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FUNDAMENTALS OF GENERAL PATHOMORPHOLOGY

A STUDY GUIDE FOR INTERNATIONAL STUDENTS OF MEDICINE
Part 1

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The guide provides detailed syllabus descriptions of practical classes and theoretical material on the discipline Pathomorphology. The handbook is designed for postgraduate students of Health Care majoring in Medicine doing their Master of Medicine degree with a Doctor as a medical professional qualification.

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Preface

The tasks of further development of medical education put forward in the Law of Ukraine "On Higher Education" (No 1556-VII of 01.07.2014) requires for its solution permanent improvement of the pedagogical process.

Pathomorphology is an important part of the system of doctor's preparation at the boundary between theoretical and clinical disciplines.

To create a complete picture of the pathological process it is necessary to comprehend the most important facts obtained by various methods, including the methods of pathomorphology, because the pathological process is impossible to consider, separating the function from the structure.

Therefore, the goals of mastering the academic discipline of general pathology are the acquisition by each student in full of knowledge of pathological anatomy in the light of modern scientific ideas about the general laws of the occurrence, development, and outcome of pathological processes, the ability to use acquired knowledge in practice and the subsequent study of other fundamental medical disciplines, to successfully study clinical specialties.

The teaching aid provides basic information on general pathology and the doctrine of tumors in the Pathomorphology study program. The advantage of this training manual for students is the conciseness and structuredness of the material presented. The presented material is sufficient for acquiring detailed familiarity with Pathomorphology within the framework of its learning at a higher medical institution.

PART 1. INTRODUCTION TO PATHOMORPHOLOGY: SUBJECT, ESSENCE, TASKS, OBJECTS, AND METHODS OF STUDY

The term “pathology”, consists of Greek words, which means “the science of disease”. This discipline in most countries has other names: pathomorphology, pathological anatomy, morbid anatomy, surgical pathology, histopathology, anatomical pathology, etc.

Pathomorphology is a science and applied discipline that studies pathological processes and diseases using macroscopic and microscopic research methods, and studies the changes occurring in cells and tissues, organs, and organ systems of the human body.

A pathological process means any violation of the structure and function that occurs in the body when exposed to a pathogenic factor, which leads to a violation of the normal course of life processes and the development of the disease. Examples of the pathological process can be dystrophy, regeneration, inflammation, and others.

A disease is a combination of one or several pathological processes with a certain etiology, pathogenesis, and clinical and morphological manifestations leading to disturbance of the normal state and vital activity of the organism.

Modern pathomorphology makes extensive use of the achievements of other biomedical disciplines (biochemistry, genetics, pathophysiology, and others) to establish the regularities of the functioning of an organ and organ system in various diseases. Pathomorphology is of particular importance among medical disciplines due to the tasks that it solves in modern science.

Tasks of pathomorphology:

1. To identify the **etiology** (cause) of pathological processes;

2. To study the **pathogenesis** (the mechanism of development of pathological processes). There are several stages in the pathogenesis of the disease: morphogenesis, sanogenesis and thanatogenesis. **Morphogenesis** is the mechanisms

of development of morphological changes. **Sanogenesis** is a mechanism of recovery. **Thanatogenesis** is the mechanism of death.

3. To study the **morphological features** of the disease, which include macroscopic and microscopic changes in the organ;

4. To study complications and outcomes of the disease;

5. To study the **pathomorphism** of diseases. **Pathomorphosis** is a change in the clinical and morphological manifestations of the disease under the influence of the external environment (natural pathomorphosis) or treatment (induced pathomorphosis);

6. To study **iatrogenic changes**. **Iatrogenic changes** are the negative consequences of medical diagnostic, therapeutic, and other influences.

Pathomorphology is divided into general and special. **General pathomorphology** studies the morphological foundations and patterns of development and outcomes of typical pathological processes that are characteristic of all diseases (degeneration, regeneration, inflammation, circulatory disorders, hypo-, hyper-, and metaplasia, tumors, and others). These changes are part of various diseases. The course of **special pathomorphology** is the science of morphological changes in individual diseases (atherosclerosis, rheumatism, tuberculosis, liver cirrhosis, etc.).

The objects studied by the pathologist can be divided into three groups: 1) cadaveric material; 2) material obtained from patients during their lifetime (organs, tissues, secretion products, fluids, etc.), and 3) experimental material.

I. Cadaveric material. The organs and tissues of people who died from diseases are the subjects of study in the course of postmortem autopsies (sections, autopsies). Cases of death that have occurred not from disease, but as a result of crime, accidents, disasters, or unclear reasons, are investigated by forensic doctors.

An autopsy is a post-mortem study of the dead body to determine the cause of death. When performing an autopsy, the pathologist performs the following tasks: macroscopic assessment of the state of organs and systems (determines the

localization, size, and nature of the pathological process), establish the final diagnosis and causes of death of the patient, assess the accuracy or inaccuracy of the clinical diagnosis, analyze the effectiveness of treatment, enrich the scientific experience of clinicians and pathologists. The postmortem examination ends with the formulation and establishment of postmortem diagnosis and postmortem epicrisis with the determination of the immediate cause and mechanism of death.

Pathological (postmortem) diagnosis is a medical report on the nature of the disease, indicating its nosology, etiology, pathogenesis, and morphological and functional manifestations provided for by international classification of diseases and an indication of causes of death. The pathological diagnosis is formulated according to the following nosological principles: a) principal disease, b) complication of the principal disease, c) concomitant diseases and their complications.

1) Principal disease is a nosological form that, by itself or as a result of its complications, leads to the death of the patient. The underlying disease can have: mono-causal diagnosis is represented by one disease; bi-causal diagnosis consists of two diseases (competing disease, comorbidities, the principal and underlying disease); multi-causal diagnosis is represented by three or more diseases.

Competing diseases are diseases that the deceased suffered at the same time, and each of them could lead to death. **Comorbidities diseases** are nosological forms, each of which is itself not fatal to the patient, but their overall negative effect on the patient is so great that it can lead to death. **Underlying diseases** are diseases that have an impact on the occurrence or unfavorable course of another (main) disease, which became the cause of death.

2) Complication of the principal disease is a pathological process, symptoms, and syndromes, or a nosological form, which are pathogenetically indirectly or directly related to the principal disease and worsened its course.

3) A concomitant disease is one or several nosological forms, which at the moment (in case of death) were not directly associated with the principal disease and did not contribute to death.

II. Material obtained from patients during their lifetime. Most often, such material comes from operating clinicians: surgeons, urologists, gynecologists, ophthalmologists, otorhinolaryngologists, and others. A **biopsy** is the taking and examination of a piece of tissue from living people for diagnostic purposes.

There are several **classifications of biopsy**.

1. According to the way of obtaining the material:

Biopsy for histological examination:

- excisional biopsy (taking of the whole material for the pathomorphological study);

- incisional biopsy (taking of the part of the pathological foci);

- puncture biopsy (a column of tissue is taken with a needle);

- scarificator biopsy (taking of the material by cutting from the surface a thin layer of tissue);

- scraping (or curettage) (taking of the material with a special instrument from the hollow organs-uterus, cervix, etc.).

Biopsy for cytology examination:

- imprints of pathological formation-erosion, ulcers (the material is transferred to a glass slide, applying it to the ulcerated surface);

- smear-imprint (the pathological material is scraped off with a spatula and then transferred to a glass slide);

- fine needle aspiration biopsy (taking of the material through a puncture needle and syringe);

2. According to the accuracy control:

Classical biopsy (obtaining material without using additional instrumental methods of accuracy control);

Target biopsy (performed under the control of ultrasound, X-ray guidance, and endoscopic).

3. According to urgency:

Planned (the result can be obtained after a few days - up to 2 weeks);

Urgent (synonyms are intraoperative biopsy, cytobiopsy) (results should be obtained no later than 30 minutes to quickly establish a histological diagnosis to determine further tactics of the surgeon).

III. Experimental material. Experimental pathology using laboratory animals makes it possible to model and study diseases and pathological processes at any stage of their development.

Modern methodological possibilities of pathomorphology are enormous. They make it possible to study pathological processes and diseases at various levels: organismic, systemic, organ, tissue, cellular, subcellular, and molecular. Since the study of an organism occurs at different levels of its organization, then all research methods can be subdivided into two large groups: macroscopic and microscopic methods.

The **macromorphological method** is a method of studying biological structures without significantly enlarging the object. Description of pathological changes in organs is carried out using the following basic parameters:

1) localization of the pathological process in the organ;

2) the size of the organ, its fragment, and its pathological area (dimensional parameter - length, width, thickness);

3) the configuration (shape) of the pathologically organ or its part;

4) the color characteristic of the tissue from the outer surface and on the cut;

5) the consistency of the pathological tissue;

6) the degree of homogeneity of the pathologically tissue by color and consistency.

The outwardly normal appearance of the organ and tissue does not guarantee the normal structure of this tissue at the histological level; therefore, externally unchanged tissues must also be taken for research.

Micromorphological (microscopic) method is a method of morphological examination under a microscope. Many variants of the microscopic method have been proposed, but the most widespread is light microscopy (light-optical studies).

Most often, various methods are used for microscopic examination: histological, cytological, immunohistochemical, molecular biological, and electron microscopy.

For the **histological method**, tissue sections for light-optical research are prepared on special devices (microtomes) and stained using various methods. A histological specimen is a stained tissue section enclosed between a microscope and a cover glass in a transparent medium (polystyrene, balsam, etc.).

Histological staining methods, the most commonly used in pathomorphology, include:

1. Routine hematoxylin and eosin (H&E) stain: cell nuclei, bacteria, deposits of calcium salts, and other structures are colored by blue (basophilic structures) hematoxylin; cell cytoplasm, erythrocytes, fibers, protein masses, most types of mucus are stained by red (eosinophilic structures) eosin. 2. Differential (special) staining techniques, including histochemical methods; are used to identify certain tissue structures and components (Tables 1 and 2).

Table 1. Some special methods of histological staining

Method of staining	Stains	Results
Mallory staining	Acid magenta, aniline blue, orange G Acid magenta, aniline blue, orange G	Collagen fibers-dark blue color; other structures - orange or red color
Orsein staining	Orsein	Elastic fibers - dark red color; other structures – light pink color
Romanowsky staining	Azur II, eosin	Erythrocytes - red color; leukocytes - light blue or blue color
Van Gieson's	Picric acid, acid	Collagen fibers - bright red

staining	fuchsine	color; other structures - yellow color
Silver impregnation	Ammoniac silver solution	Reticular fibers and elements of the nervous tissue - black color; other structures - yellow-brown color
Ziehl-Nilsson staining	Hydrochloric acid, basic fuchsin, methylene blue	Acid-fast bacteria (leprosy, mycobacterium tuberculosis) - bright red

Table 2. Some methods of histochemical staining

Method of staining	Detectable compounds	Results
Alizarin red	Calcium	Calcium - red-orange color
Congo red	Amyloid	Amyloid - bright red color
Perl’s' reaction	Iron compounds	Hemosiderin - blue-green color
Toluidine blue	Glycosaminoglycans	Glycosaminoglycans-lilac-pink color; other elements - blue color
Blue Nile stain		Neutral fats - pink color; cholesterol esters – pink or purple color; phosphatides and cerebrosides - blue color; fatty acids - dark blue color

Sudan black B, osmic acid (Osmium tetroxide)	Fats	Neutral fats - black color
Sudan III		Neutral fats-red-orange color

A cytological examination is an intravital micromorphological examination of surgical and biopsy material. It consists of a cytological examination of smears and smears of tissue prints, secretions, excretions, and cavity fluids. The most popular stains for cytological research are Azure-II-eosin (its tinctorial properties are close to hematoxylin and eosin) and Bismarck-Brown Pap.

In some pathological conditions, for example, tumors, it is difficult or impossible to determine the type of tissue or its origin (histogenesis) using histological or cytological dyes. Such verification is very important for the diagnosis and prognosis of the disease. Therefore, various additional methods are used. One of them is the **immunohistochemical study** is a method of microscopic examination of tissues, which allows the most accurate identification of unknown substances. It is based on the processing of sections with a labeled specific antibody to detect a substance, which in this situation is an antigen.

Methods of molecular biology are also used: flow cytometry and the technique of in situ hybridization, that is, on a histological section.

1. Flow cytometry is used for the quantitative analysis of DNA in tumor cells. For this purpose, a fragment of unfixed tissue with the help of enzymes is subjected to disaggregation - separation and crushing to separate cells. Then, in a special installation, isolated cells are passed through a reading laser beam.

2. In situ hybridization technology is used to determine the genome of a virus or bacteria in tissues and biological fluids; and also, to study the genome in congenital pathologies and tumors.

An electron microscopy is often used for diagnostic studies on material taken during the patient's life, which includes two types: 1) transmission (in a transmitted beam, similar to light-optical microscopy) and 2) scanning (to detect relief surface). The first type is more often used for the detailed study structure of ultrathin sections of cells, and for the identification of viruses, microorganisms, and immune complexes.

TEST YOURSELF

1. Pathogenesis is:

A. Disease of a certain type

B. The same as the pathological process

C. Section of pathology that studies the mechanisms of development of diseases

D. The cause of the disease

2. Etiology is:

A. Disease of a certain type

B. Science about the mechanisms of the development of diseases

C. Outcome of the disease four

D. Science about the causes and conditions for the development of diseases

3. Biopsy is:

A. Intravital histological examination of tissue or organ

B. Postmortem histological examination of tissue or organ

C. Intravital and postmortem histological examination of tissue or organ

4. Autopsy is:

A. Intravital histological examination of tissue or organ

B. Postmortem histological examination of tissue or organ

C. Intravital and postmortem histological examination of tissue or organ

5. According to the method of taking material, types of biopsies are distinguished (several correct answers are possible):

A. Incisional

B. Excision

C. Puncture

D. Autopsy

6. Excisional biopsy is:

A. Taking of the material with a special instrument from the hollow organs

B. Taking of the part of the pathological foci

C. Taking of the material by a puncture

D. Taking of the whole material for the pathomorphological study.

7. Needle biopsy is:

A. Taking of the material with a special instrument from the hollow organs

B. Taking of the part of the pathological foci

C. Taking of the material by puncture

D. Taking of the whole material for the pathomorphological study.

8. Principal disease is:

A. Nosological form, which leads to death

B. Pathological process, syndrome, or nosological unit that is associated with the underlying disease and affects its clinical course

C. Pathologic process, which not affected the course of the principal disease and does not lead to death.

9. Complication of the underlying disease is:

A. Nosological form, which leads to death

B. Pathological process, syndrome, or nosological unit that is associated with the underlying disease and affects its clinical course

C. Pathologic process, which not affected the course of the principal disease and does not lead to death

10. Concomitant disease is:

A. Nosological form, which leads to death

B. Pathological process, syndrome, or nosological unit that is associated with the underlying disease and affects its clinical course

C. Pathologic process, which not affected the course of the principal disease and does not lead to death

PART 2. DYSTROPHY: GENERAL ISSUES. MORPHOLOGY OF PARENCHYMATOUS DYSTROPHIES

A normal cell performs a certain number of functions. Its structure and activity are determined by the genetic programs of metabolism, proliferation, and differentiation. Collectively, the cells can provide normal homeostasis of the body. The impact of various pathogenic factors (exogenous and endogenous) leads to structural and functional disorders of the cell and its damage (alteration).

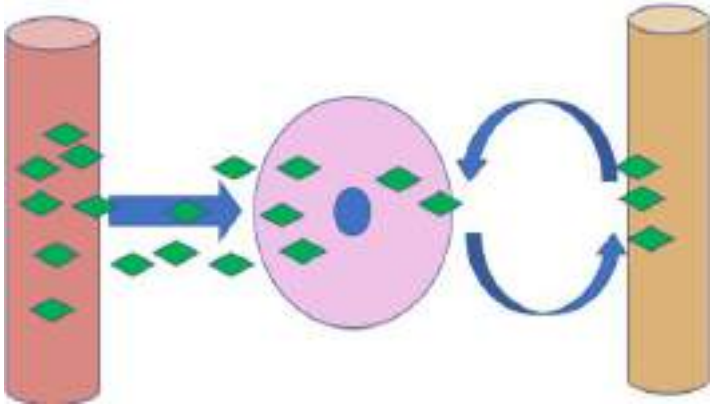
Alteration is structural changes in the cells and tissues of the body that occurs under the influence of damaging factors and are accompanied by a disruption of their vital activity. One of the types of alteration is dystrophy, which reflects metabolic disorders.

Dystrophy (degeneration) is a pathological process, which is based on a violation of the cell (tissue) metabolism, leading to structural changes. The main causes of dystrophy are hypoxia, chemical factors, physical factors, biological agents, immune processes, genetic damage, nutritional imbalance, and others.

Morphologically, this type of change is accompanied by the appearance in cells and tissues of substances that are normally absent or contain little, or from cells and tissues, their inherent substances disappear. At the heart of dystrophy is a violation of the mechanisms that ensure the metabolism and preservation of the structures of cells and tissues, such as the regulatory function of the endocrine and nervous systems, violation of blood supply and lymph circulation, disturbance of autoregulation of the cell, which leads to violation enzymatic processes in the cell.

There are the following morphogenetic mechanisms for the development of dystrophy: 1) infiltration, 2) decomposition (phanerosis), 3) perverted synthesis, 4) transformation.

1) Infiltration is an excessive penetration of metabolic products from blood and lymph into cells or intercellular substances with their subsequent accumulation. For example, infiltration of the intima of the wall of the aorta and large vessels with cholesterol and its esters in atherosclerosis. There are two types of infiltration: in the first case, the cell receives an excessive amount of substance and cannot assimilate this excess; the second type is characterized by a decrease in the functional activity of the cell, which leads to its inability to assimilate a normal amount of the incoming substance (Figure 1.).



A. B.

Figure. 1. Mechanisms of infiltration. A. Excessive intake of substances into the cell. B. Normal intake of substances into the cell.

2) Decomposition (phanerosis) is the disintegration of the ultrastructures of cells and intercellular substances, leading to the disruption of tissue or cellular metabolism and the accumulation of products of impaired metabolism in tissue or cell. For example, with diphtheria intoxication, fatty degeneration of cardiomyocytes occurs (Figure 2.).

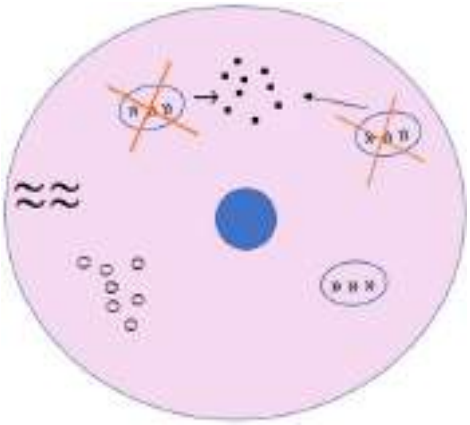


Figure. 2. Mechanisms of decomposition.

3) Perverted synthesis is the synthesis of substances in cells and tissues, which are not normal. For example, the production of abnormal amyloid protein by B-lymphocytes in multiple myeloma (Figure 3.).

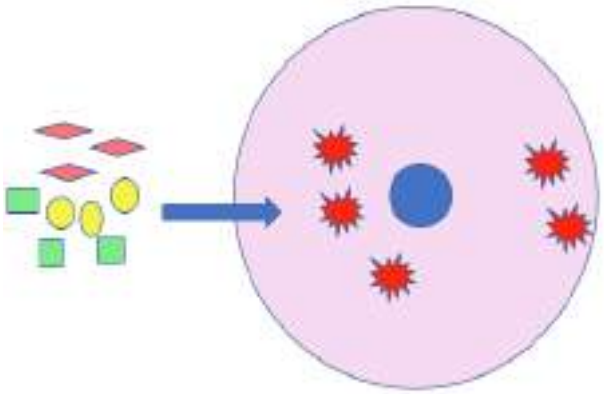


Figure. 3. Mechanisms of perverted synthesis.

4) Transformation is the formation of products of one type of metabolism instead of products of another type of metabolism. For example, the conversion of carbohydrates to fat in diabetes mellitus. (Figure 4.).

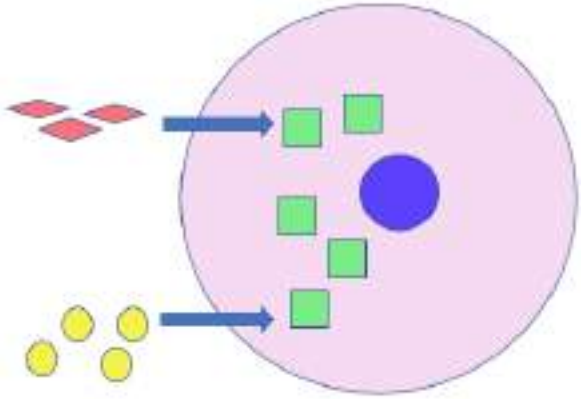


Figure. 4. Mechanisms of transformation.

Harmful factors primarily affect the molecular and cellular levels. There is a time interval between the effect of the factor and the morphological manifestations of cellular changes or cell death. The duration of this period may vary depending on the intensity of the damaging factor and the adaptive processes of the human body. Hence, the manifestations of dystrophy can differ in severity and reversibility.

When classifying dystrophies, the following features are considered: 1) the predominance of morphological changes in specialized elements of the parenchyma or the stroma and vessels (parenchymal, mesenchymal, and mixed dystrophies); 2) the prevalence of metabolic disorders (protein, fat, carbohydrate and mineral dystrophies); 3) the influence of hereditary or acquired factors (hereditary or acquired dystrophies); 4) the prevalence of the process (general and local dystrophies).

Parenchymal dystrophy (intracellular) is a pathological process with structural and functional changes observed in the cells of parenchymal organs performing a specialized function (cardiomyocytes, cells of the renal tubules, adrenal glands, hepatocytes, and others). Depending on the type of metabolic disorder, parenchymal dystrophies are divided into protein (dysproteinosis), fatty (lipidoses), and carbohydrate.

I. Parenchymal protein dystrophies (dysproteinosis) are characterized by a violation of the morphological and physicochemical properties of cellular proteins.

There are four types: 1) granular; 2) hydropic; 3) hyaline-drop; 4) keratinous dystrophies.

1) Granular dystrophy (cloudy or dull swelling).

The main causes are hypoxia, infectious agents, intoxication, impaired blood circulation and lymph circulation, and other pathogenic factors. For example, with infectious diseases, general intoxication occurs, and metabolic disorders can manifest themselves in the form of granular degeneration of the cells. Most often, granular dystrophy is found in the heart, and kidney, and less often in the liver.

Macroscopic features: the parenchyma on the cut surface is dull and protrudes. The myocardium looks like "cooked meat".

Microscopic features: the cells increase in volume, and eosinophilic granularity appears in the cytoplasm, associated with an increase in the volume of mitochondria and the expansion of the granular endoplasmic reticulum (microphotograph 1).

Some scientists dispute the existence of this type of dystrophy and consider the described changes as compensatory-adaptive reactions, which are manifested by hypertrophy of organelles (mitochondria).

Consequences: this type of dystrophy is reversible if the causative factor is eliminated.

2) Hydropic (vacuolar) dystrophy.

The main causes are toxic substances, poisoning, viral infections, allergic reactions, and others. For example, it develops in the cells of the epidermis and mucous membranes during herpes infection, chickenpox; in hepatocytes - with viral hepatitis, intoxication.

Macroscopic features: organs do not change, except the skin during the development of herpes infection or chickenpox, when bubbles (vesicles) filled with serous fluid appear.

Microscopic features: the cells are enlarged, and their cytoplasm contains vacuoles of various sizes filled with cytoplasmic fluid. Expansion of the endoplasmic reticulum is observed at the ultrastructural level (microphotograph 2). With a severe degree of the process, vacuoles merge, displacing the cell nucleus and organelles to the periphery. Intracellular structures are destroyed, and the cell takes the form of a "balloon" (balloon degeneration).

Consequences: this process is reversible when removing the causative factor in the early stages. Otherwise, focal or total colliquative (liquefactive) necrosis develops.

3) Hyaline-drop dystrophy.

The main causes are intoxication, acute and chronic infections, allergic reactions, poisoning, and others. Most often, this type of dystrophy develops in the liver, and kidneys, less often in the myocardium.

Macroscopic features: organs do not change, or depend on the diseases in which this dysproteinosis occurs.

Microscopic features: large drops appear in the cytoplasm of cells protein as a result of its coagulation often merging. For example, in chronic alcoholism, protein metabolism in hepatocytes is disrupted, and eosinophilic Mallory bodies (protein clusters) (microphotograph 3). In the kidneys with rejection, the epithelium is damaged, and hyaline casts are formed in the lumen of the kidney tubules.

Consequences: there may be necrosis, fibrosis, and portal cirrhosis in the liver; in the kidneys - focal coagulation necrosis; in the heart, this leads to a violation of the contractility of the heart muscle.

4) Keratinous dystrophy.

The main causes are disorders of skin development, chronic inflammation, chronic circulatory disorders, vitamin deficiencies, infections, tumors, and other pathological conditions.

Keratosis is the process of keratinization of the epithelium. It normally occurs in the keratinizing epithelium. With the development of dystrophy, a violation of the formation of keratin by cells occurs. There are several types of disorders: *hyperkeratosis* - a local increase in keratinization of the normal keratinized epithelium; *ichthyosis* is a congenital generalized hyperkeratosis, in some forms incompatible with life; *leukoplakia* is characterized by the formation of white spots on the mucous membranes (oral mucosa, esophageal mucosa, cervical mucosa) and is a precancerous process.

Macroscopic features: hyperkeratosis and ichthyosis are characterized by: the thickening of the skin with the growth of keratinized layer. The skin loses its elasticity, and becomes rough and dry; it resembles "fish scales". *Leukoplakia* is

characterized by the appearance of keratinizing epithelium in the form of gray-white spots or stripes of various sizes on the mucous membranes.

Microscopic features: hyperkeratosis is characterized by uneven thickening epidermis due to hyperplasia of the Malpighian layer and excessive accumulation of keratin in the cells. All layers of the epidermis are preserved. *Ichthyosis* is characterized by a pronounced hyperkeratosis with the accumulation of keratin in the enlarged hair follicle, and the granular layer of the dermis is absent. With *leukoplakia*, the appearance of keratinized epithelium with desquamation. In squamous cell carcinoma, "cancer pearls" are formed - these are structures in the form of a concentric accumulation of keratinized cells that look like rounded pinkish-layered formations that resemble "pearls" (microphotograph 4).

Consequences: In the early stages, with the elimination of the causative factor, keratinous dystrophy is reversible. Otherwise, cell necrosis will occur.

II. Parenchymal fatty dystrophies (lipidosis) are characterized by a violation of fat metabolism, predominantly neutral, in the cytoplasm of cells.

The main causes are chronic diseases of the cardiovascular system, and respiratory organs, diseases of the blood system, intoxication and infections of various origins, and general obesity.

Fatty degeneration most often develops in the heart, liver, and kidneys.

Macroscopic features: the *heart* is enlarged, its chambers are stretched, and the heart muscle is of a flabby consistency, clay-yellow in color. A feature of fatty degeneration of the myocardium is the focal nature of the lesion. Under the endocardium of the left ventricle, especially in the area of the trabeculae and papillary muscles, yellow-white stripes are visible; such a myocardium is compared to the skin of a tiger *("tiger heart"*).

The liver is enlarged, flabby consistency and yellow on the cut, a bloom of fat is visible on the cut on the knife blade. Such a liver is called a "*goose liver*" because the liver of geese, fed in a special way, looks the same.

Kidneys (lipoid nephrosis) with fatty degeneration are enlarged, flabby consistency (with the development of amyloidosis - dense), and the cortical substance is edematous, gray with yellow spots. This kidney is called a "*large white kidney*". Fatty renal degeneration often develops in the epithelial cells of the proximal and distal convoluted tubules.

Microscopic features: lipids dissolve using conventional histological staining techniques. Thus, using the routine tissue staining method (H&E) cells contain optically empty lipid vacuoles. Depending on the size of the vacuoles, there are dust-like fatty degeneration, small-drop fatty degeneration, and large-drop fatty degeneration. For differential diagnosis, special staining techniques are used to detect fat can be used.

Myocardium stained with Sudan III, lipids are determined in the cytoplasm of cardiomyocytes in the form of small drops (dust-like obesity), mainly along the venous capillaries and small veins, other muscle cells are free of fatty inclusions. In electron microscopic examination, fatty inclusions have striations and are located between intracellular structures.

In *hepatocytes*, in place of fat droplets, vacuoles are visible when stained with hematoxylin-eosin; when stained with Sudan III - yellow-red fatty drops. Large drops of fat are visible in the peripheral parts of the lobules, and small ones - in the center of the lobules. There are hepatocytes, the cytoplasm of which is filled with fat, and the nucleus is displaced to the periphery of the cell (microphotograph 5).

In *kidneys*, neutral fats, phospholipids, or cholesterol are found in the epithelium of the tubule in the stroma, dyed red-brown color.

Consequences: fatty degeneration depends on its degree. If it is not accompanied by serious damage to cellular structures, this can be a reversible process. Otherwise, in severe disorders of cell lipid metabolism, fatty degeneration leads to cell death and organ dysfunction.

There is *hereditary systemic lipidosis*, which is a group of genetic diseases with the accumulation of lipids in organs, representing diseases of accumulation

(thesaurismosis). These diseases are associated with hereditary defects in enzymes that metabolize complex fats. There are several groups of hereditary lipidoses: 1) primary dyslipoproteinemia is hereditary metabolic disorders of lipoproteins: hypolipoproteinemia, hyperlipoproteinemia, alipoproteinemia; 2) glycolipidosis is a violation of glycolipids exchange: cerebroside lipidosis (Gaucher disease), sphingomyelin lipidosis (Niemann-Pick disease), ganglioside lipidosis (Tay-Sachs disease), generalized gangliosidosis (Norman-Landing disease), etc. Bone marrow, central nervous system, liver, and spleen is most often affected. The symptoms of each disease are different and depend on the type of defect and the location of the lipid deposits.

III. Parenchymal carbohydrate dystrophies are characterized by disturbance metabolism of glycogen or glycoproteins. Depending on the type of carbohydrates that are contained in the cells, the following types are distinguished: 1) polysaccharides (glycogen), 2) glycoproteins (mucoids and mucins), 3) glycosaminoglycans (mucopolysaccharides).

1) *Violations of glycogen metabolism* are divided into two forms: acquired (for example, diabetes mellitus) and hereditary forms (glycogenosis).

Acquired disorders of glycogen metabolism are most often observed in diabetes mellitus. In this disease, there is an absolute and relative insufficiency of insulin, as a result of which the utilization of glucose is impaired and the synthesis of glycogen. The result is an increase in blood glucose (hyperglycemia), glucose appears in the urine (glucosuria), and glycogen stores in the liver and muscles are depleted. In connection with hyperglycemia and glucosuria, glucose infiltrates the tubular epithelium of the kidneys, where it usually does not exist.

Microscopic features: glycogen in hepatocytes moves from the cytoplasm to the nucleus, so the nucleus on routine slides looks light and optically empty (*"perforated" nucleus*). The amount of glycogen in the cytoplasm of hepatocytes significantly decreases and lipids accumulate instead. Sclerosis of large and small vessels develops.

Tubular epithelial cells in kidneys are characterized by significantly enhanced glycogen synthesis due to the presence of large initial amounts of glucose and its reabsorption from the urine. The cytoplasm of the tubular epithelium of the renal tubules becomes light and foamy (glycogen infiltration of the renal tubules). Glycogen grains can be detected in the lumen of the tubules. For the determination of glycogen, special methods of histological staining (PAS-reaction) can be used.

Hereditary disorders of glycogen (glycogenosis) are characterized by intracellular accumulation of glycogen due to hereditary enzymopathy (Gierke's disease, Pompe, Andersen, McArdle, etc.).

Microscopic features: morphological manifestations of glycogen storage diseases are different depending on the predominantly damaged organ. Hepatic forms are characterized by an enlarged liver. Weakness develops in skeletal muscles due to the accumulation of glycogen in the sarcoplasm muscle fibers. The systemic (generalized) form of glycogenosis affects various organs, including the heart, which is accompanied by the development of cardiomegaly and chronic heart failure.

2) *Violation of glycoproteins metabolism (mucous degeneration)* leads to the accumulation of mucoid substances (mucous and mucins) in cells. In this aspect, metabolic disorders of glycoproteins are referred to as mucous degeneration. There are two forms: acquired and hereditary.

Acquired disorders of glycoproteins metabolism are observed in inflammatory processes of the mucous membranes (bronchitis, rhinitis, gastritis, and others), which is accompanied by excessive mucus formation. Such mucus can close the lumens of the bronchi, and ducts of the glands, which leads to the formation of cysts. With colloid goiter, a mucus-like substance is produced in the thyroid gland (colloidal degeneration).

Consequences: depend on the severity and duration of excess mucus secretion. At the initial stage, this can be a reversible process, but over time it leads to atrophy and sclerosis of the organ.

A hereditary disorder of glycoproteins metabolism (mucoviscidosis) is cystic fibrosis. This is a hereditary disease with autosomal recessive inheritance.

Microscopic features: epithelial cells of the glands of the bronchi, pancreas, digestive and urinary tracts, lacrimal glands and sweat glands, and biliary tract produce thick viscous mucus. The lumens of the glands expand in the form of cysts.

Consequences: cysts compress the parenchyma organs, causing atrophy with subsequent proliferation of fibrous tissue (cystic fibrosis).

TEST YOURSELF

1. Dystrophy is:

A. Disruption of metabolism in cells and tissues, leading to a change in their functions

B. A sharp decrease in body weight

C. The death of tissue sites

D. Reducing the size of an organ or the whole body

2. What are the microscopic changes that characterize hydropic dystrophy:

A. The appearance of fat droplets in the cytoplasm

B. The appearance in the cytoplasm of cells of protein droplets such as hyaline

C. The appearance in the cytoplasm of cells and interstitial tissue of the stratum corneum

D. The appearance in the cytoplasm of cells of vacuoles with a clear liquid

3. The term "tiger heart" is used to mean:

A. Fatty degeneration

B. Granular dystrophy

C. Hyaline droplet dystrophy

D. Hydropic dystrophy

C. Carbohydrate dystrophy

4. Name the pathomorphological changes that characterize hyaline droplet dystrophy:

A. The appearance in the cytoplasm of grain cells

B. The appearance of vacuoles in the cytoplasm of cells

C. The appearance in the cytoplasm of cells of large drops of protein such as hyaline

D. The appearance of large drops of fat in the cytoplasm of cells

5. To identify parenchymal lipids, stains are used:

A. Picrofuchsin according to Van Gieson

B. Impregnation with silver salts

C. Sudan IV

D. Coloring Congo red

6. The liver with parenchymal fatty degeneration is called:

A. "Goose liver"

B. Large red liver

C. Sebaceous liver

D. "Shriveled" liver

7. Hydropic dystrophy is a manifestation of:

A. Fat metabolism disorders;

B. Protein metabolism disorders;

C. Disorders of calcium metabolism;

D. Violation of carbohydrate metabolism

8. The term «cloudy swelling» is used to mean:

A. Hyaline droplet dystrophy

B. Hydropic dystrophy

C. Horny dystrophy

D. Granular dystrophy

9. Indicate a favorable outcome of "granular" dystrophy:

A. Transformation into mucoid swelling

B. Reverse development

C. Transformation into hyaline droplet dystrophy

D. Transformation to Hydropic Dystrophy

10. With hyaline droplet dystrophy, the epithelium of the tubules of the kidneys develops:

A. Proteinuria

B. Oxalaturia

C. Uraturia

D. Lipiduria

PART 3. MORPHOLOGY OF STROMAL-VASCULAR DYSTROPHY

Stromal vascular (mesenchymal, extracellular) dystrophy is characterized by metabolic disorders in the stroma of organs and walls of the vessels. This process is accompanied by morphological changes in the histone, which is a segment of the microvasculature with the surrounding connective tissue and nerve fibers. These dystrophies develop through the mechanism of infiltration (accumulation in the stroma of blood and lymph products of metabolism), disorganization of fibers and the basic substance of connective tissue, and perverted synthesis (synthesis of abnormal protein in connective tissue). Depending on the type of metabolic disorder, stromal vascular dystrophies are divided into protein (mesenchymal dysproteinosis), fatty (mesenchymal lipidoses), and carbohydrate. Dystrophies can be acquired and hereditary.

I. Stromal-vascular protein dystrophies (mesenchymal dysproteinosis) are represented by mucoid swelling, fibrinoid swelling, hyalinosis, and amyloidosis. Mucoid and fibrinoid swelling and hyalinosis are successive stages of disorganization of the connective tissue. Amyloidosis differs from these processes in that the composition formed protein-polysaccharide complexes includes an abnormal fibrillar

protein that is not normally found which is synthesized by special cells (amyloidoblasts).

The main causes are allergic and infectious diseases, autoimmune disorders, hereditary factors, hypoxia of various origins, atherosclerosis, and arterial hypertension.

1) Mucoid swelling is a superficial and reversible disorganization of the connective tissue. The process arises as a result of an increase in the amount and redistribution of mucopolysaccharides, predominantly glycosaminoglycans in the main substance of the connective tissue due to an increase in vascular permeability against the background of immune or other mechanisms of damage. Glycosaminoglycans have pronounced hydrophilic properties, which, against the background of increased vascular tissue permeability, leads to pronounced hydration (swelling) of the main substance of the connective tissue. At the same time, the concentration of proteoglycans and, to a lesser extent, glycoproteins increase. Most often mucoid edema develops on the walls of arteries, endo- and epicardium, heart valves, and joint capsules.

Macroscopic features: organ or tissue is usually not changed.

Microscopic features: collagen fibers usually retain bundle structure, but swell and loosen up. Swelling and increase in the volume of the basic substance lead to the fact that connective tissue cells move away from each other. When stained with hematoxylin and eosin, glycosaminoglycans have slightly basophilic coloration. When stained with toluidine blue, glycosaminoglycans are stained in a lilac or purple color that is different from the dye's own color (*phenomenon of metachromasia*) (microphotograph 6).

Consequences: Mucoid swelling is a process reversible. When eliminating a pathogenic factor there is a complete restoration of structure and function; if the influence of the pathogenic factor continues, mucoid swelling progresses into the second stage - fibrinoid swelling.

2) Fibrinoid swelling is a deep and irreversible disorganization of the connective tissue. More pronounced violations of vascular permeability and tissue swelling develop, and coarse proteins are released into the intercellular substance, including fibrinogen, which turns into fibrin. The process is accompanied by the formation of *fibrinoid* - a complex substance consisting of proteins, polysaccharides, disintegrating collagen fibers, and the main substance of connective tissue, as well as blood plasma proteins and nucleoproteins of destroyed connective tissue cells. An important component of fibrinoid is fibrin.

Macroscopic features: organs and tissues are slightly changed.

Microscopic features: collagens fibers become eosinophilic, homogeneous, PAS-positive, which indicates a significant increase in the number glycoproteins. Fibrin staining is positive. The phenomenon of metachromasia is absent. This is explained complete destruction of glycosaminoglycans.

According to the prevalence of the process, fibrinoid swelling is: *systemic* (with infectious diseases, autoimmune diseases, angioedema) and *local* (with chronic inflammation. For example, at the bottom of a chronic stomach ulcer).

Consequences: may progress to fibrinoid necrosis with complete destruction of connective tissue and scar formation (*fibrinoid sclerosis*). Otherwise, fibrinoid swelling can progress to hyalinosis.

3) Hyalinosis is a pathological process in which protein accumulates in the connective tissue with the formation of translucent, homogeneous compact masses. The tissue becomes dense, similar to hyaline cartilage. This process is based on the destruction of fibrous structures and an increase in vascular permeability (plasmorrhage), infiltration of connective tissue with blood plasma proteins, and the subsequent formation of a special protein - hyaline. *Hyaline* is a fibrillar protein composed of plasma proteins, fibrin, lipids, and components of immune complexes (immunoglobulins, complement fractions). It is PAS-positive, eosinophilic, and picrinophilic.

The following types of hyalinosis are distinguished: 1. vascular hyalinosis (general, local); 2. hyalinosis of connective tissue (general, local).

General (systemic) vascular hyalinosis occurs in diabetes mellitus (diabetic microangiopathy), hypertension, and rheumatic disease. Mainly, small arteries and arterioles are affected. General hyalinosis develops due to vasospasm. With a spasm of the vessel, the vessels that feed the vascular wall are compressed, which leads to the development of hypoxia, and vascular permeability increases. The vessel wall is impregnated with plasma proteins (plasmorrhage) and thickens. Subsequently, due to enzymatic reactions (precipitation and coagulation), a new protein, hyaline, is formed.

By the mechanism of development of vascular hyalinosis, there are types of vascular hyaline: 1) simple hyaline consisted of almost intact components of the blood plasma (more common in hypertension, atherosclerosis); 2) lipohyaline contains lipids and beta-lipoproteins (most often found in diabetes mellitus); 3) complex hyaline contains immune complexes (typical for diseases with immunopathological disorders, for example, in rheumatic diseases).

Macroscopic features: the vessels are vitreous, in the form of dense tubules with a narrowed or completely closed lumen. The most noticeable changes can be seen in the vessels of the brain, retina, pancreas, kidneys, and skin. The affected organs are atrophic, deformed, and wrinkled.

Microscopic features: hyaline is found in the subendothelial space as a homogeneous eosinophilic mass. The lumen of the arterioles is sharply narrowed or completely closed. The vessel wall is thickened. The middle layer of blood vessels becomes thinner. In the end, the arterioles turn into thickened vitreous tubes (microphotograph 7).

Local vascular hyalinosis is a physiological phenomenon observed in the spleen of adults and aged people, reflecting functional and morphological features of the spleen as an organ of blood deposition.

Consequences: in most cases, this is the unfavorable outcome, since the process is irreversible. Hyalinosis of small arteries and arterioles leads to deformation and wrinkling of the organ, and atrophy (for example, the development of arteriolosclerotic nephrocirrhosis, or primary contracted kidneys). Vascular fragility leads to the development of hemorrhages (for example, hemorrhagic stroke with hypertensive disease).

General (systemic) hyalinosis of connective tissue develops as a result of fibrinoid swelling. Destruction of collagen fibers and their impregnation with plasma proteins and polysaccharides. This developmental mechanism is characteristic of diseases with immune disorders (rheumatic diseases).

Local hyalinosis of connective tissue detected in old scars, vascular wall with atherosclerosis, in the bottom of a chronic gastric ulcer, in the appendix with chronic appendicitis, fibrous adhesions of serous cavities, when organizing infarcts, thrombus, healing of wounds, ulcers, in capsules, tumor stroma, etc. In these cases, hyalinosis is based on metabolic disorders of connective tissue.

Macroscopic features: fibrous connective tissue becomes whitish, translucent, and dense, resembling hyaline cartilage. Examples: «glazed» liver, «glazed» spleen, keloid (hyalinized) scar, callous ulcer (gastric or duodenal ulcer with hyalinosis at the bottom), hyalinosis of the heart valves. "Glazed" spleen is characterized by the unevenly thickened capsule, covered with glaze or icing of whitish-gray color.

Microscopic features: collagen bundles of connective tissue are swollen, and the fibers lose fibrillarity and merge into a homogeneous dense cartilaginous mass. The cellular component is compressed, leading to atrophy. The masses are highly eosinophilic, picrinophilic and PAS-positive.

Consequences: in most cases, hyalinosis is an unfavorable process. Outcomes and consequences are different depending on the prevalence and localization of hyalinosis. This often leads to organ atrophy and functional failure. Sometimes hyalinized tissue becomes slimy. However, resorption of hyaline masses is also

possible. For example, hyaline masses in scars can exfoliate and dissolve. Hyalinosis of the breast stroma can also undergo resorption in conditions of its hyperfunction.

4) Amyloidosis is stromal-vascular dysproteinosis, accompanied by a profound violation of protein metabolism, the synthesis of abnormal amyloid protein.

Amyloid is a complex glycoprotein consisting of components: F–component (fibrillar protein), P–component (plasma protein), immune complexes, hematogenous additives, and glycosaminoglycans. The proportion of protein is 96-98% of the total mass of amyloid. Amyloid is produced by special cells called amyloidoblasts. With different forms of amyloidosis, different cells can be transformed into amyloidoblasts. In generalized forms of amyloidosis, these are mainly macrophages, plasma, and myeloma cells (possibly fibroblasts, endothelial and reticular cells). In localized forms of amyloidosis, these are cells of the APUD system and keratinocytes.

In the first stage, the formation of plasma cells in the organs of the reticuloendothelial system takes place - the so-called plasmatization of lymph nodes, bone marrow, spleen, and liver. Plasma cells are transformed into cells - amyloidoblasts, which synthesize fibrillar protein. Kupffer cells of the liver, endotheliocytes, mesangial cells of a kidney, lymphocytes, fibroblasts, and reticular cells can act as amyloidoblasts. At the next stage, when the fibrillar protein accumulates in a sufficient amount, the formation of the «amyloid skeleton» occurs. Fibrillar protein is perceived by the body as foreign. In response to its appearance, an additional group of cells appears - amyloid clusters, which try to break down amyloid. The function of such cells can be performed by macrophages. For a long time, there is a struggle between the cells that form and absorb the fibrillar component, but it always ends with the “victory” of amyloid, because there is an immunological tolerance to the amyloid fibril protein in the tissues. Plasma proteins and polysaccharides attach to the fibrillar skeleton, which leads to the formation of an abnormal protein – amyloid (Figure 5.).

Amyloid is formed outside the cells and has a strong connection with the fibers of connective tissue. If amyloid accumulates on collagen fibers, it is called pericollagen amyloid. Affects myocardial stroma, adventitia of large vessels, muscle tissue, nerve fibers, and skin. If the deposition of amyloid occurs around the reticular fibers, it is called perireticular amyloid and is observed in the spleen, adrenal glands, and intestines.

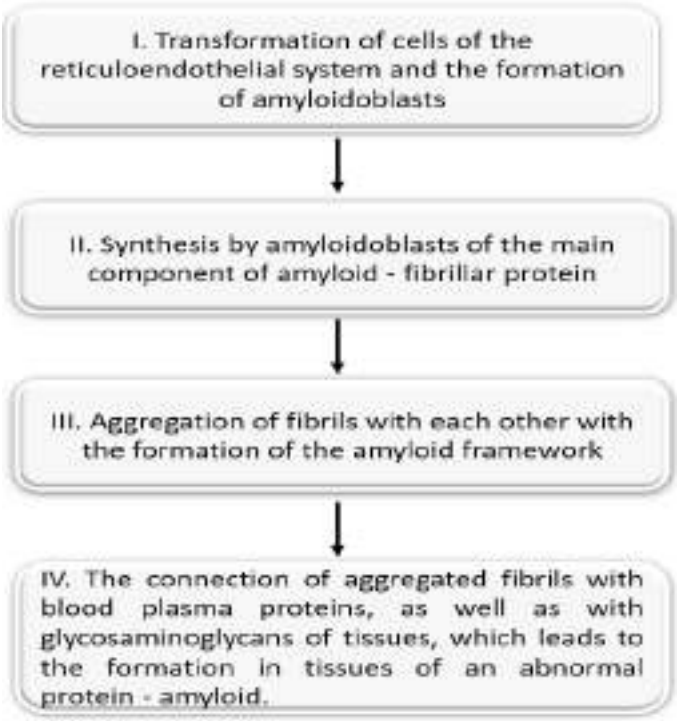


Figure. 5. Morphogenesis of amyloidosis.

Classification of amyloidosis:

According to the etiology: 1) primary (idiopathic) is a nosological form that develops without antecedent or concomitant disease; 2) secondary (reactive, acquired) occurs on the background of other diseases (e.g., suppurative destructive processes - osteomyelitis; chronic infections - tuberculosis; allergic and autoimmune diseases – rheumatoid arthritis; tumor processes); 3) hereditary (family, genetic) has a genetic predisposition (e.g., hereditary cardiopathic amyloidosis, nephropathic hereditary amyloidosis); 4) senile amyloidosis occurs in the elderly due to age-related metabolism disorders.

Depending on the clinical manifestations, the following forms are distinguished: neuropathic, cardiopathic, nephropathic, hepatopathic, mixed types of amyloidosis, and amyloidosis of APUD.

By the prevalence of the process: 1) generalized forms: primary, secondary, hereditary, senile amyloidosis; 2) local form: cerebral, cardiac, insular, senile, APUD-amyloid, etc.

According to biochemical verification of a specific fibrillar amyloid protein: AA - protein is represented by α-globulin, AL - protein consists of fragments of light chains of molecules immunoglobulins; AF - fibrillar component contains pre-albumin, AH - protein is represented by β2-microglobulin; AE - protein is composed of peptide hormone precursors (e.g. calcitonin); ASC1 - fibrillar component contains serum pre-albumin and transthyretin; Aβ - protein is represented by amyloid precursor protein.

Macroscopic features: if the amyloid deposits are small, the appearance of the organ changes little, and amyloidosis is diagnosed with a microscopic examination. With pronounced amyloidosis, the organs increase in volume, and pale, since amyloid is deposited under the vascular membrane, causing their narrowing, ischemia develops. Damaged tissue has a denser consistency compared to normal tissues. Blood vessels, those affected by amyloidosis cannot spasm and are prone to bleeding if damaged; the tissue is pale gray, on the cut-waxy («greasy») appearance.

The development of *spleen amyloidosis* occurs in two successive stages: stage 1 – «*sago spleen*» - accumulation of amyloid in the follicles of the spleen (white pulp). The follicles are enlarged, on a cut look like translucent grains. They look like sago grains, and such a spleen is called a sago spleen». Stage 2 – «*lardaceous spleen*» - amyloid diffusely spreads in the red pulp. The spleen increases in size, dense, smooth, brownish-red in section with a greasy sheen. This is called the «lardaceous spleen».

Amyloidosis of the kidney - "*lardaceous kidney*" (large, white, greasy kidney). The organ is enlarged in size, whitish in color, and of dense consistency, the border between the cortex and the medulla is not pronounced in the section.

Amyloidosis of the liver - "*lardaceous liver*" is large, dense, and light with a sebaceous shine on the cut.

Cardiac amyloidosis. The organ is enlarged (amyloid cardiomegaly), and dense, the myocardium has a greasy appearance.

Amyloidosis of the skeletal muscles - muscles become dense, and translucent.

Microscopic features: to determine amyloid, special staining “Congo red” is used, which stains the amyloid in a brick-red color.

Amyloidosis of the spleen: "*Sago spleen*" - amyloid is colored pink (H&E) or red (Congo red) color, and is located in follicles of the spleen on their periphery or in whole follicle; "*Lardaceous spleen*" - amyloid in the form of eosinophilic mass diffusely located in the intima of the arteries, the red pulp of the spleen along the reticular fibers displacing the spleen tissue. Lymphoid elements are reduced (microphotograph 8).

Amyloidosis of the kidney is characterized by the deposition of amyloid in the glomeruli, stroma, the walls of the input and output arterioles, in the capillary loops and mycangium’s of the glomeruli, under the basement membrane of the tubular epithelium. As the process progresses, the glomeruli are completely replaced by amyloid, and the connective tissue grows (amyloid wrinkling of the kidneys).

Amyloidosis of the liver - deposition of amyloid is observed among the reticuloendothelial cells of the sinusoids, along the reticular stroma of the lobules, in the walls of blood vessels, ducts, and in the connective tissue of the portal tracts. As amyloid accumulates, liver cells atrophy and die; hepatic failure develops. Central venous involvement may be accompanied by portal hypertension due to obstruction of venous outflow.

Cardiac amyloidosis - deposition of amyloid is under the endocardium, along the stroma fibers and vessels, as well as in the epicardium along the veins.

Amyloidosis of the skeletal muscles - amyloid is deposited along the intermuscular connective tissue, as well as perineural and perivascular, forming massive deposits of amyloid mass.

Consequences: amyloidosis is an irreversible process. The results and consequences depend on the location, and the degree of prevalence of amyloidosis. As a rule, this leads to the development of atrophy of the affected organ and functional failure.

II. Stromal-vascular fatty dystrophies (mesenchymal lipidoses) are characterized by a violation of the metabolism of neutral fats or cholesterol and its esters (with atherosclerosis). Neutral fats are labile fats that provide energy reserves for the body. In a free state, they localized in fat depots (subcutaneous, retroperitoneal, and mediastinal tissue, mesentery, omentum, epicardium, and bone marrow). Adipose tissue has a supportive, metabolic, and mechanical function. Violation metabolism of neutral fats and cholesterol manifests in an increase or decrease in their reserves. It can be local and general. (Figure 6.).

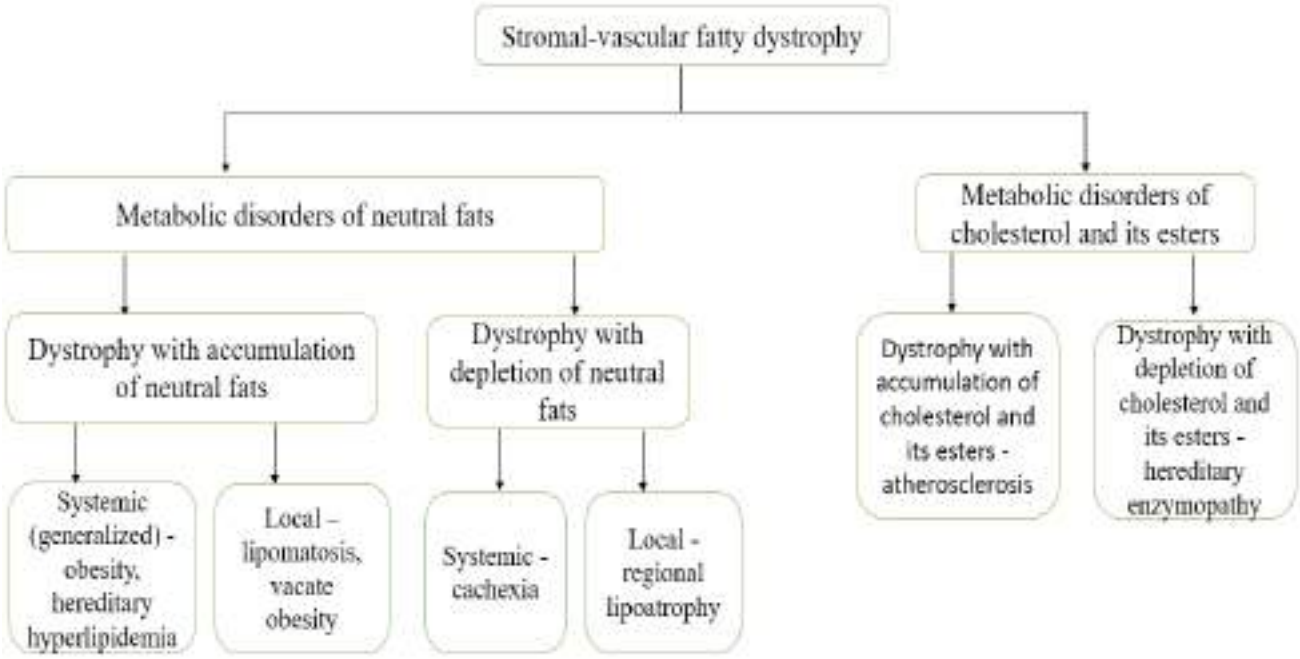


Figure. 6. Classification of stromal-vascular fatty dystrophy.

Systemic (generalized) accumulation of neutral fats - obesity is a pathological process characterized by an increase in the amount of neutral fats in the fat depots, which is of a general nature. It is expressed in excess fat deposition in the subcutaneous tissue, mesentery, omentum, epicardium, mediastinum. Adipose tissue also appears where it is usually absent or only present in small quantities (for example, in the pancreas, in the myocardial stroma).

According to the etiology, primary (idiopathic) and secondary obesity are distinguished. The cause of primary obesity is unknown. Secondary obesity is represented by the following types: 1) alimentary (e.g., physical inactivity, bulimia, or polyphagia); 2) cerebral (e.g., with neurotropic infections, trauma, brain tumors); 3) endocrine (e.g., Frohlich and Itsenko-Cushing's syndromes, hypogonadism, adiposogenital dystrophy, hypothyroidism); 4) hereditary (e.g., Laurence-Moon-Biedl syndrome and Gierke's disease).

By external manifestations, the following types of obesity are distinguished: 1) symmetric (universal) - fats are evenly deposited in different parts of the body and 2) asymmetric - uneven deposition of fat. The asymmetric type is divided into three subtypes: upper, middle, and lower. The upper type is characterized by the accumulation of fat mainly in the subcutaneous tissue of the face, occiput, neck, upper shoulder girdle, and mammary glands. The middle type is accompanied by the deposition of fat in the subcutaneous tissue of the abdominal in the form of an apron. With the lower type - in the area of the thighs and lower legs.

According to the level of increase in the patient's body weight, several degrees of obesity are distinguished. In the case of obesity of I st. degree, excess body weight is up to 30%, in case of II nd. degree - up to 50%, in case of III rd. degree - up to 99% and in case of IV th. - up to 100% or more.

The morphogenesis of obesity can be divided into two main types: hypertrophic and hyperplastic variants of general obesity. In the hypertrophic variant, the number of fat cells is not changed, but adipocytes are increased in volume and contain a large number of triglycerides. The clinical course of the disease is

malignant. In the hyperplastic variant, the number of adipocytes is increased. However, there are no metabolic changes and the function of adipocytes is not impaired; the course of the disease is benign. The most clinically important is obesity of the heart.

Macroscopic features: adipose tissue grows under the epicardium and between the muscle bundles, squeezing them. The size and weight of the heart increased due to the significantly increased in adipose tissue. These changes are more pronounced on the right side of the heart. The color is ocher-yellow, and the consistency is loose.

Microscopic features: significant deposition of adipose tissue under the epicardium, mainly along the vessels and between the muscle fibers. Cardiomyocytes are atrophied (microphotograph 9).

Consequences: obesity can be reversible. In unfavorable cases, this leads to atrophy of the organ and the development of its functional disorders. Complication such as rupture of the heart wall may develop.

Local accumulation of neutral fats – lipomatosis is an increase in the number of adipose tissues, which has a local character. For example, Dercum's disease - painful nodules of fat, similar to a lipoma, appear in the subcutaneous tissue of the limbs and trunk.

Local accumulation of neutral fats - vacate obesity is a local increase in the amount of adipose tissue on a background of organ atrophy (e.g., fatty replacement of the thymus with atrophy).

Systemic depletion of neutral fats - cachexia is an extreme depletion of the body, which is characterized by general weakness and sudden weight loss. The main causes are prolonged fasting or malabsorption (e.g., alimentary cachexia, exogenous cachexia); atrophy and/or necrosis of the hypothalamus and pituitary gland (e.g., hypothalamic-pituitary cachexia, Simmonds disease); anorexia nervosa; chronic infections (e.g., tuberculosis, HIV infection, purulent processes); burn disease; malignant tumors ("cancerous cachexia"); autoimmune diseases and others.

Macroscopic features: subcutaneous fat is significantly reduced or eliminated; the preserved adipose tissue is brown. Skin is wrinkled, flabby, and has an earthy gray color. Secondary lipofuscinosis can be seen (brown atrophy of the myocardium, kidneys, and liver). These organs are flabby, reduced in size, and brown in color.

Microscopic features: the number and size of fat cells decrease, as well as reduced amount of glycogen granules. Cell atrophy is accompanied by the accumulation of lipofuscin pigment in the form of gold or brown granules in the cytoplasm of cells.

Consequences: this can be a reversible process. It depends on the causative factor and the degree of cachexia.

Local depletion of neutral fats - regional lipoatrophy is characterized by the focal destruction of adipose tissue and the breakdown of fats with the development of an inflammatory reaction and the formation of lipogranulomas (e.g., Weber-Christian disease).

Metabolic disorders of cholesterol and its esters are the basis for the development of such a disease as atherosclerosis. With hypercholesterolemia, it penetrates from the blood into vascular intima. At the same time, cholesterol, its esters, low-density b-lipoproteins, and blood plasma proteins accumulate in the intima of the arteries. The accumulating high-molecular substances disintegrate and lead to intimal necrosis. As a result, fatty protein detritus forms in the intima, connective tissue grows, and a plaque form. Details of such disorders of fat metabolism are presented in the section «Cardiovascular diseases. Atherosclerosis».

A hereditary form of dystrophy that develops due to disturbance of cholesterol metabolism is familial hypercholesterolemic xanthomatosis. It is classified as a disease of accumulation. In this case, cholesterol is deposited in the valves of the heart, the walls of large vessels (atherosclerosis develops), the skin, and other organs.

III. Stromal-vascular carbohydrate dystrophies are pathological process, which is accompanied by a violation of the exchange of glycoproteins or glycosaminoglycans. There are two main types of stromal-vascular carbohydrate

dystrophy: 1) degeneration of stromal vessels associated with an imbalance of glycosaminoglycans (*mucopolysaccharidosis*) and 2) stromal vascular dystrophy associated with the imbalance of glycoproteins (*mucilagination of tissues*).

Stromal vascular dystrophy associated with a disturbance of glycosaminoglycan metabolism (*mucopolysaccharidosis*) is a group of genetic diseases (accumulation diseases), which are based on a deficiency of lysosomal enzymes that provide disintegration of mucopolysaccharides (glycosaminoglycans). In the absence of these enzymes, glycosaminoglycans accumulate in tissue lysosomes. Because the main localization of glycosaminoglycans in cartilage, ligaments, tendons, skin, blood vessels, heart valves, etc., the main disorders in different types of mucopolysaccharidosis are observed in organs such as liver, spleen, lymph nodes, red bone marrow, joints, cornea, vitreous, heart and blood vessels. Gargoylism syndrome has the greatest clinical significance.

Macroscopic features: Gargoylism is characterized by disproportionate growth, a deformed and massive skull ("massive skull"), a broad nose, a short neck, thick lips, a high palate, a unibrow, and a big tongue. Bone deformations: reduced and flattened vertebrae, mushroom-shaped intervertebral discs, curved tubular bones, and curved and serrated epiphyseal lines. Hepato- and splenomegaly, valvular damage and other defects.

Microscopic features: accumulation of mucopolysaccharides in phagocytes, endothelial cells, smooth muscle cells, and fibroblasts. The cells have a star shape, and increased in size with characteristic enlightenment in the cytoplasm due to numerous PAS-positive vacuoles. Affected tissue (cartilage, bone, connective tissue, and others) becomes swollen. Collagen fibers are replaced by a mucous mass.

Stromal vascular dystrophy is associated with the imbalance of glycoproteins (*mucilagination of tissues*) most often develops due to dysfunction of the endocrine glands, and depletion. For example, the development of mucosal edema (myxedema) in thyroid insufficiency. The mechanism of development is related to the destruction of proteoglycans and the release of glycosaminoglycans from them. In contrast to

mucoid swelling, collagen fibers are replaced by a mucous mass. In this case, fibrous, adipose, and cartilage tissues become translucent and swollen. Cells acquire a stellate shape, and collagen fibers are replaced with mucoid masses.

Consequences: the process can be reversible. It depends on the severity of the process, its duration, and the nature of the tissue undergoing dystrophy. Progression leads to colliquation tissue necrosis with the formation of cavities filled with mucus.

TEST YOURSELF

1. Mucoid swelling is not typical:

A. It develops in the cells of parenchymal organs

B. It develops in the stroma of organs, the walls of blood vessels

C. It often develops in rheumatic diseases

D. Reversible process

E. The phenomenon of metachromasia

2. Hyalinosis is characterized by:

A. It develops in the cells of parenchymal organs

B. It develops in the stroma of organs, the walls of blood vessels

C. Reversible process

D. The phenomenon of metachromasia

3. To refer to the amyloid lesion of the spleen, the term is used:

A. "Sago" spleen

B. Glazed spleen

C. Large variegated spleen

D. Septic spleen

4. To detect amyloid in organs and tissues, use:

A. Sudan III

B. Hematoxylin and eosin

C. Congo red

D. Impregnation with silver salts

5. To determine the phenomenon of metachromasia, use:

A. Hematoxylin-eosin

B. Toluidine blue;

C. Congo red

D. Sudan 3

6. Macroscopic view of organs and tissues with mucoid swelling:

A. Enlarged, flabby

B. Enlarged, dense

C. Reduced, flabby

D. Reduced, dense, fine-grained surface

E. Do not change visually

7. The fibrinoid swelling is based on the following connective tissue changes:

A. Edema

B. Accumulation of fat

C. Breakdown of connective tissue fibers

D. Accumulation of carbohydrates

8. Specify diseases in which fibrinoid swelling is systemic:

A. Infectious diseases

B. Rheumatic diseases

C. Obesity

D. Cachexia

9. Specify the changes in the kidneys, which are caused by common hyalinosis of arterioles:

A. Organ enlargement

B. Plethora

C. Shrinking and deformation of the organ

10. Name the diseases in which the development of cachexia is possible:

A. Atherosclerosis

B. Arterial hypertension

C. Rheumatic diseases

D. Malignant neoplasms

PART 4
MORPHOLOGY OF MIXED DYSTROPHIES

Mixed dystrophy is the dysmetabolic process of impaired metabolism in the parenchyma, as well as in the walls of blood vessels and the stroma of organs, which leads to a violation of the metabolism of complex proteins – chromoproteins (endogenous pigments), nucleoproteins, lipoproteins, and minerals. Mixed dystrophies can be both hereditary and acquired.

I. Chromoprotein (endogenous pigment) is a protein complex containing protein and pigment. Pigments contain different chemical structures and can be found normally or accumulate in pathological conditions. Pigments can be exogenous or endogenous. The most common exogenous pigment is coal dust, which enters the lungs when breathing the air. Particles of charcoal are phagocytosed by alveolar macrophages and transported to regional lymph nodes and lung tissue, where they are deposited as black inclusions (*anthracosis*). Coal dust also accumulates in the foci of pneumosclerosis. As a rule, an inflammatory reaction does not develop to coal dust, but with significant deposits, coal in combination with pneumosclerosis can cause a disease called *pneumoconiosis*. Also, sometimes there is pigment in the skin when used with certain drugs or cosmetic purposes, such as tattoos, use of mercury preparations, etc.

Endogenous pigmentation is usually associated with the excessive accumulation of pigments that are normally formed, or with the accumulation of pigments that arise only under pathological conditions. Endogenous pigments are subdivided into three groups, depending on the source of their formation: 1)

hemoglobinogenic (ferritin, hemosiderin, bilirubin, hematoidin, hematins, porphyrin); 2) proteinogenic (melanin, adrenochrome, pigment of granules of enterochromaffin cells); 3) lipidogenic (lipofuscin, lipochrome, ceroid) pigments.

1) Hemoglobinogenic pigments are a group of pigments, the formation of which is associated with the physiological and pathological destruction of erythrocytes, which include chromoprotein - hemoglobin. Pigments of this group can be found in the body in normal conditions (ferritin, hemosiderin, bilirubin) or in pathological conditions (hematoidin, hematins, porphyrins); some of them contain iron (ferritin, hemosiderin, hematins), others do not contain (bilirubin, hematoidin, porphyrins).

Ferritin is iron-containing peptide, which can be found in spleen, liver, bone marrow, and lymph nodes.

Hemosiderin is iron-containing pigment, formed mainly in macrophages of the spleen, liver, lymph nodes, and bone marrow, as well as in macrophages of almost any organ and tissue. These cells are called sideroblasts. If they die, the already synthesized pigment can be phagocytosed by other macrophages (siderophages). Hemosiderin is detected in cells when stained with hematoxylin and eosin in the form of amorphous, golden-yellow, or golden-brown grains. It is formed due to cleavage of the heme and is a polymer of ferritin in small quantities; specific stain - Perl’s reaction (blue color).

Bilirubin is a primary bile pigment formed by the metabolism of heme from biliverdin and does not contain iron. It is formed in the reticuloendothelial system during the physiological destruction of erythrocytes, enters the liver and there it is included in the bile formed by the hepatic cells. Bilirubin dissolves in bile and determines its characteristic color.

The most important are metabolic violations of hemosiderin – hemosiderosis and bilirubin – jaundice.

Hemosiderosis is an excessive deposition of hemosiderin in pathological conditions. There is general and local hemosiderosis. Local hemosiderosis occurs

with extravascular hemolysis of RBCs in the foci of hemorrhage (e.g., bruise) and with venous congestion (e.g., brown induration of the lungs). General hemosiderosis occurs due to intravascular hemolysis of RBCs (with blood diseases, poisoning with hemolytic poisons, infectious diseases, transfusion of incompatible blood groups and Rh incompatibility, etc.) or with increased absorption of iron from food. In these cases, hemosiderin is deposited in many organs and tissues, mainly in hepatocytes and macrophages of the liver, spleen, bone marrow, and other organs as well as in the extracellular space.

Macroscopic features: in the case of general hemosiderosis liver, spleen, and bone marrow have a rusty color, increase in size, and consistency become dense. In the case of local hemosiderosis, the hemorrhage area looks like rust colored area or cavity with walls of the same color.

In the foci of hemorrhage, the formation of hemosiderin occurs within 24–48 hours, then, after 7 days, it is transformed into *hematoidin* - bright yellow crystals. Hematoidin does not contain iron, and is located outside the cells, more often in the central part of the hemorrhage, where the oxygen concentration is minimal. According to this, the old hemorrhage foci change color from red to brown and then to yellow, due to the above-mentioned pigments.

Microscopic features: in the case of general hemosiderosis pigment is stored in the cytoplasm of stellate reticuloendothelial cells of the liver, macrophages in the spleen and bone marrow, and in epithelial cells as brown lumps. In the case of local hemosiderosis the pigment is detected in the cytoplasm of macrophages and extracellularly in the form of lumps at the zone of the former hemorrhage. In the Pearls reaction, these granules are bluish in color (microphotograph 10).

Jaundice is a condition caused by excessive accumulation of bilirubin in the blood plasma and tissues. According to the mechanisms of development of jaundice, there are three types of it: hemolytic; hepatic (parenchymal); obstructive (mechanical).

Hemolytic jaundice is a pathological condition caused by the accumulation of mainly indirect bilirubin because hepatocytes cannot provide conjugation of a dramatically increased level of bilirubin due to hemolysis. The amount of direct bilirubin is normal. Hemolytic jaundice occurs with intravascular hemolysis of erythrocytes. The main causes of hemolytic jaundice are the following: infection processes (sepsis, malaria), intoxications (hemolytic poisons), hemolytic anemia, leukemia, incompatible blood transfusion, Rh-conflict, autoimmune diseases, etc.

Macroscopic features: hemolytic jaundice is characterized by icteric staining of the sclera, skin, and mucous membranes with a lemon-yellow tint, hepatomegaly, splenomegaly, and systemic hemosiderosis.

Hepatic (parenchymal) jaundice is a pathological condition caused by the accumulation of both indirect and direct bilirubin. This jaundice occurs when hepatocytes are damaged, as a result of which the capture of bilirubin by them, its conjugation with glucuronic acid, and excretion are impaired. Such jaundice is observed with viral hepatitis, cirrhosis, toxic hepatic lesions, hereditary hepatosis, etc.

Macroscopic features: parenchymal jaundice is characterized by staining of the skin, sclera, mucous membranes with red-orange color, hepato- and splenomegaly.

Obstructive (mechanical) jaundice is a pathological condition caused by the accumulation of direct bilirubin due to impaired outflow of bile and its absorption into the blood. The lack of passage of bile into the intestines causes discoloration of feces due to low levels of stercobilin. This is due to obstruction and compression of the biliary tract: cholelithiasis, tumors of the liver, biliary tract, pancreatic head, parasitic invasions, and congenital malformations of the biliary tract.

Macroscopic features: obstructive jaundice is characterized by icteric staining of the sclera, skin, and mucous membranes with a greenish color with liver enlargement.

Microscopic features: with various types of jaundice, the accumulation of bilirubin is detected in the cells of various organs, the walls of blood vessels (for example, in neurons with bilirubin encephalopathy, in the epithelium of convoluted

tubules with icteric-necrotic nephrosis). With obstructive jaundice, the liver is necrotic, with foci of connective tissue and the development of liver cirrhosis (secondary biliary cirrhosis). The process becomes chronic. Bile ducts are dilated and may be ruptured. In the liver and Kupffer's cells, bile particles are found in the form of grains or lumps. With obstructive jaundice, degenerative changes and necrosis in the kidneys occur.

Hematoidin (see section «Hemosiderosis»).

Hematins are dark brown or black crystals or grains containing iron that form when hydrolysis of oxyhemoglobin. There are several types: malarial pigment (hemomelanin), hydrochloric hematin (hemin), and formalin pigment. *Malaria pigment (hemomelanin)* is a dark brown pigment formed from hemoglobin under the influence of malaria plasmodia parasitizing in erythrocytes. *Hematin hydrochloric acid (hemin)* is formed under the influence of hydrochloric acid on hemoglobin. It occurs with gastrointestinal bleeding. The mucous membrane becomes brown-black in color. *Formalin pigment* is a hematin derivative formed in histological preparations when they are fixed in acidic formalin. It looks like dark brown needles or granules.

Porphyrins are hemoglobin precursors, similar in structure to bilirubin. Violation of the exchange of porphyrins leads to the development of a disease - porphyria, which is characterized by dysfunction of the nervous system, and increased sensitivity to ultraviolet radiation. On open areas of the body, erythema, ulcers, atrophy, and depigmentation of the skin occur. Bones and teeth become brown. An increase in the content of pigments in the blood (porphyrinemia) and urine (porphyrinuria). There are two forms: acquired and congenital. The acquired form occurs with intoxication (lead, barbiturates), pernicious anemia, PP vitamin deficiencies, and some liver diseases. The hereditary form occurs when the synthesis of porphyrins is disturbed in erythroblasts (erythropoietic form) or liver cells (hepatic form).

2) Proteinogenic pigments are derivatives of tyrosine and tryptophan which include melanin, enterochromaffin cell pigment, and adrenochrome.

Melanin is a pigment of brown-black color, which is synthesized from tyrosine in the melanocytes. This pigment is found in the meninges, iris, retina, epidermis, dermis, and colon walls. There is a classification of melanin metabolism disorders: 1) according to the content of pigment: hypermelanosis and hypomelanosis; 2) according to the extent: local and systemic; 3) according to the origin: acquired and congenital.

Systemic acquired hypermelanosis (melanodermia) is manifested by skin hyperpigmentation. The main causes are vitamin deficiency (pellagra, scurvy), cachexia, hydrocarbon intoxication, endocrine disorders (hypogonadism, hypopituitarism, Itsenko-Cushing's disease), pathology of the adrenal gland of infectious or tumor nature (Addison's disease), adrenal amyloidosis.

Macroscopic features: with Addison's disease, the skin becomes bronze, dry, flaky, and dense to the touch.

Microscopic features: a large amount of melanin accumulates in melanocytes located in the basal layer of the epidermis and in the dermis.

Systemic congenital hyperpigmentation (xeroderma pigmentosum) is a hereditary disease characterized by an increase in the proliferation of melanocytes. The disease is associated with increased skin sensitivity to UV, an inflammatory reaction in the form of erythema in open areas of the body with the manifestation of pigmentation in the form of freckles. At the same time, photophobia, lacrimation, darkening, and ulceration of the cornea are observed.

Microscopic features: hyperkeratosis and edema of the dermis, a slight increase in the amount of melanin. At later stages, foci of atrophic changes, cracks, and ulcers appear in the skin. The foci of xeroderma pigmentosa are prone to malignancy and the development of a malignant tumor (melanoma).

Local hyperpigmentation (melanosis) is characterized by the development of local hyperpigmentation. The causes are: tumor nature (hereditary and acquired

melanocytic nevi, melanoma), endocrine disorders (pituitary adenomas, hyperthyroidism, ovarian tumors, during pregnancy), reactive nature (chronic dermatitis, melanosis of the colon with prolonged constipation), acanthosis black - is a nonspecific paraneoplastic process accompanied by the development of malignant tumors and characterized by thickening of the spinous layer of the epidermis and hyperpigmentation.

Systemic congenital hypomelanosis (albinism) is a hereditary absence of melanin pigment in the skin, hair, and iris. It occurs due to a genetically inherited lack of the tyrosinase enzyme. Therefore, people with this pathology have white skin, colorless hair, red iris, they have pronounced photophobia, blepharospasm, and skin burns during insolation. It may be complete or partial.

Local hereditary hypomelanosis (vitiligo) is depigmented areas of the skin due to the lack of melanin pigment. It occurs as a result of the action of certain chemicals, neuro-trophic (leprosy, syphilis), neuroendocrine (diabetes mellitus, hypoparathyroidism) factors, autoimmune disorders of melanogenesis (Hashimoto's goiter), after inflammatory and necrotic processes on the skin.

Local acquired hypomelanosis (leukoderma) is a pigmentation disorder, reflected in the disappearance of melanin pigment on separate skin areas. Most often it occurs during infectious processes (infection type) - in syphilis ("necklace of Venus"), leprosy; endocrine disorders (endocrine type) - at hypothyroidism, hyperparathyroidism, diabetes mellitus.

The pigment of the granules of enterochromaffin cells is a derivative of tryptophan and is found in the cells of the APUD-system. Pigment formation is associated with the synthesis of serotonin and melatonin. Elevated levels of this pigment can be seen in tumors from these cells (carcinoids).

Adrenochrome is a product of adrenaline oxidation. It is located in the form of small dark brown grains in the cells of the adrenal medulla. Found in pheochromocytoma cells.

3) Lipidogenic pigments are pigments containing lipids. Currently, lipopigments include lipofuscin, ceroid, and lipochromes. These pigments have practically the same histochemical and physicochemical properties. In morphology, they are distinguished by localization. Lipofuscin and lipochrome are formed in parenchymal and nerve cells. A ceroid is a lipopigment of mesenchymal cells, mainly macrophages.

Lipofuscin is a glycolipoprotein formed as a result of the destruction of the mitochondria and the cell nucleus. It is located in the cytoplasm of organ cells in the form of small yellow-brown grains. Lipofuscin metabolism disorders are usually associated with excessive accumulation - *lipofuscinosis*, which can be primary or secondary. Primary (hereditary) lipofuscinosis occurs in the cells of one organ or system. Often accompanied by damage to the nervous system and liver. Morphologically, in various parts and cells of the nervous system, excessive accumulation of lipofuscin, balloon dystrophy, destruction of nerve cells, and later - demyelination and destruction of axons are found (Spielmeyer-Sjögren's syndrome). Liver damage is characterized by the selective accumulation of lipofuscin in hepatocytes (hepatosis – Dubin-Johnson syndrome). The most common causes of secondary lipofuscinosis are: with aging ("aging pigment"), cachexia, chronic diseases of various nature, and lack of vitamin E. Morphologically when organs atrophy lipofuscin gives them a brown color (brown atrophy of the heart, spleen, liver, etc.).

Ceroid is a lipidogenic pigment produced by macrophages during lipid resorption. In pathological conditions, the formation of a ceroid is most often found in tissue necrosis, especially in areas of hemorrhage.

Lipochromes are lipid containing precursor of vitamin A (carotenoids). Accumulation of lipochromes can be observed at a sharp decrease in body mass due to condensation of lipochromes in adipose tissue, and diabetes due to metabolic disorders of lipids and vitamins. It gives a yellow color to adipose tissue, clusters of cholesterol, and other lipids.

II. Nucleoproteins are complex compounds of proteins and nucleic acids. Their decomposition is accompanied by the formation of the final product of nucleic acid metabolism - uric acid. Excessive formation and accumulation of uric acid and its salts leads to hyperuricemia (uric acid diathesis). There are main types: gout, urolithiasis, urate infarction.

Gout is a metabolic disorder characterized by urate deposition crystals in various tissues of the body. Based on the accumulation of urinary acid and a decrease in its excretion by the kidneys, which leads to an increase its concentration in the blood (hyperuricemia). There are two types here: primary and secondary gout. Primary gout is caused by congenital disorders of purine metabolism. Secondary gout is a complication: inhibition of the excretion of uric acid in the urine (renal failure of a different nature), an increase in the synthesis of uric acid (with increased destruction of tumor cells, autoimmune disease), endocrine diseases. The main manifestations of gout: acute and chronic gouty arthritis, to fuses of various localization, and gouty nephropathy.

Microscopic features: deposits of uric acid salts are found in the form of an amorphous mass or needles. Giant multinucleated cells are located around the urate deposits, granulation and fibrous connective tissue (fibrosis) grow, and areas of necrosis and inflammation are formed (microphotograph 11). In the kidneys, an accumulation of urate crystals with the development of pyelonephritis and atrophy (gouty kidney).

Consequences: gout is an irreversible process. The disease is significantly reducing the quality of life of patients, affecting primarily the musculoskeletal system (joint deformation) and urinary system (urolithiasis, renal failure).

Urolithiasis like gout, may be associated primarily with impaired purine metabolism, that is, be a manifestation of uric acid diathesis. In this case, urates are formed in the kidneys.

Urate infarction occurs in newborns who have lived for at least two days, and is associated with an intensive metabolism in the first days of a newborn's life and

reflects the adaptation of the kidneys to new conditions of existence. This is manifested by the deposition of amorphous masses in the tubules and collecting ducts of the kidneys. Macroscopically, they are visible in the form of yellow-red stripes at the papillae of the medulla of the kidney.

III. Lipoproteins are complexes of proteins and lipids. There are high-density lipoproteins (HDL), low-density (LDL), very low density (VLDL), and chylomicrons. Hyperlipidemia is an abnormally high level of lipoproteins in the blood. Violation of the exchange of LDL and VLDL leads to the development of atherosclerosis (section "Special pathomorphology").

IV. Mineral metabolism disorders include macroelements metabolism disorders (calcium, magnesium, potassium, sodium, etc.), microelement metabolic disorders (iron, copper, manganese, selenium, etc.) and the formation of stones.

Disorders of *calcium metabolism* are of great practical importance. Calcium is absorbed in the small and large intestines (90%) and in the kidneys. Metabolism is regulated by the parathyroid hormone (calcium resorption from bones and hypercalcemia) and thyroid hormone calcitonin (calcium deposition in bones and hypocalcemia). Violation of calcium metabolism in body tissues is called *calcification* (synonyms are: calcification, petrification, and calcareous degeneration). This is characterized by the precipitation of calcium salts from the dissolved state and their accumulation in cells or the intercellular substance. There are the following forms of calcification: metastatic, dystrophic, and metabolic.

Metastatic calcification occurs in normal tissues when the concentration of calcium in the blood increases (hypercalcemia). The main causes: 1) increased release of calcium salts from the depot with hyperproduction of parathyroid hormone (tumors or hyperplasia of the parathyroid glands), with a lack of calcitonin (thyroid disease); osteomalacia (multiple fractures, multiple myeloma, tuberculosis bones, tumor metastases, pregnancy pathology); 2) a decrease in the excretion of calcium salts from the body: damage to the large intestine (mercuric chloride poisoning, chronic dysentery); kidney disease (polycystic disease, chronic nephritis);

hypervitaminosis of vitamin D. Calcification most often occurs in the walls of the artery, alveolar septa of the lungs, in the gastric mucosa, in the myocardium of the left ventricle and the kidneys.

Dystrophic calcification is caused by the local disturbance of acid-alkaline balance. The calcium level in the blood does not change. It occurs in areas of necrosis (e.g., caseous necrosis in granulomas in tuberculosis and syphilis), hematomas, thrombi, exudates, etc.

Metabolic calcification is a calcification without concomitant development of hypercalcemia and local tissue changes. In this case, calcium is deposited in organs that produce acidic products (uric acid, CO2, etc.), and their tissues are more alkaline. These organs include the myocardium, arteries, lungs, stomach, and kidneys.

Macroscopic features: areas of calcification are whitish or gray in color, hard consistency (stony density).

Microscopic features: areas of calcification are basophilic when stained with hematoxylin and eosin (dark purple color). An inflammatory reaction, the formation of granulomas, is observed around calcium deposits, accumulations of macrophages, and giant cells.

Consequences: calcification is an irreversible process. In some cases, calcification is a sign of the healing of the pathological process, and in other cases, it is a complication (e.g., development of chronic renal failure with nephrocalcinosis, ischemia with extensive calcification of blood vessels, respiratory failure with damage to the pulmonary alveoli).

Stone formation is a pathological process characterized by the formation of concrements (stones) in the hollow organs (gallbladder, bladder), and in the ducts (urinary tract, bile ducts, pancreatic ducts, and salivary glands). Less commonly, concrements form in the lumen of the veins (phlebolitis), bronchi, or in large intestine (coprolites). *Concrements (stones)* are dense formations formed from the components of the secretion or excretion of organs. The causes of stone formation are varied and are determined by both general and local factors. General factors include metabolic

disorders (cholesterol, nucleoproteins, obesity, atherosclerosis, gout). Local factors include secretion disorders, secretion stagnation, and inflammatory processes in organs. Classification of stones: 1) according to the chemical composition: gallstones (cholesterol, pigment, calcareous, combined), urinary stones (urate, phosphates, oxalates, cystine, xanthine, combined); 2) according to the shape: round, dendritic, cylindrical, faceted; 3) according to the number: single, multiple; 4) according to the size: macrolites, microlites; 5) according to the surface: with smooth surface, with a rough surface.

Consequences: stone formation can lead to the development of obstructive syndrome (hydronephrosis, jaundice), inflammation (cystitis, cholecystitis), necrosis of the organ wall, followed by ulceration or perforation, adhesions, and fistula formation.

TEST YOURSELF

1. Specify the hemoglobinogenic pigment normally formed:

A. Hematoidin

B. Hematin

C. Hemosiderin

D. Porphyrin

2. Specify the hemoglobinogenic pigment formed in pathology:

A. Hematoidin

B. Ferritin

C. Hemosiderin

D. Bilirubin

3. Specify hemoglobinogenic pigments containing iron:

A. Hematoidin, ferritin

B. Ferritin, hemosiderin

C. Hemosiderin, bilirubin

D. Bilirubin, porphyrin

4. Specify hemoglobinogenic pigments that do not contain iron:

A. Bilirubin, hematoidin

B. Ferritin, hemosiderin

C. Hemosiderin, bilirubin

D. Bilirubin, hydrochloric acid hematin

5. The Perl’s reaction is used to detect:

A. Bilirubin

B. Ferritin

C. Hematoidin

D. Porphyrin

6. What is the cause of general hemosiderosis:

A. Intravascular hemolysis

B. Extravascular hemolysis

C. Impaired outflow of bile

D. Impaired outflow of urine

7. Macroscopic expression of lung hemosiderosis:

A. Rubber lung

B. Brown induration of the lungs

C. Honeycomb lung

D. Cystic lung

8. Name the pigment that provides bronze skin color in Addison's disease:

A. Bilirubin

B. Lipochrome

C. Melanin

D. Biliverdin

9. With brown atrophy of the parenchymal organ, one of the following pigments accumulates:

A. Hemosiderin

B. Lipofuscin

C. Melanin

D. Hematoidin

10. The level of calcium in the blood with metastatic calcification:

A. Not changed

B. Decreased

C. Increased

PART 5
CELL DEATH: CAUSES, MECHANISMS, TYPES OF IRREVERSIBLE DAMAGE. NECROSIS. APOPTOSIS

Necrosis is the death of a cell that occurs in a living organism as a result of the action of damaging factors. This type of cell death is not genetically controlled. The classification of necrosis is based on the stage of the process, the characteristics of its occurrence, prevalence (focal, total), clinical manifestations, and other factors.

According to etiology, there are the following types of necrosis: 1) traumatic necrosis occurs because of the effect of physical (low and high temperatures, radiation, electricity) and chemical (acids, alkalis, heavy metal salts, enzymes, drugs, ethyl alcohol) factors; 2) toxic necrosis (viruses, bacteria, protozoa); 3) allergic necrosis (endo- and exoantigens); 4) vascular necrosis (infarction); 5) trophoneurotic necrosis (non-healing ulcers, bedsores).

According to the mechanism of action of the pathogenic factors, there are: 1) direct necrosis occurs due to the direct action of the factor (e.g., toxic and traumatic necrosis); 2) indirect necrosis occurs indirectly through the vascular and neuro-endocrine system (e.g., vascular, trophoneurotic and allergic necrosis).

According to morphogenesis of necrosis, there are three successive stages: 1) paranecrosis is similar to necrotic, but reversible changes; 2) necrobiosis is irreversible dystrophic changes characterized by the predominance of catabolic

reactions over anabolic processes; 3) autolysis is the decomposition of a dead substrate under the action of hydrolytic enzymes of dead cells and cells of the inflammatory infiltrate.

To determine cell death, general morphological criteria are used.

Macroscopic features: depend on the necrotizing organ and the nature of the damaging factor. All forms of necrosis are characterized by a change in the color and consistency of the affected tissue. Color changes are due to the appearance of blood impurities. Changes in consistency are due to the development of coagulation and mummification or liquefaction.

Microscopic features: occur in the nucleus, the cytoplasm of cells, and the stroma of the organ. The following successive stages occur in the nucleus: 1) karyopycnosis – shrinking of the nucleus; 2) karyorrhexis – disintegration into fragments; 3) karyolysis – the dissolution of nuclear fragments under the action of hydrolases (ribonucleases and deoxyribonucleases). (Figure 7.). Three consecutive stages are also distinguished in the cytoplasm: 1) plasma coagulation - denaturation and coagulation of proteins in the cytoplasm of the cell; 2) plasmorrhexis – fragmentation of the cytoplasm; 3) plasmolysis – dissolution of cytoplasmic components. In the early stages, chromatin condensation is observed, then the cell swells with the destruction of cytoplasmic structures and subsequent lysis of the nucleus. Changes in the intercellular substance can be observed both in the interstitial substance and in the fibrous structures. Fibrinoid necrosis is most often observed: elastic, collagen and reticular fibers become dense, homogeneous pink or sometimes basophilic masses that can be subjected to fragmentation and disintegration. Edema, lysis, and mucilagination of fibrous structures can also be observed.

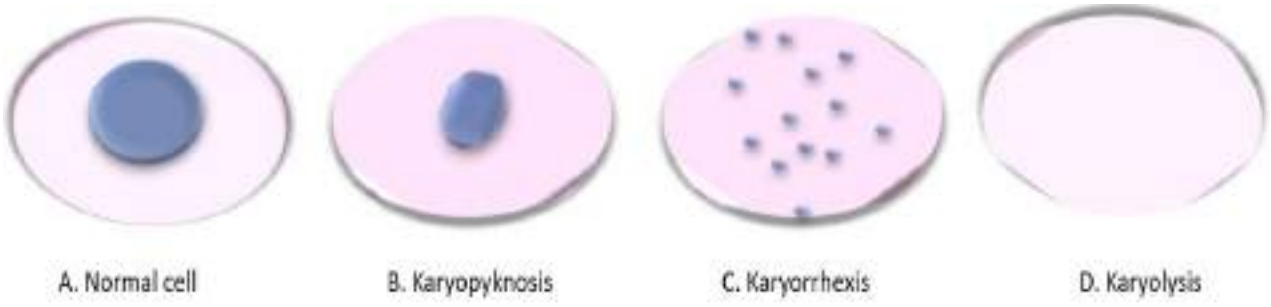


Figure. 7. Scheme of changes in cell nuclei during necrosis.

According to the functional and morphological characteristics of organs and tissues during the development of necrosis, its clinical and anatomical forms are distinguished: 1) coagulation (dry); 2) liquefactive (wet); 3) gangrene; 4) infarction; 5) sequestration, 6) bedsore.

I. Coagulation (dry) necrosis occurs in organs rich in protein and poor in fluid (e.g., myocardium, kidneys, adrenal glands, spleen). As a rule, it is the result of insufficient blood circulation and exposure to physical, chemical, and other damaging factors. With this type of necrosis, denaturation of both structural proteins and enzymes occurs, which blocks proteolysis of the cell (microphotograph 12). Special types of coagulation necrosis include waxy (Zenker's) necrosis, caseous (cheesy) necrosis, fibrinoid necrosis, and fat necrosis.

Waxy (Zenker's) necrosis is muscle necrosis, more often the anterior abdominal wall and thigh that can be seen in severe infections (cholera, typhoid fever). *Macroscopically:* the affected area is pale. The cut surface is dry and waxy, with the red foci of hemorrhages. *Microscopically*, muscle fibers are swollen and intensely stained with eosin. Sarcoplasm is presented by homogeneous lumps, which are located at some distance from each other. Fibers with ruptured sarcolemma or with complete disintegration into small lumps. Rapture of the vessels can also be observed (microphotograph 13).

Caseous (cheesy) necrosis develops in syphilis, tuberculosis, leprosy, and lymphogranulomatosis. *Macroscopically* characterized by dry, friable, limited areas of whitish-yellow color inside the internal organs. *Microscopically*, the picture is different depending on the type of pathogen. For example, in syphilis, a tissue site looks structureless, homogeneous, stained with hematoxylin and eosin pink, and lumps of nuclear chromatin (karyorrhexis) are clearly visible.

Fibrinoid necrosis is a type of connective tissue necrosis resulting from fibrinoid swelling. It is observed with allergic and autoimmune diseases (e.g., rheumatoid arthritis, rheumatism). Microscopically, it is characterized by the loss of

the normal structure of collagen fibers and the accumulation of homogeneous bright pink necrotic masses.

Fat necrosis includes two types: 1) enzymatic and 2) non-enzymatic necrosis. *Enzyme fat necrosis* is fatty necrosis that occurs in acute pancreatitis and pancreatic injury. In this case, lipase can enter the bloodstream with subsequent spread, which is the cause of fatty necrosis in many organs. Pancreatic lipase acts on triglycerides in fat cells, breaking them down into glycerol and fatty acids, which interact with plasma calcium ions to form calcium soaps. *Macroscopically*, opaque, white plaques and nodules (steatonecrosis) appear in the fatty tissue surrounding the pancreas. *Microscopically,* pancreatic tissue is present with pale color areas (steatonecrosis) surrounded with leukocytes. If the cells and their debris are not completely lysed, they undergo calcification (degenerative calcification).

Non-enzymatic fat necrosis is observed in the mammary gland, subcutaneous adipose tissue, and the abdominal cavity. Non-enzymatic fat necrosis is also referred to as traumatic fat necrosis, even if trauma is not identified as the underlying cause. *Microscopically,* non-enzymatic fatty necrosis elicits an inflammatory response characterized by the presence of numerous macrophages with foamy cytoplasm, neutrophils, and lymphocytes. The outcome is fibrosis.

II. Liquefactive (wet) necrosis is characterized by the malacia ("melting") of dead tissue. It develops in tissues with low protein content and a large amount of fluid, i.e., under conditions favorable for hydrolytic processes. Cell lysis occurs as a result of the action of its enzymes (autolysis). For example, liquefactive (wet) necrosis is gray softening (ischemic infarction) of the brain. *Macroscopically,* on the first day the affected area is bluish-soft, to the touch with unclear boundaries. By the end of the first day, the focus becomes clearer and turns pale. In the following days, the brain becomes even more flabby, yellowish in color. *Microscopically,* the brain tissue is homogeneous, structureless, and slightly pink when stained with hematoxylin and eosin.

III. Gangrene is a necrosis that develops in tissues, directly or through anatomical channels in contact with the external environment (limbs, lungs, intestines, skin of the cheeks, and other places). There are three types: dry, wet, and gas gangrenes.

Dry gangrene is necrosis of tissues in contact with the external environment, proceeding without the participation of microorganisms. With dry gangrene, necrosis is coagulative. This occurs on the limbs (for example, dry gangrene of the limb with thrombosis of its arteries, obliterating endarteritis, frostbite, and burns). *Macroscopically*, necrotic tissue is black, dry, clearly demarcated from viable tissue. *Microscopically,* demarcation inflammation occurs on the border with healthy tissues. The color change is due to the conversion of hemoglobinogenic pigments in the presence of hydrogen sulfide to iron sulfide.

Wet gangrene develops as a result of layering on necrotic tissue changes of a severe bacterial infection. Under the action of enzymes of microorganisms, secondary colliquation occurs. Wet gangrene usually develops in tissues that are rich in water. It can occur on the limbs, but more often in internal organs (intestines with obstruction of the mesenteric arteries - thrombosis, embolism, in the lungs as a complication of pneumonia - influenza, measles). Children weakened by an infectious disease may develop wet gangrene of the soft tissues of the cheeks, perineum, which is called noma. *Macroscopically,* the necrotic area becomes edematous and red-black, with extensive liquefaction of dead tissue. With wet gangrene, spreading necrotizing inflammation may occur that is not clearly delineated from healthy tissue.

Gas gangrene occurs when wounds are infected with anaerobic flora (e.g., Clostridium perfringens). It is characterized by extensive tissue necrosis and the formation of gases as a result of the enzymatic activity of the bacteria. Manifestations are similar to wet gangrene, but with the additional presence of gas in the tissues. Crepitus (cracking phenomenon on palpation) is a common clinical symptom in gas gangrene.

IV. Infarction is a tissue necrosis that occurs due to lack of blood circulation (e.g., thrombosis, embolism, prolonged spasm of the arteries, and functional overstrain of the organ under conditions of hypoxia). Distinguish infarction by shape and color. The shape of infarction depends on the angioarchitectonics of the organ and the development of collateral circulation and can be conical (regular) and irregularly shaped. The *conical shape* of infarction is characteristic of organs with poorly developed collaterals (lung, spleen, kidney). It appears as a result of obstruction of the lumen of the main artery. The base of the cone is located under the capsule, and the apex faces the hilum of the organ. *An irregular form* of an infarction occurs due to occlusion of an artery with a lot of anastomoses (brain, myocardium).

In color, infarction can be white (ischemic), white with a hemorrhagic rim (halo), and red (hemorrhagic). *White (ischemic) infarction* happens in areas with insufficient collateral circulation and violation of blood flow through the main vessel (e.g., brain, spleen). *Macroscopically*, the infarction area is white, cone-shaped, and somewhat dry and dense. *Microscopically*, the infarction zone is characterized by the presence of homogeneous pink masses with signs of karyolysis and karyorrhexis.

White infarction with a hemorrhagic rim is characterized by vasospasm that changed into their expansion and development of diapedesis hemorrhages on the border of dead and living tissues (e.g., myocardium). *Macroscopically*, the infarction zone at the kidney has an irregular shape, loose consistency, and yellowish-white in color, and is surrounded by a zone of diapedesis hemorrhages. *Microscopically*, the necrotic area is characterized by the presence of cells without nuclei. On the periphery of necrosis, there is a demarcation inflammation zone with a lot of blood vessels and infiltration of tissue with polymorphonuclear leukocytes, with hemolysis of erythrocytes and deposition of brown pigment (hemosiderin) (microphotograph 14).

Red (hemorrhagic) infarction usually occurs in case of chronic venous congestion (e.g., lungs, intestines). Blood from the pulmonary artery goes through the bronchial anastomoses to the necrosis area, resulting in the rupture of capillaries and

infiltration of necrotic tissues with blood. *Macroscopically,* the necrotic area in the lung is cone-shaped, dark red, and dense consistency. *Microscopically,* it is characterized by the destruction of interalveolar septa, lack of nuclei in the alveolar epithelium, infiltration with RBCs, and leukocytic infiltration around. leukocyte infiltration around. In healthy lung tissue, there are signs of emphysema (increased airiness).

V. Sequestration is an area of dead tissue, which is free among the living tissue, not subjected to autolysis and not replaced by connective tissue. As a rule, it occurs in the bones (e.g., with osteomyelitis); rarely found in soft tissues. It is accompanied by the development of purulent inflammation with the formation of a fistula through which fragments may be excreted.

VI. Bedsore is trophoneurotic necrosis of superficial parts of the body (skin, soft tissues) due to vascular compression and nerves between the bed and the bone. It often occurs in the area of the spinous processes of the sacral vertebrae, the greater trochanter of the femur, sacrum, etc.

Consequences: necrosis is an irreversible process. The outcomes of necrosis are associated with reactive changes - the processes of demarcation and repair. With *relatively favorable outcomes* of necrosis, the following are observed: organization (scarring) - replacement of necrotic masses with connective tissue; encapsulation - delimitation of the area of necrosis with a connective tissue capsule; petrification – impregnation of the area of necrosis with calcium salts (degenerative calcification); incrustation - impregnation of the area of necrosis with any other salts except calcium; hyalinosis - impregnation of the area of necrosis with hyaline protein; ossification - the substitution of the area of necrosis by bone tissue; cyst formation - resorption of tissue detritus with the formation of a cavity.

With *unfavorable outcomes of necrosis*, there is: purulent fusion – a purulent fusion of necrotic masses with the possible development of sepsis; sequestration is the formation of an area of dead tissue that does not undergo autolysis and is freely

located among living tissues; mummification - autoamputation of the ends of the fingers.

Apoptosis is a programmed cell death, in which internal or external factors, activating the genetic program, lead to cell death and its effective removal from the tissue. This mechanism of cell death has biochemical and morphological features. It is an important process for the body: elimination of cells in embryogenesis; involution of hormone-dependent organs after a decrease in the corresponding hormone in adults (age-related involution of the thymus, ovarian atrophy in menopause); atrophy of parenchymal organs due to obstruction of excretory ducts (parotid gland, pancreas); formation of Councilman's bodies in viral hepatitis, etc.

Morphogenesis of apoptosis proceeds in the following stages (Figure 8.): 1) decrease in cell volume; 2) condensation and fragmentation of nuclear chromatin and shrinking of cells with maintaining of the integrity of the organelles; 3) changes in the structure of the cell membrane, the formation of invaginations and membrane bodies with organelles and nuclear particles enclosed in them ("apoptotic bodies"); 4) destruction and phagocytosis of apoptotic bodies using lysosomes of surrounding cells.

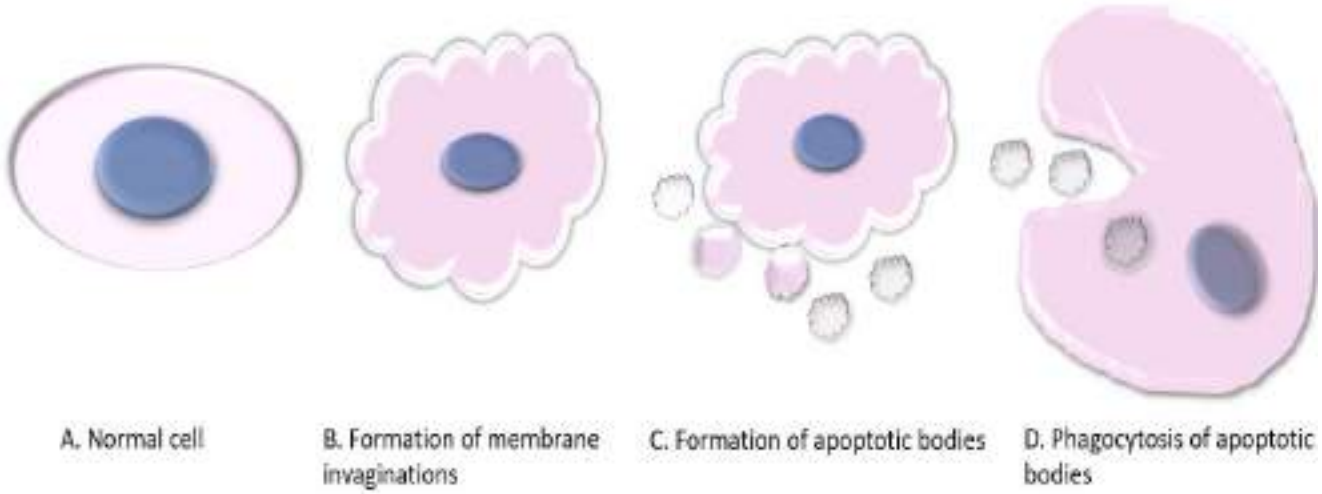


Figure. 8. Scheme of the mechanism of apoptosis.

The most important morphological features of apoptosis are: when stained with hematoxylin-eosin, apoptosis is determined in single cells or small groups of cells that look like round or oval clusters with eosinophilic cytoplasm and fragments of

nuclear chromatin; the preservation of the intracellular components in membrane structures, which allows eliminating cells without the development of inflammation.

TEST YOURSELF

1. Changes in the stroma of the organ with necrosis:

A. Ischemia

B. Hyalinosis

C. Amyloidosis

D. Fibrinoid necrosis

2. What is the typical localization of colliquation necrosis:

A. Bones

B. Connective tissue

C. Brain

D. Spleen

3. The type of necrosis that develops in the rectus abdominis muscles in acute infectious diseases:

A. Fatty

B. Waxy

C. Fibrinoid

D. Cheesy

4. Around the focus of necrosis in living tissues develops:

A. Autolysis

B. Encapsulation

C. Demarcation inflammation

D. Calcification

5. Definition of "autolysis":

A. Reversible dystrophic changes

B. Irreversible degenerative processes

C. Decomposition of the dead substrate by hydrolytic enzymes

6. In a bedridden patient with circulatory failure, immovable after a stroke, the skin and soft tissues above the sacrum turned black and swollen; after the epidermis had been rejected, ulcers opened in the black tissues. What process did the patient develop?

A. Phlegmon

B. Heart attack

C. Abscess

D. Dry gangrene

E. Bedsores

7. Microscopic examination of liver tissue revealed that some cells disintegrated into small fragments with separate organelles and remnants of the nucleus, surrounded by a membrane. There is no inflammatory response. Select the pathological process for which the described changes are characteristic.

A. Karyorrhexis

B. Plasmorrhexis

C. Necrosis

D. Plasmolysis

E. Apoptosis

8. Unfavorable outcome of necrosis

A. Petrification

B. Purulent fusion

C. Correct answer.

D. Ossification

E. Encapsulation

F. Organization

9. Disease accompanied by the development of caseous necrosis

A. Hypertonic disease

B. Tuberculosis

C. Atherosclerosis

D. Diphtheria

E. Syphilis

10. A type of necrosis that often develops in the bones

A. Heart attack

B. Bedsore

C. Sequestration

D. Gangrene

PART 6. DISORDERS OF BLOOD CIRCULATION: HYPEREMIA, ISCHEMIA, VENOUS CONGESTION, HEMORRHAGE, BLEEDING, SHOCK

Hemodynamic disorders are pathological processes that occur when the volume of blood in the bloodstream changes, its rheological properties, or the exit of blood outside the blood vessels. According to the prevalence and localization of the process, circulatory disorders are divided into local and general. Local disorders of blood and lymph circulation are caused by structural and functional damage to blood vessels in one organ, part of an organ, or part of the body (e.g., thrombosis, embolism). General disorders occur in the whole circulatory system and are associated with disturbances in the activity of the heart or changes in the volume and physicochemical properties of blood (e.g., general venous congestion; blood clotting). Blood filling disorders are manifested by: excessive blood supply (arterial hyperemia, venous hyperemia); insufficient blood supply (ischemia, anemia).

I. Arterial hyperemia is characterized by an increase in the blood supply to organs and tissues as a result of an increase in arterial blood flow. There are the following types: general and local, as well as physiological and pathological. The main causes of general arterial hyperemia: are decompression (total vacuum hyperemia), an increase in the volume of circulating blood (plethora), and an increase in the number of erythrocytes (erythremia). The causes of local physiological arterial

hyperemia are increased functional activity of an organ or tissue - «working» arterial hyperemia, local mechanical, physical, or chemical effects, and psycho-emotional stress.

The main causes of local pathological arterial hyperemia: are disturbances of vasomotor innervation, disturbances of tissue metabolism, inflammatory and allergic reactions, etc. Thus, there are main types of local pathological arterial hyperemia: 1) angioneurotic hyperemia (neuroparalytic) occurs due to stimulation of vasodilating nerves or vasoconstrictor paralysis nerves (e.g., infectious processes or trauma to sympathetic nodes); 2) collateral hyperemia occurs due to loss of blood supply through main arterial trunks (e.g., thrombosis, embolism, external compression). Then the blood is redistributed along collateral vessels; their lumens are reflexively expanded, and the flow of arterial blood increases; 3) decompression (vacate) hyperemia occurs with a rapid decrease in local barometric pressure. This hyperemia can be local (e.g., vascular thrombosis), as well as general (e.g., the rapid ascent of divers from a depth (decompression sickness); 4) hyperemia after ischemia (postischemic or postanemic) occurs after the rapid elimination of the factors compressing the artery (e.g., fluid in cavities, ligatures); 5) hyperemia due to arteriovenous fistula can be observed when pathological anastomoses (fistulas) form between an artery and a vein; 6) inflammatory hyperemia occurs due to inflammation. Vasoactive substances (e.g., histamine, prostaglandins, bradykinin, and others) act as direct effectors.

Macroscopic features: there is redness, increased tissue tension (turgor), and increased local tissue temperature.

Microscopic features: there is an increase in the number of functioning capillaries, and expansion of arterioles, arteries, and venules.

Consequences: can be divided into two types: favorable (activation of metabolism; states of increased functional activity of the cell; working hypertrophy of a tissue or organ due to prolonged, constantly repeated arterial hyperemia) and unfavorable (systemic hemodynamic disturbances with extensive arterial hyperemia

due to a decrease in peripheral resistance, increased vascular permeability and rupture of blood vessels with the formation of hemorrhages).

II. Venous hyperemia (congestion) is an increase in the blood supply to organs and tissues as a result of a decrease in blood outflow with unchanged or slightly reduced blood flow. It can be general and local, acute and chronic. The main causes of general venous hyperemia: are heart disorders (heart failure) (e.g., inflammatory heart diseases, cardiosclerosis, acquired or congenital heart defects, myocardial infarction); pulmonary diseases accompanied by the decreased volume of the pulmonary circulation (e.g., pneumoconiosis, emphysema, pulmonary fibrosis); damage of the pleura, diaphragm or chest, that accompanied by violation of the pump function of the chest (e.g., pneumothorax, deformities of the chest).

Local venous hyperemia occurs due to the disturbances of the blood outflow through the vein. Thus, there are the following types of local venous hyperemia: 1) obstructive venous congestion occurs due to the closing of the lumen of the vein by an embolus, thrombus, or inflammatory process (e.g., venous congestion of the lower extremities due to thrombophlebitis, cyanotic induration of the kidney due to thrombosis of the renal vein). It can be both acute and chronic; 2) compression venous congestion can occur due to acute or chronic compression of veins from the outside (e.g., ligature, tumor, swelling, or inflammatory exudate; 3) collateral venous congestion occurs due to difficulties in an outflow of blood through the venous trunk (e.g., portal hypertension).

Macroscopic features: with the syndrome of *acute venous congestion*, the volume and mass of the lung increase. The surface is smooth; there are depressions from the ribs. On the cut, the color of the lung tissue is variegated: dark red, cyanotic areas alternate with light pink areas of emphysema. Pink foam liquid drains from the cut surface. Areas of the lung sink in water.

With the syndrome of *chronic venous congestion*, the *skin* becomes cold to the touch and bluish (cyanosis). The veins of the skin and subcutaneous tissue are filled with blood and dilated. The *lungs (brown induration of the lungs)* become brownish;

the consistency is tightly elastic. The cut surface has a mesh pattern; there are a large number of thin whitish stripes evenly spaced over the surface. The *liver ("nutmeg liver")* is enlarged, and the consistency is dense with a thin capsule, a smooth and polished surface. The cut surface is a red and yellow mottled appearance. *Kidneys (cyanotic induration of the kidney)* enlarge and are dense with a smooth surface; the bark in the cut looks pale bluish, and the core looks dark bluish. The *spleen (cyanotic induration of the spleen)* enlarges and is dense with a smooth surface, and has a cyanotic (dark cherry) color.

Microscopic features: with the syndrome of *acute venous congestion*, there is severe venous congestion. Accumulation of the eosinophilic homogeneous serous fluid in the alveolar cavities and interstitial tissue of lungs. The alveoli's lumens are widened, and the walls are thinned due to compression. Exfoliated alveolocytes and RBCs in the lumen of the alveoli (microphotograph 15).

With the syndrome of *chronic venous congestion*, sclerosis of the vessels of the microvasculature, a decrease in their lumen and the number of capillaries. This is due to a violation of blood flow through the vessels of the microvasculature, and the development of tissue hypoxia, which leads to irreversible degenerative, atrophic, and sclerotic changes in the organs. For example, in the *liver ("nutmeg" liver)* the blood capillaries and central lobular veins are filled with blood and dilated. There are partially hemolyzed erythrocytes. Brown pigment hemosiderin is present in cells. Centrilobular hemorrhagic necrosis is possible. Hepatic laminae in the center of the lobules are thinned or absent. On the periphery of the lobule, fatty degeneration of hepatocytes is observed (microphotograph 16). In the *lungs (brown induration of the lungs)*, the interalveolar vessels are dilated. Many siderophages with hemosiderin in the lumen of the alveoli and the stroma of the lung. The alveoli are filled with serous fluid. The alveolar walls are sclerosed and thickened.

Consequences: in case of timely elimination of the causes, venous congestion is a reversible process. Otherwise, suppression of the metabolic processes in the congested tissues, which leads to a decrease in the functional activity of organs;

atrophy and sclerosis of organs occur, leading to functional failure of organs; due to the accumulation of large amounts of blood in capacitance vessels, which are dilated with extensive venous congestion.

III. Ischemia is a decrease or cessation of arterial blood flow to an organ, tissue, or part of the body. Depending on the causes, the following types of ischemia are distinguished: 1) angiospastic ischemia occurs due to spasm of the arteries due to the influence of various damaging agents; 2) obstructive ischemia occurs as a result of blockage of the lumen of the arteries (e.g., thrombosis or embolism of the arteries), as well as the growth of connective tissue in the lumen of the artery with inflammation of its wall (e.g., obliterating endarteritis) or narrowing of the lumen of the artery (e.g., atherosclerotic plaque); 3) compressive ischemia is observed as a result of compression of the artery (e.g., application of tourniquet, ligation of arteries during operations, compression by inflammatory exudate, tumor, scar or enlarged organ); 4) ischemia as a result of blood redistribution (e.g., cerebral ischemia after the rapid removal of ascitic fluid from the abdominal cavity).

Ischemia can be divided into general and local; acute and chronic. *Acute ischemia* is a complete sudden cessation of arterial blood flow to an organ or tissue (e.g., development of infarction). Details of such pathology are presented in the section "Necrosis. Infarction" and "Pathology of the cardiovascular system. Coronary heart disease". *Chronic ischemia* is a long-term gradual decrease in arterial blood flow. Tissue changes during ischemia depend on the duration of hypoxia and tissue sensitivity to hypoxia. In acute ischemia, the most pronounced changes are dystrophic and necrotic changes, and in chronic ischemia - atrophy of parenchymal and stromal sclerosis due to reduction in the collagen-synthesizing activity of fibroblasts, which are a reflection of the reaction to chronic hypoxia as compensatory and adaptive processes (e.g., development of diffuse cardiosclerosis and primary shrunken kidney - primary nephrosclerosis). Details of such pathology are presented in the section "Compensatory and adaptive processes".

Consequences: in case of timely elimination of the causes, ischemia is a reversible process. Otherwise, necrosis develops (with acute ischemia) or tissue atrophy (with chronic ischemia).

The outcome of ischemia depends on such factors: the severity of ischemia and its duration; the degree of collateral blood supply (the more developed the collateral vessels, the less severe the consequences of ischemia); the rate of occurrence of ischemia (the more sudden ischemia, the more severe the consequences, since there will not be enough time for the development of compensatory reactions and activation of collateral circulation); susceptibility to ischemia: due to the features of metabolism, some organs are extremely susceptible to ischemia (e.g., brain, myocardium) and other organs are less susceptible (e.g., skeletal muscles, bones, etc.); metabolic rate (the lower the metabolic rate, the less the effect of ischemia - hypothermia slows the rate of ischemic damage).

Vascular permeability disorders are pathological processes characterized by a change in the structure of the vascular wall (an increase or decrease of spaces between endothelial cells), which leads to an increase or decrease in the intensity of the transition of substances through the vascular wall. This occurs in many pathological conditions, for example, trauma, burns, inflammation, allergic reaction and, etc. There are two main types: bleeding and plasmorrhagia.

Bleeding (hemorrhage) is an exit of the blood from the lumen of the blood vessel or cavity of the heart into the environment - external bleeding (e.g., metrorrhagia - uterine bleeding, melena - intestinal bleeding), into the body cavity - internal bleeding (e.g., hemopericardium - into the pericardial cavity, hemothorax - into the pleural cavity, hemoperitoneum - into the abdominal cavity, hemarthrosis - into the joint cavity) or into the surrounding tissue – extravasation (e.g., hematoma - hemorrhage with loss of the integrity of tissues with the formation of cavities; hemorrhagic infiltration - hemorrhage with the preserved integrity of tissues; bruising (ecchymosis) - planar bleeding in the skin, subcutaneous tissue, and mucous membranes; petechiae - point-like hemorrhages in the skin, mucous and serous

membranes or internal organs). Depending on the source of bleeding, they are divided into arterial, venous, arterial-venous (mixed), capillary, parenchymal (capillary from parenchymal organs) and cardiac.

The mechanisms for the development of bleeding and hemorrhage include: 1) rupture (haemorragia per rhexis) resulting from trauma of vessel or necrosis (e.g., rupture of the heart in myocardial infarction), inflammation (e.g., rupture of the aorta in syphilitic mesaortitis), aneurysm of the affected vascular wall; 2) diabrosin (haemorrhagia per diabrosin) - arrosive bleeding develops when the vascular wall is destroyed by purulent inflammation, malignant tumor, necrosis (e.g., caseous necrosis in a bleeding tuberculous cavity), impact of chemical substances (e.g., gastric juice); 3) diapedesis (haemorrhagia per diapedesin) accompanied by the release of blood due to increased vascular permeability, while maintaining the integrity of the vascular wall (with severe hypoxia, intoxication, infection, various coagulopathies, hemorrhagic diathesis).

Microscopic features: the hemorrhagic focus contains clusters of RBCs around the vessel, which wall is damaged. RBCs in hematoma appeared as pale and partially lysed cells. About a day after hemorrhage macrophages loaded with hemosiderin (local hemosiderosis) can be seen on its periphery. In "old" hematomas growth of the granulation and fibrous tissue, calcium deposits, up to the formation of the bone can be seen (organization).

Consequences: depend on the type of bleeding, its severity and duration. It can be favorable - complete resorption of the extravasated blood and tissue repair, organization, encapsulation, petrification, ossification, incapsulation, the formation of a “rusty” cyst and unfavorable (suppuration when a secondary infection is attached). Significant bleeding can lead to acute ischemia, and hypovolemic shock. Prolonged bleeding from a small chronic gastric ulcer or duodenal ulcer leads to the development of chronic post-hemorrhagic anemia.

Plasmorrhagia is the exit from the lumen of the vessel of blood plasma with impregnation of surrounding tissues (plasma impregnation) due to increased vascular

permeability and changes of the blood composition. It leads to the accumulation of plasma components, damage to cells and intercellular substance in the vascular wall and perivascular tissue, which leads to hyalinosis or fibrinoid necrosis.

Microscopic features: The walls of the arterioles thicken and homogeneous. With a sharp increase of permeability in vascular development of fibrinoid necrosis is possible. Dilated blood vessels permeability is characterized by edema and thinning of the endothelial layer with the formation fenestra and wide tunnels, intercellular gaps that damage the basement membrane of the intimate membrane of the vessel.

Consequences: in the early stages and when the causative factors are eliminated, it can be a reversible process. In the other case, it leads to the development of pathological conditions such as extracellular protein degenerations, in particular - fibrinoid swelling and hyalinosis.

Shock is a severe pathological condition characterized by acute circulatory failure (circulatory collapse) after a superstrong effect on hemostasis. The main causes of shock are: decreased cardiac output due to blood loss or severe (left ventricular) heart failure; peripheral vasodilation (e.g., sepsis or severe trauma), accompanied by arterial hypotension. There are the following types: hypovolemic, cardiac, septic and vascular shock.

Hypovolemic shock is characterized by a rapid decrease in the volume of circulating blood by 20% and more; it occurs with acute blood loss, dehydration (e.g., extensive burns, severe vomiting, profuse diarrhea).

Cardiogenic shock is based on the decrease cardiac output with the rapid fall of the contractile function of the myocardium (e.g., infarction, myocarditis, acute mitral or aortic insufficiency, thrombosis of the valve, rupture of the interventricular septum).

Cardiovascular shock can be anaphylactic and neurogenic, and most often is associated with severe trauma (traumatic shock). Afferent triggers of neurogenic shock are pain impulses, resulting in reactive peripheral vasodilatation.

Septic (toxic-infectious) shock occurs in the presence of an infection caused by gram-negative (e.g., E. coli, Proteus, Klebsiella and others) or gram-positive (e.g., staphylococci, streptococci, pneumococci) microflora.

Shock has three stages in its development: 1) the non-progressive (early) stage is characterized by a decrease in blood pressure and cardiac output while maintaining a relatively normal volume of blood in the organs. It is due to compensatory vasoconstriction of blood vessels, primarily of the skin and intestines. With the depletion of the adaptive mechanisms, the shock passes into the next stage; 2) the progressive stage is characterized by pronounced clinical symptoms, deep collapse due to a decrease in blood circulation in all organs, the development of metabolic and circulatory disorders; 3) the irreversible stage is accompanied by severe circulatory failure with a violation of the integrity of the vascular wall, rapidly increasing multiple organ failure, ending with the death of the patient.

Microscopic features: generalized necrotic and dystrophic changes, disseminated intravascular coagulation (stasis, blood clots in the microvasculature) are found. In addition, due to the features of the structure and functioning of various organs, specific changes occur in each of them. Therefore, when describing shock, the term "shock organ" can be used.

Shock heart is observed small, mainly subendocardial foci of hemorrhage, myocardial necrosis, fatty degeneration of cardiomyocytes with symptoms. *Shock lung* is manifested by foci of atelectasis, serous hemorrhagic edema, sometimes with loss of fibrin filaments (hyaline membranes). *Shock kidney* is characterized by the development of necrosis of the epithelium of the convoluted tubules (necrotic nephrosis). *Shock liver* is characterized by fatty degeneration of hepatocytes and centrilobular necrosis. In the *brain* develops ischemic encephalopathy, manifested by edema, diapedesis hemorrhages and foci of necrosis. In the *adrenal cortex*, there is a decrease or disappearance of lipids used for the synthesis of steroid hormones. In the *gastrointestinal tract*, hemorrhages, erosion and acute ulcers in the mucous membrane are found.

Consequences: depends on its type, severity, stage at which treatment was started, the presence of complications. In severe cardiogenic or septic shock, mortality reaches 50% or more.

TEST YOURSELF

1. The accumulation of blood in the pericardial cavity is called:

A. Hemothorax

B. Hemangioma

C. Hemopericardium

D. Hydrothorax

E. Pericarditis

2. The accumulation of blood in the abdominal cavity is called:

A. Hemopericardium

B. Hemoperitoneum

C. Ascites

D. Peritonitis

3. Indicate the outcome of cerebral hemorrhage:

A. Rusty cyst formation

B. Scar formation

C. Inflammation

D. Hyalinosis

4. The main cause of venous hyperemia is:

A. Decreased blood flow

B. Difficulty in blood flow

C. Increased blood flow

D. Increased blood flow

5. When the "nutmeg" liver in the center of the lobule is observed:

A. Hemorrhage

B. Hyperemia

C. Atrophy of hepatocytes

D. The beginning of the proliferation of connective tissue

E. All of the above

6. An autopsy of the deceased, with a heart defect, revealed an enlarged liver of a variegated appearance, with a pattern of nutmeg on the cut. Name the type of circulatory disorder:

A. Anemia

B. General venous congestion

C. Hemorrhage

D. General arterial plethora

7. An autopsy of a 65-year-old patient who died of chronic heart failure due to rheumatic heart disease showed brown lungs, enlarged and compacted. What are these changes in the lungs called?

A. Nutmeg lungs

B. Chronic emphysema

C. Chronical bronchitis

D. Brown induration of the lungs

8. An elderly patient developed an acute disturbance of cerebral circulation from a coma and a fatal outcome. Autopsy revealed a large cavity filled with blood in the right hemisphere of the brain. What pathological process is found in the brain?

A. Brain tumor

B. Diapedesis hemorrhage

C. Hematoma

D. Hemorrhagic infiltration

9. A patient suffering from ischemic heart disease and having suffered repeated myocardial infarction died with symptoms of progressive cardiovascular failure. An autopsy revealed an enlarged dense spleen, dark

cherry in the section. Microscopic examination of the organ revealed pulp sclerosis and follicular atrophy. What is the term used to define these changes?

A. "Greasy" spleen

B. "Sago" spleen

C. Septic spleen

D. Cyanotic induration of the spleen

10. Bleeding by corroding the vessel wall develops when:

A. Purulent inflammation

B. Chronic venous stasis

C. Acute venous stasis

D. Hypertensive crisis

E. Mechanical injury

PART 7. DISORDERS OF BLOOD CIRCULATION: HEMOSTASIS, STASIS, THROMBOSIS, EMBOLIA, DIC-SYNDROME

Hemostasis is a biological system that ensures the preservation of the liquid state of the blood under normal conditions, and in case of violation of the integrity of the vessels, stopping bleeding. The normal state of blood in the vessels is maintained due to hemostasis, which reflects the interaction of four systems: coagulation, fibrinolysis, endothelial cells, and platelets. Rheological disorders of the blood (stasis, sludge phenomenon, thrombosis, embolism, disseminated intravascular coagulation) are the cause of many serious diseases.

Stasis is the stopping of blood flow in the vessels of the microvasculature. Stopping blood is usually preceded by its slowdown (pre-stasis). The causes of stasis are infections, intoxication, allergic and autoimmune diseases, shock, venous congestion, prolonged cardiopulmonary bypass, and exposure to chemical and physical factors (cold stasis with frostbite).

Microscopic features: dilated microvessels are filled with a homogeneous mass of erythrocytes, and stick together in the form of "rouleau" and polymorphic conglomerate. Hemolysis and blood clotting do not occur.

Consequences: acute stasis mostly results in reversible changes in the tissues, but in the brain, it contributes to the development of severe, sometimes fatal edema. In cases of prolonged stasis, multiple micronecrosis and diapedesis hemorrhages occur.

Stasis should be distinguished from the "sludge phenomenon".

Sludge phenomenon is the agglutination of blood cells, primarily erythrocytes, not only in capillaries but also in vessels of various calibers, including veins and arteries, which leads to significant hemodynamic disturbances - an increase in vascular permeability of capillaries and venules, edema, plasmorrhagia, and progressive ischemia. It is characterized by increased ESR. The local process, sludge develops in the pulmonary veins in such conditions as respiratory distress syndrome (acute respiratory insufficiency) and the "shock lung".

Consequences: stasis is a reversible process. The development of stasis in tissues with a low sensitivity to hypoxia can be resolved without any significant consequences. Prolonged stasis of the blood in the tissues with high oxygen consumption leads to hypoxia and necrosis of tissues, even when blood flow is restored. There are multiple hemorrhages by diapedesis and rupture of the microvessels.

Thrombosis is intravital blood coagulation in the lumen of the vessels or cavities of the heart, accompanied by the formation of a blood clot called *thrombus*.

There are general and local factors of thrombosis. Among the common factors, there is a violation of the ratio between the coagulation and anticoagulation systems of the blood, as well as a change in the quality of the blood - primarily its viscosity (e.g., multiple myeloma, hyperlipidemia in diabetes mellitus). Local factors include violation of the integrity of the vascular wall, slowing and changing blood flow. Predisposing factors increase the risk of thrombosis: prolonged bed rest after surgery,

pregnancy, chronic cardiovascular insufficiency (e.g., chronic total venous stasis), atherosclerosis, infectious processes, malignant neoplasms, acquired and congenital hypercoagulation, and other conditions.

The pathogenesis of thrombosis is based on *"Virchow's triad"*: 1) damage to the vascular wall (endothelium); it stimulates platelet adhesion and activation of the coagulation cascade. It is a significant factor in blood clotting in the arteries, and a less important factor in the formation of blood clots in the veins and microvasculature; 2) slowing and turbulent of blood flow (e.g., in the area of atheromatous plaques, a thrombus, erythrocyte aggregates, vessel aneurysms); 3) increase in the activity of the coagulation or decrease in the activity of the anticoagulant and fibrinolytic blood systems due to changes in the physical and chemical properties of blood (an increased blood viscosity, fibrinogen level and an increase in platelet count). It is a significant factor in venous thrombosis.

By the shape, the following types of thrombi are distinguished: spherical - located freely in the atrial cavity, elongated – formed in the vessel and takes its shape, «verrucose» – the formation of small blood clots resembling beads; it often occurs at the heart valve.

Due to the relation to the lumen of the vessel, there are: parietal thrombus - the lumen is free (most often white or mixed in structure); obstructive or occlusive thrombus - the lumen of the vessel is almost completely closed (usually red in structure); axial thrombus is located along the axis of the vessel or heart chamber.

Depending on the structure and appearance, there is white, red, mixed, and hyaline thrombus. *White thrombus* consists of platelets, fibrin, and leukocytes; it is formed slowly, with rapid blood flow, usually in the arteries, between the trabeculae of the endocardium, and on the heart valves in endocarditis. *Red thrombus* consists of platelets, fibrin, and erythrocytes; it occurs quickly in vessels with slow blood flow and therefore occurs usually in veins (Figure 9.). *Mixed thrombus* includes platelets, fibrin, erythrocytes, and leukocytes (microphotograph 17); is found in any part of the bloodstream, including heart cavities, and aneurysms. In this thrombus, the presence

of three parts is noted: 1. head (white thrombus in structure), 2. body (mixed thrombus), and 3. tail (red thrombus); it can detach and cause thromboembolism. *Hyaline thrombi* are usually multiple and form only in the vessels of the microvasculature (e.g., with shock, burn disease, severe trauma, DICs, dehydration, severe intoxication. etc.). They include precipitated plasma proteins and agglutinated blood cells, forming a homogeneous structureless mass with a positive histochemical reaction to fibrin.

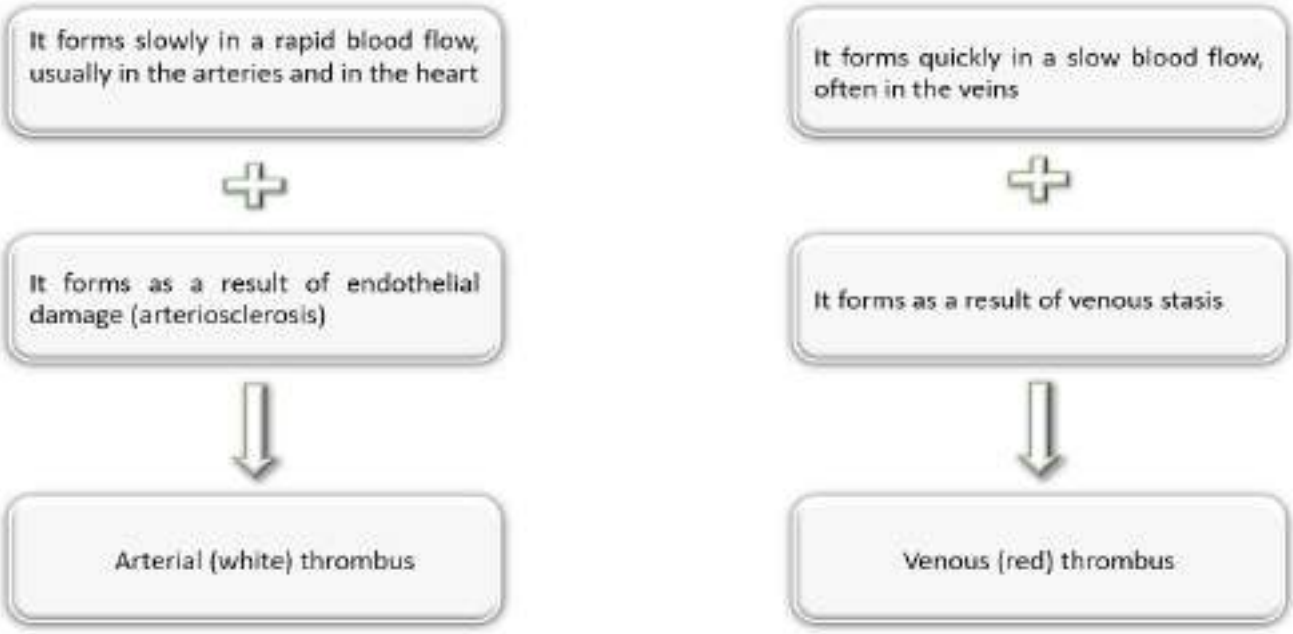


Figure. 9. Scheme of the formation of a white and red thrombus. Thrombus and the postmortem blood clot can be distinguished.

Macroscopic features: thrombus is dry, dense, crumbly, and rough and usually connected to the vascular wall; there are Zahn's lines (alternating layers of platelets and fibrin on the surface); may or may not correspond to the contours of the vessel. Postmortem clot is jelly-like, flexible, and soft; the surface is smooth, yellow, or red; it lies freely in the lumen of the vessel or heart chamber; it takes the form of the vessel.

Microscopic features: there is a clot in the lumen of the vessel, composed of fibrin in the form of pink thin fibers forming a loose mesh. There are some red blood cells and white blood cells among fibrin. Agglutinated and disintegrated platelets can

be seen as poorly stained grainy masses. Zahn's lines can be observed: the alternating lighter areas of fibrin and platelets and darker areas of erythrocyte clusters.

Consequences: thrombus outcomes can be divided into two groups: 1) favorable outcomes (relatively favorable): aseptic autolysis - complete resorption of the thrombus (with the restoration of local blood circulation); organization - replaced by the connective tissue; recanalization and vascularization - cracks can be formed within the thrombus, that looks like vascular channels lined with endothelium; calcification (petrification) deposition of calcium salts; 2) unfavorable outcomes: purulent (septic) autolysis - blood clot becomes infected with abscess formation and development of septicopyaemia; thrombus detachment with the development of thromboembolism.

Embolism is the circulation in the blood or lymph of particles (emboli) that are not found under normal conditions, followed by blockage of the lumen of the vessels.

In the direction of movement of emboli, there are 1) orthograde (direct) embolism - movement along the blood flow (e.g., from the venous system of the systemic circulation - embolism pulmonary arteries; from the left chambers of the heart or aorta - embolism of the arteries of the systemic circulation); 2) retrograde embolism – against the blood flow in the vena cava inferior (e.g., embolism by the foreign bodies due to their large mass, when the movement of the embolus is toward gravity, but against the blood flow); 3) paradoxical embolism – emboli come from the veins of the systemic circulation, but do not pass to the lungs and clog the arteries of the systemic circulation (e.g., acquired and hereditary defects of the heart).

By origin, types of embolism are possible: fat embolism, air embolism, gas embolism, cell (tissue) embolism, microbial embolism, embolism by foreign bodies, thromboembolism.

Fat embolism is embolism due to the circulating of fat particles. It occurs due to the following causes: fractures of long tubular bones, accompanied by extensive trauma and destruction of subcutaneous fat; surgeries; intravenous injections of fat-containing substances. Massive fat embolism leads to the obturation of small vessels

of the brain, lungs, kidneys, and other organs. Special staining of histological preparations shows the presence of fat droplets in the capillaries. A small amount of fat is resorbed and has a favorable prognosis.

Air embolism is embolism due to the presence of free air in the bloodstream. This is possible with open heart surgery; wounds of large veins of the neck and chest; the postpartum period; injections of air into a vein. Air emboli can pass through both the venous and arterial systems; determining the clinical and morphological picture. Most of the capillaries of the lung are obturated, but embolism of the vessels of other organs is detected - the brain, and the right parts of the heart; a foamy appearance is observed in the blood. Puncture of the right atrium under the water on autopsy allows the exit of air from its cavity.

Gas embolism is the appearance of gas in the bloodstream. It develops due to sudden changes in atmospheric pressure with the rapid rise from great depths under the water in divers, depressurization of the cabin of the aircraft at high altitude. The acute decline in pressure leads to the release of gas (nitrogen) dissolved at relatively high pressure in the blood; in this case, a lot of gas bubbles appear in the bloodstream ("foam"). Gas emboli in the systemic circulation affect various organs, including the brain and spinal cord, causing decompression sickness.

Cellular (tissue) embolism is the result of tissue destruction in diseases and injuries. An example of this is tumor cell embolism – metastases (microphotograph 18), amniotic fluid embolism, destroyed tissues of newborns due to severe birth injuries, tissue damage due to trauma or a disease that causes pulmonary vasospasm, heart failure, DIC.

Bacterial embolism is caused by circulating bacteria, fungi, animal parasites, or protozoa (e.g., alveococcus, echinococcus). This is noted with septicopyemia, purulent fusion of a thrombus, and leads to the development of multiple necrosis and metastatic abscesses.

Embolism by foreign bodies is observed when foreign fragments, medical catheters, syringe needles, bullets, and other bodies penetrate the injured large

vessels. It often leads to the development of a retrograde type of embolism due to the heavy mass of emboli. Also, this type of embolism includes calcifications and conglomerates of cholesterol crystals in atherosclerosis.

Thromboembolism is characterized by the detachment of the blood clot or its fragment and its transfer to the blood flow. It is the most common type of embolism. Its source can be blood clots of any localization - in the arteries, veins, and cavities of the heart. The most common localization of initial thrombi – veins of the systemic circulation (veins of the lower limbs). Such thromboembolism passes into the vessels of the pulmonary circulation, causing a life-threatening condition - pulmonary thromboembolism (PTE). A pulmonary embolism develops in sedentary patients (postoperative, suffering from cardiovascular diseases, malignant neoplasms, etc.). The effect depends on the size, quantity of emboli, pulmonary reaction, and thrombolytic activity. As a response, there is a reflex narrowing the lumen of blood vessels in the pulmonary circulation followed by increased pressure in the pulmonary arteries. In case of massive thromboembolism, the pulmonary-coronary reflex can be developed: the mechanical irritation of thrombotic masses of receptor endings on the intima of the pulmonary arteries leads to spasm of the coronary arteries and cardiac arrest, which is accompanied by the bronchial spasm with the development of the acute respiratory failure.

Macroscopic features: thromboembolus looks like a dense, dry, crumbly, brown mass not associated with the vascular wall. With thromboembolism of small and medium branches of the pulmonary artery, the volume of the lung is increased, and in the lumen of medium and small arteries on the cut surface there are multiple thromboemboli; there are foci of hemorrhages and hemorrhagic infarcts.

Microscopic features: thromboembolus are composed of two alternating layers (Zahn’s lines): 1. platelets and fibrin; 2. erythrocytes. In the lung tissue, edema, hemorrhagic infarcts, leukocyte infiltration, and atelectasis.

Disseminated intravascular coagulation (DIC) is characterized by the formation of multiple blood clots in the vessels of the microvasculature of various

organs and their resulting insufficiency, followed by the development of numerous hemorrhages. DIC is based on impaired coordination of blood coagulation and anticoagulant systems. Most often, DIC develops in shock of any genesis (e.g., traumatic, anaphylactic, hemorrhagic, cardiac, etc.), transfusion of incompatible blood, malignant tumors, extensive injuries, and surgical operations, severe intoxications and infections, in obstetric pathology (e.g., amniotic fluid embolism, premature detachment of the placenta, severe preeclampsia, etc.), autoimmune diseases, thermal and chemical burns, etc.

There are four clinical and morphological stages in the development of DIC: I stage – intravascular hypercoagulation and aggregation of blood cells, disseminated blood coagulation with the formation of multiple blood clots in the microvessels of organs; II stage - a significant determination of the content of platelets and fibrinogen spent on the formation of blood clots; III stage – hypocoagulation with activation of the fibrinolysis system, accompanied by lysis of previously formed microthrombi and damage to clotting factors circulating in the blood. There is the appearance of complete blood in coagulability - severe bleeding and hemorrhage, microangiopathic hemolytic anemia; IV stage - recovery, complications, and outcomes, characterized by dystrophic, necrotic, and hemorrhagic changes in organs. In most cases, restoration of tissue changes occurs, however, in severe cases of DIC, mortality is 50% due to acute multiple organ failure (e.g., renal, hepatic, adrenal, pulmonary, cardiac).

Macroscopic features: multiple hemorrhages in the skin and mucous membranes, mostly petechial, rarely extensive, combined in some cases with small necrotic foci caused by microthrombi. In the mucous membranes of the gastrointestinal tract, multiple small hemorrhages develop, as well as erosions and acute ulcers.

Microscopic features: the presence of multiple microthrombi in the microvasculature: fibrin thrombi (consisting of fibrin with erythrocytes), hyaline, white (leukocyte), red (erythrocyte). In addition, there are phenomena of stasis in

capillaries and venules, as well as hemorrhages, and necrotic and dystrophic changes in organs.

Consequences: with adequate treatment, the prognosis is favorable; with pronounced dystrophic and necrotic changes, the prognosis is unfavorable.

TEST YOURSELF

1. Define thrombosis:

A. Circulation of formed elements in the blood

B. Intravital blood coagulation in the cavities of the heart and the lumen of blood vessels

C. Postmortem blood clotting

D. Stopping blood flow

2. List the elements that make up a white blood clot:

A. Erythrocytes, fibrin, leukocytes

B. Plasma proteins

C. Platelets, leukocytes, fibrin

D. Fibrin, erythrocytes

E. Platelets, fibrin, erythrocytes

3. Indicate the elements that make up a red blood clot:

A. Plasma proteins

B. Erythrocytes, fibrin, platelets

C. Fibrin, leukocytes

D. Leukocytes, platelets, fibrin

E. Red blood cells

4. Give the definition of embolism:

A. Intravital blood clotting

B. Circulation in the blood of normally non-occurring particles and blockage of blood

vessels by them

C. The exit of blood from the vascular bed

D. Stopping blood flow

E. Postmortem blood clotting

5. Reasons for the development of fat embolism:

A. Tumors

B. Ulceration of an atherosclerotic plaque

C. Fractures of tubular bones

D. Burns

E. Increased consumption of fatty foods

6. The mechanism of death in thromboembolism of the pulmonary artery trunk:

A. Heartbreak

B. Cardiac arrest due to coronary pulmonary reflex

C. Acute venous congestion

D. Pulmonary edema

7. Name the factor that determines the form of a heart attack in the organs:

A. Organ shape

B. Thromboembolic size

C. Angio-architectonics

D. The functional state of the organ

E. The reactivity of the body

8. What blood clots are formed with a very slow current

blood in the vessels:

A. Red

B. Parietal

C. White

D. Hyaline

9. Name the parts of a mixed blood clot (several answers are possible):

A. Head

B. Abdomen

C. Body

D. Tail

E. Appendages

10. Favorable outcomes of thrombosis include:

A. Sepsis

B. Septic autolysis

C. Thromboembolism

D. Recanalization

PART 8. INFLAMMATION: CAUSES, MORPHOGENESIS. PATHOMORPHOLOGY OF EXUDATIVE INFLAMMATION

Inflammation is a complex response to injury, aimed at destroying the damaging factor and restoring damaged tissues, which is manifested by characteristic changes in the microvasculature and mesenchyme. The name of inflammation in tissues originates from the name of the organ in Latin or Greek and the suffix "itis". For example hepar, hepatitis – inflammation of the liver; gaster, gastritis – inflammation of the gastric mucosa. There are goals of inflammation: isolation of the damaging factor; destruction of the damaging factor; creation of optimal conditions for recovery.

Any damaging agent that exceeds the adaptive capacity of the body in strength and duration can cause inflammation. All factors are divided into exogenous and endogenous. Exogenous factors include biological factors (e.g., bacteria, viruses, fungi, protozoa, etc.); chemical factors (e.g., acids, drugs, toxins, poisons, alkalis, etc.); physical factors (cold, heat, X-ray, radioactive, ultraviolet rays); mechanical factors (e.g., foreign body, pressure). Endogenous factors include those that occur in the body as a result of another disease (e.g., reaction to a tumor, stones, or a blood

clot in the vessels. According to etiological factor, the following types of inflammation are distinguished: 1) specific inflammation is caused by certain pathogens and having characteristic morphological features (e.g., inflammation in tuberculosis, leprosy, syphilis, actinomycosis); 2) non-specific inflammation is caused by non-specific factors and does not have specific signs (e.g., staphylococcal and streptococcal infections, physical or chemical factors).

Depending on the reactivity of the body, the following types of inflammatory reactions are distinguished: 1) normergic inflammatory reaction - the intensity of inflammation adequately corresponds to the strength of the pathogenic factor; the result of this inflammatory reaction is healing, as it occurs under the influence of neutralization, suppression or complete elimination of harmful agents, excretion, absorption or isolation (encapsulation) of foreign bodies; 2) hyperergic inflammatory reaction - the intensity of inflammation exceeds the strength of the pathogen (e.g., allergic reactions). It is characterized by very severe and insufficiently harmful damage. Necrotic processes prevail over regenerative; 3) hypoergic inflammatory reaction - inadequately weak response to the harmful effects of the damaging agent; it is typical for people with reduced reactivity (e.g., ionizing radiation injury, anaerobic infections, physical overwork, starvation). This type of inflammatory response contributes to the development of progressive and generalized severe infection.

There are also 3 types of inflammation according to duration: 1) acute-inflammatory reaction, develops immediately after exposure to a damaging agent and is characterized by a predominance of an exudative tissue reaction, and completion of the process with the elimination of damaging factors and restoration of tissues (duration from 7 to 10 days); 2) subacute - characterized by duration between acute and chronic (duration up to 3 months); 2) chronic - long process (duration - 6 months or more) with tissue damage, reactive changes, and healing processes occur simultaneously, and periods of exacerbation are replaced by remissions.

Common clinical and morphological signs of inflammation: signs of inflammation: 1) rise of the temperature (fever) – calor, 2) redness of the

inflammatory focus – rubor. Fever and redness are associated with increased blood flow in the inflamed area; 3) swelling of the inflammatory focus – tumor. It occurs due to the accumulation of inflammatory fluid, 4) pain – dolor due to a variety of biologically active substances that irritate the damage of the nerve endings, 5) loss of functions – functio leasea is caused by a combination of these factors.

The pathogenesis of inflammation consists of three successive phases: 1) alteration, 2) exudation, 3) proliferation.

I. Alteration is the initial stage of inflammation, characterized by the excessive release of biologically active substances, lysosomal enzymes and a violation of the structure and function of the tissue. There are two types of alteration: primary and secondary. *Primary alteration* occurs in response to a direct effect of the inflammatory factor. The extent and nature of the alteration depend on the quality and intensity of the pathogenic factors and their localization, damage area, and resistance of the damaged structures and the whole body. *Secondary alteration* occurs under the influence of various pathogenetic factors both as the local (chemical and physical factors, amount and activity of inflammation mediators, vascular reactions, etc.) and systemic (humoral and nervous, including endocrine and immune reactions) changes.

II. Exudation is the exit of the liquid part of the blood, electrolytes, proteins, and cells from the vessels into the tissues. It occurs at different times after damage to cells and tissues under the influence of inflammatory mediators. In the mechanism of the exudation stage, two phases are distinguished: the first is *plasma exudation* associated with the expansion of the vessels of the microvasculature, increased blood flow to the focus of inflammation, which leads to an increase in hydrostatic pressure in the vessels, the release of plasma and its components from the vessels into the surrounding tissues; the second is *cell infiltration*, characterized by the marginal standing of leukocytes, monocytes, platelets, and other blood cells, followed by their migration into altered tissues.

III. Proliferation is the final stage of the inflammatory process characterized by anabolic processes, an increase in the number of stromal and parenchymal cells, as

well as the formation of an intercellular substance in the focus of inflammation. These processes are aimed at the regeneration or replacement of damaged tissue elements. During this period, the hyperemia of the inflamed tissue and the intensity of the emigration of blood cells, especially neutrophilic leukocytes, decrease. It occurs when a large number of macrophages enter the focus of inflammation and cleanse this aria by phagocytosis. They not only multiply in this zone but also secrete interleukins that attract fibroblasts and stimulate their reproduction, as well as the formation of blood vessels. The accumulation of cells in the focus of inflammation is called an inflammatory infiltrate. Detects cells of the immune system (e.g., T- and B-lymphocytes, plasma cells, and macrophages). The forms and degree of cell proliferation are different and are determined by the nature of cell populations. For example, cells of such organs as the liver, skin, gastrointestinal tract, and respiratory tract have a high proliferative capacity sufficient to eliminate structural defects in the focus of inflammation. In other organs, this ability is limited (e.g., tissues of tendons, cartilage, ligaments, kidneys, etc.). There are also organs and tissues whose parenchymal cells practically do not have proliferative activity (e.g., myocytes, neurons). Therefore, at the end of the inflammatory process in the tissues of the myocardium and the nervous system, the proliferation of stromal cells, mainly fibroblasts, occurs in the focus of inflammation, resulting in the formation of a connective tissue scar.

Basic morphological types of inflammation are determined by the predominance of one of the main components of inflammation in its dynamics: alterative inflammation, exudative inflammation, and proliferative (productive) inflammation.

Alterative inflammation is characterized by a pronounced lesion of the parenchyma of the organ. The vascular reaction is weakly expressed. The degree of damage is varied: dystrophy with a mild degree of damage or necrotic damage with more severe forms. *Consequences:* depend on the localization and severity of the process. Small lesions heal completely; in place of large foci, scar tissue is formed.

Exudative inflammation is characterized by the formation of exudate, the composition of which is determined by the cause of the inflammatory process and the corresponding reaction of the body to the damaging factor. The exudate is a muddy fluid enriched by proteins (more than 2%) and hematogenous cells and inflammatory nature histogens, which exits from small blood vessels in the site of inflammation. By the nature of the exudate, 7 types of exudative inflammation are distinguished: serous, fibrinous, purulent, putrid, hemorrhagic, catarrhal, and mixed.

1) Serous inflammation is characterized by the formation of fluid containing 1.7 to 2.0 g/L of protein and a small number of cells. The course of inflammation is acute. The main causes are thermal, chemical, infectious factors, the action of toxins and poisons, intoxication, etc. It is more often localized in the serous cavities (e.g., cardiac, abdominal, pleural), meninges, and stroma of the liver, myocardium, and kidneys. *Macroscopically,* serous exudate is a slightly hazy opalescent yellowish liquid. *Consequences:* serous inflammation is usually favorable - the exudate dissolves. Sometimes diffuse sclerosis develops in parenchymal organs (e.g., liver, kidneys, myocardium).

2) Fibrinous inflammation is characterized by the formation of an exudate containing a lot of fibrin. The course is acute and chronic. Etiological factors can be diphtheria corynebacterial, various coccal flora, Mycobacterium tuberculosis, some viruses, causative agents of dysentery, and exogenous and endogenous toxic factors. Serous and mucous membranes are affected more often, less often the stroma of organs. There are two types of inflammation: croupous and diphtheritic.

Croupous fibrinous inflammation is developed on serous and mucous membranes covered with a single-layered cylindrical epithelium (e.g., mucosa of the trachea, bronchi); characterized by the formation of a fibrinous gray-yellow film. The film is loosely connected to the surface of the necrotic mucosa or serous membrane. When the film is separated, a surface defect is detected.

Macroscopic features: the *fibrinous pericarditis* – epicardium is dull and covered with grayish-yellow rough masses in the form of strands ("shaggy heart").

Those masses can be easily removed. *Croupous laryngitis, tracheitis, bronchitis* - is characterized by a whitish-gray film on the surface of the mucous membrane of the larynx and trachea. The mucous membrane is thickened and swollen. The film is loosely adhered to the underlying tissues and can be easily detached; there is a defect on the place of the rejected film. *Croupous pneumonia* - affected lobe of the lung has increased density (like hepatic tissue); on the section, it looks gray and grainy (gray hepatization stage). There are fibrinous films that are easily detached on the pleura.

Microscopic features: the *fibrinous pericarditis* - the pericardium is thickened due to edema, congestion, and proliferation of cells. On the surface, there are fibrinous deposits. *Croupous laryngitis, tracheitis, bronchitis* - mucous membrane of organs is necrotized. Detritus and fibrinous exudate form a film (fibrinous-necrotic film) that covers the underlying tissues. Small vessels are hyperemic and dilated. *Croupous pneumonia* - exudate in the lumen of the alveoli, consisting of fibrin and leukocytes (gray hepatization stage).

Consequences: the *fibrinous pericarditis* - formation of adhesions between the layers of the pericardium (adhesive pericarditis) with the obliteration of the pericardial cavity. Sometimes sclerotic membranes become calcified or ossified ("stone heart"). *Croupous laryngitis, tracheitis, bronchitis* – superficial completely regenerating (healing) ulcers following detachment. However, easily separated fibrinous films can cause asphyxia due to mechanical obstruction of the upper airways ("true croup"), requiring emergency tracheostomy. *Croupous pneumonia* - organization of the intraalveolar fibrinous exudate (lung carnification).

Diphtheritic fibrinous inflammation is developed in the mucous membranes covered with stratified squamous epithelium. The fibrinous film of gray-yellow color is tightly soldered to the underlying tissues; it is difficult to separate, resulting in deep ulcers. Diphtheritic inflammation occurs in various types of pathology (e.g., bacteria: streptococci, staphylococci, bacilli - tuberculosis, diphtheria, etc., viruses, kidney failure (uremia), exogenous poisoning, and others).

Macroscopic features: for example, with *diphtheritic colitis* – intestinal wall is thickened; the mucous membrane gray, without folds due to the presence of a fibrinous film. Ulcerative defects may be visible in areas of film rejection.

Microscopic features: mucosa is partially necrotized. There is detritus and fibrinous exudate in the form of film-coated submucosa. The vessels are dilated and congested. There is a cell inflammatory infiltrate in the perivascular tissue. There are ulcers in areas of the film detachment.

Consequences: on the mucous membranes: small defects heal, scar tissue forms at the site of large defects with the possible development of stenosis. On serous membranes: fibrous adhesions are formed, which can lead to adhesive disease when localized in the abdominal cavity and intestinal obstruction. Due to the formation of ulcers, perforation of the intestinal wall and bleeding are possible.

3) Purulent inflammation is characterized by the formation of a purulent exudate containing a lot of polymorphonuclear leukocytes. The causes are most often pyogenic microorganisms (all types of coccyx infections), tuberculosis bacilli, fungi, etc.). Purulent exudate contains various proteolytic enzymes of leukocytes - neutral proteases (e.g., collagenase, elastase, cathepsin, and acid hydrolases). They can lyse dead and altered structures in the lesion, including collagen and elastic fibers, so tissue lysis is characteristic of purulent inflammation. It occurs in all tissues and all organs. Its course can be acute (occurs in the form of diffuse or limited inflammation) and chronic (occurs for a long time with the development of fibrosis around the purulent process). There are two main types of purulent inflammation: limited purulent inflammation (abscess, furuncle, and carbuncle) and diffuse purulent inflammation (phlegmon, cellulitis, and empyema).

Abscess is delimited purulent inflammation, accompanied by the formation of a cavity filled with a purulent exudate. Localization is different: skin, head, kidneys, liver, lungs, and other internal organs. The course of abscesses is: acute and chronic. An acute abscess is formed by a pyogenic membrane, through the vessels of which leukocytes enter the abscess cavity and partially remove decay products from it. A

chronic abscess is represented by a pyogenic membrane and the presence of a peripheral fibrous capsule and fistulas, through which pus periodically exits.

Macroscopic features: the cavity is filled with purulent yellow-green exudate.

Microscopic features: the abscess wall is covered with purulent fibrinous deposits and fragments of necrotic tissues. On the periphery of the abscess, there is a demarcation zone of inflammation, which is the basis of the formation of the pyogenic membrane. In the case of chronic abscess pyogenic membrane forms two layers: an inner one facing the cavity and consisting of granulation tissue and an outer one, which is formed by mature connective tissue (microphotograph 19).

Furuncle is a purulent inflammation of the hair follicle caused by pyogenic bacteria, especially Staphylococcus aureus.

Carbuncle is a purulent inflammation of a group of hair follicles and subcutaneous tissue; it tends to spread rapidly.

Phlegmon is purulent, unlimited diffuse inflammation, in which purulent exudate spreads through intermuscular spaces, fatty tissue, fascia, tendons. Phlegmon can be soft if lysis of necrotic tissues predominates, and hard when coagulative necrosis of tissues occurs in the phlegmon, which is gradually rejected. *Microscopically,* there are numerous neutrophilic granulocytes around the fibers of striated muscle and adipose cells. The decaying neutrophils form a purulent exudate (microphotograph 20).

Cellulitis is an acute diffuse purulent inflammation of the subcutaneous fat.

Empyema is a purulent inflammation of body cavities (e.g., pleural, abdominal, joints) or hollow organs (e.g., gallbladder, bladder, uterus).

Consequences: an abscess usually ends with spontaneous emptying and release of pus to the surface of the body, into hollow organs or cavities, after which the abscess cavity is scarred. Sometimes the abscess becomes encapsulated and the pus thickens. The healing of phlegmon begins with delimitation, followed by the formation of a rough scar. With an unfavorable course, purulent inflammation may spread to the blood and lymphatic vessels with possible bleeding and generalization

of infection with the development of sepsis. Prolonged chronic purulent inflammation often leads to the obliteration of hollow organs and the development of amyloidosis.

4) Putrid inflammation is developing when a putrefactive anaerobic infection (e.g., C. perfringens, C. novyi and C. septicum) enters the inflammation zone. Usually, it occurs in debilitated patients with extensive, long-term non-healing wounds or chronic abscesses. It is characterized by severe tissue necrosis with the formation of fetid gas.

Macroscopic features: wound edges are cyanotic; there is swelling of the subcutaneous adipose tissue. Subcutaneous adipose tissue is pale, and necrotic muscles are present. On palpation, there can be crepitating sound, and the wound has an unpleasant smell.

Microscopic features: progressive tissue necrosis predominates, without a tendency to delimitation. Neutrophils migrate into the inflammatory focus and die. The presence of a large number of WBCs is a favorable prognostic sign that indicates the decay of the process.

Consequences: with the use of antibiotics in combination with surgery, recovery is possible. An unfavorable outcome often develops due to massive destruction and reduction of body resistance. Necrotized tissues turn into fetid masses, which is accompanied by increasing intoxication, from which patients usually die.

5) Hemorrhagic inflammation is characterized by high permeability of the vessels of the microvasculature, and penetration into the exudate of erythrocytes. Usually, hemorrhagic inflammation develops with very high intoxication, accompanied by a sharp increase in vascular permeability (e.g., plague, anthrax, smallpox, severe forms of influenza).

Macroscopic features: for example, with hemorrhagic pneumonia, the mucous membrane of the large bronchi is edematous, with dark red spots - areas of hemorrhage. There are dark red lung lesions. Tissue in these foci is airless. With the

breakdown of red blood cells and the transformation of hemoglobin, the exudate may become black.

Microscopic features: interalveolar walls are thickened due to edema and moderate lymphohistiocytic infiltration. The exudate is visible in the lumen of the alveoli and contains many erythrocytes (hemorrhagic exudate), alveolar macrophages, and desquamated alveolocytes.

Consequences: the favorable outcome is possible with complete resorption of exudate.

6) Catarrhal inflammation is not an independent form; characterized by inflammation of the mucous membranes with the formation of mucus and admixture of mucus to any exudate. It can be caused by various infections, metabolic products, allergic reactions, thermal and chemical factors, etc. For example, in allergic rhinitis, mucus is mixed with serous exudate. The course of catarrhal inflammation is acute and chronic.

Macroscopic features: the mucous membrane is full-blooded and swollen; exudate drains from the mucous surface.

Microscopic features: the mucous membrane is edematous, infiltrated with leukocytes and plasma cells, vascular hyperemia; a lot of goblet cells of the mucous membrane. The exudate contains desquamated epithelial cells and some leukocytes.

Consequences: acute catarrhal inflammation lasts 2-3 weeks and, as a rule, ends with recovery. As a result of chronic catarrhal inflammation, atrophic or hypertrophic changes in the mucous membrane may develop. In this case, there is a violation of the function of the organ with the development of chronic gastritis, enteritis, colitis, bronchitis, pneumosclerosis and, etc.

7) Mixed inflammation is characterized by the presence of mixed exudate. It usually develops when a new infection joins in the course of inflammation or the reactive properties of the body change significantly. For example, serous-purulent inflammation, serous-fibrinous, purulent-fibrinous and others. *Morphologically,* it is

determined by a combination of morphological features characteristic of different types of exudative inflammation.

Consequences: often has an unfavorable outcome.

TEST YOURSELF

1. Phlegmon is:

A. Diffuse inflammation of cell spaces

B. Purulent muscle fusion

C. Limited accumulation of pus in tissues

D. A type of proliferative inflammation

2. The initial phase of inflammation is:

A. Exudation

B. Proliferation

C. Alteration

D. Phagocytosis

3. In purulent exudate, in contrast to serious, prevail:

A. Desquamated cells of the integumentary epithelium

B. Desquamated cells of the mesothelium

C. Neutrophils

D. Slime

E. Fibrin

4. Types of fibrinous inflammation:

A. Abscess, phlegmon

B. Phlegmon

C. Catarrhal, diphtheria

D. Diphtheria, croupous

E. Croupous, catarrhal

5. The type of fibrinous inflammation on the mucous membranes determines:

A. Number of vessels

B. Features of the organ stroma

C. Epithelium type

D. Stage of the disease

E. Type of pathogen

6. Localization of catarrhal inflammation:

A. Organ stroma

B. Serous membranes

C. Liver parenchyma

D. Mucous membranes

E. Organ capsule

7. What is the unfavorable outcome of purulent inflammation:

A. Organization

B. Petrification

C. Encapsulation

D. Generalization of infection

8. Name a symptom that is not typical for inflammation:

A. Temperature increase

B. Pale color

C. Increased organ volume

D. Pain

E. Functional impairment

F. Hyperemia

9. Name the type of inflammation depending on the etiology (several answers are possible):

A. Acute

B. Exudative

C. Chronic

D. Specific

E. Nonspecific

10. The most common outcome of fibrinous inflammation in the serous membranes:

A. Organization with the formation of adhesions

B. Empyema

C. Gangrene

D. Purulent fusion

E. Heart attack

PART 9. PATHOMORPHOLOGY OF PROLIFERATIVE INFLAMMATION

Proliferative (productive inflammation) is a process characterized by the predominance of the proliferation of cellular elements over alteration and exudation. Productive inflammation can be acute (in acute infectious diseases - typhoid fever, rabies, epidemic encephalitis, tularemia, brucellosis, etc.), but more often it is a chronic process. There are four main forms of productive inflammation: interstitial; granulomatous; hyperplastic growth as polyps and condylomas; inflammation around animal parasites and foreign bodies.

I. Interstitial proliferative inflammation is characterized by the predominant formation of diffuse-cellular growth in the stroma of the organ with less pronounced dystrophic and necrotic changes. This form of inflammation is caused by chronic viral infections, autoimmune processes, or long-term chemical intoxication. It can occur in all parenchymal organs and is localized in their stroma, where inflammatory cells accumulate. The most pronounced morphological changes of interstitial proliferative inflammation are observed in acute and chronic interstitial pneumonia, interstitial myocarditis, interstitial hepatitis, and interstitial nephritis.

Macroscopic features: the consistency of the organ is dense, the surface is smooth or granular, and gray-brown; on the cut surface – the diffuse proliferation of connective tissue.

Microscopic features: in acute inflammation, there is focal or diffuse inflammatory cell infiltration in the stroma of the lungs, myocardium, liver, and kidney; pronounced dystrophic and necrotic changes can be found in the parenchyma of the organs. In the chronic form – the diffuse proliferation of fibrous connective tissue (fibrosis) and sclerosis of the organ.

Consequences: the most common outcome of proliferative inflammation is sclerosis, accompanied by deformation of organs and damage to the parenchyma with the development of atrophy and wrinkling of organs (cirrhosis), which can lead to dysfunction of organs (e.g., liver cirrhosis, nephrocyrrhosis, etc.). With interstitial myocarditis, diffuse cardiosclerosis develops, leading to chronic heart failure. Interstitial lung disease often leads to interstitial pulmonary fibrosis with the formation of so-called "honeycombed" lungs and progressive cardiopulmonary failure.

II. Granulomatous proliferative inflammation is inflammation in which infectious focal accumulations (granulomas) and diffuse tissue infiltrates are formed. The predominant type of cells in the infiltrates are cells: macrophages, epithelioid cells, giant multinucleated cells of foreign bodies, and Pirogov-Langhans cells. Granulomas are sometimes called "nodules". Granulomatous inflammation is usually chronic (e.g., rheumatism, tularemia, tuberculous mycoses, syphilis, leprosy, etc.). However, it can also be acute (e.g., typhoid fever, typhus, and other infections). In the formation of granulomas, successive stages are distinguished: 1) the accumulation of monocytes in the focus of inflammation (from the bloodstream); 2) the maturation of monocytes and the formation of macrophages; 3) transformation of macrophages into epithelioid cells; 4) fusion of epithelioid cells with the formation of giant multinucleated cells of two types - giant multinucleated cells of the Pirogov-Langhans type and giant multinucleated cells of foreign bodies.

Epithelioid cells are large cells with a large pale oval nucleus and pale pink granular cytoplasm; do not form secondary lysosomes, which indicates a low phagocytic potential. At the same time, these cells have a well-developed rough endoplasmic reticulum and synthesize cytokines that stimulate sclerotic processes in tissues. They are called epithelioid because of some resemblance to epithelial cells.

Pirogov-Langhans giant cells are characterized by large sizes and the presence of a large number (up to 20) of nuclei on the cell periphery.

Giant cells of foreign bodies contain up to 30 nuclei located randomly, mainly in the center of the cell. Both types of giant cells have a small number of lysosomes, therefore, capturing pathogenic factors, giant cells are not able to completely digest them - phagocytosis is incomplete.

According to the predominance of the cellular composition, granulomas are divided into three types: macrophage granuloma, epithelioid cell granuloma, and giant cell granuloma.

Classification of granulomas by etiology: 1) infectious granulomas-granulomas (e.g., with typhus and typhoid fever, rabies, viral encephalitis, tuberculosis, leprosy, syphilis; 2) non-infectious granulomas develop when exposed to organic and inorganic dust (e.g., wool, asbestos; drug exposure). Classification of granulomas by pathogenesis: 1) immune granulomas develop as a result of a delayed-type hypersensitivity reaction (e.g., tuberculosis, leprosy, syphilis). Morphologically, they contain epithelioid cells or macrophages and contain Pirogov-Langhans giant cells, as well as an admixture of a large number of lymphocytes and plasma cells (at later stages, fibroblasts); 2) non-immune granulomas develop around foreign bodies, consisting of particles of inorganic dust, suture material. Morphologically, it consists of macrophages and giant multinucleated cells of foreign bodies. Compared to immune granulomas, the number of lymphocytes and plasma cells is minimal. According to morphology, two types are distinguished: 1) non-specific granulomas and 2) specific granulomas.

1. Non-specific granulomas do not have distinctive morphological features; for example, inflammation around foreign bodies and parasites of animal origin (e.g., echinococcus, alveococcus of the liver).

Macroscopic features: the liver is enlarged, and dense, and most of the liver is occupied by alveococcus. It is represented by a white dense node without clear boundaries; spreads through the vessels to the brain, lungs, and other organs, where the secondary nodes could be found.

Microscopic features: alveococcus cysts are surrounded by a chitinous membrane, intensely colored pink. Around - a zone of necrosis with granulomatous inflammation with the presence of giant cells of foreign bodies, fibroblasts, lymphocytes, plasma cells; a connective tissue capsule is formed outside.

Consequences: if the alveococcus dies, the cyst petrifies and has a stony density. With extensive damage to the organ, it leads to dysfunction of this organ.

2. Specific granulomas are inflammations in which the nature of the pathogen can be determined by its morphology, which causes this inflammation. For example, granulomas in tuberculosis, syphilis, leprosy, and rhinoscleroma.

Tuberculous granuloma (tuberculoma) is caused by Mycobacterium tuberculosis and is observed in pulmonary tuberculosis and other organs.

Macroscopic features: the lung is enlarged in size, from the surface (on the pleura) and on the section, numerous white-yellow tubercles are visible, of a dense consistency. The tubercles are submiliary in size up to 1 mm, miliary - 2-3 mm, and solitary - up to several cm in diameter.

Microscopic features: numerous granulomas are visible. In the center, there is a rounded zone of caseous necrosis, which occurs due to the direct action of secreted cytotoxic products of sensitized T-lymphocytes and macrophages, as well as the indirect action of these products that cause vasospasm. Around the focus of necrosis are activated macrophages (histiocytes) - epithelioid cells and giant multinucleated Pirogov-Langhans cells. Mycobacterium tuberculosis is found in the cytoplasm of epithelioid and giant cells when stained by Ziehl–Neelsen. The external layers of the

granuloma are represented by sensitized T-lymphocytes. There are no blood vessels in tuberculoma.

Consequences: a relatively favorable outcome for granulomas is the formation of a scar or hyaline changes, and for caseous necrosis - petrification. An unfavorable course leads to an increase in exudative-necrotic changes with the development of infiltrative and destructive forms of tuberculosis. It leads to pulmonary and respiratory failure and arrosive bleeding. The disease is complicated by the development of cachexia and secondary amyloidosis.

Syphilitic granuloma (gumma) is caused by Treponema pallidum observed in tertiary syphilis (an infection that occurs several years after invasion). Most often they are found in the skin and mucous membranes, in the liver, bones, testicles, etc.

Macroscopic features: there is a whitish-grayish node; on the section, there is a yellow jelly-like mass that looks like glue - gum Arabic (gumma means glue). Gummas can be single (solitary) or multiple. Their sizes range from 0.3-1.0 cm (on the skin) to the size of a chicken egg (in the internal organs). They are usually surrounded by scar tissue.

Microscopic features: there is a focus on caseous necrosis in the center, larger than with tuberculous granuloma. There are many lymphocytes, plasma cells, and fibroblasts along the periphery of the necrosis zone. Epithelioid cells, macrophages, and single Pirogov-Langhans giant cells can be found in small numbers in the gumma. A feature is the presence of a large number of small vessels with a narrowed lumen due to productive endovasculitis. Syphilitic granuloma is characterized by the rapid growth of connective tissue that forms capsules.

Consequences: scar formation; in the presence of multiple gummas, and rough deformation of the organ.

With tertiary syphilis, in addition to gumma, diffuse *granulomatous inflammation (gumma infiltrate)* may be observed with the formation of perivascular inflammation. It is an analogue of gumma, characterized by diffuse infiltration and the absence of caseous necrosis, which occurs in large vessels. This can lead to the

development of aortic mesaortitis; it often occurs in the ascending aorta and aortic arch.

Macroscopic features: the affected areas become wrinkled and rough with many small scar retractions that look like «shagreen skin». The elastic wall of the aorta becomes thinner, expands, and bulges like a bag (syphilitic aortic aneurysm). The destruction of the middle layer is caused by cellular infiltrates and vasculitis associated with productive inflammation of the own vessels of the aorta.

Microscopic features: gumma infiltrate consists of plasma cells, lymphocytes with an admixture of epithelioid cells, and fibroblasts mainly in the middle layer of the aorta; destruction of the elastic frame of the aorta. Areas of lysis of elastic fibers are replaced by connective tissue.

Consequences: aortic aneurysms can lead to atrophy from sternum and rib pressure.

Possible dissection and rupture of the aneurysm with fatal hemorrhage. In the aortic valves, a syphilitic aortic defect can form, more often in the form of aortic valve insufficiency. The spread of the infiltrate to the coronary arteries can lead to myocardial infarction.

Lepromatous granuloma (leproma) is caused by Mycobacterium leprosy and is observed mainly in the skin. Granulomas in leprosy have a different morphological structure depending on the form of the disease. There are several types of leprosy: 1) tuberculoid leprosy; 2) lepromatous leprosy.

1) Tuberculoid leprosy develops with the high resistance of the host organism. It is a clinically benign form and sometimes self-healing process under the condition of the expressed immune properties of the body.

Macroscopic features: diffuse skin lesions in the form of plaques and papules, with areas of depigmentation. Changes in the internal organs are not typical.

Microscopic features: there are diffuse infiltrates of polymorphic cellular composition: macrophages, epithelioid cells, giant cells, plasma cells, and fibroblasts.

Mycobacteria are rarely detected. It confirms the hypersensitive mechanism of the delayed type of leprosy development.

2) Lepromatous leprosy develops with a low resistance of the host organism. It is characterized by the development of diffuse granulomatous inflammation.

Macroscopic features: there are skin lesions of diffuse character with the damage of skin derivates - sebaceous and sweat glands, as well as blood vessels. Diffuse infiltration of the skin sometimes leads to deformation of the skin with complete disFigurement («lion face»).

Microscopic features: it is characterized by the presence of well-vascularized granulation tissue, forming nodules merging, consisting mainly of macrophages with a small amount, of plasma cells, and histiocytes. These patients have very low resistance and therefore no destruction of the bacilli occurs. Therefore, electron microscopy in macrophages detects a large number of viable mycobacteria, the arrangement is similar to a «pack of cigarettes». Macrophages become very large, and in them, there is a partial disintegration of bacilli, which stick together in the form of balls «leprosy balls» (Virchow cells), which are detected using Ziehl-Nilsson staining; fat vacuoles appear. With the death of macrophages, these "balls" are located freely in the tissue. Subsequently, they are phagocytosed by giant multinucleated Pirogov-Langhans giant cells. Accumulations of macrophages are surrounded by lymphocytic infiltration (microphotograph 21).

Consequences: with effective treatment, a complete cure is possible. Unfavorable outcomes are associated with tissue destruction with the formation of extensive areas of necrosis, and ulcers, up to autoamputation (mutilation) of body parts.

4) Granuloma with rhinoscleroma (scleroma) is caused by Klebsiella rhinoscleromatis observed in the mucosa and skin of the vestibule of the nasal cavity, nasopharynx, choanes, soft and hard palate, larynx, trachea, bronchi.

Macroscopic features: on the skin and mucous membranes diffuse or nodular soft consistency bright pink or dark red thickening, not prone to ulceration. Over time, this becomes cartilage density.

Microscopic features: characterized by granulation tissue with an accumulation of macrophages, lymphocytes, a large number of plasma cells, and their degradation products - eosinophilic Roussel bodies. Specific for granuloma scleroma are large macrophages with vacuolated light cytoplasm - Mikulicz cells. In the cytoplasm of these cells, gram-negative bacilli Klebsiella rhinoscleromatis (Frisch-Volkovich bacillus) are detected by Gram staining. There are also pronounced sclerosis and hyalinosis of the granulation tissue.

Consequences: the proliferation of granulomas leads to the narrowing of the airways, which leads to respiratory failure, and sometimes to asphyxia.

III. Hyperplastic growth as polyps and condylomas is a productive inflammation in the stroma of the mucous membranes, in which there is a proliferation of stromal cells and hyperplasia of the epithelium of the mucous membranes with the formation of polyps (e.g., polyposis rhinitis, polyposis uterus, polyposis colitis, etc.), as well as hyperplastic growths that occur on the border of the mucous membranes with a squamous or prismatic epithelium with the formation of condylomas (e.g., condylomas of rectum or external genitalia).

Hyperplastic growth as polyps is a polyetiological process.

Macroscopic features: papillary or fungiform exophytic outgrowth on the mucous membrane on the peduncle or the wide basis.

Microscopic features: growth of hyperplastic epithelium; peduncle is formed by the connective tissue with vessels. According to the histological structure, the following types of polyps are distinguished: fibrous type - the stromal component predominates, glandular type - the glandular component predominates, glandular-fibrous (mixed) type - the fibrous and glandular components are equally developed (microphotograph 22).

Consequences: inflammatory processes, malignization, necrosis with perforation of a hollow organ, torsion of the polyp pedicle with bleeding.

Hyperplastic growth as condylomas is caused by human papillomavirus (HPV) infection (sexual transmission).

Macroscopic features: it looks like a lobed structure in the form of a "cock's comb" or "cauliflower" on the skin, pink or whitish in color, on the wide basis or peduncle, from a few millimeters to dozens of centimeters.

Microscopic features: the villous proliferation of the stroma, covered with squamous epithelium with acanthosis.

Consequences: inflammatory processes, malignization.

IV. Inflammation around animal parasites and foreign bodies is the formation of a granuloma in the presence of parasites in the tissues (even the dead) or foreign bodies located inside the parenchymal organs and not amenable to phagocytosis and elimination. It occurs when the foreign material is so large that it cannot be phagocytosed by a single macrophage (e.g., echinococcus, alveococcus), or the material is inert and non-antigenic (does not elicit an immune response) (e.g., suture material, coal, asbestos). Therefore, a non-immune productive inflammation is formed around, aimed at delimiting these agents by a connective tissue capsule.

Macroscopic features: deformation of the organ; the consistency is dense.

Microscopic features: granuloma contains macrophages, fibroblasts, lymphocytes, as well as giant cells of foreign bodies, which are characterized by the presence of numerous nuclei randomly located in the cell. Foreign material is usually found in the center of the granuloma. Tissue necrosis does not occur.

Consequences: formation of a connective tissue capsule, sclerosis, and deformation of the organ.

TEST YOURSELF

1. Define productive inflammation:

A. Inflammation characterized by the formation of mucous exudate

B. Inflammation characterized by the formation of a purulent exudate

C. Inflammation characterized by the formation of fibrinous exudate

D. Inflammation, characterized by the proliferation of cells of histiocytic and hematogenous origin

2. The type of tissue reaction that predominates in productive inflammation:

A. Exudation

B. Sclerosis

C. Proliferation

D. Destruction

3. The type of productive inflammation that develops in the liver with tuberculosis:

A. Interstitial

B. Granulomatous, nonspecific

C. Polyps

D. Granulomatous, specific

4. A type of productive inflammation that develops around foreign bodies:

A. Interstitial

B. Granulomatous, nonspecific

C. Polyps

D. Granulomatous, specific

5. Tuberculous granulomas are characterized by:

A. Virchow cells

B. Pirogov-Langhans cells

C. Mikulicz cells

D. Neutrophils

E. Eosinophils

6. In the focus of productive inflammation proliferate:

A. Macrophages

B. Erythrocytes

C. Neutrophilic leukocytes

D. Eosinophils

7. The term "proliferation" means:

A. Cell death

B. Cell damage

C. Inflammation outcome

D. Reproduction of cells

E. Regeneration

8. Synonym for syphilitic granuloma:

A. Petrificat

B. Tubercle

C. Gumma

D. Leproma

E. Tuberculoma

9. Typical outcome of granulomas:

A. Sclerosis

B. Suppuration

C. Slime

D. Resorption

E. Cyst formation

10. An infectious granuloma in leprosy is called:

A. Petrificat

B. Tubercle

C. Gumma

D. Leproma

E. Tuberculoma

PART 10. COMPENSATORY AND ADAPTIVE PROCESSES

Adaptation is the process by which the body responds to changes in living conditions (e.g., changes in temperature, atmospheric pressure, radiation exposure, the influence of microorganisms, nutritional factors, psychological stress, and others) and maintains the constancy of the internal environment (homeostasis). In other words, adaptation is the body's reactions to such influences that are not accompanied by significant destructive changes in tissues and therefore are neutralized by an increase in functions that do not significantly exceed their physiological parameters. Adaptation of the body to the environment is continuous from birth.

Compensation is a type of adaptation to restore the disturbed structure and function in case of a disease. In other words, compensation is the body's reactions to such influences, which are accompanied by pronounced dystrophic and necrotic changes in the organ; at the same time, there is a need for other organs to “come to help the damaged organ” by strengthening their function, compensate (restore) the damaged tissue and dysfunction through compensatory reactions of the body.

Adaptive processes include atrophy, metaplasia, dysplasia, and organization; compensatory processes include regeneration, hypertrophy, and hyperplasia. Such reactions are related processes; therefore, they are considered compensatory-adaptive reactions of the body. The processes of adaptation and compensation in their formation and development have the following phases: 1) formation phase is an acute stage, as a result of the action of pathogenic factors in the body, all resources are mobilized - an increase in the intensity of metabolism with the inclusion of reserve structures in the work, an increase in the function of the structural components of cells and organs; 2) fixing phase is characterized by a relatively stable morphological and functional compensation of dysfunction or increased workload, which can continue a very long time (e.g., compensated heart defect, vicarious enlargement of one kidney, an increased function of the lymph nodes with atrophy of the spleen); 3) phase of decompensation (exhaustion) may occur at different times after complete or

incomplete recovery as a result of congenital or acquired insufficiency of compensatory-adaptive processes.

I. Atrophy is a lifetime decrease in the volume of organs, tissues, and cells due to the reduction of parenchymal elements, accompanied by a decrease or cessation of their functions. Atrophy must be distinguished from hypoplasia is a congenital underdevelopment of organs and tissues. Atrophy is divided into physiological and pathological.

1) Physiological atrophy occurs under normal conditions throughout a person's life (e.g., in newborns, the umbilical arteries, arterial (Botallo's) ducts atrophy; in the elderly, the thymus, sex glands, intervertebral cartilage, muscles, etc. atrophy).

2) Pathological atrophy develops as an adaptation to changes caused by diseases. There are general atrophy and local pathological atrophy.

General pathological atrophy or cachexia (exhaustion) can develop during starvation, cancer, tuberculosis, and brain diseases. The appearance of patients: emaciation, skin is dry and wrinkled, lack of adipose tissue. Its remaining parts have a brown color due to the accumulation of lipochromes. In the liver, myocardium, muscles, and other parenchymal organs there are signs of brown atrophy with an accumulation of lipofuscin in their cells (see section "Lipidogenic pigments"). Internal organs, and endocrine glands are reduced in size.

Local pathological atrophy occurs for various reasons. According to etiology, the following types of local pathological atrophy are distinguished: a) dysfunctional atrophy (atrophy from inactivity) develops with a decrease in the function of the organ (e.g., muscle atrophy in case of a bone fracture, atrophy of the optic nerve after removal of the eye); b) dyscirculatory atrophy (atrophy caused by insufficient blood supply) occurs when the blood supply to the organ is disturbed, leading to ischemia and hypoxia (e.g., cerebral atrophy due to atherosclerosis of the cerebral arteries, atrophy of the kidneys with hyalinosis of the renal arterioles.); c) atrophy due to the pressure occurs due to compression of the tissues leading to disruption of the microcirculation and ischemia (e.g., atrophy of the kidneys due to the damaged

outflow of urine - hydronephrosis, atrophy of the brain due to the damaged outflow of CSF); d) neuropathic atrophy (atrophy due to the denervation) is associated with a violation of the innervation of a tissue or organ (e.g., injury of the functioning of the motor neurons, such as polio or neuritis, leads to atrophy of muscle groups innervated by the nerve); e) atrophy under the influence of chemical (e.g., thyroid gland atrophy due to iodine deficiency) and physical factors (e.g., atrophy of the bone marrow and gonads under the influence of ionizing radiation); f) atrophy due to lack of hormone (e.g., hypofunction of adenohypophysis leads to atrophy of the thyroid gland, adrenal glands and gonads).

Macroscopic features: atrophied organs are reduced in size; their surface is smooth or granular.

Microscopic features: accumulation of lipofuscin in the cells of an atrophied organ - brown atrophy (brown atrophy of the myocardium, liver, etc.). A decrease in the volume of the parenchymal component; the stroma of the organ usually retains its volume and, at the same time, is often sclerotic (microphotograph 23).

Consequences: in the early stages, atrophy is a reversible process, and if its cause is eliminated, the function of the organ can be restored.

II. Hypertrophy is an increase in the volume and mass of an organ due to an increase in the volume of its cells. The increase of cells in size happens due to increasing the number of intracellular structures. Thus, the macroscopic "hypertrophy" is caused by the microscopic manifestation of hyperplasia. The main goal of this process is to increase the functional activity of organs. There are 1) true hypertrophy - an increase in mass due to an increase in the number of functioning cells; 2) false hypertrophy – the organ is enlarged in size due to non-parenchymal elements - connective tissue, adipose tissue, blood vessels (e.g., in diabetes mellitus, adipose tissue grows between the lobules of the pancreas; skeletal muscles are replaced by connective and adipose tissue; an increase of the kidney due to hydronephrosis).

There is physiological hypertrophy that occurs in healthy people as an adaptive response to an increase in the function of individual organs (for example, an increase in muscle volume in athletes); pathological hypertrophy that occurs in diseases is a compensatory reaction that allows saving the function of individual organs in pathological conditions.

There are the following clinical and morphological types of hypertrophy:

1) Working (compensatory) hypertrophy occurs under the influence of an increased load on an organ or tissue. It can be physiological and pathological. An example of physiological hypertrophy is an increase in the mass of striated muscles or the heart in athletes and people involved in heavy physical labor. Under conditions of a disease or pathological process, an organ or part of it must function intensively, which leads to an increase in the volume of cells in this organ. This type of hypertrophy is usually found in hollow organs: the gastrointestinal tract, and the bladder (e.g., with hyperplasia (adenoma) of the prostate, which narrows the urethra). In clinical practice, working hypertrophy of the heart is of great importance (e.g., with heart defects, hypertension disease). Morphologically, two types of hypertrophy of this organ are distinguished: concentric (tonogenic) hypertrophy - thickening of the myocardium occurs without expansion of the heart cavities (compensation phase) and eccentric (myogenic) hypertrophy - accompanied by a significant expansion of the heart cavities (phase decompensation).

Macroscopic features: the mass of the heart increases; it can be up to 1 kg or more ("beef heart" or cor bovinum); myocardium thickens, and the ventricular septa, trabecular and papillary muscles increase. With compensated hypertrophy, the cavities of the heart are narrowed (concentric hypertrophy), and with decompensated hypertrophy, the heart cavity is extended (eccentric hypertrophy). The myocardium is flabby and clay-like (fatty degeneration).

Microscopic features: cardiomyocytes increase in volume, and unevenly thicken. Their nuclei become large and hyperchromic. In the stage of decompensation, fatty degeneration develops in cardiomyocytes, which leads to a

decrease in myocardial function. In the myocardial stroma, the number of capillaries increases and interstitial sclerosis develops.

Consequences: with the elimination of the causative factor, working hypertrophy is a reversible process. Otherwise, there is a cardiac failure (chronic ischemia) associated with a lack of blood supply to the hypertrophied organ that leads to the development of dystrophic, necrotic, and sclerotic processes in it.

2) Vicarious (replacement) hypertrophy develops in paired organs due to the death or removal of one of them (e.g., lungs, kidneys), or due to the removal of part of the organ (e.g., liver). The preserved organ (or part of the organ) takes over the function of both hypertrophies.

3) Neurohumoral hypertrophy (correlative) hypertrophy occurs when the function of the endocrine organs is impaired. Physiologically, these changes are observed in the uterus and mammary glands during pregnancy and lactation. Pathological conditions are also accompanied by hormonal hypertrophy (e.g., glandular cystic endometrial hyperplasia, gynecomastia, acromegaly, and dyshormonal glandular prostatic hypertrophy).

III. Hyperplasia is an increase in the size of an organ or tissue as a result of an increase in the number of their cells. It occurs due to the stimulation of the mitotic activity of cells, which leads to increasing their number. The main goal of this process is to increase the functional activity of organs. There are reactive (protective) hyperplasia, neurohumoral (hormonal) hyperplasia, and substitution or compensatory hyperplasia.

1) Reactive hyperplasia occurs in the immune organs (e.g., lymph nodes, tonsils, thymus, spleen, bone marrow, intestinal lymphatic apparatus, and others). Hyperplasia of the lymph nodes happens mainly in response to antigenic stimulation; spleen hyperplasia - in septic conditions. Myeloid hyperplasia of the bone marrow is most often due to an increased need for neutrophils (e.g., inflammation).

2) Hormonal hyperplasia occurs in target organs through the action of hormones. It may be observed both physiological conditions (e.g., hyperplasia of the

mammary gland during pregnancy and lactation) and pathological conditions (e.g., glandular hyperplasia of the endometrium is the result of increased estrogen stimulation of the endometrium; thyroid hyperplasia occurs due to the increased amount of thyroid-stimulating hormone, or due to the action of autoantibodies; prostatic hyperplasia occurs in elderly and is associated with a reduction in the level of androgen production).

Macroscopic features: glandular hyperplasia of the endometrium is characterized by thickening of the endometrium, it becomes friable, and easily rejected.

Hyperplasia of the thyroid gland is characterized by an increase in the glandular epithelium in size; the surface often becomes uneven due to the presence of nodes of various sizes.

Prostatic hyperplasia is characterized by an increase in the size of the organ, the consistency is dense. It compresses the urethra and prevents urination. In the bladder, this leads to working hypertrophy of the muscle membrane.

Microscopic features: glandular hyperplasia of the endometrium is characterized by thickening of the endometrium, due to an increased number of glands that have different sizes and shapes; some of them may be cystic expanded. Endometrial glands become corkscrewed and convoluted. The glandular epithelium has signs of proliferation. In addition, there is the proliferation of stroma.

Hyperplasia of the thyroid gland is characterized by the proliferation of the follicle epithelium that forms "pillows" (Sanders pillows) in the lumen of the follicles; papillary outgrowths into the lumen of the follicles. There are signs of lacunar or diffuse resorption of the colloid (appearance of enlightenments of various sizes on the periphery).

Prostatic hyperplasia is characterized by hyperplasia of glandular tissue and stroma.

IV. Regeneration is restoration by the body of tissues, cells, and intracellular structures damaged as a result of their physiological death or as a result of

pathological influences. The main purpose of this process is to maintain normal organ function. Regeneration is a continuous process that provides recovery at all levels: ultrastructural, cellular, tissue, and organ. There are three forms of regeneration: 1) cellular occurs due to cell reproduction, 2) intracellular occurs due to hyperplasia of ultrastructures of the cell, and 3) mixed – both cellular and intracellular regeneration occurs. Regeneration in different organs occurs in different ways. It depends on the regenerative ability of the cells, which are divided into labile cells, relatively stable cells, and stable (permanent) cells.

Labile cells are characterized by a cellular form of regeneration, they are actively dividing throughout life, being a source of cells to replace the dead; their number is maintained due to the proliferation of labile stem cells. Damage of tissue containing labile parenchymal cells is accompanied by rapid regeneration. For example, this occurs during the regeneration of bone tissue cells, epidermis, gastrointestinal mucosa, respiratory mucosa, mucosa of the genitourinary system, endothelium, mesothelium, loose connective tissue, and hematopoietic system. Cessation of the function of tissue cells during their differentiation is not significant for the function of these organs.

Relatively stable cells have both cellular and intracellular forms of regeneration; are usually characterized by a long period of life, and low mitotic activity. However, they retain the proliferation ability and begin to divide, if necessary. For example, cells of the liver, kidneys, pancreas, lungs, smooth muscles, autonomic nervous system, and endocrine system regenerate both due to the formation of new cells to replace the dead ones, and as a result of the regeneration of only intracellular structures while maintaining cells.

Stable cells are characterized only by the intracellular form of regeneration. complete recovery is not possible; therefore, damage to the organ and tissue is always accompanied by scar formation. Thus, the loss of the permanent cell due to necrosis leads to disruption of the function of these organs. For example, organs such as the heart, brain, skeletal muscles (mainly), and ganglion cells of the CNS require

simultaneous and synchronous cellular development, therefore, they regenerate only by restoring their intracellular structures, while the cells do not cease to function. This principle is determined both in the norm and in pathology.

According to morphogenesis, there are two subsequent stages of regeneration: 1) the stage of proliferation (reproduction) of undifferentiated, blast cells; 2) the stage of differentiation of young cells into mature cells that are capable to perform a specialized function. These stages are regulated by humoral, immunological, nervous, and functional mechanisms.

Regeneration is: 1) physiological, 2) pathological, and 3) reparative.

1) Physiological regeneration is the restoration of cell and tissue elements as a result of their natural death. The body continuously renews itself throughout life. Physiological regeneration occurs in all organs, but in some more, in others less.

2) Pathological regeneration is a perversion of the regenerative process, a violation of the change of phases of differentiation and proliferation. Most often occurs as a result of a violation of general (e.g., age, protein, and vitamin starvation) and local (e.g., impaired blood and lymph circulation, chronic inflammation, etc.) regeneration factors. There are the following types of pathological regeneration: a) hyperregeneration – excessive formation of regenerating tissue (e.g., keloid scars, callus); b) hyporegeneration – insufficient formation of regenerating tissue (e.g., prolonged wound healing); c) metaplasia - the transition of one type of tissue to another within one germ layer (e.g., the transition of prismatic glandular epithelium of bronchi into stratified squamous keratinizing epithelium).

3) Reparative regeneration is the restoration of lost tissue as a result of pathological processes. It is divided into a) complete (restitution) and b) incomplete (substitution).

a) complete regeneration is characterized by the replacement of a defect with a tissue identical to the dead one (if the epithelium is damaged, the epithelium is restored; if the bone tissue is damaged, the bone tissue is restored); therefore, this type of regeneration is typical for tissues where there is cellular regeneration.

b) incomplete regeneration is characterized by the replacement of a tissue defect with a connective tissue scar, and the restoration of function occurs due to regenerative hypertrophy (an increase in the size of the preserved part of the organ and tissue), which ensures the preservation of the function of the damaged organ. It is typical for organs and tissues in which the intracellular form of regeneration predominates, or cellular and intracellular forms. For example, in the heart with myocardial infarction, necrosis occurs, which is replaced by connective tissue leading to the development of macrofocal cardiosclerosis.

Macroscopic features: in the wall of the ventricle, a thick, irregularly shaped area of whitish color with clear boundaries (scar) is visible.

Microscopic features: in the myocardium there is dense fibrous connective tissue, cardiomyocytes are enlarged along the periphery, and their nuclei are enlarged and hyperchromic.

A special case of reparative regeneration is wound healing, which has several stages:

1) Lysis and removal of necrotic detritus (debris of dead cells, inflammatory exudate). The detritus is lysed by lysosomal enzymes of neutrophilic leukocytes, which migrate to this area and are subsequently eliminated by the lymphatic system. Particles are removed by macrophages through phagocytosis.

2) The proliferation of granulation tissue. It is a highly vascularized connective tissue containing newly formed capillaries and connective tissue proliferating cambial cells that fill the damaged area.

3) The maturation of granulation tissue. It is characterized by a progressive increase in collagen content; cells and vessels become less. A young scar contains a large number of fibroblasts and capillaries, and a moderate amount of collagen. The mature scar consists of a massive accumulation of collagen with few fibroblasts and almost no blood vessels.

Macroscopic features: granulation tissue is soft and looks pink and granular due to the presence of numerous capillaries.

Microscopic features: there are many capillaries surrounded by undifferentiated connective tissue cells (microphotograph 24).

4) The reduction and compaction of the scar. It is the final stage of healing. Contraction begins in the early stages of healing due to the active contraction of myofibroblasts and continues as the scar matures.

Depending on the degree of the defect and the type of tissue, 4 types of wound healing predominate:

1) Direct closure of an epithelial defect is the simplest healing, characterized by the closure of a defect in the surface epithelium by epithelial cells.

2) Wound healing under a scab occurs with small defects. The wound healing process begins with the clotting of blood or lymph, which, when dried, forms a scab. Under it, there is a rapid regeneration of the epidermis (within 3-5 days), then the scab is separated.

3) Wound healing by primary intention (primary union) occurs with clean lacerated (surgical) wounds with edges that are close to each other. With minor tissue trauma and small microbial invasion, dystrophic and necrotic cell changes are minimal. There is a rapid cleansing of the wound and a transition to the proliferative phase of regeneration. The small gap in the epidermis and dermis is filled with clotted blood that forms a scab. By the 5th day, the dermal defect is filled with granulation tissue and a small amount of loose connective tissue. The surface of the defect is covered with epithelium and a tender scar is formed in place of the granulation tissue.

4) Wound healing by secondary intention (secondary union or healing through suppuration) occurs with large and deep, open tissue defects, with active microbial invasion, and also when foreign material is present in the wounds or there is extensive tissue necrosis. In such cases, demarcation purulent inflammation develops on the border with dead tissue. Purulent inflammation within 5-6 days contributes to the rejection of necrotic masses (there is a secondary cleansing of the wound), and granulation tissue begins to form at the edges of the wound. Granulation tissue, gradually filling the wound defect, has pronounced signs of inflammation. In the

future, granulation tissue matures and transforms into connective tissue. A mature scar is formed at the site of injury.

Another special case is the regeneration of bone tissue (regeneration of bone fractures), which occurs in two ways:

1) Primary bone fusion is bone regeneration in an uncomplicated fracture when the bone fragments are well-matched and fixated, and there is no infection. There are successive stages:

The first stage is the activation of the proliferation of osteoblasts with the formation of soft callus (osteoblastic granulation tissue consisting of a large number of newly formed thin-walled vessels of capillary type and a large number of dividing cells of the connective tissue);

The second stage is a differentiation of cells to bone cells (osteocytes), which produce an extracellular matrix and form osteoid;

The third stage is the formation of the final callus, which differs from bone tissue in the chaotic arrangement of bone beams;

The fourth stage is a newly formed bone tissue that is subjected to restructuring using osteoclasts and osteoblasts; bone marrow appears in the medullary canal; there is a restoration of innervation and vascularization.

2) Secondary bone fusion is the regeneration of bone tissue with extensive fractures, mobility of bone fragments, and blood circulation disorders of bone tissue, leading to bone regeneration violation. *The first stage* is the formation of a preliminary osteochondral callus, which is eventually replaced by bone tissue. *The second stage* – is the formation of a mature bone. It proceeds for a longer time; the result may be the formation of a false joint.

V. Organization is the replacement of a tissue defect, area of necrosis, thrombus, or fibrinous exudate with connective tissue. In the beginning, the dead tissue or thrombus is lysed and granulation tissue grows into them, which turns into scar tissue. Encapsulation is a type of organization in which connective tissue grows around dead parasites, foreign bodies, and necrotic tissue that has undergone

petrification. The processes of the organization include sclerosis, fibrosis, cirrhosis, and scar.

Sclerosis is a pathological process leading to diffuse small-focal or local compaction of internal organs due to excessive growth of dense connective tissue.

Fibrosis is moderate sclerosis without the prominent hardening of the tissue, although a clear separation of these terms does not exist.

Cirrhosis is pronounced sclerosis with the deformation and restructuring of the organ (cirrhosis of the lung, liver cirrhosis, cirrhosis of the kidneys, etc.).

The scar is local sclerosis, replacing necrotic focus or wound defect.

Consequences: these processes may be reversible after cessation actions of the pathogenic factor, partially reversible after the treatment, and irreversible with pronounced changes.

VI. Metaplasia is the transition of one type of tissue to another within one germ layer. The main causes of metaplasia are the following: chronic inflammation, dyshormonal diseases, and lack of vitamins in the body. These causes can lead to violation of tissue regeneration (perverted regeneration) and the development of metaplasia. Most often, metaplasia occurs in the epithelium (one type of epithelium transforms into another type) or in connective tissue (connective tissue is transformed into cartilage or bone tissue).

According to morphogenesis, there are successive stages in the development of metaplasia: 1) the proliferation stage is characterized by the proliferation of undifferentiated cells, and 2) the stage of cell maturation and differentiation into another type of tissue. According to the pathogenetic principle, two types of metaplasia are distinguished: 1) direct metaplasia - tissue replacement occurs due to changes in its structural elements by transforming mature cells into another type (e.g., fibrocytes are transformed into osteocytes, etc.); 2) indirect metaplasia - the formation of a new tissue due to the proliferation of undifferentiated (immature) cells and their subsequent differentiation into another type of tissue.

Also, according to the histogenetic principle, there are 1. Epithelial metaplasia: a) squamous metaplasia - single-layer cuboidal or prismatic glandular epithelium is replaced by stratified squamous keratinizing or nonkeratinizing epithelium (e.g., in the bronchial mucosa, cervix, endometrium, urinary bladder mucosa); b) glandular metaplasia - stratified squamous epithelium is replaced by nonkeratinizing glandular epithelium (e.g., gastric or intestinal type); 2. Mesenchymal metaplasia occurs in tumors or chronic inflammation (e.g., cells of the fibrous connective tissue transform into cartilage or bone).

Consequences: metaplasia can be a reversible process when the pathological influence ceases. Otherwise, metaplasia can provoke the development of functional disorders of organs that contribute to the development of other pathological processes. Also, on the background of metaplasia, dysplasia can develop, which increases the risk of developing a tumor.

VII. Dysplasia is a pathological process accompanied by violation proliferation and differentiation of cells (cellular atypia) with a change in the histoarchitectonics of the tissue. Cellular atypia is represented by a different size and shape of cells, an increase in the size of the nuclei and their hyperchromia, an increase in the number of mitotic Figures, the appearance of atypical mitoses; their gradual accumulation of atypical properties, ending with tumor growth. Violations of histoarchitectonics in dysplasia are manifested by a loss of the polarity of the epithelium. Dysplasia occurs in inflammatory and regenerative processes, reflecting a violation of cell proliferation and differentiation.

According to the degree of proliferation and the severity of cellular and tissue atypia, three stages (degrees) of dysplasia are distinguished: I - mild; II - moderate; III - severe.

Consequences: I and II stages of dysplasia are most often reversible. Changes in severe dysplasia (stage III) are less prone to regression and are regarded as a precancerous process. Sometimes it is difficult to distinguish it from carcinoma in situ.

TEST YOURSELF

1. Define adaptation:

A. The transition from one type of fabric to another

B. Sclerosis

C. Life processes aimed at preserving the species

D. Decrease in organ mass

E. Hypertrophy

2. Define regeneration:

A. The transition from one type of fabric to another

B. Increase in the cell, tissue, and organ volume

C. Replacement of necrosis focus with connective tissue

D. Restoration of the structure of tissue elements to replace the dead

E. Decrease in cell volume

3. Define hypertrophy:

A. Tissue necrosis

B. Restoration of tissue to replace the lost one

C. Decrease in cell volume

D. Replacement with connective tissue

E. Increase in the volume of cells, tissues, organs

4. Define hyperplasia:

A. Decrease in the volume of cells, tissues

B. Growth of the stroma at the site of the parenchyma

C. Restoration of tissue to replace the lost one

D. An increase in the number of structural elements of tissue, cells

E. Less quantity of structural elements of tissue, cells

5. Define atrophy:

A. Decrease in fat

B. Restoration of tissue to replace the lost one

C. Sclerosis

D. Intravital decrease in the size of organs, tissues, cells

E. The transition from one type of fabric to another

6. Type of bronchial epithelium formed during its metaplasia:

A. Ciliary

B. Glandular

C. Cylindrical

D. Stratified squamous

E. Transition

7. Synonym for general atrophy:

A. Obesity

B. Cachexia

C. Brown atrophy

D. Necrosis

C. Dwarfism

8. Define granulation tissue:

A. Young, rich in cells and thin-walled vessels, connective tissue

B. Tissue that rich in pigment granules

C. Immature adipose tissue

D. Muscle tissue

E. Scar tissue

9. Vicarious hypertrophy is characteristic for:

A. Spleen

B. Brain

C. Kidney

D. Hearts

E. Liver

10. Organization is:

A. Wound formation

B. Replacement of necrosis with connective tissue

C. Inflammatory infiltration

D. Deposition of calcium salts

PART 11. TUMORS: ETIOLOGY, PATHOGENESIS, MAIN PROPERTIES OF TUMORS. MORPHOLOGICAL CHARACTERISTICS OF EPITHELIAL TUMORS

Tumor is a pathological process characterized by changes in the genetic apparatus of cells, which leads to a violation of the regulation of their growth and differentiation, and cell apoptosis. Pathology of growth is characterized by its autonomy, uncontrollability, the presence of pathological Figures of mitosis, invasiveness, and metastasis. Pathology of differentiation is associated with the absence or decrease in maturation (differentiation) of tumor cells. The pathology of apoptosis is manifested in its relative insufficiency and incomplete character. Synonyms of "tumor" are the following terms: neoplasm, neoplastic process, and blastoma.

The etiology of tumors has not been established, but it is associated with the action of various endogenous and exogenous factors - carcinogens. The main theories of the occurrence of tumors are as follows: 1) theory of chemical carcinogens (e.g. aflatoxin B – liver carcinoma; asbestos – mesothelioma, lung carcinoma; aromatic amines – urinary bladder carcinoma; benzene – acute leukemia; foods rich in nitrosamines – stomach carcinoma; smoking – lung carcinoma; polyvinylchloride – liver angiosarcoma); 2) theory of physical carcinogens (e.g., ionizing radiation – leukemia, thyroid carcinoma; sun (UV) radiation – skin carcinoma, skin melanoma); 3) viral theory (e.g., DNA viruses: EBV (Epstein-Barr virus) – Burkitt's lymphoma, nasopharyngeal carcinoma; Of HBV, HBC (hepatitis B, C) – hepatocellular carcinoma; HPV (human papillomavirus) – cervical and precancer carcinoma. RNA viruses: HTLV-1 (HTLV) – T-cell leukemia/lymphoma); 4) theory of genetic

disorders (e.g., presence of families with a high incidence rate of certain malignant tumors; the presence of oncogenetic syndromes - hereditary diseases, often accompanied by the genesis of certain tumors: Down syndrome (trisomy of chromosome 21) – often occurs with acute lymphoblastic leukemia; dysplastic nevus syndrome (abnormality of chromosome 1) – skin melanoma often develops); 5) infectious theory (e.g., chronic inflammation); 6) dysontogenic theory (e.g., tumors form as a result of embryonic primordia dystopia during embryogenesis; 7) polyetiological theory (combines all other theories).

The main properties of tumors are autonomous growth and the presence of atypia. Atypism is a deviation from the norm. There are 4 types of atypia in tumors: 1) morphological, 2) biochemical, 3) antigenic, 4) functional.

1) Morphological atypism (or atypism of the tumor structure) is expressed in the fact that the tumor tissue does not repeat the structure of a similar mature tissue, and tumor cells may not look like mature cells of the same origin. Morphological atypism is represented by three variants: tissue, cellular and ultrastructural. *Tissue atypism* is characterized by a change in the ratio between the parenchyma and the stroma of the tumor. The parenchyma of the tumor is represented by tumor cells, the stroma is formed by fibrous connective tissue with vessels and nerves, in which the parenchymal elements of the tumor are located. Depending on the pronounced stroma, two types of tumors are distinguished: the organoid type (tumors with a pronounced stroma) and the histioid type (tumors with a pronounced parenchyma). *Cellular atypism* is characterized by the appearance of cellular polymorphism both in shape and size, enlargement of nuclei in cells, an increase in the nuclear-cytoplasmic ratio, and the appearance of large nucleoli. As a result of pathological mitoses, cells with hyperchromic nuclei, giant nuclei, multinucleated cells, and pathological mitotic Figures are found in tumor cells. *Ultrastructural atypism* of the tumor cell is also characterized by changes in the structure of the nucleus with chromatin margination, the presence of heterochromatin, a decrease in the number of nuclear pores, pronounced mitotic activity and the presence of pathological forms of mitosis.

2) Biochemical atypism is expressed in violation of the metabolism of tumor tissue. All changes in tumor metabolism are aimed at ensuring its growth and adaptation to the relative oxygen deficiency that occurs with the rapid growth of neoplasm. Biochemical atypism can be studied using morphological methods such as histo- and immunohistochemical methods, therefore it is also called histochemical atypism.

3) Antigenic atypism characterized by the appearance of new antigenic properties in the tumor tissue. The identification of these antigens by immunological and immunohistochemical methods is widely used in the diagnosis of tumors.

4) Functional atypism characterized by the loss of specialized functions by tumor cells that are inherent in similar mature cells, and/or the appearance of a new function that is not characteristic of cells of this type (e.g., cells of poorly differentiated scirrhous gastric cancer stop producing secretion and begin to intensively synthesize collagen in the tumor stroma).

Morphogenesis of malignant tumors can occur in two ways: 1) tumor development de novo - occurs without previous visible precancerous changes; 2) staged carcinogenesis (oncogenesis) - the development of a tumor at the site of precancerous changes (in the case of cancer, the term "precancer" is used to refer to precancerous changes). There are two forms of precancer: obligate precancer - a precancer that sooner or later transforms into a malignant tumor (e.g., skin changes with xeroderma pigmentosum); facultative precancer - a precancer that does not transform into cancer in all cases (e.g., leukoplakia, smokers' bronchitis or chronic atrophic gastritis). The morphological expression of obligate precancer is severe cellular dysplasia, which are classified as "grade III intraepithelial neoplasia" along with carcinoma in situ. In the pathogenesis of the development of immature malignant tumors, four main stages are distinguished: 1) precancerous stage (hyperplasia and precancerous dysplasia occur); 2) non-invasive tumor stage («carcinoma in situ»); 3) stage of tumor progression (tumor invasion); 4) stage of metastasis (Figure 10).

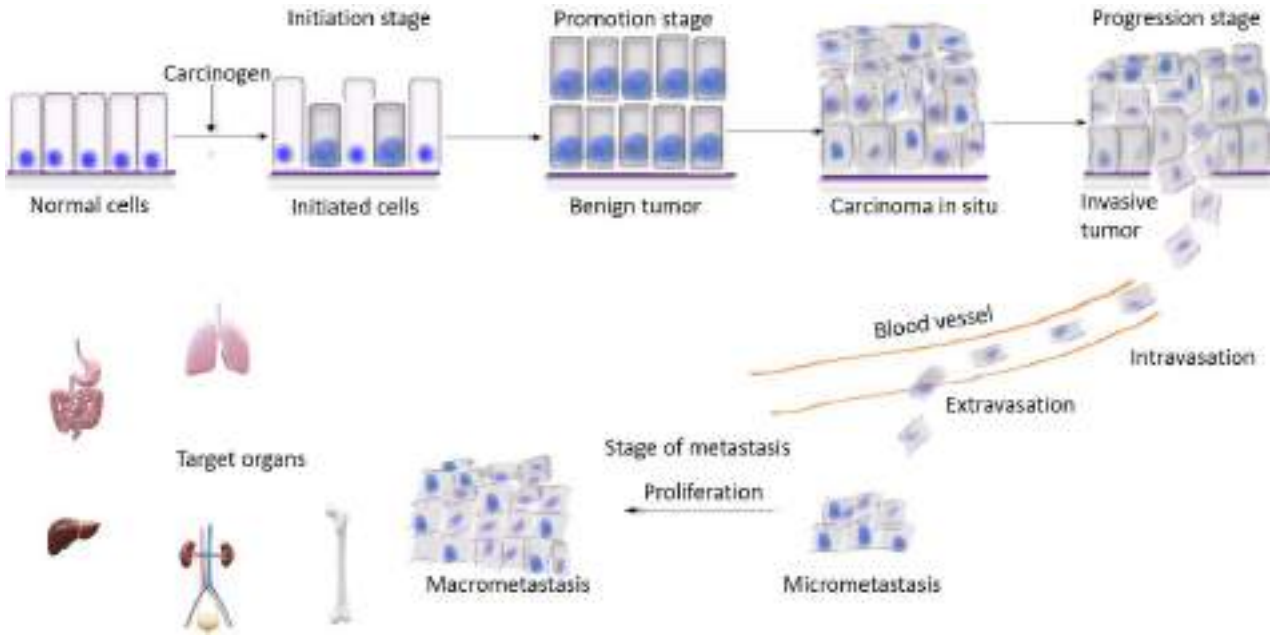


Figure. 10. Scheme of pathogenesis of malignant tumors.

1. Precancerous stage is characterized by the transformation of a normal cell into a tumor cell. At the first stage - the stage of initiation - a somatic mutation occurs, as a result of which oncogenes appear in the genome of tumor cells; at the second stage - the stage of promotion, the proliferation of initiated cells begins. Oncogenes (onc) are any genes that cause the transformation of a normal cell into a tumor cell. Oncogenes, depending on their origin, are divided into two groups: cellular oncogenes (c-onc) and viral oncogenes (v-onc). Cellular oncogenes are formed from normal cellular genes called proto-oncogenes.

2. Non-invasive tumor stage («carcinoma in situ», intraepithelial cancer, or stage 0 cancer) is characterized by the accumulation of histologically altered cells without invasion into the underlying tissue (without destruction of the basement membrane). A malignant cell that divides forms a node (clone) of similar cells that feed on the diffusion of nutrients from the tissue fluid and surrounding normal tissues, and do not grow into them. At this stage, the tumor node does not yet have its vessels. The reason for this is unknown. Perhaps, it is due to the small mass of the tumor, which leads to insufficient production of factors that stimulate angiogenesis

and the formation of stroma in the tumor. The duration of this stage can be 10 years or more.

3. Stage of tumor progression is characterized by infiltrative growth. A developed vascular component appears in the tumor, the stroma is expressed to varying degrees, and there are no borders with the surrounding non-tumor tissue due to the invasion of tumor cells into it.

4. Stage of metastasis is characterized by the formation of secondary foci of tumor growth (metastases) as a result of the spread of cells from the primary tumor to other tissues. There are the subsequent stages in the process of metastasis: 1) separation of tumor cells from the group of cells of the primary tumor node; 2) invasion of the wall of the blood or lymph vessel (intravasation); 3) tissue embolism; 4) secondary intravasation and extravasation - invasion into the surrounding tissue. There are different ways of metastasis: lymphogenous route – through the lymphatic vessels to regional and then to distant lymph nodes (more characteristic for carcinomas); hematogenous route – spread through the bloodstream (more characteristic for sarcomas); implantation route – through direct contact with the tumor tissue (e.g., peritoneal dissemination of the tumor); intracanalicular route – through natural anatomic channels, spaces.

Tumor growth (neoplasia or neoplastic process) in relation to the surrounding tissues can be: 1) expansive growth - tumor grows "from itself", with the formation of a connective tissue capsule and pushing the surrounding tissues; it is slow tumor growth; it is typical for mature benign tumors; 2) infiltrative (invasive) growth – the tumor grows into the surrounding tissues and destroy them (destructive growth); 3) apposition growth – occurs due to neoplastic transformation of normal cells into the tumor cells, that is observed in the tumor field. Depending on the relation of the tumor to the lumen of hollow organs, 2 types of growth are distinguished: 1) exophytic - expansive growth of the tumor into the cavity of the organ; the tumor looks like a plaque or nodule on superficial tissues - skin or mucous membrane; 2)

endophytic – infiltrative growth of the tumor into the wall of the organ; the tumor does not rise above the surface of the skin or mucous membrane.

Depending on the number of primary tumor foci, neoplasms can have unicentric growth - one primary tumor focus and multicentric growth - two or more primary tumor foci.

The main principles of the classification of tumors are clinical-morphological and histogenetic (tissue origin). According to clinical and morphological features (which are determined by the degree of maturity - differentiation of the tumor), all tumors are divided into benign (differentiated) tumors, malignant (undifferentiated) tumors, and borderline tumors. Benign tumors - tumors that do not cause severe complications and do not lead to the death of the patient. A benign tumor can transform into a malignant one. Malignant tumors - tumors that cause severe violations of life and lead to disability and death (Figure 11). Borderline tumors – tumors are intermediate between benign and malignant tumors: they have signs of locally destructive infiltrating growth, but do not metastasize.

The name of a benign tumor is formed from the name of the tissues of which it consists, and the suffix "-oma". For example, a benign tumor of fibrous tissue – fibroma, adipose tissue – lipoma, glandular epithelium – adenoma, cartilage – chondroma. Malignant tumors of epithelial origin are called cancers or carcinomas, mesenchymal origin – sarcomas. The words "cancer", "carcinoma" or "sarcoma" are added to the name of the tissue from which the tumor originated: adenocarcinoma – cancer from glandular epithelium, squamous cell carcinoma – from stratified squamous epithelium, transitional cell carcinoma – cancer from transitional epithelium, fibrosarcoma – malignant connective tissue tumor, etc. There are numerous exceptions to these rules. For example, lymphoma and seminoma are malignant tumors; many tumors are called with names of authors, who described them: Kaposi sarcoma (angiosarcoma), Hodgkin's disease (one of malignant lymphomas), and others.

Benign tumor	Malignant tumor
1. Slow expansive growth	1. Rapid infiltrating and invasive growth
2. Encapsulated and well-circumscribed	2. Poorly- circumscribed and irregular
3. Size is usually small	3. Size is often large
4. Secondary changes occur less often	4. Secondary changes occur more often
5. Function is usually well maintained	5. Function may be retained, lost or become abnormal
6. Contains mature differentiated cells (tissue atypism)	6. Contains immature undifferentiated cells (cellular and tissue atypism)
7. Basal polarity is retained	7. Basal polarity is lost
8. Nucleus-cytoplasmic ratio is normal	8. Nucleus-cytoplasmic ratio is increased
9. Anisonucleosis is absent	9. Anisonucleosis is present
10. Hyperchromatism is absent	10. Hyperchromatism is present
11. Mitoses are present, but always typical mitoses	11. Mitotic Figures increased and are generally atypical and abnormal
12. Cytoplasmic elements are normal	12. Normal cytoplasmic elements are reduced or lost
13. Tumor giant cells may be present but without nuclear atypism	13. Tumor giant cells present with nuclear atypism
14. Histological pattern resembles the tissue of origin closely	14. Histological pattern has a poor resemblance to a tissue of origin
15. Does not metastasize	15. Often metastasizes
16. Does not recur after removal	16. Often recurs after removal
17. Does not have a general effect on the body, only local	17. Has both local and general effect on the body

Figure. 11. The key differences between benign and malignant tumors.

According to the histogenetic (tissue origin) tumors are divided into 1) epithelial tumors (organ-specific and organ-non-specific) are tumors with epithelial differentiation of the parenchyma (organ-non-specific are found in various organs, organ-specific – mainly in any one organ); 2) mesenchymal tumors – tumors with differentiation of the parenchyma in the direction of fibrous connective, fatty, muscle, vascular and skeletal (cartilaginous and bone) tissues, as well as tumors of synovial and serous membranes; 3) melanocytic tumors; 4) tumors of the nervous tissue and membranes of the brain; 5) hemoblastoses – tumors of the hematopoietic (myeloid and lymphoid) tissue; 6) teratomas - tumors and tumor-like processes that develop from embryonic structures.

To determine the prognosis of the tumor, it is necessary to consider the morphological degree of malignancy and the stage of the tumor process.

The degree of malignancy depends on the degree of tumor differentiation, which is determined by the severity of cellular atypism. There are 3 degrees of malignancy (Grading): low (G1), intermediate (G2), and high (G3). Low-grade tumors are well-differentiated tumors with minimally pronounced signs of cellular atypism (G1); intermediate-grade tumors are moderately differentiated tumors (G2); high-grade tumors are poorly differentiated tumors with pronounced signs of cellular atypism (G3).

For an additional assessment of the degree of malignancy, the gradation of the National Federation of Cancer Centers of France (FNCLCC) is used: 1) the degree of tumor differentiation; 2) the number of mitoses; 3) the severity of secondary necrotic changes. According to these criteria, the higher the score, the more aggressive the tumor (Figure 12).

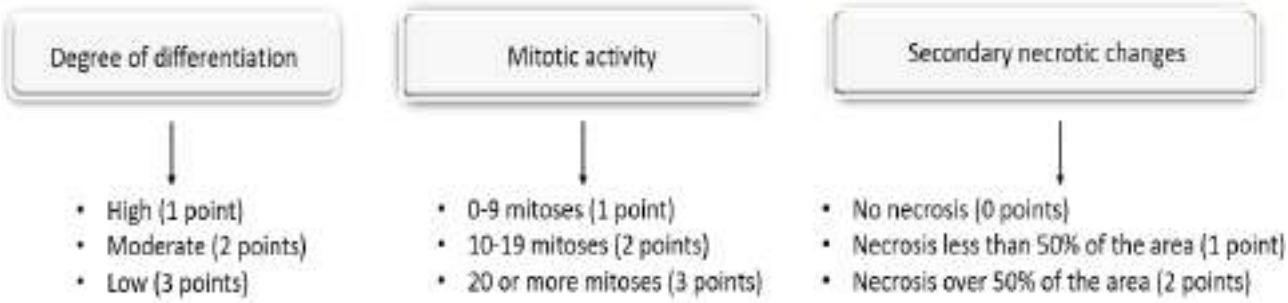


Figure. 12. Assessment of the degree of malignancy of the tumor according to the criteria of FNCLCC.

To determine the stage of the tumor process TNM classification is used (from the Latin words: Tumor – tumor, Nodulus – lymph node, Metastases – metastases). It considers the size and spread of the tumor (T), the presence of metastases in regional lymph nodes (N), and distant metastases (M):

Tx - primary tumor can't be assessed; T0 - no evidence of primary tumor; Tis - carcinoma in situ; T1–T4 - increase in tumor size and/or local spread of the primary node in the organ and surrounding tissues;

Nx - the presence of metastases in regional lymph nodes is unclear; N0 - metastases into regional lymph nodes are absent; N1-N3 - the severity of regional metastasis;

Mx - the presence of distant metastases is unclear; M0 - no distant metastases; M1 - there are distant metastases. In each case, different combinations of TNM can be.

Epithelial tumors are formed from glandular and surface squamous (transitional) epithelium. Tumors from the epithelium are the most common among tumors. According to the degree of differentiation, epithelial tumors can be benign (mature) and malignant (immature). Depending on the histogenesis of the tumor, there are 1) squamous epithelium (stratified and transitional epithelium - urothelium); 2) glandular epithelium. A mature benign tumor from the surface (stratified squamous or transitional) epithelium is called a papilloma. A mature benign tumor of the glandular epithelium is called an adenoma. Immature malignant tumors from the

glandular epithelium are called carcinomas, and from the surface (stratified squamous or transitional) epithelium are called cancer.

1) Papilloma is a benign tumor from the surface (stratified squamous or transitional) epithelium. Squamous cell papillomas are formed on the skin and mucous membranes covered with stratified squamous epithelium (e.g., oral cavity, pharynx, esophagus, vocal cords of the larynx, vagina, and vaginal portion of the cervix). Transitional cell papilloma is localized in the urinary tract, mainly in the bladder. Therefore, papillomas are non-organ-specific tumors.

Macroscopic features: spherical formation on a wide base or a thin peduncle, movable. The surface of the tumor is covered with small papillae. The consistency can be dense or soft. In dense papillomas, the stroma is well expressed, represented by dense fibrous connective tissue. In soft papillomas, the parenchyma predominates in volume, the stroma is formed by loose fibrous connective tissue with many thin-walled vessels. The tumor rises above the surface of the skin or mucosa; the size varies from a few millimeters to centimeters.

Microscopic features: tumor consists of many papillary vegetations of stratified squamous (or transitional) epithelium that lying on the basement membrane, maintains the polarity; uneven development of the epithelium and stroma and excessive formation of small blood vessels, which is a manifestation of tissue atypia.

Consequences: papilloma can recur and become malignant (e.g., larynx, urinary bladder).

2) Adenoma is a benign tumor from glandular epithelium. Adenomas are found in all glandular organs, as well as in the mucous membranes (e.g., nasal cavity, trachea, bronchi, stomach, intestines, endometrium), where they protrude above the surface in the form of a polyp. They are called adenomatous (glandular) polyps. Adenomas of endocrine glands (e.g., pituitary, adrenal, ovary) may retain functional features of the cells of the original tissue and produce the corresponding hormones in excess. These hormonally active adenomas give characteristic clinical syndromes that make it possible to diagnose these neoplasms in the clinic. Depending on the

histological structure of the epithelial component, the following variants of adenomas are distinguished: 1) alveolar (acinar) adenoma is characterized by multiple small round bubble-like formations, covered with columnar or cuboidal epithelium; 2) tubular adenoma, preserving the ductal nature of epithelial structures; 3) trabecular adenoma, having a beam structure; solid, in which there is no lumen of glandular structures; 4) cystic adenoma with a pronounced ectasia (expansion) of the lumen of the glands and the formation of cavities (cystadenoma). According to the ratio of parenchyma and stroma, adenomas are divided into 1) simple adenoma (parenchyma predominates over stroma); 2) fibroadenoma (approximately equal ratio of parenchyma and stroma); 3) adenofibroma (pronounced predominance of stroma, resembles fibroma in structure, but contains single glands). The most significant types of adenomas are cystadenoma and fibroadenoma.

Cystadenoma is an adenoma with the presence of cysts (cavities). In this case, the cyst may precede the development of an adenoma (primary cyst) or occur in the tissue of an already-formed tumor (secondary cyst).

Macroscopic features: cysts are filled with fluid, mucus, coagulated blood, and mushy or dense masses. Cystadenomas most commonly occur in the ovaries (ovarian cystadenoma). There are cysts: single-chamber (single-cavity) and multi-chamber (multi-cavity).

Microscopic features: the tumor is formed by the glands, the lumens of which are cystically dilated. Epithelium that lines cysts (columnar or cuboidal) forms numerous papillary vegetations; maintains the basement membrane and polarity. Depending on the state of the inner layer of the cyst, there are: smooth-walled and papillary (papillary protrusions of the epithelial lining inside of the cavity). There are true and false papillae. True papillae are epithelial protrusions with stroma and vessels. False papillae are represented by proliferating epithelium. The papillary formation is an indicator of the intensity of proliferative processes in the cystadenoma epithelium. It is a morphologically unfavorable sign, which indicates the possibility of malignancy of the tumor (microphotograph 25).

Consequences: an ovarian tumor has a high potential for malignancy: infiltrative growth and a malignant course are possible. It is also possible torsion of the cyst with the development of necrosis of the wall, its rupture and bleeding; suppuration of cysts.

Fibroadenoma is a benign tumor with a well-expressed stroma and poorly developed parenchyma. It is an organ-specific tumor. The typical localization of fibroadenoma is the mammary glands (breast fibroadenoma).

Macroscopic features: movable, thick, painless, well-circumscribed white node no more than 3 cm in diameter with slit-shaped cavities on the cut. Sometimes it can be large sizes – a giant fibroadenoma.

Microscopic features: the tumor is composed of glandular structures of different sizes and shapes. Stroma is represented by a large amount of connective tissue, which dominates the parenchyma. The epithelium lies on the basement membrane, and maintains the polarity. There are the following histological types of fibroadenoma: a) pericanalicular fibroadenoma - connective tissue grows around the intralobular ducts, so that they have the form of small round tubules, b) intracanalicular fibroadenoma - connective tissue grows into intralobular ducts and giving them a bizarre slit-like shape, c) leaf-shaped (phyllodes) fibroadenoma - a node of lobed structure with a reticulate pattern resembling the structure of a leaf; slit-like and cystic cavities, foci of necrosis and hemorrhages are visible.

Consequences: fibroadenoma malignization is rare; in most cases, carcinoma in situ is detected.

3) Carcinoma (cancer) is an immature malignant epithelial tumor that develops from undifferentiated or poorly differentiated epithelial cells. There are two main morphological forms of cancer: intraepithelial (non-invasive or carcinoma in situ) and invasive (infiltrating) cancer. Carcinoma in situ is characterized by the absence of invasive growth; all malignant cells are concentrated in the thickness of the epithelial layer. In accordance with histogenesis, numerous variants of invasive carcinomas are distinguished, the most common of which are: basal cell carcinoma, squamous cell

carcinoma, transitional cell (urothelial carcinoma) carcinoma, adenocarcinoma, undifferentiated (anaplastic) carcinoma.

Basal cell carcinoma is characterized by the formation of polymorphic tumor epithelial cells that resemble the cells of the basal layer of stratified squamous epithelium. Cells are small, prismatic, or polygonal in shape, with hyperchromic nuclei and a narrow rim of the cytoplasm; located perpendicular to the basement membrane. Most often, basal cell carcinoma occurs on exposed areas of the skin; grows slowly, and often ulcerates with the formation of a deep ulcer. It is characterized by a slow course, pronounced destructive growth, and metastasizes late. With localization in the internal organs, the prognosis is less favorable.

Squamous cell carcinoma is developed from a stratified squamous epithelium. There are two main variants of squamous cell carcinoma: a) keratinizing squamous cell carcinoma (highly differentiated) and b) non-keratinizing squamous cell carcinoma (poorly differentiated).

a) keratinizing squamous cell carcinoma is characterized by the formation of extracellular keratin as "carcinomatous pearls". They got their name based on the macroscopic picture. On the cut, they are visible in the form of small grains of a grayish-white color with a pearly sheen. Squamous cell carcinoma grows relatively slowly; development in the skin, on the mucous membranes, are covered with squamous or transitional epithelium (e.g., oral cavity, esophagus, cervix, vagina, etc.). In mucous membranes covered with prismatic epithelium, squamous cell carcinoma develops only on the background of metaplasia and dysplasia of the epithelium.

b) non-keratinizing squamous cell carcinoma is a poorly differentiated cancer without keratinization (keratin is absent). It is characterized by polymorphism of cells and nuclei, a large number of mitoses. Compared to keratinizing squamous cell carcinoma, it grows quickly, and has a less favorable prognosis.

Transitional cell (urothelial carcinoma) carcinoma is a highly differentiated cancer and is sometimes very difficult to distinguish from transitional cell papilloma.

A distinctive feature is the destruction of the basement membrane and infiltration by tumor cells of their layer mucous membrane. It is characterized by more pronounced cellular atypism, multi-layering, complete or partial loss of polarity, and the presence of pathological forms of mitosis. Most often, transitional cell carcinoma develops in the mucous membrane of the urinary tract, primarily the bladder.

Adenocarcinoma (glandular cancer) is immature malignant tumor from prismatic epithelium, lining the mucous membranes and glandular epithelium of various organs. There is a pronounced cellular atypia, manifested by cell polymorphism, hyperchromia of the nuclei. The basement membrane of the glands is destroyed. Glandular structures are of various shapes and sizes, formed by stratified epithelium; their lumen is always preserved; grows into surrounding tissues, and destroys them (microphotograph 26).

Depending on the degree of differentiation there are distinguished: high-, moderate- and low-grade forms. There are glandular adenocarcinoma, tubular adenocarcinoma, and papillary adenocarcinoma. Special variants of adenocarcinoma include mucinous adenocarcinoma and signet ring cell carcinoma. Mucinous adenocarcinoma is characterized by the formation of a large amount of extracellular mucus in the tumor tissue. Signet ring cell carcinoma is formed by rounded cells, the cytoplasm of which contains mucus, which deforms and pushes the nucleus to the periphery, which makes the cell look like a ring.

Undifferentiated (anaplastic) carcinoma is a highly malignant neoplasm, characterized by the absence of signs of tissue differentiation. The use of special methods (immunohistochemical and electron microscopy) makes it possible to detect these signs. Tumor cells may be arranged in trabeculae (trabecular carcinoma) or in layers (solid carcinoma).

The cell size of undifferentiated carcinoma varies greatly: large cell carcinoma, giant cell carcinoma, and small cell carcinoma (often in the lung). Undifferentiated carcinoma can develop in any organ.

The most common organ-specific cancers are renal cell carcinoma and hepatocellular carcinoma. Depending on the severity of the stroma, two types of cancer are distinguished: medullary and fibrous (skirr). Medullary (medullary carcinoma) - cancer with a small amount of stroma, fibrous (fibrous carcinoma) - cancer with a pronounced stroma. The tissue of medullary carcinoma is usually gray-pink, soft, or elastic, resembling the substance of the brain (from the Latin "medulla" - the brain). Fibrous cancer is characterized by the density of tumor tissue due to the presence of collagen fibers in the stroma. Medullary carcinoma is more common in the thyroid and breast; fibrous - in the mammary gland and the stomach.

TEST YOURSELF

1. Name a benign tumor from squamous and transitional epithelium:

A. Adenoma

B. Fibroadenoma

C. Polyp

D. Papilloma

E. Condyloma

2. Name a benign tumor from the glandular epithelium:

A. Adenoma

B. Fibroadenoma

C. Polyp

D. Papilloma

E. Condyloma

3. Ways of metastasis of a malignant tumor:

A. Hematogenous

B. Lymphogenous

C. Implantation

D. All answers are correct

4. Local effect of the tumor on the body:

A. Increased erythrocyte sedimentation rate

B. Anemia

C. Cachexia

D. Destruction of surrounding tissue

E. Hormonal Disorders

5. Highlight a feature inherent in papilloma:

A. Tissue atypism

B. Cellular atypism

C. Metastasis

D. Invasive growth

E. Cancer pearls

6. The general effect of a malignant tumor on organism:

A. An increase in the number of red blood cells

B. Obesity

C. Hyperproteinemia

D. Increased blood lipids

E. Cachexia

7. Cancer (cancerous) is an immature tumor from:

A. Epithelium

B. Fibrous tissue

C. Hematopoietic tissue

D. Serous membranes

E. Mesenchymal tissue

8. Tumor recurrence is:

A. Development of a new tumor

B. Resumption of tumor growth in the same place

C. Increased tumor growth rates

D. A kind of metastasis

9. Early cancer metastases appear in:

A. Regional lymph nodes

B. Distant lymph nodes

C. Lungs

D. Liver

E. Bones

10. Sign of a malignant tumor:

A. Expansive growth

B. The presence of cellular atypism

C. Lack of metastases

D. Does not recur

E. Slow growth

PART 12. MORPHOLOGICAL CHARACTERISTICS OF MESENCHIMAL TUMORS. TUMORS OF MELAN PRODUCING TISSUE

Mesenchymal tumors are tumors that develop from mesenchyme derivatives: connective (fibrous), fat, muscular (smooth and striated), vascular (blood and lymphatics vessels), bone, cartilage tissues, as well as synovial and serous membranes. The source of mesenchymal tumors is a pluripotent mesenchymal cell. The level of tumor transformation of the cell, and the direction of differentiation determines the type of tumor. It can be a one-component tumor containing derivatives of one tissue (adipose, fibrous, etc.); multicomponent (mesenchymoma) - the tumor contains derivatives of various tissues (fibrous, fatty, vascular, etc.). The tumor may be heterotopic, i.e., consisting of tissue uncharacteristic for this organ (e.g., osteoma of the lung, retroperitoneal synovioma, etc.). They do not have organ specificity (may occur in any organ).

Main characteristics of mesenchymal tumors:

1) the nature of neoplasms: benign (their names are formed by adding the suffix –«oma» to the end of the original tissue, for example, fibroma, lipoma, etc.); malignant (their names are formed by adding «sarcomas» (from Greek «*sarcos*» - fish meat, with which these tumors are similar in appearance) to the end of the original tissue, for example, fibrosarcoma, liposarcoma, etc.);

2) tumor grade (high, moderate, low), set by the severity of signs of cellular atypia;

3) tumor stage (several classifications are used to assess the tumor stage, in particular, this is the TNM classification).

I. Tumors of connective (fibrous) tissue:

1) Benign, mature tumors: fibroma, dermatofibroma, fibromatosis.

Fibroma is a benign tumor of the connective (fibrous) tissue. It occurs predominantly in women. Most often localized in the skin, ovaries, and limbs.

Macroscopic features: a rounded or oval formation of a dense consistency with clear contours, separated from the surrounding tissues by a capsule. On the surface of the cut - whitish-gray colors, a fibrous structure.

Microscopic features: there are two types of fibroma: 1) soft fibroma consists of a large number of connective tissue cells (fibroblasts, fibrocytes) and a small number of connective tissue collagen fibers; 2) dense fibroma consists mainly of connective tissue fibers and a small number of connective tissue cells.

Dermatofibroma (fibrous histiocytoma) is a benign intradermal tumor that develops from the undifferentiated reticular cells (from which endothelial cells, histiocytes, and fibroblasts are formed). It is localized in the skin (usually the limbs), and subcutaneous tissue.

Macroscopic features: the tumor is represented by a small painless brown nodule (rarely exceeding 1 cm in diameter) protruding above the surface of the skin.

Microscopic features: the tumor contains fibroblasts, histiocytes, macrophages, Tuton cells (large multinucleated cells with foamy cytoplasm); a small number of connective tissue fibers, and sometimes there are hemosiderin deposits.

Fibromatosis is connective tissue tumors with locally destructive growth. Arise along the fascia, aponeuroses, and other connective tissue formations. Some researchers suggest that this tumor is a tumor-like (reactive, hyperplastic, dysplastic) proliferation of connective tissue. Currently, fibromatosis is considered as a tumor. They have infiltrating growth but do not metastasize.

Macroscopic features: fibromatosis is presented by diffuse or nodular vegetations of varying density.

Microscopic features: fibromatosis has a microscopic structure, which is identical to fibromas, but does not form capsules and infiltrates the surrounding tissues.

There are the following types of fibromatosis: desmoid, palmar, plantar, penile fibromatosis, etc.

Desmoid (deep fibromatosis) is the most common type of fibromatosis characterized by locally destructive growth; recurs after removal. It can be abdominal, intra-abdominal or extra-abdominal. *Abdominal desmoid* is a dense tumor-like whitish formation that occurs in the muscular-aponeurotic structures of the anterior wall of the abdomen, mainly in women 20-40 years old, more often during pregnancy and after childbirth. Often recurs. *Extra-abdominal desmoid* is localized in the muscles of the shoulder, chest wall, back, and thigh in both sexes. *Intra-abdominal desmoid* is localized in the mesentery, pelvis, and retroperitoneal in both sexes.

2) Malignant, immature tumors: fibrosarcoma, malignant fibrous histiocytoma.

Fibrosarcoma is a malignant tumor of the connective tissue. It is founded more often in the shoulder and hip.

Macroscopic features: the tumor is represented by single or multiple nodes that invade the underlying tissues or skin. The tumor is associated with aponeurosis or fascia, located in the thickness of the muscles. In section, the tumor tissue resembles "fish meat", gray in color. The color of the tumor in the section depends on the presence of foci of necrosis and hemorrhage. Often the tumor has cysts filled with mucous secretion.

Microscopic features: the tumor contains atypical fibroblasts and immature collagen fibers. There is highly differentiated fibrosarcoma - the fibrous component prevails over the cellular component; gives late metastases. Poorly differentiated fibrosarcoma consists of immature cells with multiple polymorphic mitoses; has more pronounced malignancy and gives early metastases.

Malignant fibrous histiocytoma is a malignant tumor of mixed origin. It is the most common malignant mesenchymal tumor. It is localized more often on the lower extremities; retroperitoneal localization is also characteristic. The tumor grows slowly, infiltrating the surrounding tissues, and may recur, but rarely metastasize.

Macroscopic features: the tumor is presented by a dense nodule, with signs of invasion into the underlying tissues. Vascularization of the tissue can be different; the density of the tissue depends on the amount and composition of the fibrous component.

Microscopic features: the tumor is formed by fibroblast-like cellular elements and histiocytes with signs of cellular atypia (polymorphism of cells and nuclei, the presence of mitoses, etc.). A microscopic feature of the tumor is the presence in the tissue of a large number of giant multinucleated cells.

II. Tumors of adipose tissue:

1) Benign, mature tumors: lipoma, hibernoma.

Lipoma is a benign tumor of the white adipose tissue. It is one of the most common. The tumor can be localized both under the skin and on the internal organs and omentum.

Macroscopic features: this is a demarcated node of various sizes, light yellow in color with a thin capsule, soft consistency; yellowish on the cut, resembling adipose tissue.

Microscopic features: the tumor contains mature lipocytes with a small amount of connective tissue. Vascularization of the tissue is different; signs of secondary inflammation may be detected, with large tumors with a diameter of more than 10 cm - foci of necrosis.

Hibernoma is a benign tumor of brown fat (brown fat is present in newborns, and plays an important role in heat production since most of the energy produced by these cells is released in the form of heat). It more often occurs in women of elderly and middle age in the interscapular region.

Macroscopic features: the tumor is formed by a soft-elastic encapsulated node with a lobed structure.

Microscopic features: the tumor consists of round or polygonal cells with centrally located nuclei; the cytoplasm is fine-grained or foamy.

2) Malignant, immature tumors: liposarcoma, malignant hibernoma.

Liposarcoma is a malignant tumor of the white adipose tissue, which is relatively rare. Liposarcomas grow slowly and metastasize late.

Macroscopic features: tumor may be large; has the appearance of a node or a conglomerate of nodes with infiltration of surrounding tissues. The consistency is dense; the cut surface is motley - with foci of mucus, hemorrhages, and necrosis.

Microscopic features: the tumor consists of lipoblasts of varying degrees of maturity; giant cells are found; pronounced tissue and cellular polymorphism. Depending on the predominance of cellular forms, several types of liposarcoma are distinguished: 1) highly differentiated - consists of mature adipocytes with slight pleomorphism and a small admixture of lipoblasts, 2) myxoid - is characterized by round and spindle-shaped cells located in a vascularized myxoid matrix, containing lipoblasts, 3) round cell - contains primitive round cells, 4) polymorphic cell (poorly differentiated) - contains pleomorphic spindle-shaped and round cells, varying numbers of pleomorphic lipoblasts.

Malignant hibernoma is a malignant tumor of brown fat. Tumor localization, sex, and age of patients are the same as in hibernoma. The tumor recurs. It rarely metastasizes - mainly to the lungs by the hematogenous route.

Macroscopic features: the tumor has a lobular appearance, brownish color. When localized under the skin, it often ulcerates and is partially necrotic.

Microscopic features: the tumor is characterized by a pronounced polymorphism of cells that have a polygonal shape. There are many giant single and multinucleated cells with basophilic homogeneous and fine-grained cytoplasm. There are few mitoses.

III. Tumors of muscle tissue (from smooth and striated):

1) Benign, mature tumors: leiomyoma, rhabdomyoma.

Leiomyoma is a benign tumor of the smooth muscle. It occurs at any age in both men and women. The tumor may be located in the uterus, muscular layer of the gastrointestinal tract, skin (from the muscles that raise the hair, from the walls of the

vessels), and mammary gland. Leiomyoma of the uterus is one of the most common tumors in women. There are submucosal, intramural subserous uterine leiomyomas.

Macroscopic features: the tumor is a clearly delimited node of dense consistency, fibrous on the cut. The size of the tumor is variable, sometimes up to 30 cm and more. Leiomyomas can be multiple or isolated or form a conglomerate of nodes.

Microscopic features: leiomyoma is formed from spindle-shaped tumor cells that form bundles going in different directions. With special research methods, myofibrils are detected in the cytoplasm. There may be a predominance of the connective tissue component – fibromyoma. The more connective tissue in the tumor, the slower it grows.

Rhabdomyoma is a benign tumor of the striated muscle. It occurs rarely in all age groups, more often in children and newborns. The tumor is localized on the head, neck, and torso, upper and lower extremities. Clinically, they proceed benignly, except for rhabdomyomas of the heart and tongue, which are the cause of death of patients.

Macroscopic features: the tumor is represented by a node, sometimes reaching 10-15 cm in diameter, dense elastic consistency, movable, with a pronounced capsule.

Microscopic features: it develops from striated muscle structures of cells of various shapes - large oval, strip-like, ribbon-like. Striations are detected with difficulty, mainly in elongated ribbon-shaped cells. Glycogen is found in the cytoplasm of cells. Mitotic Figures are absent.

2) Malignant, immature tumors: leiomyosarcoma, rhabdomyosarcoma.

Leiomyosarcoma is a malignant tumor of smooth muscle. It is localized more often in the gastrointestinal tract, mainly in the large intestine, retroperitoneally, in the soft tissues of the extremities, and the uterus. It occurs more often at a young age and rarely occurs in children. The tumor metastasizes early, predominantly by the

hematogenous route, giving multiple metastases to the liver, lungs, and often to the brain and other organs.

Macroscopic features: the tumor is represented by a node of dense elastic consistency, which can be more than 30 cm in diameter. The boundaries are unclear; it grows into the surrounding tissues. The cut surface of the tumor is gray-red, often motley due to foci of hemorrhages and necrosis.

Microscopic features: the tumor is characterized by a pronounced polymorphism of cells and nuclei - large elongated cells with rounded hyperchromic nuclei and a large number of pathological mitoses; the presence of giant multinucleated cells. The stroma is represented by a loose network of argyrophilic fibers with numerous vessels.

Rhabdomyosarcoma is a malignant tumor of the striated muscles. Rhabdomyosarcoma is one of the most common tumors in children. It is localized in the muscles of the lower, less often upper limbs, in the retroperitoneal tissue, mediastinum, on the face, neck, nasopharynx, and in the urinary organs. Rhabdomyosarcoma is characterized by a high degree of malignancy; often recurs, and gives multiple hematogenous metastases to the liver and lungs.

Macroscopic features: the tumor is represented by a node with a diameter of up to 20 cm or more without clear contours. The tissue on the cut surface has the appearance of "fish meat".

Microscopic features: the tumor is represented by rhabdomyoblasts with granular eosinophilic cytoplasm with thick and thin filaments. Rhabdomyoblasts have a polymorphic structure - they can be round or oval and have striations. There are the following types of rhabdomyosarcoma: 1) alveolar - characterized by the formation of pseudo-glandular and pseudo-alveolar structures, 2) embryonal - characterized by the presence of myxoid, spindle-shaped, and round cells, 3) pleomorphic - characterized by rounded, polymorphic or large spindle-shaped and stellate cells; syncytial masses and vacuolated arachnid-shaped cells.

IV. Tumors of vessels (blood and lymphatics vessels):

1) Benign, mature tumors: hemangioma, glomus-angioma, hemangiopericytoma, lymphangioma.

Hemangioma is a benign tumor of the endothelium of blood vessels. In most cases, it appears during the first days and weeks of life, and most actively grows during the first six months. Depending on which vessels are affected, there are the following types of hemangiomas: 1) capillary; 2) venous; 3) cavernous; 4) arterial.

Macroscopic features: 1) *capillary hemangioma* is more often localized in the skin, mucous membranes of the gastrointestinal tract, and liver; is represented by a red or bluish node with a smooth, tuberous, or papillary surface, on the cut it has a cellular structure. If the tumor is localized in the skin when pressed, the node becomes white; 2) *venous hemangioma* is localized deep in the soft tissues, between the muscles; is represented by the red or bluish node; 3) *cavernous hemangioma* is more often localized in the liver, gastrointestinal tract, brain; it has an appearance of a red-blue spongy node, which is well delimited from the surrounding tissue; 4) *arterial hemangioma* resembles a capillary hemangioma, represented by a conglomerate of vessels of bright red color.

Microscopic features: 1) *capillary hemangioma* consists of branching capillary type vessels with narrowed lumens; is characterized by multinucleated endothelial cells; stroma is loose or fibrous (microphotograph 27); 2) *venous hemangioma* consists of vessels of the venous type, forming cavities; 3) *cavernous hemangioma* consists of large thin-walled vascular cavities (caverns) lined by endothelial cells and filled with liquid и clotted blood; 4) *arterial hemangioma* consists of many vessels of arterial type.

Glomus-angioma is a benign tumor of arteriovenous anastomoses. The preferential localization is fingers and toes in the nail bed area, rarer on the skin of the shin, thigh, and torso. It can be a single (solitary) or multiple. It occurs with the same frequency in both men and women, mostly of mature age.

Macroscopic features: the tumor is represented by a single node with a diameter of 0.3-0.8 cm, soft consistency, and grayish-pink color.

Microscopic features: it consists of sinusoid-type slit-like vessels lined with endothelium and surrounded by epithelioid cells resembling glomus cells.

Hemangiopericytoma is a tumor of vascular origin, characterized by the formation of vessels, as well as the proliferation of perivascular cells (pericytes). The tumor occurs at any age, more often in children; may happen again in a few years.

Macroscopic features: the tumor is represented by a nodule, has a porous structure, and is pinkish-red in section, with abundant vessels.

Microscopic features: the tumor is characterized by a large number of capillaries lined with endothelium and surrounded by oval, rounded, or spindle-shaped cells with dark nuclei and pale cytoplasm. The cells are braided by a network of argyrophil fibers. There is a massive proliferation of perivascular cells (pericytes).

Lymphangioma is a benign tumor from the lymphatic vessels. More often it happens in children. It is localized mainly on the neck, the oral mucosa, the retroperitoneal space, and the mesentery. There are the following types of tumors: 1) capillary, 2) cavernous, and 3) cystic.

Macroscopic features: 1) *capillary lymphangioma* is located on the face (cheeks and upper lip); is swollen, covered with intact skin; consistency is elastic; 2) *cavernous lymphangioma* is soft tumor nodules covered with intact skin and causing a pronounced deformation of affected areas; in some cases, grows into the skin and forms on its surface the thin-walled vesicles filled with lymph; 3) *cystic lymphangioma* is the soft hemispherical painless formation of large size, as a rule, is not fused with the skin.

Microscopic features: 1) *capillary lymphangioma* consists of a network of dilated lymphatic capillaries; 2) *cavernous lymphangioma* is represented by many small and large cavities lined with endothelium; 3) *cystic lymphangioma* contains single large cavities lined with endothelium and filled with serous fluid mixed with detritus.

2) Malignant, immature tumors: hemangiosarcoma, Kaposi's sarcoma, lymphangiosarcoma.

Hemangiosarcoma is a malignant tumor of the blood vessels. The tumor is characterized by rapid growth, early metastasis, and high malignancy. It is found in the skin, skeletal muscles, and liver.

Macroscopic features: the tumor is represented by grayish-pink or brown nodes; they are soft. The tumor infiltratively grows into the tissue.

Microscopic features: the tumor consists of spindle-shaped, rounded, and polymorphic atypical cells – endotheliocytes (malignant hemangioendothelioma) or periocytes (malignant hemangiopericytoma). The cells form strands and are associated with well-developed newly formed vessels and vascular cavities. Some of the cells (periocytes) may retain muff-like locations around the vessels.

Kaposi's sarcoma (multiple idiopathic hemorrhagic Kaposi's sarcoma, Kaposi's angiosarcoma, angioendotelioma of the skin) is one of the specific types of angiosarcoma; is a malignant neoplastic disease of reticulo-histiocytic system with a primary lesion of the skin. The disease is accompanied by lesions of the oral mucosa and lymph nodes. Prognosis is poor: death occurs as a result of hemorrhage in the internal in organs case of generalization of the process or progressive cachexia. There are 3 clinical forms: 1) sporadic, 2) endemic, and 3) epidemic.

1) *Sporadic form* (classic variant, European type) - a rare tumor; that occurs in older men; localized on the skin of the legs, symmetrical lesions are frequent. Tumor is a low degree of malignancy, characterized by a long course with possible metastasis.

Macroscopic features: the tumor is represented by spots and plaques - cyanotic, purple, often with ulceration, spontaneous scarring of the foci is possible.

2) E*ndemic form* (African type) is common in some parts of Africa, accounting for up to 10% of all malignant tumors. It occurs in children; is characterized by an aggressive course with injury of the internal organs and lymph nodes.

3) *Epidemic form* (AIDS-related type) occurs with immunodeficiency and refers to HIV-associated diseases. The direct etiological role of the virus (HIV) in Kaposi's sarcoma has not been proven. Kaposi's sarcoma in HIV infection occurs regardless of gender and age often localized in the internal organs with the development of widespread lesions of the gastrointestinal tract, lungs, etc. It occurs more aggressively with the early development of metastases.

Microscopic features: in any clinical form, the tumor is represented by vascular cavities lined with endothelial cells and filled with erythrocytes, and bundles of elongated fibroblast-like cells; hemorrhages, hemosiderosis are found.

Lymphangiosarcoma is a malignant tumor of the lymphatic vessels; occurs in the background of chronic lymphostasis. It is characterized by rapid infiltrative growth and early metastasis.

Macroscopic features: the tumor is localized mainly superficially in the skin and subcutaneous tissues. It has the appearance of flat purple-bluish spots or slightly elevated plaques, and then becomes nodular, often ulcerate and bleed.

Microscopic features: the tumor is represented by anastomosing vascular slits of capillary type with proliferating atypical endothelial cells (malignant lymphangioendothelioma) and hyperchromic nuclei. Hyalinosis of perivascular spaces and vascular walls is found. Significant lymphoplasmacytic infiltration is found in the stroma.

V. Tumors of bone tissue:

1) Benign, mature tumors: osteoma, osteoblastoclastoma.

Osteoma is a benign bone tumor. The predominant localization of osteomas is the bones of the skull, especially the paranasal sinuses. Osteoma of tubular bones is rare. It is more often detected in childhood.

Macroscopic features: the tumor has the appearance of a node, and dense consistency compared to the surrounding tissues. In the paranasal sinuses of the skull, it is sometimes multiple, growing in the form of a pedunculated polyp. Concerning bone, the osteoma can be periosteal, cortical, or endosteal.

Microscopic features: there are two types of osteoma: compact and spongy. *Compact osteoma* consists of a bone mass of fine-fiber or lamellar structure with very narrow vascular channels. *Spongy osteoma* is represented by a clear network of bone beams chaotically located. Interfascicular spaces are filled with cellular-fibrous tissue. It has no clear boundaries with the surrounding bone tissue.

Osteoblastoclastoma (giant cell tumor) contains multinucleated giant cells (osteoclasts) and small cells (osteoblasts). The predominant localization is the jaws, epiphyseal and metaphyseal parts in long bones. The tumor recurs, and sometimes metastasizes (even in a benign course) by the hematogenous route.

Macroscopic features: the tumor has a motley appearance (brown tumor): on the cut surface red and gray sections alternate with brown centers of hemosiderosis, yellowish areas of necrosis, whitish areas of fibrosis, and cystic cavities containing serous or bloody fluid. At the same time with the prevailing soft masses, denser areas of ossification and fibrosis can be seen. A pathological fracture often occurs in the area of the tumor.

Microscopic features: the tumor contains anastomosing small osteoid and calcified bone beams, between which there are many vessels and fibrous tissue with multinuclear osteoclasts.

2) Malignant, immature tumors: osteosarcoma, malignant osteoblastoclastoma.

Osteosarcoma (osteogenic sarcoma) is a malignant tumor that develops from bone and is characterized by the formation of atypical bone-osteoid. Most often, the tumor occurs in males aged 10-20 years. The most typical localization is long bones. Osteosarcoma can also occur in various bones in the elderly on the background of bone pathology (Paget's disease, etc.).

Macroscopic features: the tumor has a motley appearance - from white-gray to brown-red in color, with loose consistency, despite the presence of focal calcification.

Microscopic features: the tumor is represented by bone and osteoid structures lined with atypical osteoblasts, with the presence of many thin-walled vessels, and there are many atypical mitotic Figures. Metastasis is predominantly hematogenous,

mainly in the lungs. Depending on the predominance of bone formation or bone destruction, osteoblastic and osteolytic forms of osteosarcoma are distinguished.

Malignant osteoblastoclastoma is characterized by a pronounced structural atypism; in the case of expressed anaplasia it can take the character of fibro-, polymorphocellular or osteogenic sarcoma. Other features, in general, correspond to benign osteoblastoclastoma (see above).

VI. Tumors of cartilage tissue:

1) Benign, mature tumors: chondroma.

2) Malignant, immature tumors: chondrosarcoma.

Chondroma is a benign tumor of hyaline cartilage. The most common localization is the hands and feet, vertebrae, sternum, and pelvic bones. It occurs in all age groups but is more common in children. Clinically, it grows slowly, over the years. Depending on the location of the tumor, there are two types: *ecchondroma* - the tumor is localized in the peripheral parts of the bone; *enchondroma* - the tumor is localized in the central parts of the bone.

Macroscopic features: chondroma is represented by a nodular of lobular structure, dense consistency, and bluish-white color, resembling cartilage.

Microscopic features: the tumor consists of mature hyaline cartilage cells enclosed in the main substance. Cartilage cells with one, sometimes with two small nuclei are located chaotically in typical lacunae (microphotograph 28).

Chondrosarcoma is a malignant tumor of hyaline cartilage. The tumor grows slowly, and gives late metastases.

Macroscopic features: the tumor is formed by lobules of a bluish-white color, of different sizes and shapes, separated by layers of connective tissue. The consistency may be dense (calcification and endochondral bone formation) or liquid (cystic cavities filled with mucous mass).

Microscopic features: the tumor is characterized by a pronounced polymorphism of atypical cells of the chondroid type with atypical mitoses, the formation of a chondroid intercellular substance. There may be foci of osteogenesis,

mucus, and necrosis. Depending on the degree of differentiation, there are the following types of tumors: high, moderate, and poorly differentiated.

VII. Tumors of synovial membranes:

1) Benign, mature tumors: benign synovioma.

2) Malignant, immature tumors: synovial sarcoma.

Benign synovioma is a benign tumor that develops from the synoviocytes of the tendon sheaths and tendons. The tumor is localized on the extremities in the area of the joints; occurs more often at the age of 30-40 years, more often in men.

Macroscopic features: the tumor is represented by a dense nodule 5 cm or more in size, homogeneous on the cut surface, whitish-pink in color.

Microscopic features: the tumor contains polymorphic large cells; has cracks and cysts of various sizes, lined with oval, cubic, prismatic cells, resembling cells of glandular epithelium. In addition, there are spindle-shaped cells that form the stroma of the tumor. They are also polymorphic. There are single giant multinucleated cells (gigantoma) and xanthoma cells.

Synovial sarcoma (malignant synovioma) is a malignant tumor of the synovial elements (synoviocytes). The tumor is localized in large joints; grows rapidly, metastasizes early.

Macroscopic features: the tumor is represented by a limited shapeless mass, usually of large sizes. On the section it is homogeneous, soft-elastic consistency; sometimes there are areas of bone, cartilage, calcifications, and cysts.

Microscopic features: the tumor has a polymorphic structure; in some cases, light polymorphic cells, pseudoepithelial glandular formations, and cysts predominate; in other cases, fibroblast-like atypical cells and collagen fibers predominate, as well as tendon-like structures.

VIII. Tumors of serous membranes:

1) Benign, mature tumors: mesothelioma.

2) Malignant, immature tumors: malignant mesothelioma.

Mesothelioma is a benign tumor that develops from cells of the mesothelium. Mesothelioma occurs more often in the visceral and parietal pleura and peritoneum and; in rare cases – in the pericardium and testicle membranes. The tumor is relatively rare.

Macroscopic features: the tumor is represented by a slowly growing, clearly demarcated, dense, layered nodule in the serous membranes (most often in the visceral pleura).

Microscopic features: the tumor consists of light neoplastic cells forming solid fields or tubular structures, which are located in the connective tissue, with small lymphoid infiltrates.

Malignant mesothelioma is a malignant tumor that develops from mesothelial cells. It is found in the peritoneum, less often in the pleura and pericardium. It is a rare neoplasm. The development of this tumor is triggered by exposure to asbestos.

Macroscopic features: the tumor looks like a dense infiltrate with a thickness of 2-3 cm or more on the serous membranes. In the pericardium and omentum it appears as indistinctly demarcated nodules with a villous surface.

Microscopic features: the tumor consists of atypical cells with vacuolated cytoplasm, forming papillary or tubular structures.

Tumors of melanin-producing tissue are a group of tumors that develops from neurogenic melanin-producing cells (melanoblasts and melanocytes). These are cells that, under the influence of tyrosinase, synthesize the pigment melanin, painted in a dark brown color. Benign tumors include a nevus; a malignant tumor is called melanoma.

Nevus is a benign tumor-like formation from melanin-producing cells. Nevi are localized on the skin, more often on the face, torso in the form of protruding dark-colored formations. According to the origin, the nevi can be divided into acquired and hereditary. Depending on their location and morphological classification, there are the following types of nevi: 1) junctional, 2) intradermal, 3) compound (mixed), 4) epithelioid (spindle-cell), 5) blue.

1) Junctional nevus is located at the border of the epidermis and dermis, mainly in the papillary layer of the dermis.

Macroscopic features: the nevus is represented by a dark brown, dark gray, or black nodule that slightly protrudes above the skin; is usually not more than 1 cm in diameter with a smooth, dry, hairless surface. The border nevus has clear contours. It can be located on different parts of the body.

Microscopic features: nests of nevus cells with pigment are elongated, rounded, or polygonal in shape with a homogeneous or slightly granular cytoplasm, and a large oval or round nucleus (microphotograph 29).

2) Intradermal nevus is located deep in the dermis. It is the most common type of melanoform nevus.

Macroscopic features: papillomatous nodular or warty formation pale brown or black in color with a diameter from 2 mm to several centimeters.

Microscopic features: nevus consists of nests and strands of nevus cells, which are located only in the dermis. Nevus cells contain a lot of melanin. Often found multinucleated giant cells of the nevus.

3) Compound (mixed) nevus is a transitional form; it has the characteristics of both junctional and intradermal nevus.

Macroscopic features: the nevus looks like a mole: it rises on the skin and can have a different color - from light brown to almost black. It often has hair on it. A mixed nevus has a smooth surface and can be found anywhere on the body.

Microscopic features: in the dermis nests of nevus cells that are clearly demarcated from the surrounding tissue are found. In the deeper layers of the dermis nevus cells become elongated.

4) Epithelioid (spindle-cell) nevus occurs on the face mainly in children (juvenile nevus).

Macroscopic features: the nevus is represented by a spherical or flat single node, clearly delimited from the surrounding tissue, pale red, yellowish-gray, brown or black in color with a smooth, sometimes warty, and papillomatous surface.

Microscopic features: the nevus consists of spindle-shaped cells and epithelioid cells with a light cytoplasm. There are multinucleated giant cells resembling Pirogov-Langhans cells or Touton cells. There is little or no melanin in the cells. Nevus cells form nests both at the border with the epidermis and in the deep layers of the dermis.

5) Blue nevus occurs more often in people 30-40 years old in the buttocks and limbs. The structure of the blue nevus is similar to melanoma, but is a benign neoplasm; sometimes it recurs.

Macroscopic features: it looks like a blue nodule with a bluish tinge.

Microscopic features: the nevus consists of proliferating melanocytes that can grow into the subcutaneous tissue.

Dysplastic nevus is a separate group because it is a precancerous condition, which leads to the development of melanoma.

Macroscopic features: these are flat maculae or plaques that protrude slightly above the surface of the skin and have a "motley" surface.

Microscopic features: nevi are characterized by cellular and tissue atypism. Nests of nevus cells are large and often merge. The single nevus cells replace the basal layer of cells along the border with the epidermis, leading to the development of lentiginous hyperplasia.

There are signs of nevus progression: an increase or decrease in pigmentation; the formation of small pigmented satellite nodules; change to a dense consistency; the appearance of areas of bluish-red color; the appearance of radiating streak-like pigmentation. Progression of dysplastic nevi can lead to the development of melanoma.

Melanoma (melanoblastoma, malignant melanoma) is a malignant tumor of melanin-producing cells. It is one of the most malignant tumors, metastasis by both lymphogenous and hematogenous routes to almost all organs. It is localized in melanin-producing tissue - more often in the skin (face, limbs, and torso) and eyes,

less often in the pia mater, adrenal glands, and colon mucosa, less often - in the mucous membranes of the oral cavity, genital organs, esophagus, and anus.

Most melanomas occur de novo, rarely on the background of pre-existing pigmented lesions (e.g., lentigomaligna, dysplastic nevi) (Figure 13).

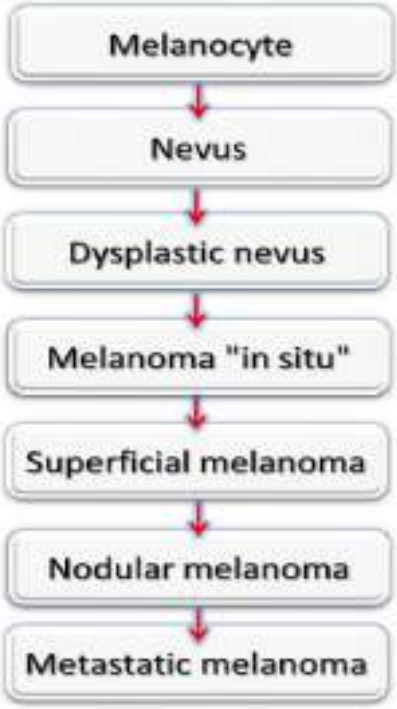


Figure. 13. Stages of biological progression of melanoma.

There are the following risk factors: ultraviolet radiation is the leading risk factor; phenotype (light skin, light (blue) eyes); sunburns in anamnesis; heredity; xeroderma pigmentosum; age over 50, etc.

Test ABCDE, helps to identify the signs of transformation of nevus (mole) in melanoma: **A**symmetry: half or part of the mole does not look like its other half (or its part); **B**order: birthmark borders are irregular, blurred, vague, and badly defined; **C**olor: birthmark color is not uniform, varies from one part of the mole to another; **D**iameter: birthmark diameter is greater than 6 millimeters; **E**volving: the size or shape, or color of a birthmark changes over time (Figure 14).

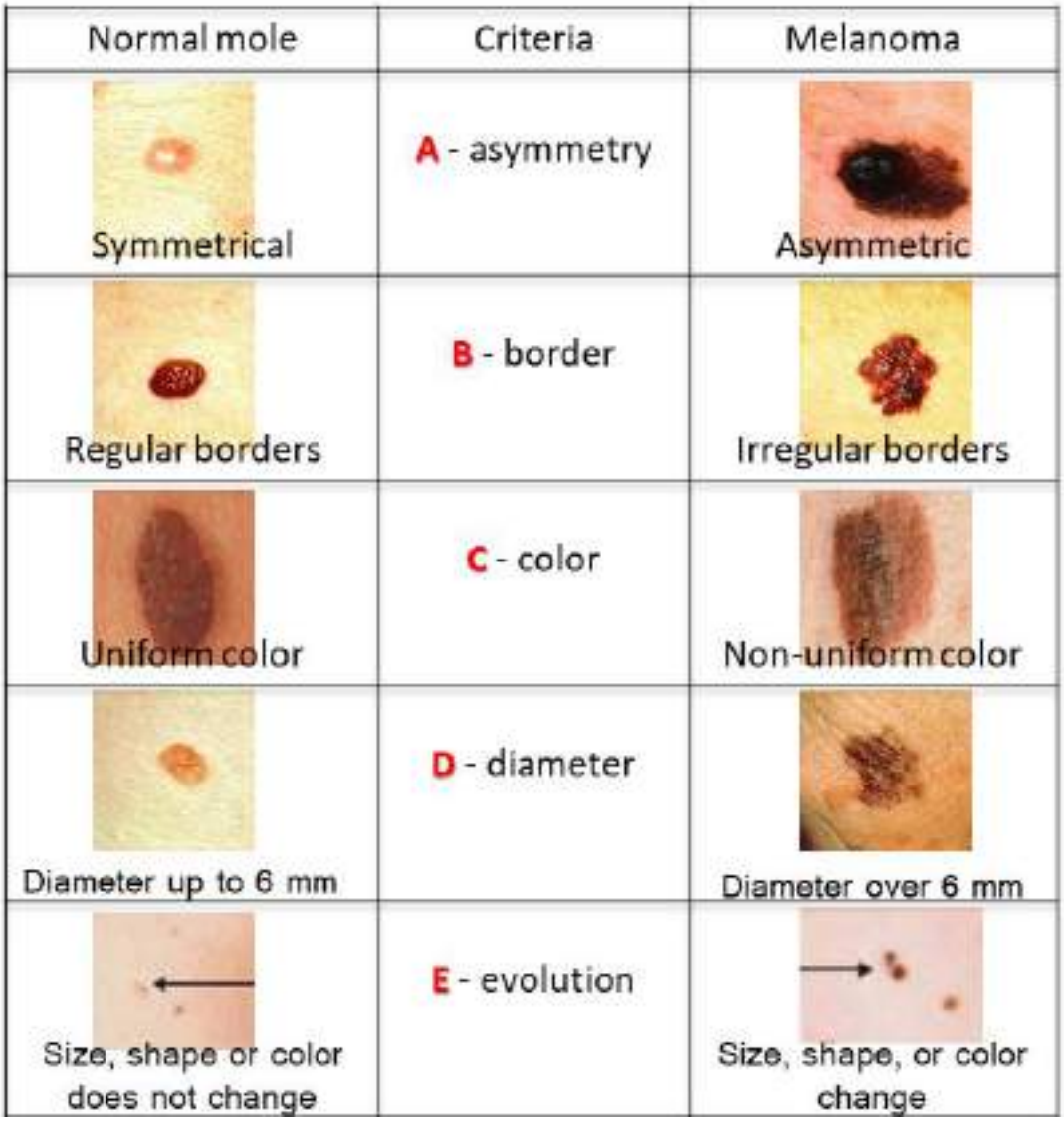


Figure. 14. ABCDE criteria for the evaluation of melanocytic tumors

Melanoma growth phases: 1) radial (horizontal) growth phase - the tumor grows inside the epidermis without spreading into the dermis (tumor in situ). 2) vertical growth phase - the tumor spreads into the dermis and subcutaneous tissue. It is characterized by the appearance of metastases. Over time, radial growth changes to a vertical type of growth.

Macroscopic features: melanoma may appear as patches of pink and black (superficially spreading melanoma), blue-black, soft nodules or plaques (nodular melanoma) often with ulceration. Occasionally, there are isolated areas of white or

flesh-colored hypopigmentation. The borders of melanoma are unclear, convoluted, and the shape is rounded.

Microscopic features: the tumor is characterized by intraepidermal proliferation of large melanocytes of spindle-shaped, epithelioid, neocellular and mixed forms, containing a large amount of pigment, and their invasion into the dermis; the papillary dermis is enlarged, there is an inflammatory infiltrate. These cells form solid nests, or grow in small groups in all layers of the epidermis or the dermis. There are many mitoses in the tumor, foci of hemorrhages and necrosis are noted. When the tumor decays, a large amount of melanin and promelanin is released into the blood, which may be accompanied by melaninemia and melaninuria.

There are the following clinical and morphological forms of melanoma (main forms): 1) superficial spreading melanoma, 2) nodular melanoma, 3) acral lentiginous melanoma, 4) lentiginous melanoma.

1) Superficial spreading melanoma is the most common type; typical localization - limbs, and torso. It has the appearance of a spot or plaque without clear boundaries, various colors - from pink-brown to dark brown. Microscopically, the tumor is represented by monomorphic atypical melanocytes forming nests. Horizontal growth (in situ) prevails. There are possible foci of invasion into the dermis.

2) Nodular melanoma is characterized by vertical growth. It occurs at an earlier age on any part of the skin. It has the worst prognosis. The tumor appears as a bluish-black plaque or pigmented nodule (black or brown), often ulcerated. Microscopically, the tumor consists of polymorphic (spindle-shaped, lamellar, and irregularly shaped, often multinucleated) cells containing granules of a black-brown pigment - melanin. The nuclei are irregular in shape, with large nucleoli, and numerous mitoses. The tumor infiltrates the dermis and subcutaneous tissue.

3) Acral lentiginous melanoma - the most typical localization is the palms and soles, the mucous-epidermal zones of the oral cavity, nose, and anus. Microscopically, the tumor contains intraepidermal proliferation of large, pigment-

rich, polymorphic melanocytes and their invasion into the dermis; the papillary dermis is expanded, and there is an inflammatory infiltrate.

4) Lentiginous melanoma occurs on areas of the skin exposed to insolation. It has a long phase of radial growth and a low grade of malignancy. Microscopically, the tumor consists of atypical, polymorphic, often spindle-shaped melanocytes infiltrating the dermis.

The prognosis of melanoma is determined by: 1) the stage of the tumor; 2) the level of invasion by Clark; 3) the depth of invasion (tumor thickness) by Breslow:

1) Stages of melanoma development:

Stage I - local lesion;

Stage II - regional skin metastases (satellites) or metastases to regional lymph nodes;

Stage III - the presence of distant metastases.

2) Levels of melanoma invasion by Clark:

1. All tumor cells are found in the epidermis, upper the basement membrane;

2. Tumor cells infiltrate the papillary layer of the dermis;

3. The tumor is found in the boundary between the papillary and reticular layers of dermis;

4. Tumor cells are found in the reticular layer of the dermis;

5. Tumor invades the fatty tissue.

3) Breslow’s depth indicates the absolute depth of tumor invasion into the dermis. It is considered the thickness from the upper layer to the deepest layers:

1. Superficial – less than 0.75 mm invasion;

2. Intermediate – from 0.76 to 3.99 mm;

3. Deep – invasion more than 4 mm.

The deeper invasion is associated with a worse prognosis. At levels of invasion 1 - 2, 5-year survival is 100%, at levels 3 - 88%, 4 - 66%, 5 - 15%.

TEST YOURSELF

1. Lipoma is characterized by:

A. Hematogenous metastasis

B. Lymphogenous metastasis

C. Cellular atypism

D. Tissue atypism

2. What are the malignant tumors of muscle tissue?

A. Rhabdomyoma, leiomyoma

B. Leiomyosarcoma, rhabdomyosarcoma

C. Hemangioma, hemangiosarcoma

D. Fibroma, fibrosarcoma

E. Melanoma

3. What is the characteristic of rhabdomyoma?

A. Malignant tumor of the striated musculature

B. Benign striated muscle tumor

C. Cellular and tissue atypism

D. Benign smooth muscle tumor

E. Malignant tumor of smooth muscle

4. The most common localization of fibroadenoma:

A. Stomach

B. Rectum

C. Mammary gland

D. Pancreas

E. Ovary

5. Melanoma is:

A. Benign tumor of the glandular epithelium

B. Benign tumor of melanocytes

C. Malignant tumor from melanocytes

D. Tumor from muscle tissue

6. Name an immature tumor of mesenchymal origin:

A. Fibroma

B. Sarcoma

C. Lipoma

D. Leiomyoma

7. A 28-year-old man with a history of an elbow bruise 3 years ago presented with a tumorous growth in the area of an epiphysis of a humeral bone. The formation did not have accurate borders. A histological investigation of biopsy material revealed a considerable quantity of polymorphic cells of osteoblastic type with numerous pathological mitoses. Make the presumable diagnosis.

A. Osteosarcoma

B. Chondrosarcoma

C. Fibrosarcoma

D. Lipoma

8. A 15-year-old young man presented with a tumorous formation in the central site of his wrist bone. The node grew slowly within the last three years. Histological research of a removed neoplasm revealed mature chondrocytes without mitoses, which are randomly located in chondral lacunas. Cartilages of a capsule had different forms and sizes due to the variable quantity of chondral cells, between which there was a basic substance with liquid layers of connective tissue. What is the most likely diagnosis?

A. Chondrosarcoma

B. Chondroma

C. Osteosarcoma

D. Leiomyoma

9. A 14x6x5 cm neoplasm excised from a retroperitoneum of a 66-year-old woman in the surgery department. Microscopic investigation revealed atypical anaplastic cells, which contained round cytoplasmic vacuoles of lipid that scallop

the nucleus. The majority of cells were pleomorphic, and some of them were round with chromosomal abnormalities. What is the most likely diagnosis?

A. Fibrosarcoma

B. Lipoma

C. Myosarcoma

D. Liposarcoma

E. Mesothelioma

10. A 20-year-old man has had a slowly growing reddish nodule on his upper lip. He finally decides to have a surgeon remove it. Microscopically the nodule is composed of benign varying-sized tiny blood vessels. What is the most likely diagnosis?

A. Myosarcoma

B. Capillary hemangioma

C. Fibroma

D. Myoma

E. Lipoma

PART 13. TUMORS OF THE HEMOPOETIC AND LYMPHOPROLIFERATIVE TISSUE

Hemoblastoses are tumor diseases of the hematopoietic and lymphatic tissue. Hemoblastoses are polyetiological diseases. Various factors can cause mutation of hematopoietic and lymphatic tissue cells: 1) biological factors (human T-lymphotropic virus (HTLV-I, HTLV-II), Epstein-Barr virus); 2) chemical factors (benzene, chloramphenicol, phenylbutazone, etc.); 3) environmental factors (ionizing radiation); 4) chemotherapy; 5) suppression of the immune system; 6) lifestyle factors (alcohol abuse, smoking, unhealthy eating habits, prolonged insolation, etc.); 7) hereditary factors.

According to the International Histological and Cytological classification of tumor diseases of the hematopoietic and lymphoid tissues, which is based on the cellular composition of neoplasms and the nature of the distribution, all hemoblastoses are divided into two main groups: 1) leucosis (leukemia) - systemic tumor diseases hematopoietic tissue; 2) lymphomas - regional tumor diseases of the hematopoietic and/or lymphoid tissue. The division of hemoblastoses into systemic and regional tumors is conditional since limited tumor growth and diffuse tumor infiltration can occur simultaneously or sequentially in one patient.

I. Leucosis (leukemia) is a systemic progressive proliferation of immature tumor tissue with the initial localization in the bone marrow and with hematogenous spread to other organs and tissues. The process is characterized by the rapid dissemination of tumor cells in the hematopoietic system. As a result, in the early stages, the disease becomes systemic.

In leukemia, tumor tissue initially grows into the bone marrow and gradually replaces normal hematopoietic cells. It leads to the development of various cytopenias – anemia (leukoanemia), thrombocytopenia, lymphocytopenia, leukocytopenia. Such violations are accompanied by increased bleeding, hemorrhage, and suppression of immunity with the development of infectious complications. Metastasis is accompanied by the appearance of leukemic infiltrates in various organs - the spleen, lymph nodes, lymph formations (Peyer's patches, solitary lymphoid follicles) along the gastrointestinal tract, liver, and other organs. Heart attacks, ulcerative-necrotic changes develop in organs due to the blockage of blood vessels by tumor embolisms. There are main syndromes that occur in patients: tumor intoxication (fatigue, night sweats, decreased performance, fever over 38 ° C in the absence of infection, weight loss); leukemic proliferation syndrome (a systemic increase of all groups lymph nodes, hepato- and splenomegaly, hypertrophic gingivitis, cutaneous leukemids, diffuse or local tumor cells infiltration in the bone marrow); anemic syndrome (paleness of mucous membranes and skin, fatty degeneration and atrophy of parenchymal organs, sclerotic changes, etc.);

hemorrhagic syndrome (bleeding and massive hemorrhages, DIC - syndrome can develop); infectious lesions (development of agranulocytosis in association with the features of the course of leukemia or on the background of cytostatic therapy).

Depending on the degree of differentiation of tumor cells and the course pattern, all leukemias are divided into two main groups: 1) acute leukemias (myeloblastic, lymphoblastic, monoblastic and undifferentiated, erythromyeloblastic and megakaryoblastic); 2) chronic leukemias (myeloid, lymphocytic, monocytic leukemias, erythremia, osteomyelofibrosis, multiple myeloma - Kahler's disease, Waldenström's macroglobulinemia, heavy chain disease - Franklin's disease).

Depending on the number of leukocytes in the peripheral blood, leukemia is divided into leukemic leukemia (more than 25 thousand leukocytes); subleukemic (15-25 thousand); aleukemic leukemia (the normal content of leukocytes, and even blast cells in the blood may be absent) and leukopenic leukemia (the number of leukocytes in the blood is reduced).

1) Acute leukemia starts acutely and rapidly progresses, undifferentiated (blasts) or poorly differentiated blood cells undergo tumor transformation. Their number is increasing (more than 30%). Due to the sharp inhibition of blood cell differentiation and the predominance of blast forms, all acute leukemias are characterized by severe anemia and thrombocytopenia, a significant decrease in the number of leukocytes in the blood, and the appearance of "leukemic hiatus". "*Leukemic hiatus*" is a sharp increase of blast cells and the presence of single mature elements segmented (e.g., leukocytes, monocytes, lymphocytes). Transitional maturing forms (from blast cells to mature) are present in very small amounts or completely absent.

Bone marrow is characterized by a significant amount of blast cells, which supplant other normal cells present in normal conditions. In remission content of blast cells in the bone marrow is less than 5%.

Nervous system is characterized by the infiltration of nerve trunks, brain membranes, and brain substances by the blast cells (neuroleukemia) with appropriate clinical symptoms of the nervous system injury.

Heart is characterized by the presence of whitish foci. Histologically blast cell accumulations are visible in myocardium.

Lungs are characterized by the thickening of interalveolar walls due to leukemic cell infiltration, and the formation of infiltrates, consisting of blast cells, around the bronchi (leukemic pneumonitis). It is also possible pleura involvement with effusion into the pleural cavity and the pleurisy development.

Liver enlarges, and becomes denser, with the front edge rounded. The infiltration of the liver tissue by leukemic cells: in the lymphoblastic leukemia as well-circumscribed clusters in the portal tracts, while in myeloblastic it has a diffuse character. It is accompanied by the destruction of the hepatic lobules, degenerative changes in hepatocytes, and focal necrosis.

Kidneys are usually bilateral in the form of diffuse infiltration or foci of proliferation of leukemic cells. The kidneys are increased in size, under the capsule on their external surface and the cut surface foci of tumor growth are seen as different sizes, rounded areas of whitish colors. Tumor cells are located in the stroma of the kidney around glomeruli and tubules.

Lymph nodes and spleen increase in size, and thicken.

Skin – dermal lesions (leukemids) are multiple and more common in the later stages of the disease. Dense and soft formations raised above the surface of the skin, pink or light brown. Blast infiltration of the dermis, predominantly around vessels, hair follicles, and sweat glands. It may be accompanied by necrosis and ulceration of the epidermis; may spread to the subcutaneous fat.

Mucous membrane of the oral cavity and gums is characterized by the increase in the size of the gums, their hyperemia, and the presence of ulceration areas and necrosis. Necrosis can be caused by leukemia infiltrates narrowing the lumen of blood vessels.

With leukemia, death can occur due to a number of syndromes associated with damage to organs and organ systems: bleeding (hemorrhagic diathesis), hemorrhage in organs; intoxication - due to the leukemic cells destruction; development of infections (sepsis), and others.

The most common forms of acute leukemia are acute lymphoblastic leukemia and acute myeloid leukemia.

Acute lymphoblastic leukemia is more common in childhood (85%); leukemic infiltrates are characteristic in the substance of the brain (meninges) and spinal cord, as well as lymph nodes, spleen, liver, thymus, urinary system, and skin. Diffuse tissue damage is noted in the bone marrow; tumor cells displace other hematopoietic germs and adipose tissue. The bone marrow of spongy and tubular bones with lymphoblastic leukemia becomes crimson-red ("*raspberry jelly*" appearance). Hemorrhagic syndrome is not always characteristic. Ulcerative-necrotic lesions are not expressed. The treatment gives a good effect on long-term remissions.

Acute myeloid leukemia occurs in adults (85%). The location of leukemic infiltrates is noted in the spleen, liver, lymph nodes, mucous membranes of the gastrointestinal tract, lungs, meninges. Diffuse damage to bone marrow tissue is characteristic. The bone marrow becomes greenish, so it is called pyoid (greenish, purulent). Hemorrhagic syndrome and ulcerative-necrotizing lesions pronounced. Remissions are unstable, short, and milder in children.

2) Chronic leukemias begins slowly with a prolonged increase in symptoms. Mature cellular elements undergo tumor transformation. Cell differentiation is largely preserved. The blood usually contains immature cells (less than 30%), but tends to mature. Slowly progressing anemia is typical. There is no "leukemic hiatus".

Chronic lymphocytic leukemia is a tumor disease arising from mature lymphocytes. It is more common in old age (40-60 years). Typical manifestations are a sharp enlargement of the lymph nodes, infectious complications, hemolytic anemia, thrombocytopenia. With lymphocytic leukemia, monomorphic infiltrates are

represented by small, approximately identical, rounded shapes with hyperchromic lymphocytic tumor cells.

Bone marrow is crimson red.

Spleen is increased in size to 1 kg. Follicles with their sharp increase.

Lymph nodes are significantly enlarged, and soft; they merge into huge dense packages; on the cut, juicy, white-pink, the drawing of the lymph node is erased as a result of the growth of tumor tissue.

Liver is slightly enlarged; focal lymphoid infiltrates are located outside the lobule (along the Glisson capsule and triads) (microphotograph 30).

Tonsil tissues, group and solitary lymphatic follicles of the intestines, kidneys, skin, and sometimes the brain and its membranes are characterized by severe leukemic infiltration.

Lungs are characterized by peribronchial lymphoid infiltration.

Chronic lymphocytic leukemia has a favorable course.

Chronic myelogenous leukemia is a tumor disease arising from mature granulocytes and their precursors. It is more common in ages 30-40 years. It is one of the most common leukemias, its marker is the detection of the Philadelphia chromosome. Typical manifestations are a sharp enlargement of the spleen, leukemic thrombi in the vessels of many organs, "blast crises" (a manifestation of tumor progression in the final stage chronic leukemia; a blood test in terms of the number of blast cells resembles that in acute leukemia and can exceed 30%, and the number of the same cells in the bone marrow is more than 50%). The disease occurs in two stages: monoclonal (benign) and polyclonal (malignant). Leukemic infiltrates in myelocytic leukemia are more polymorphic (due to more transitional forms), the cytoplasm in the cells is clearly expressed, and the nuclei are light, and contain loose, diffusely located chromatin.

Bone marrow is pyoid.

Spleen is significantly enlarged, its weight can reach 5-6 kg (normally 120-150 g), and the pulp looks like a rotten plum.

Lymph nodes are greatly enlarged, and soft, on the cut - gray-red. The drawing of the lymph node is erased as a result of the growth of tumor tissue.

Liver is greatly enlarged due to leukemia; diffuse infiltrates are located mainly inside the lobule between the hepatic beams (microphotograph 31).

Lungs are characterized by lymphoid infiltration of the interalveolar walls.

Paraproteinemic leukemias are the diseases representing tumors of B-lymphocytes system capable to synthesize homogeneous immunoglobulins or their fragments, the so-called paraproteins (pathologic monoclonal immunoglobulins).

Tumor cells in paraproteinemic leukemia differentiate according to the plasmocytic type, preserving in a perverted form the peculiarity of plasma cells to synthesize immunoglobulins. This group includes three diseases: multiple myeloma (Kahler's disease), primary Waldenström's macroglobulinemia, and heavy chain disease (Franklin's disease). Multiple myeloma is the most important among paraproteinemic leukemias.

Multiple myeloma is characterized by tumor proliferation plasmablasts with the production of paraproteins (immunoglobulins) or their fragments. It occurs mainly in adults. Name the disease and the tumor cell are obtained due to the predominant localization of the process in the bone marrow.

Depending on the class and type of synthesized and secreted paraproteins, the following immunochemical variants are distinguished: G-, A-, D-, E-myeloma, Bence-Jones myeloma (light chain disease), etc. Depending on the nature of myeloma infiltrates in the bone marrow, the following forms are distinguished: nodular, diffuse, and diffuse-nodular. Myeloma can occur in a solitary form, in the form of a single node, but more often it is multiple. According to the cellular composition, myeloma can be plasmocytic, plasmoblastic, polymorphic cell or small cell myeloma.

Tumor infiltrates are most often found in flat bones (ribs, skull bones) and the spine, less often in tubular bones (humerus, femur). The proliferation of myeloma cells in the bone marrow leads to the destruction of bone tissue due to the synthesis of osteoclast activating factors by them. The growth of tumor tissue leads to the

destruction of bone tissue - osteolysis, osteoporosis, and axillary resorption, which leads to the development of pathological bone fractures. Bone tissue defects become rounded smooth-wall cavities with clear margins ("stamped" defects). *Microscopically,* the diffuse-focal proliferation of myeloma cells in the bone marrow with a displacement of normal myeloid cells. In the case of focal growth stroma sclerosis is observed around myeloma nodes. If it affects the bone tissue – neoplastic myeloma cells grow in the lumen of the central channel of the osteon or the bone beam, leading to osteolysis with endosteum detachment and osteoporosis.

In addition to the bone marrow and bones, myeloma cells, and infiltrates are observed in the internal organs (the extramedullary tumor proliferates). Hepato- and splenomegaly – due to the proliferation of neoplastic myeloma cells.

Myeloma nephropathy (paraproteinemic nephrosis) – the formation of the so-called "myeloma shrunken kidney" is characterized by amyloidosis of stroma, leukemic infiltration, paraprotein deposition in the tubules of the nephron, calcification, and ascending urinary tract infection. *Microscopically,* deposition of amyloid-like substances in the mesangium and basement membranes of glomerular capillaries, afferent blood vessels with subsequent sclerosis of them. In the majority of the patients, there are signs of necrotic nephrosis - acute renal failure. Developing uremia is the cause of death in patients with myeloma in 30% of cases. Another common cause of death is the development of infections.

II. Lymphomas are neoplasms of lymphoid tissue, occurring primarily in the central or peripheral organs of immunogenesis. Malignant lymphomas most commonly affect lymph nodes and less often lymphoid tissue in other organs (pharyngeal tonsils, solitary follicles, and Peyer's patches of the small intestine, spleen). The clinical course of many lymphomas is characterized by low growth speed and prolonged survival periods. All lymphomas are divided into two main groups: 1) lymphogranulomatosis (synonyms: Hodgkin's disease, Hodgkin's lymphoma); 2) non-Hodgkin's lymphomas (B-cell, T-cell, peripheral lymphomas).

1) Hodgkin's lymphoma (lymphogranulomatosis) is a malignant disease of the lymphoid tissue which can occur in the central and the peripheral organs of the immune system and characterized by the presence of Reed-Berezovsky-Sternberg cells in the affected tissue. It has a chronic (rarely acute) course with the predominant development of tumor tissue in the lymph node. In this case, cervical, mediastinal, and retroperitoneal lymph nodes are most often affected, less often inguinal, and axillary. This disease accounts for 15% of all lymphomas.

The disease has a certain clinical stage. The criteria that determine the stages of development of lymphomas are the localization of the tumor and its spread beyond the primary localization. Stage I – damage of one or two lymph nodes located on one side of the diaphragm, or damage of one extralymphatic organ; stage II - damage of two or more lymph nodes on one side of the diaphragm or damage of one extralymphatic organ and its regional lymph nodes; stage III - damage of the lymphatic system on both sides of the diaphragm or damage of one extralymphatic organ with involvement of the adjacent lymph nodes or spleen in the process; stage IV - diffuse lesion of one or more extralymphatic organs with or without involvement of the lymph nodes.

There are two variants of lymphogranulomatosis: isolated (local) with damage of one group of lymph nodes; generalized, in which the growth of tumor tissue is found not only in the lymph nodes, but also in the spleen, liver, lungs, stomach, and skin. With an isolated form, the lymph nodes of the neck, mediastinum, retroperitoneal tissue, and inguinal are most often affected.

Macroscopic features: lymph nodes are enlarged, have a soft consistency, have clear contours, are not fused with the skin and are movable. Over time, the lymph nodes increase in size, and become dense, dry, and motley, with areas of caseous necrosis and hemorrhages. They merge and form large conglomerates.

Microscopic features: see description of histological variants of Hodgkin's lymphoma.

In a generalized process, the spleen is usually affected.

Macroscopic features: the spleen increases in size, and becomes dense; has areas of light-gray color (foci of tumor growth) on a dark-red background are visible on the cut surface in the spleen tissue. The appearance of the cut surface is compared with "porphyry stone" (red granite with gray inclusions and streaks) - "porphyry spleen".

Microscopic features: a focal or diffuse proliferation of lymphoid tissues, the presence of hemosiderin deposits, foci of caseous necrosis, diffuse or focal sclerosis.

The histological features of Hodgkin's lymphoma are complex and specific. The ratio of Reed-Berezovsky-Sternberg cells (and Hodgkin mononuclear cells), lymphocytes, histiocytes and the severity of fibrosis is the basis for the classification of Hodgkin's lymphoma.

Reed-Berezovsky-Sternberg cells are large cells with two "bean-shaped" mirror located nuclei with large eosinophilic nucleoli. *Small Hodgkin's cells* are mononuclear, lymphoblast analogues. *Large Hodgkin's cells* are large mononuclear cells with oxyphilic or slightly basophilic cytoplasm.

Histopathological variants of lymphogranulomatosis are represented by the following types: 1) lymphohistiocytic (with a predominance of lymphoid tissue), 2) nodular sclerosis, 3) mixed cellularity, 4) with suppression of lymphoid tissue.

Lymphohistiocytic variant (lymphoid predominance) occurs at any age but is the most common in young men. It is about 10% of cases. There is the reactive proliferation of lymphocytes and histiocytes, with few or no plasma cells, and few Reed-Berezovsky-Sternberg cells. Pronounced foci of necrosis and sclerosis are not observed. This variant is the most favorable, as there is a pronounced immune reaction.

Nodular sclerosis occurs more commonly in women. It is about 45% of cases of the disease. There are collagen fibers overgrowth in the form of annular bands dividing tumor tissue into small rounded shape sections. At the center of these nodules are clusters of cells, mainly mature lymphocytes, large Reed-Berezovsky-

Sternberg cells: typical double-nucleated and atypical with a large number of small nuclei.

Mixed cellularity is more often observed in patients of average age. It is about up to 40% of cases. Cellularity is noted here and pronounced cellular polymorphism is detected - typical Reed-Berezovsky-Sternberg cells, eosinophils, and neutrophils, leukocytes, lymphocytes, histiocytes, plasma cells, epithelioid cells (histocytes), fibroblasts. There is diffuse fibrosis and foci of necrosis.

Lymphoid suppression (depletion) usually occurs in the elderly. It is less than 1%. It is characterized by diffuse sclerosis in the form of the overgrowth of rough strands of fibrous connective tissue with the shedding of amorphous protein masses. There are clusters of typical and atypical Reed-Berezovsky-Sternberg and Hodgkin's cells, fibroblasts with few lymphocytes.

The histopathological variants described may be successive stages in disease progression and have prognostic and therapeutic differences. With the progression of the disease, lymphocytes disappear from the lesions. Lymphoid depletion variant is considered the most unfavorable. The most stable variant is nodular sclerosis.

The course of lymphogranulomatosis can be complicated by compression by a rapidly growing lymph node conglomerates of other organs, which can lead to acute asphyxia, obstructive jaundice, and intestinal obstruction. In addition, there is a frequent development of amyloidosis (kidneys, intestines), cachexia, and infections. The cause of death in most cases is progressive pulmonary-cardiac or hepatic-renal failure, bleeding, and intoxication.

2) Non-Hodgkin's lymphomas (lymphosarcomas) are a group of malignant tumors of B- and T-cell origin. Classification of Non-Hodgkin's lymphomas means division depending on 1) sizes and morphology of the cells; 2) origin (T-cell and B-cell); 3) spread and type of growth in the lymph nodes (follicular, diffuse, mixed); 4) degree of differentiation and malignancy (low malignancy, moderate malignancy, high malignancy).

B-cell lymphomas occur frequently (up to 85%). The most common histological types are: 1) follicular lymphoma, 2) lymphoma from the small lymphocytes, 3) lymphoma of the cells of the mantle zone (mantle-cell), 4) extranodal B-cell lymphoma of the marginal zone, 5) diffuse large -cell B-cell lymphoma, 6) Burkitt's lymphoma.

Follicular lymphoma occurs in up to 30-35% of lymphomas. *Microscopically,* it is represented by the lymphoid follicles that do not have a typical mantle zone, are poorly demarcated, located densely, and tend to merge, forming diffuse growth zones. Sclerotic changes are found in diffuse areas. Cells are represented mainly by centrocytes - they are larger than lymphocytes, and have a deeply split nucleus with indistinguishable nucleoli; a different number of centroblasts - they are 2-3 times larger than small lymphocytes with a large rounded light nucleus with 1-3 small nucleoli on the periphery.

Lymphoma from the small lymphocytes occurs in about 7% of lymphomas. *Microscopically,* it is characterized by the diffuse proliferation of small lymphocytes. Homogeneous, round nuclei with basophilic compact chromatin and inconspicuous nucleoli. The narrow rim of light cytoplasm. Largely transformed lymphocytes and mitoses are rare.

Lymphoma of the cells of the mantle zone (mantle-cell) accounts for 4-6% of lymphomas. *Microscopically,* it is characterized by a follicular or diffuse proliferation of cells in the mantle zone surrounding the follicle. Cells are medium-sized with an irregularly shaped nucleus with a serrated contour, dispersed chromatin, and poorly distinguishable nucleoli. Small vessels are hyalinized.

Extranodal B-cell lymphoma of the marginal zone is accompanied by the spread of tumor infiltration around relatively intact reactive lymphoid follicles, outwards from the mantle zone with the formation of wide tumor fields. The presence of lymphoepithelial lesions with accumulations of three or more lymphocytes in epithelial structures with degenerative changes in epithelial cells.

Diffuse large-cell B-cell lymphoma occurs in about 30-40% of all non-Hodgkin's lymphomas. It is characterized by an aggressive course. The cellular composition is polymorphic and is represented by centroblasts (cells of medium or large size, round or oval light nuclei with 2-4 nucleoli), immunoblast cells (cells with multilobed rounded light nuclei, a single centrally located nucleolus, visible basophilic cytoplasm), pleomorphic cells (large cells with deformed nuclei) - an anaplastic variant.

Burkitt's lymphoma is about 2% of all lymphomas. It has a highly malignant course, but despite this, the tumor is successfully treated. Localization of the lesion - lymph nodes, extranodal lesion. Several variants are possible: 1) epidemic variant - predominant localization of the primary focus on different parts of the face, especially on the jaw; 2) sporadic variant; 3) associated with an immunodeficiency variant - with HIV infection. *Microscopically,* it is characterized by the presence of medium-sized tumor cells with a high nuclear-cytoplasmic ratio, high mitotic activity, and a high level of tumor cell death due to the presence of numerous macrophages (histiocytes). The cells are tightly arranged, forming a dark background, on which many light macrophages can be depicted - a picture of the "starry sky".

T-cell lymphomas are less common than B-cell lymphomas (about 15%). There are several histological types: 1) cutaneous T-cell lymphoma; 2) extranodal T-cell lymphoma from the natural killers; 3) T-cell lymphoma with enteropathy; 4) T-cell panniculitis-like lymphoma of subcutaneous tissue; 5) angioimmunoblastic T-cell lymphoma; 6) anaplastic large cell lymphoma.

Cutaneous T-cell lymphoma (mycosis fungoides, Sezary's syndrome – leukemic form) accounts for 1% of the total number of lymphomas. Predominant localization in the skin, lymph nodes, and bone marrow. Nodules of soft consistency protrude above the surface of the skin (mycosis fungoides). *Microscopically*, multiple tumor nodes in the skin are represented by large proliferating cells. In the case of *Sezary's disease* - in the tumor infiltration of the skin, bone marrow, and blood, the presence of atypical mononuclear cells with crescent nuclei (Sezary's cells).

Extranodal T-cell lymphoma from natural killers is characterized by a predominant lesion of the skin, lungs, and central nervous system. *Microscopically*, neoplastic infiltrate consists of small lymphocytes with split or round nuclei and atypical small and large lymphoid cells. Tumor cells infiltrate blood vessels with their destruction.

T-cell lymphoma with enteropathy is more common in people with gluten sensitivity. Predominant localization in the small intestine.

T-cell panniculitis-like lymphoma of subcutaneous tissue is a variant of extranodal lymphoma; frequency is less than 1%. Primary localization in the skin.

Angioimmunoblastic T-cell lymphoma is a rare form characterized by rapid growth. *Microscopically*, tumor infiltration of the lymph nodes by immunoblasts is characteristic of the subsequent erasure of the histological structure and the pathological formation of new vessels.

Anaplastic large-cell lymphoma accounts for less than 2% of all lymphomas. Predominant localization in the lymph nodes. *Microscopically*, complete erasure of the histological picture of the lymph node is characteristic. Very polymorphic cells grow in large sheets and nests. The distribution of cells in the sinuses of the lymph nodes is characteristic. A marker is the presence of large cells with eccentric nuclei and eosinophilic inclusions in the Golgi apparatus.

TEST YOURSELF

1. Name a disease that belongs to systemic tumor diseases of the hematopoietic tissue:

A. Leukemia

B. Cancer

C. Sarcoma

D. Lymphoma

E. Anemia

2. Lymphosarcoma is:

A. Pretumor disease

B. Immune disease

C. Regional tumor disease of hematopoietic tissue

D. Systemic tumor disease of the hematopoietic tissue

E. Malignant tumor from the mesenchyme

3. Cellular elements from which malignant lymphomas are built:

A. Only from stromal elements

B. From the cells of the integumentary epithelium

C. From hematopoietic cellular elements and stromal cells

D. Only from lymphoid cells

E. From undifferentiated blood cells

4. Give a synonym for the term "leukemia":

A. Malignant lymphoma

B. Leukemia

C. Dysplasia

D. Anemia

E. Sarcoma

5. List the organs and organ systems in which tumor cells grow in the initial stage of hemoblastosis:

A. In the organs of hematopoiesis;

B. In the organs of the cardiovascular system;

C. In the musculoskeletal system;

D. In the organs of the respiratory system;

E. In the gastrointestinal tract

6. What are the reasons for the sharp increase in organs with leukemia?

A. Granuloma formation

B. Edema

C. Stagnation of blood

D. Sclerosis

E. Tumor cell metastases

7. Proliferation of undifferentiated or poorly differentiated blast blood cells is characteristic for:

A. Lymphogranulomatosis

B. Acute leukemia

C. Anemia

D. Lymphosarcomas

8. Proliferation of differentiated leukemic blood cells is characteristic for:

A. Lymphogranulomatosis

B. Kaposi's sarcomas

C. Acute leukemia

D. Chronic leukemia

9. At autopsy an elderly female is found to have enlarged groups of neck, axillary, and mediastinal lymph nodes matted together. They were firm and rubbery. The cut surface was gray-white, producing a "fish-flesh" appearance. Microscopy revealed heterogeneous cellular infiltrate which contained lymphocytes, and classic and mononuclear Reed-Berezovsky-Sternberg cells. What is the most likely diagnosis?

A. Lymphogranulomatosis

B. Chronic lymphatic leukemia

C. Lymphosarcoma

D. Retikulosarcoma

E. Mycosis fungoides

10. A liver biopsy was taken from a 66-year-old man, with a history of increased quantity of lymphocytes and pro-lymphocytes in his blood. Histological investigation of the liver: sample revealed plural accumulations of the lymphocytes and pro-lymphocytes, mainly between hepatic segments. For what disease above the listed changes are characteristics?

A. Chronic lymphatic leukemia

B. Acute lymphatic leukemia

C. Lymphogranulomatosis

D. Chronic persistence hepatitis

E. Hepatocellular carcinoma of the liver

PART 14. ANEMIA. THROMBOCYTOPATHY

Anemia is a group of diseases characterized by a decrease in hemoglobin and the number of red blood cells per unit volume of blood leading to tissue hypoxia. With anemia, erythrocytes of various sizes (poikilocytosis) and shapes (anisocytosis), varying degrees of color (hyperchromia, hypochromia), sometimes inclusions are found in erythrocytes (remnants of nuclei – Jolly bodies – basophilic grains, Cabot rings - basophilic rings.) which are normally removed by the spleen.

Depending on the content of hemoglobin, anemia is divided by severity: mild – 100 g/l – the symptoms of anemia are leveled by compensatory mechanisms and clinical manifestations may be absent; moderate – 70 – 100 g/l – accompanied by moderate clinical symptoms (e.g., pallor of the skin and mucous membranes, tachycardia, tachypnea); severe – less than 70 g/l – clinical manifestations are pronounced (e.g., signs of angina pectoris, syncope, weakness in the limbs).

Of greatest interest to the practitioner is the etiopathogenetic classification of anemia: I. Anemia due to blood loss (posthemorrhagic): a) acute posthemorrhagic anemia, b) chronic posthemorrhagic anemia; II. Anemia due to insufficient production of erythrocytes: a) iron deficiency anemia, b) iron-redistributive anemia, c) iron-saturated anemia, d) megaloblastic anemia, e) hypo- and aplastic anemia; III. Anemia due to increased destruction of erythrocytes (hemolytic): a) acquired hemolytic anemia, b) hereditary hemolytic anemia (anemia associated with changes in erythrocyte membranes – membranopathies; anemia associated with changes in the metabolism of erythrocytes – erythrocytoenzymopathy; anemia associated with a defect in hemoglobin synthesis – hemoglobinopathies).

Acute posthemorrhagic anemia is caused by rapid and massive blood loss. The main causes: are significant blood loss in injuries and wounds, accompanied by damage of blood vessels, and also bleeding from internal organs in diseases (from the digestive tract, kidneys, lungs, from the bladder) and hemorrhagic diathesis, uterine bleeding, ruptures of aneurysmally altered vessels. The pathogenesis is characterized by a simultaneous decrease in blood plasma and red blood cells, which leads to acute hypoxia. It manifests in the form of shortness of breath and palpitations.

Macroscopic features: paleness of the skin and internal organs are noted. The red bone marrow of flat bones pink. Absence of blood in large vessels, a small number of post-mortem cloths, and severe anemia of internal organs.

Microscopic features: posthemorrhagic anemia is represented by granular degeneration.

The larger the damaged vessel, the more dangerous bleeding. Damage to the aorta causes a sudden drop in blood pressure, which is fatal. With bleeding from smaller vessels and with the loss of more than half of the total blood volume, death occurs due to acute heart failure.

Chronic posthemorrhagic anemia occurs with moderate prolonged blood loss. The main causes of their occurrence are gastric ulcers complicated by bleeding, tumors, varicose hemorrhoidal veins, hemophilia, and severe hemorrhagic syndrome. In the initial stage of chronic bleeding, the regenerative function of the bone marrow compensates for the loss of red blood cells; the peripheral blood formula is practically unchanged. However, due to increasing hypoxia caused by the loss of red blood cells, there is an increase in erythropoietin, which leads to increased proliferation of red bone marrow cells. It is manifested by an increase in reticulocyte number in peripheral blood. But at the same time as red blood cells, the patient loses the iron contained in hemoglobin. Therefore, posthemorrhagic anemia becomes iron deficiency anemia.

Macroscopic features: paleness of the skin and pallor of internal organs are noted.

Microscopic features: hypoxia of organs and tissues leads to the fatty degeneration of the myocardium of the liver and kidneys. Sclerosis in parenchymal organs. The hemorrhagic syndrome is often expressed due to the loss of platelets during bleeding, which manifests in the form of hemorrhages on the mucous and serous membranes. Focal transformations of yellow bone marrow into red are observed, and foci of extramedullary hematopoiesis appear in the liver and spleen.

The cause of death is the development of heart failure.

Iron deficiency anemia is anemia caused by iron deficiency in the blood serum, and bone marrow. Iron deficiency anemia is most common in children, adolescents, women of reproductive age, and the elderly. Causes of iron deficiency anemia: insufficient intake of iron from food - alimentary anemia (e.g., premature babies, vegetarianism), with increased consumption of iron (in pregnant and lactating women), insufficient absorption of iron (in diseases of the gastrointestinal tract and after resection of the stomach or intestines).

Macroscopic features: skin, mucous membranes, and internal organs are pale. Dystrophic changes in the skin and its appendages (dryness, peeling, a tendency to rapid cracking; dullness, brittle hair; thinning, brittleness, transverse striation, flattening, dullness of nails). Angular stomatitis - cracks in the corners of the mouth. Glossitis leading to atrophy of the tongue papillae.

Microscopic features: atrophic changes in the mucosa of the gastrointestinal tract. Fatty degeneration of the myocardium, kidneys, and liver, and degenerative changes in brain cells (due to chronic hypoxia).

Megaloblastic anemia is a group of anemias caused by violation DNA synthesis in nucleated erythrokaryoblasts due to deficiency of vitamin B12 and/or folic acid and characterized by megaloblastic type of hematopoiesis. For normal erythropoiesis in red bone marrow vitamin B12 and folic acid should be taken participates in DNA synthesis during cell proliferation.

Causes of vitamin B12 deficiency: violation intake of vitamin B12 from food (e.g., vegetarianism), violation absorption of the vitamin (e.g., autoimmune gastritis,

total or subtotal gastrectomy, malabsorption syndrome of various origins), increased intake of vitamin B12 (e.g., chronic hemolytic anemia, thyrotoxicosis), a decrease in vitamin B12 reserves (e.g., pronounced cirrhosis of the liver), a violation of the transport of vitamin B12 of hereditary origin (e.g., lack of transcobalamin II or the appearance of antibodies to it).

Causes of folic acid deficiency: alimentary (e.g., especially common in old age, as well as during starvation), malabsorption in the gastrointestinal tract (e.g., celiac disease, extensive resection of the small intestine), increased folate utilization (e.g., physiological: pregnancy, lactation, puberty; pathological: hematological diseases, oncological diseases, inflammatory diseases - Crohn's disease, rheumatoid arthritis), increased loss of folic acid (e.g., heart failure, hemodialysis, liver cirrhosis), taking certain drugs (e.g., 5-fluorouracil, anticonvulsants, sulfasalazine, cycloserine).

The skin is pale, with a yellow tint, yellowness of the sclera. Petechia hemorrhages are found in the skin, mucous and serous formations. The changes in the nervous system are characterized by a pronounced disintegration of myelin and axial cylinders in the spinal cord, in the posterior and lateral columns – "funicular myelosis". In patients, it manifests as a decrease in sensitivity, a decrease in motor function, etc. There may be foci of ischemia and softening of the brain and spinal cord.

Changes in the blood system.

Macroscopic features: bone marrow of flat bones crimson-red, and juicy; in tubular bones, it looks like "raspberry jelly". Enlargement of the spleen.

Microscopic features: bone marrow hyperplasia with a predominance of immature forms of erythropoiesis (erythroblasts, normoblasts, and megaloblasts - a large cell with an eccentrically located nucleus without nucleoli), changes in myeloid cells (increase in size, hypersegmentation), a decrease in the number of megakaryocytes. In peripheral blood – macrocytosis, anisocytosis, poikilocytosis, thrombocytopenia, and leukopenia as a result of the neutrophil number decrease.

Changes in the digestive tract.

Macroscopic features: gastrointestinal tract lesions include: glossitis, atrophic gastritis, and atrophic changes in the intestinal mucosa. In the oral cavity – Gunter's tongue – changes in the tongue. At the beginning of the disease, the edges and tip of the tongue are bright red, then the inflammation disappears, and the papillae of the tongue atrophy, it becomes "varnished".

Microscopic features: atrophy of the epithelium and the papillae of the tongue, with the presence of diffuse, predominantly subepithelial, lymphoplasmacytic infiltrates, pronounced dilation of the vascular bed. The mucous membrane of the bottom of the stomach is thinned, the epithelium of the glands is atrophied, it is found only in the main cell, the glands are located at a considerable distance from each other, and subsequently sclerosis develops (microphotograph 32).

Hypo- and aplastic anemia (pancytopenia) is characterized by a progressive decrease in erythropoiesis, granulopoiesis, and thrombopoiesis, up to complete depletion of the bone marrow. Red bone marrow is replaced by yellow (fat). The causes can be endogenous (e.g., Fanconi's congenital aplastic anemia - bone marrow aplasia is combined with malformations) and exogenous (e.g., radiation exposure, drugs - cytostatics, barbiturates, amidopyrine; and other toxic substances - benzene, phenol, etc.). With exogenous hypoplastic anemia, unlike endogenous, hematopoiesis is not completely inhibited at first. In the punctate from the sternum, young forms of the erythropoietic and myelopoietic series are found. However, with prolonged exposure to a pathogenic factor, there is a devastation of the red bone marrow and an almost complete replacement of the red bone marrow with adipose tissue – panmyelophthisis.

Clinical manifestations are associated with the severity of hematopoiesis suppression of the bone marrow: anemic syndrome, hemorrhagic diathesis, multiple bleeding, general hemosiderosis develops, jaundice (with the concomitant hemolytic syndrome), fatty degeneration of parenchymal organs, infectious complications, ulcerative necrotic processes.

Fanconi's congenital aplastic anemia is an autosomal recessive hereditary disease. The first clinical manifestations are usually observed at the age of 4-10 years; boys get sick more often. A feature is the presence of congenital somatic anomalies. There is the pigmentation of the skin (bronze or bronze-brown) due to the deposition of melanin in the cells of the basal layer of the epidermis. Pigmentation occurs due to the excessive release of adrenocorticotropic hormone in adrenal insufficiency. Decrease in body weight and height of the child at birth, as well as a lag in growth and development after birth due to a decrease in the function of the adenohypophysis. Anomalies of the bones of the skull and skeleton (small head, absence or significant shortening of the thumb, insufficient development of the radius, congenital dislocation of the hip, etc.). Neurological disorders (retraction of the eyeball, ptosis of the upper eyelid, underdevelopment of the cerebral hemispheres, microgyria, hydrocephalus, optic nerve atrophy, etc.). Violation of the genital organs (cryptorchidism, hypospadias, epispadias). Anomalies in the development of the kidneys and urinary tract, congenital heart defects, congenital anomalies of the lungs, and intestine, and enzymopathies. Changes in peripheral blood are similar to those in other types of aplastic anemia but less pronounced. The disease progresses gradually. The average life expectancy is 7-10 years.

Hemolytic anemias are a group of anemias characterized by hemolysis syndrome - increased destruction of red blood cells. Hemolytic anemias are divided into anemias due to intravascular and extravascular hemolysis.

Hemolytic anemia due to intravascular hemolysis for reasons of occurrence is divided into 1) toxic (occurs under the influence of poisons, toxins); 2) infectious (malaria); 3) post-transfusion; 4) immune hemolytic anemia (hemolytic disease of the newborn); 5) autoimmune hemolytic anemia (systemic lupus erythematosus, with viral infections, with treatment with certain drugs, etc.). Hemolytic anemia due to extravascular hemolysis is often hereditary. Anemias of this group are characterized by a triad of signs: anemia, splenomegaly, and jaundice.

Manifestations are characterized by permanent general hemosiderosis. In some cases, "acute nephrosis" occurs with hemolysis products – hemoglobinuric nephrosis. The bone marrow reacts to the destruction of red blood cells by hyperplasia and therefore becomes pink-red, juicy in spongy bones, and red in tubular bones. Microscopically, in the bone marrow, pronounced hyperplasia of erythroid cells is detected, and the number of erythrokaryocytes is 70% or more. Accelerated leaching of erythrocytes from the bone marrow explains the entry of polychromatophiles into the blood. The appearance of megaloblasts is possible, which is explained by the relative insufficiency of folic acid during the active regeneration of erythroblasts. In the spleen, liver, and lymph nodes - foci of extramedullary hematopoiesis.

Hemolytic anemias of a hereditary nature include membranopathies, which are based on defects in the erythrocyte cell membrane, which causes their instability and destruction by the reticuloendothelial system of the spleen, bone marrow, lymph nodes, and liver by macrophages. The main erythromembranopathies include ovalocytic hemolytic anemia and microspherocytic hemolytic anemia.

Microspherocytic hemolytic anemia (Minkowski–Chauffard syndrome) is inherited in an autosomal dominant type. There is a violation of the synthesis of the membrane protein ankyrin, as a result, erythrocytes acquire a spherical shape and reduced size. Damaged erythrocytes lose their membrane when passage through the reticuloendothelial system, especially through the spleen. Manifestations are characterized by anemia of varying degrees, a color index of about 1.0, mild jaundice, spleen hyperplasia, pain in the right hypochondrium, and a tendency to stone formation due to the high content of bilirubin in bile. There are hemolytic crises, which are most often provoked by any infection. Bone marrow hyperplasia of tubular and flat bones is observed.

Thrombocytopathies are a group of diseases and syndromes, which are based on hemostasis disorders caused by qualitative disorders or dysfunction of platelet with hemorrhagic manifestations at the level of microvasculature vessels.

Thrombocytopathies are divided into hereditary (e.g., Glanzmann's thrombasthenia - membrane abnormalities of platelets; Chediak-Higashi syndrome - the absence of type I dense bodies and their components in platelets) and acquired. Acquired thrombocytopathies develop under various pathogenic influences and occur in many diseases and syndromes: 1) hemoblastoses; 2) myeloproliferative diseases and essential thrombocythemia; 3) B12 deficiency anemia; 4) cirrhosis, tumors and parasitic diseases of the liver; 5) hormonal disorders (e.g., hypothyroidism, hypoestrogenism); 6) scurvy; 7) radiation sickness; 8) DIC-syndrome and activation of fibrinolysis; 9) massive blood transfusions; 10) drugs and toxins (e.g., in the treatment with non-steroidal anti-inflammatory drugs, acetylsalicylic acid, indomethacin, etc.; in alcoholism).

Morphological manifestations of thrombocytopathy are characterized by the development of hemorrhagic syndrome and anemia with more or less severe thrombocytopenia.

Thrombocytopenia is a group of diseases in which there is a decrease in the number of platelets due to their increased destruction or consumption, as well as their insufficient formation. Increased platelet destruction is the most common mechanism for the development of thrombocytopenia.

There are hereditary and acquired forms of thrombocytopenia. With hereditary thrombocytopenia, changes in various properties of platelets are observed, which allows us to consider these diseases in the group of thrombocytopathies (see «Thrombocytopathies»). Depending on the mechanism of platelet damage, acquired thrombocytopenia is divided into immune and non-immune. Among immune thrombocytopenias, there are alloimmune (incompatibility in one of the blood systems), transimmune (penetration of autoantibodies of a mother suffering from autoimmune thrombocytopenia through the placenta), heteroimmune (violation of the antigenic structure of platelets) and autoimmune (production of antibodies against own unchanged platelet). Non-immune thrombocytopenia can be caused by mechanical damage of platelets (with splenomegaly), inhibition of bone marrow cell

proliferation (with radiation or chemical damage of the bone marrow, aplastic anemia), bone marrow replacement (overgrowth of tumor cells), somatic mutation (Marchiafava-Micheli disease), increased consumption of platelets (with DIC), lack of vitamin B12 or folic acid (with anemia). Immune forms of thrombocytopenia are more common than non-immune forms.

Morphological manifestations of thrombocytopenia are characterized by the development of hemorrhagic syndrome with hemorrhages and bleeding. Hemorrhages occur more often in the skin in the form of petechiae and ecchymosis, less often in the mucous membranes, and in the parenchyma of internal organs (e.g., hemorrhages in the brain). Bleeding is possible in the stomach, intestines, and lungs. Often there is an increase in the spleen as a result of hyperplasia of its lymphoid tissue, and an increase in the number of megakaryocytes in the bone marrow. Hemorrhages can lead to the development of anemia.

TEST YOURSELF

1. Post-hemorrhagic anemias in the course can be:

A. Intravascular

B. Acute and chronic

C. Extravascular

D. Benign and malignant

2. A 38-year-old man, with a history of an ulcer, which resulted in a stomach resection, in his blood test had a normal quantity of erythrocytes, but reduced hemoglobin concentration and decreased color index. An autopsy revealed pale skin and visible mucous membranes; the bone marrow of long tubular bones was brightly red. Erythrocytes in a smear had a normal form and size. They look very pale because of bad staining by dyes. What pathological process took place in this case?

A. Hypochromic iron deficiency anemia

B. B12-folic acid deficiency anemia

C. Acute lymphoblast leukemia

D. Sickle cell anemia

E. Aplastic anemia

3. A 44-year-old man presented to a gastroenterologist with pains in his epigastrium. A physical examination revealed an icteritious of his skin and scleras, an alteration of a tongue's mucous membrane. A tongue grossly looked shining, smooth, with red spots. In peripheral blood smear, there were found enlarged erythrocytes (megaloblasts). A histological study of a gastrobiopsy from a body of a stomach showed a thinning of mucosa, a reduction of glands quantity, and superfluous growth of connective tissue. Specify, which of the diagnoses is the most probable in this case:

A. Chronic myeloid leukemia

B. Chronic posthemorrhagic anemia

C. Hemolytic anemia

D. B12-folic acid deficiency anemia

E. Aplastic anemia

4. A man, with a history of getting a high dose of ionizing radiation, presented to his physician with marked stomatorrhagia (gingival hemorrhage), spontaneous skin, and mucosas' hemorrhages. A blood test showed normochromic anemia and pancytopenia. The concentration of iron in the blood's serum was normal. A histological investigation of a bone marrow puncture sample revealed a replacement of a hemopoietic tissue by the fatty tissue. What is the most likely diagnosis?

A. Aplastic anemia

B. B12-folic acid deficiency anemia

C. Hemolytic anemia

D. Chronic posthemorrhagic anemia

5. Morphological changes in the spleen with anemia due to a lack of vitamin B12:

A. Dense, reduced

B. Enlarged, flabby

C. Spleen follicular hyperplasia

D. There are always no foci of extramedullary hematopoiesis

E. Septic spleen

6. What is the etiological factor of pernicious anemia?

A. Iron deficiency

B. Vitamin B12 deficiency

C. Vitamin B6 deficiency

D. Vitamin B1 deficiency

E. Deficiency of vitamin B12 and iron

7. How does the level of serum iron change with iron deficiency anemia:

A. Sharply increased

B. Reduced

C. Never changes

D. Increased slightly

8. What is the main symptom of the diagnosis of hypochromic anemia?

A. Decreased platelets

B. Decrease in red blood cells

C. Increased reticulocytes

D. Low color index

9. Anemia is characterized by a decrease in blood levels:

A. Red blood cells

B. Leukocytes

C. Platelets

D. Plasma cells

E. Plasma proteins

10. With a single massive blood loss occurs:

A. Iron deficiency anemia

B. B-12 deficiency anemia

C. Acute hemolytic anemia

D. Acute post-hemorrhagic anemia

Recommended literature

Compulsory*:*

1. Патологическая анатомия: учебник в 2 т. / под ред. В.С. Паукова. – 2-е. изд., доп. – М.: ГОЭТАР – Медиа, 2016. – Т. 1. Общая патология. – 728 с.

2. Sorokina I.V. Pathomorphology / Sorokina I.V., Markovskyi V.D., Halata D.I. – Kyiv: AUS Medicine Publishing, 2019 – 327 p.

3. Патологическая анатомия: учебник / А.И. Струков, В.В. Серов; под. Ред. В.С. Паукова. – 6-е изд. – М.: ГОЭТАР – Медиа, 2015. – 880 с.

4. Патоморфологія: нац. підруч. / В.Д. Марковський, В.О. Туманський І.В. Сорокіна П20 та ін., за ред. В.Д. Марковського, В.О. Туманського. — К.: ВСВ «Медицина», 2015 — 936 с., кольор. вид. ISBN 978-617-505-450-5.

5. Anderson's Pathology // Edited by John M. Kissane. The 1. Kumar V. Robbins Basic Pathology tenth edition / Kumar V., Abbas A.K., Aster J.C. – Canada: Elsevier Health Sciences, 2017 – 910 p.

Optional:

1. Клатт Э. Атлас патологии: пер. с англ. / Э. Клатт. - Элби СПб, 2010. – 532 с.

2. Патологическая анатомия: учебник C.V. Mosby Company. – Toronto – Philadelphia, 1990. –2196 p.

6. Mohan H. Textbook of Pathology. – 7th ed. – New Delhi: Jaypee. – The Health Sciences Publ., 2015. – 954 p.

7. Robbins and Cotran Pathologic Basis of Disease / ed.: V. Kumar et al. – 9th ed. – Philadelphia: Elsevier / Saunders, 2015. – 1391 p.

8. Roberts F. Pathology Illustrated. – 8th ed., international. – (S.1.): Elsevier, 2018. – 714 p.

9. Rubin’s Pathology: clinicopathologic foundations of medicine / ed. by D.S. Strayer et al. – 7th ed. – Philadelphia: Wolters Klumer / Lippincott Williams and Wilkins, 2015. – 1602 p.

10. Shafer’s textbook of oral pathology / ed. R. Rajendran, B. Sivapathasundharam – Philadelphia: Elsevier / Sunders. – 6th ed. – 2009. – 963 p.

11. Sorokina I.V. Lectures in Pathological anatomy / I.V. Sorokina, A.F. Yakovtsova. – Kharkiv: Tornado, 2000. – 254 p.

12. Thomas C. Macropathology / Thomas C. – Toronto, Philadelphia: B.C. Decker Inc., 1990. – 355 p.

The internet resources:

1. Центр тестування – база ліцензійних тестових завдань «Крок-1».

2. http://library.med.utah.edu/WebPath/webpath.html

3. http://www.webpathology.com/

4. https://www.geisingermedicallabs.com/lab/resources.shtml.

Appendix 1

ANSWERS

PART 1

1	C	6	D
2	D	7	C
3	A	8	A
4	B	9	B
5	A, B, C	10	C

PART 2

1	A	6	A
2	D	7	B
3	A	8	D
4	C	9	B
5	C	10	A

PART 3

1	A	6	E
2	B	7	C
3	A	8	B
4	C	9	C
5	B	10	D

PART 4

1	C	6	A
2	A	7	B
3	B	8	C
4	A	9	B
5	B	10	C

PART 5

1	D	6	E

2	C	7	E
3	B	8	B
4	C	9	B
5	C	10	C

PART 6

1	C	6	B
2	B	7	D
3	A	8	C
4	B	9	D
5	E	10	A

PART 7

1	B	6	B
2	C	7	C
3	B	8	A
4	B	9	A, C, D
5	C	10	D

PART 8

1	A	6	D
2	C	7	D
3	C	8	B
4	D	9	D, E
5	C	10	A

PART 9

1	D	6	A
2	C	7	D
3	D	8	C
4	B	9	A
5	B	10	D

PART 10

1	C	6	D
2	D	7	B
3	E	8	A
4	D	9	C
5	D	10	B

PART 11

1	D	6	E
2	A	7	A
3	D	8	B
4	D	9	A
5	A	10	B

PART 12

1	D	6	B
2	B	7	A
3	B	8	B
4	C	9	D
5	C	10	B

PART 13

1	A	6	E
2	C	7	B
3	C	8	D
4	B	9	A
5	A	10	A

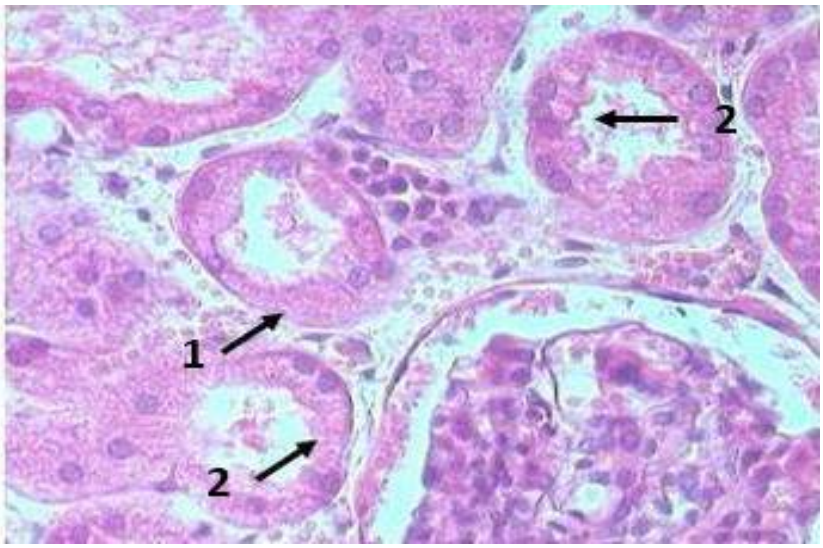
PART 14

1	B	6	B
2	A	7	B
3	D	8	D

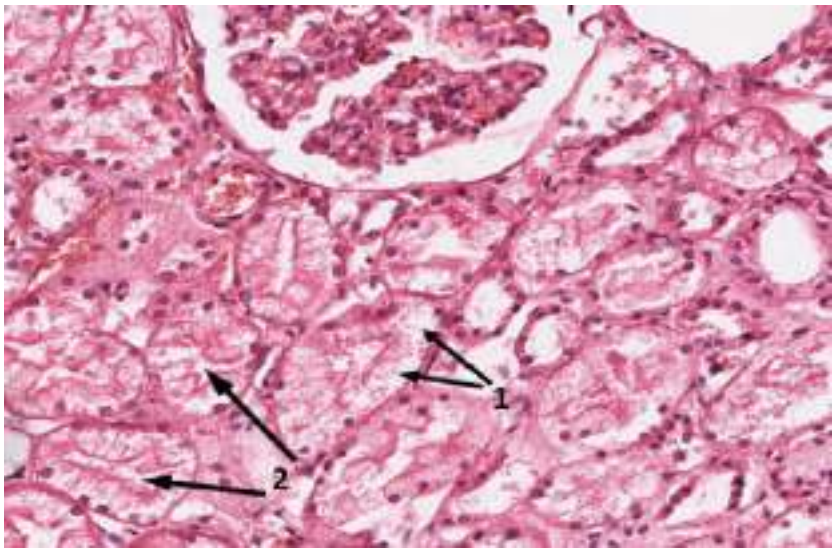
4	A	9	A
5	B	10	D

Appendix 2

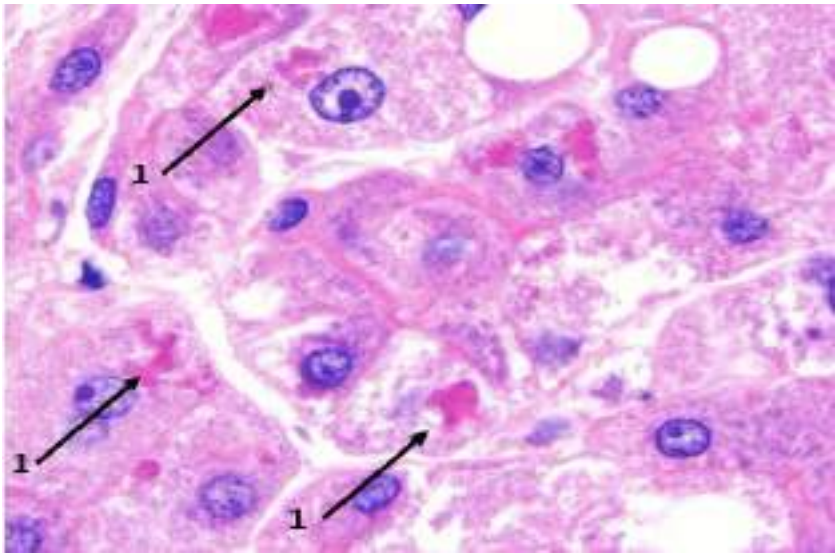
Microphotographs



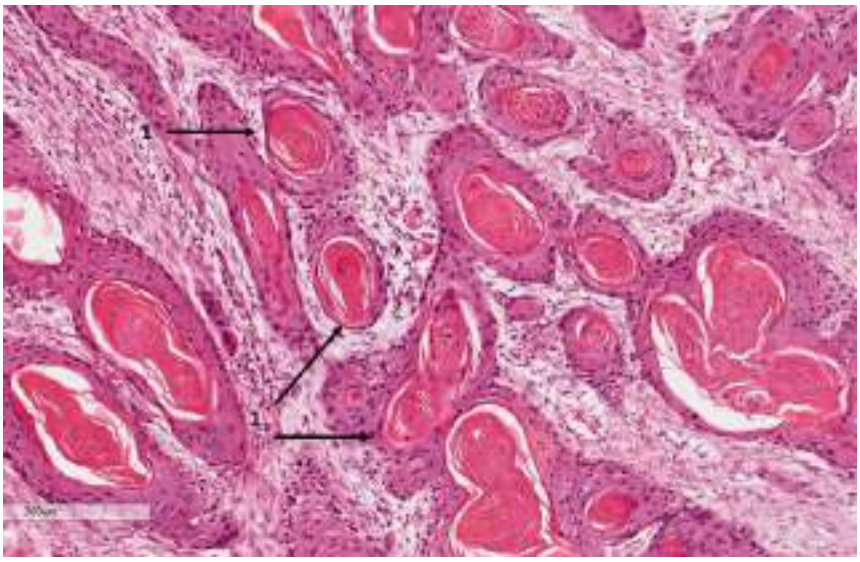
1. Granular dystrophy of the kidney. In the cytoplasm of the epithelium of the convoluted tubules of the kidney, there are numerous small eosinophilic grains (1) - hypertrophied intracellular organelles. The apical cytoplasm is destroyed and becomes stellate (2).



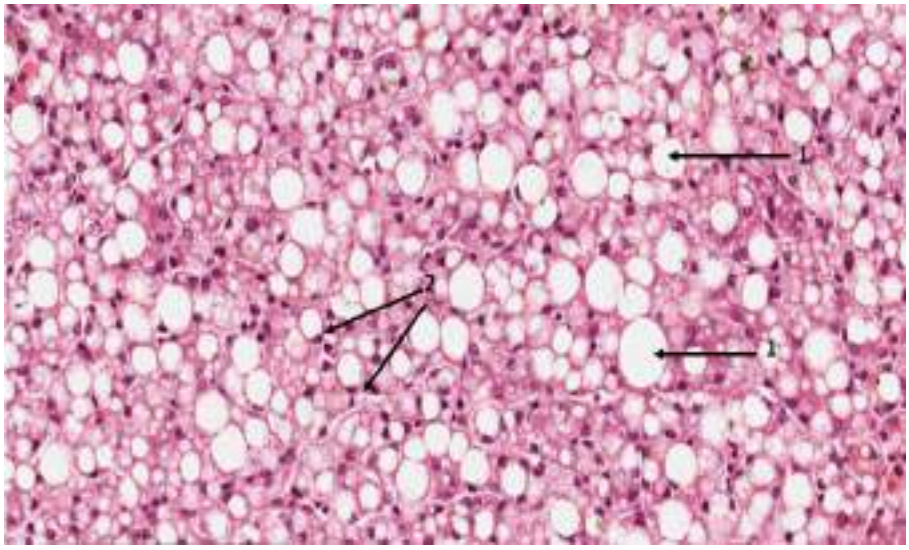
2. Hydropic (vacuolar) dystrophy of the kidney. The volume of epithelial cells is increased due to excessive hydration of the intracellular space with the formation of optically empty vacuoles filled with cytoplasmic fluid (1). Vacuolization also affects cell organelles (e.g., mitochondria, Golgi apparatus, endoplasmic reticulum). The lumen of the tubules is narrowed or completely absent (2).



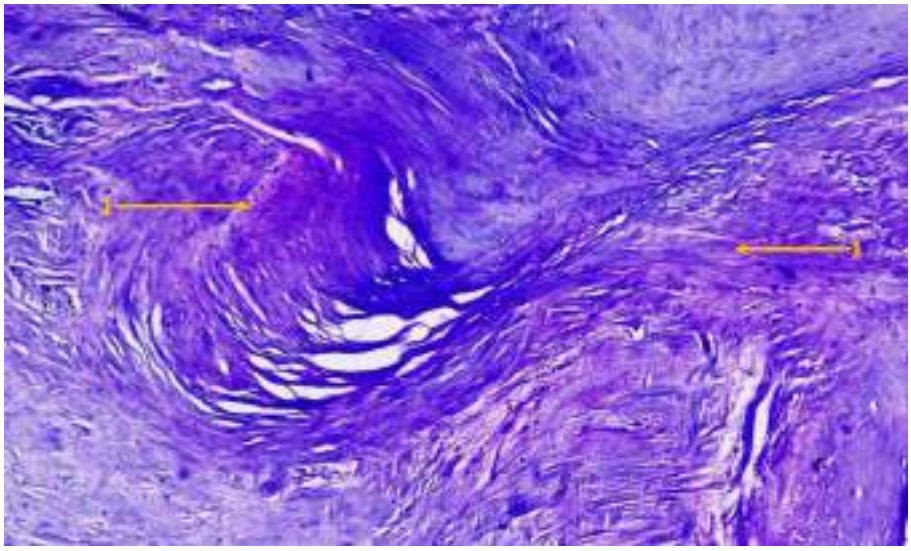
3. Hyaline-drop dystrophy of the liver. In the cytoplasm of cells, hyaline-like homogeneous eosinophilic inclusions (Mallory bodies) appear, located in the form of drops or merging (1). These changes are characteristic of alcoholic liver damage - alcoholic hepatosis.



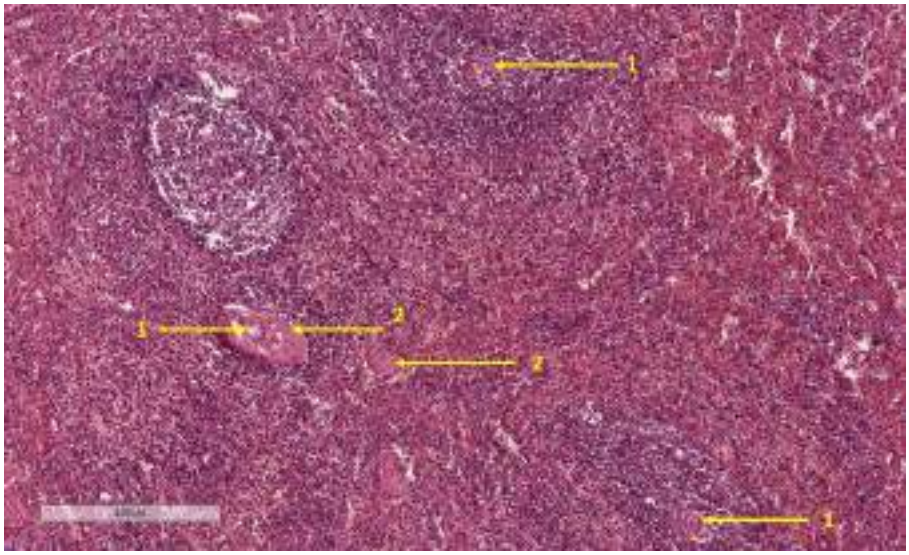
4. Squamous cell carcinoma with keratinization. Concentric accumulations of keratinizing cells, having the appearance of rounded pinkish layered formations - "cancer pearls" (1).



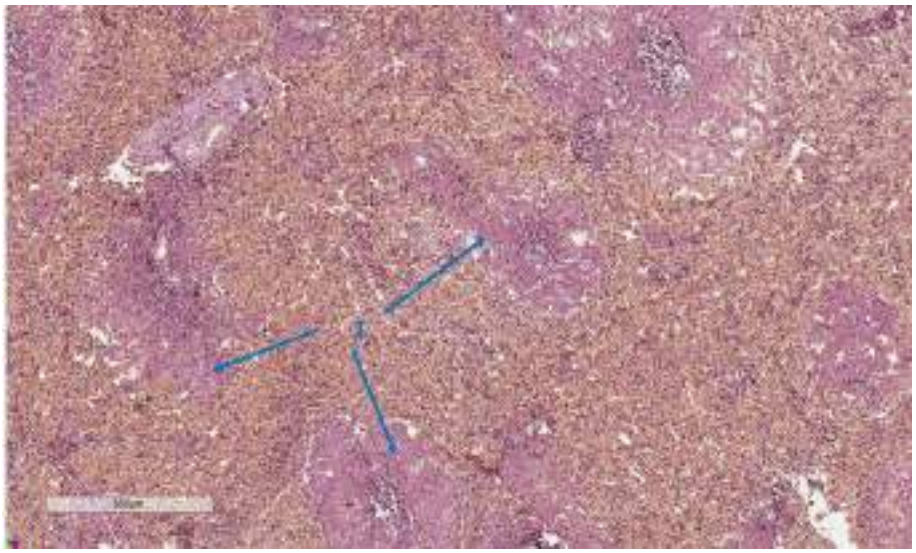
5. Parenchymal fatty dystrophies of the liver. In the cytoplasm of hepatocytes, there are large optically empty fat vacuoles (when stained with (H&E) (1). The sizes of hepatocytes are increased, and the nucleus is displaced to the periphery of the cell (2). Macroscopically, such a liver is called «goose liver».



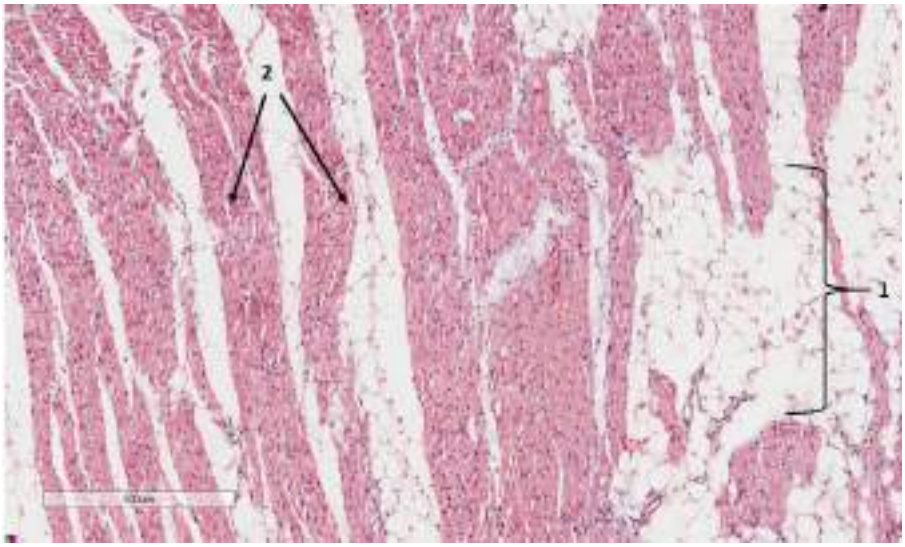
6. Mucoid swelling of the mitral valve of the heart in rheumatism (staining with toluidine blue). The main substance swells and volume increases, which leads to the removal of connective tissue cells from each other. The valve tissue loses its fibrillar structure due to swelling and homogenization of collagen fibers and stains pinkish-violet (metachromasia) (1).



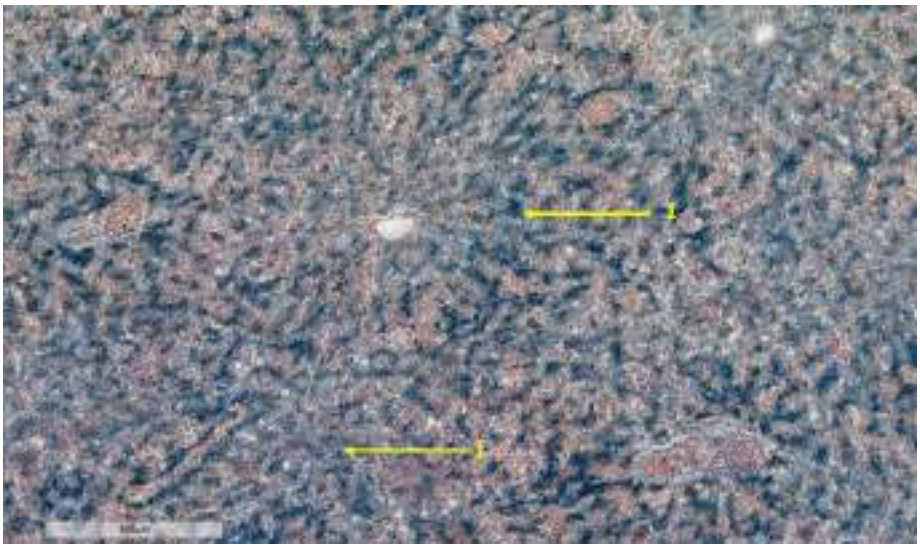
7. Hyalinosis of the vessels of the spleen. In the centers of the follicles, arterioles have a narrowed lumen (1) and a thickened wall due to the deposition of a homogeneous eosinophilic mass under the endothelium – hyalinosis (2).



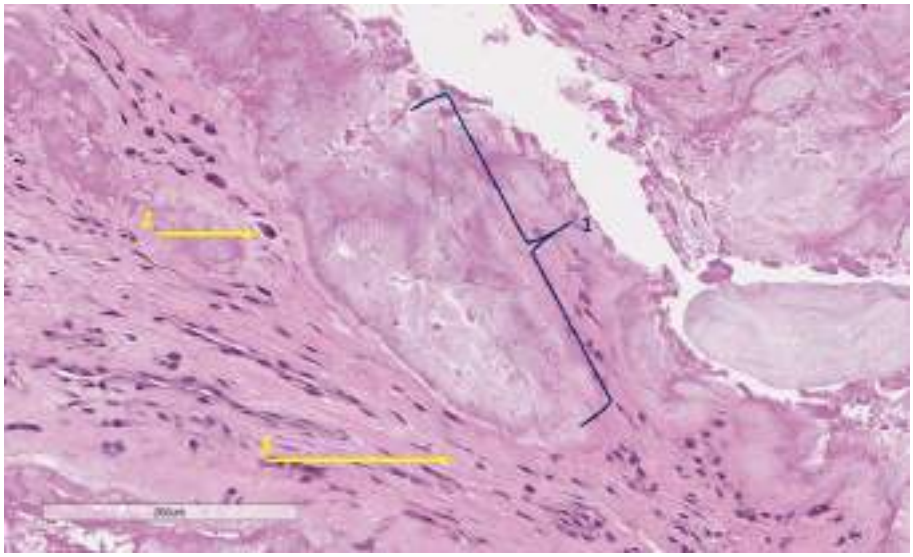
8. Amyloidosis of the spleen ("sago spleen"). Amyloid masses stain pink with eosin and are located predominantly in the peripheral part of the spleen follicles or replace the entire follicle and displace cells (1).



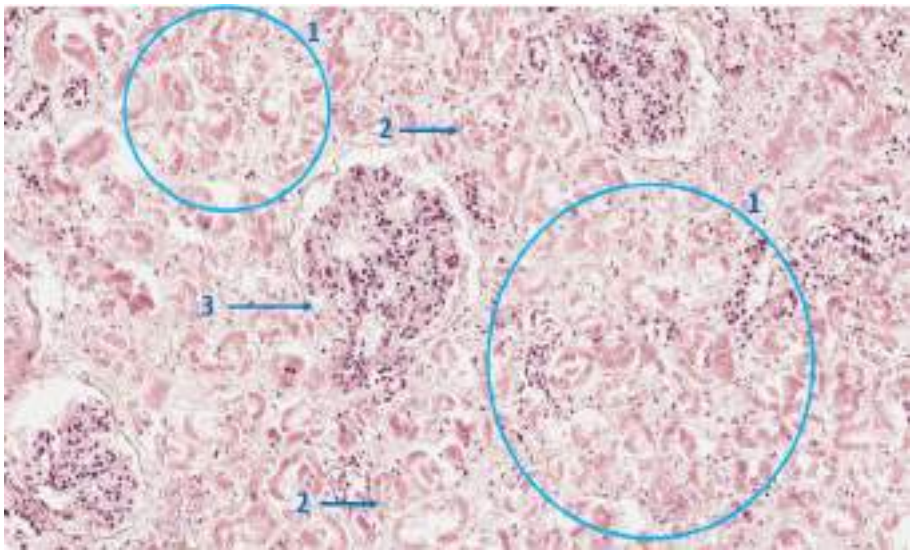
9. Obesity of the heart. Between the muscle fibers there is a deposition of adipose tissue in the form of large optically empty vacuoles that grow from the side of the epicardium (1). Muscle fibers are compressed and atrophied (2).



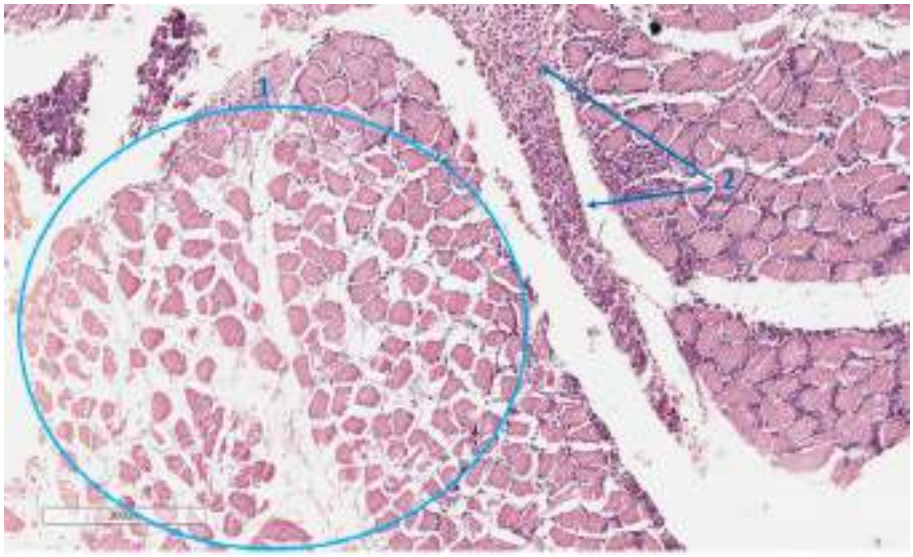
10. Hemosiderosis of the liver (staining for iron - Perl's reaction). Deposition of greenish-blue granules of hemosiderin in the cytoplasm of hepatocytes, as well as in the tissue of the organ (1).



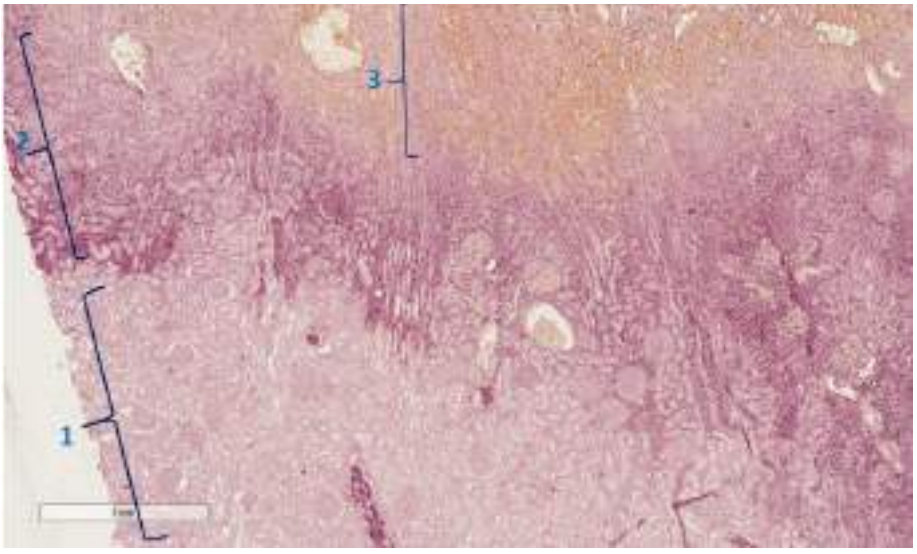
11. Skin with gout. There is a deposition of salts of uric acid in the form of amorphous or needle-shaped crystals (1), the presence of giant multinucleated cells of foreign bodies (2) around the deposition of urates. The presence of fibrous connective tissue around the deposition of salts with the formation of a capsule (3), as well as the presence of areas of necrosis and proliferative inflammation.



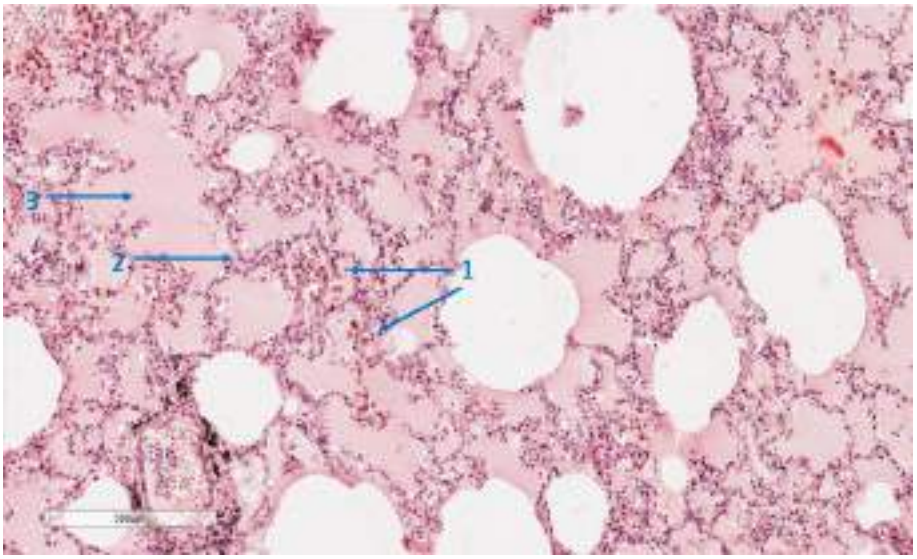
12. Necrotic nephrosis. The nephrocytes of the proximal tubules are enlarged, and nuclei are absent in them (karyolysis) (1). The convoluted tubules of the kidney look like homogeneous eosinophilic formations with a narrowed lumen (2). Vascular glomeruli are preserved (3).



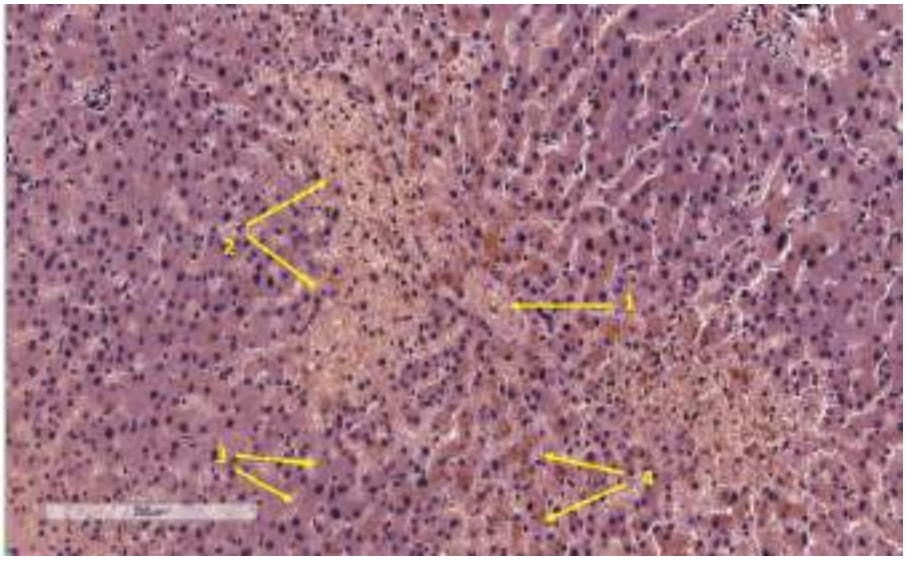
13. Waxy (Zenker's) necrosis of muscles. In areas of necrosis, muscle fibers are swollen, and thickened, and do not have nuclei and transverse striation (1). The stroma is swollen. The marginal areas of necrosis are infiltrated with leukocytes (2).



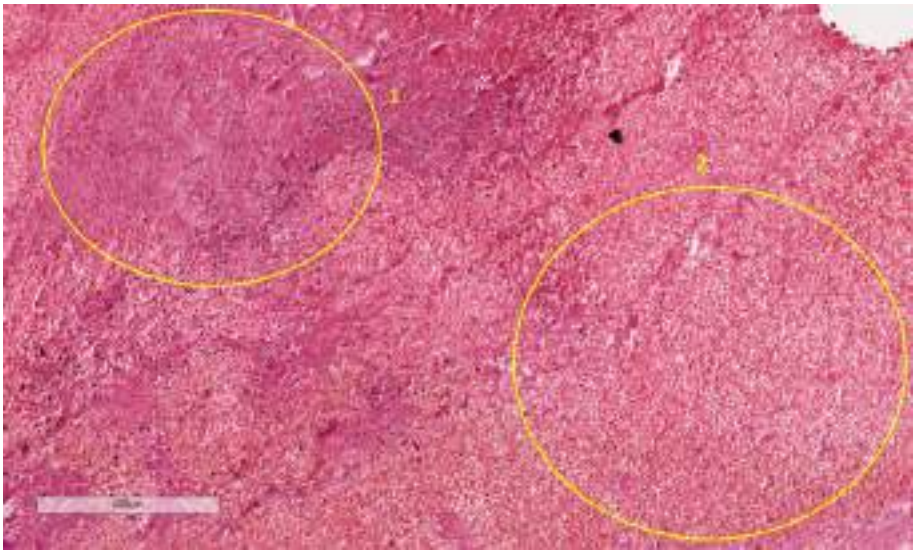
14. White infarction of the kidney with a hemorrhagic rim. In the zone of infarction, the structure of the organ is broken, the nuclei do not stain (karyolysis), there are accumulations of lumps of chromatin (karyorrhexis), all structural elements merge into a homogeneous eosinophilic mass (1). The zone of necrosis is delimited from the preserved kidney tissue by leukocyte infiltration (demarcation line) (2). On the periphery of the infarction, there is a zone of hemorrhage with hemolysis of erythrocytes and the deposition of brown pigment (hemosiderin) (3).



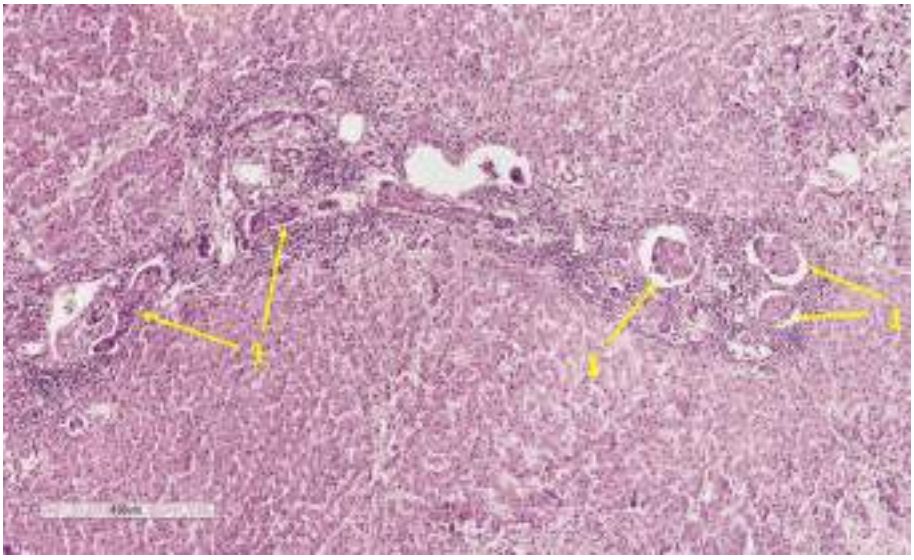
15. Acute pulmonary edema. In the lumen of the alveoli, there are accumulations of alveolar macrophages with a dark brown pigment - hemosiderin in the cytoplasm (siderophages) (1). The interalveolar septa are thickened due to the expansion of capillaries (2). Part of the alveoli is filled with edematous fluid (3).



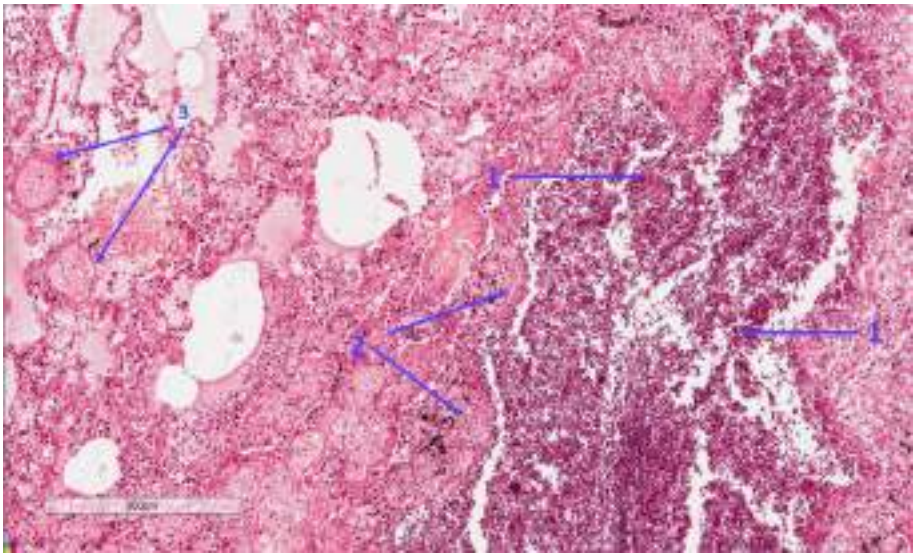
16. "Nutmeg" liver. Blood capillaries and veins in the centers of the lobules are dilated and filled with blood (1). Some erythrocytes are hemolyzed (2). Hepatic beams are thinned, and sometimes absent (3). The cells contain the brown pigment hemosiderin (4).



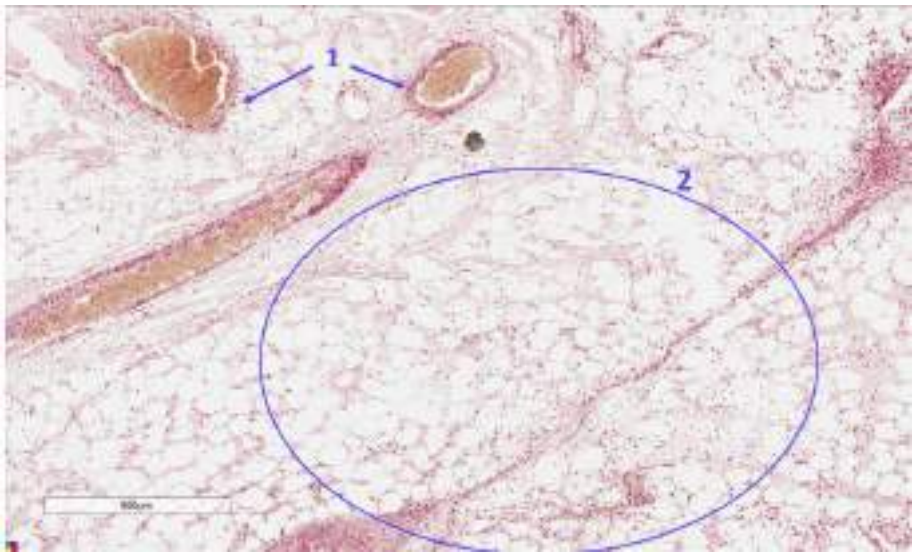
17. Mixed thrombus. Thrombotic masses contain fibrin, leukocytes, platelets (1) and hemolyzed erythrocytes (2).



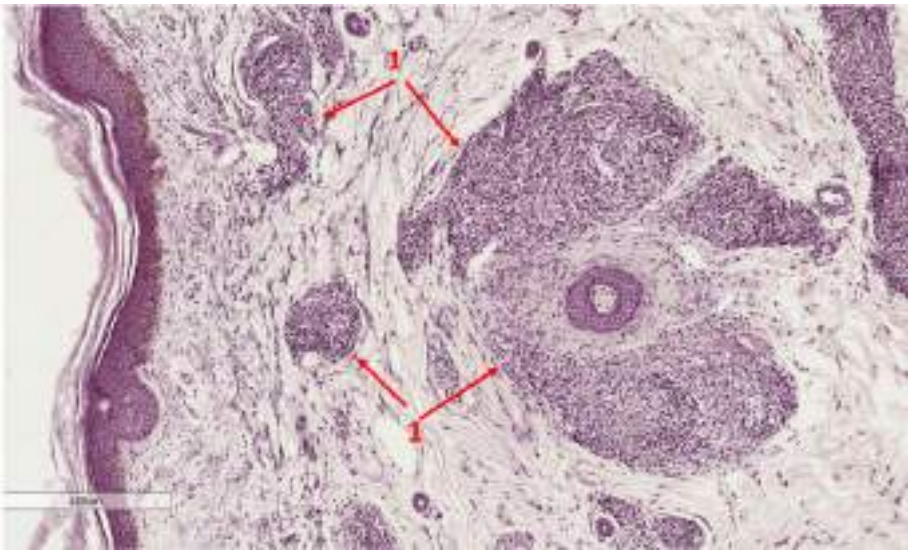
18. Embolism by cancer cells of the lymphatic vessels of the liver. Most triads contain complexes of intensely stained cancer cells that form compact clusters (1). They are located in the lumen of the lymphatic vessels located between the components of the triads, but sometimes in the lumen of the veins.



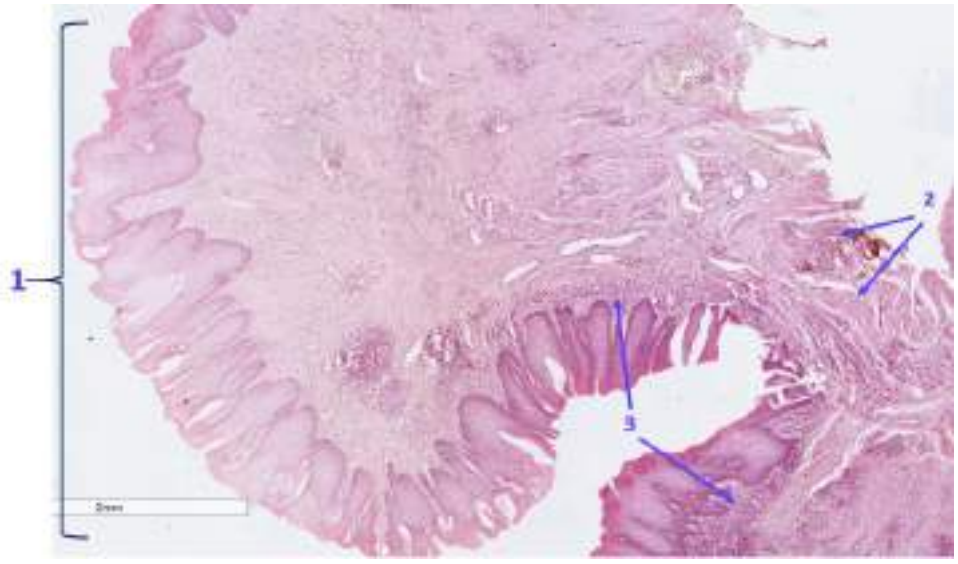
19. Acute abscess of the lung. The formation of a cavity with significant focal inflammatory infiltration, represented mainly by neutrophilic leukocytes, as well as pronounced tissue and cellular detritus, is noted (1). The wall of the abscess is thin and is formed by single cells of the connective tissue and the surrounding lung parenchyma (2). There is hyperemia of the vessels of the microvasculature (3).



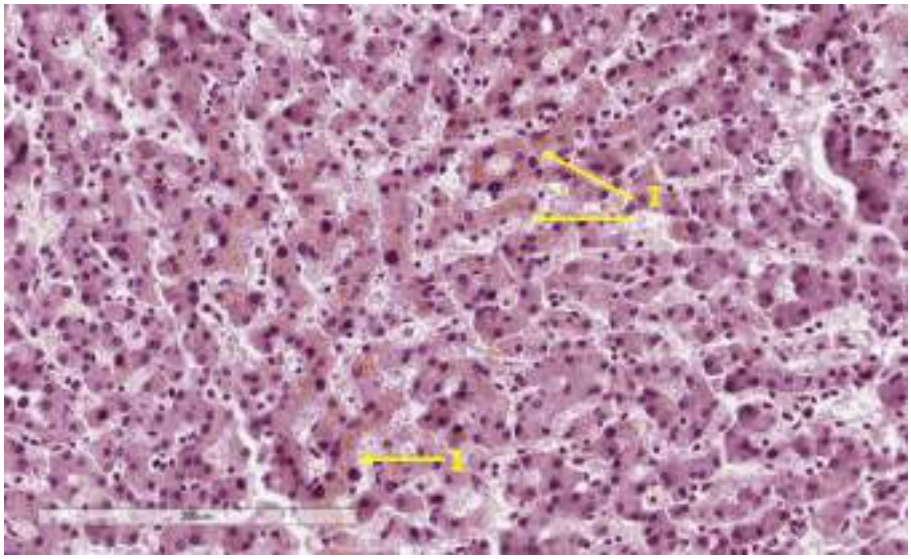
20. Phlegmonous inflammation of the thigh. Edema, hemorrhages, inflammatory hyperemia (1), and diffuse infiltration of adipose tissue by leukocytes (2) are noted.



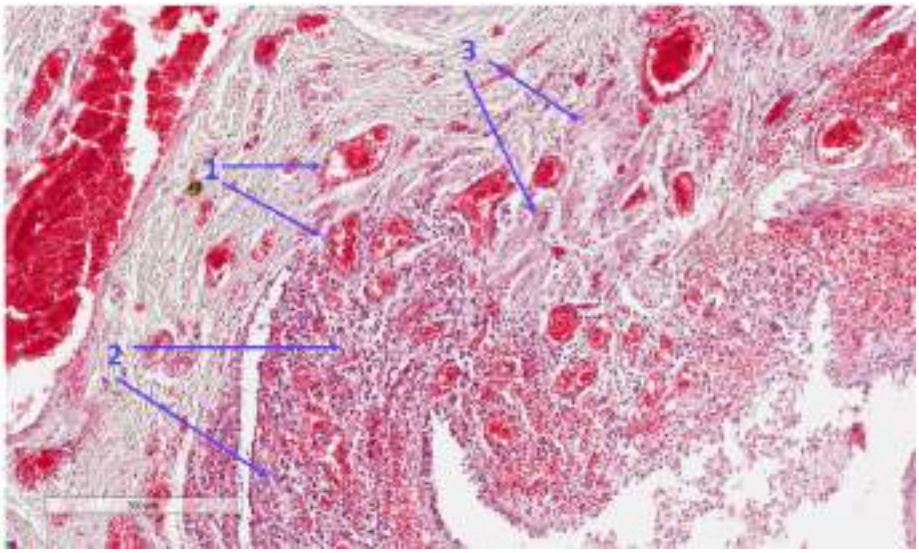
21. Leprosy (tuberculoid type). Formation of epithelioid cell granulomas in the dermis (1) without a focus on caseous necrosis. Also, a large number of lymphocytes and plasma cells are involved in the formation of granulomas. Single multinucleated cells are formed.



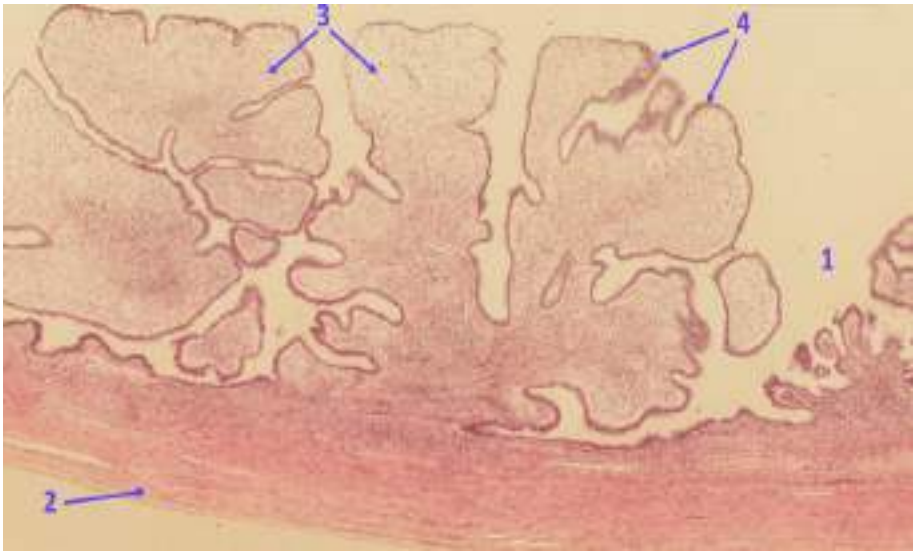
22. Polyp of the stomach. Villous growths of the hyperplastic epithelium (1); the peduncle is represented by connective tissue with vessels (2) and inflammatory lymphohistiocytic infiltration (3).



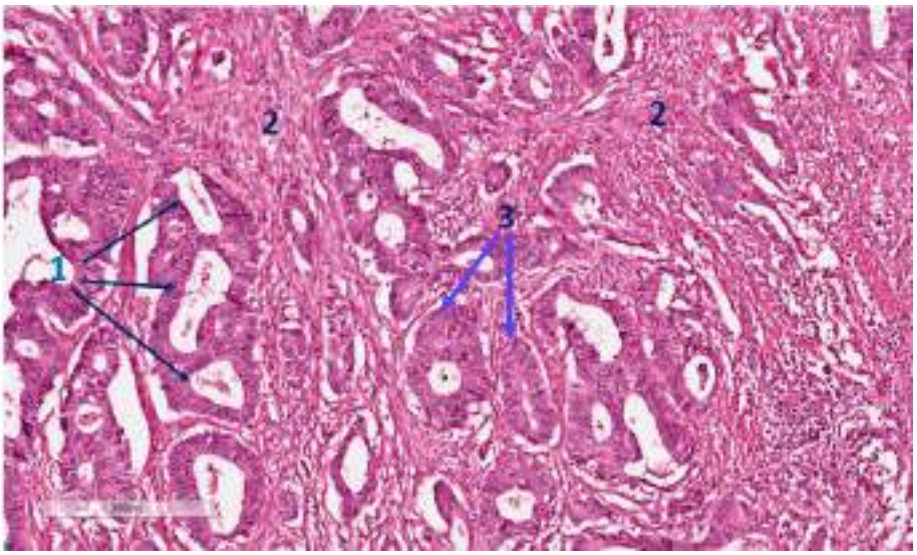
23. Atrophy of the liver. Accumulation of the brown lipidogenic pigment lipofuscin in the cytoplasm of hepatocytes (1) («brown atrophy of the liver»).



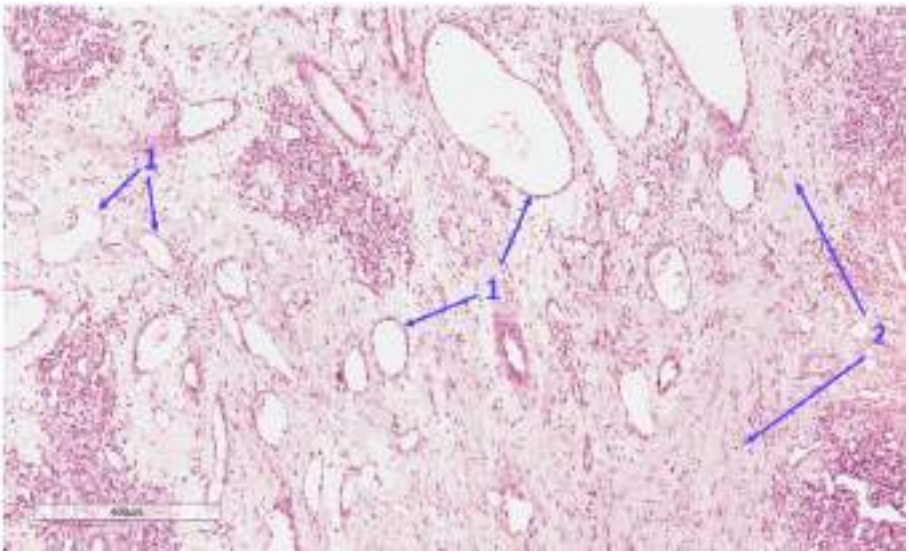
24. Granulation tissue. A large number of young vessels of the microvasculature are located in parallel (1). Between them are leukocytes and macrophages (2), as well as young elements of connective tissue (fibroblasts, myofibroblasts) (3).



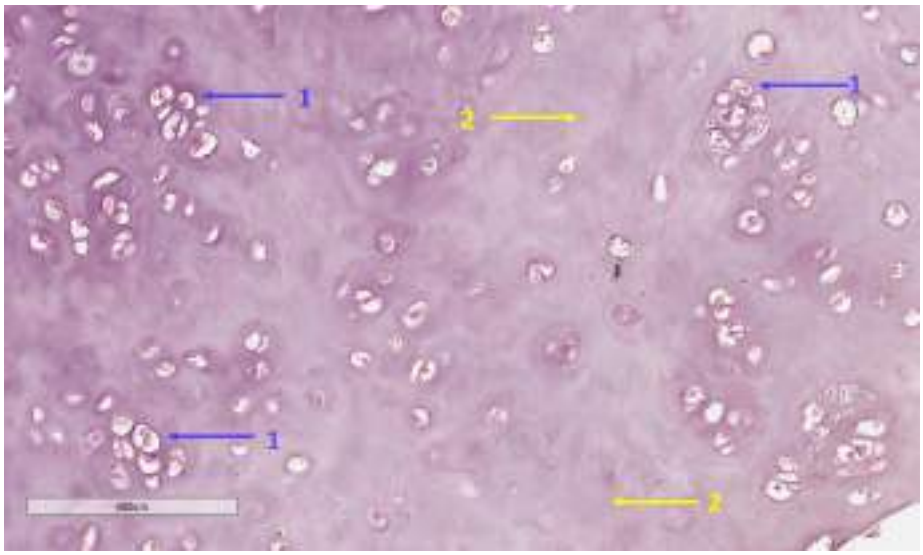
25. Papillary adenocystoma. Adenocystoma contains cavities (1), the walls of which are represented by fibrous connective tissue (2) and papillary epithelial growths, different in size and shape (3). A single layer and stratified columnar epithelium located on the basement membrane are determined (4).



26. Adenocarcinoma of the intestine. Germination of the mucous and submucosal layers of the intestinal wall with atypical glands of various shapes and sizes: elongated-rounded, irregular in shape, large and small (1). The glands are unevenly located among the fibrous tissue (2). Epithelial cells lining the glands are atypical: their nuclei are polymorphic, with different content of chromatin and mitoses, cells of different shapes and sizes can be arranged in several layers (3).

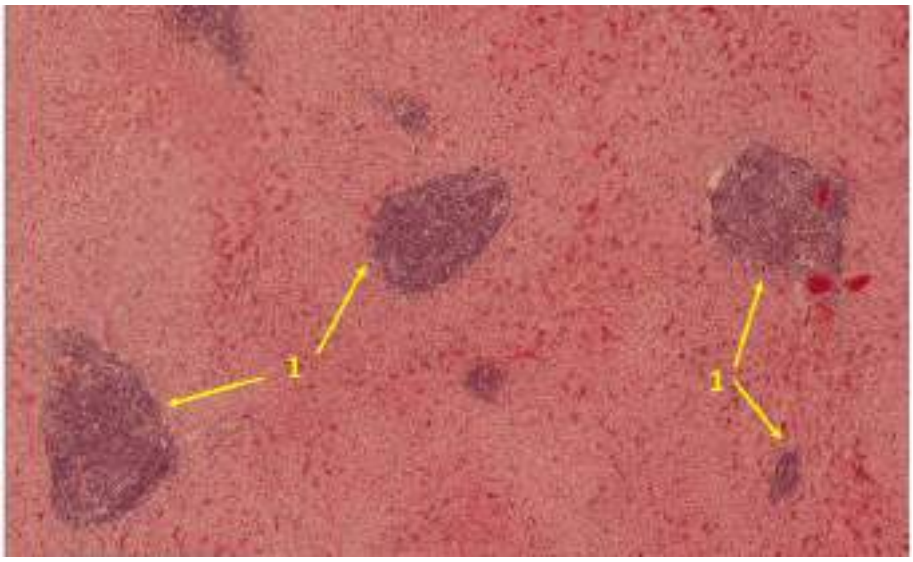


27. Capillary hemangioma. The tumor consists of small capillary-type vessels lined with typical endothelial cells (1) and surrounded by connective tissue (2).

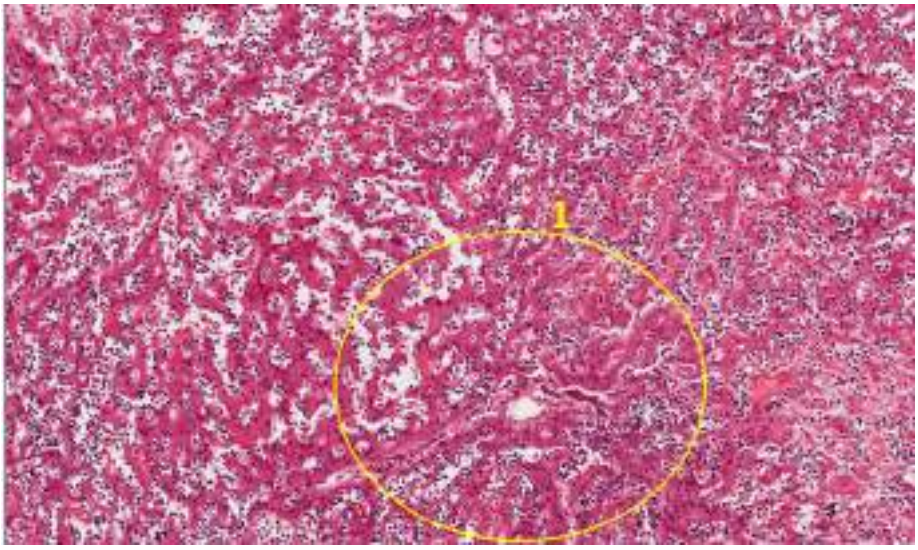


28. Chondroma. Tumor chondrocytes are polymorphic - different sizes and shapes, with one or two nuclei (1); located chaotically in the lacunae of the main substance of the cartilage (2).

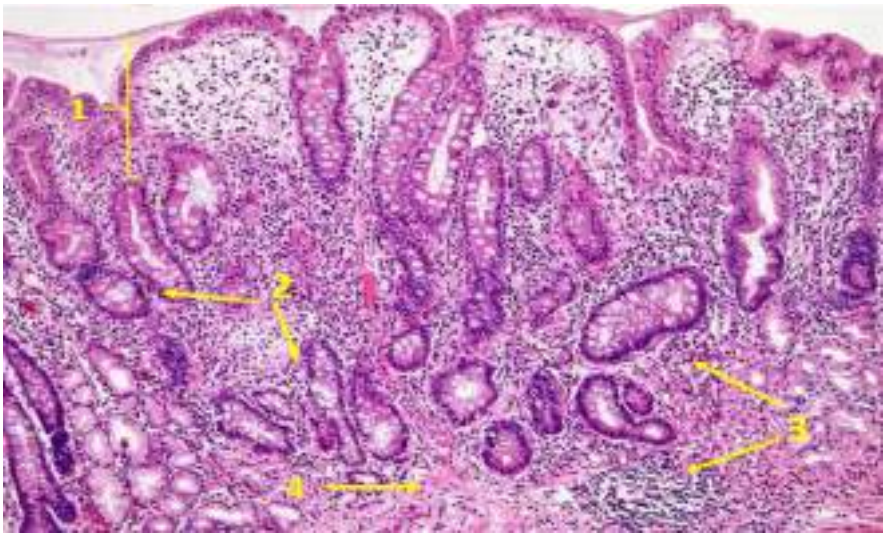
29. Junctional nevus. Nested accumulations of large nevus cells with the presence of pigment on the border between the epidermis and the papillary dermis (1). There is a massive focal lymphohistiocytic infiltration in the underlying papillary layer of dermis (2).



30. The liver in chronic lymphocytic leukemia. Leukemic infiltrates are represented by atypical lymphocytes, and have a nested arrangement along the triads (1).



31. The liver in chronic myelogenous leukemia. Inside the lobules, along the interbeam capillaries, immature elements of the myeloid series are diffusely located, forming leukemic infiltrates (1).



32. Atrophy of the gastric mucosa. The mucous membrane is thinned (1). Reducing the number and size of glands, increasing the distance between them (2). Lymphohistiocytic infiltration of the lamina propria (3), pronounced sclerosis near the gastric glands (4). Intestinal and pyloric metaplasia is also noted.