consists of epithelioid and giant cells.
- Two types of granuloma:

  1. Foreign Body granuloma-formed in response to indigestible materials

  2. Allergic granuloma-formed in delayed hypersensitivity reactions

Granulomatous inflammation

- Characterized by the predominance of activated macrophages and / or their derivatives;
- **Morphological substrate** - granuloma;
- **Granuloma** is a focal cluster of cells capable of phagocytosis monocyte-macrophage nature.

Etiology of granulomatous inflammation

Endogenous factors:

1. poorly soluble products of damaged tissues, especially adipose tissue,
2. products of impaired metabolism (urate).

Exogenous factors:

1. biological (bacteria, fungi, protozoa, helminths);
2. organic and inorganic substances (dust, fumes, medicines, etc.)

Classification of granulomas (by etiology)

Granulomas of known etiology

1. **Infectious granulomas** (in typhus and typhoid fever, rabies, viral encephalitis, actinomycosis, schistosomiasis, tuberculosis, leprosy, syphilis, etc.)

2. **Noninfectious granulomas** (organic and nonorganic dusts - wool, flour, silicon oxide, asbestos, etc., foreign bodies, medicinal effects).

Granulomas of unknown etiology

1. sarcoidosis,
2. Crohn's disease,
3. primary biliary cirrhosis of the liver, etc.

Morphogenesis of granuloma

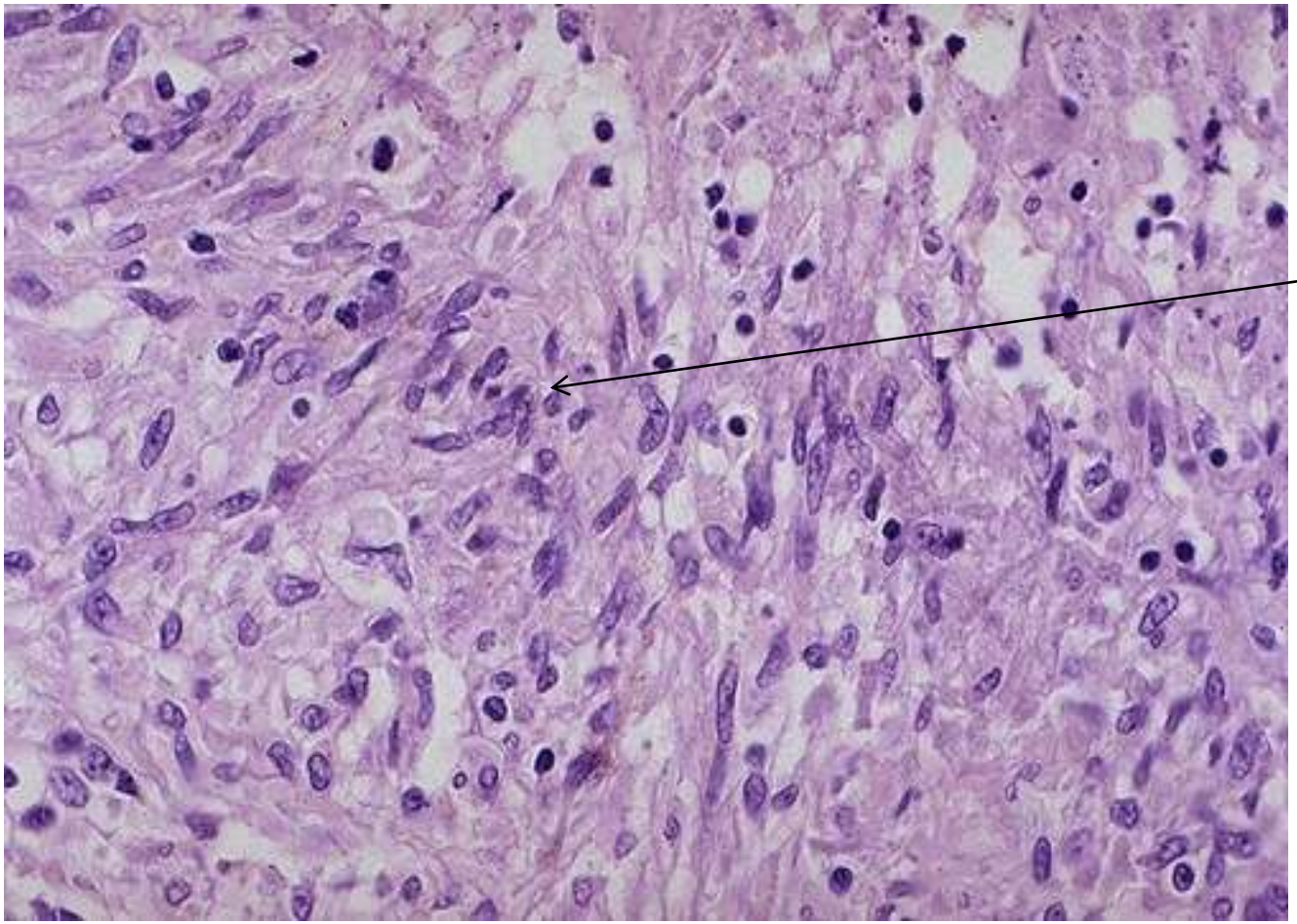
I stage. Accumulation in the lesion of tissue damage of young monocytic phagocytes.

II stage. Maturation of these monocytic phagocytes into macrophages and the formation of macrophagial granuloma.

III stage. Maturation and transformation of monocytic phagocytes and macrophages into epithelioid cells and formation of epithelioid-cell granuloma.

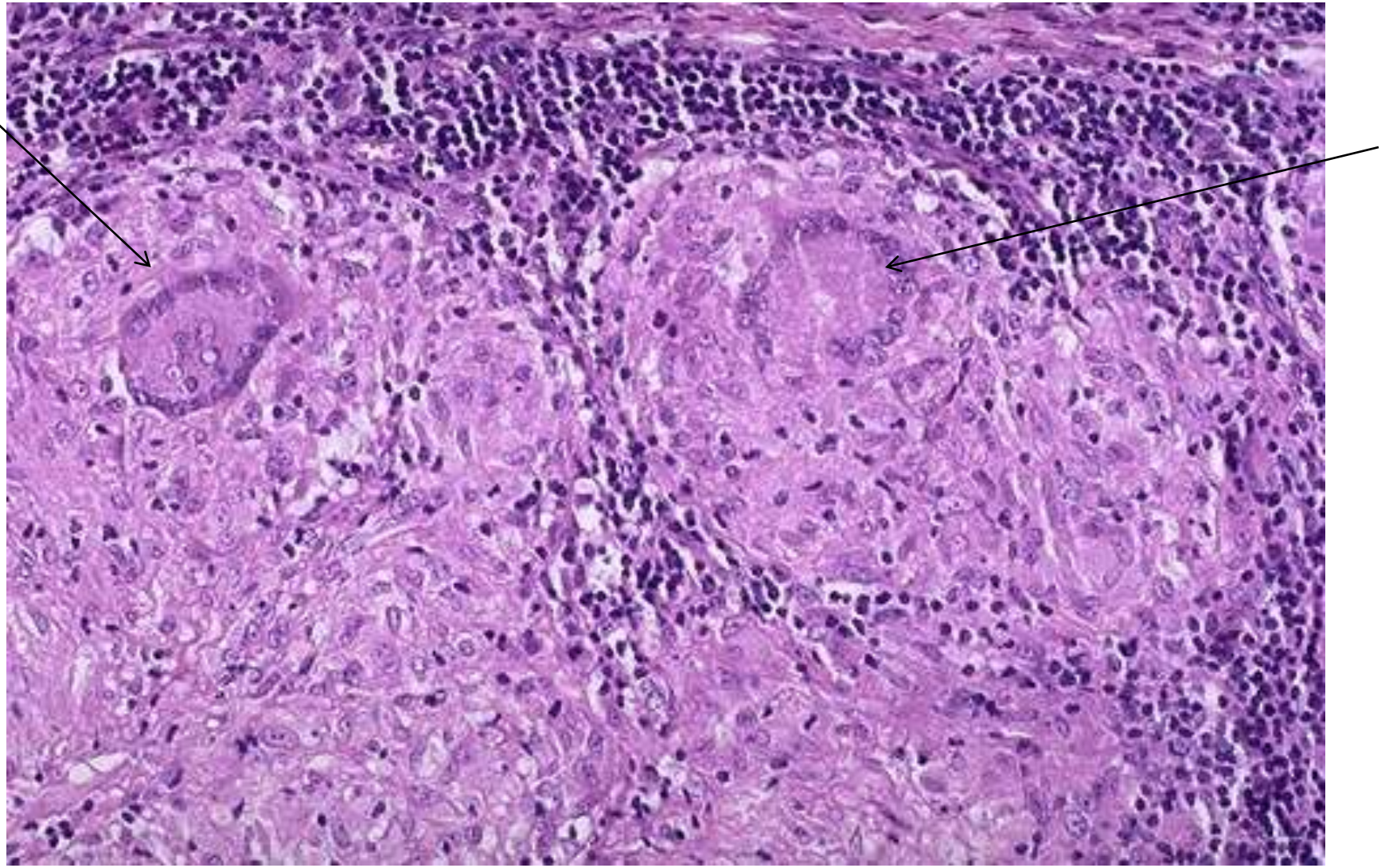
IV stage. Transformation of epithelioid cells into multinuclear giant cells and formation of giant cell granuloma.

Granulomatous inflammation

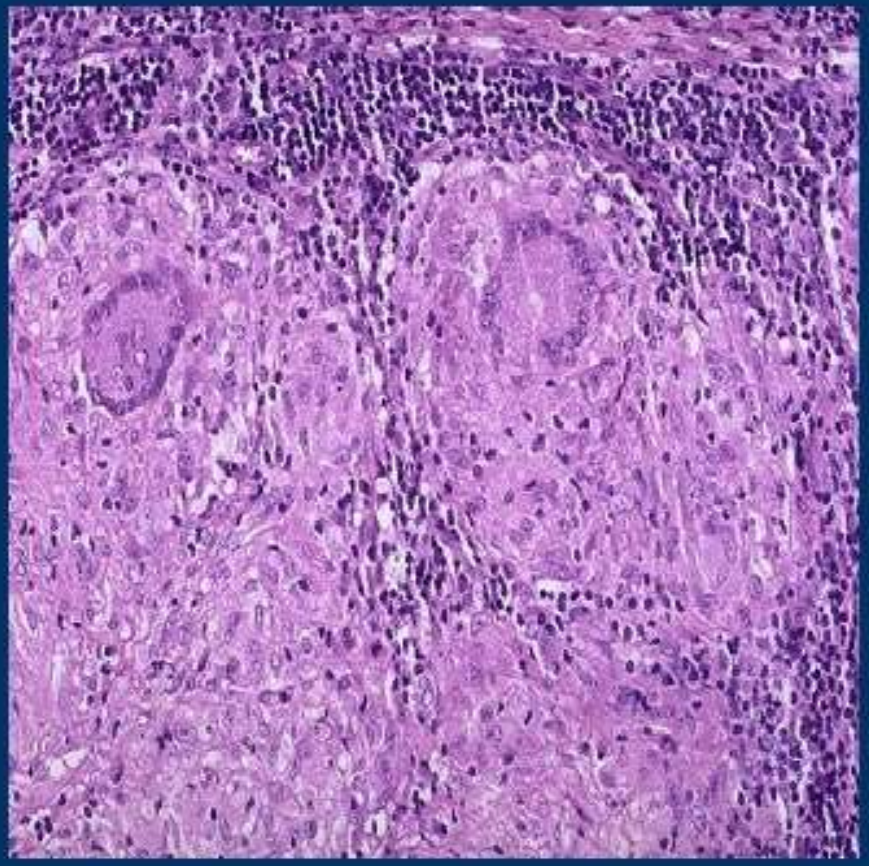


- Epithelioid cells;

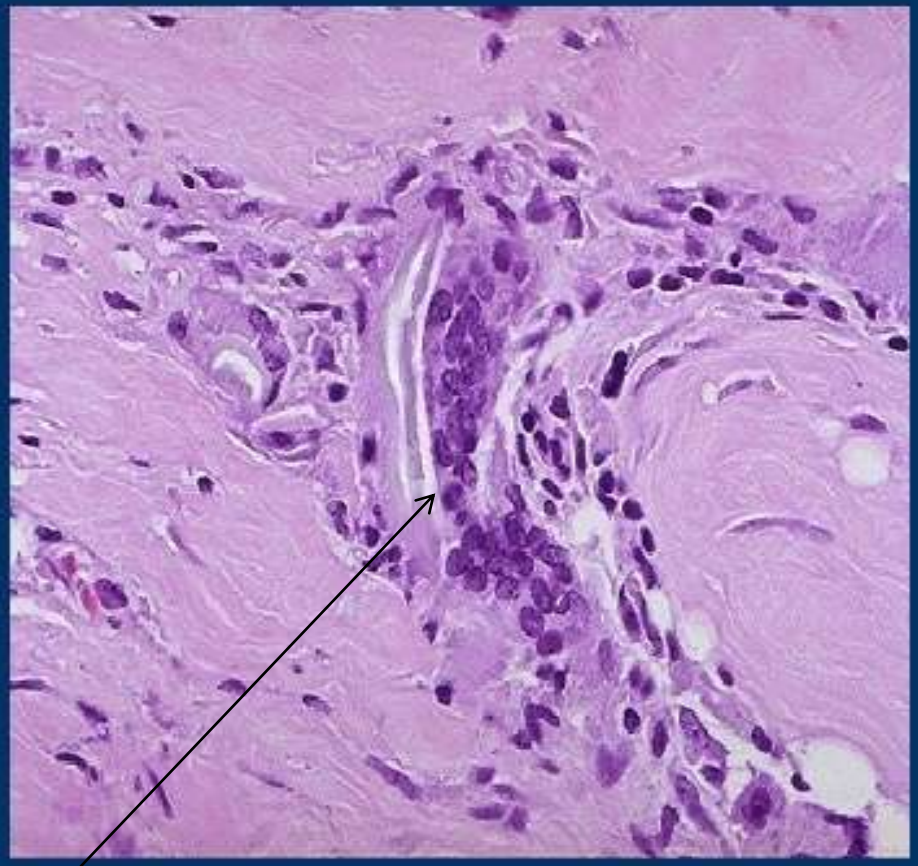
Pirogov-Langhan's multinuclear giant cells



LANGHAN'S GIANT CELLS

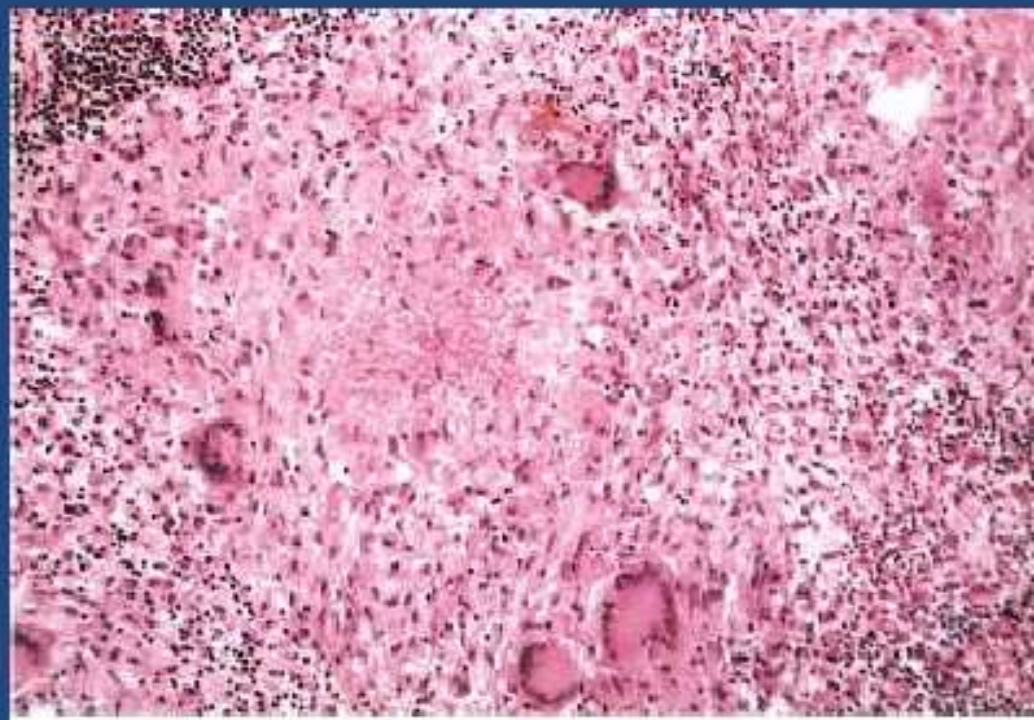


FOREIGN BODY GIANT CELL- IN SUTURE LINE



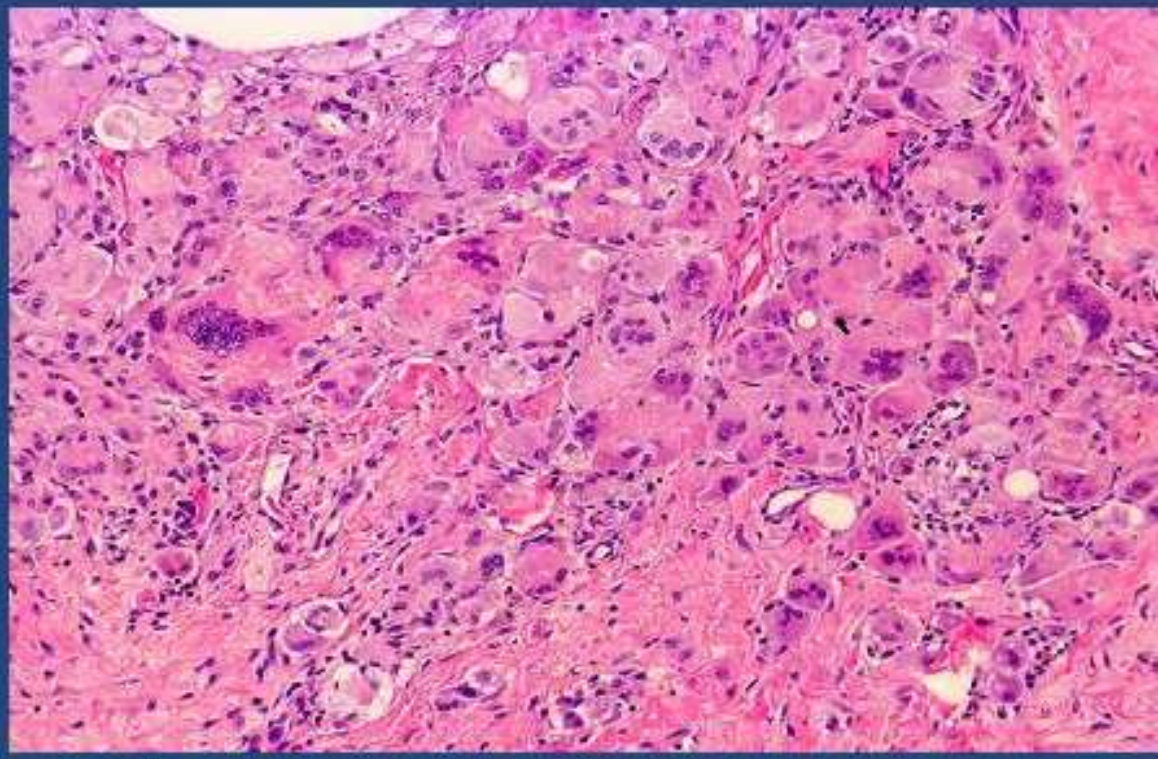
Granuloma

- Focus of chronic inflammation
- May have central necrosis
- Aggregation of macrophages that are transformed into epithelioid cells
- Epithelioid cells fuse to form Giant Cells
- Surrounded by lymphocytes and plasma cells



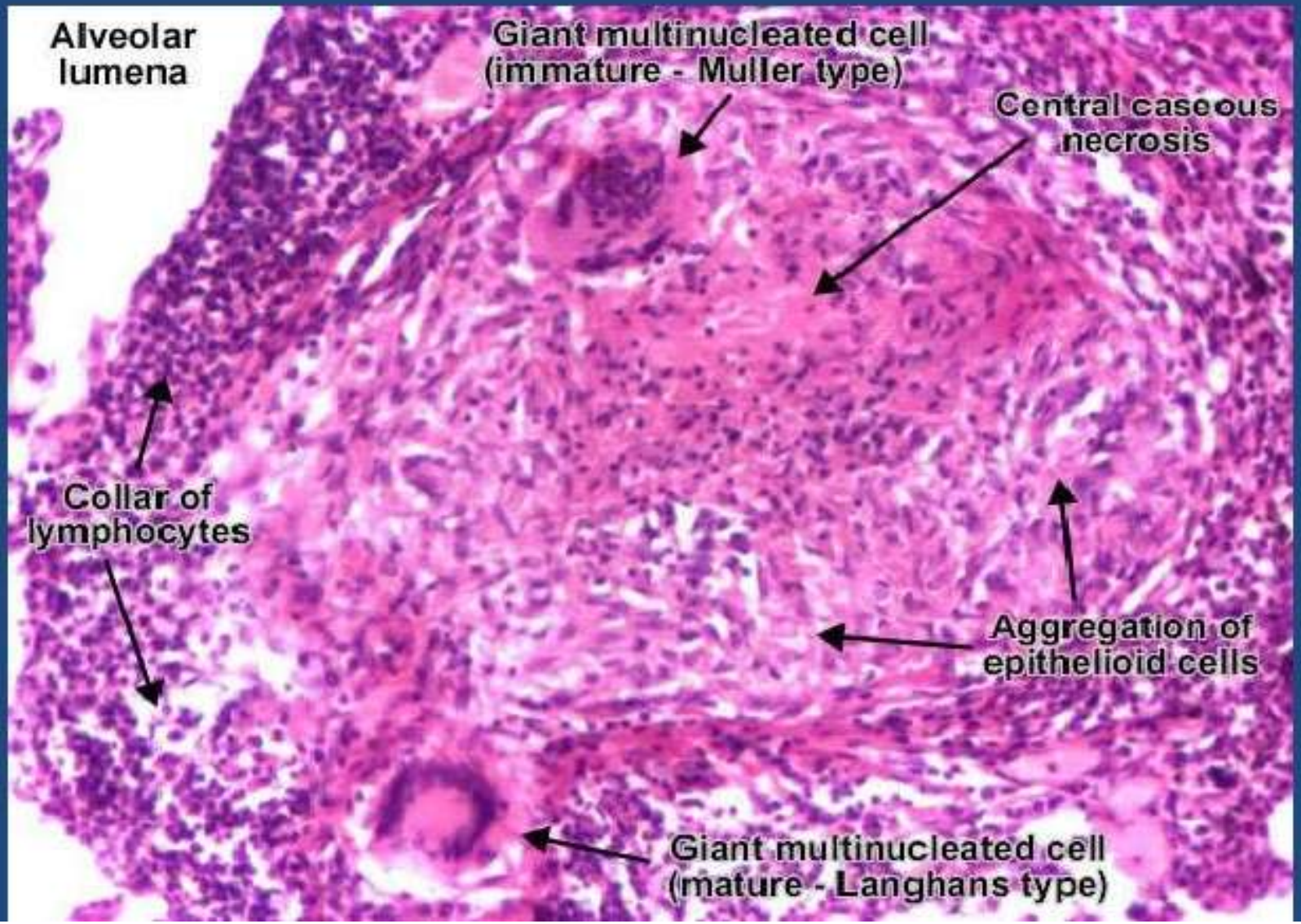
Foreign Body Granuloma

- Inert foreign bodies
  - Talc
  - Sutures

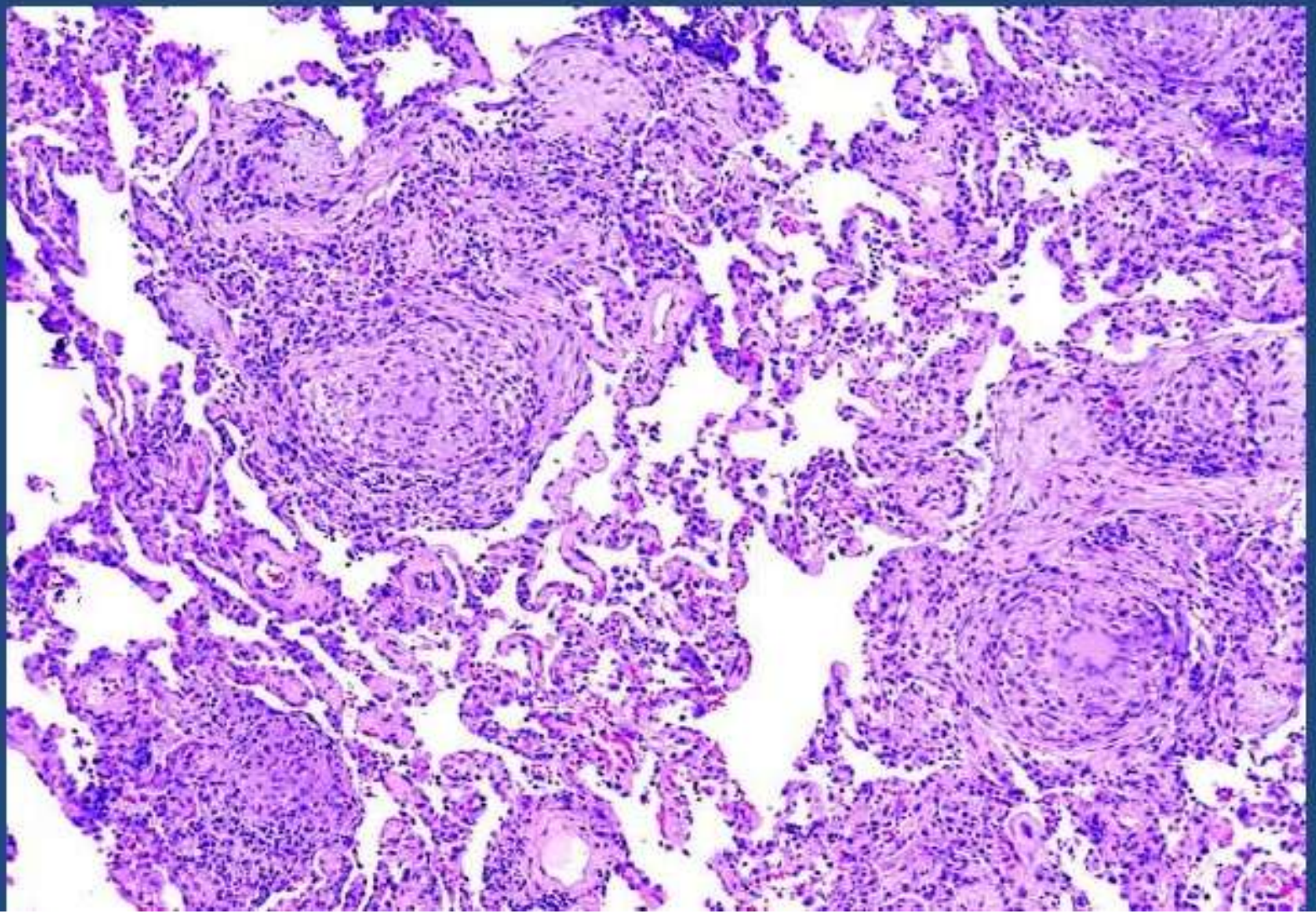


- Foreign Body-type Giant Cells
  - Haphazardly arranged nuclei

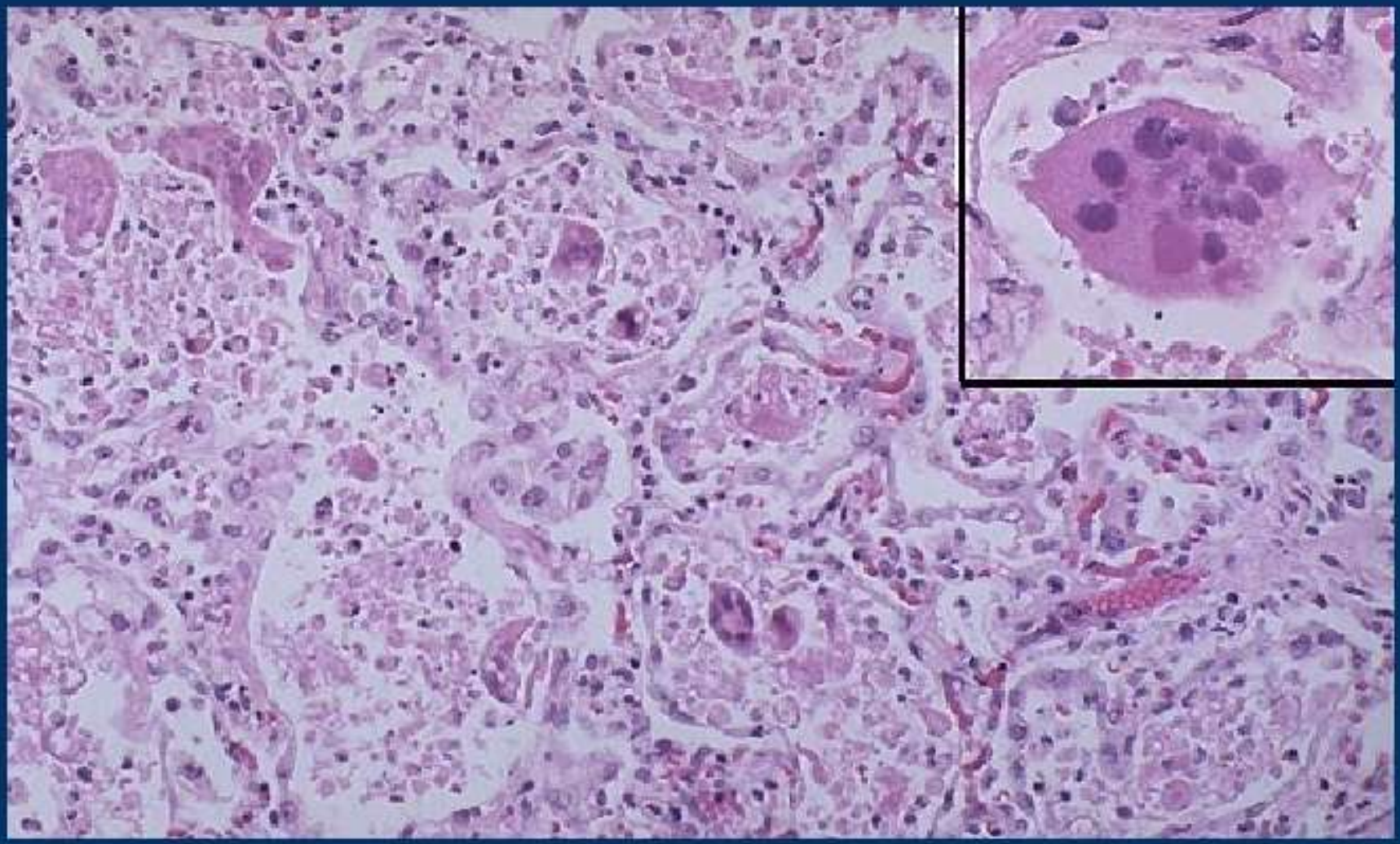
Immune Granuloma - TB



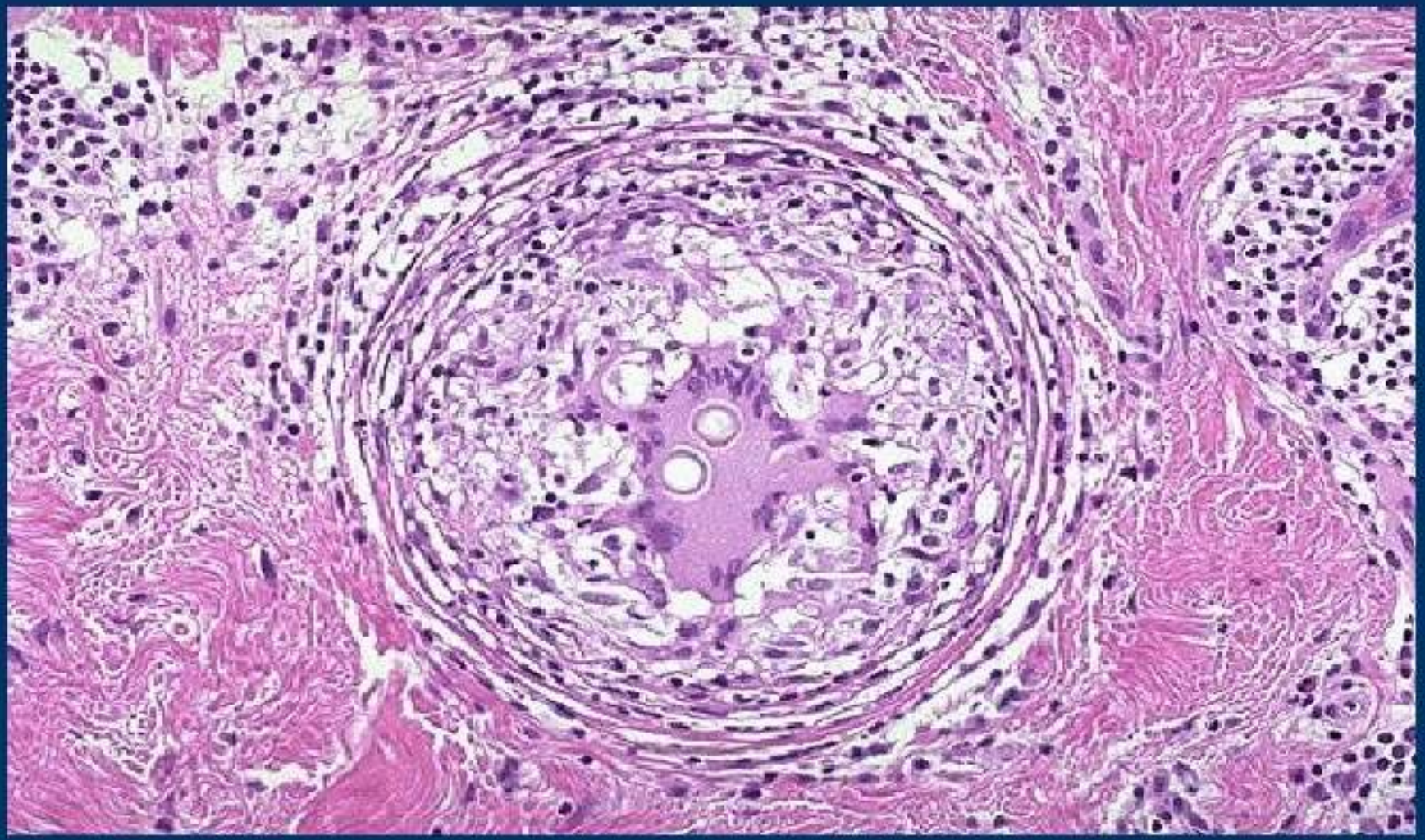
Immune Granuloma - Sarcoidosis



SYNCYTHIAL GIANT CELLS



GRANULOMATOUS INFLAMMATION WITH SPHERULES



Classification of granulomas

Immune granulomas

- Predominantly epithelioid-cell;
- A large number of lymphocytes and plasma cells;
- in tuberculosis, leprosy, syphilis, sclera,
- in exposed to organic dust particles, aerosols containing the proteins of birds, fish, animal hair.

Non-immune granulomas

- Primarily macrophagal or giant cell;
- around foreign bodies (suture material), animal parasites, particles of inorganic dust.

Classification of granulomas (depending on the degree of rapidity of cell exchange within the granuloma)

Rapidly updated granulomas

- Update for 1-2 weeks (cells quickly die and replaced with new ones);
- Granulomas produce very toxic substances (tuberculosis, leprosy);
- Predominantly epithelioid-cell;
- Alien material is only partially located in macrophages.

Slowly updated granulomas

- The kinetics of cell metabolism is sharply delayed;
- Occur when exposed to inert, low-toxic substances;
- Predominantly giant-celled;
- The pathogen is entirely located in macrophages.

Outcomes of granulomas

1. Resolution of cellular infiltrate (a rare option, acute infections - rabies, abdominal and typhus);

2. Sclerosis - with the formation of a scar or fibrous nodule - most often;

3. Necrosis of granuloma - tuberculosis granuloma, etc.

4. Suppuration of granuloma - mycoses, sap, yersiniosis, tularemia.

Tuberculosis granuloma

Macroscopically:

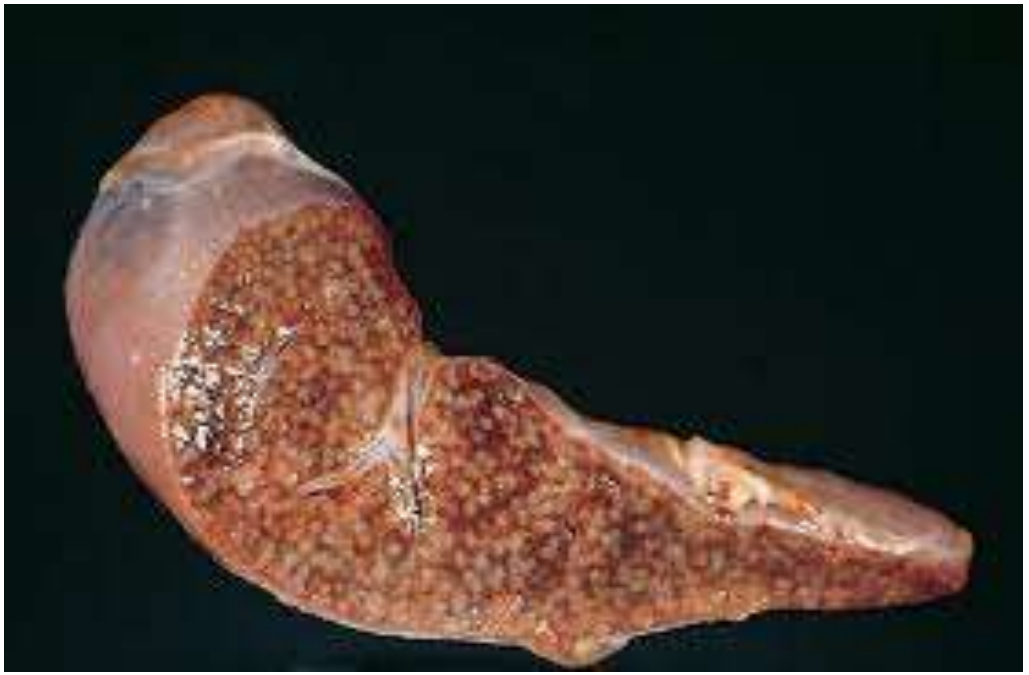
- The diameter of the granulomas is 1-2 mm,
- Numerous confluent granulomas - small, millet-like tubercles -> miliary (from the Latin miliarius - millet) tuberculosis.

Microscopically:

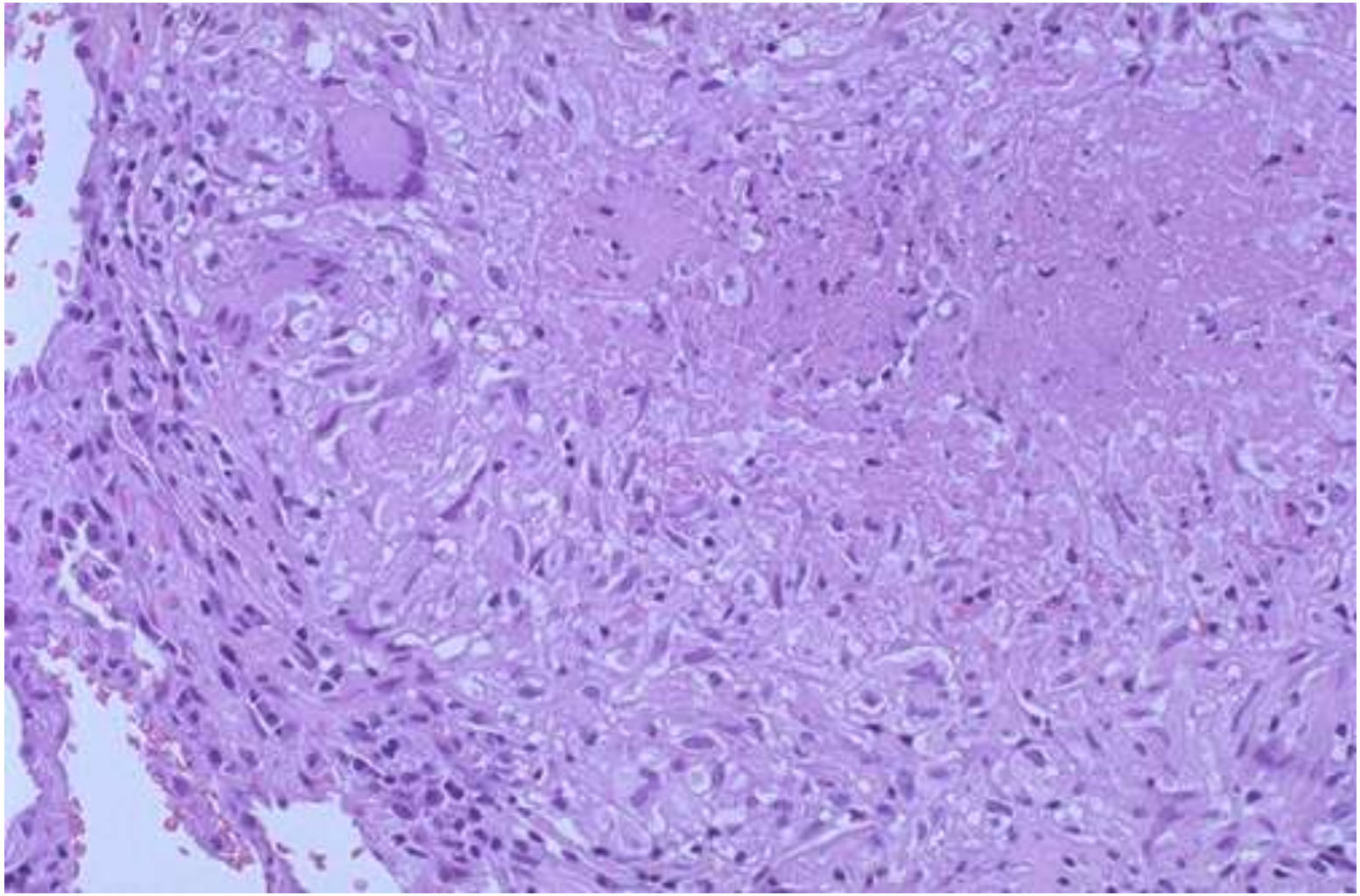
- In the center - a focus of caseous necrosis,
- Around - a shaft of epithelioid cells,
- Further - a shaft of lymphocytes with an admixture of giant multinucleated cells Pirogov-Langhans.
- When impregnating with silver salts - a network of argyrophilic fibers;
- There are no blood vessels;
- In giant cells when stained according to the Tsil-Nielsenumycobacterium tuberculosis.

Granulomatous inflammation

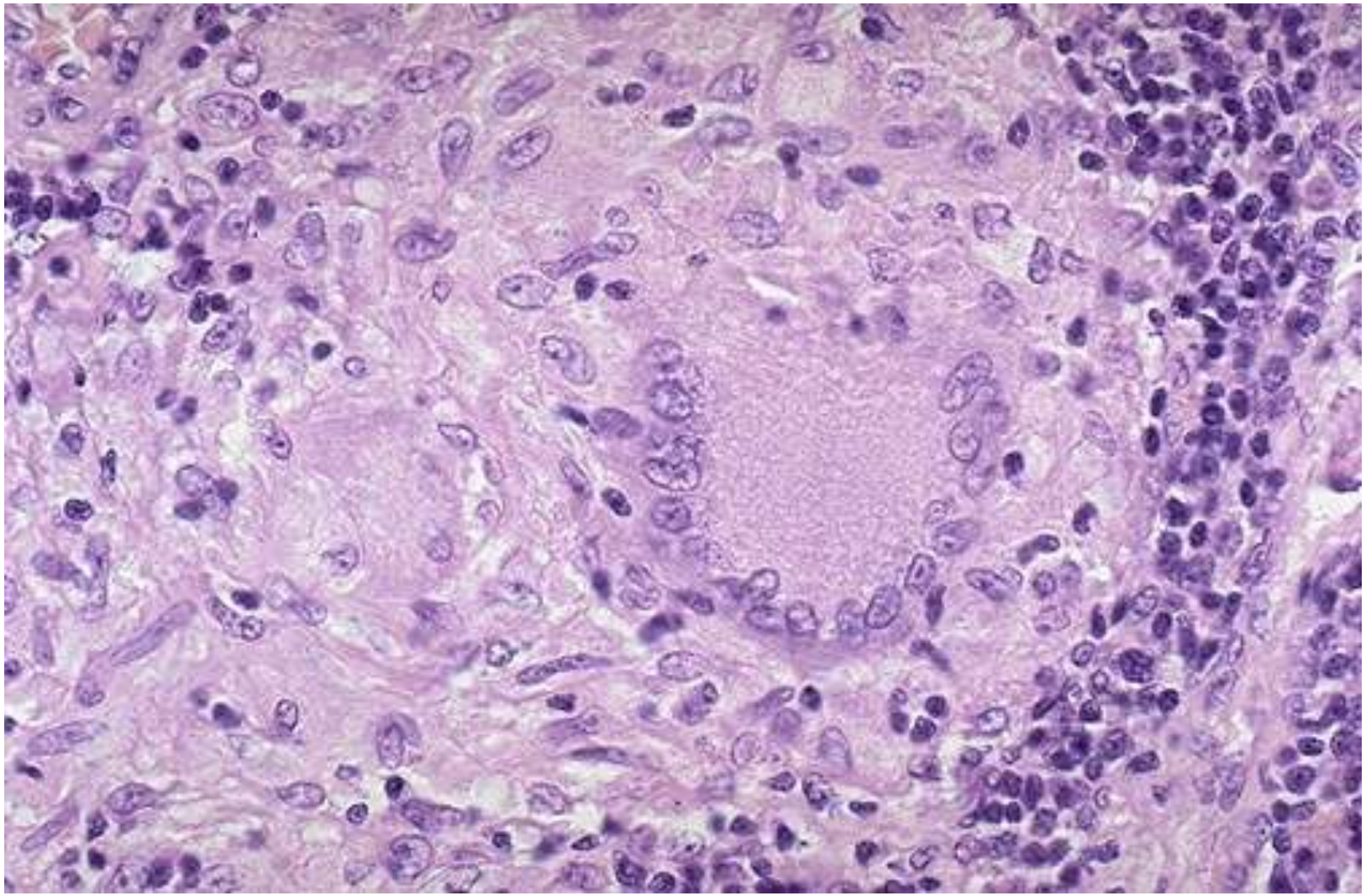
- Miliary tuberculosis of the lungs / spleen



Granuloma in tuberculosis



Granuloma in tuberculosis



Syphilitic granuloma (gumma)

- It is characteristic for the tertiary period of syphilis;

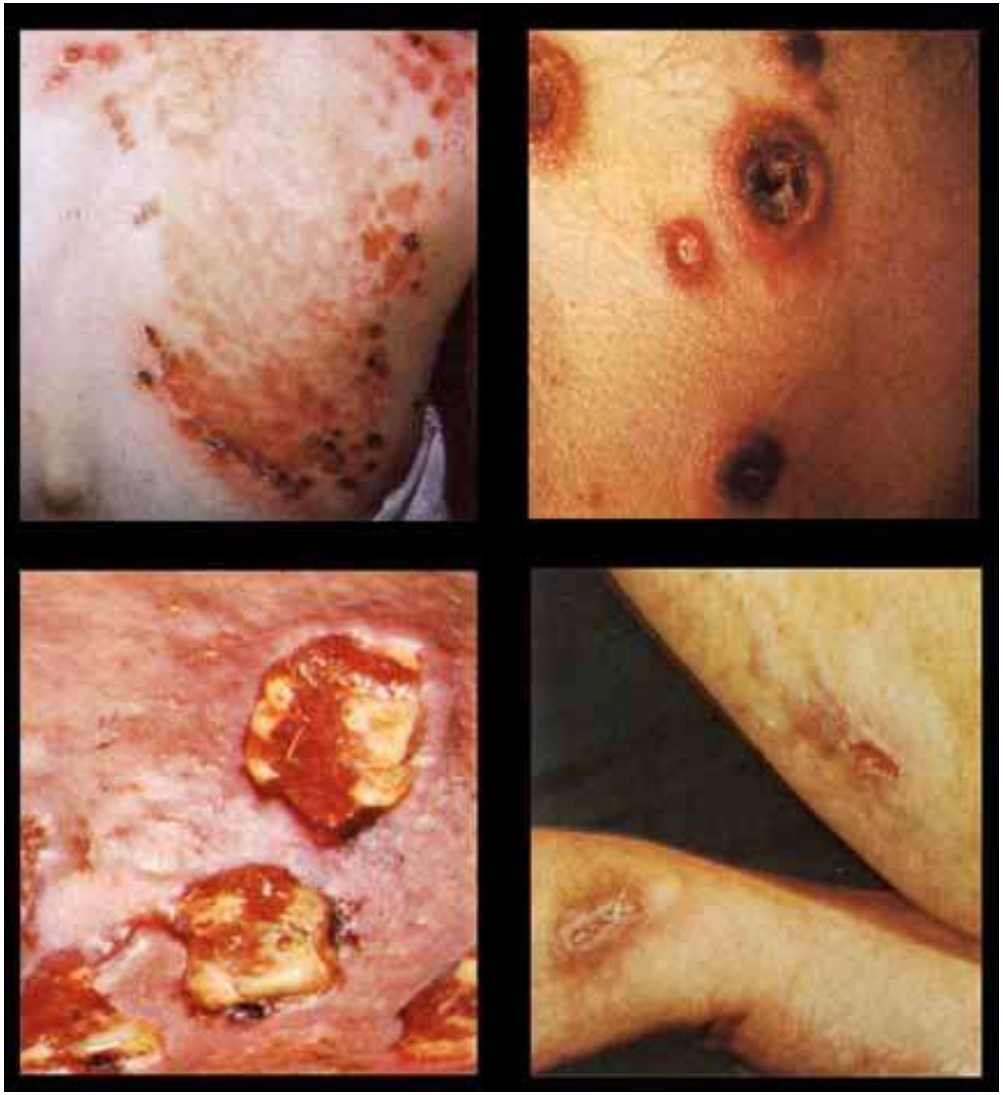
Macroscopically:

- Nodes - with a diameter of 0.3-1.0 cm on the skin - up to 4-5 cm in internal organs (bones, brain, liver, etc.);
- On the cut at the nodes - jelly-like mass of yellow color (similar to glue gum arabic).

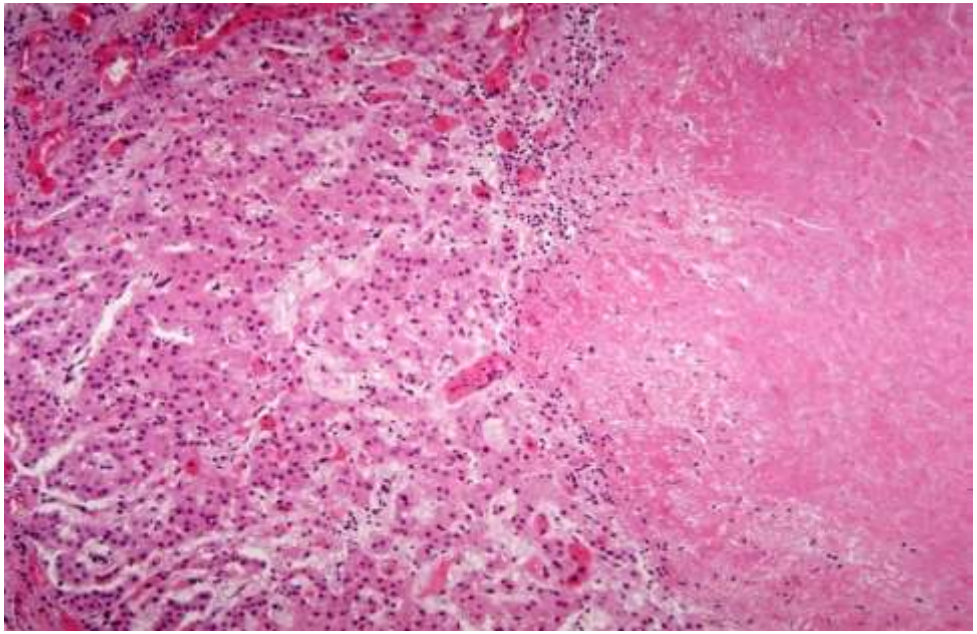
Microscopically:

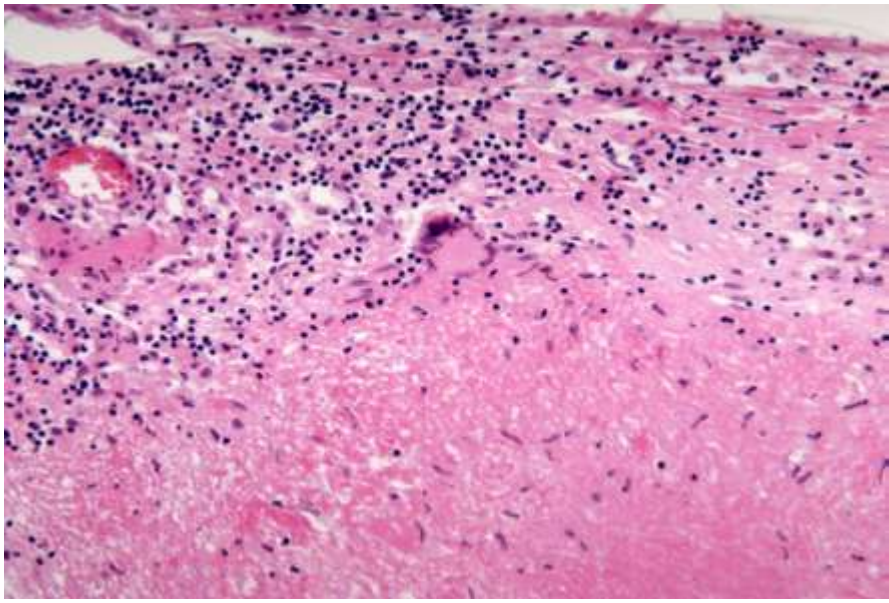
- In the center there is a foci of caseous necrosis (larger than in tuberculosis);
- In the periphery - a lot of lymphocytes, plasma cells and fibroblasts;
- characteristic - the rapid formation of massive dense connective tissue (a kind of capsule);
- On the inside of the capsule are numerous small, and outside - larger vessels with signs of productive endovascularity;
- Pale treponema is extremely rare (with Levadity silvering).

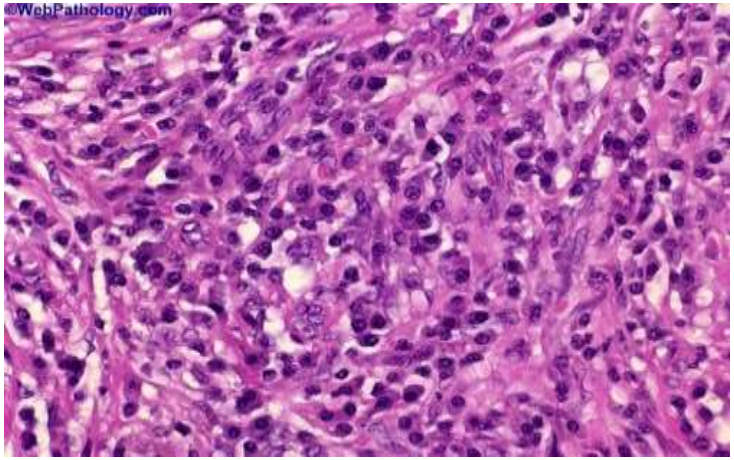
Gumma in syphilis



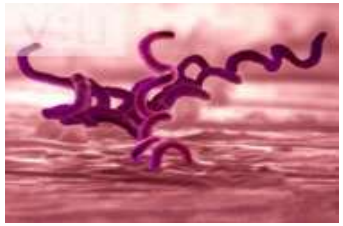
Gumma in syphilis

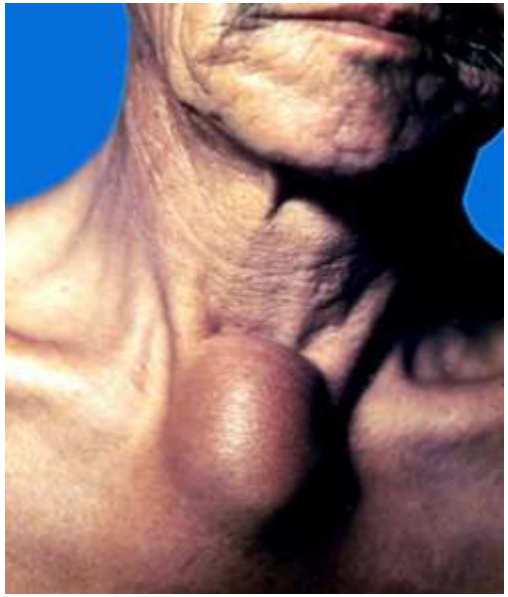


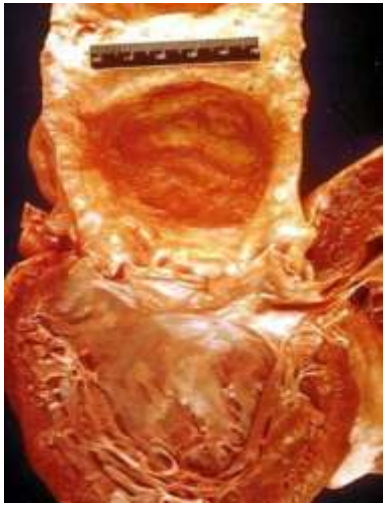


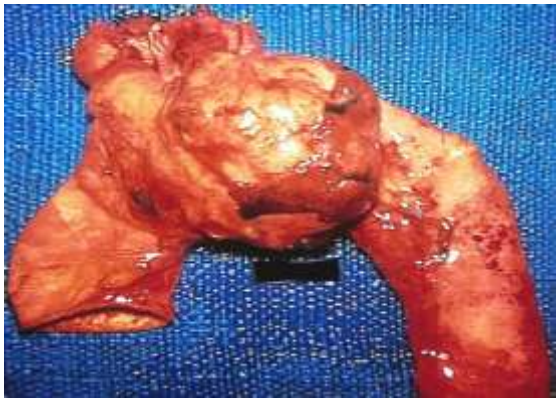


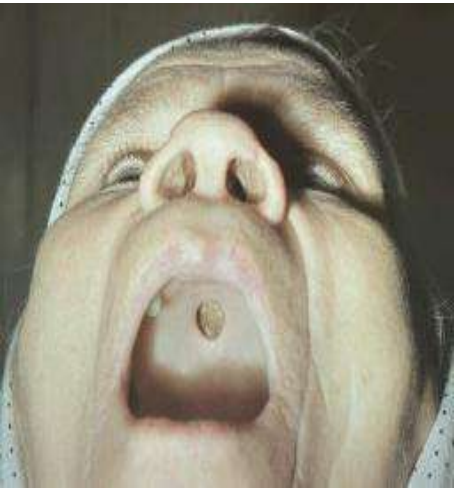
Syphilis

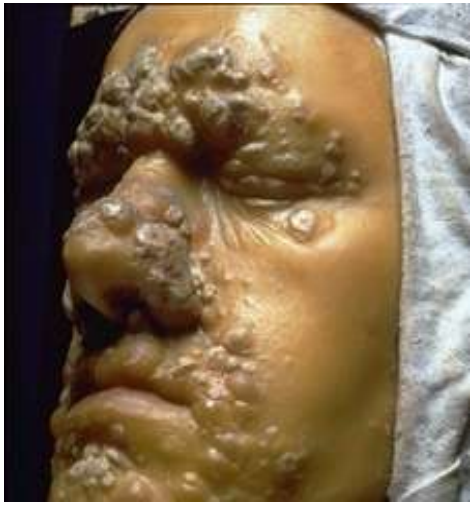












Tertiary syphilis: Typical gummas. A. Wisdom. Color

Leprosy granuloma

- The causative agent is Mycobacterium Hansen-Neisser (coloration according to Tsil-Nielsen).

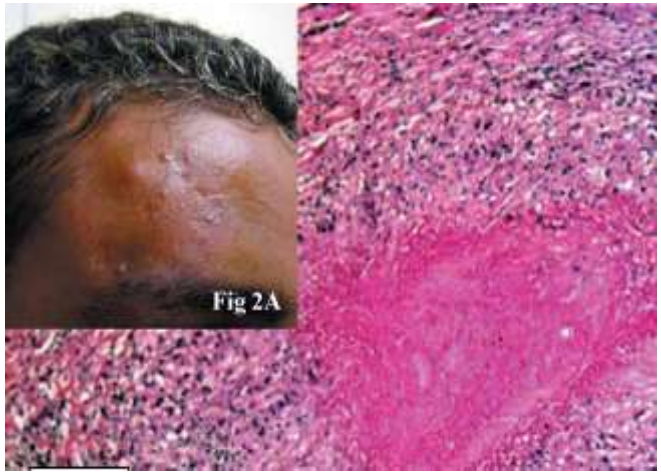
Cellular composition:

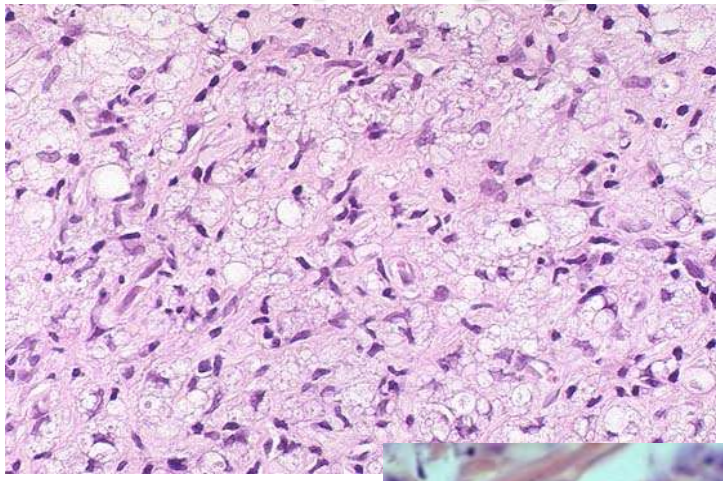
1. macrophages,
2. epithelioid cells,
3. giant cells,
4. plasma cells,
5. Fibroblasts.

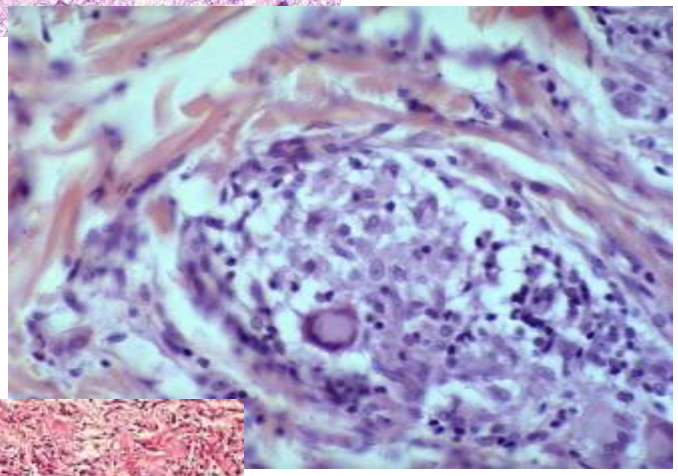
- Unfinished phagocytosis - in the cytoplasm of macrophages - Mycobacterium Hansen-Neiser in the form of strictly ordered series (like cigarettes in a pack) -> increase in macrophages + appearance of fatty inclusions.
- Bonding of mycobacteria -> formation of leprosy balls
- Destruction of macrophages
- Phagocytosis of leprosy balls dropped by giant cells of foreign bodies.

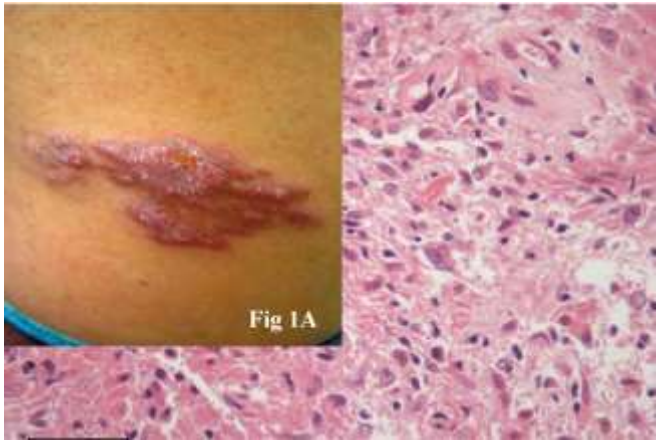
- in 1 g of "blossoming" leprom - 5x109 mycobacteria

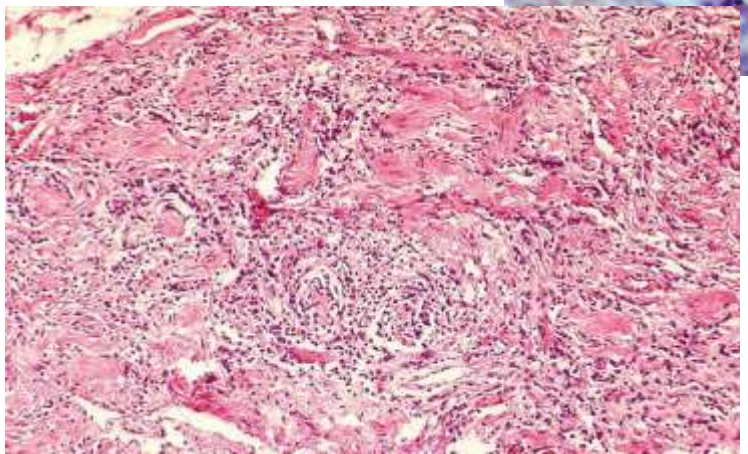
Leprosy granuloma



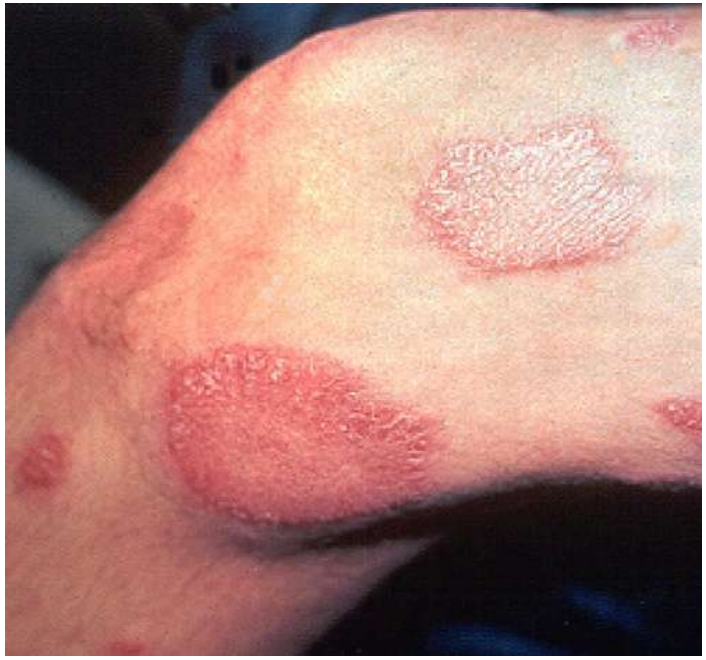


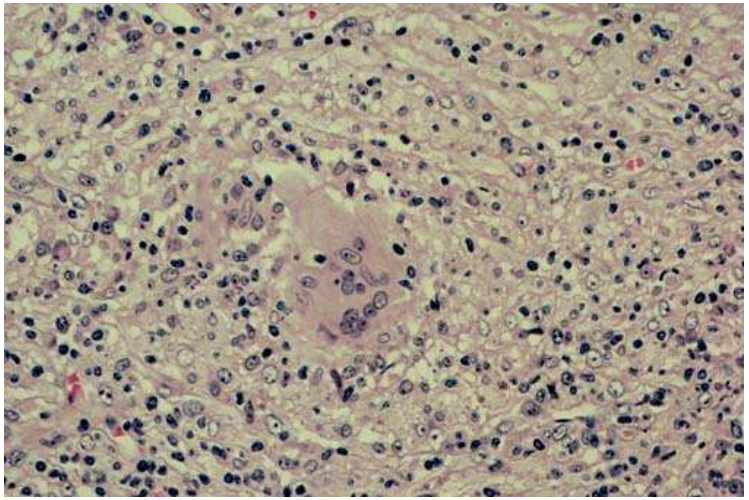


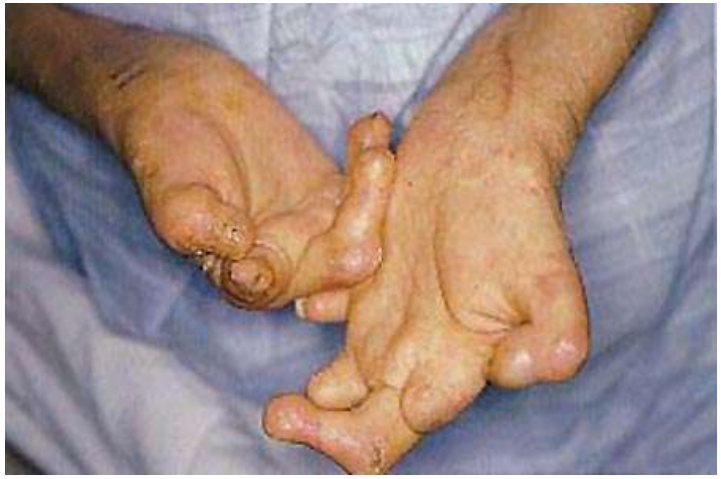




Leprosy granuloma







Granuloma in scleroma

- Pathogen: wand of Volkovitch-Frish.

Cellular composition:

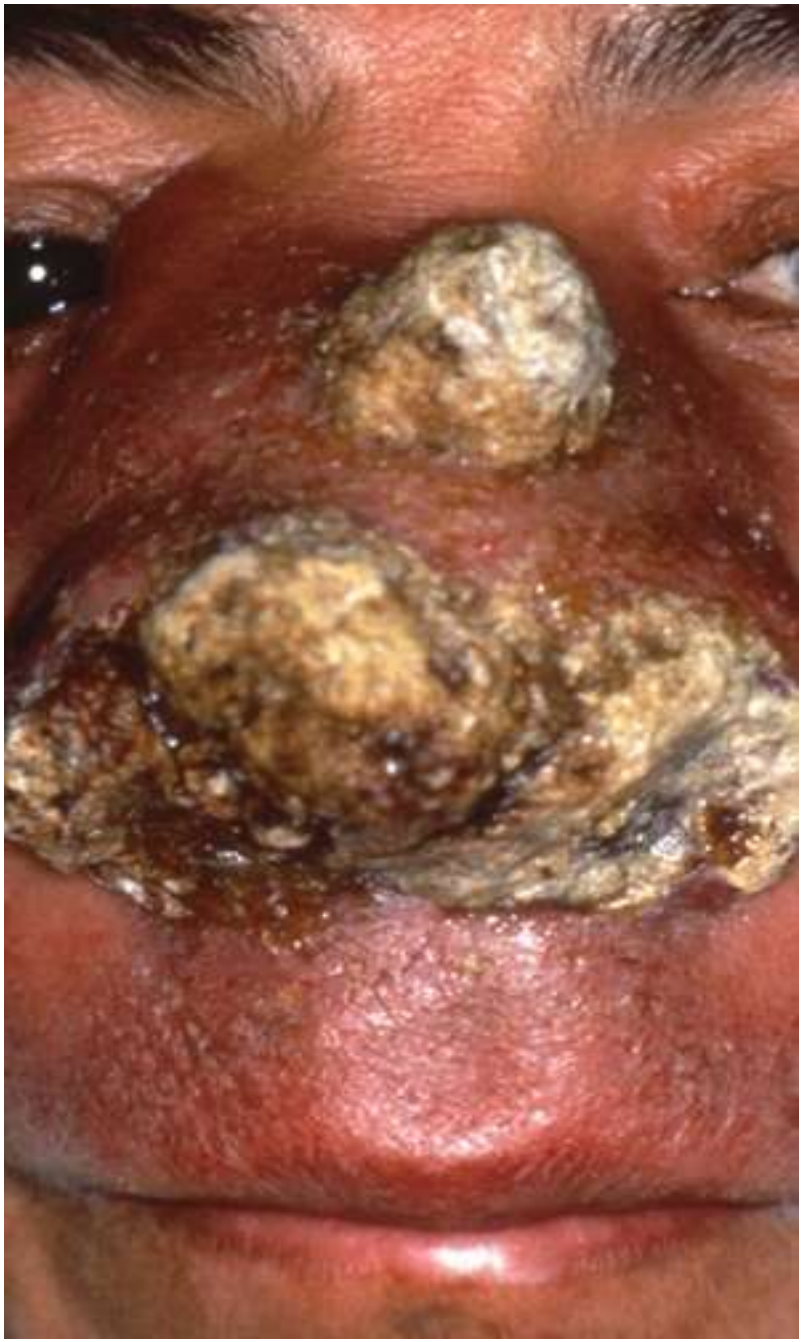
1. Macrophages,
2. Lymphocytes,
3. Plasma cells,
4. Eosinophilic corpuscles Roussel (products of degradation of plasma cells),
5. Mikulich cells are specific cells - very large single-nucleated macrophages with vacuolated cytoplasm + wolkovich-Frish sticks.

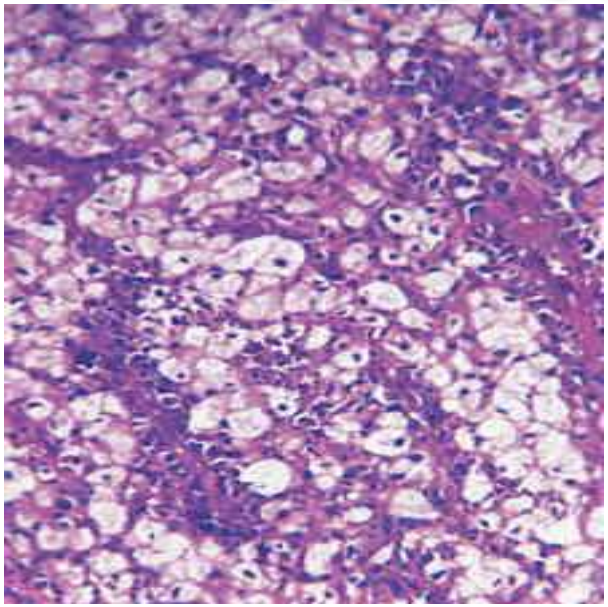
Granuloma in scleroma

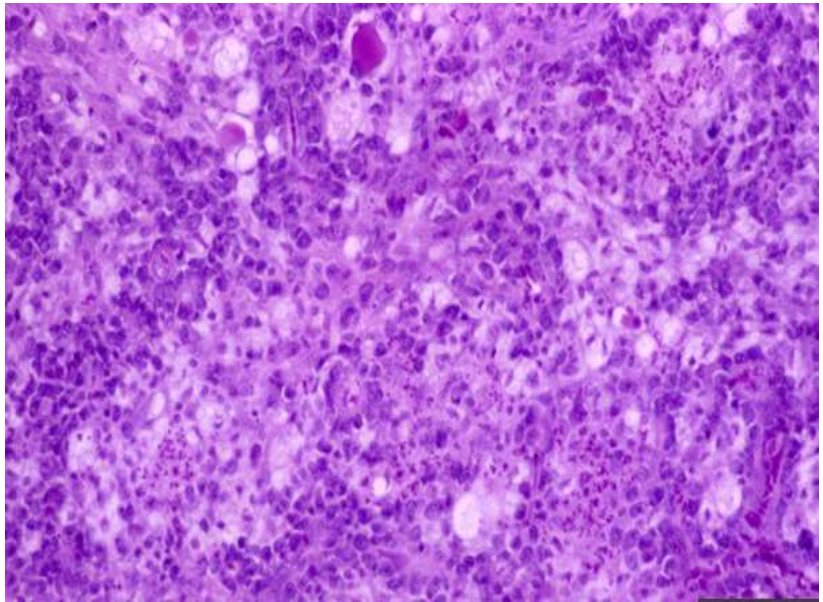
- Localization: the mucous membrane of the upper respiratory tract - nose, larynx, trachea, less often - bronchi.

- Outcome - sclerosis -> deformation of the mucosa - narrowing of the respiratory tract -> sometimes - asphyxiation.

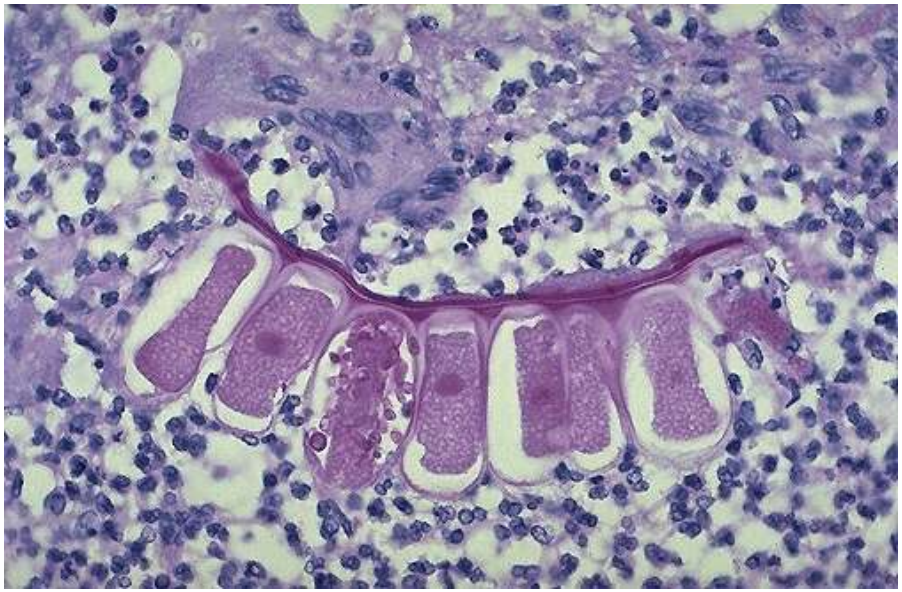
Scleroma

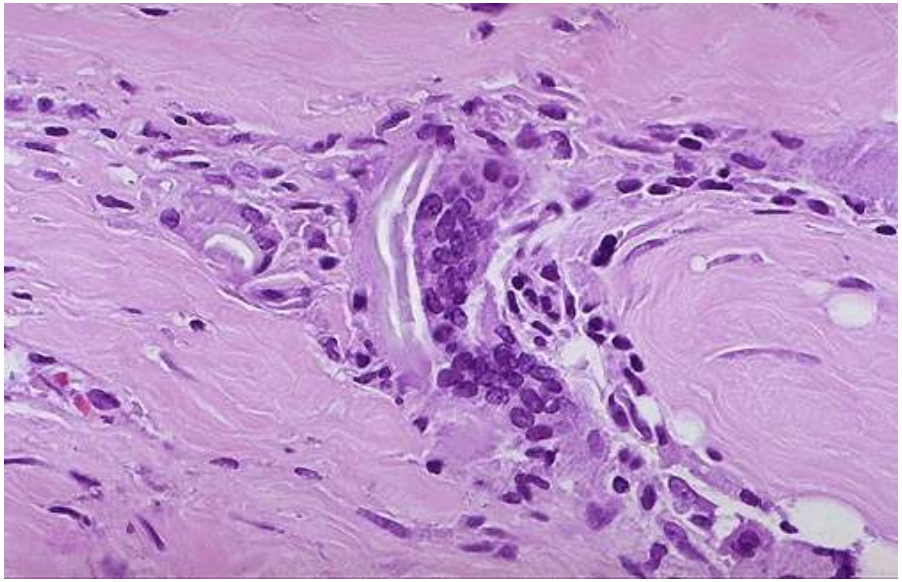






Granulomatous inflammation



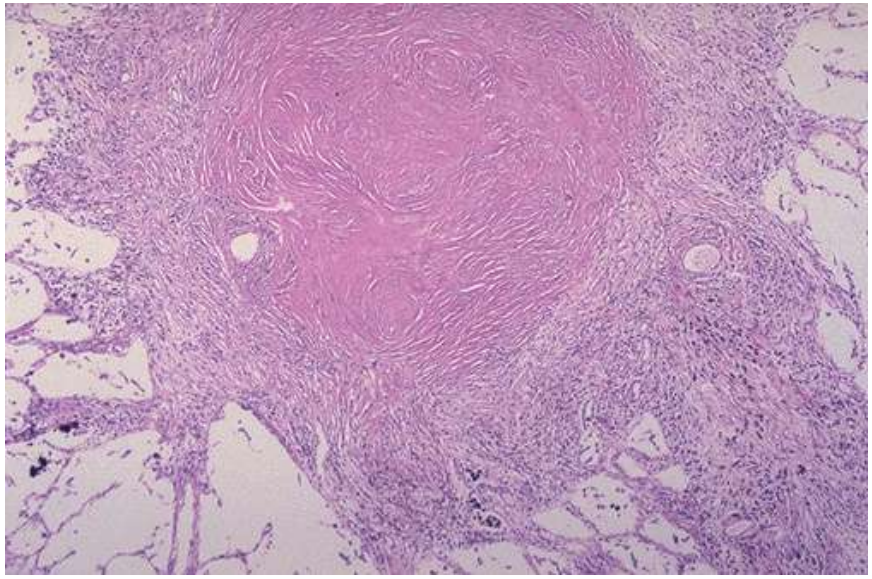


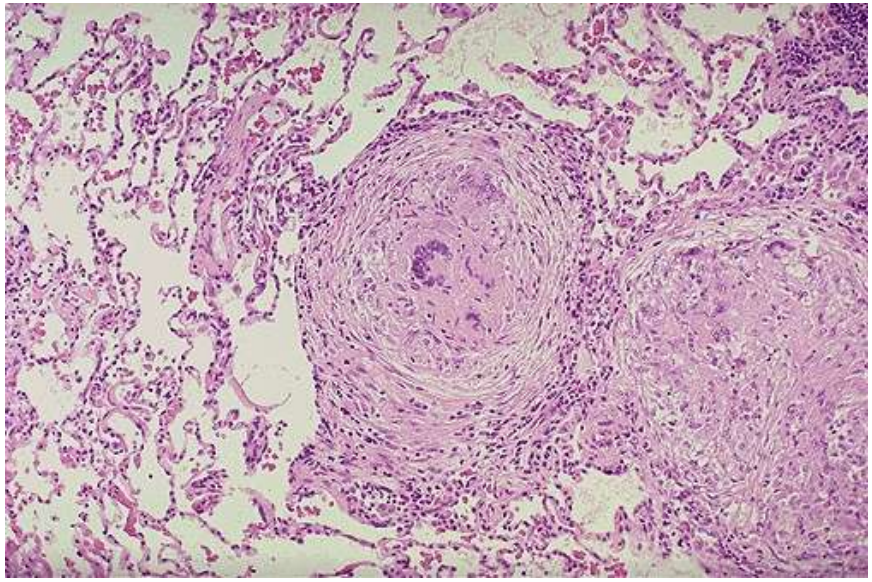
Inflammation around foreign bodies:

- Aspiration pneumonia (inflammation around plant fibers) with giant cells of foreign bodies;

- Inflammation around the suture (stitches)

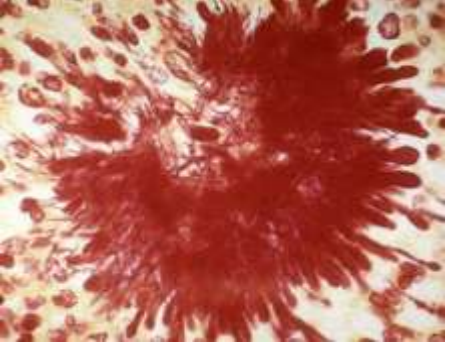
Granulomatous inflammation





- **Granuloma in silicosis:**
- (macrophages, lymphocytes, plasmocytes, fibrosis);

- **Granuloma in sarcoidosis:**
- "stamped" appearance,
- the central part - from the epithelioid and giant multinucleated cells of Pirogov - Langhans,
- on the periphery - lymphocytes, macrophages, plasma cells and fibroblasts.



Actinomycosis

1. systemic infection prone to sluggish, chronic course; characterized by the development of granulomas (actinomycetics), fistulas and abscesses.

2. Pathogen - various types of actinomycetes - gram-positive bacteria of the genus Actinomyces, which can branch (form a mycelium).

3. Forms: cervico-facial, thoracic, abdominal and generalized.

4. Druses, surrounded by macrophages and neutrophils.

Actinomycosis

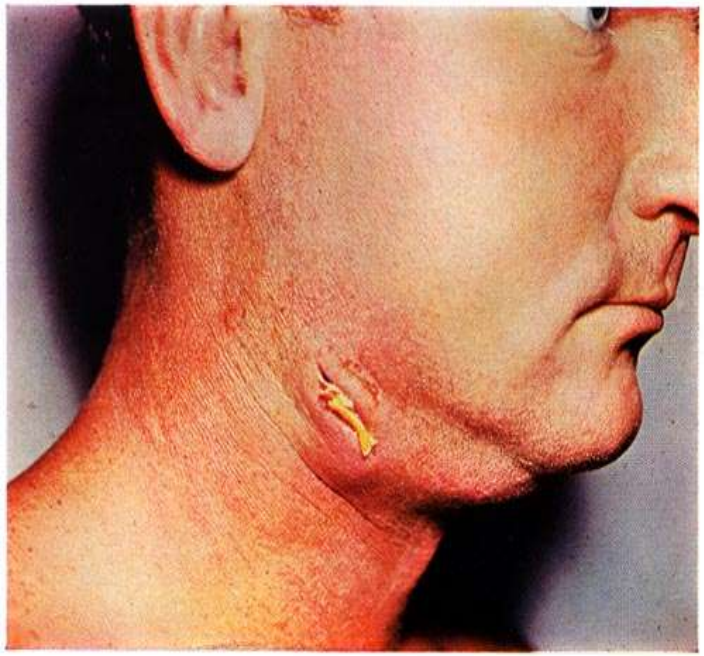
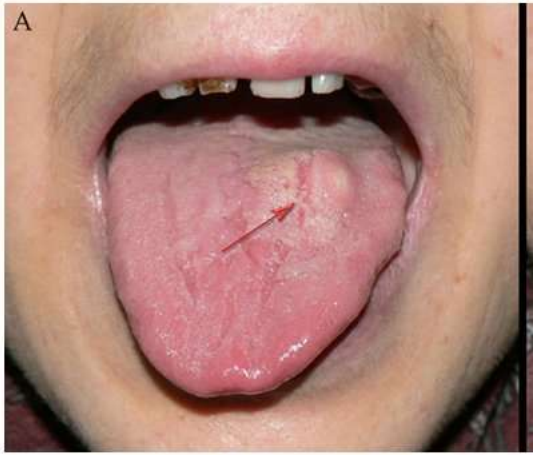
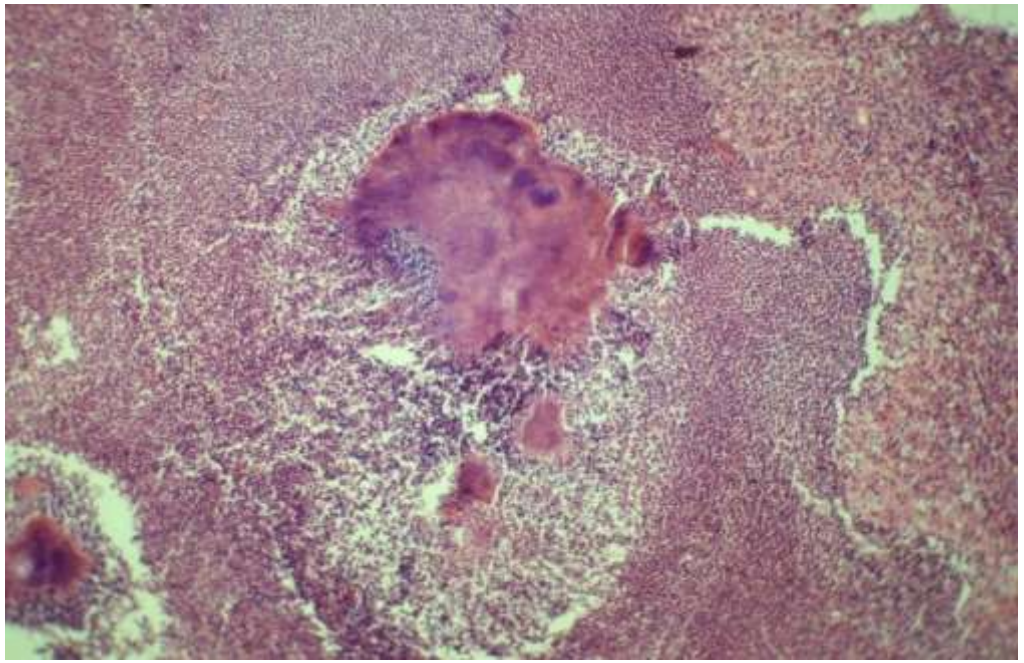


FIGURE 1.—Actinomycosis, jaw, observed at Letterman General Hospital, San Francisco, Calif., in a sergeant who had punctured the floor of his mouth with a weed stem while picking his teeth.





Trichinosis

- Helminthiasis from the group of nematodes,

- Characteristic: fever, myalgia, face swelling, skin rash, eosinophilia of the blood, and in severe cases - damage to internal organs and the central nervous system.

- Young larva through sarcolemma -> into muscle fiber, partially destroying it.
- Around the larva is a cellular infiltrate, and after 3-4 weeks. after the invasion - a fibrous capsule with a network of blood vessels.
- The walls of the capsule gradually thicken, impregnated with calcium salts.
- The larvae remain viable for many years.

Trichinosis

Ingestion of meat scraps or animals

Ingestion of undercooked meat (esp. pork)

Encysted larva in striated muscle

Pigs

Carnivorism

Carnivorism

Rodents

Larva released in small intestine

Encysted larva in striated muscle

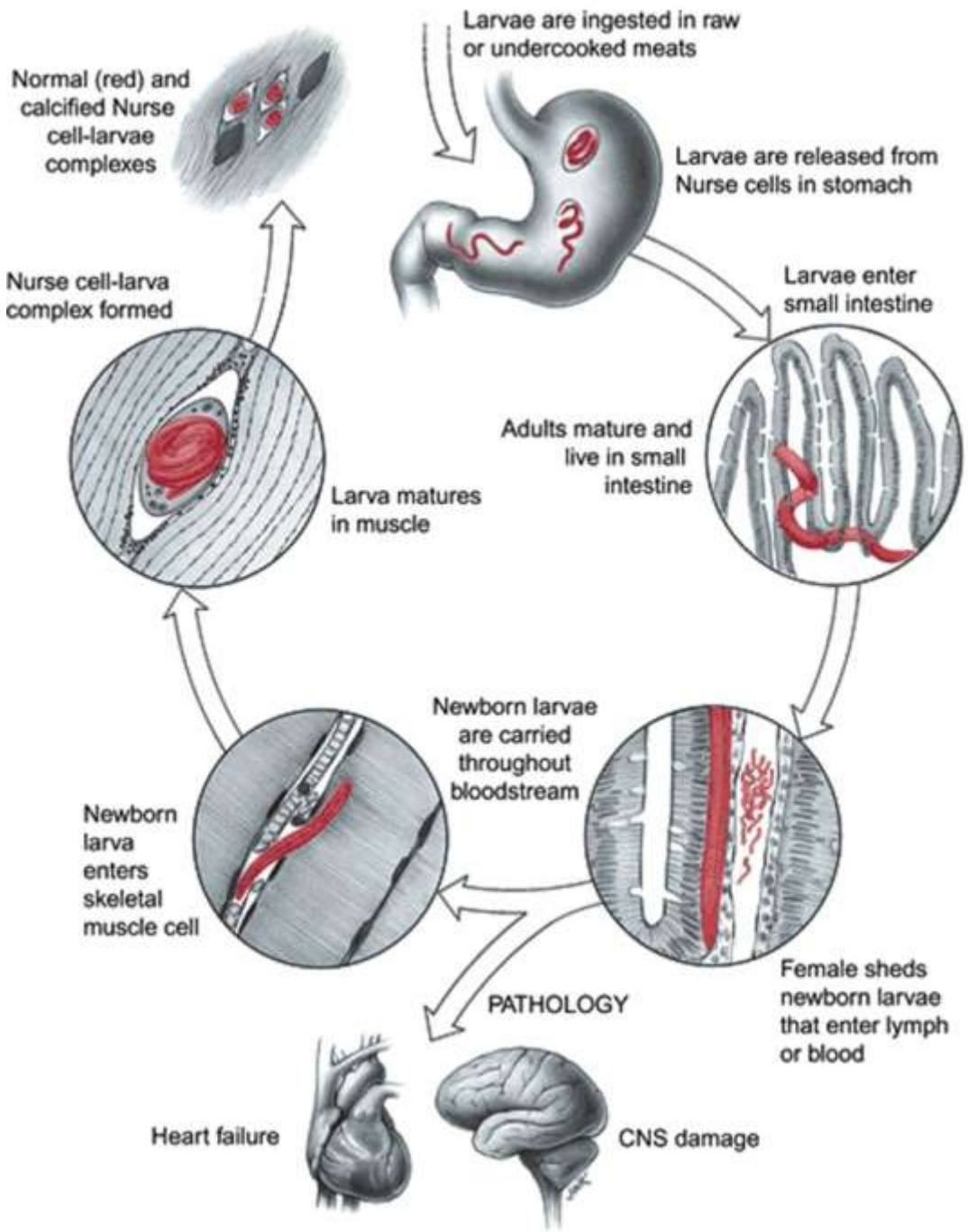
Adults in small intestine

Circulation

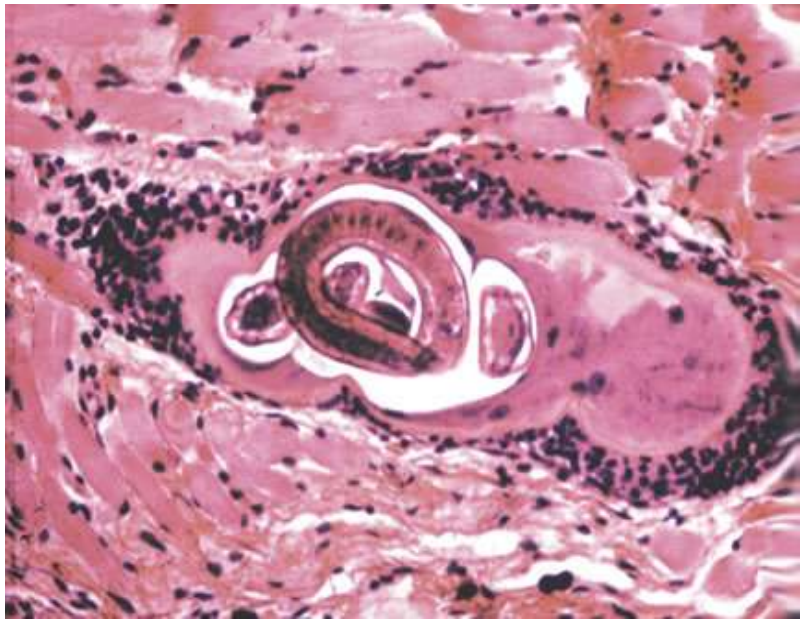
Larva deposited in mucosa

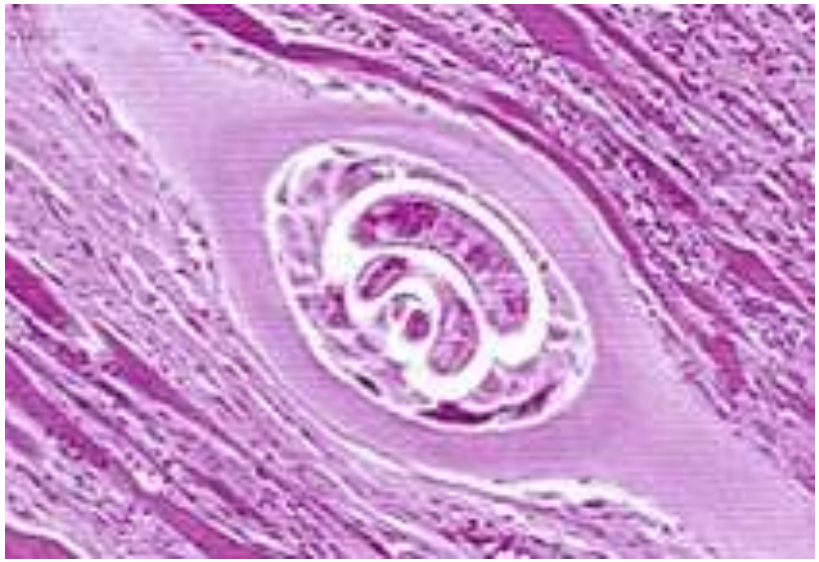
i = Infective Stage

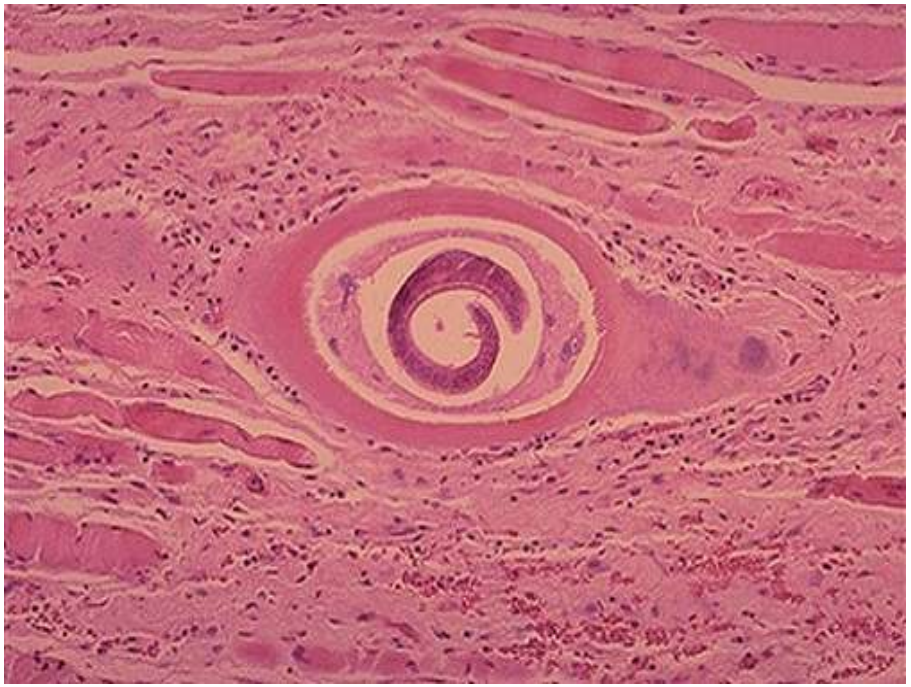
d = Diagnostic Stage


Larvae are ingested in raw or undercooked meats
Larvae are released from Nurse cells in stomach
Larvae enter small intestine
Adults mature and live in small intestine
Female sheds newborn larvae that enter lymph or blood
Newborn larvae are carried throughout bloodstream
Newborn larva enters skeletal muscle cell
Larva matures in muscle
Nurse cell-larva complex formed
Normal (red) and calcified Nurse cell-larvae complexes
PATHOLOGY
Heart failure
CNS damage

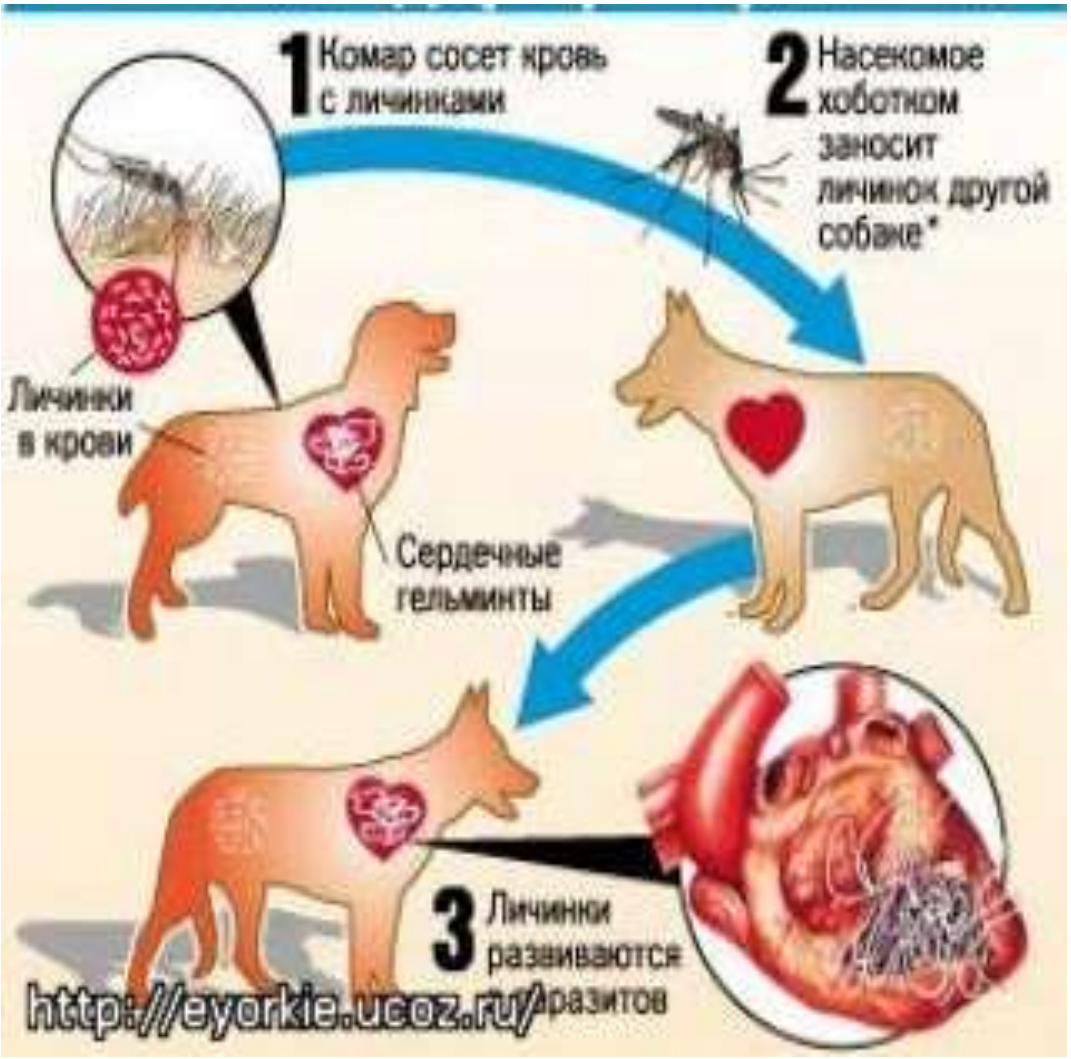
Trichinosis



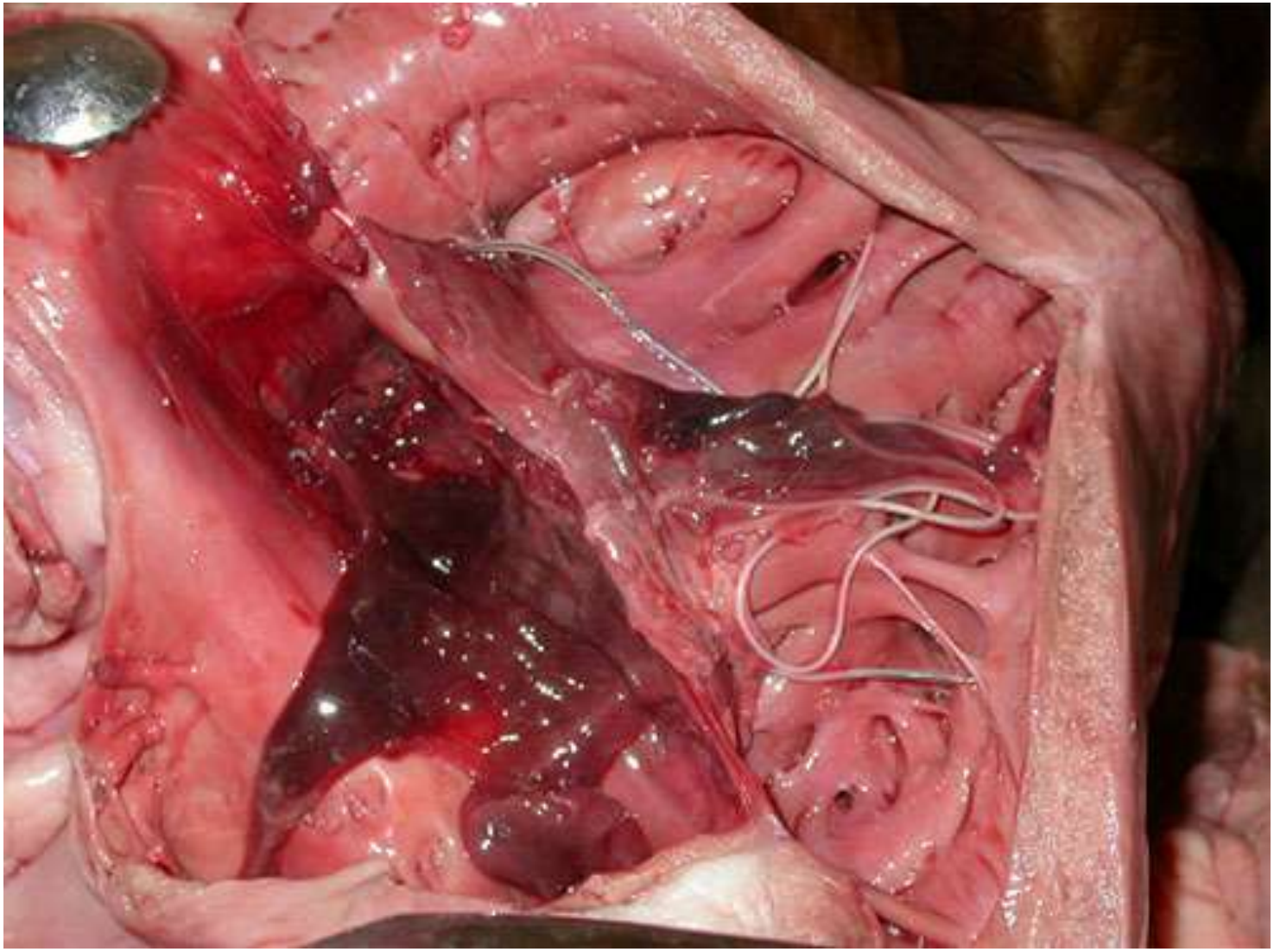


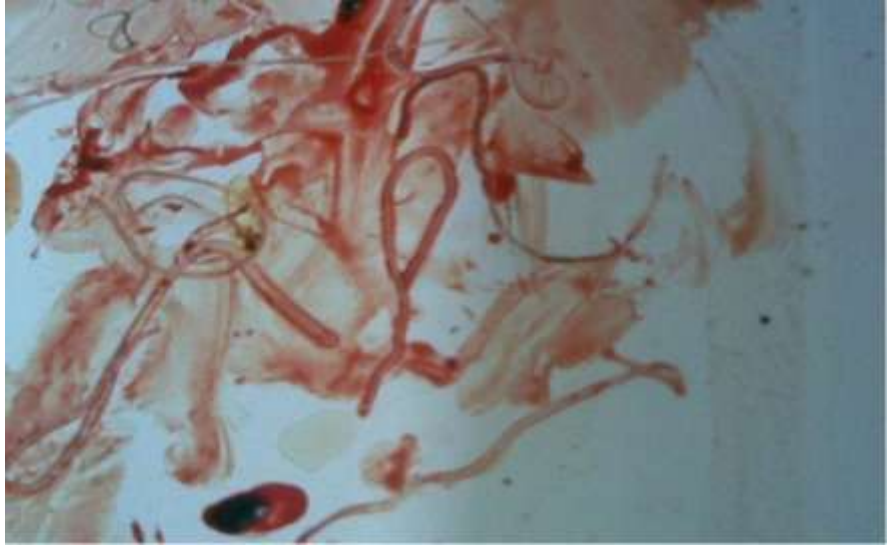


Dirofilariasis

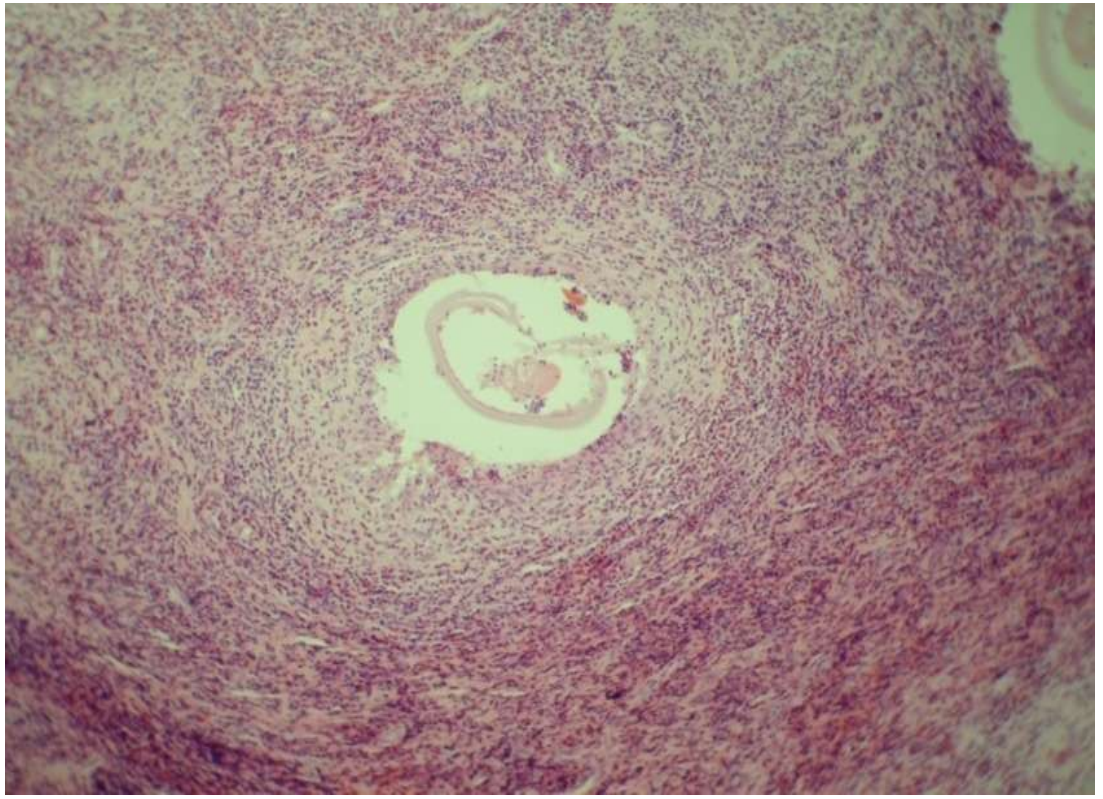


Dirofilariasis

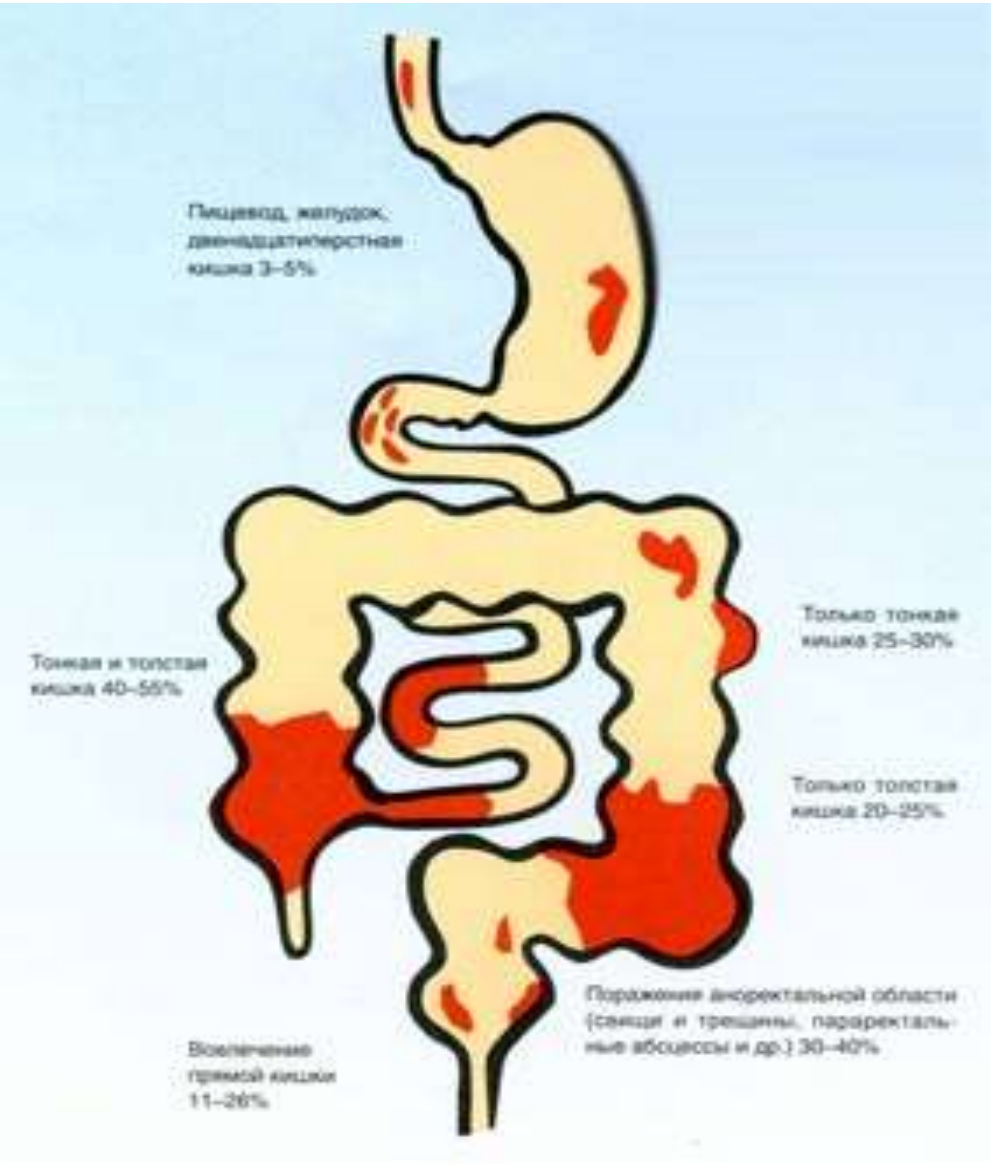




Dirofilariasis

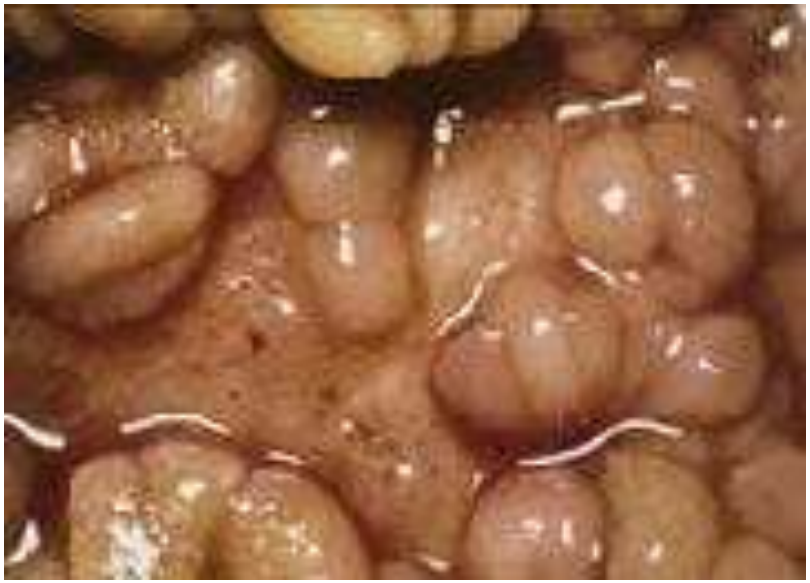


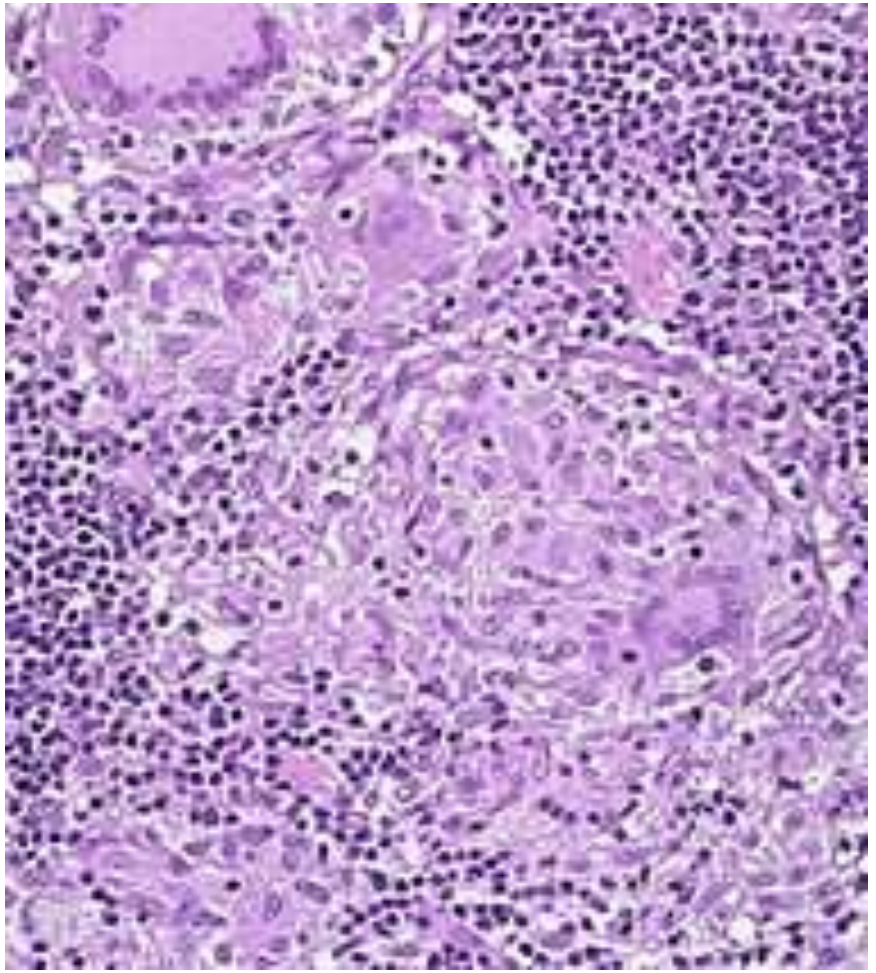
Crohn's disease



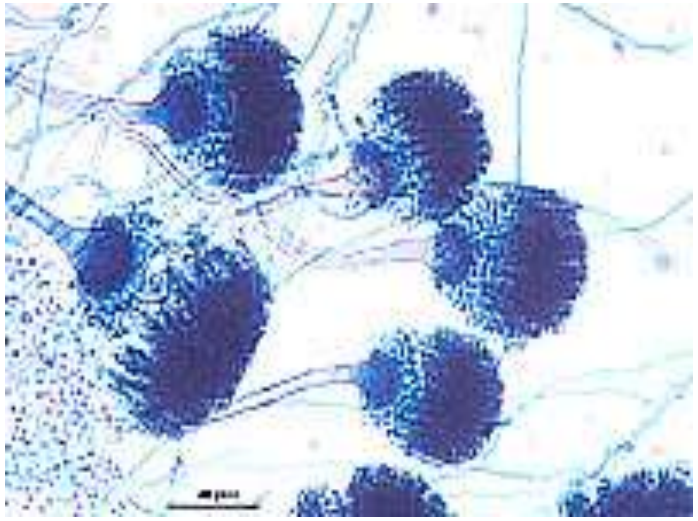
- nonspecific disease of any part of the gastrointestinal tract.
- It is manifested by transmural inflammatory infiltration and sarcoid granulomas of the gastrointestinal tract.

Crohn's disease



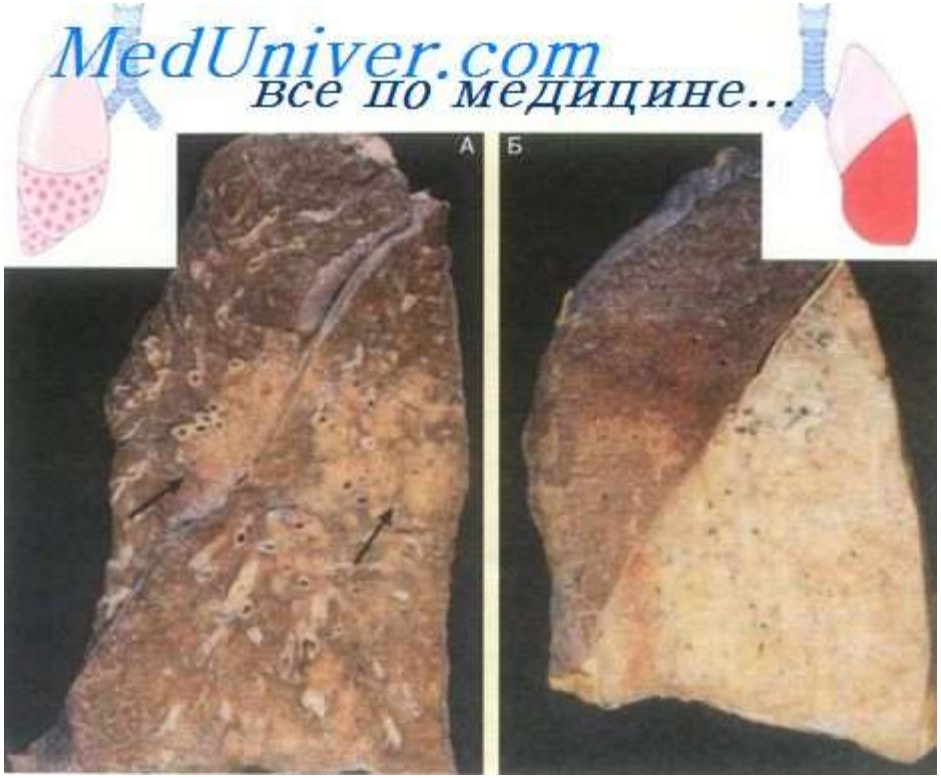


Aspergillosis



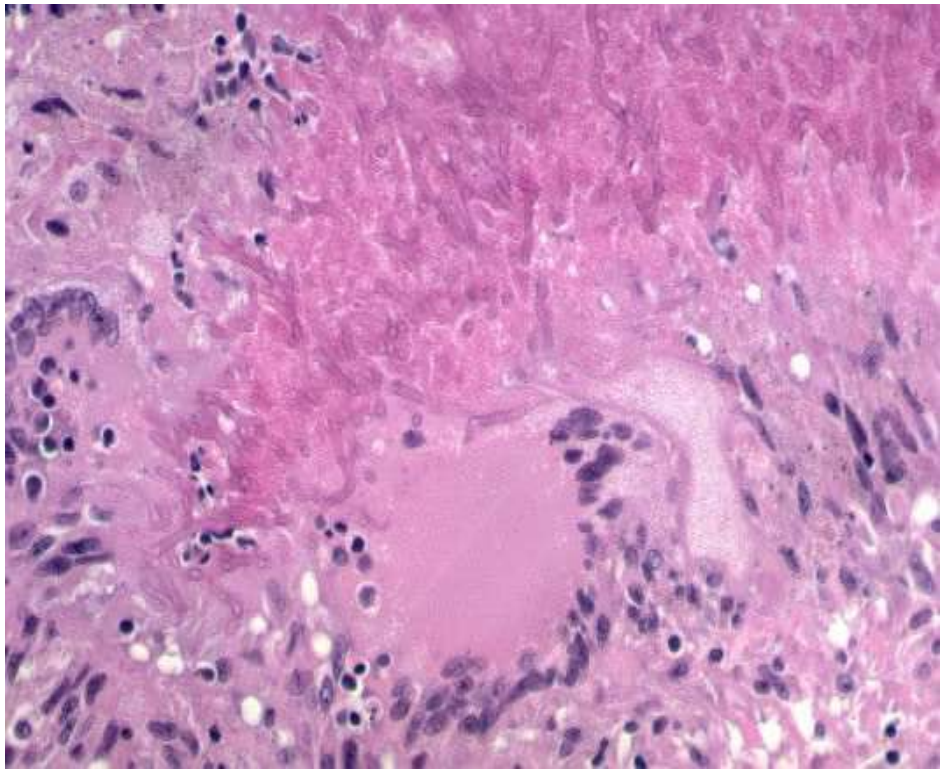
- Fungi - aspergillus.
- May complicate chronic diseases of the lungs such as bronchial asthma, chronic obstructive pulmonary disease.

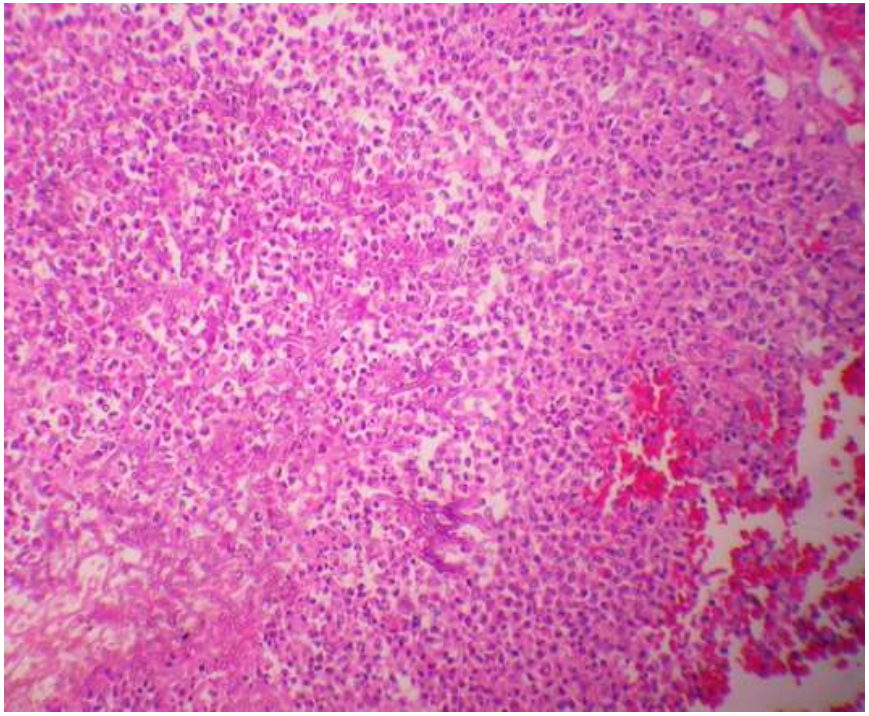
Aspergillosis

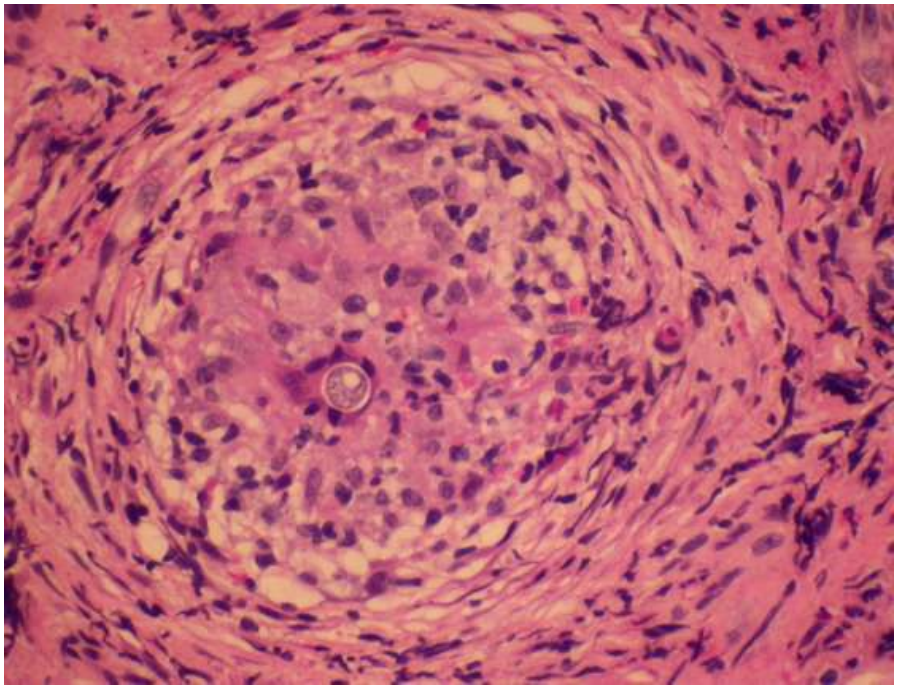


- Ussually develops in patients with decreased immunological reactivity, caused by different diseases, genetic factors or due to treatment by cytostatics and immunosupressions.

Granuloma in aspergillosis

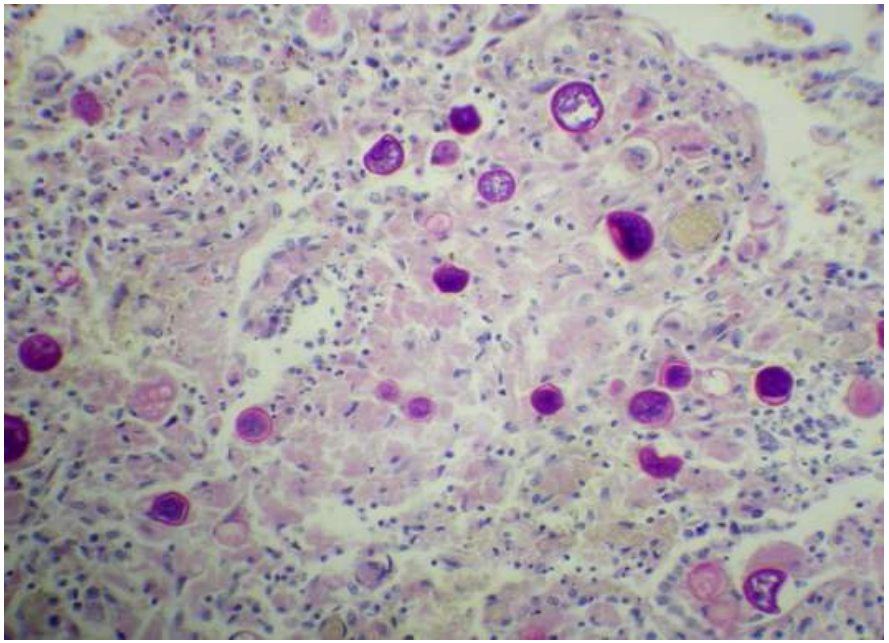




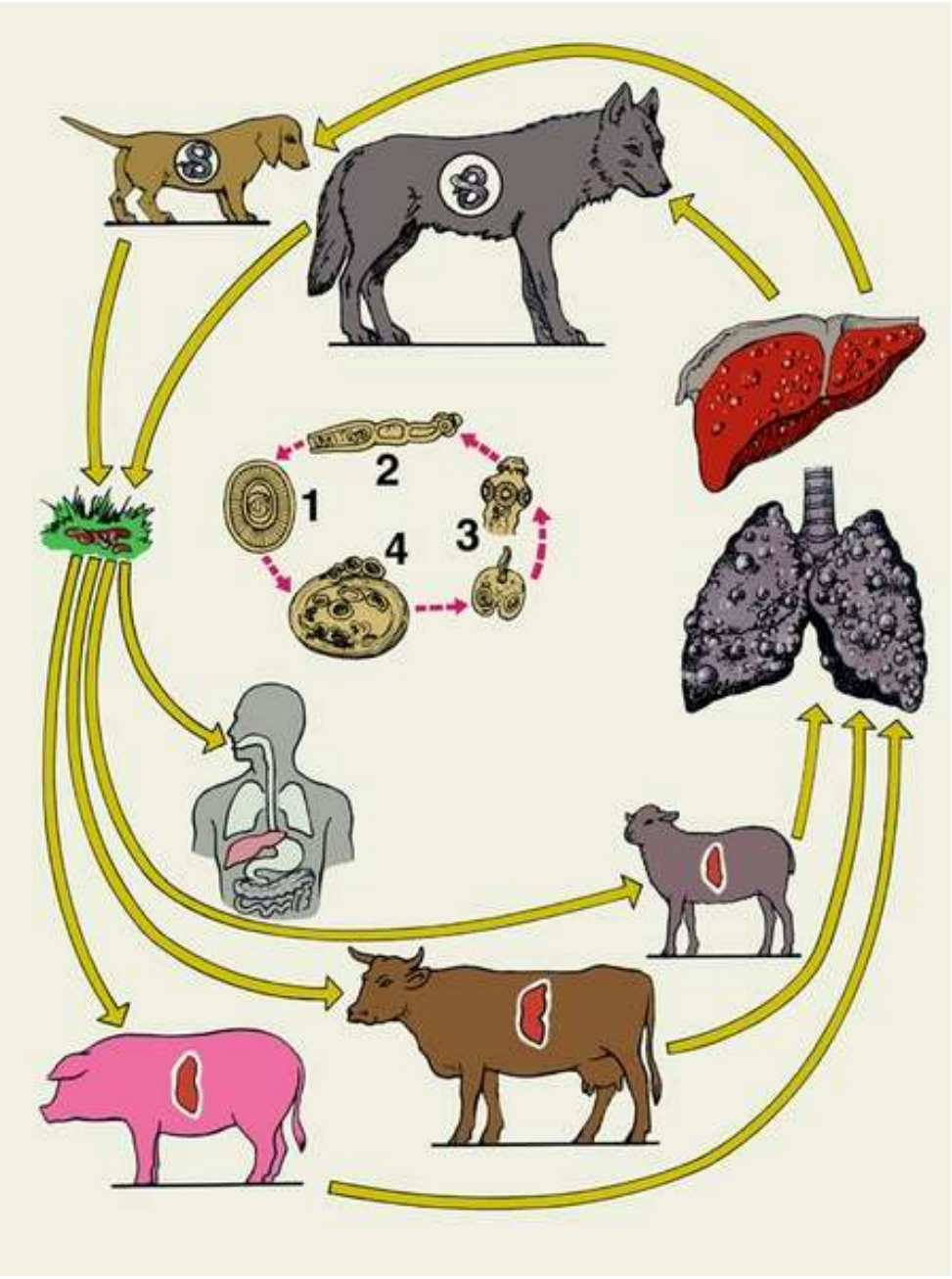


Coccidiodomycosis

- H&e,

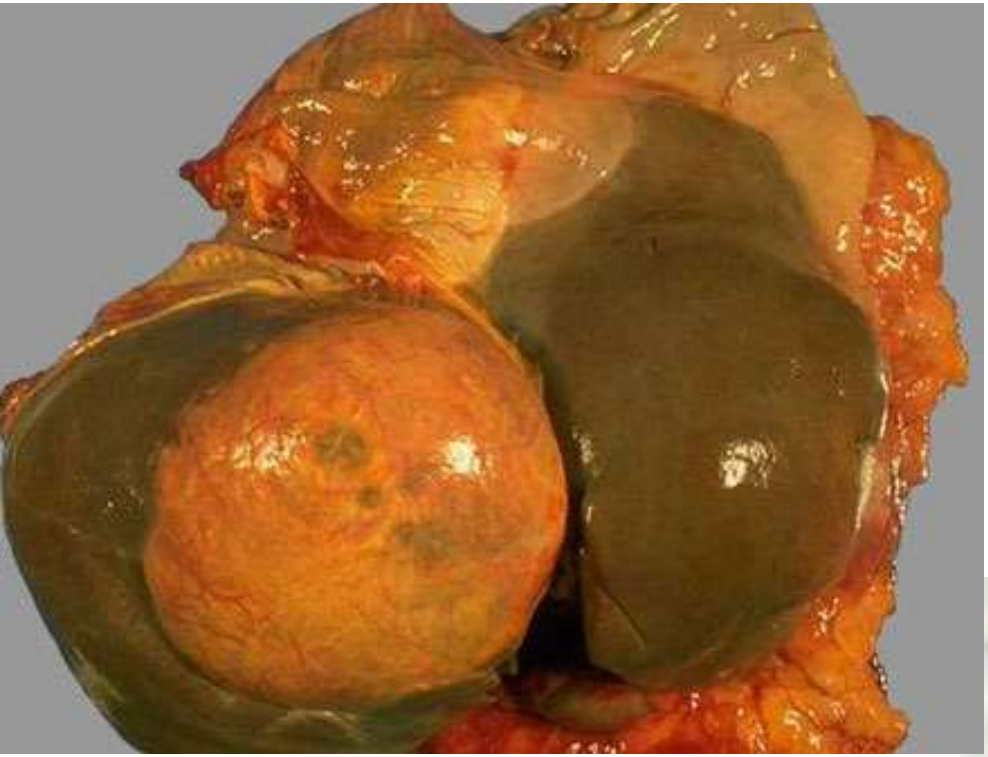


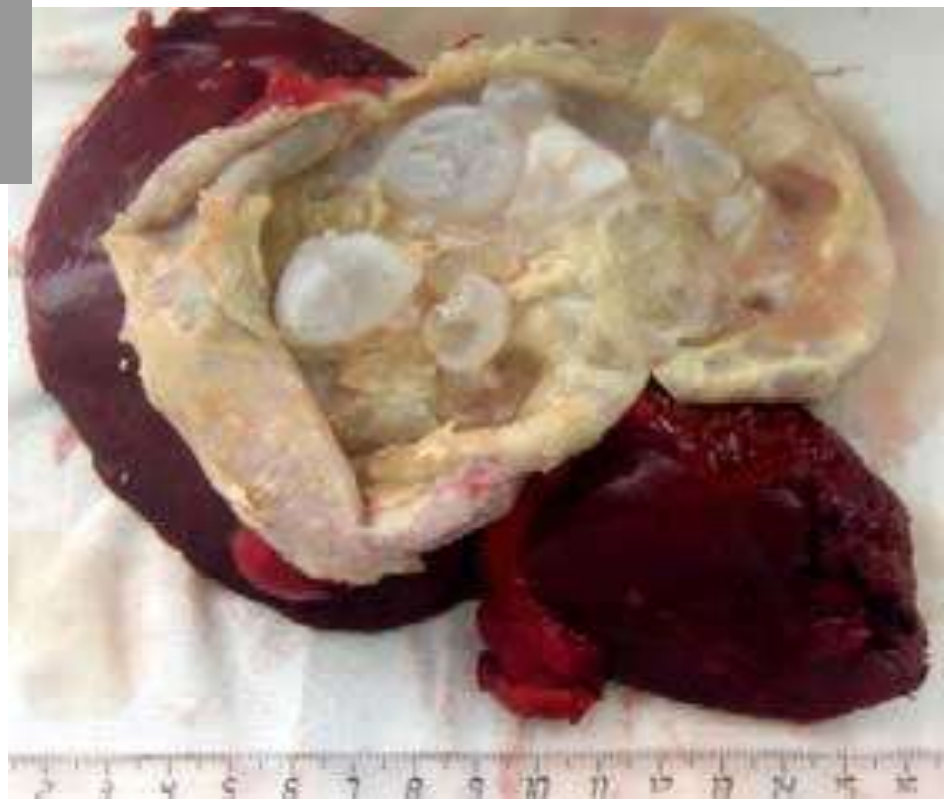
- PAS-reaction.



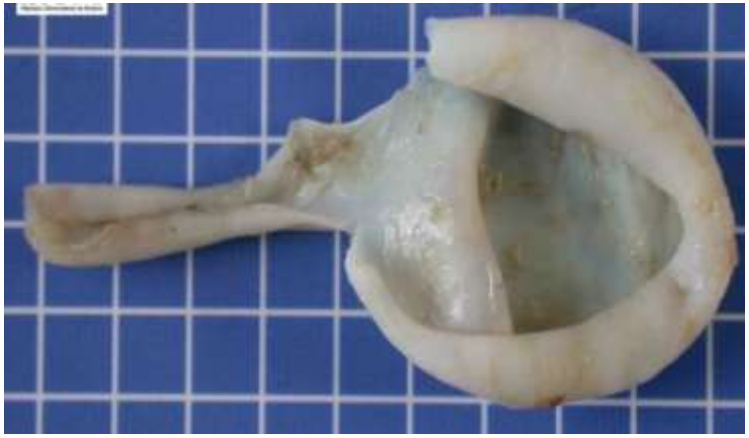
Echinococcosis

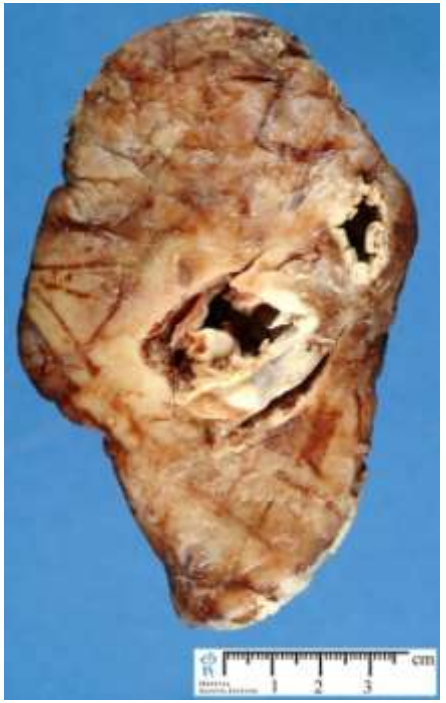
Echinococcosis

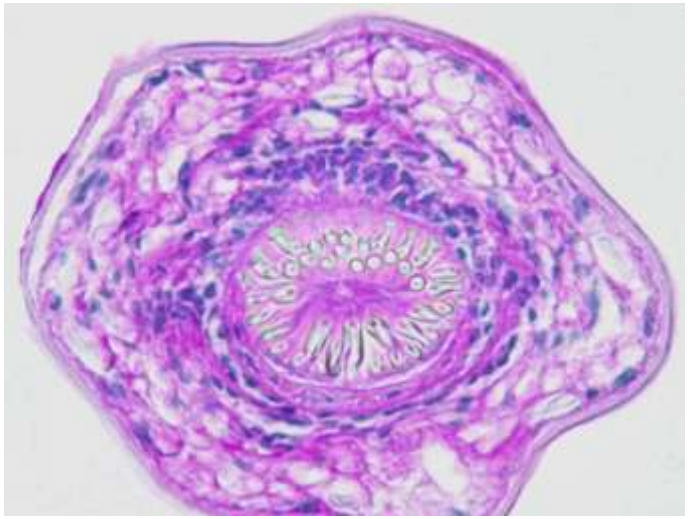


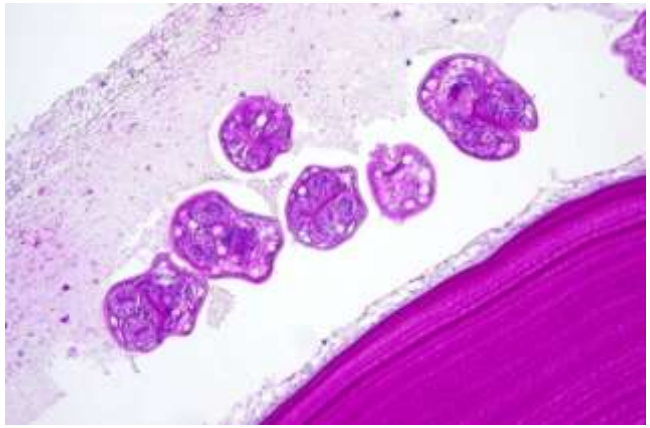


Echinococcosis

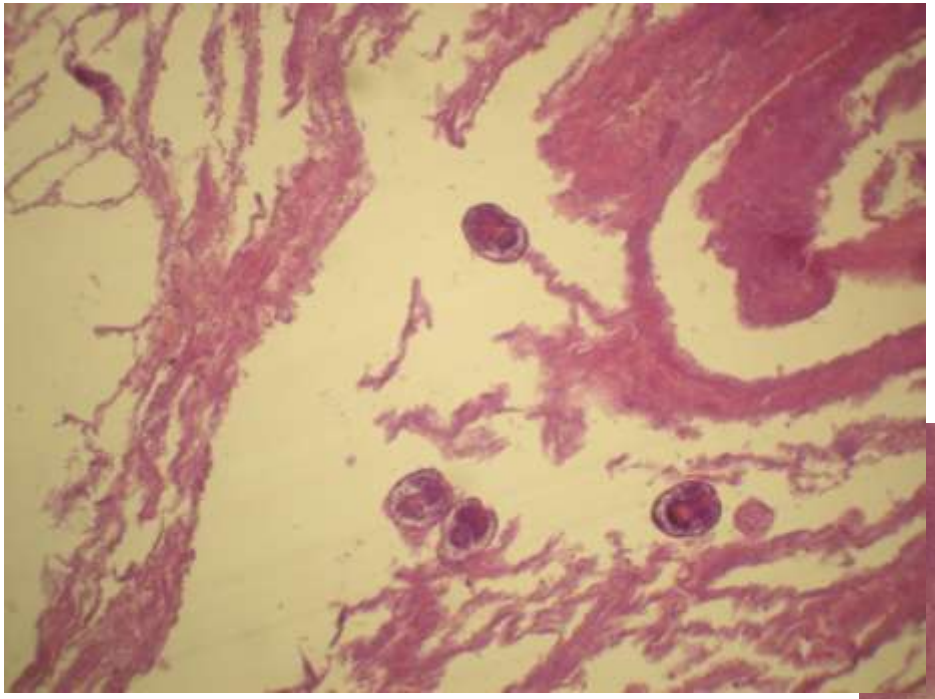


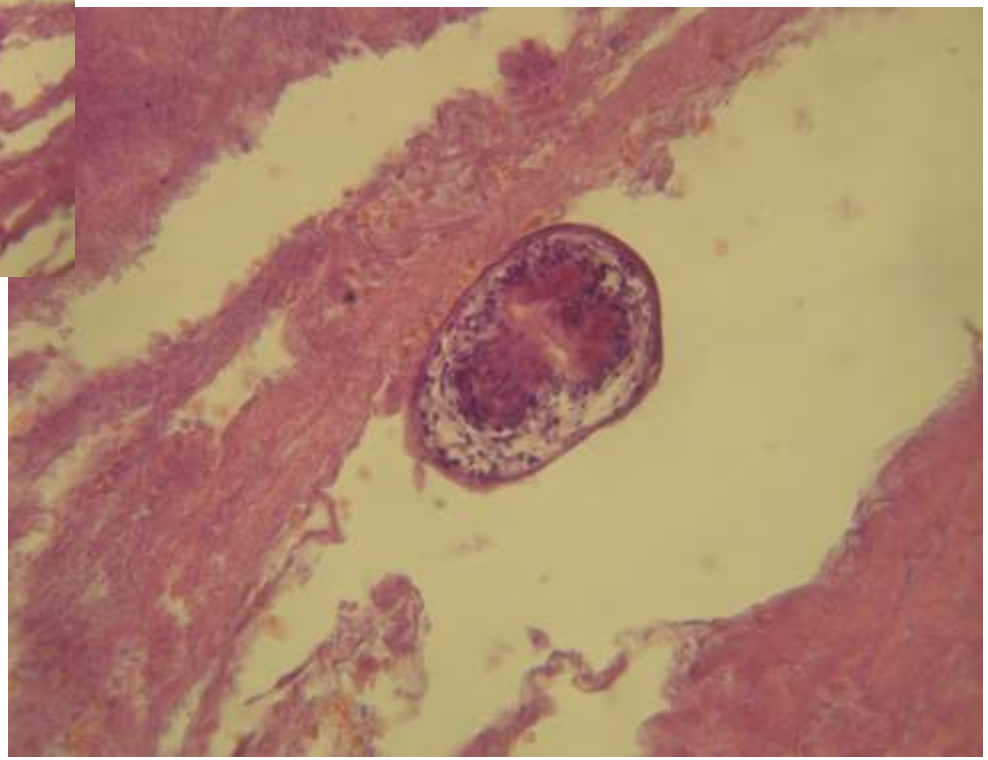






Echinococcosis





Outcomes of chronic inflammation

- Fibrosis
- Chirrosis
- Chronic organ insufficiensy

Inflammation

Acute

- Rapid onset
- Short duration
- Neutrophils
- Exudation of fluid and plasma proteins
- Inflammation followed by Repair

Chronic

- Slow onset; may follow acute
- Longer duration
- Lymphocytes and Macrophages
- Proliferation of blood vessels
- Simultaneous Inflammation and Repair